Smooth Pursuit and Antisaccade Eye Movements as Endophenotypes in Schizophrenia Spectrum Research

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Abstract

Smooth pursuit eye movement (SPEM) and antisaccade deficits have been proposed as schizophrenia spectrum endophenotypes. An endophenotype is a behavioural or biological deficit thought to represent, more closely than the disease phenotype, the effects of an underlying disease gene. Oculomotor endophenotypes possess phenotypic homogeneity, well-understood neural correlates and objective assessment and may thus be used as phenotypes in linkage studies. This thesis investigated a number of issues concerning the reliability and validity of the SPEM and antisaccade tasks as schizophrenia spectrum endophenotypes (and two tasks thought to be unimpaired in the schizophrenia spectrum, visual fixation and prosaccades). The schizophrenia spectrum encompasses not only people with schizophrenia but any population with an increased frequency of schizophrenia-related phenotypes or genotypes, such as schizotypal individuals or first-degree relatives of schizophrenia patients. A valid endophenotype should thus be detected in these populations. Study I investigated reliability, namely internal consistency and temporal stability, of eye movements in healthy individuals. Study II utilised first-episode psychosis patients and healthy controls, aiming to detect behavioural oculomotor deficits in the absence of secondary confounds that may be encountered in chronic schizophrenia. Study III assessed performance in siblings discordant for schizophrenia. Study IV explored the relationship between psychometric schizotypy and oculomotor performance. Study V examined possible state effects of procyclidine, an anticholinergic compound often administered to schizophrenia patients, on performance in a patient group. The results generally confirmed the validity of the SPEM and antisaccade deficits as schizophrenia spectrum endophenotypes: Oculomotor performance was mostly stable both within and between assessments. SPEM and antisaccade impairments were observed in first-episode psychosis patients and schizophrenia patients and their healthy siblings. Antisaccade, but not SPEM, impairments were associated with high levels of schizotypy. State effects of procyclidine on SPEM and antisaccade performance were observed, suggesting the need to consider the influence of pharmacological treatment in future patient studies. These findings suggest that SPEM and antisaccade deficits may be studied profitably as endophenotypes in schizophrenia spectrum research.

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Für Martina

und meine Eltern

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Chapter One

Introduction to the Schizophrenia Spectrum

1.1 Chapter Overview

This chapter will provide an introduction to schizophrenia spectrum research. First, important issues relating to the definition, description and diagnosis of schizophrenia will be addressed. Then, the epidemiology and treatment of schizophrenia will be described and the key findings of structural and functional brain changes in this condition will be reviewed. The concepts of schizotypy and the schizophrenia spectrum will be introduced. A particular focus of the chapter will be on the genetics of schizophrenia. The chapter will conclude with a delineation of the research problem that this thesis addresses. The research problem focuses on strategies needed in order to overcome the clinical and biological heterogeneity and genetic complexity of schizophrenia in the identification of disease genes. The approach to the research problem that this thesis is advocating is the endophenotype approach, which will be outlined.

1.2 Definition, Description and Diagnosis of Schizophrenia

Schizophrenia is the term used to describe a severe psychiatric syndrome including the symptoms of hallucinations, delusions, disordered thought, abnormal affect and loss of volition. The influential Diagnostic and Statistical Manual of Mental Disorders, Version IV (DSM-IV), of the American Psychiatric Association (1994), defines schizophrenia as a "disturbance that lasts for at least 6 months and includes at least 1 month of active-phase symptoms (i.e. two [or more] of the following: delusions, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour, negative symptoms)" (p. 273). The criteria required in establishing a clinical diagnosis of schizophrenia according to DSM-IV are listed in Table 1.1.

Table 1.1: Diagnostic Criteria for Schizophrenia according to DSM-IV (American Psychiatric Association 1994)

Criterion	Specifications
A. Characteristic Symptoms	Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated): (1) delusions (2) hallucinations (3) disorganised speech (e.g., frequent derailment or incoherence) (4) grossly disorganised or catatonic behaviour (5) negative symptoms, i.e., affective flattening, alogia, or avolition **Note:** Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts, or two ore more voices conversing with each other.
B. Social-occupational Dysfunction	For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement)
C. Duration	Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).
D. Schizoaffective and Mood Disorder Exclusion	Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either (1) no Major Depressive, Manic, or Mixed Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.
E. Substance/general medical condition exclusion	The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.
F. Relationship to a Pervasive Developmental Disorder	If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

A similar definition is offered by the International Statistical Classification of Diseases and Related Health Problems, Version 10 (ICD-10), of the World Health Organization (1992):

"The schizophrenic disorders are characterised in general by fundamental and characteristic distortions of thinking and perception, and affects that are inappropriate or blunted. Clear consciousness and intellectual capacity are usually maintained although certain cognitive deficits may evolve in the course of time. The most important psychopathological phenomena include: thought echo; thought insertion or withdrawal; thought broadcasting; delusional perception and delusions of control; influence or passivity; hallucinatory voices commenting or discussing the patient in the third person; thought disorders and negative symptoms. The diagnosis of schizophrenia should not be made in the presence of extensive depressive or manic symptoms unless it is clear that schizophrenic symptoms antedate the affective disturbance. Nor should schizophrenia be diagnosed in the presence of overt brain disease or during states of drug intoxication or withdrawal." (World Health Organization 1992; p. 325).

The most important signs and symptoms of schizophrenia are defined according to DSM-IV as follows (American Psychiatric Association 1994).

Hallucinations are sensory experiences that are not due to real stimuli, as they are experienced only by the sufferer. In schizophrenia, hallucinations may occur in any modality (e.g. tactile, olfactory) but are most commonly auditory (e.g. hearing voices). Auditory hallucinations of human voices most commonly provide a running commentary on the sufferer's actions, directly address the sufferer or consist of a dialogue between two or more people. The content varies, but is often pejorative.

Delusions are erroneous, often bizarre, beliefs, which are incongruent with one's cultural norms, are held despite evidence to the contrary and are resistant to logic or persuasion. Delusions often have common themes, the most common of which include persecution (the sufferer believes s/he is being followed or spied on), reference (the sufferer believes that gestures, comments or passages from the media or other people are directed at him/her), religion (the sufferer believes s/he has special religious significance) or grandiosity (the sufferer believes s/he has special status in a variety of contexts, such as being a celebrity, great discoverer etc.).

Disorganised thinking, or formal thought disorder, may be detected through a number of abnormal speech patterns, including loose associations (moving quickly from one

topic of conversation to another), providing answers that are unrelated to questions or displaying incoherent or incomprehensible speech.

Grossly disorganised behaviour includes a variety of disturbances, such as child-like ('silly'), agitated, unplanned, unpredictable, or inappropriate behaviours.

Catatonic motor behaviours refer to a significant decrease in motor responsivity to the environment, maintaining a rigid pose, resistance to instructions or attempts to be moved, or, alternatively, excessive unstimulated motor behaviour.

Negative symptoms include flattening of affect, alogia (poverty of speech) and avolition (inability to execute goal-directed, purposive behaviours).

A number of clinical subtypes of schizophrenia are specified in DSM-IV; these are the *Paranoid, Disorganised, Catatonic, Undifferentiated* and *Residual* types.

Historically, schizophrenia was called *dementia praecox* by Kraepelin (1971). Kraepelin observed cognitive decline (*dementia*) but recognised that the early (*praecox*) onset of illness distinguished this condition from other dementias. Dementia praecox was also distinguished from the other major psychotic disorder, namely manic depression, which was thought to be associated with better prognosis (Kraepelin 1971). The term 'schizophrenia' was first introduced by Bleuler (1950), derived from the Greek words *schizo* (split) and *phrene* (mind), referring to fragmentation of the mind and the often-observed dissociation of affect from reality. Bleuler discarded the term dementia, as he did not observe frequent deterioration over the course of the illness. Interestingly, Bleuler referred to the *schizophrenias*, proposing the now popular notion of multiple disease processes and/or subtypes instead of a unitary, homogenous disease category.

Despite the consistent observation of a common set of schizophrenic symptoms the clinical presentation is highly variable, both within and between individuals. Thus, there is no single core symptom that is observed in all patients with a diagnosis of schizophrenia; indeed, a popular criticism of the concept of schizophrenia is that there may be two individuals with the same diagnosis who differ widely in their clinical presentation and do not share a single symptom (Rosenhan & Seligman 1995).

One of the key clinical features of schizophrenia is *psychosis*, most narrowly defined as hallucinations and delusions. Broader definitions of psychosis include symptoms such as disordered speech and grossly disorganised or catatonic behaviour (American Psychiatric Association 1994).

Diagnosis of schizophrenia is based on information available from clinical interviews and observations. This reliance on clinical information is critical, as no valid biological (or neuropathological) markers of the disease are available (as in other neuropsychiatric conditions, such as Alzheimer's disease; Bertram & Tanzi 2001). Similarly, the aetiology of schizophrenia is essentially unknown. A number of genetic and non-genetic factors are likely to play a role; however, these are not, at present, utilised in the diagnostic process.

Differential diagnosis of schizophrenia involves the exclusion of a number of other psychiatric and neurological conditions whose symptoms may overlap with those of schizophrenia, such as schizoaffective disorder, bipolar affective disorder (especially in the manic phase), depression with psychotic features, dementia, certain types of drug abuse and severe forms of obsessive-compulsive disorder (American Psychiatric Association 1994).

Symptoms of hallucinations, delusions and thought disorder have been theoretically grouped together as *positive* symptoms, with avolition, reduced or flattened affect, alogia and social withdrawal representing *negative* symptoms (American Psychiatric Association 1994; Crow 1980a, 1980b). Positive symptoms in this categorisation are, therefore, defined by being abnormal through their presence, while negative symptoms are defined as the abnormal absence of psychological function. Factor analytic studies of clinical symptom ratings have shown, however, that symptoms tend to cluster more reliably into three dimensions, commonly labelled as *reality distortion* (including delusions and hallucinations)[1], *disorganisation* (including inadequate affect and disordered thought and speech) and *psychomotor poverty* (including poverty of speech, paucity of facial and other emotional expressions, reduced motor behaviour and social withdrawal)[2] (Liddle 1987b). The first two of these dimensions thus constitutes positive symptoms; the last constitutes negative symptoms (Crow 1980a, 1980b).

Just as the inter-individual presentation of schizophrenia is variable, the course of the illness is often not linear and differs between people. Evidence from retrospective as well as prospective studies points to extended premorbid and prodromal phases. The

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[1] This dimension is called the "psychotic dimension" by DSM-IV (American Psychiatric Association 1994; p. 275).

[2] This dimension is called "negative symptoms" by DSM-IV (American Psychiatric Association 1994; p. 275).

premorbid phase is characterised by subtle cognitive, emotional, social and motor deficits in otherwise clinically healthy children and adolescents. The prodromal phase immediately precedes illness onset and is characterised by an increase in socially deviant behaviour, eccentric ideas, unusual perceptions and experiences and disordered speech (Allin & Murray 2002). Onset of illness is often insidious, making it difficult to distinguish from the clinically similar but more subtle prodromal phase (American Psychiatric Association 1994).

The observation of pronounced premorbid and prodromal symptoms has led to the formulation of one of the most influential accounts of schizophrenia to date, namely the neurodevelopmental model. This general model, posited in several variations by a number of scientists (Allin & Murray 2002; Andreasen et al 1999; Luna & Sweeney 2001; Sawa & Snyder 2002; Tsuang et al 2001), argues that schizophrenia is a developmental brain disorder. Abnormal brain development, resulting from genetic predisposition and/or early lesions, is thought to result in behavioural and subclinical abnormalities throughout development, culminating in clinical psychosis after brain maturational processes in early adulthood. Pre-clinical abnormalities concern schizophrenia-related (sub-)clinical symptoms, motor deficits, cognitive deficits and social and interpersonal problems (Allin & Murray 2002; McDonald & Murray 2000).

The neurodevelopmental model, or at least aspects of it, is widely accepted in biological schizophrenia research. However, as Allin and Murray (2002) pointed out, the model cannot at present explain the precise mechanisms by which early brain damage and genetic predisposition result in full-blown illness after a 'latency period' of about two decades. Moreover, a number of cases with schizophrenia, such as late-onset cases, are clearly not of a neurodevelopmental nature (Allin & Murray 2002).

Following an acute initial phase with severe, mostly positive symptoms, some cases (about 20%) completely remit, whereas the majority go on to experience further psychotic episodes. For about 35% of sufferers the course of illness from first episode is chronic, resulting in greater functional impairments with each episode. However, there is also evidence that some features of schizophrenia, in particular positive symptoms, improve after the initial acute phase (Green 2001). Factors that are associated with good outcome include an acute rather than insidious onset, older age at onset, a short initial psychotic phase, a relative absence of previous psychiatric history and fewer functional and structural brain impairments. Men are thought to have an earlier onset of illness and worse prognosis than women (American Psychiatric Association 1994).

1.3 Epidemiology of Schizophrenia

Epidemiology is concerned with the frequency and determinants of disease in a population (i.e. the prevalence, incidence and risk factors; Bromet & Fennig 1999). Epidemiological studies of schizophrenia are limited by a number of factors, such as less than perfect reliability in obtaining the diagnosis, difficulties in determining the date of illness onset (which has serious consequences for the identification of risk factors) and difficulties in obtaining data from entire populations or, at least, truly representative samples. Nevertheless, there is some agreement on basic epidemiological findings in schizophrenia research.

The lifetime prevalence of schizophrenia (the percentage of the population who at any point in time have schizophrenia) is thought to be about 0.7%. The incidence (the rate of new cases each year) varies but is estimated to be about 0.2 per 1000 (American Psychiatric Association 1994; Bromet & Fennig 1999).

Schizophrenia does not strike at random; its onset is often preceded by a number of risk factors. A risk factor is a determinant of the illness, which antedates its onset (Bromet & Fennig 1999). The identification of risk factors is of obvious importance in providing a better understanding of the aetiology of schizophrenia. As noted above, the aetiology of schizophrenia is essentially unknown, but a number of risk factors may be causally implicated. The following are amongst the most reliably identified risk factors (for review, see Allin & Murray 2002; Bromet & Fennig 1999; McDonald & Murray 2000; Sawa & Snyder 2002; Torrey & Yolken 2000; van Os & Marcelis 1998).

Family history of schizophrenia. This is arguably the greatest known risk factor and is discussed in more detail in Section 1.6.1.

Social class. Schizophrenia is somewhat more common in lower socio-economic classes. Two hypotheses have been proposed to account for this finding. First, the adverse physical and social environment of low socio-economic status might contribute to the development of schizophrenia. On the other hand, the generally more accepted view holds that downward social drift takes place before and/or after illness onset, due to the functional, social and professional impairments associated with the illness.

Age and gender. There is a slight male excess of schizophrenia diagnoses, especially with onset under age 35.

Season of birth. People with schizophrenia are slightly more likely to be born in late winter or early spring; this effect is more pronounced in females than in males and in people with no family history of schizophrenia compared to those who have relatives with schizophrenia. However, the effect is small, and season of birth may be a proxy for other variables, such as maternal virus infection or diet.

Obstetric and early childhood complications. Obstetric complications are more common in schizophrenia, possibly causing early brain damage, which may have a small contribution to disease development. However, birth complications could already be a consequence of genetic factors or prenatal environmental factors.

Viruses. Viral infection of the mother might affect brain development *in utero*; alternatively, viruses transmitted in early childhood could have adverse effects.

Substance abuse. Cannabis use is common in the premorbid, prodromal and clinical phases of schizophrenia. The direction of this effect, however, is unclear. While stimulation of dopamine neurotransmitter systems may precipitate a psychotic episode, cannabis consumption in schizophrenia has also been thought to reflect self-medication of psychotic symptoms. The contribution of cannabis to the development of schizophrenia is further unclear, as the general increase in cannabis consumption in many Western countries over the last decades has not been matched by a corresponding increase in the incidence of schizophrenia.

Maternal stress. The presence of extreme stressors, such as war, during pregnancy appears to contribute to the later development of schizophrenia. The precise mechanisms of this effect are unclear, but may involve increased smoking (to relieve stress), dietary changes of the mother or stress-induced preterm delivery.

Geographic location. Schizophrenia has similar incidences around the world; however, higher rates of schizophrenia are observed in urban than rural areas. The direction of this relationship is unclear, possibly reflecting adverse effects of an urban environment on the developing brain (e.g. toxins, viruses, diet, stress) or, alternatively, a trend for schizophrenia-prone individuals to move into cities.

Migration. There is a slightly elevated incidence of schizophrenia amongst Afro-Caribbean immigrants in Great Britain, possibly reflecting difficulties in adjusting to a new (and hostile) cultural environment.

It becomes apparent that there is no single major environmental risk factor for schizophrenia. Each of the above variables is likely to exert relatively small influence on the development of schizophrenia and may act in conjunction with other risk factors as well as genes. Notably, psychological factors, such as parenting in general and mothering in particular, do not feature prominently in most recent reviews of non-genetic schizophrenia risk factors (Bromet & Fennig 1999; Green 2001). The current scientific focus on genetic risk is probably supported not only by considerable evidence but also by the relative absence of viable models of psychological risk factors. One psychological approach, however, that has met with some success is that focussing on *expressed emotions (EE).* Individuals high in EE tend to be overly protective and/or critical of other people and tend to express emotional content more directly and frequently than others. Returning to high EE family environments has been shown to facilitate relapse into psychosis (Green 2001; Wearden et al 2000).

The study of non-genetic risk factors is further complicated by gene-environment interactions and correlations (see Section 1.6). Thus, the likely presence of several environmental risk factors, gene-environment interactions and correlations as well as interactions amongst risk factors make the unambiguous identification of either genes or environmental risk factors difficult (van Os & Marcelis 1998).

1.4 Structural and Functional Brain Changes in Schizophrenia

1.4.1 Brain Structure

The presence of structural brain changes was long postulated in schizophrenia. Neuropathological studies began with Kraepelin's, Bleuler's and Alzheimer's work (Shenton et al 2001) but waned somewhat over subsequent decades during the middle of the 20th century, when psychological and psychosocial theories of schizophrenia were more dominant than biological ones (Green 2001). Modern research into brain structure in schizophrenia arguably began with Johnstone et al's (1976) landmark report of increased ventricular volume using computed tomography (CT). It was the advent of neuroimaging methods such as CT that allowed the study of brain structure *in vivo* and the simultaneous demise of a number of psychological theories of schizophrenia that led to a renewed interest in brain research in schizophrenia.

Since Johnstone et al's (1976) report, a large number of publications have documented the existence of subtle volumetric changes of specific brain structures in people with schizophrenia. These studies are based on the assumption that the volume of a brain structure is an important tissue property intimately related to its function (Caviness et al 1999). Volumetric neuroimaging studies of schizophrenia patients usually aim to clarify whether the volume of a given brain structure is reduced, increased or unchanged relative to a healthy comparison group. Volume reductions are taken to indicate the existence of a pathophysiological process such as cell death or shrinkage, reduced neural interconnectivity, abnormal growth or excessive neuronal pruning (Caviness et al 1999; Shenton et al 2001). Increases in volume may reflect, amongst others factors, effects of pharmacological treatment such as an increase in receptor growth (Shenton et al 2001).[3] Findings from volumetric structural neuroimaging studies using techniques such as CT or magnetic resonance imaging (MRI) have been summarised in a number of reviews (Henn & Braus 1999; Lawrie & Abukmeil 1998; Pearlson & Marsh 1999; Shenton et al 2001; Weinberger & McClure 2002; Wright et al 2000). The key findings are as follows.

The most consistent reports of structural brain changes in schizophrenia concern *increased* lateral and third ventricular volume. Medial temporal lobe structures, such as amygdala, hippocampus, superior temporal gyrus or parahippocampal gyrus have frequently been found to be of *reduced* volume. There is moderate evidence of frontal, in particular prefrontal and orbitofrontal, and parietal, in particular inferior parietal lobule, grey matter volume *reductions*. Amongst subcortical structures, the thalamus, cerebellum and corpus callosum have been found to be of *reduced* volume in some but not all studies. Basal ganglia structures have been shown to be of *increased* volume in medicated patients, most probably reflecting pharmacological treatment effects.

These findings generally corroborate neuropathological post-mortem examinations (Harrison 1999). However, the precise role of the observed grey matter volume changes in the pathophysiology of schizophrenia remains unclear. Similarly, the full clinical and cognitive correlates of these structural brain changes remain to be elucidated; however, there is growing evidence of relationships between (cortical) volume reductions and

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[3] In addition to *volumetric* analyses, recent techniques have allowed the assessment of *morphology*, the shape or form of a brain structure (e.g. Frumin et al 2002).

neurocognitive impairments, suggesting that structural brain abnormalities may be accompanied by functional decline (Bigler 1998; Szeszko et al 2000).

Two interrelated issues that may be addressed using structural neuroimaging methods are: first, whether brain changes exist at illness onset or whether they are a function of chronic illness, and second, whether they are static or whether they deteriorate further over the course of the illness.

Findings from first-episode psychosis studies furnish support for the existence of structural brain changes early in the disease process (Copolov et al 2000; Ettinger et al 2001; Fannon et al 2000; Hirayasu et al 2001; Lim et al 1996; Sumich et al 2002; Zipursky et al 1998). First-episode studies circumvent certain methodological confounds encountered in studies of chronic schizophrenia patients, such as long-term antipsychotic medication, functional and social isolation, hospitalisation and putative effects of disease chronicity and neurotoxicity. These studies, therefore, discount the notion that structural changes in schizophrenia are entirely due to these secondary factors.

To address the second point, there are some longitudinal studies demonstrating further decreases in grey matter volumes and increases in ventricular volumes over periods of several months and years, suggesting a neurodegenerative component of schizophrenia (Lieberman 1999). However, the overall evidence of neurodegenerative processes in schizophrenia is weak. As Weinberger and McClure (2002) pointed out, many of these studies are fraught with serious methodological shortcomings. Additionally, neurodegeneration appears unlikely, as the process of gliosis (an increased growth of supportive glial cells in response to neural damage) has not been demonstrated in post-mortem studies. Likewise, expression of genes known to modulate the cellular response to injury has not been observed (Weinberger & McClure 2002).

A final remark on structural neuroimaging studies in schizophrenia concerns the effect size of the differences in brain structural volumes between schizophrenia patients and healthy participants. As shown in quantitative reviews of this research (Wright et al 2000), the volumetric brain changes seen in schizophrenia are very subtle (in the region of 1-5%); indeed, overlap in variance between the two groups is probably as prominent as the statistical significance of the differences in group means. These findings then indicate the existence of reliably identified but rather subtle brain changes in this condition.

1.4.2 Brain Function

Brain function of people with schizophrenia has been examined in relation to specific clinical symptoms as well as using cognitive tasks as behavioural probes. These studies have used neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). Regarding the neural correlates of schizophrenia symptoms, it has, for example, been demonstrated that auditory hallucinations are associated with neural activation in auditory association cortex (Shergill et al 2000). Negative symptoms have been linked to reduced frontal activation (Liddle et al 1992).

Concerning neural activation in response to behavioural or cognitive probes, the behavioural deficits observed on many neuropsychological measures of frontal cortex integrity, such as those of planning, working memory, or executive function, appear to be accompanied by reduced activation in (pre)frontal areas (Weinberger et al 2001). This 'hypofrontality' is thought to be one of the most robust findings in biological schizophrenia research, believed to be of paradigmatic status by some (Tandon 1999). Interestingly, however, *increased* brain activation has also been observed during cognitive performance in schizophrenia patients. This 'neural inefficiency' is chiefly observed during performance of well-practised, easy tasks and is thought to reflect the increased neural resources required by schizophrenia patients to achieve normal or close to normal cognitive performance (Weinberger et al 2001).

Brain function in schizophrenia has, of course, also been studied behaviourally. A vast number of studies have demonstrated that one of the core features of this condition is impaired cognition (Green 2001). Cognitive deficits have been demonstrated using standard neuropsychological measures and have been related chiefly to frontal and temporal lobe deficits (Cornblatt & Malhotra 2001; Green 2001; Park et al 1995; Sharma & Harvey 2000).

1.4.3 Neurochemistry

A number of neurotransmitter systems have been implicated in the pathophysiology of schizophrenia; the most prominent of which is dopamine (DA). The *dopamine hypothesis* of schizophrenia, in its original form, assumed that the positive psychotic symptoms of schizophrenia were due to deficient DA transmission, particularly of projections originating in the ventral tegmental area (Leonard 1997). This hypothesis

was based on the psychotomimetic properties of dopaminergic compounds, the antipsychotic effects of DA antagonists and the observation of side effects after prolonged treatment with DA antagonists bearing resemblance to Parkinson's disease, a condition with known DA deficiency (Leonard 1997). The revised dopamine hypothesis accommodates the complexity of cortical and subcortical dopaminergic projections as well as the existence of several symptom dimensions of schizophrenia and argues that *hyper*dopaminergic state in the mesolimbic pathway is associated with positive symptoms, while *hypo*dopaminergic function in the prefrontal cortex is associated with negative (and cognitive) symptoms (Friedman et al 1999).

In vivo PET studies have shown a correlation between binding affinity of antipsychotics to DA (in particular D2-type) receptors and clinical efficacy of the drug. Imaging studies of DA receptor density in schizophrenia have yielded inconsistent results (Leonard 1997).

Other neurotransmitter systems have also received attention, particularly those interacting with DA. A role of glutamatergic dysfunction has arisen from animal and human psychopharmacological models of drug-induced schizophrenia (e.g. using ketamine and phencyclidine; Radant et al 1998; Weiler et al 2000). The major glutamatergic projections extend from cortex to striatum and are compatible with a role of these areas and their interconnectivity in schizophrenia. The serotonergic system has also been implicated, not only because of its putative role in mediating the effects of some pharmacological antipsychotic treatments (see Section 1.5).

Studies using magnetic resonance spectroscopy (MRS) have the potential to probe for neurochemistry *in vivo*. These studies have provided evidence of reductions in N acetyl-aspartate (NAA) in frontal and temporal brain regions. NAA is a measure of neuronal integrity, suggesting abnormal neurochemistry in these areas (Leonard 1997).

1.5 Treatment of Schizophrenia

The treatment of choice for schizophrenia is pharmacological (Kapur & Remington 2001; Leonard 1997). Effective pharmacological treatment of schizophrenia began with the serendipitous discovery of the antipsychotic properties of chlorpromazine in the early 1950s (Leonard 1997). Chlorpromazine is still used in the treatment of schizophrenia, although a large variety of other neuroleptic compounds exist. These compounds are most commonly classified as typical and atypical antipsychotics. The

definition of what constitutes a typical antipsychotic varies but usually involves action on dopaminergic, in particular D2-type, receptors, and the generation of catalepsy in animals or extrapyramidal side effects (EPS) in humans. Typical antipsychotics have been shown to be clinically successful, in particular in the treatment of positive psychotic symptoms (Leonard 1997). Atypical antipsychotics, on the other hand, compounds that do not induce catalepsy or EPS, are generally held to be more successful in the treatment of negative symptoms and cognitive deficits (Leonard 1997; Sharma & Harvey 2000).

The main mechanism of action of typical antipsychotics is via the D2 dopamine receptor (Kapur & Remington 2001). The action of the more heterogeneous group of atypical drugs is less clear and is thought to involve other neurotransmitter systems in addition to DA, such as serotonergic (in particular the 5-HT2 receptor subtype), histaminergic, adrenergic and muscarinic systems. While associated with reduced probability of EPS, atypical antipsychotics still produce side effects, such as sedation, seizures or sexual dysfunction. In order to counter antipsychotic-induced EPS, anticholinergic compounds are often administered (Leonard 1997).

Psychological approaches, such as cognitive behavioural therapy (CBT), play second fiddle in the treatment of schizophrenia, probably due to the severity of the illness as well as the lack of good basic cognitive function and the communication skills crucial for the success of such therapies. There is, however, evidence of the usefulness of psychoeducative programs on patients' knowledge of their own disease and its day-to-day management (Penn & Mueser 1996). Further, CBT has been shown to be useful in some studies in the remediation of core psychotic symptoms, such as delusions and hallucinations (Turkington & Kingdon 2000).

1.6 Genetics of Schizophrenia

In addition to environmental risk factors (Section 1.3), the aetiology of schizophrenia involves genetic factors. These will be discussed in the following sections, with consideration of both behavioural and molecular genetic studies.

1.6.1 Behavioural Genetics

There is ample evidence of a genetic contribution to schizophrenia. This evidence stems from genetic epidemiologic and behavioural genetic studies, such as family, twin and

adoption studies. Studies of families with one (simplex) or more than one (multiplex) members with schizophrenia have demonstrated that the risk of schizophrenia, which is estimated to be at just under 1% in the general population, is significantly increased, at about 16% in first-degree relatives of people with schizophrenia (Bromet & Fennig 1999; Hallmayer 2000; Lichtermann et al 2000). The risk is slightly higher when the schizophrenic relative is a parent rather than a sibling (Torrey & Yolken 2000).

Family studies cannot, of course, distinguish between familial and genetic factors. Thus, the increased risk of first-degree relatives could be due to shared genes or shared non-genetic factors, such as parenting, life-events, diet or exposure to teratogens and viruses (Ott 1991; Torrey & Yolken 2000).

Other studies have compared the concordance rates of schizophrenia in monozygotic twins, who have identical genes, and dizygotic twins, who, like siblings, share on average 50% of their genes. Concordance is observed when both twins in a pair carry a diagnosis of schizophrenia; discordance is noted when only one in the pair has the diagnosis. Recent concordance rates for monozygotic twins are estimated to be between 45-75%, whereas those for dizygotic twins range between 4-15%, similar to those amongst full biological relatives (Lichtermann et al 2000). Twin studies have also allowed estimating the heritability of schizophrenia as well as the proportion of variance due to shared and non-shared environmental factors. Heritability is thought to be at about 50-87%, with most non-genetic influence due to non-shared environmental factors (Kringlen 2000; Lichtermann et al 2000).

Perhaps the most convincing evidence of a genetic contribution to schizophrenia comes from adoption studies. These studies have used the *adoptees' family study approach*, where the biological families of individuals with schizophrenia are studied, and the *high-risk adoptees approach*, where the adopted-away children of people with schizophrenia are studied (Ingraham & Kety 2000). These studies, while open to methodological criticisms of sample selection, have produced the following findings. High-risk adoptees studies have shown that these individuals are at higher risk of developing schizophrenia than adoptees of non-schizophrenic parents. Adoptees' family studies have demonstrated that these individuals have an excess of schizophrenia amongst their biological, but not adoptive, families; they also have a higher rate of schizophrenia amongst their biological families compared to non-schizophrenic control adoptees (Ingraham & Kety 2000).

Evidence concerning genetic influence on specific clinical subtypes of schizophrenia (e.g. catatonic, hebephrenic, disorganised, undifferentiated, paranoid) is weak, suggesting that the overarching syndrome of schizophrenia has a genetic basis, but not its clinical (DSM-IV) subtypes (Lichtermann et al 2000). It has, however, been demonstrated that an illness course defined by prominent, primary negative symptoms may be more genetic than one defined by positive symptoms (Kirkpatrick et al 2001; Lichtermann et al 2000).

One important finding from schizophrenia family studies was that first-degree relatives of schizophrenia patients are at increased risk of developing not only schizophrenia, but also other, related disorders, such as schizotypal personality disorder, schizoaffective disorder and other psychotic disorders (Lenzenweger 1994). These disorders are collectively known as schizophrenia spectrum disorders (see Section 1.7).

While family, twin and adoption studies, therefore, agree on a considerable genetic contribution to schizophrenia, the mode of inheritance in multiply affected families is less clear. The observed pattern of inheritance and the existence of non-genetic factors, however, suggest that a single gene, transmitted in a Mendelian fashion, is extremely unlikely.

1.6.2 Molecular Genetics

The key strategies that have been used in the search for 'schizophrenia genes' are linkage and association studies. *Linkage* studies examine families multiply affected with schizophrenia and investigate the co-transmission of the disease and genetic markers of known chromosomal location (Ott 1991). *Association*, e.g. case-control, studies examine candidate genes in affected and unaffected individuals. Candidate genes are genes whose protein product is known and is thought to play a role in the pathophysiology of the disorder, such as the D3 dopamine receptor gene or the catechol-*O*-methyltransferase gene in schizophrenia (Egan et al 2001b; Rybakowski et al 2001).

While there have been many positive findings from linkage studies, suggesting an association between the schizophrenia phenotype (i.e. the diagnosis of schizophrenia based on observable signs) and a large number of chromosomes, there has been a large number of failures to replicate. Studies have implicated chromosomes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 13, 14, 15, 18, 20, 22 and the X (Lichtermann et al 2000; Pulver 2000; Riley & McGuffin 2000). Of these, the most promising chromosomal sites are likely to be 1q, 5q,

6p, 8p, 10p, 13q, 18p and 22q, given the evidence from replication of linkage, candidate gene studies and other molecular genetic evidence (e.g. 22q deletions or velo-cardio-facial syndrome) (Lichtermann et al 2000; Murphy 2002; Pulver 2000; Riley & McGuffin 2000).

Molecular genetic studies, therefore, suggest that a large number of genetic loci could be associated with schizophrenia. This evidence, and a comparison of molecular genetic schizophrenia studies with the success of molecular genetics in identifying major genes in other neuropsychiatric disorders (e.g. Alzheimer's disease or Huntington's disease; Bertram & Tanzi 2001; Ho et al 2001), rules out the existence of a single, major schizophrenia gene (Kato et al 2002; Tsuang & Faraone 2000). A more likely scenario is that the genetic contribution to schizophrenia stems from a number of genes, each contributing a small or moderate effect. *Polygenic* models assume the existence of many genes of small effect; *oligogenic* models assume the existence of a few genes varying from small to large effect; and *mixed* models assume the existence of a single gene of large effect against a polygenic background (Iacono 1998). Traditional polygenic models assumed that genes co-act in an additive fashion. An alternative to additive action is *epistasis,* which is defined as the interactive action of several susceptibility genes (Skuse 2001). Which of these models best identifies transmission of schizophrenia is unclear; however, any of these mechanisms could account for the observed clinical and biological heterogeneity of the disorder and its non-dichotomous presentation, as well as the non-Mendelian pattern of transmission within families (Kato et al 2002; Tsuang & Faraone 2000).

The role of the environment in schizophrenia may not be ignored; indeed, the list of possible environmental risk factors is extensive (Section 1.3). It is at present unknown how environmental factors may contribute over and above the effects of genes; however, it is thought that they precipitate the onset or relapse of schizophrenia (McDonald & Murray 2000; van Os & Marcelis 1998). This then suggests an interplay between a predisposing genotype and risk-conferring non-genetic factors. This interplay may take on at least two different forms, namely *gene-environment interactions* and *gene-environment correlations* (van Os & Marcelis 1998). In gene-environment interactions genes are thought to increase the sensitivity for a certain (pathological) reaction to an environmental stimulus, such as physical or psychological abuse. In gene-environment correlations genes are thought to increase the likelihood of the individual seeking out a certain (risk-conferring) environment, such as drug abuse. It is believed that both types

of gene-environment interplay, sometimes in conjunction, occur in schizophrenia (van Os & Marcelis 1998).

Schizophrenia is thus a genetically *influenced* but not *determined* disease (Gottesman & Erlenmeyer-Kimling 2001). Schizophrenia is not alone in its status as a genetically complex disease; indeed, comparisons with diabetes mellitus (Type-I or insulin dependent) and coronary artery disease (leading to heart failure) have been made (Gottesman & Erlenmeyer-Kimling 2001).

1.7 Schizotypy and the Schizophrenia Spectrum

The operational definitions of DSM and ICD for a diagnosis of schizophrenia are used in clinical practice as well as in many scientific investigations in order to achieve objective and reliable agreement on an individual's diagnostic status. One of the consequences of the application of rigid diagnostic criteria is the creation of the dichotomies of affected/unaffected, or ill/healthy. While useful in clinical and research settings (Rosenhan & Seligman 1995), there is growing dissatisfaction with this perceived oversimplification of the schizophrenia phenotype (e.g. Tsuang et al 2000). Indeed, it has been argued for a long time that schizophrenia may represent one state along a continuum, encompassing severe psychosis as well as less severe disorders and traits (Tsuang et al 2000).[4]

The *schizophrenia spectrum* approach to the study of the etiology, pathophysiology and genetics of schizophrenia, therefore, focuses not only on individuals with a formal diagnosis of schizophrenia, but on any population whose members have a greater occurrence of schizophrenia-related genotypes or phenotypes. The spectrum includes people with schizotypal personality disorder (SPD), subclinically elevated schizotypal traits or a family-history of schizophrenia (Claridge 1990; Eysenck 1992; Lenzenweger 1994; Tsuang et al 2000).

The key application of this approach to date lies in research; indeed, only SPD has made the transgression from theory to clinical practice, being incorporated into the DSM-IV. SPD is defined, according to DSM-IV, as "a pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close

[4] Interestingly, continuity of symptom severity and the existence of subclinical symptom dimensions was also recognised in DSM-IV (American Psychiatric Association 1994; p. 710-711).

relationships as well as by cognitive or perceptual distortions and eccentricities of behaviour. This pattern begins in early adulthood and is present in a variety of contexts." (American Psychiatric Association 1994; p. 641).

The key symptoms of SPD, according to DSM-IV, are: ideas of reference; odd beliefs or magical thinking that influences behaviour and is inconsistent with subcultural norms (e.g. superstitiousness, belief in clairvoyance, telepathy, or 'sixth sense'); unusual perceptual experiences, including bodily illusions; odd thinking and speech (e.g. vague, circumstantial, metaphorical, overelaborate, or stereotyped); suspiciousness or paranoid ideation; inappropriate or constricted affect; behaviour or appearance that is odd, eccentric, or peculiar; lack of close friends or confidants other than first-degree relatives; excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears rather than negative judgements about self (American Psychiatric Association 1994).

Much more common than SPD in the general population, however, are subclinical schizotypal personality traits. In contrast to a diagnosis of SPD, which requires clinical interview and DSM criteria, subclinical schizotypal personality traits in the general population are most commonly measured using self-administered questionnaires (Johns & van Os 2001). The traits under study are features phenomenologically related to but clinically less severe than symptoms of schizophrenia, including unusual perceptions and experiences, suspiciousness, delusional ideas, magical thinking, oddness, disordered thought structure and speech, social isolation and withdrawal and physical and social anhedonia (Claridge 1990; Gruzelier 2002; Lenzenweger 1994).

Theories of schizotypy have emphasised the relatedness to schizophrenia and SPD as well as the increased risk of schizophrenia. Indeed, a striking similarity between schizotypy and schizophrenia concerns their symptom factor structure as obtained through factor analysis. Schizotypy is generally thought not to be a unitary construct but consists of a number of dimensions, most commonly including positive features (perceptual-cognitive signs and symptoms such as delusions, thought disorder, hallucinations and unusual experiences and beliefs) and negative features (mainly social-interpersonal signs and symptoms such as social withdrawal and isolation, poor rapport, aloof and odd social interactions and social and physical anhedonia) (Vollema & van den Bosch 1995). Other dimensions that have been found in factor analyses of psychometric schizotypy questionnaires include anxiety-related traits and psychoticism/nonconformity (Vollema & van den Bosch 1995). Still other studies have

shown an occurrence of more than one positive schizotypy factor, akin to Liddle's (1987b) factors of reality distortion and thought disorder in schizophrenia (Mason et al 1995; Vollema & van den Bosch 1995).

This similarity in factor structure, particularly of the overarching dimensions of positive and negative symptoms, has led some to speculate on the possible continuity between schizotypy and schizophrenia (Johns & van Os 2001; Vollema & van den Bosch 1995).[5] Powerful evidence for this proposed continuity was obtained by Fanous et al (2001). In a large sample of schizophrenia patients and their first-degree relatives, these researchers demonstrated an association between levels of positive and negative schizophrenic symptoms in the patients and levels of positive and negative schizotypal symptoms, respectively, in their relatives.

Additional evidence for the relatedness between the constructs of schizotypy and schizophrenia stems from similarities in their psychophysiological and neuropsychological correlates. Non-clinical samples of individuals scoring high in schizotypy have significantly impaired performance on a number of tests shown to be sensitive to schizophrenia, such as neuropsychological measures of temporolimbic and frontal cortex function or psychophysiological measures of information processing (Croft et al 2001; Dinn et al 2002; Kumari et al 1997b; Nunn & Peters 2001; Steel et al 1996).

Finally, college students with high scores on psychometric self-report measures of schizotypy are at significantly increased risk of developing psychosis over a ten-year period (Chapman et al 1994b).

Given the hypothesised and observed similarity of schizophrenia and schizotypy, schizotypal individuals represent an ideal population in which to assess the validity of a biological or neurocognitive marker of the schizophrenia spectrum. A considerable methodological advantage of studying schizotypy is the relative absence of secondary confounds commonly observed in the schizophrenia patient group, such as antipsychotic medication, disease chronicity, institutionalisation, variable motivation and social and professional impairments.

Another schizophrenia spectrum population that has received considerable research interest is that of first-degree relatives of schizophrenia patients. These individuals,

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[5] However, see Stuart et al (1999) for a criticism of factor analytic studies supporting the three-syndrome model of schizophrenic symptoms.

expected to have in common some of the genes that led to the expression of schizophrenia in their relatives, have increased rates of SPD and subclinical schizotypy when established using clinical interviews (Kendler et al 1995).[6] Relatives have also been shown to have a number of neurocognitive, e.g. brain structural, psychophysiological and neuropsychological deficits, similar in kind but of reduced magnitude compared to the patient group (Clementz et al 1998; Egan et al 2000; Egan et al 2001a, 2001c; Saoud et al 2000).

Like schizotypy research, the study of healthy first-degree relatives of schizophrenia patients overcomes some of the confounds encountered in studies of schizophrenia patients. The likely existence of schizophrenia disease genes, the observation of increased rates of SPD and the evidence of neurocognitive deficits make this population ideally suited for the assessment of the validity of schizophrenia spectrum endophenotypes.

1.8 The Research Problem

The above overview points to the identification of 'schizophrenia genes' as one of the most urgent and difficult questions in schizophrenia research. Identification of genes is crucial not only for a better understanding of the pathophysiology of schizophrenia but may also be expected to lead to improvements in the pharmacological treatment of this disorder (Mancama et al 2002; Scharfetter 2001). To summarise, the search for schizophrenia genes is made difficult by the complex and heterogeneous phenotype of schizophrenia (including schizophrenia spectrum phenotypes); the unknown (but non-Mendelian) mode of transmission of schizophrenia; the likely existence of a number of causal genes; the small effect of each (or most) of these genes; the existence of environmental risk factors and interplay between genes and risk factors; and the large gap between a putative gene and the schizophrenia phenotype. It is probably due to these difficulties that linkage studies – one of the best methods to date in the search for disease genes – have been inconsistent or unsuccessful. The variable phenotype of schizophrenia means that it is unlikely to reflect accurately an underlying disease

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[6] Relatives do not, however, attract significantly higher scores on psychometric self-report measures of schizotypy; in fact, they sometimes obtain lower scores than healthy controls. This paradox has most parsimoniously been explained as a defensive response set, given the apparent nature of many schizotypy questionnaire items in a schizophrenia-related research project that the relative agreed to take part in (Catts et al 2000; Claridge et al 1983; Katsanis et al 1990).

genotype in a one-to-one fashion (Hyman 1999); the (assumed) existence of multiple genes with small effect means that it is statistically difficult to confirm the action of any such gene (Iacono 1998).

A number of strategies have been proposed to circumvent these difficulties. Leboyer et al (1998) suggested either widening or narrowing the phenotype of a complex medical condition (such as schizophrenia). Both approaches propose studying a biologically, and, by extension, genetically, more homogeneous phenotype.

The narrowing of the phenotype is referred to as the candidate symptom approach (Leboyer et al 1998). This approach aims to identify a symptom or symptom cluster potentially involved in the condition under study; such a symptom is required to be clinically homogeneous, to have circumscribed biological correlates and to show a simpler pattern of inheritance than the overall disease phenotype. It can thus be used as a phenotype in linkage studies. One version of the candidate symptom approach involves narrowing of the disease phenotype along clinical criteria, such as age at onset or disease severity. An example of the success of this approach is the amyloid precursor protein gene on chromosome 21q for early onset Alzheimer's disease (Bertram & Tanzi 2001).

Within schizophrenia research, a distinction between early and late age at onset has demonstrated high and low familiality, respectively, but has not yet yielded susceptibility genes (Leboyer et al 1998). Identification of a homogeneous symptom cluster, however, may be more successful. For example, the deficit syndrome (consisting of primary, enduring negative symptoms) is thought to be a promising phenotype in the candidate symptom approach (Carpenter et al 1999).

An alternative to narrowing the phenotype is the endophenotype approach, which will be discussed in the following section.

1.8.1 The Endophenotype Approach

An *endophenotype* (also termed *trait marker* or *intermediate phenotype*) is a specific biological or behavioural deficit thought to be a more direct expression of a disease-related gene than the disease phenotype (Iacono 1998; Leboyer et al 1998; Lenzenweger 1999; Ott 1991; Stoltenberg & Burmeister 2000). Endophenotypes are objective, reliable and phenotypically homogenous deficits, and are typically assessed using biochemical, endocrinological, neurophysiological, psychophysiological, psychometric or

experimental psychological means.[7] The crucial point is that, due to its assumed influence by a disease-related gene, an endophenotype is expected to be observed at increased frequency not only in the patient group but also in clinically unaffected individuals with a genetic predisposition to the illness, such as first-degree relatives. Indeed, the study of clinically unaffected individuals marks the aforementioned widening of the phenotype (Leboyer et al 1998). This then means that an individual with observed endophenotypic impairment may be identified as a 'gene carrier' with regard to the hypothesised endophenotype/disease gene despite the absence of a clinical diagnosis. This feature opens up new avenues for genetic linkage and other molecular genetic studies (Ott 1991).

An endophenotype is thought to reflect the action of a disease-related gene, or the action of a gene in linkage disequilibrium with a disease-related gene. Hence, endophenotypes have been used in linkage studies. Their advantages over disease phenotypes in linkage studies include the arguably more direct biological reflection of the effects of a disease gene, the objective and less ambiguous definition and measurement and the greater statistical power through the identification of clinically unaffected gene carriers (Iacono 1998; Ott 1991). Additionally, as some endophenotypes are assumed to reflect the action of a major gene, the pattern of transmission of such a deficit may be simpler than that of a complex disease phenotype (Iacono 1998).

Endophenotypes have been used profitably in medical genetics. Indeed, Stoltenberg and Burmeister (2000) argued that the novel strategies of the endophenotype and candidate gene approaches represent a "paradigm shift" in genetic research (p. 931). For example, studies of serum iron concentrations in idiopathic haemochromatosis have led to the observation of linkage to the HLA-A locus (Leboyer et al 1998). The inclusion of electroencephalographic (EEG) abnormalities as an endophenotype in genetic studies of juvenile myoclonic epilepsy has led to identification of linkage (Leboyer et al 1998). Endophenotypes are also being studied in psychiatric disorders other than schizophrenia, including bipolar affective disorder (Ahearn et al 2002), attention-deficit/hyperactivity disorder (ADHD; Castellanos & Tannock 2002), and borderline personality disorder (Siever et al 2002). Additionally, endophenotypes have been used in studies of complex traits such as general intelligence (de Geus et al 2001).

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[7] The prefix *endo-* suggests that this phenotypic expression is not visible to the unaided naked eye and thus differs from the external phenotype, or *exo*phenotype (John & Lewis 1966).

It becomes clear from the definition of the endophenotype that this approach aims to circumvent some of the most serious problems of genetic schizophrenia research, such as phenotype heterogeneity and genetic complexity. The study of more confined aspects of brain function reduces this heterogeneity. As de Geus et al (2001) put it, "the use of endophenotypes to find genes influencing a complex trait fully obeys Caesar's adage of '*divide et impera*'" (p. 490; italics added).

A second advantage of this approach is that the extension of investigation to non-clinical samples allows the confirmation of any given behavioural or biological deficit in the absence of methodological confounds, such as pharmacological treatment and hospitalisation, often encountered in the patient group.

A further benefit of the phenotypic homogeneity of endophenotypes is that investigation of not only causal genes but also the neural correlates of disease is possible. Hence, a growing body of research aims to clarify the functional brain correlates of some of the behavioural endophenotypic impairments (McDowell & Clementz 2001; O'Driscoll et al 1999). Knowledge of the underlying neural correlates of an endophenotype, in addition to the identification of causal genes, could provide a powerful tool in investigating the pathophysiology of the disease under study. Indeed, the assumed genetic simplicity of the endophenotype implies that a relatively specific neural site or mechanism (e.g. dorsolateral prefrontal cortex or specific dopaminergic projections; Egan et al 2001b) mediates the chain of events from disease gene to disease phenotype via endophenotype. Relatedly, Castellanos and Tannock (2002) suggested that it should be a *requirement* of an endophenotype in neuropsychiatry to be "anchored in neuroscience" (p. 619).

A variety of schizophrenia endophenotypes have been suggested, including psychophysiological and electrophysiological deficits of information processing (Cadenhead & Braff 2002; Clementz 1998; Iacono 1998), impairments in cognitive measures of attention (Cornblatt & Malhotra 2001) and working memory (Park et al 1995) and brain structural abnormalities (Dickey et al 1999).

In order to qualify as a promising endophenotype, a behavioural or biological deficit must fulfil a number of criteria. These criteria, adapted from other authors (Cadenhead & Braff 2002; Calkins & Iacono 2000; Clementz 1998; de Geus et al 2001; Gottesman & Erlenmeyer-Kimling 2001; Iacono 1998; Leboyer et al 1998; Lenzenweger 1999; Ott 1991; Stoltenberg & Burmeister 2000), are as follows.

Presence in the patient group and low base rate in the general population. In order to be considered as an endophenotype in genetic studies, a deficit must be unambiguously present in the patient group. Additionally, it should have a low base rate (i.e. be uncommon) in the general population.

Heritability. There must be good evidence that the behaviour under observation has significant heritability. Heritability can be established through adoption studies as well as studies of healthy monozygotic and dizygotic twins.

Temporal stability. An endophenotype should be a trait not a state deficit. State deficits, such as those accompanying changes in medication or exacerbation of clinical symptoms, are not temporally stable and are thus unlikely to represent important underlying genetic factors.

Specificity. It is sometimes suggested that a homogeneous endophenotypic marker will improve the identification of disease-related genes if it is observed only in the patient group under study and the associated spectrum (e.g. relatives). Specificity is, of course, important; a deficit that is, for example, observed in every psychiatric patient group may be an indicator of general brain dysfunction. Evidence of considerable clinical and biological overlap between related conditions, such as schizophrenia and bipolar affective disorder, however, may also suggest genetic overlap. Indeed, some of the most promising susceptibility loci in schizophrenia genetics also appear to be implicated in bipolar affective disorder (Jorgensen et al 2002). Consequently, it is possible that lack of specificity of a given endophenotype concerning clinically related disorders might not represent a serious weakness; alternatively, such an endophenotype might be the expression of a shared, predisposing disease gene (Stoltenberg & Burmeister 2000).[8]

Family studies. Given the increased genetic risk for many complex disorders in first-degree relatives of patients, and the putative action of a disease gene on an endophenotype, increased frequencies of endophenotype impairments should be observed in clinically unaffected and affected relatives. The levels of deficit in unaffected relatives may be expected to be between those of the patients and healthy controls, due to the putative influence of other (genetic and non-genetic) factors, likely to be more concentrated in the patient group.

Independence of secondary factors associated with patient status. In addition to being temporally stable and independent of short-term fluctuations in clinical state, endophenotypic measures should be observed in the absence of factors secondary to the disease, such as chronic medication, institutionalisation or effects on the brain of disease chronicity itself. Recent-onset patients may be studied to address this question.

Schizotypy. Elevated levels of impairments on a schizophrenia endophenotype should be observed in individuals with an increased frequency of subclinical schizophrenia spectrum symptoms, such as otherwise healthy people with elevated scores on self-report measures of schizotypy, or individuals with SPD. Due to the somewhat lower levels of severity of subclinical schizotypal signs and symptoms in these individuals, performance impairments may be expected to be less severe than those of the schizophrenia patient group. On the basis of the assumed genetic and biological similarity between schizophrenia and subclinical schizotypy, however, the pattern of impairments should be similar in quality to those of schizophrenia patients.

A thorough examination of the validity of any endophenotype should thus address these points. If these criteria are met, an endophenotype may be used in order to advance the search for genes involved in the development of schizophrenia by inclusion as a phenotype in linkage studies or in assessments of candidate genes.

Although several schizophrenia spectrum endophenotypes have been proposed, deficits in specific aspects of *eye movement control* have been argued to be particularly promising trait markers (Calkins & Iacono 2000; Clementz 1998; Flechtner et al 2000; Holzman 2000). These deficits comprise of reduced accuracy of smooth pursuit eye movements and an increased error rate on the antisaccade task. Several lines of evidence argue that eye movement (or oculomotor) impairments might be a very suitable schizophrenia spectrum endophenotype. This evidence includes, in addition to the considerable body of evidence from previous schizophrenia spectrum studies reviewed in Chapter 2, the advantage of a good understanding of the neural correlates of eye movements and the relatively unambiguous assessment of these deficits. This thesis will focus on eye movement endophenotypes in the schizophrenia spectrum and will address some of the above criteria in order to investigate their validity.

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[8] The acceptable non-specificity of an endophenotype within a class of related disorders is also necessitated by the less than perfect clinical delineation of overlapping disorders such as schizophrenia and bipolar affective disorder (Iacono 1998).

Chapter Two

Eye Movements in the Schizophrenia Spectrum

2.1 Chapter Overview

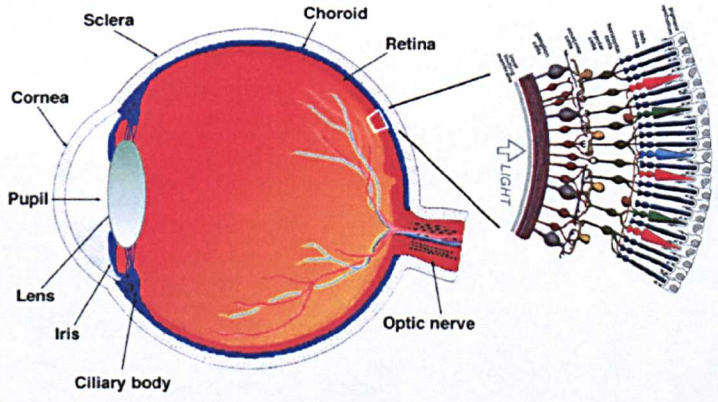
This chapter will review the literature of eye movement tasks as endophenotypes in schizophrenia spectrum research. Basic principles of eye movement research will be outlined first. Each eye movement task applied in this thesis, i.e. the smooth pursuit, visual fixation, antisaccade and prosaccade tasks, will be reviewed separately. As the smooth pursuit task was, historically, the first oculomotor endophenotype proposed in the literature it will be discussed first, followed by the fixation task, a task often used as an oculomotor control condition for smooth pursuit. The antisaccade, and its suggested control condition, the prosaccade task, will be similarly reviewed. For each task, methodological issues, such as stimulus presentation and data scoring, will be considered first, before addressing the task's validity as a schizophrenia endophenotype. The criteria relating to the validity of these tasks as schizophrenia endophenotypes that will be addressed here are based on those listed in Chapter 1 and include: performance levels in the patient group; neural, cognitive, clinical and pharmacological correlates; heritability in healthy humans; temporal stability; specificity to schizophrenia; performance levels in family members of people with schizophrenia; performance levels in first-episode psychosis patients; association with schizotypy; and evidence from molecular genetic studies. Following this review, other eye movement tasks that have been studied in the schizophrenia spectrum, such as memory-guided and predictive saccades and visual scan paths will be considered briefly. Finally, a comparison of and examination of the relationships between the most promising of these oculomotor endophenotypes, the smooth pursuit and the antisaccade tasks, will be undertaken. The chapter will conclude with an overview of the remainder of this thesis, including the rationale for the experimental studies reported in the thesis and the hypotheses.

2.2 Introduction to Eye Movements

Why move the eyes if we can move the head? is the title of a review article by Delgado-Garcia (2000); *Why study eye movements?* is the title of the first section of Leigh and Zee's (1999) authoritative book on the neurology of eye movements. Both questions will be addressed briefly in the following introduction to eye movement research.

The eye is the organ for vision. The fovea is the part of the retina that is specialised for high-acuity vision and optimal processing of colour and shape (Figure 2.1). Most detailed processing of a visual stimulus is, therefore, achieved by retaining its image within about 0.5° of the centre of the fovea (Leigh & Zee 1999). Stimulation of retinal neurons (rod and cone cells) by light waves causes the transmission of neural signals down the optic nerves via the lateral geniculate body of the thalamus to the primary visual area of the occipital lobe, resulting in the experience of vision (Leigh & Zee 1999; Reid 1999).

Figure 2.1: Cross-sectional Diagrammatic Representation of the Human Eye



In foveate animals, the existence of constant, small (or large) head movements in an absence of the ability to move the eyes would result in slippage of visual input across the retina, thus causing blurred vision whenever the image has left the fovea. One purpose of eye movements is, therefore, to enable high-acuity vision by compensating for head movements. As accurate visual perception is only possible when images on the retina are stable, most processing of visual information takes place when the eye fixates a stimulus. A second main purpose of eye movements is to allow foveate animals to bring or retain an image on the fovea independently of, thus without requiring, head movements (Delgado-Garcia 2000; Reid 1999).

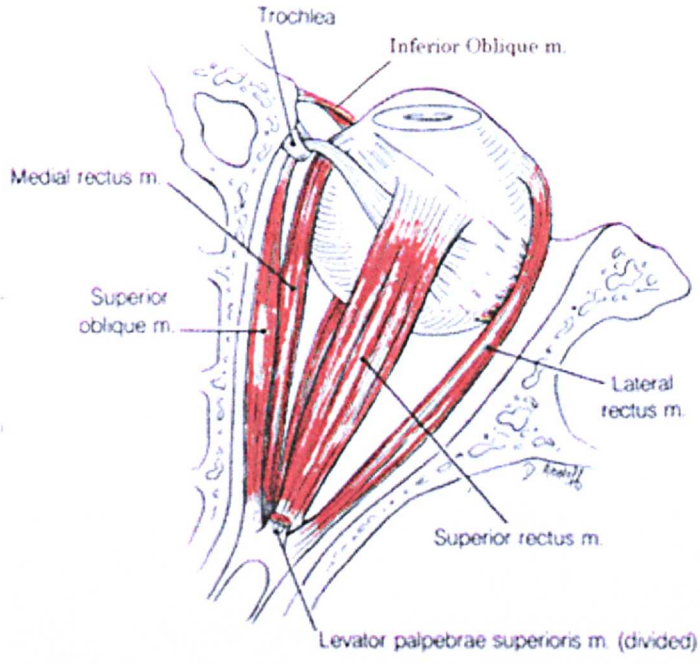
Eye movements fall into several categories. Leigh and Zee (1999) classified eye movements on the basis of their functions into vestibular, visual fixation, optokinetic, smooth pursuit, nystagmus quick phase, saccades and vergence eye movements; their key functions are described in Table 2.1. These eye movements may be summarised further into two broad functional categories, *gaze-shifting* (those that bring an image onto the fovea) and *gaze-stabilising* (those that retain an image on the fovea) eye movements (Leigh & Zee 1999).

Table 2.1: Functional Classification of Eye Movements (Leigh & Zee 1999)

Type	**Key function**
Smooth pursuit	To retain the image of a moving object on the fovea
Visual fixation	To retain the image of a stationary object on the fovea
Saccades	To bring the image of an object of interest onto the fovea
Vestibular	To retain the image of an object on the fovea during brief head rotation
Optokinetic	To retain the image of an object on the fovea during prolonged head rotation
Nystagmus quick phase	To reset the eye during prolonged self-rotation to oncoming stimuli
Vergence	To retain an image on both eyes' foveae by moving eyes in opposite directions

The eye is held and moved in its socket by three pairs of extra-ocular muscles (Figure 2.2): the *superior* and *inferior recti* move the eye up and down; the *lateral* and *medial recti* move the eyes from side to side; and the *superior* and *inferior obliques* allow eye rotation within the socket. The eye muscles are innervated by brainstem motoneurons, the oculomotor (ipsilateral medial and inferior rectus, inferior oblique and contralateral superior rectus), trochlear (contralateral superior oblique) and abducens (ipsilateral lateral rectus) motoneurons. Neural control of eye movements above the brainstem level is discussed in the relevant sections below (Sections 2.3.5.2, 2.4.4.2, 2.5.4.2 and 2.6.4.2).

Figure 2.2: Diagrammatic Representation of the Extra-ocular Muscles



Why do people study eye movements? To the scientist (and the layperson!), the eye may be a rich source of information about perceptual, cognitive and affective processes; indeed, the eye has been called the "window to the soul" (Stern & Dunham 1990; p. 513). Consequently, eye movements have been studied in a wide variety of contexts, including biomedical research; research into various psychological processes, such as visual perception, reading, or visual art appreciation; and topics in applied psychology such as car driving, the use of visual media and human-computer interaction (Andreassi 1995; Leigh & Zee 1999; Stern & Dunham 1990).

2.2.1 Why Study Eye Movements in Schizophrenia?

As Everling and Fischer (1998) pointed out, there are two streams of research into eye movements in schizophrenia. The first stream of research focuses on the endophenotypic nature of eye movement deficits in schizophrenia. This literature, which originates in the observation of impaired smooth pursuit performance in first-degree relatives in schizophrenia patients (Holzman et al 1974), is based on the hypothesis that eye movement dysfunction may be the behavioural expression of a schizophrenia-related gene. The endophenotype approach to eye movements in schizophrenia has generated the largest amount of research in this field and has mainly focussed on the

smooth pursuit task (Holzman 2000), although the antisaccade task has, more recently, also been suggested to be a useful endophenotype (Clementz et al 1994).

The second stream of oculomotor research in schizophrenia, most clearly delineated by McDowell and Clementz (2001) and Broerse et al (2001a), follows methods of neurology (Kennard et al 1994) and proposes the use of oculomotor tasks to study the cognitive and neural components of the pathophysiology of schizophrenia. According to this approach, the use of specific eye movement measures allows the identification of brain areas involved in task performance in healthy individuals and laboratory animals; the assessment of specific behavioural performance deficits in people with schizophrenia; pin-pointing the underlying neural deficits in the patient group (using neuroimaging methods, or on the basis of behavioural data, by comparison with brain-lesioned individuals); and, by deduction, the identification of brain areas likely involved in the pathophysiology of schizophrenia (Broerse et al 2001a; Kennard et al 1994; McDowell & Clementz 2001).

This approach has mainly focussed on the antisaccade task, probably given its origins in the human brain lesion literature (Guitton et al 1985). More recent attempts at delineating the cognitive and neural substrates of smooth pursuit dysfunction, however, have also adopted this approach (Chen et al 1999a, 1999c; Sweeney et al 1998a).

Importantly, the two approaches have recently begun to converge, such as in studies aiming to elucidate the neural correlates of oculomotor endophenotypes in first-degree relatives of schizophrenia patients (O'Driscoll et al 1999).

The research reported in this thesis is concerned with an evaluation of the validity of the first stream of research, the *oculomotor endophenotype approach.* However, hypotheses concerning the likely neural and cognitive correlates of eye movement dysfunction and implications for the pathophysiology of schizophrenia will be made wherever possible.

2.2.2 Eye Movements in the Schizophrenia Spectrum

The following review will consider four eye movement tasks commonly studied in the schizophrenia spectrum, namely the smooth pursuit, visual fixation, antisaccade and prosaccade tasks. After definition of each task, methodological issues, such as stimulus presentation and data scoring, will be discussed before turning to the findings from schizophrenia spectrum populations.

2.3 Smooth Pursuit Eye Movements

2.3.1 Definition

Smooth pursuit eye movements (SPEM) are gaze-stabilising eye movements executed in order to maintain the image of a slowly moving visual object on the fovea. Smooth pursuit eye movement accuracy was the first oculomotor endophenotype suggested in schizophrenia research. The key findings from the many studies of the smooth pursuit task in schizophrenia will be described in the following sections.

2.3.2 Smooth Pursuit Stimulus

Stimulus presentation requires attention to two points; first, the type of physical stimulus presented, and second, the temporal characteristics of the stimulus.

2.3.2.1 Hardware

In the first schizophrenia spectrum SPEM studies participants were required to follow with their eyes a pendulum often consisting of improvised material, such as fishing line and sinker, swung about 1m in front of them (Diefendorf & Dodge 1908; Holzman et al 1973; Pass et al 1978; Salzman et al 1978; Shagass et al 1974; Siever et al 1986; Spohn et al 1988). While this technique was reliable and inexpensive (Lipton et al 1983) and provided a useful starting point for research in this field, its weaknesses are obvious. Target characteristics such as frequency of oscillation, amplitude and waveform cannot be precisely controlled and target position cannot be recorded.

Some subsequent studies have used cathode-ray oscilloscope (CRO) stimuli (Amador et al 1995; Gooding et al 1994; Iacono et al 1981; Levin et al 1982a; Malaspina et al 1998); however, the most commonly used methods nowadays include light emitting diode (LED) arrays, laser spots and video or computer monitors.

Light-emitting diodes are sources of (red) light that are commonly used in a variety of settings, such as display panels or rear car lights. LEDs have the advantage over conventional light bulbs of responding, i.e. being turned on and off, quickly, and being robust and long lasting. Typically, LEDs are presented at eye-level to participants at a distance of 1-2m, horizontally aligned in a purpose-built hardware array. Diodes can be controlled by a computer; concurrent logging of eye and target data is possible. LEDs

are still being used and present a well-established and flexible means of displaying pursuit stimuli. Studies reported in Chapters 4-6 employed LEDs (Section 3.2.2.1).

The laser spot method allows the presentation of a small visual target, usually projected onto a clear background screen (Arolt et al 1998; Hutton et al 1998a; Rosenberg et al 1996). As the stimulus can be precisely controlled by purpose-written software, target movement is sufficiently accurate and flexible for eye movement studies.

Most recently, however, the method of choice for stimulus presentation has been the computer or video monitor (Clementz et al 1995; Clementz & McDowell 1994; Friedman et al 1995b; Keefe et al 1997; Litman et al 1994; Olincy et al 1998; Sweeney et al 1992a, 1994a; Thaker et al 1999). Studies reported in Chapters 7 and 8 used computer screen based stimulus presentation (Section 3.2.2.2).

One advantage of computer monitor based presentation is that stimulus properties, such as shape or colour, can easily be manipulated. Such manipulations may be useful in the investigation of cognitive processes during smooth pursuit or saccadic eye movements (Rosenberg et al 1997c; Sweeney et al 1994b). Additionally, computer screen based stimulus presentation lends itself to functional neuroimaging studies. The disadvantage of such a stimulus display is the restricted horizontal range, making it inappropriate for certain clinical assessments (Leigh & Zee 1999). However, the horizontal range of computer or video monitors is fully compatible with target eccentricities used in schizophrenia studies.

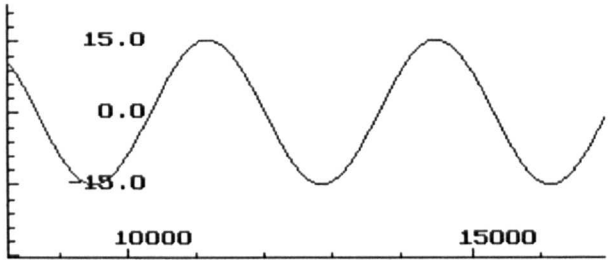
The target used in studies using computer or video monitors most often consisted of a small, coloured, square or round dot (Cegalis & Sweeney 1981; Clementz et al 1995; Clementz & McDowell 1994; Friedman et al 1995b; Ross et al 1999c), although letters, numbers and other symbols have also been used (Cegalis et al 1983; Keefe et al 1997; Sweeney et al 1992a; Thaker et al 1999). The monitor is usually presented at a distance of about 40-60cm at eye level from participants, approximating the average computer reading distance (Clementz et al 1995; Clementz & McDowell 1994; Litman et al 1994; Ross et al 1998e; Rybakowski et al 2001; Sweeney et al 1992a; Thaker et al 1999).

2.3.2.2 Stimulus Properties

In SPEM tasks, the target is usually first presented in the centre of the participant's visual field and is then moved horizontally to one side until it reaches the end point and reverses. It is important to note the difference between sinusoidal and constant velocity

(triangular or trapezoidal waveform) stimuli. The *sinusoidal* waveform essentially replicates the pendulum design (Figure 2.3).[9]

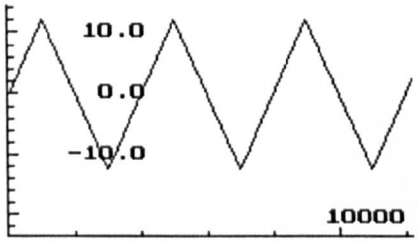
Figure 2.3: Example of a Sinusoidal Target Waveform



Legend: x-axis, time (ms); y-axis, degree of visual angle

In the *triangular* smooth pursuit waveform the target never stops or changes velocity, and experiences an abrupt direction reversal at the extreme eccentricity of each half-cycle (Figure 2.4). In the *trapezoidal* waveform the target stops at the end of each half-cycle and remains stationary for durations of typically a few hundred milliseconds, before initiating a new half-cycle (Figure 2.5). A *half-cycle* is defined as the target excursion between the most eccentric peripheral locations.

Figure 2.4: Example of a Triangular Target Waveform



Legend: x-axis, time (ms); y-axis, degree of visual angle

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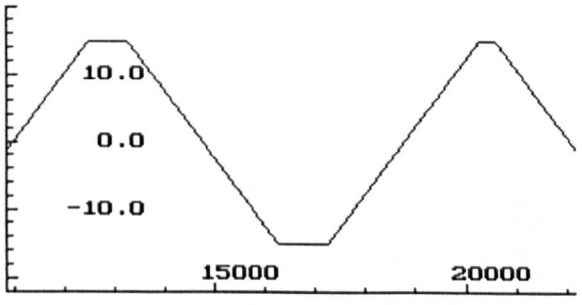
[9] The representation of eye movement data in Figure 2.3 is identical in principle to other graphs used in this and the following chapters: The vertical axis displays stimulus amplitude, with the participant's centre of the visual field (0°) displayed as the midline. Target movements to the participant's right visual hemifield are depicted as an upward movement of the target line in the graph; target movements to the participant's left are reflected by the line going down. The horizontal axis displays units of time, usually milliseconds.

Both sinusoidal (Gooding et al 1994; Green et al 2000; Holzman et al 1973; Pivik 1991; Rosenberg et al 1996; Spohn et al 1988) and constant-velocity (Arolt et al 1998; Clementz & McDowell 1994; Hutton et al 1998a; Lencer et al 1999; Litman et al 1994; O'Driscoll et al 1998; Ross et al 1999c) targets have been used in schizophrenia spectrum research. The key findings in schizophrenia spectrum research have been replicated irrespective of target waveform. Investigations using sinusoidal as well as constant-velocity targets have found high correlations between these measures and have generally not reported differences between them in discriminating between schizophrenia spectrum individuals and healthy controls (Amador et al 1995; Bartfai et al 1983; Iacono et al 1981; Shagass et al 1974; Siever et al 1994).

Figure 2.5: Example of a Trapezoidal Target Waveform



Legend: x-axis, time (ms); y-axis, degree of visual angle

A range of different *target velocities* has been used. Velocity of sinusoidal targets is usually expressed in frequency (Hertz; Hz) and peak velocity (degrees per second). Velocity of triangular or trapezoidal targets is usually expressed in degrees per second (°/s). As the human smooth pursuit system may comfortably follow targets of velocities up to 30-40°/s (Carpenter 1988; Leigh & Zee 1999), most studies have employed velocities ranging from 10°/s to about 40°/s, or 0.3Hz to 0.6Hz (e.g. Cegalis et al 1983; Cegalis & Sweeney 1981; Gambini et al 1993b; Pass et al 1978; Radant et al 1997; Roitman et al 1997; Salzman et al 1978; Shagass et al 1974; Spohn et al 1988; Thaker et al 1999; Van Gelder et al 1990), although faster targets have also been used (Iacono et al 1981; Levin et al 1982a; Schwartz et al 1999; Versino et al 1993). As accuracy of the smooth pursuit system is affected by target velocity, and it has been suggested that

target velocity also affects the effect size of comparisons between schizophrenia patients and controls, a number of studies have combined different target velocities (Abel et al 1991; Hutton et al 2001a; Lipton et al 1980a; May 1979; Pivik 1979b).

Another issue that needs to be addressed is that of the *range* of horizontal target excursions. Due to restrictions of the linearity of infrared oculographic recording systems, and to minimise strain on the eyes, most studies have used comfortable horizontal target excursions of ±10°, ±12°, or ±15° (Litman et al 1991; Matsue et al 1994b; Nkam et al 2001; Roitman et al 1997; Ross et al 1997, 1999c; Stuve et al 1997; Van Gelder et al 1990).

Instructions to participants in the smooth pursuit task are typically to follow the target, with their eyes, as accurately as possible wherever it goes. In order to avoid contamination by movement artefacts, participants are required to keep their head and other parts of the body still during the task.

In addition to this regular type of smooth pursuit task, which will be the main focus of this thesis, other tasks, such as step-ramp and predictive pursuit tasks have been applied to schizophrenia spectrum populations.

In a horizontal *step-ramp*, or *Rashbass task* (Rashbass 1961), the target first appears in the central location, then abruptly moves to the side (the step), and then immediately starts to move slowly at a constant velocity (the ramp). In *foveopetal* step-ramp tasks the direction of the ramp is opposite to that of the step, so that the target moves back towards and crosses the central fixation point. In *foveofugal* tasks the target continues the ramp in the direction of the step, away from the central fixation point.

Step-ramp tasks allow the assessment of closed-loop pursuit performance, similar to the standard pursuit task, but also provide additional information on motion processing and open-loop pursuit performance, obtained from the first few hundred milliseconds of this task. Open-loop pursuit occurs in the first 100-200ms of pursuit initiation, when perceptual feedback about pursuit performance is not yet available. Pursuit in this phase is initiated, therefore, on the basis of sensory and motion input. Closed-loop pursuit refers to the later phase of pursuit, where perceptual information of pursuit performance can be utilised in improving accuracy of performance (Sweeney et al 1999). These measures have been studied in attempts to locate the neuroanatomic deficit underlying SPEM impairment in schizophrenia spectrum (Clementz & McDowell 1994; Sweeney et al 1999).

Some researchers have used predictive pursuit tasks (Thaker et al 1996b, 1998, 1999). Thaker et al's task consisted of a predictable triangular waveform target, which was occasionally blanked out (masked) for durations of 500ms, thereby allowing measurement of gain during predictive pursuit in the absence of a physical target. Trillenberg et al (1998) used a sinusoidal target that abruptly stopped after a number of predictable half-cycles at the most extreme target eccentricity, again allowing the assessment of predictive pursuit eye movements.

2.3.3 Recording

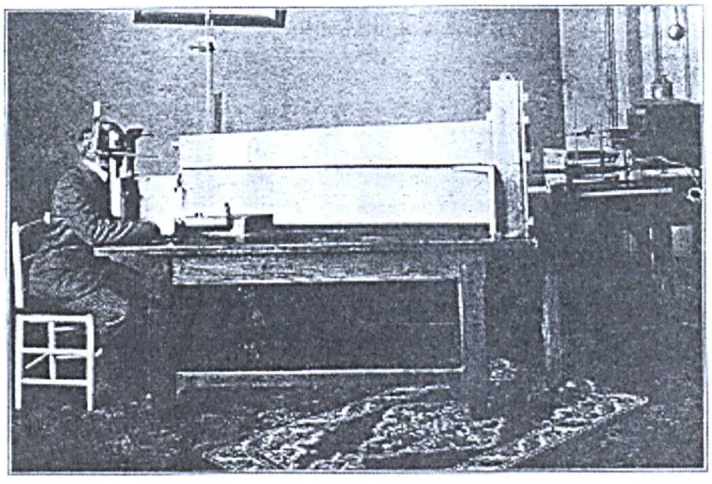
This section discusses eye movement recording techniques of relevance to schizophrenia spectrum research. Recording techniques do not generally differ across the (smooth pursuit, fixation, antisaccade and prosaccade) eye movement tasks discussed in this thesis; therefore, methods discussed in this following section apply to other tasks as well.

A wide variety of techniques have been used to record oculomotor activity (for review see (Carpenter 1988, Appendix 1; Clementz & Sweeney 1990; Iacono & Lykken 1983; Leigh & Zee 1999, Appendix B). In the field of schizophrenia spectrum research, the vast majority of studies have employed either the electrooculographic (EOG) or the infrared oculographic (IRO) techniques.

Historically, the first schizophrenia study employed a photographic method (Diefendorf & Dodge 1908). The *Dodge Photochronograph* (Figure 2.6) made photographic recordings of the eye using the movement of a sensitive photographic plate. Briefly, the photographic plate captured filtered light rays of an electric arc, which reflected from the cornea of the eye back to the plate. The light ray consisted of an arc light with horizontal upper carbon and was projected onto one of the participant's eyes from behind a condensing lens through an opening in an otherwise opaque screen placed in front of the participant. From the cornea the light was then reflected onto the photographic plate. An enlarging camera of fixed length (153cm) and a device for producing regular motion of the sensitive photographic plate were used.

This ingenious method has proved to be of considerable accuracy; "it is fair to say that the precision of those recordings has not been matched even with today's electronic technology" (Holzman 1983; p. 33).

Figure 2.6: Dodge Photochronograph



from Diefendorf and Dodge (1908), p. 456

Probably the most reliable and accurate method in neuro-ophthalmology is the magnetic search coil (MSC) technique (Stahl et al 2000; Van Der Geest & Frens 2002). This technique involves the participant wearing a silastic annulus under their eyelid containing two coils of wire, wound in the frontal and sagittal planes. The participant is placed in a magnetic field and the voltages that are induced in the coils can be recorded to determine eye position. Despite its excellent resolution the main disadvantage of this technique is its invasiveness, as the participant must wear a contact lens and can usually not endure test session of longer than 30 minutes (Leigh & Zee 1999). The MSC technique has met with little acceptance in schizophrenia spectrum research (however, see (Levin et al 1988; Nieman et al 2000), presumably due to its invasive nature which might pose a problem in the assessment of psychiatric patients, especially those acutely ill. Further, the assessment of large number of individuals is time consuming.

Most early studies of eye movements in schizophrenia have used the EOG method (Iacono & Lykken 1983; Levin et al 1982b; Lipton et al 1983). This technique has a number of advantages (Table 2.2). It is a relatively inexpensive, reliable, accurate (to within 1 or 2 degrees of visual arc) and unobtrusive method, which is readily available in most psychophysiology laboratories. The method works on the differences in voltage generated by shifts in the position of the eyes. A standing potential of 1mV exists between the cornea and the fundus of the eye. Eye movements create a change in

voltage potential generated by shifts in the position of the two globes and can be monitored from periorbital electrodes, such as silver/silver chloride electrodes placed on the outer canthi of the eyes (tin and gold electrodes may also be used). Electrodes may be referenced to each other or to a neutral reference electrode placed in an area of low electrical activity (e.g. earlobe, or mastoid). An additional electrode is used as ground electrode for participants' safety and to reduce ambient electrical artefact. The main disadvantages of the EOG technique are its restricted precision and its susceptibility to effects of bioelectric noise. Factors such as facial muscle activity, eye-blinks and twitches, skin resistance, sweat, changes in retinal metabolism due to light changes and brain electrical activity may introduce artefacts into the recordings.

Most recent studies of eye movements in the schizophrenia spectrum have used the infrared oculographic (IRO) method. IRO is a photoelectric technique that exploits the reflection characteristics of infrared light when projected onto the boundary between iris and sclera (i.e. the limbus, see Figure 2.1). Infrared light beamed onto the limbus is reflected and subsequently picked up by detectors on both the nasal and temporal side of the eye. With horizontal movements of the eye the detectors will pick up increases and decreases in limbus reflection, together giving a measure of eye position (Iacono & Lykken 1983; Reulen et al 1988).

Various commercially available apparatuses have been developed based on this technique (for review, see Reulen et al 1988). The equipment usually involves the participant wearing a light plastic helmet containing the infrared emitters and detectors, ensuring minimal disruption due to head movements while at the same time guaranteeing little discomfort to the participant. Importantly, unlike other methods (e.g. MSC), IRO does not involve physical contact with the eye. However, the headset is usually more obstructive to vision than, for instance, electrodes in the EOG technique.

The main advantage of IRO over EOG is its excellent precision (Table 2.2). Additionally, IRO does not experience the problems of bioelectric noise encountered in EOG. IRO, however, has a number of disadvantages (Carpenter 1988; Iacono & Lykken 1983; Leigh & Zee 1999; Lipton et al 1983; Reulen et al 1988).

Table 2.2: Advantages and Disadvantages of the Electro-Oculographic (EOG) and Infrared Oculographic (IRO) Techniques in the Recording of Eye Movements

	EOG	IRO
Robustness to bioelectric noise	-	+
Robustness to ambient light	+	-
Precision	-	+
Range of linearity in horizontal target/eye excursions	+	-
Unobtrusiveness of equipment	+	-
Usability for prolonged recording	+	-
Suitability for participants with glasses	+	- *
Recording of vertical eye movements	+	-

Legend:
+ denotes strength of the method
- denotes weakness of the method
* see Iacono and Lykken (1983)

First, photodetectors and infrared light emitters mounted close to the participant's eye may restrict the field of view. Second, most IRO headsets cannot be applied to people with glasses.[10] Third, sources of ambient light introduce noise into the recordings. Fourth, prolonged exposure to infrared light may cause irritation or drying of the eye. Fifth, the range of horizontal recordings is larger with EOG than IRO. Lastly, vertical eye movements may be more reliably recorded with EOG than IRO.

Given these disadvantages, it may seem surprising that IRO is now one of the most widely used techniques in schizophrenia spectrum oculomotor research. However, most of these problems are relatively easily circumvented, e.g. by using brief assessment durations and controlled light conditions. Others, such as restriction to horizontal tasks of limited range, do not pose a threat to the most commonly used tasks in schizophrenia spectrum research. As outlined above, most studies use horizontal targets with maximum excursions of ±30°, well within the possibilities of most IRO systems. It may be argued, therefore, that the key advantages of IRO over EOG, its excellent resolution and robustness to bioelectric noise, outweigh its problems.

A number of studies have addressed the similarities and differences between IRO and EOG in recording eye movements in schizophrenia patients and healthy individuals. Generally, these studies have demonstrated a high degree of qualitative similarity and

[10] Iacono and Lykken (1983) demonstrated a system that may be worn over glasses thus circumventing this problem.

high correlations of quantitative SPEM and prosaccade measures for simultaneous EOG and IRO recordings (Iacono & Lykken 1981; Lindsey et al 1978; Ong & Harman 1979).

It has, however, been found that EOG recordings contained more spiky interruptions of pursuit, masking as small saccades (Iacono & Koenig 1983; Iacono & Lykken 1981, 1983). These small spikes (2-3°) most likely did not reflect eye movements, but unspecified biological signals or EEG activity, such as alpha or kappa waves (Holzman & Levy 1977; Iacono & Koenig 1983; Lindsey et al 1978).

Concerning the similarities and differences between the IRO and EOG methods, the Clinical Research Branch of the National Institute of Mental Health and the Center for Studies of Schizophrenia convened a small conference in August 1981 to resolve methodological issues, differences and misunderstandings between SPEM researchers (editorial to Schizophrenia Bulletin; Volume 9, Number 1; 1983; see also the reviews therein). It was commented that "methodological disputes about recording techniques were more apparent than real since the basic findings were robust enough to transcend even primitive recording methods" (p. 11).

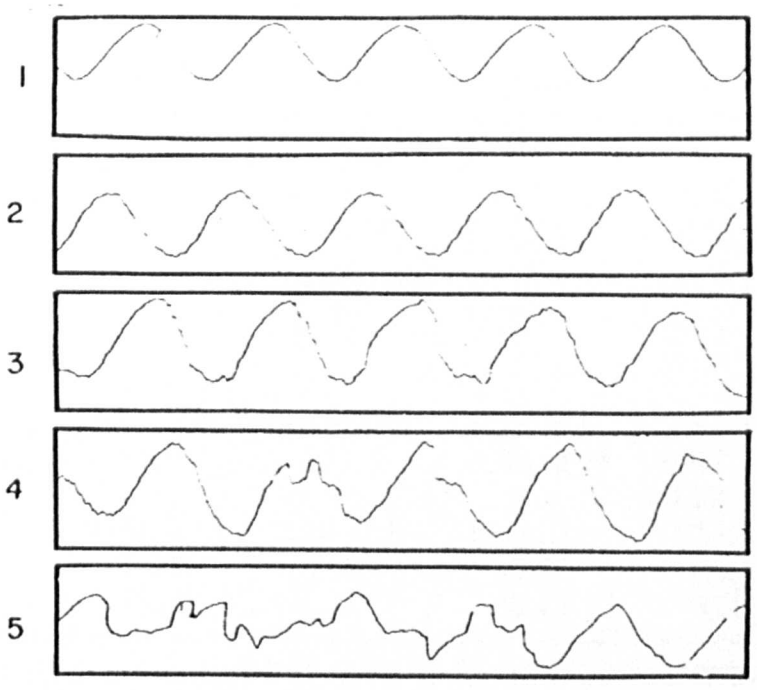
2.3.4 Smooth Pursuit Scoring

"Despite decades of research, the field of eye-tracking disorder in schizophrenia continues to struggle with questions about which measures should be used" (Ross et al 1998c; p. 184). It becomes obvious from this quote that analysis of SPEM data is riddled with problems. The reason for disagreements between researchers on SPEM analysis, according to Braff (1998), is probably the complexity of smooth pursuit performance itself, involving a variety of cognitive (and neural) processes. The SPEM task complexity is reflected in the number of subcomponents that can be studied. Previous approaches to SPEM scoring can be grouped into global and specific (Clementz & Sweeney 1990) methods, although a distinction along the quantitative-qualitative spectrum has also been made (Braff 1998).

The first studies by Holzman's group and subsequent replications employed *qualitative assessments* of SPEM data as 'normal' or 'deviant' performance. Categorisation was based on visual inspection of the congruence of eye movement recording with the target waveform (Holzman et al 1973, 1974; Holzman & Levy 1977). Reasons for adopting this method were its simplicity, the fact that target traces were not recorded (and thus could not be used in quantitative analysis) and the use of similar measures in previous

studies (Benitez 1970). Shagass et al (1974) elaborated on Holzman's method and provided examples of a 5-point qualitative rating scale (Figure 2.7), rating performance from 1 (best) to 5 (worst). This scale, or variations of it, has been widely used (Keefe et al 1989; Lencz et al 1993; Siever et al 1994).

Figure 2.7: Example of 5-point Smooth Pursuit Rating Scale



from Shagass et al (1974), p. 249; 1 = best, 5 = worst

In addition to this qualitative dichotomy Holzman and colleagues (1978b) distinguished between Type I and Type II eye-tracking dysfunction. Type I dysfunction was described by large amplitude, inaccurate saccades largely replacing the smooth pursuit component. In Type II dysfunction small amplitude saccades and frequent, brief eye arrests intruded on pursuit. This distinction, however, has not been widely used by others.

Qualitative assessment has the advantage of providing a simple summary score. A considerable number of studies have applied this method to schizophrenia spectrum samples, yielding important findings. Some of the most important findings obtained with qualitative ratings are those of SPEM dysfunction in first-degree relatives and

schizotypal individuals, SPEM concordance in twins discordant for schizophrenia, effects of lithium treatment in bipolar patients and independence of eye-tracking dysfunction from typical antipsychotic drug treatment (Holzman et al 1974, 1977, 1980, 1991; Levy et al 1983b, 1985; Siever et al 1994).

However, qualitative ratings may be criticised on a number of grounds. First, scoring involves a subjective component which, despite good inter- and intra-rater reliability (O'Driscoll et al 1998; Rosse et al 1992a; Siever et al 1994; Spohn et al 1988), may be undesirable. For this reason, researchers have strived to employ *objective* measures of pursuit. Second, and more importantly, qualitative ratings do not specify what exactly the oculomotor deficit underlying 'abnormal' pursuit is (e.g. Abel 1986). For this reason, researchers have developed *specific* measures.

Amongst the earliest *quantitative* measures were frequency of *velocity arrests* and frequency of *positive saccades* (Holzman et al 1973; Pivik 1979b; Salzman et al 1978). Velocity arrests were measured as the number of times pursuit velocity reached zero or came near zero (Holzman & Levy 1977). Positive saccades were counted when eye velocity exceeded target velocity by 33.33%. These measures were shown to be reliable and correlated with qualitative ratings (Coursey et al 1989; Holzman et al 1973, 1974). The validity of both measures, however, has been seriously challenged (Troost et al 1974) on the grounds of their arbitrary nature, the possibility of EOG recording artefacts and their lack of relatedness to previously used measures of pursuit. Lindsey et al (1978) confirmed that velocity arrests were significantly increased in EOG compared to IRO recordings, suggesting contamination by bioelectric noise.

Given these criticisms, these measures were rapidly succeeded by other quantitative procedures. At around the same time Lindsey et al (1978) and Iacono and Lykken (1979a, 1979b) developed *global quantitative measures* of smooth pursuit. These were developed given the newly emerged possibility of obtaining a record of the target trace and advances in the development of microcomputers.

Lindsey et al's (1978) *natural logarithm of the signal-to-noise ratio*, or *ln(S/N)*, determines the amount of 'noise' in the eye movement, or its deviation from the target movement. For a sinusoidal target at a given frequency (e.g. 0.4Hz), eye pursuit frequency within this frequency range defined as 'signal' and a predefined range of frequencies is defined as 'noise' (e.g. 1.2-12Hz). The natural logarithm of the ratio between the two is taken as performance index, with higher scores indicating better performance. ln(S/N) has the

advantage of being scored relatively easily and objectively. It has been shown to be correlated with qualitative and quantitative measures, and to discriminate between healthy controls and patients, furnishing evidence of its validity (Grawe & Levander 1995; Levin et al 1981b; Lindsey et al 1978; Siever et al 1989; Spohn et al 1988).

However, as a global measure ln(S/N) suffers a similar problem to qualitative ratings, i.e. the lack of information regarding specific oculomotor deficits. Abel and Ziegler (1988) undertook a computer simulation of poor ln(S/N) performance in hypothetical groups differing considerably and systematically in precise measures (such as the frequencies of different kinds of saccades). ln(S/N) scores were identical across groups, demonstrating that this global measure might be informative in establishing an abnormality without specifying where exactly the abnormality lies.

Iacono and Lykken's (1979a, 1979b) *root mean square error*, or *RMSE*, is a mathematically related procedure (Lykken et al 1981). It expresses the overall deviation of eye from target and can be used for targets of all waveforms. RMSE is calculated as the difference between eye and target position for every recorded data point. This difference at each data point is then squared and the average of all terms is taken. Higher scores indicate worse performance.

RMSE has been used by a number of laboratories in studies of schizophrenia spectrum populations (Clementz et al 1992; Friedman et al 1995b; Iacono et al 1992; Ross et al 1996c; Sweeney et al 1993). Its advantages include the simple and linear quantification of overall pursuit, the objective nature of the scoring procedure and its established validity. Clementz et al (1996b) most vigorously pointed out the advantages of RMSE. They argued that RMSE correlates highly with alternative measures, is temporally stable in schizophrenia patients and normals and has been successful in discriminating between different clinical and non-clinical groups. However, similar to qualitative ratings and ln(S/N), RMSE does not provide specific oculomotor performance scores.

Other quantitative measures that have been used in schizophrenia spectrum research include phase-lag (Ross et al 1996a; Trillenberg et al 1998) and indirect measures such as the amount of time spent in pursuit (Schwartz et al 1999).

Leigh and Zee (1999) summarise the usefulness of global (qualitative and quantitative) measures as follows: "RMSE values are estimates of overall tracking, not just smooth pursuit" and "finally, qualitative rating scales of pursuit as relatively "normal" or "deviant" are of little value in determining the nature of the deficit" (p. 180). Abel and

Ziegler (1988) in a widely cited review of smooth pursuit scoring techniques in schizophrenia come to a similar conclusion. Despite these criticisms, ln(S/N) and RMSE have been widely used in schizophrenia spectrum research. Most recent studies, however, have taken heed to Abel and Ziegler's (1988) call for the use of specific oculomotor measures. The most frequently used specific measures are those of smooth pursuit gain and the frequency of saccades.

Gain is arguably the best measure of smooth pursuit system integrity (Leigh & Zee 1999) and has been widely used in schizophrenia spectrum research (Clementz et al 1990; Hutton et al 1998a; Levin et al 1988; Litman et al 1989; Ross et al 1998c; Schmid-Burgk et al 1982; Yee et al 1987). Gain is most commonly calculated by dividing eye velocity by target velocity. A score of 1 (or 100, if multiplied by 100), therefore, indicates perfect match of eye and target velocity. As it is the function of the pursuit system to match eye and target movement (Leigh & Zee 1999), the gain measure is often considered sufficient for assessment of pursuit system integrity. Gain is usually calculated for small segments (e.g. 50-500ms) of steady-state mid-cycle pursuit for constant velocity target waveforms or segments during peak target velocity in sinusoidal target waveforms (Flechtner et al 1997; Gooding et al 2000b; Hutton et al 2000, 2001a; Levy et al 1994; Siever et al 1994; Thaker et al 1996b) after eye-blinks, saccades and artefacts have been excluded.

Another widely used measure is the *frequency of saccades*, usually expressed as the number of saccades per unit of time. Different types of saccades are observed during smooth pursuit. The most common distinction is that of intrusive vs. corrective saccades. Intrusive saccades consist of anticipatory saccades and square-wave jerks; corrective saccades consist of catch-up saccades and back-up saccades.

The first studies to evaluate saccadic frequency in schizophrenia, however, did not always distinguish between different subtypes of saccades (Cegalis et al 1983; Cegalis & Sweeney 1979; Mialet & Pichot 1981), or used coarse categories such as large and small saccades (Spohn et al 1988), saccades in target motion and in opposite direction (Van Gelder et al 1990), or saccadic intrusions and saccadic pursuit (Levin et al 1982a). With increasing awareness of saccade subtypes and improvements in recording and analysis techniques, more recent investigations have focussed on specific subtypes.

Anticipatory saccades (AS) are defined as saccades in direction of target motion, which end ahead of the target and increase position error (i.e. the difference between eye and

target position). AS are followed by about 50-300ms of reduced eye velocity, often operationally defined as less than 50% of target velocity. Return saccades (to target) may occur after a long inter-saccadic interval (Ross et al 1998e, 1999c, 2001). Initial studies suggested minimum amplitude criteria of about 5° (Whicker et al 1985).

Ross and colleagues have stressed the importance of the AS as a potential genetic marker and have further characterised it. Ross et al (1999c) investigated the effect of required minimum amplitude for the inclusion of AS on schizophrenia-control group effect sizes. It was found that inclusion of smaller AS (1°) improved the statistical separation between groups. More recently, Ross et al (2001) characterised the amount of post-saccadic slowing required for reliable detection of AS. Most previous studies have assumed that AS are followed by post-saccadic slowing of approximately ≤50% of target velocity (Clementz et al 1990; Litman et al 1994; Radant & Hommer 1992; Rosenberg et al 1997c; Sweeney et al 1994b). Ross et al (2001) found that focusing this criterion on 50ms rather than 300-400ms after the saccade maximised statistical separation of schizophrenia and control groups. However, it also becomes clear from their analyses (their Table 2, p. 331) that AS differentiated patients and controls irrespective of post-saccadic slowing criteria. Additionally, as small AS (1-2°) were unlikely to be followed by 300-400ms of slowed pursuit (≤50%), it is not clear how AS amplitude affected these results. This point is particularly important given the authors' earlier finding of increased separation between schizophrenia and control groups with the inclusion of smaller AS, obtained in the same sample (Ross et al 2001).

A considerable body of research has confirmed the validity of AS as a specific oculomotor endophenotype in schizophrenia spectrum research (Lencer et al 1999; Rosenberg et al 1997c; Ross et al 1998e), although evidence to the contrary has also been presented (Clementz et al 1990). The main attractions of this measure are probably its face validity as an inhibitory saccadic failure and its well-characterised appearance.

Catch-up saccades (CUS) serve to reduce position error when the eye is lagging behind the target. CUS are usually defined as saccades that begin behind the target. As their function is to move the eye back to the target, a correctly executed CUS should end on target. However, CUS often begin and end behind the target, or begin behind the target and end ahead of it (Friedman et al 1991; Radant & Hommer 1992; Ross et al 1997). If the latter is the case, a criterion of postsaccadic position error of at most 50% of presaccadic error has been suggested, i.e. the saccade has to significantly reduce

position error. Post-saccadic slowing criteria are not usually applied to the identification of CUS (Ross et al 2001). Instead, Levy et al (1994) suggested that CUS are typically *preceded* by reduced velocity gain, a feature which additionally serves to distinguish them from AS.

Square-wave jerks (SWJ) are intrusive saccades that consist of pairs of saccades in opposite direction. The first saccade usually takes the eye ahead of the target. The second saccade returns it after about 50-500ms. Importantly, (parafoveal) pursuit continues between the pair of saccades. This feature serves to distinguish SWJ from AS (Ross et al 2001). Macro-SWJ have also been identified (Clementz & Sweeney 1990); these are defined as pairs of saccades of larger amplitude than SWJ but relatively short inter-saccadic interval (100-125ms)

Back-up saccades (BUS) are compensatory saccades that return the eye to the target when it moved ahead of it. BUS may also occur after post-saccadic slowing following an AS. BUS have not been studied in detail in the schizophrenia spectrum.

In addition to saccadic frequency, some studies have investigated the amplitudes of saccades during pursuit (Cegalis et al 1983; Mather & Putchat 1982) or the 'desired CUS amplitude' (Ross et al 1998c), i.e. the amplitude a CUS would require to move the eye precisely onto the target.

An important question in smooth pursuit analysis concerns the relationship between global and specific, or qualitative and quantitative measures. While most measures of pursuit – not surprisingly – tend to be correlated, a number of studies have attempted to examine the amount of variance of qualitative and global quantitative measures that is explained by specific measures.

Ross et al (1998c) aimed to explain qualitative ratings (1-5) in terms of RMSE, gain, variability (SD) of gain, CUS frequency, CUS amplitude, desired CUS amplitude and phase lag in 76 schizophrenic patients. Multiple regression showed that 4 of the 6 specific measures (gain, SD of gain, CUS amplitude, desired CUS amplitude) were accepted by the model as significant predictors of qualitative ratings. Spohn et al (1988) demonstrated that 79% of the variance of ln(S/N) was accounted for by the frequency of 'small' and 'large' saccades.

Variance in RMSE has also been partially explained by specific measures. Ross et al (1997) used mixture analysis to obtain two groups of schizophrenic patients, with high

and low RMSE scores. SPEM was also scored for gain, SD of gain, AS frequency and CUS frequency, amplitude and desired amplitude. Gain, gain SD, CUS amplitude and desired amplitude significantly discriminated between the high and low RMSE groups. Similarly, Levy et al (2000) found that poor and good performers (based on qualitative ratings) could be differentiated primarily by CUS and gain and secondarily by SWJ frequency.

Taken together, these findings indicate that global qualitative and quantitative measures may be largely, but not completely, explained statistically by specific measures. This should come of no surprise, as both measures assess the same overall behaviour, i.e. SPEM performance, in the same individuals. More importantly, these results support the concurrent validity of specific measures, in particular reduced gain and increased saccadic frequency (especially CUS), in describing global eye-tracking dysfunction of schizophrenia patients.

What are the implications of this plethora of different scoring methods for the analysis of SPEM performance in schizophrenia spectrum individuals? As Levy et al (2000) pointed out, "ETD [eye-tracking dysfunction] is a multivariate process" (p. 172). Similarly, Braff (1998) pointed to the complex (cognitive) nature of this task. Given these assertions, the use of specific measures may be encouraged. Specific measures are of particular importance, and in fact essential, if one wishes to pinpoint precise neural abnormalities based solely on behavioural data (Clementz 1996a; Clementz & McDowell 1994; Sweeney et al 1999; Thaker et al 1996b, 1998, 1999). Similarly, Hutton and Kennard (1998) pointed to the importance of *combining* measures of saccadic frequency and pursuit gain. For example, information on CUS frequency is invaluable in the interpretation of reduced gain in schizophrenia. Reduced gain in the presence of increased CUS frequency might indicate intact position error detection mechanisms, while reduced gain in the absence of increased CUS frequency might indicate impaired position error detection mechanisms (Hutton & Kennard 1998).

However, the validity of global measures has been demonstrated. Moreover, two studies demonstrated that qualitative ratings were superior to measures of gain and saccadic frequency in statistically separating healthy individuals from relatives of schizophrenia patients (Keefe et al 1997) or SPD patients (Siever et al 1994). Interestingly, global (categorical) performance measures continue to be used successfully in functional neuroimaging studies (O'Driscoll et al 1999) and genetic analyses of the ETD phenotype (Rybakowski et al 2001). In linkage studies it may be advantageous to classify

individuals as 'affected' or 'unaffected' based on SPEM performance, ignoring further between-subject variance. It may, therefore, be concluded, that different study designs and research questions require different analysis techniques.

A further problem, however, is that while a number of specific measures have been proposed, "...no one has definitely offered a compelling taxonomy and scoring method that has convinced the qualitative "supporters" to adopt a fully quantitative approach" (Braff 1998; p. 185). Although considerable work has been carried out on the description of some specific measures, different laboratories continue to differ in their use of scoring techniques, software packages and specific criteria. Until common criteria are established which can be implemented objectively across different software packages and laboratories, researchers will likely continue to disagree. It is, however, reassuring that the basic finding of SPEM dysfunction in schizophrenia spectrum individuals has been replicated many times, over almost 100 years, using the multitude of scoring approaches and criteria described above (Section 2.3.5.1).

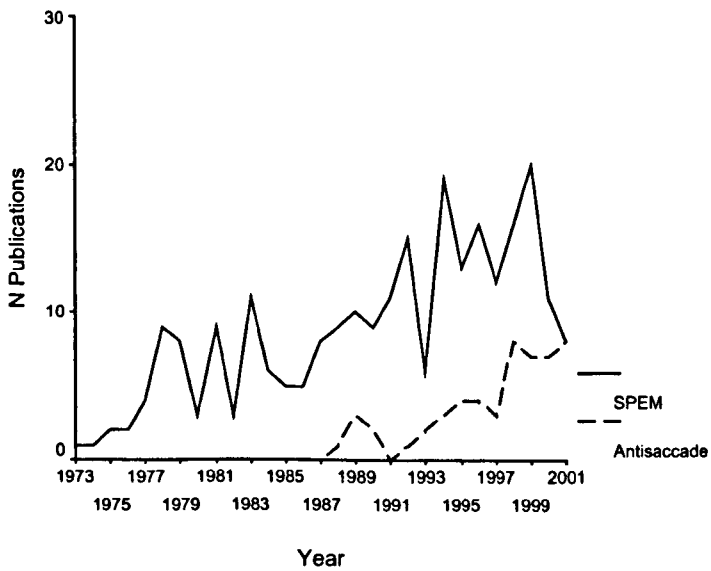
2.3.5 Smooth Pursuit Eye Movements in the Schizophrenia Spectrum

2.3.5.1 Behavioural Characterisation of Smooth Pursuit Eye Movements in Schizophrenia Patients

The finding of 'impaired' SPEM in individuals with schizophrenia is believed to be one of the most robust in schizophrenia research. Indeed, SPEM abnormalities were judged by a panel of experts to be amongst the top 18% of most reproducible findings in schizophrenia research (Tandon 1999). Observations of SPEM abnormalities were judged as more reproducible than, for example, findings that stimulants such as amphetamines model schizophrenia, that obstetric complications increase the risk of schizophrenia or that schizophrenia is characterised by hypofrontality or reduced grey matter volume (Tandon 1999). Since Holzman et al's (1973) seminal study, there have been several dozens of replications of this finding. A large number of literature overviews are available (Abel et al 1992; Arolt et al 1993; Clementz & Sweeney 1990; Flechtner et al 2000; Holzman 1985, 1992, 2000; Holzman & Levy 1977; Hutton & Kennard 1998; Lee & Williams 2000; Levin 1984; Levy et al 1993, 1994; MacAvoy & Bruce 1995; Schwartz & Evans 1999). The rising number of peer-reviewed journal publications on SPEM in schizophrenia since 1973 (including reviews) parallels the

steady increase in the research effort into this phenomenon and is depicted in Figure 2.8.

Figure 2.8: Number of Publications in *Medline* on Smooth Pursuit and Antisaccade Eye Movements in the Schizophrenia Spectrum since 1973



Chronicling the research of SPEM in schizophrenia patients over the past 30 years essentially parallels the development of ever more sophisticated recording and analysis techniques, as described above (Section 2.3.4). Briefly, the early finding of a qualitative disturbance of smooth pursuit eye movements in schizophrenia (Holzman et al 1973) was soon replicated by other research groups (Brezinova & Kendell 1977; Kuechenmeister et al 1977; Shagass et al 1974). Importantly, this observation could be replicated irrespective of methodological variations in stimulus display (Cegalis & Sweeney 1979; Shagass et al 1974) and recording techniques (Iacono & Lykken 1981; Lindsey et al 1978; Ong & Harman 1979), supporting the notion that SPEM impairments in schizophrenia are not bound to specific target characteristics and are not due to recording artefacts.

Research in the following years began to use quantitative measures of pursuit in order to overcome some of the problems of qualitative ratings, again replicating the early findings. Thus, when compared to healthy individuals, schizophrenia patients demonstrated increased frequency of velocity arrests (Holzman et al 1973; Pass et al 1978), increased phase-lag (Ross et al 1996a; Trillenberg et al 1998), increased RMSE

(Clementz et al 1992; Friedman et al 1995b; Iacono et al 1992; Ross et al 1998c, 1996c; Sweeney et al 1993) and worse ln(S/N) (Grawe & Levander 1995; Levin et al 1981b; Lindsey et al 1978; Siever et al 1989; Spohn et al 1988).

Improvements in recording techniques and analysis software as well as a better understanding of the neurophysiology of eye movements, however, now allow a more precise characterisation of the smooth pursuit deficits in schizophrenia patients. Mainly since Abel and colleagues' (Abel 1986; Abel & Ziegler 1988) repeated attacks on non-specific pursuit measures, schizophrenia researchers have adopted specific, ophthalmologically informed measures. Thus, recent evidence paints the following picture. When compared to healthy individuals, people with schizophrenia have reduced pursuit gain (Friedman et al 1991; Levin et al 1988; Radant & Hommer 1992; Schmid-Burgk et al 1982; Yee et al 1987) as well as increased frequency of saccades during pursuit. The increase in saccadic frequency is mostly due to the occurrence of compensatory catch-up saccades (Abel et al 1991; Friedman et al 1991; Hutton et al 1998a; Radant & Hommer 1992; Sweeney et al 1992a); intrusive anticipatory saccades have also been observed by some (Ross et al 1999b, 1999c, 2000, 2001) but not others (Hutton et al 2000). Frequencies of intrusive square-wave jerks (Campion et al 1992; Clementz et al 1990; Friedman et al 1992a; Hutton et al 2000; Lencer et al 1999; Levin et al 1988; Litman et al 1994; Radant & Hommer 1992) and compensatory back-up saccades (Lencer et al 1999; Litman et al 1994) are generally not found to be elevated in the patient group, despite some reports to the contrary (Flechtner et al 1997).

Studies using multiple target velocities have found evidence of greater impairments at faster velocities (Abel et al 1991; Hutton et al 2001a; Lipton et al 1980a; May 1979; Pivik 1979b), likely due to increased task difficulty. Other studies, however, have failed to replicate this effect (Hutton et al 1998a; Sweeney et al 1999). Gender appears to have no consistent influence on SPEM and differences between schizophrenia patients and healthy individuals (Iacono et al 1992; Pivik 1979a). SPEM performance worsens with age, but the differences between schizophrenia patients and healthy individuals appear to remain (Muir et al 1992; Ross et al 1999a). SPEM deficits in schizophrenia have been observed in a number of different geographic locations and ethnic groups, indicating universality of the finding (Allen et al 1990b; Allen 1997; Allen & Johnson 1995).

An early criticism was that SPEM dysfunction in schizophrenia might be due to general inattentiveness and lack of motivation. While variable motivation is, of course, a pervasive feature of schizophrenia (Brown & Pluck 2000), experimental studies have

demonstrated that superficial manipulation of state motivation as well as attentiveness is unlikely to fully account for the SPEM deficits seen in this disorder. First, incentives such as money and cigarettes do not appear to improve SPEM performance in schizophrenia (May 1979). Second, reiteration of instructions during the task does not lead to significant improvements (Brezinova & Kendell 1977; Holzman et al 1974; Pivik 1979a; Shagass et al 1974). Third, presentation of distracting visual and auditory stimuli (without the requirement of further cognitive processing) does not significantly impair SPEM in schizophrenia patients (Pass et al 1978). Fourth, Pivik (1979b) could show that an indirect measure of attentiveness, EEG alpha activity, was not associated with SPEM dysfunction. Fifth, SPEM impairments in schizophrenia were found to be comparable across high and low distracting room conditions (Mather et al 1989).

More evidence against an explanation of generalised inattentiveness or lack of motivation stems from studies of other types of eye movements (Sections 2.4.4.1 and 2.6.4.1) which are often found to be unimpaired in the same patients who display impaired SPEM (Iacono et al 1981; Levin et al 1982b). Other studies have shown that patients are in general able and willing to follow complex task instructions, casting doubt over the assumption that SPEM deficits are due to a failure to understand or comply with instructions (McDowell & Clementz 1997). Additionally, studies of psychiatrically and neurologically healthy and, presumably, normally motivated first-degree relatives as well as healthy and discordant twins suggest that individual differences in performance levels are mostly due to genetic factors and unlikely to be related exclusively to *state* effects of motivation (Section 2.3.5.5.4). Due to the profound levels of clinical impairments and drug-induced side effects seen in some schizophrenia patients, however, the possibility cannot be excluded that poor motivation or inattentiveness accounts for a small proportion of variance in SPEM deficits in schizophrenia patients, similar probably to other neurocognitive tasks used in schizophrenia research.

2.3.5.2 Neural and Cognitive Basis of Smooth Pursuit Eye Movements

2.3.5.2.1 Neural Substrates of Smooth Pursuit Eye Movements

Generation and control of smooth pursuit in humans involves a widespread cortical and subcortical network. On the basis of evidence from animal lesion, human lesion and

human functional neuroimaging studies, Leigh and Zee (1999) outlined the following model, which is acknowledged by others as well (MacAvoy & Bruce 1995).

Visual input from the retina reaches occipital visual areas (striate cortex V1) via the lateral geniculate body of the thalamus. Further processing of the pursuit stimulus in extrastriate cortex is mostly localised to V5 (in humans; MT/MST in monkey) and posterior parietal cortex (PPC). The importance of V5 (MT/MST) in smooth pursuit lies principally in the processing of motion related information (e.g. velocity and direction), as indicated by inaccurate saccades to moving targets after lesions to this area (Newsome et al 1985). PPC appears to be concerned more with the semantic nature of the target stimulus, suggesting attentional processing capacities. MT/MST and PPC project directly to the frontal eye fields (FEF), which contain an area (in the inferior lateral part) selectively involved in pursuit eye movements. FEF, MT/MST and PPC project to the supplementary eye fields (SEF), which have also been implicated in pursuit.

Descending projections from these cortical areas (directly or via the nucleus of the optic tract) are those to pontine nuclei, which in turn project to various site in the cerebellum. Cerebellar areas involved in pursuit include the posterior vermis, the paraflocculus, the flocculus and the fastigial oculomotor region.

2.3.5.2.2 Neuroimaging Studies in Schizophrenia

Only a small number of studies have investigated the neural correlates of SPEM impairments in schizophrenia patients. Such studies are of importance, as a precise understanding of the neural structures and networks underlying impaired SPEM in the patient group would aid the understanding of the effects of a putative gene on the behavioural deficit.

The only functional neuroimaging study of SPEM in the patient group to date demonstrated lower glucose metabolism in left and right frontal cortex during a pursuit task; deficits were more pronounced for patients with negative symptoms (Volkow et al 1987). Restrictions in spatial resolution of Volkow et al's (1987) imaging method, however, did not allow a more detailed anatomic description of the deficit. A more recent study compared functional activation of two groups of schizophrenia patients' first-degree relatives with impaired and unimpaired performance during pursuit (O'Driscoll

et al 1999). Differences in cerebral blood flow between the two groups were localised to the FEF.

Blackwood et al (1994a) observed a relationship between SPEM and cerebral blood flow in frontal areas, indicating that *normal* SPEM was associated with *reduced* blood flow in bilateral frontal lobe and left anterior and posterior cingulate cortex. SPEM and cerebral blood flow were measured on different occasions. Blackwood et al (1994a) argued that this finding indicates the existence of "separate pathological processes" (p. 164). However, if separate processes were at operation one might expect a zero correlation not a negative one.

Ross et al (1995) observed correlations between RMSE and glucose utilisation in the FEF and caudate nucleus. In this study, glucose utilisation was assessed using PET during an attentional task; SPEM was measured on a separate occasion. Correlations indicated that worse SPEM was associated with reduced metabolism in the FEF and increased metabolism in the caudate, consistent with previous observations of hypofrontality during cognitive tasks (Weinberger et al 2001) and the notion that FEF damage might at least partially underlie the SPEM impairments seen in schizophrenia (MacAvoy & Bruce 1995; O'Driscoll et al 1999). However, as glucose metabolism was not obtained during eye movements in this study it is difficult to evaluate the specificity of this finding.

Other researchers have studied the structural brain correlates of SPEM abnormalities in schizophrenia. These investigations are based on the hypothesis that greater brain structural abnormalities, such as reduced grey matter or increased ventricular volume, might be associated with greater SPEM impairments, due to effects of illness severity or a common neurodevelopmental insult. To summarise the key findings, three studies (Bartfai et al 1985; Blackwood et al 1991; Weinberger & Wyatt 1982) obtained evidence of an association between increased ventricle size and abnormal SPEM. Other studies failed to obtain significant associations between SPEM and measures of brain structure (Jacobsen et al 1996; Katsanis et al 1991; Katsanis & Iacono 1991; Siever et al 1986), while two studies obtained evidence of an inverse association between structural brain

and SPEM abnormalities, suggesting that temporal lobe (Levy et al 1992)[11] and ventricular (Smeraldi et al 1987) *abnormalities* are associated with *normal* pursuit.

Unfortunately, most of these investigations suffered serious methodological shortcomings, such as the use of low-resolution brain imaging techniques (Bartfai et al 1985; Katsanis et al 1991; Siever et al 1986; Smeraldi et al 1987) and non-specific SPEM (Bartfai et al 1985; Smeraldi et al 1987; Weinberger & Wyatt 1982) and brain structure (Jacobsen et al 1996; Katsanis et al 1991; Katsanis & Iacono 1991; Siever et al 1986; Smeraldi et al 1987; Weinberger & Wyatt 1982) analysis methods.

To conclude, three neuroimaging studies (O'Driscoll et al 1999; Ross et al 1995; Volkow et al 1987) have demonstrated a co-occurrence of functional frontal lobe underactivity and SPEM dysfunction in the schizophrenia spectrum. However, evidence from a fourth study (Blackwood et al 1994a) is somewhat incompatible. Concerning the structural brain correlates of SPEM in schizophrenia, the largely inconsistent findings from studies with mostly inadequate methods necessitate further research. Future structural neuroimaging studies of eye movements may benefit from using sensitive eye movement recording and scoring techniques as well as volumetric measures of anatomically defined brain areas known to be implicated in schizophrenia and oculomotor control (Ettinger et al 2002).

2.3.5.2.3 Experimental Cognitive Studies

Attempts at delineating the cognitive basis of the SPEM impairments seen in schizophrenia have used both experimental manipulations and correlational studies. The key cognitive processes thought to underlie impaired SPEM in schizophrenia include attention, motion perception and working memory, and will be discussed in turn.

A well-established phenomenon is that SPEM accuracy can be improved through a simple manipulation of the visual target. These manipulations include the attaching of letters to the target pendulum (Holzman et al 1976; Shagass et al 1976), the employment of changing letters as targets (Clementz et al 1990; Rosenberg et al 1997c; Sweeney et al 1994b) and changes in colour (Schlenker et al 1994; Schlenker & Cohen

[11] Lieberman et al (1993) reported the same relationship in an extension of the sample by Levy et al (1992).

1995; Yee et al 1998) or other physical properties (Iacono et al 1981, 1982; Van Gelder et al 1990) of the target during pursuit.

Such target manipulations have ubiquitously been shown to lead to improvements in SPEM accuracy on a variety of measures, such as gain, RMSE, spectral purity, anticipatory saccades and catch-up saccade amplitude (but not square-wave jerk frequency) in samples of schizophrenia patients, their first-degree relatives and healthy individuals (Clementz et al 1990; Holzman et al 1976; Rosenberg et al 1997c; Schlenker et al 1994; Shagass et al 1976; Sweeney et al 1994a, 1994b; Van Gelder et al 1990; Yee et al 1998). It is important to note that some – but not all – studies have required participants to count the frequency of changes in target characteristics or respond to them with button presses. Improvements in SPEM accuracy are, therefore, achieved despite the introduction of a secondary task.

Importantly, statistical differences between schizophrenia patients and healthy controls become smaller but generally persist during target manipulation (although Rosenberg et al, 1997c, found that differences between first-degree relatives and controls were abolished) and return to original magnitude after the removal of the attention-facilitation condition, thus excluding the possibility of practice effects (Holzman et al 1976; Rosenberg et al 1997c; Yee et al 1998). Additionally, participants appear to be unaware of their subtle improvements in SPEM accuracy during target manipulation, suggesting automatic rather than voluntary processes (Van Gelder et al 1990).

While scientists, therefore, agree on the effectiveness of these manipulations in improving pursuit accuracy, it is less clear how these improvements come about. The most reasonable hypothesis appears to be that changes in the target characteristic lead to improved attentional processing of the target, thereby 'locking' the eye more closely on the target and improving smooth pursuit accuracy. A link between smooth pursuit and attention has been suggested: Schwartz et al (2001) argued that people with schizophrenia have particular problems with attentional tasks involving the integration of temporal and spatial information, such as smooth pursuit eye movements. This finding, although its precise mechanisms are not well understood, suggests that the SPEM impairments seen in schizophrenia might be at least partly due to attentional deficits. Kathmann et al (1999) argued that SPEM might be executed in an automatic, rather than controlled, mode of attention. This assumption was based on the failure to obtain a dose-dependent reduction in SPEM accuracy with the introduction of tasks with low and high attentional requirements (Kathmann et al 1999).

A hint regarding the neural substrate of a putative attentional effect comes from animal studies. These studies have shown that posterior parietal cortex is particularly involved in processing the nature of the visual target during pursuit (Lynch et al 1977). It is a possibility, therefore, that relatively intact posterior parietal processing during pursuit of an attention-demanding target in people with schizophrenia partially compensates for SPEM deficits due to lesions in other (e.g. frontal) areas.

Other studies have linked smooth pursuit impairments in schizophrenia to deficits in motion processing. Stuve et al (1997) reported a relationship between motion processing and SPEM, which could not be accounted for by deficits in sustained attention. Their motion perception test required participants to detect the direction of movement of a sample of dots within a large cluster of stationary dots. Chen et al (1999a, 1999c) demonstrated further that deficits in motion perception in schizophrenia were not due to deficient sensitivities for orientation discrimination or contrast detection and were selectively correlated with measures of open- and closed-loop pursuit gain but not saccadic frequency or qualitative ratings of pursuit.

As damage to cortical motion-processing areas (MT/MST; V5) may result in reduced pursuit accuracy (Newsome et al 1985), it has been speculated that SPEM impairments in schizophrenia might be related to disturbed motion processing and abnormalities in relevant cortical areas (Chen et al 1999a; Stuve et al 1997). While this hypothesis is promising, a recent functional neuroimaging study failed to find an association between abnormalities in V5 activation and SPEM impairments in relatives of schizophrenia patients (O'Driscoll et al 1999).

Thaker and colleagues demonstrated that SPEM impairments in schizophrenia patients (Thaker et al 1999) as well as their first-degree relatives (Thaker et al 1998) might be due to deficits in the predictive mechanism of pursuit. As these researchers argued, the brain has two sources of information on target motion available during smooth pursuit: first, retinal slip (i.e. the difference in target and eye velocity), and second, an internal representation of past target motion. The former may be expected to lead to a 'reflexive' response; the latter results in a predictive response. In Thaker et al's (1998, 1999) studies the pursuit target was blanked out temporarily (for about 500ms). During this interval, slow pursuit eye movements are generated by the stored representation of target movement, in other words based on predictive pursuit to extra-retinal motion signals. Patients' gain, as well as their relatives', was particularly impaired under this

condition, even at slow target velocities where gain to a regular (physical) pursuit target was normal.

The generation of a predictive (pursuit) response relying on stored information from past target motion resembles some conceptualisations of working memory (Abel 1999; Thaker et al 1999). Relatedly, an inability to keep information on-line has been argued to be one of the core cognitive deficits in schizophrenia, related to prefrontal dysfunction (Goldman-Rakic 1999). Thus, it may be speculated that at least some of the SPEM impairments seen in schizophrenia might be due to working memory deficits (see also Section 2.3.5.2.4 on neuropsychological tests of working memory). Further evidence for this hypothesis comes from studies of healthy individuals, which have demonstrated that blocking working memory capacity (e.g. through arithmetic tasks, such as subtracting series of 7s or 13s from 200), but not simple distraction, impairs smooth pursuit (Acker & Toone 1978; Brezinova & Kendell 1977; Pass et al 1978). However, these early studies used non-specific SPEM analyses and, therefore, require replication. One working memory task that has not been used in schizophrenia SPEM studies is the n-back task. It would be valuable to use this well-established measure of working memory during predictive and non-predictive components of pursuit.

To conclude, the cognitive basis of SPEM impairments in schizophrenia is not entirely clear. While some evidence points to an involvement of attentional processes, other studies favour motion processing or working memory. The possible neural correlates of these proposed deficits implicate frontal and parietal sites. Most likely smooth pursuit tracking is a multivariate process, requiring all of these processes to different degrees.

2.3.5.2.4 Neuropsychological Studies

In a second main approach to studying the cognitive and neural components of smooth pursuit impairments in schizophrenia, scientists have examined the pattern of correlations between SPEM measures and clinical neuropsychological tests. Neuropsychological tests have the advantage of being standardised using normative samples, thus allowing comparisons with the general population; tapping well-established psychological and cognitive processes, thus providing a *lingua franca* to interpret oculomotor deficits in psychological terms; and being sensitive to fairly localised brain damage, thus allowing attempts to pinpoint the cortical/subcortical correlates of oculomotor dysfunction (Lezak 1983).

The pattern of correlations between SPEM and neuropsychological tests is not entirely consistent, partly due to differences across studies in SPEM analysis methods and sample characteristics such as disease chronicity and drug treatment. The bulk of the research has focussed on two aspects of cognition, namely 'frontal lobe tests' and attentional tests.

A first conclusion from the evidence to date may be that smooth pursuit performance is modestly related to neuropsychological tests sensitive to frontal lobe function. The tests that have been studied most often are the Wisconsin Card Sorting Test (WCST), measuring set shifting, working memory and executive function; the Trail Making Test A (TMT-A), measuring psychomotor coordination and motor speed and the Trail Making Test B (TMT-B), measuring the ability to shift strategy, visuospatial working memory and visual sequencing; and the finger tapping test, measuring motor speed.

Correlations with WCST (Grawe & Levander 1995; Litman et al 1991; Schlenker et al 1994), TMT (Bartfai et al 1985; Grawe & Levander 1995) and finger tapping (Bartfai et al 1985; Grawe & Levander 1995) have been observed on more than one occasion. Radant et al (1997) observed these correlations only for predictive but not regular pursuit. Other studies, however, failed to find a correlation between WCST and SPEM (Friedman et al 1995b; Gambini & Scarone 1992; Nkam et al 2001; Tien et al 1996). Interestingly, three of the studies showing no relationship as well as the study by Radant et al (1997) used specific pursuit measures such as gain and frequency of saccades, whereas two of three studies showing a relationship (Grawe & Levander 1995; Katsanis & Iacono 1991) used global pursuit measures, suggesting effects of poor measurement in some of the studies showing a relationship between WCST and SPEM disturbance.

In one of the most comprehensive examinations to date, Katsanis and Iacono (1991) assessed correlations between RMSE and WCST, verbal fluency, auditory verbal learning, the Benton memory test, TMT, finger tapping and the Wechsler Adult Intelligence Scale (WAIS; Wechsler 1981). The pattern and magnitudes of the observed correlations indicated that tests sensitive to frontal lobe function were better predictors of SPEM performance than measures of temporal lobe (e.g. auditory verbal learning) and global function.

Additionally, SPEM measures were found to be correlated with Necker cube reversals (Bartfai et al 1985), word fluency (Friedman et al 1995b) and delayed response task performance (Snitz et al 1999), further supporting the notion of frontal involvement.

The second main focus of neuropsychological research has concerned tests of attention, in particular the Continuous Performance Test (CPT). The interest in tests of attention stems from the early findings of an involvement of attentional components in smooth pursuit (Section 2.3.5.2.3). The CPT involves the serial presentation of visual stimuli (e.g. digits) for very brief durations (e.g. 50ms). The participant's task is to respond (e.g. through a button press) to the rare presentation of a target stimulus (e.g. a certain digit, or sequence of digits). Given the visual attentional demands of this and the pursuit tasks, correlations may be expected. The evidence, however, is fairly inconclusive.

Roitman et al (1997) reported a modest correlation between CPT and RMSE in male chronic schizophrenia patients. Van den Bosch (1984) found inconsistent correlations between RMSE and CPT in patients and controls. Three studies have failed to find a significant relationship in patients and controls (Siever et al 1982; Stuve et al 1997) as well as in first-degree relatives of schizophrenia patients (Keefe et al 1997).

To conclude, the evidence linking performance on the smooth pursuit task and neuropsychological tests is not entirely consistent, but provides modest support for a frontal lobe involvement in SPEM. This literature is characterised by failures to replicate, probably partly due to differences in SPEM analysis methods as well as small samples (Bartfai et al 1985; Litman et al 1991; Stuve et al 1997). Replication studies are clearly needed, utilising larger samples and comprehensive neuropsychological test batteries. One mistake made in some studies (e.g. Bartfai et al 1985) was to use only tests sensitive to frontal lobe function, thereby failing to provide evidence of the discriminant validity of the relationship between these tests and SPEM performance, akin to 'searching under the lamppost'.

2.3.5.2.5 Neural Correlates – Conclusion

The smooth pursuit performance patterns of schizophrenia patients appear to indicate two deficits: first, reduced gain and increased frequency of compensatory catch-up saccades; and second, increased frequency of intrusive anticipatory saccades (MacAvoy & Bruce 1995). In an attempt to integrate the review of the neural and cognitive correlates of SPEM in schizophrenia and healthy individuals, several lines of evidence appear to suggest that the frontal lobe may be the source of both types of impairments (Calkins & Iacono 2000; Levin 1984; MacAvoy & Bruce 1995).

First, MacAvoy and Bruce (1995), in a comparison of animal lesion and schizophrenia patient studies, came to the conclusion that pontine or cerebellar lesions are unlikely to account for the specific impairments seen in schizophrenia. Impairments seen in laboratory animals after lesions to these areas tend to be qualitatively different and more severe. MacAvoy and Bruce (1995) argued that FEF lesions in monkeys best mimic the pattern of SPEM impairments in schizophrenia, including reduced gain and increased frequency of compensatory catch-up saccades as well as somewhat increased frequency of intrusive saccades.

Second, a frontal lobe involvement in SPEM impairments in schizophrenia is modestly supported by evidence from functional neuroimaging and neuropsychological studies.

Third, a number of studies have indicated that the vestibulo-ocular reflex (VOR; fixating eyes on a stationary target while rotating the head) and the nystagmus response are relatively unimpaired in schizophrenia, suggesting intact midbrain and brainstem eye movement areas (Latham et al 1981; Levin 1983; Levy et al 1978, 1983a; Lipton et al 1980b).

Third, PPC recruitment during smooth pursuit in schizophrenia patients may be argued to be relatively intact, given the normal improvements due to attentional facilitation. More evidence suggesting that parietal areas recruited during pursuit are intact came from a study of the optokinetic reflex (OKR; Hutton et al 2000). Smooth pursuit of a target moving across a (randomly) structured background invokes the OKR, which, if incompletely inhibited, results in reduced smooth pursuit accuracy. Hutton et al (2000) observed similar reductions in pursuit accuracy in schizophrenia patients and healthy individuals during pursuit of a target over a structured background. This finding suggests similarly incomplete inhibition of OKR in both groups, pointing to relatively intact inferior parietal cortex in schizophrenia.

Fourth, deficits in motion and velocity sensitive areas (MT/MST, V5) in schizophrenia remain debated. Although there is evidence for an association between motion processing and SPEM deficits (Chen et al 1999a, 1999c; Stuve et al 1997), studies of step-ramp tasks have shown that damage to MT/MST should lead to inaccurate saccades to moving targets (Newsome et al 1985). A number of studies have demonstrated *accurate* saccades to moving targets in schizophrenia (Clementz 1996a; Sweeney et al 1999; Thaker et al 1996b). More damagingly to this hypothesis, Newsome et al (1985) also observed normal steady-state pursuit after lesions to MT/MST. This

pattern of findings strongly argues that MT/MST/V5 damage *alone* cannot produce the SPEM deficits seen in schizophrenia. Additionally, O'Driscoll et al (1999) did not find evidence of V5 underactivation during pursuit in poorly performing relatives of schizophrenia patients.

Fifth, a particularly important role of the FEF (relative to other cortical areas) in predictive pursuit has been described (Leigh & Zee 1999; MacAvoy & Bruce 1995). Significant impairments in predictive pursuit in schizophrenia (Thaker et al 1998, 1999) are in agreement with FEF dysfunction.

Finally, Levin (1984) suggested that SPEM deficits in schizophrenia might be largely due to saccadic disinhibition. Levin argued that the failure to suppress saccades during pursuit likely originates in dysfunctional frontal areas.

An important distinction, however, concerns that between the two different parts of the FEF related to saccades and smooth pursuit, respectively (Berman et al 1999). Given this distinction it is important to note that some frontal lobe hypotheses of SPEM dysfunction in schizophrenia point to the saccadic FEF, such as the increase in intrusive saccades during pursuit (Levin 1984), whereas others emphasise the smooth pursuit FEF (Sweeney et al 1998a).

2.3.5.3 Clinical Correlates

A number of possible clinical correlates of SPEM dysfunction in schizophrenia have to be considered. First, relationships between SPEM and severity of clinical symptom dimensions have been addressed in a large number of investigations. Relatedly, differences between acutely ill and remitted (asymptomatic) patients have been addressed. Second, variables such as duration of illness, number of hospitalisations and time spent in psychiatric hospitals have been investigated in relation to smooth pursuit performance. Finally, a small number of studies have examined the relationship between SPEM and neurological soft signs.

Two key findings concerning the symptom correlates of SPEM emerge from a review of relevant studies. First, a relationship between SPEM and negative symptoms has been reported on several occasions. This relationship was most clearly articulated by Ross (2000). Second, however, a recent conjecture (Lee & Williams 2000) and evidence (Lee et al 2001) suggest that SPEM dysfunction might be associated specifically with the symptom dimension of thought disorder. As outlined in Section 1.2, schizophrenic

symptoms tend to fall into positive and negative dimensions, with thought disorder being one facet of the positive dimension. The two hypotheses by Ross (2000) and Lee and Williams (2000) are thus conflicting, which may be explained in methodological terms, as outlined below.

A number of researchers have observed a relationship between SPEM and negative symptoms, using global as well as specific smooth pursuit measures and symptom scales such as the Schedule for the Assessment of Negative Symptoms (SANS; Andreasen 1984) or the Brief Psychiatric Rating Scale (BPRS) (Blackwood et al 1991; Ciuffreda et al 1994; Katsanis & Iacono 1991; Matsue et al 1993; Roitman et al 1997; Sweeney et al 1992a, 1994a). These reports contrast with other studies reporting an absence of this relationship using similar measures and scales (Cegalis & Sweeney 1979; Flechtner et al 1997, 2002; Gooding et al 1994; Kelly et al 1990; King et al 1999; Litman et al 1997; Rosenberg et al 1996; Schlenker et al 1994).

A relationship between negative symptoms and SPEM disturbance may be integrated with the putative frontal lobe involvement in both (Kelly et al 1990; Volkow et al 1987). Ross et al (1996b) argued that the expected relationship has not been observed consistently as less than optimal measures of negative symptoms have been used. One scale that has been used particularly often is the SANS. This scale assesses primary as well as secondary negative symptoms, thereby introducing confounding variance due to effects of medication or hospitalisation. Ross et al (1996b) suggested instead focussing on primary and enduring negative symptoms. These symptoms are referred to as the deficit syndrome and have been argued to occur in a significant proportion of schizophrenia patients (Carpenter et al 1999).

In agreement with this hypothesis, Ross et al (1996b) observed a relationship between specific SPEM measures and a diagnosis of the deficit syndrome. This relationship was replicated and extended by Ross et al (1997) in a larger sample of patients, including some of the 1996 study. A relationship between SPEM dysfunction and the deficit syndrome had been observed in an earlier study by the same group (Thaker et al 1989a) and was recently independently replicated (Malaspina et al 2002). Nkam et al (2001), however, observed only a weak, non-significant relationship.

Ross (2000) argued that the co-occurrence of SPEM dysfunction and the deficit syndrome may represent a homogenous subtype of schizophrenia, possibly indicating a shared genetic basis. This hypothesis was based on the observed relationship between

the two deficits, as well as similarities in their familial patterns of occurrence, their status as trait markers and their neural and cognitive correlates. Wolff and O'Driscoll (1999) arrived at a similar conclusion in a review of motor abnormalities in the schizophrenia spectrum. These authors suggested the existence of a "triad" (p. 309) of negative symptoms, cognitive deficits and motor abnormalities including, but not restricted to, smooth pursuit eye movements. Further evidence for the pervasiveness of this constellation of signs comes from studies demonstrating a relationship between SPEM and subclinical negative features of schizotypy in healthy individuals (see Section 2.3.5.5.6).

Somewhat conflicting with the deficit syndrome hypothesis, however, a small number of studies have observed a relationship between SPEM and the positive symptom category of thought disorder (Keefe et al 1989; Lee et al 2001; Solomon et al 1987; Tien et al 1996).

Lee et al (2001), in the most comprehensive investigation so far, factor analysed symptom scores from 78 schizophrenia patients, obtaining factors of Unreality, Disorganisation and Psychomotor Poverty. A robust relationship with SPEM was observed only for the Disorganisation dimension. Lee et al (2001) argued that disorganisation symptoms (tapping thought disorder) might be central to the pathophysiology of schizophrenia.

Difficulties in reconciling the hypotheses by Ross (2000) and Lee and Williams (2000) may be at least partly due to methodological reasons. The majority of the studies reviewed here have used small sample sizes (N<30); large samples are needed to reliably address individual differences in neurocognitive measures (Detterman 1989). Further, studies are often difficult to compare due to differences in sample composition, utilising first-episode, chronic or mixed samples. Additionally, antipsychotic treatment might be at least partly blamed for inconsistencies as well as systematic failures to observe relationships. It is well known that typical antipsychotic treatment alleviates positive symptoms to a greater extent than negative symptoms (Leonard 1997). It is, therefore, a possibility that relationships between temporally stable measures of SPEM and temporally fluctuating measures of positive symptoms cannot be detected in samples of largely typically medicated patients (Anastasi & Urbina 1997). Finally, no previous study has combined designated measures of the deficit syndrome and of thought disorder in one investigation, allowing a direct comparison of the magnitude of each measure's correlations with SPEM.

A number of other clinical factors merit consideration. First, evidence suggests that SPEM abnormalities are observed in remitted and asymptomatic as well as acutely ill patients (Arolt et al 1998; Bartfai et al 1985; Iacono et al 1981; Muir et al 1992; Salzman et al 1978), suggesting they are not an epiphenomenon of acute symptom levels. Second, a small number of studies have compared SPEM performance across different subtypes of schizophrenia, such as paranoid/non-paranoid, hebephrenic and disorganised, and have obtained no significant differences (Campion et al 1992; Holzman et al 1974). Third, there appear to be no strong relationships between SPEM and number and duration of hospitalisations, duration of illness, or age of onset (Flechtner et al 1997, 2002; Katsanis & Iacono 1991; Kelly et al 1990; King et al 1999; Schlenker et al 1994; Sweeney et al 1994b), although some studies have found worse SPEM in patients with later age of onset (Bartfai et al 1983; Siever et al 1986; Sweeney et al 1994a), longer durations of illness (Litman et al 1997) and more frequent or longer hospitalisations (Bartfai et al 1985; Keefe et al 1989). However, most of these studies were not designed and powered to detect effects of disease chronicity; large-scale longitudinal studies are required to systematically address this issue.

Finally, only relatively little evidence has been obtained regarding relationships between SPEM and neurological soft signs (NSS). NSS constitute motor and neurocognitive abnormalities detected in a neurological examination and have been shown to be abundant in schizophrenia patients and their relatives (Wolff & O'Driscoll 1999). As Ross et al (1998b) have pointed out, it is surprising that the two research areas of NSS and SPEM have been carried out virtually in parallel over the past decades, given the evidence of general motor deficits in schizophrenia (Wolff & O'Driscoll 1999).

Schlenker et al (1994) reported associations between SPEM and 'sensory integration', 'motor coordination', 'sequencing of complex motor acts' and other subcomponents of NSS. Ross et al (1998b) observed a relationship with 'sensory integration' but not the other components from the Schlenker et al (1994) study, thus replicating an observation in healthy individuals (Siever et al 1989). Clearly, more research is needed to clarify the NSS correlates of SPEM dysfunction in schizophrenia patients.

To summarise the clinical correlates of smooth pursuit dysfunction in schizophrenia, the most common symptom correlates appear to be those of negative symptoms (or the deficit syndrome) and thought disorder (or the disorganisation syndrome). At present, the literature is inconsistent as to which of these symptom dimensions represents the more reliable correlate. SPEM dysfunction appears not to be a mere epiphenomenon of

illness state, as studies of acute and remitted patients have demonstrated. It remains to be investigated whether SPEM impairments become more pronounced with more frequent hospitalisations, i.e. with a chronic course of the disease. Future studies might also aim to confirm the link between SPEM and soft neurological motor abnormalities as well as the negative or disorganised symptom dimensions.

2.3.5.4 Pharmacology

2.3.5.4.1 Treatment Effects

Treatment effects in schizophrenia research are ubiquitous and merit careful evaluation in research (Spohn & Strauss 1989). Given the widespread use of pharmacological agents in the treatment of schizophrenia, a large number of studies have investigated the effects of these drugs on clinical symptoms, behaviour, cognition and biological markers, including the smooth pursuit task.

The very early schizophrenia eye movement studies are sometimes quoted as evidence that SPEM dysfunction in this patient group "is not merely a motor side effect of neuroleptic or other antipsychotic medications" (Levin 1983; p. 37). However, patients in the early studies were treated with other drugs such as tranquillizers and barbiturates, some of which are known to disrupt SPEM (Holzman et al 1975).

Holzman and colleagues as well as others established that short-, medium- and long-term typical neuroleptic treatment is not associated with SPEM abnormalities in schizophrenia patients. This conclusion stems from a multitude of designs, including correlations between drug dose levels and SPEM (Flechtner et al 2002; Schlenker et al 1994; Spohn et al 1985; Thaker et al 1989a), comparisons of treated and untreated patients (Friedman et al 1992a; Holzman et al 1974; Karson 1979; Litman et al 1989; Shagass et al 1974; Siever et al 1986; Thaker et al 1999), studies of never-medicated patients (Campion et al 1992; Hutton et al 1998a; Sweeney et al 1999) and longitudinal studies of treatment and drug withdrawal effects (Campion et al 1992; Flechtner et al 2002; Gooding et al 1994; Levy et al 1983b; Rosenberg et al 1996; Schlenker & Cohen 1995; Shagass et al 1974; Siever et al 1986; Spohn et al 1988; Sweeney et al 1998a).

However, there are also findings indicating the existence of drug effects. Two studies using longitudinal designs have found that clozapine (but not typical antipsychotics or placebo) exacerbates quantitative SPEM measures over treatment intervals of several weeks (Friedman et al 1992b; Litman et al 1994). Rea et al (1989) found that after one

month of antipsychotic treatment the number of small saccades during pursuit increased, while the number of large AS decreased; the magnitude of this decrease was associated with neuroleptic dosage. Hutton et al (2001a) observed that long- but not short-term treatment led to reduced pursuit gain. Sweeney et al (1994b) found that antipsychotic treatment led to *improvements* in some SPEM measures. Bartfai et al (1983, 1985) showed that previously treated patients had significantly impaired SPEM compared to patients without previous treatment. It is, however, possible that in the Bartfai et al studies previous treatment was confounded with longer duration of illness or number of psychotic episodes.

It has also been demonstrated that treatment with clinical doses of lithium improves symptoms of bipolar psychosis patients but impairs their smooth pursuit, leading to qualitative abnormalities, reduced gain and increased saccadic frequency (Holzman et al 1991; Iacono et al 1982; Levy et al 1985), although one study did not find this effect (Gooding et al 1993).

Another drug effect that has received attention concerns tardive dyskinesia (TD). TD is a syndrome characterised by abnormal, involuntary movements, thought to be caused by long-term treatment with typical antipsychotic agents (Leonard 1997). As its pathophysiology is likely to involve dopaminergic neurons in the basal ganglia, TD could affect the neural control of any motor system.

Worse SPEM in patients with TD was reported by a number of investigators, in line with the expected disruption of motor systems (Oepen et al 1990; Spohn et al 1988; Thaker et al 1989a). However, a later replication failed (Ross et al 1998a). These authors argued that earlier studies might have found effects of TD because they employed the EOG recording technique, allowing for artefacts of face muscle activity to yield an 'abnormal' pattern of pursuit.

Another important issue concerning the pharmacology of eye movements in schizophrenia is the role of nicotine. People with schizophrenia have a prevalence rate of smoking of between 74% and 92% compared to 30% to 35% of the general population and take in more nicotine from cigarettes than non-schizophrenic individuals (Olincy et al 1997). Interestingly, the α7 nicotinic receptor subunit has been implicated as a genetic marker of schizophrenia (Freedman et al 1994).

Experimental findings regarding the effects of smoking on SPEM are inconsistent. Olincy et al (1998) found that cigarette smoking acutely improved SPEM abnormalities

in schizophrenia patients, but had no effect on healthy controls. Domino et al (1997) found that smoking slightly improved SPEM in healthy individuals. Two studies (Sibony et al 1988; Thaker et al 1991) observed increases in square-wave jerk rate during SPEM after smoking. Additionally, it has been shown that nicotine can induce nystagmus (Pereira et al 2001); how this is related to SPEM remains to be investigated.

Other agents acting on the cholinergic system have not been explored systematically. Schizophrenia patients with extrapyramidal side effects are often prescribed anticholinergic drugs, such as procyclidine (Leonard 1997); the effects of procyclidine on smooth pursuit in people with schizophrenia have not been addressed.

To conclude, the bulk of the literature suggests that the robust SPEM impairments seen in schizophrenia are unlikely to be *entirely* due to medium- or long-term treatment with typical antipsychotic drugs. While some deleterious effects on SPEM have been demonstrated, allowing for the possibility of a further exacerbation of SPEM with long-term treatment, the evidence from studies of never-medicated patients is conclusive. The question of whether TD contributes to SPEM abnormalities needs to be addressed further using infrared light oculographic recording techniques. Finally, the effects of atypical antipsychotics, especially the newer ones, have not been studied intensively.

2.3.5.4.2 Effects of Pharmacological Manipulation in Healthy Individuals

A number of pharmacological compounds interfere with the control of smooth pursuit eye movements when administered to healthy individuals. The most relevant to the present discussion are drugs frequently administered to schizophrenia patients.

Given the widespread treatment of schizophrenia patients with typical antipsychotics, it was examined early whether these drugs could affect SPEM in healthy volunteers. Holzman et al (1975) demonstrated no effect of chlorpromazine (but of barbiturates) on SPEM; Lynch et al (1997) similarly did not observe significant effects of haloperidol. In contrast, King (1994) reported that haloperidol dose-dependently impaired SPEM; Malaspina et al (1994b) similarly showed disrupted SPEM after haloperidol (but not amphetamine) administration.

These inconsistencies need to be resolved in future studies. However, the relevance of these studies to the validity of SPEM as a schizophrenia endophenotype has to be questioned. First, these studies used individuals without schizophrenia; drug effects in these individuals may be very different from those in patients with schizophrenia.

Second, effects of acute administration might be significantly different from those of medium- or long-term treatment with antipsychotics.

More consistent evidence concerns the effects of benzodiazepines, suggesting that SPEM is reliably interrupted by administration of this sedative (Green et al 2000; Iwata et al 1999; Lynch et al 1997; Masson et al 2000; Norris 1971; Roy-Byrne et al 1993). This finding suggests the necessity to examine the effects of benzodiazepines in schizophrenia patients and the role of this compound in between-group differences. Lithium does not appear to impair pursuit in healthy individuals (Flechtner et al 1992).

2.3.5.5 Validity as Endophenotype

2.3.5.5.1 HERITABILITY

Studies of healthy, reared-together twins have been carried out in order to assess the heritability of smooth pursuit performance. Given the small number of these studies, and the importance of demonstrating heritability in the validation of an endophenotype, these studies will be discussed individually.

Identical (monozygotic) twins are genetically identical; fraternal (dizygotic) twins share on average 50% of their genes. Therefore, comparing within-twin pair correlations for a quantitative biobehavioural measure between monozygotic and dizygotic twins will indicate the amount of variance in the measure accounted for by genetic and (shared or non-shared) environmental factors (Plomin et al 2000).

In the first investigation of SPEM in healthy twins, Iacono and Lykken (1979a, 1979b) observed correlations for RMSE in 32 pairs of monozygotic (MZ) twins ranging between 0.49 and 0.65. Iacono (1982) later extended this sample, adding 24 pairs of dizygotic (DZ) twins. Within-twin pair correlations were higher for MZ than for DZ twins, indicating substantial heritability.

Bell et al (1994) investigated smooth pursuit gain in eight pairs of MZ twins and found within-pair intraclass correlations (ICC) ranging from 0.91 and 0.98. However, the study used a small sample size and no DZ twins. In an extension of this sample including dizygotic twins Blekher et al (1997) observed low ICC in dizygotic twins, suggesting that SPEM is under influence of multiple genes and/or common environmental influences. Litman et al (1997) reported ICC in MZ twins for SPEM gain

and frequency of saccades of 0.60 and 0.68, respectively, but did not include a group of healthy DZ twins.

In the most comprehensive investigation to date, Katsanis et al (2000) examined global as well as specific SPEM measures in 64 MZ and 48 DZ adolescent (11 and 17 year old) twin pairs. With two exceptions, correlations between SPEM measures were substantially higher for MZ twins than DZ twins. In an examination of the specific influences of genetic and environmental causes of variance it was found that SPEM variance was accounted for by roughly equal shares of additive genetic and non-shared environmental factors.

It may be concluded from these studies that SPEM performance is largely heritable, although environmental factors also influence individual differences in performance. As most studies have used relatively small sample sizes, and few have compared monozygotic and dizygotic twins, future studies employing large samples of monozygotic and dizygotic twin pairs are needed.

2.3.5.5.2 Temporal Stability

A number of studies have investigated the key criterion of temporal stability of SPEM performance. These studies have indicated that performance is relatively stable in schizophrenia patients and healthy controls over time intervals ranging from one week to two years, with most correlation coefficients ranging between about 0.5 and 0.9 (Campion et al 1992; Gooding et al 1994; Holzman et al 1973; Iacono & Lykken 1981; Kufferle et al 1990; Rea et al 1989; Roy-Byrne et al 1995; Schlenker & Cohen 1995; Shagass et al 1974; van den Bosch & Rozendaal 1988; Yee et al 1998).

Importantly, this moderate-to-good temporal stability has been demonstrated using all available SPEM measures, including global qualitative and quantitative measures, velocity arrests, gain, as well as frequency of saccades. The magnitude of reliability coefficients appears to be unaffected by the length of the time interval between test and retest. Additionally, performance is relatively stable irrespective of sample characteristics, as studies of first-episode (Gooding et al 1994; Yee et al 1998) as well as chronic (Campion et al 1992; Schlenker & Cohen 1995) patients have demonstrated. Importantly, a number of studies have demonstrated reliable performance despite changes in medication status and levels of symptom severity between first and second

assessment (Campion et al 1992; Kufferle et al 1990; Rea et al 1989; Schlenker & Cohen 1995).

Related evidence of the trait nature of SPEM deficits concerns the lack of significant improvements in SPEM performance levels between first and second assessment, irrespective of changes in treatment status and reductions in symptom levels (Campion et al 1992; Gooding et al 1994; Kufferle et al 1990; Levy et al 1983b; Rea et al 1989; Schlenker & Cohen 1995; Shagass et al 1974).

Taken together, these findings indicate that SPEM performance is relatively stable over time. Despite the likely influence of state measures (as indexed by the less than perfect correlations), SPEM deficits in schizophrenia may not be considered a mere epiphenomenon of clinical state.

2.3.5.5.3 Specificity to Schizophrenia

Smooth pursuit deficits are not specific to the schizophrenia spectrum. Impaired smooth pursuit has been observed in a number of neurological and psychiatric conditions, including cocaine addiction (Rosse et al 1992b), in particular with a paternal history of alcoholism (Bauer 1997), Pick's disease (Hutton et al 1987), dyslexia in children (Eden et al 1994), progressive supranuclear palsy (Vidailhet et al 1994), Alzheimer's disease (Zaccara et al 1992), Parkinson's disease (Lekwuwa et al 1999; Rottach et al 1996), Huntington's disease (Collewijn et al 1988), anorexia nervosa (Pallanti et al 1998), in HIV-1 seropositive individuals (even before onset of overt symptoms of the AIDS Dementia Complex) (Sweeney et al 1991) and in university students with a childhood history of emotional and physical abuse (Irwin et al 1999).

The existence of SPEM impairments in obsessive-compulsive disorder (OCD) is unclear, with some studies obtaining deficits (Gambini et al 1993a; Pallanti et al 1996; Sweeney et al 1992b) but others not (Farber et al 1997; Nickoloff et al 1991). It appears that individuals with OCD have impairments particularly at faster target velocities (Clementz et al 1996a). Adults or children with ADHD generally appear not to have impaired SPEM (Castellanos et al 2000; Jacobsen et al 1996; Ross et al 2000).

Deficits in these widely different neuropsychiatric conditions have most commonly been attributed to damage to cortical and subcortical areas involved in smooth pursuit, in particular FEF and basal ganglia.

The most relevant patient group in which to examine the proposed specificity of SPEM dysfunction to schizophrenia, however, is that of affective disorder. This disorder, particularly in combination with psychotic features, has been argued to be related to schizophrenia at genetic, biological and clinical levels (Berrettini 2000a, 2000b; Maier et al 1999). Given the proposed nature of the SPEM task as a schizophrenia endophenotype, therefore, a number of studies have aimed to examine the putative specificity of SPEM deficits. Evidence from these studies is mixed. Although some studies have found SPEM deficits to be relatively specific to schizophrenia (Diefendorf & Dodge 1908; Friedman et al 1995a; Iacono et al 1992; Muir et al 1992; Tien et al 1996), others have observed impairments similar in kind and magnitude in (unipolar and bipolar) affective disorder and schizophrenia (Amador et al 1991, 1995; Couch & Fox 1934; Friedman et al 1992a; Iacono & Koenig 1983; Kufferle et al 1990; Lipton et al 1980b; Shagass et al 1974; Sweeney et al 1999; van den Bosch 1984).

More positive evidence of specificity, however, has been obtained in some studies showing similar performance levels of schizophrenia and affective disorder patients on certain measures (e.g. gain) but worse performance in schizophrenia patients on other measures (e.g. catch-up saccade rate; Abel et al 1991; Flechtner et al 1997; Sweeney et al 1994a).

A number of explanations have been offered for the observation of SPEM impairments in affective disorder, in particular bipolar patients. First, it has been shown that SPEM impairments in affective disorder might be state-related and affected by treatment. Malaspina et al (1994a) showed that SPEM dysfunction in major depression improved with ECT treatment. Other studies have shown that lithium salts, which are commonly used in the treatment of bipolar patients, impair SPEM in this patient group (Holzman et al 1991; Iacono et al 1982; Levy et al 1985). However, a more recent study failed to observe this effect (Gooding et al 1993). Additionally, there is evidence of SPEM impairments in affective disorder patients *never* medicated with lithium (Kufferle et al 1990) or unmedicated at time of assessment (Sweeney et al 1994a). It remains, therefore, debated whether SPEM impairments in affective disorder represent a state variable, as some have argued (Levy et al 1994).

A second explanation that has been proffered to support the assumed specificity of SPEM dysfunction to schizophrenia is the failure to observe SPEM impairments in first-degree relatives of affective disorder patients (Holzman et al 1984; Levy et al 1983c). This evidence indicates that SPEM deficits may be observed in affective disorder, but

are not an expression of the genetic liability. However, the two relevant investigations (Holzman et al 1984; Levy et al 1983c) suffer from poor methodologies, thus requiring replication. Additionally, more recent studies did observe some levels of SPEM impairments in relatives of unipolar or bipolar patients (Blackwood et al 1996; Rosenberg et al 1997c), thereby challenging this argument of specificity.

More research is needed to establish whether SPEM impairments are indeed specific to schizophrenia. This research could benefit particularly from the use of unmedicated patients with affective disorders and the inclusion of their unaffected first-degree relatives. If future studies will indeed demonstrate relative non-specificity for SPEM impairments across the nosological boundaries of schizophrenia and bipolar affective disorder, then this might still not, however, present a serious challenge to the SPEM endophenotype approach. Recent evidence suggests that some of the most promising genetic susceptibility loci are associated with schizophrenia as well as bipolar affective disease (Berrettini 2000b). Given the clinical overlap between the two conditions, it may turn out that SPEM dysfunction is an indicator of general vulnerability to the psychosis spectrum, rather than to schizophrenia *per se*.

2.3.5.5.4 Family and Twin Studies

Studies of first-degree relatives have been the focus of the SPEM research program in schizophrenia since the mid 1970s (Holzman et al 1974). These studies are based on the assumption that SPEM dysfunction may serve as an endophenotype, as outlined in Section 1.8.1. The demonstration of subtle SPEM deficits in first-degree relatives of schizophrenia patients is, therefore, an important piece of evidence concerning the validity of this approach.

Historically, the first studies by Holzman and colleagues (Holzman et al 1974, 1976) demonstrated global SPEM abnormalities in first-degree relatives, including parents, siblings and offspring. The percentage of relatives with SPEM dysfunction (about 30-50%) fell between that of patients (50-80%) and healthy controls as well as relatives of non-psychiatric patients (about 8-10%).

Later studies replicated these findings by employing quantitative global and specific measures. Relatives' levels of RMSE and ln(S/N) were found to fall between those of patients and healthy controls (Iacono et al 1992; Ross et al 1996c; Schlenker et al 1994).

The pattern of performance deficits in the first-degree relatives group described by specific measures is very similar to that observed in the patients, including reduced gain (Clementz et al 1990; Lencer et al 1999; Ross et al 1996c) and increased frequency of saccades (Clementz et al 1990; Lencer et al 1999; Rosenberg et al 1997c; Ross et al 1996c, 1998e), although some have failed to find reduced gain (Keefe et al 1997; Thaker et al 1998). Other, specific, deficits previously observed in the patient group, such as those in predictive pursuit (Thaker et al 1999; Trillenberg et al 1998) and pursuit initiation (Sweeney et al 1998a) were similarly replicated in the relatives (Clementz et al 1995; Thaker et al 1998). Chen et al (1999b) demonstrated similar associations between SPEM deficits and motion/velocity processing in both patients and first-degree relatives. These similarities further underscore the validity of the assumption that SPEM performance may be a schizophrenia spectrum marker, transcending the borders of people with and without a diagnosis of schizophrenia.

In addition to observations of impaired performance levels in first-degree relatives, a number of other findings merit consideration. First, it has been reported that SPEM deficits in first-degree relatives are not due to increased levels of psychiatric symptoms in these individuals (Iacono et al 1992). This finding is of importance, as it indicates that SPEM dysfunction in relatives is not merely a consequence or an epiphenomenon of psychiatric symptoms. It has, however, been shown that relatives with subclinical schizophrenia spectrum symptoms have particularly impaired performance (Clementz et al 1991; Thaker et al 1996a), similar perhaps to the relationship between schizotypy and SPEM observed in healthy individuals (Gooding et al 2000b; O'Driscoll et al 1998).

Second, a small number of studies have investigated the specificity of SPEM deficits to first-degree relatives of schizophrenia patients. Given the presumed and observed overlap between bipolar affective disorder and schizophrenia, it is of importance to determine whether SPEM dysfunction is a genetic marker specific to schizophrenia (Levy et al 1994) or non-specific within the wider psychosis spectrum. Evidence to date appears to indicate that SPEM dysfunction characterises relatives of schizophrenia but not bipolar disorder patients (Holzman et al 1984; Levy et al 1983c). Iacono et al (1992) observed no significant differences between relatives of bipolar patients and healthy individuals; however, their Figure 1 clearly indicates that performance levels of these relatives fell in between those of relatives of schizophrenia patients and healthy individuals. Blackwood et al (1996) described SPEM abnormalities in a large family of relatives of bipolar patients. Unfortunately, no control group was used in this study and

comparisons were based on performance levels of healthy individuals from a previous study (Muir et al 1992). Rosenberg et al (1997c) observed worse global pursuit in adult offspring of depressed patients. Therefore, the assumed specificity to relatives of people with schizophrenia remains debated.

Third, SPEM performance levels appear to be correlated within families, such that relatives of patients with poor performance tend to have poorer performance than relatives of patients with good performance (Iacono et al 1992; Rybakowski & Borkowska 2002). These patterns of within-family correlations complement studies of healthy twins, indicating a familial, and possibly genetic basis of SPEM dysfunction.

Fourth, first evidence of the neural correlates of SPEM dysfunction in first-degree relatives of schizophrenia patients points to the FEF. In the above-mentioned study, O'Driscoll et al (1999) demonstrated that relatives with and without global SPEM dysfunction differed only in FEF activation (but not in activation of posterior areas) during pursuit. FEF activation levels further correlated with pursuit gain scores.

Fifth, one specific measure of SPEM that has attracted attention as a particularly promising endophenotype is the increased AS frequency during pursuit (Whicker et al 1985). Ross et al (1996c) demonstrated increased AS (but not CUS) frequency in children of schizophrenia patients compared to normally developing children. AS frequency was subsequently shown to be a specific discriminator between adult offspring of schizophrenia patients and depressed patients (Rosenberg et al 1997c), were observed in childhood onset schizophrenia patients aged 10-18 (Jacobsen et al 1996), were found to be more frequent in childhood than adult-onset schizophrenia and associated with bilineal inheritance (Ross et al 1999b) and were found to characterise the more-likely gene carrier in families multiply affected with schizophrenia (Ross et al 1998e).

However, the validity of AS as a specific oculomotor endophenotype was challenged in studies showing that differences between schizophrenia spectrum individuals and healthy controls could be abolished by attention-facilitating target characteristics (Clementz et al 1990; Rosenberg et al 1997c). Relatedly, Rea et al (1989) found a decrease in large AS frequency after neuroleptic treatment. One interpretation of these findings is that AS frequency reflects superficial inattention and is not a 'hardwired' expression of a genetic deficit (Clementz et al 1990). A more positive interpretation, however, might be that AS frequency does indeed reflect attentional processes, a

suggestion that is compatible with propositions that attention may be a useful schizophrenia endophenotype (Cornblatt & Malhotra 2001).

Sixth, a distinction is sometimes made in the schizophrenia literature between familial and non-familial schizophrenia. Familial (or multiplex) schizophrenia is observed in individuals with families characterised by multiple occurrences of the illness; non-familial (or simplex, or sporadic) schizophrenia is described when the proband does not have relatives with the disorder. Only a small number of studies have addressed this distinction with regard to SPEM performance. Schwartz et al (1995b) found that patients with familial schizophrenia had reduced rightward SPEM gain compared to controls; non-familial patients performed intermediate. Lencer et al (2000) failed to obtain differences between simplex and multiplex schizophrenia families, suggesting that a degree of SPEM abnormalities and, arguably, genetic factors, might be observed in both.

Finally, probably the best test of the validity of the proposed SPEM dysfunction endophenotype is the examination of its concordance in twins discordant for schizophrenia. If variance in SPEM performance was entirely due to genetic influences, perfect concordance of SPEM dysfunction should be observed in twin pairs despite discordance in clinical status (i.e. one twin has schizophrenia, the other twin does not). Such a situation would indicate the influence of non-genetic factors on the clinical expression of schizophrenia but not SPEM dysfunction and would strengthen the validity of the SPEM endophenotype. However, as described in Section 2.3.5.5.1, SPEM variance is only partially accounted for by genetic factors, including substantial variance from environmental sources.

Holzman et al (1977) were the first to investigate SPEM in twins discordant for schizophrenia. Eleven sets of MZ twins and 15 sets of DZ twins were selected from Kringlen's Norwegian twin sample. Of the MZ twins, 7 pairs were discordant and 4 pairs were concordant or "partially concordant" (i.e. "manifested some behavioural peculiarity"; Holzman et al 1978a; p. 116). All 7 discordant pairs were concordant for global SPEM quality ('good', 'bad'). The correlation for velocity arrests between pairs was 0.77 for all MZ twins and 0.40 for all DZ pairs. These findings clearly indicate strong genetic influence on SPEM performance in discordant twins.

Holzman et al (1980) replicated the twin design using a different sample of slightly younger twins (10 MZ and 15 DZ pairs). Six of the MZ pairs were discordant and four

remaining co-twins had psychotic disorders (schizophrenia, schizoaffective condition, reactive psychosis, manic-depressive illness). DZ twin pairs were discordant. Data were scored both qualitatively and quantitatively (ln S/N). According to Holzman et al (1980), findings indicated higher concordance of abnormal SPEM in MZ than in DZ, supporting the genetic hypothesis. Correlations for ln(S/N) were 0.80 for MZ and 0.39 for DZ pairs (across diagnoses), indicating good heritability. Qualitative SPEM concordances were also higher for MZ than DZ twins.

However, a number of criticisms of this study must be made. First, the probands in the MZ sample had a number of psychiatric diagnoses. In effect, there were only three pairs of twins truly discordant for schizophrenia (all of which were concordant for qualitative SPEM scores). A second apparent anomaly in these data is the finding that only 6 of 20 MZ twins had 'bad' eye-tracking. These individuals all had psychosis and all except 5 of the remaining twins had a psychiatric diagnosis. Third, the three twin pairs with concordant 'bad' performance were the oldest pairs (ages: 35, 36, 36), suggesting an age effect (only one pair with 'good' performance was aged 35).

A recent attempt at replicating the Holzman twin findings failed. Litman et al (1997) obtained detailed quantitative measures of SPEM performance using thorough operational definitions and criteria for data scoring amongst 12 pairs of MZ twins discordant for schizophrenia and 12 pairs of healthy twins. Affected twins showed decreased gain and increased numbers and amplitudes of total and intrusive saccades during pursuit. Unaffected twins performed similarly to healthy controls. These findings imply that SPEM abnormalities seen in schizophrenia are associated with the phenotype, i.e. the clinical expression of schizophrenia, and not the genotype, casting serious doubt on the validity of this endophenotype.

In a response to this study, Holzman and colleagues (1997) pointed out a number of methodological weaknesses in the Litman et al study. First, the small sample size may have allowed for non-random error to confound the results and generally weaken any interpretation of the findings. Second, two of the affected twins had also suffered brain trauma, which may have affected SPEM. These participants possibly increased the differences between the schizophrenic and the other groups. If the two twin pairs with brain trauma had been removed from the analyses, Holzman et al (1997) argued, the performance of the schizophrenic twins would have been in the range of the normal. The inclusion of these two pairs would have, therefore, masked true differences between

groups. Third, two of the control twins displayed deviant SPEM and may have, therefore, blurred differences between this group and the unaffected twins.

Further, Holzman et al mentioned that the data by Litman et al had also been scored by Holzman and Levy to assign qualitative scores, as done in previous studies by these researchers. According to Holzman et al the concordance of the qualitative scores in a subsample of the discordant twins (8 pairs) was 100%. These data, not reported by Litman et al, are, of course, in accordance with earlier findings (Holzman et al 1977, 1980), pointing to a genetic basis of SPEM dysfunction in schizophrenia. Holzman et al also attacked Litman et al's claim that quantitative measures of gain and frequency of saccades provide a more superior index of eye-tracking dysfunction than the qualitative measures favoured by Holzman's group.

While this is an ongoing debate (Clementz et al 1997; Ross et al 1997), the claim that quantitative measurement of SPEM may have masked between-group differences appears questionable. Holzman et al's criticism of Litman et al's small sample size is, of course, correct, but likewise concerns their own earlier studies (Holzman et al 1977, 1980), which used very similar sample sizes (N=10-15). Additionally, the Holzman et al (1977, 1980) studies may themselves be criticised for their methodology, employing EOG recordings, less than optimal testing conditions (in various hospital settings or participants' homes) and global qualitative SPEM ('good', 'bad') analysis. Also, as mentioned, the sample in the 1980 study was very heterogeneous with regard to clinical status.

Clearly, further studies of discordant twins are needed. Given the advantages of specific measures (Abel 1986; Abel & Ziegler 1988), future studies should use precisely defined measures of gain and saccadic frequency. In order to allow comparisons with the Holzman et al (1977, 1980) studies, however, global measures might also be included. Future studies should also use large samples of accurately diagnosed twin pairs.

In conclusion, evidence from studies of first-degree relatives of people with schizophrenia lends support to the hypothesis that SPEM dysfunction may be a genetic marker of risk for schizophrenia. First-degree relatives consistently show subtle SPEM impairments when compared to healthy controls; their performance levels tend to fall between those of the patients and healthy controls. Within-family correlations, evidence from healthy twin studies (Section 2.3.5.5.1) and similarities in the specific SPEM deficits between patients and relatives further support the usefulness of the SPEM

endophenotype. Future studies should a) clarify the specificity of SPEM dysfunction to schizophrenia by studying families with bipolar disorder, b) further investigate the neural correlates of SPEM performance in the relatives, and c) replicate observations of SPEM concordance in MZ and DZ twins discordant for schizophrenia.

2.3.5.5.5 First-episode Psychosis

First-episode psychosis patients constitute an important sample in which to confirm the validity of a schizophrenia endophenotype. Studies of this patient group have the advantage of circumventing a number of methodological difficulties encountered in the study of chronic patients. These include factors possibly influencing, i.e. worsening performance in samples of chronic patients, such as prolonged antipsychotic drug treatment, long-term hospitalisation, or functional, social and professional impairment. An additional advantage of first-episode studies is the improved sample homogeneity with regard to disease stage and illness duration. Finally, it has been argued that there might be detrimental, e.g. neurotoxic, effects on the brain of the illness itself, which could affect performance in chronic patients (Weinberger & McClure 2002). SPEM abnormalities seen in the first psychotic episode are, therefore, thought to be linked to the primary disease process and the genetic basis rather than secondary confounds or the effects of disease chronicity (Copolov et al 2000; Lieberman et al 1993; Lieberman et al 1992; Lieberman et al 2001; Spohn & Strauss 1989; Waring 1995).

There are, however, also methodological difficulties of first-episode studies. First, it has been argued that the subgroup of acutely ill schizophrenia patients who are willing to and capable of performing psychophysiological assessments may not be representative of the patient group at large (Clementz 1998). Second, it remains a possibility that the onset of illness disrupts eye movement performance in an all-or-none fashion. Longitudinal studies tracking individuals' performance before and after onset of illness are required to address this issue.

In line with observations of impaired performance on a number of proposed endophenotypes in first-episode psychosis (Copolov et al 2000; Ettinger et al 2001; Hirayasu et al 1998; Hutton et al 1998b; Riley et al 2000; Salisbury et al 1998), SPEM deficits have also been described in this patient group.

Importantly, the types of abnormalities seen in the first episode mirror those seen in chronic patients, including global qualitative (Levy et al 1992; Yee et al 1998) and

quantitative (Iacono et al 1992; Yee et al 1998) abnormalities as well as specific deficits, such as reduced gain (Hutton et al 1998a; Levy et al 2000; Sweeney et al 1992a) and increased saccadic frequency (Levy et al 2000; Sweeney et al 1992a, 1998a).

In addition to demonstrating performance deficits in the first episode, it is of interest to compare performance levels in first-episode psychosis with those observed in chronic schizophrenia. While most of the clinical exacerbation in schizophrenia is observed in the first five years of the illness (Lieberman et al 1992), studies of *cognition* have provided no consistent evidence of deterioration, with some indication of selective improvements in function following recovery after illness onset (Censits et al 1997; Hoff et al 1999).

Evidence concerning changes in SPEM through the first months of the illness is mixed, with one study showing no change in global SPEM performance over approximately 9.5 months, despite changes in medication status and clinical improvement (Gooding et al 1994), but another study (Yee et al 1998) showing significant deterioration over a period of one year.

Evidence from cross-sectional studies indicates that SPEM deficits are more pronounced in chronic than in recent-onset patients (Holzman et al 1974; Hutton et al 2001a; Sweeney et al 1992a). It appears, therefore, that SPEM performance deteriorates with the occurrence of multiple psychotic episodes; however, this issue needs to be resolved using longitudinal studies[12]. The failure to obtain consistent correlations between SPEM and indirect measures of disease chronicity (e.g. number of hospitalisations) (Section 2.3.5.3) might be due to methodological reasons, such as small samples and small range of scores.

What implications would deteriorations in performance over multiple psychotic episodes have, if observed, for the validity of oculomotor measures as schizophrenia endophenotypes? First, the observation of SPEM deficits in the first psychotic episode renders it unlikely that deviant performance in the schizophrenia patient group at large is *entirely* due to secondary confounds. Second, it is possible that secondary effects of schizophrenia, such as social and functional impairments, chronic drug treatment and disease chronicity do adversely affect performance levels. These factors in the chronic

[12] Lieberman et al (1992) report that the first-episode patients in their Hillside Hospital study have been followed up using SPEM (and other) assessments at 18, 30, and 60 months after baseline tests. However, at present these data have not been published.

group might lead to a systematic overestimation of differences with groups of relatives or healthy controls, and might have to be considered in genetic studies using quantitative performance scores (Arolt et al 1999; Rybakowski et al 2001). Finally, genetic research has shown that levels of expression of a gene may vary over time (Plomin et al 2000). It remains a possibility that worse SPEM in chronic patients represents a greater reflection of genetic influence.

2.3.5.5.6 Schizotypy

Given the hypothesised proximity of schizotypy to clinical schizophrenia, a number of investigations have combined SPEM and psychometric schizotypy questionnaires in otherwise healthy individuals, mainly university students. Other studies have examined individuals with a DSM Axis II diagnosis of schizotypal personality disorder (SPD). Studying schizotypy in healthy individuals (e.g. university students) is an advantageous strategy in schizophrenia spectrum research as it overcomes many of the methodological confounds of patient studies, such as antipsychotic and adjunctive drug treatment, hospitalisation and social and functional impairments.

Studies of schizotypy in healthy individuals and SPD patients mirror those of clinical schizophrenia in their methodological approaches. Thus, first evidence of a relationship between SPEM and schizotypy and SPD was obtained and subsequently replicated using global qualitative as well as non-specific quantitative measures (Coursey et al 1989; O'Driscoll et al 1998; Siever et al 1982, 1989, 1990). As in the schizophrenia studies, these deficits were also shown using more refined methods (Gooding et al 2000b), although one study found differences between individuals with SPD and healthy controls on global qualitative ratings, but not specific quantitative measures (Siever et al 1994). While most researchers have either compared high and low schizotypal individuals, or investigated correlations between schizotypy levels and SPEM, an inverse sampling strategy has also been used successfully. Siever et al (1984) selected college students with good and poor SPEM; a diagnosis of SPD or schizophrenia was more common in the poor SPEM group.

Few failures to replicate these findings have been reported. A study by Simons and Katkin (1985) is often quoted as demonstrating worse SPEM in high schizotypy scorers. In fact, high and low scorers on the Chapmans' Physical Anhedonia (Chapman et al 1980) scale in this study did not differ on qualitative SPEM ratings, although performance in the high scorer group was more variable and there were three

individuals with severely impaired performance. Blackwood et al (1994b) found no differences on the ln(S/N) measure of SPEM between adults who were in childhood diagnosed as schizoid and control adults (who had other psychiatric disturbances in childhood). However, the two groups also did not differ on another measure of susceptibility to schizophrenia, the event-related potentials measure P300, thus suggesting the finding was not a failure specific to SPEM.

One issue of particular interest is that of the specific relationship between SPEM and symptom dimensions of schizotypy. As discussed in Section 1.7, the symptom dimensions of schizotypy appear to somewhat map those of clinical schizophrenia (Vollema & van den Bosch 1995); as summarised in Section 2.3.5.3, a number of studies have demonstrated a relationship between SPEM and negative features of full-blown schizophrenia. Interestingly, a remarkably similar relationship has been obtained in a number of (but not all) studies of schizotypy.

An association between SPEM and social introversion in healthy individuals has been found (Siever et al 1982, 1989); Coursey et al (1989) similarly found a correlation between ln(S/N) and interpersonal but not affective symptoms in students. Siever et al (1994) showed that poor qualitative SPEM was associated with negative, deficit like, but not positive, psychotic like symptoms in a group of mixed personality disorder patients; the association was even stronger amongst individuals with SPD.

While these findings are intriguing, as they appear to demonstrate a continuum between schizophrenia and schizotypy at the phenomenological as well as the biological level, other studies have found comparable associations between SPEM and negative as well as positive symptoms (Gooding et al 2000b; O'Driscoll et al 1998).

A second point of interest concerns the relationship between measures of schizotypy and trait emotionality. A number of studies have demonstrated a correlation between trait emotionality and schizotypal personality traits (Bentall et al 1989; Braunstein-Bercovitz et al 2002; Eysenck & Barrett 1993; Lipp et al 1994; Muntaner et al 1988; O'Driscoll et al 1998; Rust & Chiu 1988; Tien et al 1992a; Wuthrich & Bates 2001) as well as increased levels of neuroticism in schizophrenia (Catts et al 2000; Gurrera et al 2000; van den Bosch 1984). The reasons for this association are not well understood. One possibility is that increased levels of neuroticism are observed as a consequence of distressing psychosis-like symptoms (Claridge & Broks 1984). Alternatively, it has been suggested that neuroticism may be a non-specific measure of many different types of

psychopathology, not specific to psychosis (Claridge & Davis 2001). Finally, high levels of neuroticism might produce symptoms typically associated with the schizophrenia spectrum, such as thought disorder (Vollema & van den Bosch 1995).

Irrespective of the precise causal relationships at operation, Raine and Lencz (1995) have argued for the need to examine the specificity of proposed behavioural or biological markers to schizotypy and schizophrenia, while minimising the risk of statistically – or through sampling – correcting for comorbid features, such as anhedonia or social anxiety, which may in fact be essential to the construct under study. No previous study has examined whether trait emotionality impacts on the relationship observed between SPEM performance and schizotypal traits in healthy individuals. Such an observation would be of importance in order to establish the relative specificity of the relationship between SPEM and schizotypy symptoms.

2.3.5.5.7 The Latent Trait Model

In attempting to explain the pattern of inheritance of SPEM dysfunction, Holzman and colleagues made an observation that rendered a Mendelian pattern unlikely (Matthysse et al 1986): A number of schizophrenia patients with normal SPEM had first-degree relatives with impaired SPEM; the opposite pattern was also observed. This finding indicates that SPEM dysfunction cannot be a *necessary* genetic marker in schizophrenia. In order to explain this finding, as well as the observed frequencies of SPEM dysfunction in patients (50-80%) and relatives (30-50%), Matthysse et al (1986) developed the *latent trait model.*

The latent trait model holds that SPEM dysfunction and clinical schizophrenia are two expressions of an underlying, hence latent, trait. This trait is transmitted in a quasi-Mendelian fashion, determined by a single major locus. Matthysse et al (1986) argued that the disease process linked to the latent trait has a greater probability of manifesting itself as SPEM dysfunction (which is more common in the general population) than schizophrenia, thereby explaining the observation of schizophrenia patients with good SPEM and the increased frequencies of SPEM and schizophrenia in first-degree relatives, the former being more frequent than the latter.

The expression of a gene as more than one phenotypes is called pleiotropy (Plomin et al 2000). Holzman and colleagues (Holzman 2000; Matthysse & Holzman 1987) have compared their SPEM model to a similar observation in neurofibromatosis, where

benign café-au-lait spots represent the more common and less pathological phenotype (comparable to SPEM dysfunction) than the neurofibromata (comparable to schizophrenia-related symptoms). Another example is phenylketonuria (PKU), where a single gene causes light hair and skin colour as well as mental retardation (Plomin et al 2000). In comparison to these conditions, Matthysse and Holzman (1987) argued that the two expressions of the latent trait (schizophrenia and SPEM dysfunction) "are very different from each other" (p. 272).

The latent trait model makes a very strong prediction: SPEM performance should be clearly bimodally distributed, if not dichotomous, in families with multiplex schizophrenia (allowing for random error of measurement and non-specific sources of variance). Early studies by Holzman and colleagues, of course, used dichotomous SPEM scoring methods, thereby artificially creating groups with and without SPEM dysfunction. Later studies using statistical techniques such as mixture analysis could demonstrate that the distribution of quantitative SPEM scores is indeed best fit by two distributions. Mixture of distributions indicates that a sample is more likely to be taken from two different populations than the same population (one distribution). These studies indicate that one of the patient subgroups appears to display abnormal pursuit, underperforming normal controls, while the other, worse performing, group cannot be easily distinguished from controls.

Mixture distributions were obtained for RMSE (Clementz et al 1992; Iacono et al 1992; Ross et al 1988, 1996a, 1997; Sweeney et al 1993), ln(S/N) (Gibbons et al 1984) and gain (Clementz et al 1992) and were demonstrated in schizophrenia patients and their first-degree relatives but not in healthy controls.

The statistical features of the latent trait model were tested on SPEM data from schizophrenia patients, their first-degree relatives and discordant twins. In different datasets Holzman and colleagues found that the genetic transmission of SPEM dysfunction and schizophrenia could be best explained by a single, autosomal dominant gene (Holzman et al 1988). However, as Grove et al (1992) pointed out, this study did not compare the dominant gene model to a polygenic one. Additionally, the study used qualitative SPEM ratings, thereby losing important between-subject variance. McGue and Gottesman (1989) have argued further that a shortcoming of the model was not to consider familial environmental as well as polygenic components.

Grove et al (1992) provided more evidence of a major gene effect on SPEM deficits in schizophrenia, but observed polygenic factors as well. Pooling together samples of schizophrenia patients and their first-degree relatives, they found that a (simulated) major gene in the presence of residual, polygenic variance accounted for about two thirds of the variance in RMSE in their sample.

The evidence from the Holzman et al (1988) and Grove et al (1992) studies is promising, but should be considered preliminary. As outlined below, there is no firm, consistent evidence of linkage between SPEM dysfunction and a specific genetic locus as yet. Given Holzman et al's report of a single gene effect in 1988, it may be all the more surprising that their group has not published a linkage study of the SPEM phenotype. Additionally, evidence from healthy twin studies appears to indicate a polygenic pattern of SPEM inheritance. Finally, Matthysse and Holzman's (1987) assumption that SPEM dysfunction and schizophrenia represent two very different phenotypes may be challenged. While the most prominent application of the SPEM task in schizophrenia spectrum research to date has been investigations of its endophenotypic properties (the 'first' stream of research; Section 2.2.1), there is also evidence linking it to schizophrenia at cognitive and biological levels (the 'second' stream of research; Section 2.2.1). It may be argued that although SPEM and schizophrenia may indeed represent two pleiotropic manifestations of an underlying trait, their shared putative frontal lobe correlates may be more than accidental. This speculation requires more research, combining genetic, cognitive and biological approaches.

2.3.5.5.8 Molecular Genetic Studies

The ultimate purpose of an endophenotype is to be used in genetic linkage studies. It is, therefore, surprising that despite almost thirty years of family and twin research of SPEM in schizophrenia, only two linkage studies (with overlapping samples) of this endophenotype have been reported.

The first study was reported by Arolt et al (1996). These researchers carried out a scan limited to the 6p21-23 region to test for linkage between chromosomal markers and SPEM dysfunction as well as schizophrenia. Two lod scores of 3.51 for D6S271 and 3.44 for D6S282 on chromosome 6p21-23 were obtained for SPEM dysfunction (but not for a diagnosis of schizophrenia) in 8 families with multiplex schizophrenia. These markers are close to regions previously implicated in linkage studies of the schizophrenia phenotype (Moises et al 1995).

A second linkage study by the same group replicated this finding using an extension of the original sample (Arolt et al 1999). Linkage of SPEM dysfunction – but not schizophrenia – was found to markers on chromosome 6p21, while there was no convincing linkage to chromosomes 8, 9, 20 and 22.

Additionally, a recent study demonstrated a link between SPEM impairments and polymorphisms of the dopamine D3 receptor on chromosome 3q (Rybakowski et al 2001). The serine-serine polymorphism of the D3 receptor gene was found to be associated with worst SPEM dysfunction in 119 schizophrenia patients and 85 healthy controls; serine-glycine heterozygotes performed in-between and glycine-glycine homozygotes performed best. This finding is of considerable interest given the proposed role of the dopaminergic system in the pathophysiology of schizophrenia (Kapur & Remington 2001; Leonard 1997).

While the two studies demonstrating linkage of SPEM dysfunction to chromosome 6p21 are very promising, they will need to be replicated. Additionally, the finding by Rybakowski et al (2001) is difficult to reconcile with these linkage studies. While Arolt et al (1999) argued that a single gene on the 6p21 locus may account for SPEM dysfunction in their families, a different gene was implicated by Rybakowski et al (2001). It is, however, important to note that Arolt et al (1996) restricted their search to the 6p21-23 region, thus not allowing the detection of other genetic loci. These contradictory findings are not inconsistent with the notion that more than one gene is implicated in schizophrenia. Given the heterogeneity of SPEM itself (Levy et al 2000) it may further be argued, contrary to the latent trait model (Matthysse et al 1986; Matthysse & Holzman 1987), that this heterogeneity may also be reflected genetically.

2.4 Visual Fixation

2.4.1 Definition

Visual fixation describes the controlled focus of gaze onto a stationary target. Because of relatively spared visual fixation capacities in people with schizophrenia and the proposed similarities between fixation and smooth pursuit, this task is often considered a 'control' condition for the smooth pursuit task rather than a genetic marker in schizophrenia spectrum research. Visual fixation methods and key findings will, therefore, be considered only relatively briefly here.

2.4.2 Visual Fixation Stimulus

2.4.2.1 Hardware

Visual fixation tasks involve the presentation of a stationary stimulus for lengthy periods of time. The types of stimulus display are similar to those of smooth pursuit tasks, using computer screens (Clementz et al 1994; Curtis et al 2001b; Gooding et al 2000a; Kissler & Clementz 1998; Levin et al 1982a; Paus 1991; Rosse et al 1992a; Rybakowski et al 2001), CRO (Amador et al 1995; Matsue et al 1986; Mialet & Pichot 1981) and laser spots (Ross et al 1988).

2.4.2.2 Stimulus Properties

Stimuli usually consist of simple targets, such as dots, crosses, or squares, similar to those used in smooth pursuit trials. The target stimulus is usually presented in the centre of the participant's visual field (0°), or in a peripheral horizontal location. The use of more than one horizontal location allows investigation of laterality and amplitude effects (Clementz et al 1994; Kissler & Clementz 1998).

Kissler and Clementz (1998) suggested using at least one horizontal stimulus *amplitude* that is taxing for the visual fixation system (e.g. ±20°), in order to probe effectively for drift. Regarding the *temporal characteristics* of visual fixation trials, previous research has employed stimulus durations of about 10,000-30,000ms per location. *Instructions* to participants are usually to keep their eyes on the target at all times.

A variant of this task, the fixation with distractors task, has also been used in schizophrenia spectrum research (Curtis et al 2001b; Hutton et al 2002). In this task peripheral targets appear briefly, introducing a challenge for the saccadic inhibitory component of the fixation system. As the simple fixation task in the present research serves primarily as a control condition for the SPEM task, the fixation with distractors and tasks using semantic stimuli (Paus 1991) are not discussed further.

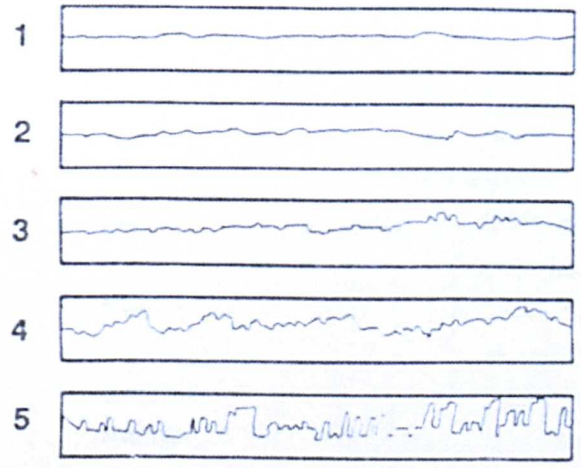
2.4.3 Visual Fixation Scoring

Scoring methods for visual fixation tasks somewhat overlap with those for SPEM and have ranged from qualitative to quantitative. Leigh and Zee (1999) described a clinical assessment of fixation stability, which does not involve recording or analysis equipment. While such a bedside assessment is indicated for gross neurological

disorders, it is likely to obscure the subtle fixation abnormalities that may be observed in schizophrenia.

Rosse et al (1992a) published examples of a 5-point *qualitative rating scale* for visual fixation performance, based on the SPEM scale of Shagass et al (1974). This scale ranged from 1 (best) to 5 (worst), presumably based on accuracy and consistency of fixation as well as frequency of saccades (Figure 2.9).

Figure 2.9: Example of a 5-point Visual Fixation Rating Scale



from Rosse et al (1992), p. 413; 1 = best, 5 = worst

Kissler and Clementz (1998) undertook a detailed quantitative analysis of fixation data in schizophrenia patients and healthy controls. The *frequency of saccades* was assessed. SWJ were defined as pairs of saccades separated by a 100-450ms interval, with only the first saccade in each pair counted. Single saccades were also observed. After exclusion of saccades and eye-blinks, fixation stability was further evaluated as the average and standard deviation of the eye position and eye velocity. Other researchers (Clementz et al 1994; Curtis et al 2001b; Gooding et al 2000b; Levin et al 1982a; Mialet & Pichot 1981; Silverman & Gaarder 1967) have also assessed saccade frequency as a measure of fixation stability. Ross et al (1988), following the SPEM literature, calculated *RMSE* for fixation. Minimum amplitudes for the identification of saccades were reported by Gooding et al (2000b: 1°) and Curtis et al (2001b: 0.5°).

2.4.4 Visual Fixation in the Schizophrenia Spectrum

2.4.4.1 Behavioural Characterisation of Visual Fixation in Schizophrenia Patients

A number of studies have indicated relatively unimpaired visual fixation in patients with schizophrenia (Clementz et al 1994; Gooding et al 2000a; Kissler & Clementz 1998; Mather & Putchat 1982; Radant et al 1997; Ross et al 1988). However, other studies have indicated the existence of subtle disruptions of fixation (Amador et al 1991, 1995; Curtis et al 2001b; Matsue et al 1986; Mialet & Pichot 1981; Rybakowski & Borkowska 2002; Silverman & Gaarder 1967). These abnormalities most commonly consist of saccades away from and back to the target as well as slow drift away from the target. It is important to note that the two methodologically most detailed studies (Gooding et al 2000a; Kissler & Clementz 1998) observed no impairments in schizophrenia and that many of the studies observing impairments used either qualitative ratings of fixation performance or the electrooculographic recording technique, thereby allowing for possible bioelectric artefacts.

An intact fixation system in schizophrenia is sometimes postulated as evidence of the specificity of SPEM impairments across oculomotor functions. The two tasks have been related to each other, as visually attending to a stationary target may be equivalent to smooth pursuit eye movements at zero target velocity (Leigh & Zee 1999). However, the evidence from a number of studies of fixation impairments in schizophrenia argues against the presumed specificity of SPEM impairments.

2.4.4.2 Cognitive and Neural Basis of Visual Fixation in Schizophrenia Patients

Gaze-holding of a stationary target is a cognitively relatively undemanding task. Therefore, deficits seen during this task do not necessarily imply disturbance of higher cognitive functions. Lesions to a variety of brain areas can induce fixation impairments. These areas include the cerebellum (in particular the flocculus), frontal cortex (in particular the FEF, dorsolateral prefrontal cortex [DLPFC] and supplementary motor area), occipito-parietal cortex (in particular the inferior parietal lobule), the basal ganglia and the superior colliculus (Anderson et al 1994; Leigh & Zee 1999; Petit et al 1999).

Neuroimaging studies of healthy humans have shown mainly frontal areas to be involved in the control of fixation. In particular, activation has been observed in precentral gyrus, supplementary eye fields, cingulate and ventromedial and anterolateral prefrontal cortex (Anderson et al 1994; Petit et al 1999).

To probe for fixation deficits in schizophrenia by increasing cognitive load, a commonly used variation of the task presents peripheral visual distractors (such as flashing targets) during fixation of the central target. The participant is in this task required to actively inhibit the initiation of saccades towards the peripheral targets, thereby increasing the (frontal) cognitive demands (Petit et al 1999). Although a recent study failed to find differences between first-episode schizophrenia patients and healthy controls on this task (Hutton et al 2002), a previous study showed that the distractor condition led to increased impairments in schizophrenia (Curtis et al 2001b).

In an elegant experimental task manipulation, Paus (1991) observed an increased frequency of saccades away from the fixation stimulus only during fixation of a semantically inert stimulus, but not during a categorisation task of semantically meaningful stimuli. This finding somewhat resembles the attentional manipulations of target characteristics in the SPEM task (Section 2.3.5.2.3) as it demonstrates normal performance in schizophrenia after focussing patients' attentional (or other cognitive) processing capacities onto the stimulus.

Malaspina et al (1999) observed that neuroleptic-free schizophrenia patients had significantly reduced rCBF in the left medial frontal, superior frontal, middle frontal and anterior cingulate cortex during visual fixation when compared to controls. Increased rCBF in the patient group was observed in the left and right parahippocampal gyrus and right fusiform gyrus. The finding of frontal hypoactivity is consistent with the hypofrontality hypothesis of schizophrenia (Section 1.4.2), but is intriguing given the low cognitive demands of the task.

More evidence for a frontal involvement in fixation deficits in schizophrenia was obtained by Paus (1991) who observed a correlation between fixation performance and neuropsychological tests of frontal lobe function, such as WCST.

Based on the inconsistent evidence of fixation abnormalities in schizophrenia it is difficult to infer a specific neural abnormality. However, one hypothesis is that fixation impairments, when seen in this patient group, might be due to frontal lobe dysfunction (Malaspina et al 1999; Paus 1991). Findings indicating intact visual fixation, conversely,

might suggest that lower brain areas involved in fixation, such as the nucleus prepositus hypoglossi or the medial vestibular nucleus (Kissler & Clementz 1998), are spared by the schizophrenic disease process.

2.4.4.3 Clinical Correlates

Little is known about the clinical correlates of fixation control in schizophrenia. Rosse et al (1992a) observed a correlation between visual fixation impairments and Mini Mental State Examination, a measure of dementia, implying effects of general cognitive decline. Paus (1991) noted a correlation with BPRS thought disorder. Thaker et al (1989c) did not find differences between patients with and without tardive dyskinesia in fixation performance.

2.4.4.4 Treatment Effects in Schizophrenia and Pharmacological Manipulation in Healthy Individuals

Little is known about antipsychotic treatment effects on fixation in schizophrenia. Amador et al (1995) observed no significant correlation between neuroleptic dose and fixation quality. Similarly, Gooding et al (2000a) observed no differences between patients on and off medication.

It has, however, been demonstrated that lorazepam (but not sertraline or chlorpromazine) administration leads to increased saccades during the fixation with distractors task in healthy individuals (Green et al 2000; Green & King 1998).

2.4.4.5 Validity as Endophenotype

2.4.4.5.1 Heritability

No study examining the heritability of fixation performance in healthy monozygotic and dizygotic twins could be identified.

2.4.4.5.2 Temporal Stability

Fixation performance appears to be stable in healthy individuals over several weeks (Roy-Byrne et al 1995).

2.4.4.5.3 Specificity to Schizophrenia

Due to the basic neural control of visual fixation, the task has been used widely as a neurological assessment tool. Patients with a number of neurological conditions, including Friedreich's ataxia, progressive supranuclear palsy and acquired lesions to the cerebellum have been demonstrated to have poor abilities to maintain fixation (Leigh & Zee 1999). Bipolar psychotic patients do not appear to have fixation abnormalities (Amador et al 1991, 1995).

2.4.4.5.4 Family and Twin Studies

Despite the presumed stability of visual fixation in schizophrenia, there are two reports showing fixation impairments in first-degree relatives of schizophrenia patients (Amador et al 1995; Rybakowski & Borkowska 2002). Curtis et al (2001b) observed increased saccades during fixation in first-degree relatives only on the fixation with distractors but not the simple fixation task.

2.4.4.5.5 First-episode Psychosis

Hutton et al (2002) did not observe increased saccadic frequency during the fixation with distractors task in patients within their first psychotic episode.

2.4.4.5.6 Schizotypy

Fixation performance does not appear to be related to levels of psychometric schizotypy in healthy individuals (Gooding et al 2000b).

2.4.4.5.7 Molecular Genetic Studies

The study by Rybakowski et al (2001) already mentioned above (Section 2.3.5.5.8) also included the fixation task. Fixation disturbance (like SPEM) was significantly associated with the Ser-Ser genotype in schizophrenia patients and healthy controls; weaker fixation abnormalities were observed in Ser-Gly homozygotes and Gly-Gly homozygotes had best fixation scores. These findings indicate that, despite many reports to the contrary, the fixation task may be studied with profit as a schizophrenia spectrum endophenotype, possibly in conjunction with the SPEM task. However, the finding awaits replication.

2.5 Antisaccade Eye Movements

2.5.1 Definition

An antisaccade is a saccadic eye movement in direction opposite to a peripheral target. The antisaccade task has over the last decade been suggested to be an oculomotor endophenotype in schizophrenia spectrum research (Calkins & Iacono 2000; Clementz 1998). Due to this promising evidence, methodological considerations as well as performance patterns and correlates in the schizophrenia spectrum will be described in detail.

2.5.2 Antisaccade Stimulus

2.5.2.1 Hardware

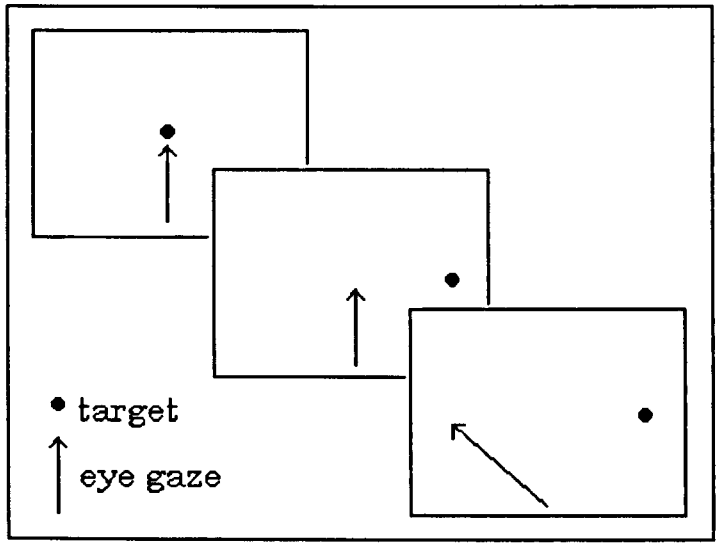
Most schizophrenia antisaccade studies have used computer monitors (Broerse et al 2001b; Clementz et al 1994; Curtis et al 2001a; Klein et al 2000b; McDowell et al 1999), LED arrays (Crawford et al 1995a, 1995b; Fukushima et al 1990b; Hutton et al 1998a; Karoumi et al 1998b) or laser targets (Maruff et al 1998) to present target stimuli.

Similar to SPEM studies, computer monitor targets are presented at distances of about 40cm to 60cm from participants. LED arrays are presented at slightly greater distances (Fukushima et al 1990b; Hutton et al 1998a; Karoumi et al 1998b). Computer screen-based antisaccade targets are usually made up of simple shapes, such as dots or squares, varying in colour and size.

2.5.2.2 Stimulus Properties

An antisaccade trial usually begins with the presentation of a central target (0°). After a brief duration, the target is abruptly moved to a peripheral location. Participants are required to initiate an eye movement in opposite direction, without first following the target movement (see Figure 2.10)

Figure 2.10: Flowchart of the Antisaccade Task



Different *peripheral target locations* have been used, typically ranging between ±5° and ±25°. McDowell et al (1999) have highlighted the importance of using more than one amplitude. These researchers found that a 'far' target (±16°) provided patient-control separations about 2.5 times larger than a 'near' target (±8°). Some researchers (Burke & Reveley 2002; Crawford et al 1998; Hutton et al 1998a; Karoumi et al 1998b; Larrison et al 2000) additionally presented participants with an auditory stimulus (buzzer) coinciding with peripheral target onset.

Of equal importance is the *duration of central and peripheral targets.* In schizophrenia spectrum studies no one single protocol of these factors has been established. Durations of the central and peripheral targets have varied between about 1,000ms and 3,000ms. While some antisaccade tasks have used fixed central target durations (Crawford et al 1998; Hutton et al 1998a; Ross et al 1998d), others have varied the duration quasi-randomly across trials (Clementz et al 1994; Curtis et al 2001a; Karoumi et al 2001; Katsanis et al 1997; Thaker et al 2000). Quasi-random duration of central targets may be advantageous, making the peripheral target appearance temporally unpredictable.

Most previous studies have used the regular, or 'non-overlap' antisaccade task, where the peripheral target appears immediately as the central target disappears. Two variations of this task have been studied, i.e. the 'overlap' and the 'gap' antisaccade tasks (Fischer et al 2000; McDowell & Clementz 1997), following the gap and overlap

reflexive saccade tasks (Fischer et al 1993). In the gap task, a brief temporal gap of about 200ms is introduced between central and peripheral target presentation, in which the screen is blank. In the overlap task, the central and peripheral targets overlap by about 200ms. Previous studies have shown that the gap condition leads to a reduction in latency and an increase in error rate. Conversely, the overlap task is associated with a prolongation of latency and a reduction in error rate (Fischer & Weber 1997; McDowell & Clementz 1997). While these task manipulations have been studied with profit, the bulk of the literature (including the research conducted as part of this thesis) has used the regular (non-overlap) task.

The *number of trials* in an antisaccade assessment is typically about N=20 (Clementz et al 1994; Crawford et al 1998; Curtis et al 2001a; Hutton et al 1998a; Katsanis et al 1997), although larger numbers have also been used (N=60) (Karoumi et al 2001; McDowell et al 1999) and Maruff et al (1999) argued for the use of at least 40 trials. *Practice trials* are usually given to familiarise participants with the task requirements. *Instructions* to participants usually focus on the inhibition of reflexive saccades towards the peripheral target and the immediate initiation of a saccade in opposite direction. Most, but not all (Thaker et al 2000), researchers additionally require participants to match, with their saccade, the peripheral target amplitude.

Some researchers have chosen to provide feedback to participants concerning the spatially correct saccadic response. This involves a stimulus appearing in the location where participants were required to look, i.e. opposite to the peripheral target location (Burke & Reveley 2002; Crawford et al 1995a, 1995b; Karoumi et al 2001; McDowell et al 1999; Nieman et al 2000; Ross et al 1998d; Tien et al 1996). This addition may have the advantage of providing the individual with important information concerning their performance. However, feedback on cognitive task performance may improve performance and induce arousal and may, therefore, lead to complex cognitive processing, affecting performance differences between schizophrenia spectrum participants and healthy individuals in an unknown way.

2.5.3 Antisaccade Scoring

The antisaccade task, as a competing endophenotype to the SPEM task, has the advantage of possessing clearly defined analysis criteria. The key measure of antisaccade performance, and the most promising saccadic endophenotype, is the *error rate.* Probably every schizophrenia spectrum study of the antisaccade task has reported

the average error rate (Allen et al 1996; Broerse et al 2001b; Burke & Reveley 2002; Clementz et al 1994; Crawford et al 1995a, 1995b, 1996, 1998; Curtis et al 2001a, 2001b; Dursun et al 1999; Fukushima et al 1988, 1990b, 1990c; Gooding 1999; Gooding & Tallent 2001; Hutton et al 1998a, 2001a, 2001b; Karoumi et al 1998b, 2001; Katsanis et al 1997; Klein et al 2000b, 2000c; Maruff et al 1998; McDowell et al 1999, 2002; McDowell & Clementz 1997; Müller et al 1999; Nieman et al 2000; O'Driscoll et al 1998; Ross et al 1998d; Rosse et al 1993; Schlenker & Cohen 1995; Sereno & Holzman 1995; Straube et al 1999; Thaker et al 1989b, 1989c, 1996a, 2000).

Figure 2.11: Example of an Antisaccade Error with Subsequent Corrective Saccade

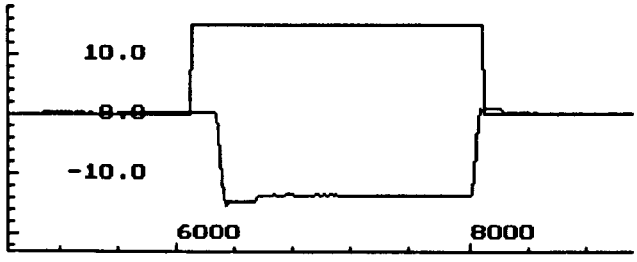
Legend: x-axis, time (ms); y-axis, degree of visual angle

An antisaccade error is counted – quite unambiguously – when the participant initiates a saccade towards the peripheral target. Errors may even be counted by visual inspection (Figure 2.11). The error rate reflects the percentage of error trials over the total number of correct antisaccade trials, and is calculated as follows:

$$\frac{N_{err}}{N_{tot}} 100\%$$

where N_{err} is the number of errors, and N_{tot} is the total number of antisaccades.

Figure 2.12: Example of a Correct Antisaccade



Legend: x-axis, time (ms); y-axis, degree of visual angle

A correct antisaccade trial is counted when the participant performs a saccade in opposite direction to the peripheral target (Figure 2.12). Criteria for detection of saccades in automatic, computer-based analyses of this task have varied across studies. A saccade is usually defined as a change in eye velocity, with velocity exceeding about 5°/s (Clementz et al 1994) to 30°/s (Crawford et al 1998). Most researchers are likely to have employed criteria of minimum amplitude, although these are rarely reported (Broerse et al 2001b: 3°; Gooding 1999: 2°; Straube et al 1999: 5°). Transforming visual input into an eye movement response requires time (Carpenter 1988; Leigh & Zee 1999); therefore, saccades in response to a target are considered predictive, and subsequently excluded from analysis, if the latency is less than about 70-100ms (Clementz et al 1994; Evans & Schwartz 1997; Gooding 1999; Katsanis et al 1997; Klein et al 2000c; McDowell et al 1999; Nieman et al 2000).

Some – but not all – studies have investigated the antisaccade error *correction rate* (Clementz et al 1994; Crawford et al 1998; McDowell & Clementz 1997). Usually, an antisaccade error is corrected by the participant through the execution of a saccade in opposite direction (Figure 2.11). The correction rate is calculated as the percentage of corrective saccades over error trials. This measure (usually close to 100% in healthy individuals) can taken as an indication of whether participants understood the task instructions and were in principle willing and able to perform the task (McDowell & Clementz 1997).

Most studies have analysed antisaccade *latency*. Latency is defined as the time, in milliseconds, from target appearance to saccade initiation. Only a few studies have provided an index of antisaccade *accuracy*. The most frequent measure of accuracy is

that of primary antisaccade gain (Crawford et al 1995a, 1995b, 1998; Karoumi et al 1998b, 2001; Nieman et al 2000). Primary antisaccade gain is calculated as follows:

$$\frac{ampl_{sacc}}{ampl_{trgt}}100\%$$

where $ampl_{sacc}$ is the primary saccade amplitude in degrees, and $ampl_{trgt}$ is the target amplitude in degrees.

As the antisaccade amplitude is opposite in valence to that of the target, the resulting percentage measure of accuracy will be negative for correctly executed antisaccades. A gain score of -100%, therefore, reflects perfect accuracy of a primary antisaccade. This measure of gain minimises effects of drift and is, therefore, preferable over a direct measure of eye position.

As an additional measure of accuracy, some investigators (Crawford et al 1995a, 1995b, 1998; Hutton et al 1998a) have reported *final eye position*, reflecting the average fixation position after primary and subsequent corrective saccades. Ross et al (1998d) measured antisaccade accuracy as *residual error*, defined as a percentage of post-saccadic position error divided by the distance from initiation of saccade to target location. Accuracy and latency measures are usually reported only for correct antisaccades, although some investigators have also studied the saccadic metrics of error saccades (Fischer & Weber 1997).

Only a few studies have reported other antisaccade characteristics, such as *peak velocity* (in degree per second) or *duration* (in milliseconds) (Fukushima et al 1990b, 1994; Nieman et al 2000; Straube et al 1999). However, probably due to the role of the error rate as the most promising antisaccadic endophenotype, most schizophrenia spectrum studies have not used these measures.

2.5.4 Antisaccade Eye Movements in the Schizophrenia Spectrum

2.5.4.1 Behavioural Characterisation of Antisaccade Eye Movement Impairments in Schizophrenia Patients

The most robust observation of antisaccade abnormalities in schizophrenia is undoubtedly that of an increased error rate on the antisaccade task. No study to date has failed to replicate this finding. Average error rates in the patient group tend to range

from about 25% to over 70%; the range in healthy individuals is from just over 0% to about 30%. Percentages are difficult to compare across studies, however, due to differences in task design that may affect performance levels.

Most (Fukushima et al 1990c; Karoumi et al 1998b; Klein et al 2000b; Maruff et al 1998; Matsue et al 1994b), but not all (Nieman et al 2000), studies have demonstrated longer latency in schizophrenia. Hutton et al (1998) observed prolonged latency only in antipsychotic treated, but not untreated, first-episode patients. The third main measure, spatial saccadic accuracy, has not been studied comprehensively. There is, however, some evidence of reduced antisaccade gain in schizophrenia (Karoumi et al 1998b; McDowell et al 1999).

The correction rate (initiation of antisaccades after the committal of an error) has been considered by some to indicate whether patients have understood task instructions and are willing to comply. Correction rates are generally high, reducing the possibility of a generalised cognitive, motor or motivational deficit underlying poor antisaccade performance (Crawford et al 1995a, 1995b; McDowell & Clementz 1997).

There are reliable age effects on antisaccade performance: Young children have difficulty performing the task (Klein & Foerster 2001); amongst adults, older individuals tend to make more errors and take longer to initiate correct antisaccades (Gooding & Tallent 2001; Klein et al 2000a; Olincy et al 1997). Some studies have shown that females make more errors than males (Crawford et al 1998; Tien et al 1996); however, the majority of studies have not observed this relationship.

2.5.4.2 Neural and Cognitive Basis of Antisaccade Eye Movements

2.5.4.2.1 Neural Substrates of Antisaccade Eye Movements

The precise neural correlates of the antisaccade remain debated (Broerse et al 2001a; Everling & Fischer 1998). It is thought that antisaccades share with simple reflexive saccades the basic saccadic circuitry, including FEF, parietal eye fields (PEF), superior colliculus (SC), brainstem reticular formation and cerebellum. In addition, however, further cortical areas are likely to be required for the successful suppression of reflexive errors. Early human lesion studies have primarily implicated the FEF (and SEF) in the suppression of reflexive errors (Guitton et al 1985). However, more recent lesion studies have found increased error rate after lesions to the DLPFC but *not* FEF/SEF (Fukushima et al 1994; Gaymard et al 1990, 1998b, 1999; Pierrot-Deseilligny et al

1991). Nevertheless, lesions to the FEF lead to increased antisaccade latency (Rivaud et al 1994), in line with the well-established role of the FEF in the generation of voluntary saccades (Pierrot-Deseilligny et al 1995).

Increased rates of antisaccade errors have also been observed after lesions to the superior colliculus and anterior cingulate (Gaymard et al 1998b). Conversely, lesions to globus pallidus and putamen appear not to result in increased errors (Vermersch et al 1996). Nonhuman primate recording studies have confirmed a role of the frontal lobe, in particular FEF, during preparation and execution of antisaccades (Everling & Munoz 2000).

Functional neuroimaging studies of healthy humans have essentially replicated these findings, including the lack of clarity concerning the roles of FEF and DLPFC in error suppression. Compared to oculomotor control conditions with low inhibitory demand, activation during antisaccades has been observed most consistently in DLPFC (Müri et al 1998; Sweeney et al 1996) and FEF (Cornelissen et al 2002; O'Driscoll et al 1995; Sweeney et al 1996). Specifically, Cornelissen et al (2002) could show that FEF activity rose before initiation of correct antisaccades but not error saccades, likely indicating presaccadic inhibitory processes. Similarly, increased FEF activation during a (covert) inhibitory task has been observed (Perry & Zeki 2000). Paus et al (1993) observed involvement of the anterior cingulate, in agreement with some lesion evidence (Gaymard et al 1998b).

Although functional imaging techniques have the advantage of providing relatively good spatial resolution their key disadvantage is probably the low temporal resolution. Electroencephalography (EEG) shows the inverse pattern of excellent temporal but poor spatial resolution. This technique has been used to examine cortical brain activity preceding pro- and antisaccades in healthy individuals. Studies appear to agree on an increase in electrical (neural) activity observed in the frontal cortex preceding antisaccades but not prosaccades, possibly due to processes of presaccadic inhibition (Evdokimidis et al 1996; Everling et al 1997). However, due to limitations in spatial resolution these studies have not been able to address the relative involvements of specific frontal areas.

2.5.4.2.2 Neuroimaging Studies in Schizophrenia

The first functional neuroimaging study of the antisaccade in schizophrenia was reported by Crawford et al (1996).[13] In this single photon emission tomography (SPET) study schizophrenia patients with normal and high antisaccade error rate were compared during task performance. Patients with high error rate showed decreased regional cerebral blood flow (rCBF) in anterior cingulate, insula and left striatum. This design has the advantage of avoiding non-specific differences between groups, such as patient status, drug treatment or disease severity. In addition to lending support to the involvement of the anterior cingulate in antisaccade performance (Gaymard et al 1998b), these findings also point to a role of the basal ganglia.

A recent fMRI study provided clear evidence of DLPFC involvement (McDowell et al 2002). During a prosaccade task, schizophrenia patients demonstrated normal FEF, SEF and PPC activation. Reduced DLPFC activation relative to healthy controls was observed during antisaccade performance, which according to McDowell et al (2002) presents "corroborative evidence that prefrontally mediated inhibition is functionally impaired among schizophrenia subjects" (p. 222).

In contrast, a second fMRI study of the same year (Raemaekers et al 2002) obtained no evidence of DLPFC deficits in schizophrenia, but observed that reductions in neural activity associated with saccadic inhibition in patients (relative to controls) were localised to the striatum. The difference between this study and that by McDowell and colleagues (2002) is most likely to lie in the type of stimuli that were used. The McDowell et al study used a 'traditional' antisaccade stimulus, similar to those used previously (Section 2.5.2) and to that used in this thesis (Chapter 3). Thus, central and peripheral targets alternated with inter-stimulus intervals of about 1,000-2,000ms. Additionally, the antisaccade block used in the McDowell et al study interleaved prosaccades and antisaccades; the type of eye movement required was indicated to the participant by a change in colour of the central target (green: prosaccade; red: antisaccade) at the beginning of each trial. This design, therefore, placed heavy demands on (prefrontal) attentional and working memory resources, as the participant

[13] In an earlier study, Nakashima et al (1994) observed reduced FEF and DLPFC activation in patients relative to controls during an uncommon version of the antisaccade task: Participants were required to follow a spatially (but not temporally) predictable target, while inhibiting a distractor stimulus at the opposite side. The extent to which this finding generalises to the antisaccade task used in most other studies and in this thesis thus remains unclear.

had to constantly focus on the task, maintain instructions on-line and make the correct decision concerning which type of eye movement to initiate at the beginning of each trial.

The Raemaekers et al study, on the other hand, used an event-related fMRI design in order to study neural activation associated with individual trials. Inter-stimulus intervals were more than 12,000ms, thus isolating the inhibitory component in the relative absence of continuous working memory or sustained attentional processing. It is likely that these differences in stimulus sequence led to the failure to observe DLPFC activation in the Raemaeker et al study. Although Raemaeker et al (2002) ruled out medication effects as a possible explanation for the striatal underactivation in the patients, the finding does provide a suggestive link to studies showing increased error rate in patients with tardive dyskinesia (Thaker et al 1989b, 1989c).

The implications of the Raemaeker et al study for the antisaccade error rate as a (prefrontal) schizophrenia endophenotype (Calkins & Iacono 2000; Clementz 1998) are not yet clear. What the findings do appear to indicate is that DLPFC underactivation might not be *necessary* to explain inhibitory deficits in schizophrenia. The traditional antisaccade task, on the other hand, does appear to be a good measure of DLPFC activation in humans (McDowell & Clementz 2001), whether or not this may be due to saccadic inhibition, sustained attention, or task complexity.

A recent brain activation study using EEG methods observed significantly reduced cortical activity (the contingent negative variation; CNV) in schizophrenia patients before antisaccade performance compared to healthy controls (Klein et al 2000b). The CNV has been argued to be a measure of prefrontal working memory function, thus providing some support for frontal hypoactivation during antisaccades in schizophrenia.

The only structural neuroimaging studies of the antisaccade in schizophrenia to date indicated an association between increased errors and frontal lobe atrophy (Fukushima et al 1988, 1990b). Unfortunately, however, these studies used small sample sizes, a low-resolution neuroimaging technique (CT) and qualitative interpretation of brain structure, necessitating further research in this field.

2.5.4.2.3 Experimental Cognitive Studies

Antisaccade performance may be dissected into three cognitive components: first, the inhibition of a prepotent response to a peripheral visual target; second, covert

attentional processes to encode target location; and third, initiation of a voluntary saccade in opposite direction of the target. Since its first administration to brain damaged patients, the antisaccade task has been argued to be a measure of frontal lobe integrity (Guitton et al 1985). Prefrontal cortex is critically involved in processes of working memory, response inhibition and keeping plans and thoughts 'online' (Goldman-Rakic 1999). The response inhibition component of the antisaccade task may be related to the visual grasp reflex (Everling et al 1997). A number of experimental cognitive studies support the hypothesis that response inhibition, or suppression of the visual grasp reflex, and working memory are interrelated functions and are required for successful antisaccade performance. Other studies have pointed to the (covert) attentional requirements of this task.

One of the key functions of prefrontal cortex is the inhibition of reflex-like, prepotent responses (Roberts et al 1994). By its face validity, therefore, an antisaccade error reflects a failure to inhibit a prepotent response, that is a reflexive saccade towards the target. Using up working memory resources increases the probability to respond in a reflex-like manner to a prepotent stimulus, similar to everyday action errors during distraction (taking the 'old' route to a new place of work when one's thoughts are occupied during driving; Roberts et al 1994). Following this rationale, Roberts et al (1994) experimentally 'impaired' working memory resources in healthy individuals during prosaccade and antisaccade task performance through simultaneous performance of arithmetic calculations. This manipulation increased antisaccade error rate and latency but did not affect prosaccade metrics. Effects were stronger with increasing working memory load and were not accounted for by non-specific effects of task performance (such as listening or speech).

Stuyven et al (2000) could demonstrate that another working memory measure (internally generated, arrhythmic finger taps) but not a control condition (regular finger taps) increased antisaccade error rate and latency. Similarly, a recent study showed increased antisaccade errors during a well-known working memory task, the n-back task (Mitchell et al 2002). These authors observed non-linear increases in antisaccade errors, which paralleled increases in DLPFC activation observed in previous studies in response to the increasing working memory loads of this task (0-back, 1-back, 2-back). The authors concluded that the most likely neural site of interference of the n-back task with antisaccade performance might be the DLPFC. Further supporting the involvement

of the frontal lobe in antisaccade performance, Gooding and Tallent (2001) observed a relationship with a delayed-response working memory test.

A second line of research has implicated attentional processes in the antisaccade. Maruff and colleagues (1996; 1998) have pointed to the overlap in reflexive saccades and overt attentional shifts. Likewise, the first phase of the antisaccade is likely to involve a *covert* attentional shift (without eye movement) towards the target, in order to encode target location. It was shown that schizophrenia patients have difficulties inhibiting both overt and covert reflexive shifts of attention (Maruff et al 1996, 1998). Given the observation of intact disengagement of attention to cued targets it was argued that damage in schizophrenia may not be localised to parietal cortex but probably frontal attentional areas (Maruff et al 1998). More recently, it was observed that distracting (covert) attention briefly before an antisaccade eye movement increased or decreased its latency, depending on its timing (Kristjánsson et al 2001).

The processes required between the response inhibition and the initiation of a voluntary saccade in opposite direction were illuminated by Krappmann et al (1998). These processes may be referred to as sensorimotor coordinate transformations and require the transforming of spatial representations between sensory input and motor output. Likely neural correlates of sensorimotor coordinate transformations are frontal and parietal areas (Krappmann et al 1998; Leigh & Zee 1999).

Taken together, studies of working memory manipulation during task performance suggest a necessary prefrontal component in the generation and control of antisaccades, but not prosaccades. Other studies have pointed to the role of covert attentional processes and internal manipulation of spatial signals in the initiation of a motor response. It becomes clear from this brief discussion that successful antisaccade performance is a multivariate, cognitively (and neurally) complex task. The implications of this complexity for the endophenotype hypothesis will be discussed later (Section 9.3).

2.5.4.2.4 Neuropsychological Studies

The notion that the antisaccade might be a 'frontal' task has also been supported by a number of studies of standardised neuropsychological tests. The most robust finding is that of a correlation between error rate and WCST (Crawford et al 1995a, 1995b, 1996; Karoumi et al 1998b; Radant et al 1997; Rosse et al 1993; Tien et al 1996). Less

consistent evidence was obtained by Broerse et al (2001b), who found no strong associations of antisaccade errors with 'frontal' neuropsychological tests (e.g. Stroop test, TMT-B, verbal fluency), but instead with psychomotor speed (e.g. TMT-A).

The extent to which relationships between antisaccade and 'frontal' neuropsychological tests can be explained by overall intelligence (IQ), remains unclear, although most studies appear to suggest that antisaccade deficits remain after covarying (or matching) for IQ (Crawford et al 1995b, 1995a; Gooding & Tallent 2001; Nieman et al 2000; Tien et al 1996).

2.5.4.2.5 Neural Correlates – Conclusion

Researchers have attempted to pinpoint the neural correlates of antisaccade impairments in schizophrenia on the basis of findings from lesion, neuroimaging, cognitive and neuropsychological studies. It appears that the pattern of increased antisaccade error rate and prolonged latency in schizophrenia is most compatible with DLPFC and/or FEF damage, consistent with evidence from functional neuroimaging studies. Cognitive and neuropsychological studies of working memory and covert attention similarly suggest DLPFC and FEF involvement, respectively. However, functional imaging studies in the patient group, probably the best evidence of the neural correlates of antisaccade impairments, remain ambiguous, implying deficits in frontal (anterior cingulate, DLPFC) and subcortical areas (striatum).

2.5.4.3 Clinical Correlates

There is little consistent evidence of clinical symptom correlates of antisaccade performance; most schizophrenia studies do not report correlations with severity of symptoms. One study showed an association between increased antisaccade errors and conceptual disorganisation as well as motor retardation, with 14 other (positive, negative, cognitive and emotional) symptom scales showing no effect (Fukushima et al 1990c). Some (Crawford et al 1995b; Müller et al 1999; Tien et al 1996) but not other (Crawford et al 1996; Karoumi et al 1998b; Raemaekers et al 2002; Rosse et al 1993) authors observed a relationship with negative symptoms (SANS) and thought disorder (Tien et al 1996). Additionally, one study (Tien et al 1996) found fewer positive symptoms to be associated with more antisaccade errors.

Due to the relatively small number of studies of the antisaccade task in schizophrenia (compared to SPEM), the small samples used in some of these studies and the fact that

several studies did not report relationships with clinical symptom ratings, more research into the clinical correlates of antisaccade performance in schizophrenia is required. Given the evidence of an association between motor abnormalities and negative symptoms (Wolff & O'Driscoll 1999), future studies should focus on relationships between antisaccade performance and a) robust measures of negative symptoms and b) neurological soft signs.

2.5.4.4 Pharmacology

2.5.4.4.1 Treatment Effects

A small number of cross-sectional as well as longitudinal studies have examined drug effects on antisaccade performance. In the first systematic investigation of treated and untreated schizophrenic patients, Crawford et al (1995a, 1995b) demonstrated increased error rate and reduced gain in both unmedicated (but previously treated) and (typically) medicated patients. In post-hoc analyses of (lithium, neuroleptic, anti-parkinson, antidepressant, anxiolytic, anticonvulsant) medication effects, no relationships with error rate were obtained in a number of studies (Gooding & Tallent 2001; Maruff et al 1998; Sereno & Holzman 1995). No differences between risperidone and olanzapine treated first-episode patients were observed in one study (Nieman et al 2000). Müller et al (1999) observed that treatment over 1-4 months with a variety of typical and atypical antipsychotics did not affect antisaccade error rate.

Significant increases in error rate have been observed in patients with TD compared to patients without TD (Thaker et al 1989b, 1989c). Additionally, it was shown that the amount of GABA agonist-induced reductions in antisaccade errors were correlated with the amount of changes in dyskinesia ratings (Cassady et al 1992). The relationship between antisaccade and TD might be due to the effects of long-term antipsychotic treatment, possibly mediated by GABAergic neurons in the basal ganglia (Thaker et al 1989b, 1989c).

Two recent studies point to the existence of positive treatment effects on the error rate. In an elegant cross-over longitudinal design, Burke and Reveley (2002) demonstrated that patients had lower error rate under risperidone than typical antipsychotic treatment. This effect was not caused by practice effects as it was observed after 'switching' in both directions (risperidone → typical and typical → risperidone); it was also independent of changes in psychotic symptoms. As error rate worsened after a

switch from risperidone to typical antipsychotics, the improvement effected by risperidone treatment may be only temporary. Risperidone has previously been shown to improve core schizophrenic symptoms as well as neurocognitive deficits when compared to typical antipsychotics (Honey et al 1999), possibly due to its antagonism of 5-HT2 receptors. This hypothesis was supported by a recent study showing beneficial effects of the 5-HT2 antagonist cyproheptadine on antisaccade error rate and other 'frontal' neuropsychological tests (Chaudhry et al 2002). 5-HT2 antagonism is thought to activate dopaminergic neurons projecting to the prefrontal cortex, thus increasing DA turnover in this area (Friedman et al 1999).

It appears, therefore, that typical antipsychotic treatment has little effect on the key measure of antisaccade error rate but antagonism of 5-HT2 receptors (and, indirectly, action on prefrontal DA transmission) may improve performance. An alternative explanation of the findings by Burke and Reveley (2002), however is that reduced DA occupancy of the basal ganglia (and associated motor side effects) led to the observed improvements in error rate with risperidone. This finding might be compatible with the observed association between error rate and TD (Thaker et al 1989b, 1989c) and the involvement of the striatum in saccadic disinhibition in schizophrenia (Raemaekers et al 2002). The extent to which clinical doses of anticholinergic treatments affect antisaccade performance is unknown.

2.5.4.4.2 Effects of Pharmacological Manipulation in Healthy Individuals

Antisaccade errors are increased dose-dependently in healthy individuals by administration of a benzodiazepine drug, lorazepam (Green et al 2000; Green & King 1998). These impairments were associated with increased latency and slowed peak velocity and were specific to lorazepam; chlorpromazine and sertraline had no effect on error rate. In contrast, McCartan et al (2001) recently observed an increase in error rate with chlorpromazine.

These studies leave open the question of whether administration of typical antipsychotics causes antisaccade impairments in schizophrenia, and call for caution in the interpretation of findings from patient groups receiving benzodiazepines.

Evidence for an involvement of dopaminergic pathways in antisaccade performance was obtained in further studies. Dursun et al (1999) found that a small number of amphetamine (a drug of abuse acting on the DA system) users had higher error rates

than non-users. Duka and Lupp (1997) observed reduced antisaccade error rates in healthy individuals during monetary incentives (but no effects on other saccadic paradigms). Additionally, Duka and Lupp (1997) found that the dopaminergic agonist levodopa led to increased antisaccade errors in healthy volunteers. Error rate was also increased by overnight withdrawal from smoking in smokers and reduced by smoking before testing (Powell et al 2002). Due to the action of nicotine on dopaminergic pathways (Powell et al 2002), and as the same participants also displayed reduced responsiveness to incentive motivation during abstinence, it is likely that dopamine mediated motivational stimulus properties affect antisaccade performance. Relatedly, Klein et al (2002) showed improvements in antisaccade errors during methylphenidate administration (an indirect dopamine agonist often used in the treatment of ADHD) in adults with ADHD.

A role of dopamine in antisaccade performance is, of course, also consistent with the prefrontal neural correlates of this task (Section 2.5.4.2). It has, for example, been established that disruption of DA projections to prefrontal cortex impairs working memory performance (Friedman et al 1999); working memory relies on intact prefrontal cortex and is thought to be a key cognitive component of antisaccade performance. Similarly, acute administration of amphetamine (a dopamine agonist) *improves* prefrontal cortex function during WCST performance, a test shown to be correlated with antisaccade error rate (Daniel et al 1991; Rosse et al 1993).

2.5.4.5 *Validity as Endophenotype*

2.5.4.5.1 *Heritability*

A recent study observed considerable heritability of the antisaccade error rate in healthy, adolescent twins (Malone & Iacono 2002). Using biometric model-fitting analysis, additive genetic factors were found to account for more than half of the variance in antisaccade performance. Amongst non-genetic factors, the largest source of variance was found to be non-shared environmental factors.

2.5.4.5.2 *Temporal Stability*

Surprisingly few studies have investigated the temporal stability of antisaccade performance. Roy-Byrne et al (1995) reported non-significant intraclass correlations (ICC) for antisaccade error rate but good reliabilities for latency. Correlations for

reflexive saccade latency and SPEM measures in the same sample were considerable and significant. The failure to obtain significant ICC for antisaccade error rate might have been due to the restricted range of scores (the number of reflexive errors ranged from 0-2) and the very small sample (N=8). Similarly, Klein and Berg (2001) reported low reliability of antisaccade error rate, but good reliability of antisaccade latency over a four-week interval in twenty healthy individuals.

More positive results were obtained by Thaker et al (1989a), who mentioned (but did not provide detailed data of) test-retest reliabilities for antisaccade latency and error rate of r>0.75 over periods of one week to one year.

Apart from the parenthetic report by Thaker et al (1989a), no study has, therefore, demonstrated good antisaccade reliability in healthy individuals or schizophrenia patients. Such a demonstration is urgently required in order to confirm the antisaccade's status as a schizophrenia spectrum endophenotype.

2.5.4.5.3 Specificity to Schizophrenia

Antisaccade impairments are not specific to schizophrenia but are observed in a number of psychiatric and neurological disorders. Most antisaccade studies in these disorders may, for the purpose of this review, be classified into two categories: first, those relating to affective disorder; and second, those relating to disorders of fronto-striatal networks. In addition to these two disease categories, however, antisaccade abnormalities have also been discovered in conditions such as Alzheimer's disease (Abel et al 2002; Currie et al 1991) (although no clear evidence of abnormalities was obtained in dementia by Mulligan et al, 1996), persistent whiplash syndrome (Mosimann et al 2000), neurological impairments after cardiac surgery (BhaskerRao et al 1998) and autism (Minshew et al 1999).

The evidence from studies of patients with affective disorders is somewhat mixed, but appears to indicate that antisaccade errors are moderately increased in this disorder. This has been confirmed for both unipolar depressed, manic and bipolar patients (Crawford et al 1995a; Curtis et al 2001a; Gooding & Tallent 2001; Katsanis et al 1997; Sereno & Holzman 1995; Sweeney et al 1998b; Tien et al 1996), although normal performance has also been reported (Fukushima et al 1990c). Generally, performance levels of affective disorder patients fall between those of schizophrenia patients and

healthy controls, similar perhaps to those of first-degree relatives of schizophrenia patients (Curtis et al 2001a).

A number of studies have demonstrated that patients with presumed fronto-striatal atrophy have difficulties on the antisaccade task, as indexed by increases in error rate and, less consistently, prolongations of latency. These patient groups include OCD (Rosenberg et al 1997a, 1997b; Tien et al 1992b; however, see Maruff et al, 1999, for a failure to replicate increased antisaccade errors), attention deficit/hyperactivity disorder (Aman et al 1998; Mostofsky et al 2001a; Nigg et al 2002), Tourette's syndrome (Dursun et al 2000b; Farber et al 1999; Straube et al 1997), progressive supranuclear palsy (Pierrot-Deseilligny et al 1989; Vidailhet et al 1994) and Huntington's disease (these deficits appear to be independent of antipsychotic drug treatment; Dursun et al 2000a; Lasker & Zee 1997).

Antisaccade abnormalities in Tourette's syndrome may be due to co-morbidity with ADHD (Mostofsky et al 2001b) and people with cocaine dependence may have increased error rate if they display foraging behaviours related to drug craving (Rosse et al 1994). Conversely, Parkinson's disease patients have inconsistent antisaccade performance (Crevits et al 2000; Fukushima et al 1994; Lueck et al 1990; Vidailhet et al 1994).

These diverse patient groups are thought to have in common structural and functional neural abnormalities centred on prefrontal cortex and basal ganglia, in particular the striatum (caudate and putamen). While symptoms and course of illness clearly differs between these different disorders, findings of antisaccade deficits have most commonly been attributed to abnormalities in the fronto-striatal network. The precise abnormalities of fronto-striatal connections and possible overlap with the pathophysiology of schizophrenia remain to be investigated more closely.

This pattern of findings across a large number of studies clearly challenges the assumption of specificity relating to the antisaccade error rate as a schizophrenia endophenotype. However, a number of issues must first be considered before discarding the antisaccade task on these grounds.

First, little is known about the nature of antisaccade deficits in affective disorder patients. It remains to be investigated whether heightened antisaccade error rate is a trait or state measure in this population and whether their first-degree relatives also share this abnormality. A first hint for differences in the type of antisaccade impairments in schizophrenia and bipolar disorder comes from studies suggesting

different neurocognitive correlates of the error rate in bipolar and schizophrenic patients (Gooding & Tallent 2001; Sereno & Holzman 1995; Tien et al 1996).

Second, antisaccade impairments in non-schizophrenic (especially affective disorder) patient groups appear to be of modest magnitude (performance levels often fall between those of schizophrenia patients and healthy people) and less consistent, as some failures to replicate have been observed. These failures to replicate contrast with the very robust observation of antisaccade impairments in schizophrenia across a large number of studies.

Third, a shared neural substrate at a macro-level (e.g. 'prefrontal-striatal dysfunction') between schizophrenia and other disorders may not in itself be damaging to the validity of the antisaccade endophenotype in schizophrenia research. The precise neural deficits within these (large) structures remain to be investigated. With regard to schizophrenia and bipolar disorder in particular, recent views hold that there may be a shared genetic basis of these two disorders, in addition to common clinical and neurocognitive features (Maier et al 1999). In contrast, however, antisaccade impairments do not appear to be a genetic marker for Huntington's disease. Rothlind et al (1993) found no differences between presumed Huntington's disease gene carriers and non-carriers on antisaccade performance; this finding, of course, contrasts with the evidence of antisaccade impairments in the family members of schizophrenia patients (Section 2.5.4.5.4).

2.5.4.5.4 Family and Twin Studies

Since the first observation of increased antisaccade error rate in first-degree relatives of schizophrenia patients (Clementz et al 1994), a number of studies have replicated this finding in parents, siblings and offspring (Curtis et al 2001a, 2001b; Karoumi et al 2001; Katsanis et al 1997; Ross et al 1998d; Thaker et al 2000). However, two studies failed to find statistically significant differences in error rate between relatives and healthy controls (Crawford et al 1998; Thaker et al 1996a).

A number of additional findings relating to the validity of the antisaccade endophenotype have emerged from these family studies. First, increased error rate has been observed in relatives with and without psychiatric symptoms, suggesting an independence of acute psychiatric symptoms (Curtis et al 2001a; Katsanis et al 1997). Second, antisaccade errors, like SPEM performance scores, show a familial pattern: Relatives of patients with high error rate have higher error rate than relatives of patients

with low error rate (Crawford et al 1998; Curtis et al 2001a). Third, antisaccade latency is not generally found to be prolonged in first-degree relatives (Clementz et al 1994; Crawford et al 1998; Karoumi et al 2001; Katsanis et al 1997; McDowell & Clementz 1997; Ross et al 1998d); however, see (McDowell et al 1999; Thaker et al 1996a, 2000). Fourth, deficits appear to be most severe in relatives with schizophrenia spectrum symptoms (Thaker et al 2000). Fifth, performance may be worse in multiplex than simplex schizophrenia family members (McDowell et al 1999), suggesting an effect of increased genetic loading (or familiality).

2.5.4.5.5 First-episode Psychosis

Antisaccade impairments have been replicated in samples of first-episode patients, supporting the notion that they might be intrinsic to the disease process or the genetic disposition. Hutton et al (1998a) observed substantially increased error rates in both drug-naïve and neuroleptic treated patients. Treated but not drug-naïve patients had reduced primary antisaccade gain; final eye position, however, did not differ between groups. Drug-naïve patients had longer latency than treated patients and healthy controls. Nieman et al (2000) observed similar increases in error rate in the patient group. Additionally, patients had reduced primary gain.

2.5.4.5.6 Schizotypy

Increases in error rate, but not latency, have been related to higher scores on psychometric measures of schizotypy in university students, further supporting the association between this measure and the schizophrenia spectrum (Gooding 1999; Larrison et al 2000; O'Driscoll et al 1998).

The scales that were used in these studies focussed on positive schizotypal signs and symptoms, including the Chapmans' Perceptual Aberration (Chapman et al 1980) and Magical Ideation (Eckblad & Chapman 1983) scales as well as the Rust Inventory of Schizotypal Cognitions (Rust 1989), but also the Schizotypal Personality Questionnaire (Raine 1991) and the Chapmans' Social Anhedonia Scale (Mishlove & Chapman 1985). This pattern of findings suggests antisaccade errors are associated with both positive and negative dimensions of schizotypy; however, the negative dimension has not been explored in great depth.

A recent study failed to obtain differences between healthy schizotypy high and low scorers (Klein et al 2000c), possibly due to methodological reasons.[14] The only investigation of the antisaccade in people with schizotypal personality disorder (SPD) observed no statistically significant differences compared to a control group (Brenner et al 2001). However, as Brenner et al (2001) claimed, a subgroup of SPD patients had a significantly increased error rate.

Effects of *trait* emotionality on the association between antisaccade impairments and schizotypy have not been explored. O'Driscoll et al (1998) observed that high scorers on the Chapmans' Perceptual Aberration scale also had higher scores on measures of *state* anxiety and depression (Beck Depression Inventory; BDI) and that there was a correlation between BDI scores and antisaccade errors. Importantly, however, neither of these measures fully accounted for the relationship between SPEM and antisaccade dysfunction and positive schizotypal traits.[15]

2.5.4.5.7 Molecular Genetic Studies

Only one molecular genetic study to date has used the antisaccade task as an endophenotype. This study combined the error rate with a measure of sensorimotor gating (from the P50 event-related potentials paradigm) into a "composite inhibitory phenotype" (p. 544) and observed linkage to a locus on chromosome 22q11-q12 in eight multiplex schizophrenia families (Myles-Worsley et al 1999). Importantly, this chromosomal region has been implicated in schizophrenia linkage as well as other genetic studies, thus providing suggestive evidence of an important susceptibility locus (Egan et al 2001b; Jorgensen et al 2002).

Clearly, given the otherwise promising evidence of the antisaccade error rate as a schizophrenia endophenotype, further linkage and other molecular genetic studies are required.

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[14] For a more detailed discussion of the Klein et al (2000c) study, see Section 7.5.3.

[15] Shafiq-Antonacci et al (1999) observed a correlation between heightened trait anxiety and increased antisaccade errors, however, did not include measures of schizotypy.

2.6 Prosaccade Eye Movements

2.6.1 Definition

A prosaccade, or reflexive saccade, is a rapid eye movement in response to a (visual) stimulus of abrupt onset. It serves to bring the image of an object of interest onto the fovea. As prosaccade performance has been found to be unimpaired in schizophrenia in a number of studies, and due to the physiological similarity with the antisaccade, this task is often considered a 'control' condition for the antisaccade task rather than a genetic marker in schizophrenia spectrum research and will, therefore, be considered only relatively briefly. The terms *prosaccade* and *reflexive saccade* are used interchangeably in this thesis, as both refer to a reflex-like saccadic eye movements in response to a visual stimulus. The term *pro*saccade further underscores the methodological differences between the antisaccade and prosaccade tasks.

2.6.2 Prosaccade Stimulus

2.6.2.1 Hardware

Stimulus display methods in the prosaccade task mirror those of the antisaccade, using computer monitors (Curtis et al 2001a; Klein et al 2000c), LEDs (Crawford et al 1998; Fukushima et al 1990a; Hutton et al 1998a; Karoumi et al 2001; Schwartz et al 1995a) and laser targets (Maruff et al 1998). Physical targets properties are likewise similar to those of the antisaccade, consisting of common shapes, such as squares or dots.

2.6.2.2 Stimulus Properties

The most commonly used laboratory-based horizontal prosaccade trial begins with the target in the central location (0°), which then moves abruptly horizontally to one of a number of peripheral locations. *Instructions* to participants are to follow the target movement, with their eyes, as accurately and quickly as possible.

About 20-60 trials are carried out in a standard prosaccade task (Broerse et al 2001b; Crawford et al 1998; Karoumi et al 1998b; Klein et al 2000c; Thaker et al 2000). Some researchers have presented an auditory stimulus (e.g. buzzer) simultaneously with the peripheral target (Burke & Reveley 2002; Crawford et al 1998; Hutton et al 1998a;

Karoumi et al 1998b; Larrison et al 2000). Different *peripheral target amplitudes* have been used, typically ranging between ±5° and ±30°.

Some researchers have used random rather than fixed horizontal target locations (Müller et al 1999; Straube et al 1999). This specification has the advantage of making targets completely spatially unpredictable; however, it makes analysis of specific target amplitudes difficult. As target amplitude might affect between-group differences (Schreiber et al 1997) it may be beneficial to use at least two different visual angles on either side of the central fixation point, possibly dividing each hemi-field equally. This allows the comparison of saccades of small and large amplitude.

Regarding the *temporal characteristics* of prosaccade targets, a number of studies have adopted a fixed duration of central fixation point presentation, typically in the range of 500-1,000ms (Broerse et al 2001b; Crawford et al 1998; Hutton et al 1998a). Other tasks have employed randomised central target durations, most commonly ranging between 1,000ms and 3,000ms (Fukushima et al 1990c; Karoumi et al 1998b; Levin et al 1981a; Sweeney et al 1997; Thaker et al 2000), thereby making target appearance temporally unpredictable. Peripheral target durations are usually fixed for about 1,000-2,000ms.

A number of variations of the standard prosaccade paradigm have been employed in schizophrenia spectrum research. The gap task introduces a temporal gap of about 200ms between fixation point and peripheral target appearance (Cavegn & Biscaldi 1996; Fischer 1986; Wenban-Smith & Findlay 1991). This gap has been shown to reduce saccadic latency, produce an increased number of so-called express saccades (latency<100ms) and induce the so-called gap negativity, i.e. a negative electrical brain wave peaking 200ms after the fixation point has disappeared. Conversely, in the overlap task the central and peripheral targets overlap by about 200ms, leading to increased latency (Cavegn & Biscaldi 1996; Fischer 1986; Fischer et al 1997; Klein et al 2000c; Reuter-Lorenz et al 1991; Spantekow et al 1999; Wenban-Smith & Findlay 1991).

Some researchers (Clementz et al 1994; Schmid-Burgk et al 1983; Schreiber et al 1995) have used target movements slightly departing from the regular prosaccade task. In these studies, the target stepped (quasi-)randomly between a number of horizontal target locations. Thus, a trial did not consist of a central-peripheral step, but of steps in either horizontal direction, foveofugal or foveopetal. This task has the advantage of making the target appearance spatially unpredictable. However, as it has been shown

that saccadic metrics differ between foveofugal and foveopetal steps (Leigh & Zee 1999), a (quasi-)random selection of such trials increases the heterogeneity of the task.

2.6.3 Prosaccade Scoring

The two most commonly used measures of prosaccade performance in schizophrenia spectrum research are those of latency and gain. Criteria of minimum amplitude (2°-5°; Broerse et al 2001b; Gooding 1999; Straube et al 1999), latency (about 70-100ms; Fischer et al 1997) and velocity at saccade initiation (5°-30°/s; Clementz et al 1994; Crawford et al 1998; Sweeney et al 1997) have been used in the automatic detection of saccades.

Primary saccade gain is calculated as outlined above (Section 2.5.3). A gain score of 100%, therefore, reflects perfect primary saccade accuracy. Additionally, final eye position has been reported, as defined above (Crawford et al 1995a, 1995b, 1998; Hutton et al 2000). The *latency* reflects the time, in milliseconds, between target appearance and saccade initiation.

In addition to gain and latency, some previous studies have reported measures of average and peak *velocity* and *duration* (Clementz et al 1994; Fukushima et al 1994; Levin et al 1981a, 1982b; Sweeney et al 1997; Thaker et al 2000). Reflexive saccade peak velocity has been widely studied in pharmacological research, due to its sensitivity to CNS active pharmacological agents (Griffiths et al 1984). Most studies of schizophrenia spectrum participants, however, have not included measures of velocity.

2.6.4 Prosaccade Eye Movements in the Schizophrenia Spectrum

2.6.4.1 Behavioural Characterisation of Prosaccade Eye Movements in Schizophrenia Patients

According to some (e.g. McDowell & Clementz 2001), prosaccade performance is *unimpaired* in patients with schizophrenia. This claim is supported by numerous studies demonstrating normal latency (Clementz et al 1994; Couch & Fox 1934; Crawford et al 1995a, 1995b, 1998; Curtis et al 2001a; Diefendorf & Dodge 1908; Karoumi et al 1998b; Klein et al 2000b; Krebs et al 2001; Maruff et al 1998; Matsue et al 1994b; Müller et al 1999; Schwartz et al 1995a; Sweeney et al 1997), accuracy (Clementz et al 1994; Crawford et al 1995a, 1995b, 1998; Hommer et al 1991; Karoumi

et al 1998b, 2001; Krebs et al 2001; Levin et al 1981a, 1982b; Maruff et al 1998; Müller et al 1999; Park & Holzman 1992; Sweeney et al 1997; Yee et al 1987) and velocity (Clementz et al 1994; Levin et al 1981a, 1982b; Mather & Putchat 1982; Sweeney et al 1997) in this patient group. Additionally, the relationship between saccade amplitude and duration as well as peak velocity (the *main sequence;* Leigh & Zee 1999) has been shown to be comparable to healthy individuals (Clementz et al 1994; Fukushima et al 1990b; Levin et al 1981a, 1982b).

Studies of the gap prosaccade task have indicated that schizophrenia patients are able to display reduced latency and increased frequency of express saccades compared to non-overlap stimuli similar to healthy individuals (Clementz 1996b; Matsue et al 1994a; Sereno & Holzman 1993). However, Currie et al (1993) observed fewer express saccades in the patient group.

Based on these findings it is often claimed that the schizophrenic disease process spares the basic saccadic neural circuitry and the prosaccade task may, therefore, be used as a control condition for the cognitively more complex antisaccade task (e.g. McDowell & Clementz 2001). Unimpaired prosaccade performance has also been interpreted as indicating, in addition to an intact basic saccadic neural circuitry, sufficient levels of motivation and compliance, supporting the specificity across oculomotor tasks of antisaccade (and SPEM) impairments.

While this line of reasoning is important and supported by considerable evidence, there is also evidence of impaired prosaccades in schizophrenia. Patients with schizophrenia have been shown to display longer prosaccade latency (Evans & Schwartz 1997; Mackert & Flechtner 1989), decreased and increased peak velocity (Cegalis et al 1982, 1983; Fukushima et al 1990a, 1990b, 1990c; Mahlberg et al 2001; Schwartz et al 1995a) and reduced accuracy (Cegalis et al 1982; Mather & Putchat 1982; Schmid-Burgk et al 1982, 1983; Schwartz et al 1995a).

The reasons for these discrepancies between studies are unclear, but may involve treatment factors or stimulus characteristics. One hint concerns stimulus amplitude: Two independent investigations (Schreiber et al 1997; Schwartz et al 1995a) observed reduced saccadic gain in schizophrenia spectrum individuals only for large-amplitude targets, not commonly used in other studies. It is, therefore, a possibility that saccadic deficits in the schizophrenia spectrum are restricted to large saccades. In concordance with this assumption, Levin et al (1981a) observed a trend for longer latency to larger

amplitude targets in schizophrenia. Clearly, the claim of *unimpaired* prosaccades in schizophrenia has to be treated with caution.

2.6.4.2 Cognitive and Neural Basis of Prosaccade Eye Movements in Schizophrenia Patients

Given the inconsistency of prosaccades performance in schizophrenia it is difficult to deduce a specific neural or cognitive substrate of impairments when seen. Indeed, a number of writers have argued that, given the behavioural data, the basic saccadic neural circuitry is likely to be intact (e.g. McDowell & Clementz 2001). Cortical areas most likely involved in triggering reflexive saccades are FEF and PEF (Gaymard et al 1998a; Pierrot-Deseilligny et al 1995). Patients with FEF lesions have increased latency of voluntary saccades, but not consistently of simple reflexive saccades. PEF damage, on the other hand, appears to prolong latency of reflexive saccades (Pierrot-Deseilligny et al 1991). Neural projections important for the generation of reflexive saccades are those from PEF to FEF and from both PEF and FEF to the SC; the SC (as well as the FEF) projects to the brainstem reticular formation. The cerebellar vermis, in concert with other areas, plays a crucial role in determining saccadic accuracy (Barash et al 1999; Bötzel et al 1993; Ettinger et al 2002; Hashimoto & Ohtsuka 1995; Takagi et al 1998; Vahedi et al 1995).

Observations of *normal* prosaccade latency and accuracy in some schizophrenia studies might thus argue for an intact saccadic neural circuitry, including brainstem, SC, cerebellum and PPC. This assumption is further supported by a functional neuroimaging study (McDowell et al 2002) already discussed, which obtained normal levels of activation in FEF, SEF and PPC during prosaccade performance in schizophrenia patients. Raemaekers et al (2002), on the other hand, observed slightly reduced – but not absent – activation in visual cortex, FEF, SEF and PEF in schizophrenia patients compared to controls.

Findings of impaired saccadic accuracy in some studies (Cegalis et al 1982; Mather & Putchat 1982; Schmid-Burgk et al 1982, 1983; Schwartz et al 1995a) may at first be interpreted as indicating subtle impairments of cerebellar vermis. It is, however, important to note the difference between the hypometric saccades of lesioned humans (and nonhuman primates) (Barash et al 1999; Bötzel et al 1993; Takagi et al 1998; Vahedi et al 1995) and people with schizophrenia. Individuals with cerebellar or brainstem lesions are usually *unable* to perform spatially accurate saccades (Schmid-

Burgk et al 1983; Schreiber et al 1997). Patients with schizophrenia, however, tend to make saccades of variable amplitudes, some of which are hypometric, resulting in overall between-group differences in some studies. Therefore, the neural substrate of reduced saccadic accuracy in schizophrenia is unlikely to be found in the brainstem or cerebellum, but may possibly be localised to cortical areas such as FEF (Schreiber et al 1997) or PEF (Gaymard et al 1998a).

Studies of gap prosaccades have shown that lesions to the FEF, SC and PPC disrupt the generation of express saccades. Based on observations of normal or increased frequency of express saccades in schizophrenia patients, McDowell and Clementz (McDowell & Clementz 2001) argued that these brain areas are, therefore, unlikely to be impaired in schizophrenia. Additionally, as Clementz (1996b) argued, damage to DLPFC can lead to an *increased* generation of express saccades, suggesting DPLFC damage in schizophrenia. Conflicting with this conclusion is, of course, the observation of fewer express saccades in schizophrenia by some researchers (Currie et al 1993).

Cognitive interpretations of prolonged prosaccade latency in schizophrenia have drawn on attentional processes (Mackert & Flechtner 1989), such as impairments in the disengagement of covert attention from the central fixation target (Evans & Schwartz 1997). Similarly, Schwartz and Evans (1999) could show that reflexive saccade latency in schizophrenia patients increased during the introduction of a peripheral distractor, likely due to the interference with overt as well as covert attentional processes. Attentional hypotheses of problems in saccade initiation are in accord with studies showing overlap in the neural networks mediating covert and overt shifts of attention (Beauchamp et al 2001; Nobre et al 2000).

Taken together, evidence from studies of reflexive saccade control in schizophrenia patients argues for relatively intact basic saccadic neural circuitry, including brainstem and cerebellum, with inconsistent evidence concerning the roles of FEF and PPC.

2.6.4.3 Clinical Correlates

Prosaccade metrics are not consistently correlated with clinical symptom ratings in schizophrenia patients (Clementz 1996b; Evans & Schwartz 1997; Karoumi et al 2001; Mackert & Flechtner 1989; Mahlberg et al 2001).

2.6.4.4 Treatment Effects in Schizophrenia and Pharmacological Manipulation in Healthy Individuals

A large variety of pharmacological compounds interfere with saccadic control in healthy individuals. Indeed, the susceptibility of prosaccades to centrally mediated drug effects makes this task an ideal tool for the detection of CNS activity of novel compounds (Griffiths et al 1984). Compounds with relevance to schizophrenia research which disturb prosaccade control include benzodiazepines, opiates, antipsychotics, monoamine oxidase inhibitors, alcohol and others (Blekher et al 2002; Griffiths et al 1984; Roy-Byrne et al 1993; Schmid-Burgk et al 1982).

A longitudinal study of risperidone treatment in schizophrenia patients showed adverse effects of this drug on latency, peak velocity and accuracy (Sweeney et al 1997), a finding later partly replicated in a cross-sectional design (Nieman et al 2000). However, Burke and Reveley (2002) found no differences between risperidone and typical antipsychotic treated patients. Curtis et al (2001a) observed reduced prosaccade gain in patients taking anxiolytics, but no effects of antipsychotics or anticholinergics. Other studies have found no associations between prosaccade metrics and treatment variables (Clementz 1996b; Crawford et al 1995a; Karoumi et al 2001; Mahlberg et al 2001; Schmid-Burgk et al 1982).

Given the effects of pharmacological compounds on prosaccades demonstrated in some studies, research addressing comparisons between schizophrenia patients and healthy individuals not adjusting for these effects have to be treated with caution.

2.6.4.5 Validity as Endophenotype

2.6.4.5.1 *Heritability*

In a study already described (Section 2.3.5.5.1), Bell et al (1994) investigated prosaccade performance in eight pairs of healthy twins and found ICC between twins of 0.64 (latency) and 0.83 (gain). However, the absence of a group of dizygotic twins makes the assessment of heritabilities impossible. Blekher, Gale and colleagues (Blekher et al 1998; Gale et al 1996) observed high within-twin pair correlations for prosaccade latency, accuracy and peak velocity in MZ but not in DZ twins and suggested that variance might be best accounted for by multiple genes and/or prenatal environmental factors; the MZ twins were the same as those studied by Bell et al (1994).

2.6.4.5.2 Temporal Stability

Measures of prosaccade latency, accuracy and amplitude-duration as well as amplitude-velocity relationships are stable over durations ranging from several weeks to two years (Iacono & Lykken 1979a; Versino et al 1993; Wilson et al 1993).

2.6.4.5.3 Specificity to Schizophrenia

Reflexive saccade eye movement abnormalities are observed in a number of neurological conditions (Leigh & Zee 1999). Patterns of abnormalities in these patient groups include prolonged latency and reduced accuracy, similar to some schizophrenia patients. However, many individuals with neurological disorders or acquired brain lesions also display evidence of main sequence perturbances, not observed in schizophrenia. Additionally, as outlined above, many individuals with acquired brain damage or neurological disorders appear to have more severe, and qualitatively different, abnormalities than people with schizophrenia.

2.6.4.5.4 Family and Twin Studies

While most studies have found normal prosaccade performance in first-degree relatives of schizophrenia patients (Crawford et al 1998; Curtis et al 2001a; Karoumi et al 2001; Thaker et al 2000), there are some reports to the contrary. Hypometric (reduced accuracy) prosaccades have been observed in a mixed sample of first-degree relatives (Schreiber et al 1995) as well as adolescent offspring of schizophrenia patients (Mather 1985; Schreiber et al 1997). Interestingly, in the Schreiber et al (1997) study, relatives showed hypometric saccades most reliably to large amplitude targets (>30°), mirroring those observed in the patient group (Section 2.6.4.1). Most previous studies have not used such large amplitudes, possibly explaining the failures to obtain this finding.

2.6.4.5.5 First-episode Psychosis

Prosaccade metrics appear to be relatively normal in patients in their first psychotic episode (Hutton et al 1998a, 2002), although Nieman et al (2000) observed prolonged latency in risperidone treated first-episode patients (suggesting a treatment effect; see Section 2.6.4.4).

2.6.4.5.6 SCHIZOTYPY

There is no consistent evidence of an association between levels of schizotypy and prosaccade metrics in healthy individuals (Gooding 1999; Klein et al 2000c; Larrison et al 2000), although Iacono and Lykken (1979b) observed an association between longer latency and higher scores on the psychoticism dimension (Eysenck & Eysenck 1976).

2.6.4.5.7 MOLECULAR GENETIC STUDIES

No study to date has employed the prosaccade task as a phenotype in schizophrenia linkage studies.

2.7 Other Eye Movement Tasks

In addition to the SPEM, fixation, antisaccade and prosaccade tasks, a number of other experimental paradigms involving the recording of eye movements have been used in schizophrenia spectrum research. Some of these (e.g. predictive saccade and memory-guided saccade tasks) are similar to the tasks discussed above in terms of stimuli and procedure; others focus on the processing of complex semantic stimuli.

The predictive saccade task involves a spatially as well as temporally predictable visual target stepping between two peripheral locations (e.g. ±12°). In this task, predictive saccadic behaviour is usually established in healthy individuals after a few target oscillations. Predictive behaviour is indicated by reduced saccadic latency and an increased frequency of 'anticipatory saccades'; these are saccades made not in response to but in anticipation of the target movement (e.g. latency<100ms).

People with schizophrenia appear to be as able as healthy individuals to make anticipatory saccades (Litman et al 1994); indeed, some reports observed faster latency and greater frequency of anticipatory saccades in schizophrenia (Karoumi et al 1998a; McDowell et al 1996). The second characteristic of predictive saccade performance in schizophrenia is that of reduced amplitude saccades, or hypometria (Hommer et al 1991; Hutton et al 2001b; Krebs et al 2001; McDowell et al 1996). This finding was initially thought to be mediated by typical neuroleptic drug treatment (as similar deficits were observed in Parkinson's disease; Crawford et al 1995b, 1995a; Hommer et al 1991); however, a recent report observed hypometric predictive saccades in never-medicated patients, suggesting a working memory deficit (Hutton et al 2001b). Predictive saccades have not yet been examined closely in first-degree relatives, making

it difficult to estimate whether this task might constitute an oculomotor endophenotype. In one investigation, Clementz et al (1994) did not find impairments.

In the memory-guided saccade, or oculomotor delayed response task, participants are presented with a central fixation point. During fixation of this target a peripheral target appears briefly (e.g. 500ms); participants are instructed not to saccade towards this target. Upon disappearance of the central target participants are required to initiate a saccade to the remembered location of the peripheral target. This task, therefore, requires the inhibition of a reflexive saccade towards the saccade, the covert encoding and memorisation of the spatial location of the peripheral target and the initiation of a voluntary saccade towards the remembered target location.

People with schizophrenia tend to make an increased number of reflexive errors to target (Crawford et al 1995a, 1995b; McDowell & Clementz 1996), consistent with the demonstration of reflexive errors on the antisaccade task. Additionally, memory-guided saccades in schizophrenia tend to be of prolonged latency and reduced accuracy (i.e. hypometric) (Everling et al 1996; Krappmann & Everling 1998; McDowell & Clementz 1996; Park & Holzman 1992). Similar deficits of reflexive errors and hypometric saccades were observed in first-degree relatives of schizophrenia patients (McDowell et al 2001; Park et al 1995). On the basis of these observations, and as memory-guided saccade task performance appears to rely on DLPFC integrity (Pierrot-Deseilligny et al 1995), it has been suggested that this task might be useful to study both the pathophysiology and genetics of schizophrenia (McDowell et al 2001; Park et al 1995).

In contrast to the predictive and memory-guided saccade tasks as well as the tasks studied in this thesis, further paradigms involve the recording of eye movements while participants are viewing semantically meaningful stimuli, such as pictures, complex shapes, or faces.

A number of authors have noted visual scan paths of reduced area and fewer but longer fixation periods in people with schizophrenia when viewing drawings or complex figures (Kojima et al 1992; Kojima et al 2001; Matsushima et al 1992). Scan paths are the records of eye movements made by an individual while freely viewing a stimulus over a certain period of time. Associations with psychiatric symptoms have been described (Gaebel 1989; Tsunoda et al 1992). Gaebel (1989) observed *excessive* scanning in patients with predominantly positive symptoms and *reduced* scanning (with longer fixation) in patients with predominantly negative symptoms. Tsunoda et al (1992)

argued that the assessment of scanning eye movements may be a good and objective measure of symptom severity in schizophrenia. Matsushima et al (1998) observed good sensitivity and specificity of exploratory eye movement abnormalities to schizophrenia and argued that these abnormalities point to the existence of pathological visual information processing in schizophrenia.

Exploratory eye movements to complex stimuli may, therefore, be studied profitably to detect deficits in schizophrenia. However, the cognitive and neural correlates of scanning eye movements in response to these artificial and complex stimuli, as well as their relevance to the genetics of schizophrenia, remain unclear.

Other studies have used images of human faces as stimuli. Unlike artificial geometric figures, faces have the advantage of being naturally and evolutionarily salient stimuli, with evidence of specific face-processing areas (Bruce & Young 1998). Studies of visual scanning of face stimuli in schizophrenia patients have demonstrated reduced fixation periods, fewer fixations, reduced scan paths and increased processing of extra-facial features (Gordon et al 1992; Loughland et al 2002; Manor et al 1999; Phillips & David 1997, 1998).

More recently, the neural correlates of impaired face processing in schizophrenia have been studied. Phillips et al (1999) observed differential neural responses associated with incorrect classification of facial emotions in paranoid and non-paranoid patients with schizophrenia. Non-paranoid patients were more likely to categorise faces expressing disgust as fearful or angry and displayed greater activation of amygdala (typically associated with fearful stimuli).

To conclude, studies of eye movements during face processing have the advantage of using graphic representations of naturally occurring stimuli. Due to the importance of face processing in humans in a variety of social contexts, schizophrenia studies may build on a large body of knowledge concerning the cognitive and neural mechanisms underlying face processing (Bruce & Young 1998). As facial stimuli can be manipulated easily to depict mood states (happiness, sadness, disgust, etc.), these paradigms may also be used to study affective processing in schizophrenia.

2.8 Relationship between Smooth Pursuit and Antisaccade

One issue that has received relatively little attention is that of the relationship between SPEM accuracy and antisaccade errors in the schizophrenia spectrum. The majority of

studies of the SPEM and antisaccade tasks in the schizophrenia spectrum have focussed on either task, but have rarely combined both. Previous studies addressing this question remain inconclusive. While some studies (Matsue et al 1994b; Schlenker & Cohen 1995; Sereno & Holzman 1995) found higher antisaccade error rate to be associated with worse SPEM performance, others did not (Hutton et al 1998a; Nkam et al 2001; Thaker et al 1989c; Tien et al 1996).

It thus remains to be investigated conclusively whether SPEM and antisaccade deficits independently characterise schizophrenia patients or whether the two tasks may be used interchangeably due to shared variance. Investigating the relationship between SPEM and antisaccade performance is of interest as it has been suggested that both measures may be schizophrenia endophenotypes tapping frontal function (Calkins & Iacono 2000).

If performance on the two measures was indeed *unrelated* in schizophrenia patients and healthy individuals, and patients' performance was characterised by deficits on both tasks, then a combination of the two tasks might improve the statistical separation between the patient and a control group, with possible implications for the diagnostic process (Arolt et al 1998; Robins & Guze 1970; Sponheim et al 2001). Statistical overlap between two conceptually related eye movement measures, on the other hand, would suggest that these measures might be profitably combined in the development of a 'composite oculomotor endophenotype' for linkage studies (cf. Cadenhead et al 2002; Myles-Worsley et al 1999). Genetic linkage requires labelling individuals as 'affected' or 'unaffected'. In many diseases this dichotomy is achieved through the combined observation of a number of diagnostic signs and symptoms (Ott 1991). Similarly, an endophenotype could consist, not of the dichotomisation of a single variable (e.g. antisaccade error rate), but of a combination of two or more such variables (e.g. antisaccade error rate and saccadic frequency during smooth pursuit). A composite (oculomotor) endophenotype would thus have the advantage of providing a more reliable identification of individuals as affected or unaffected (Ott 1991).

Given the evidence from some studies (Matsue et al 1994b; Schlenker & Cohen 1995; Sereno & Holzman 1995) of a relationship between SPEM and antisaccade performance, and the putative shared frontal involvement in both tasks (Calkins & Iacono 2000; Clementz 1998; Levin 1984; MacAvoy & Bruce 1995), it may be argued that these two measures are to some extent related. More research, however, is required to fully characterise this relationship. In particular, a number of previous studies have used

non-specific SPEM measures. It is a possibility that the use of specific measures would facilitate the study of this relationship, in particular if certain specific measures were more closely related (biologically) to antisaccade errors than overall smooth pursuit performance.

One particularly interesting lead in the literature stems from research into the anticipatory saccade during smooth pursuit (Rosenberg et al 1997c; Ross et al 1998e). This type of intrusive saccade has been described as a failure of inhibitory processes due to frontal dysfunction (Sweeney et al 1994a), a feature it shares at face level with antisaccade errors. This putative shared inhibitory component underlying both types of saccades suggests that the relationship between these measures in schizophrenia spectrum populations would deserve to be explored; no study to date has observed an association. However, there are, of course, phenomenological differences between anticipatory saccades and antisaccade errors, including the role of the visual target: Anticipatory saccades during smooth pursuit occur *away from* and in anticipation of the physical target, whereas in the antisaccade task errors reflect a reflexive response *towards* the target. Therefore, differences in the cognitive and neural substrates may be observed in addition to a possibly shared inhibitory component.

A similar approach to combining neurocognitive schizophrenia endophenotypes was adopted recently by Myles-Worsley and colleagues (1999). These researchers combined antisaccade errors and a measure of inhibitory function derived from an event-related paradigm, the P50 suppression, into a "composite inhibitory phenotype" (p. 544). This phenotype showed linkage to a locus on chromosome 22q11-q12, supporting the validity of combining conceptually related measures in the identification of schizophrenia genes. The relationship between antisaccade errors and P50 suppression (but not prepulse inhibition, another measure of inhibitory function) has subsequently been confirmed (Cadenhead et al 2002).

2.9 Evaluation of the Validity of the Smooth Pursuit and Antisaccade Tasks as Schizophrenia Endophenotypes

A large body of evidence relating to the endophenotypic nature of oculomotor tasks has been reviewed. The key conclusions from this body of evidence may be as follows.

- The most promising oculomotor schizophrenia endophenotypes are those of reduced smooth pursuit accuracy and increased antisaccade errors. Reduced

smooth pursuit accuracy in the schizophrenia spectrum appears to be best characterised by reduced gain and increased frequency of (catch-up and anticipatory) saccades. Back-up saccades and square-wave jerks during smooth pursuit as well as antisaccade latency are less promising endophenotypes; antisaccade gain has not been studied sufficiently.

- Smooth pursuit and antisaccade deficits are argued by most researchers to be relatively specific on the background of less consistent impairments in visual fixation and reflexive saccades, making the existence of a generalised oculomotor deficit in schizophrenia unlikely.

- Deficits in the patient group are unlikely to be entirely due to factors such as typical neuroleptic treatment, hospitalisation, disease chronicity or psychiatric symptom severity.

- SPEM and antisaccade deficits in the patient group are at present most parsimoniously explained by frontal and fronto-striatal dysfunction, respectively.

- SPEM and antisaccade deficits in schizophrenia show familial patterns compatible with genetic influence; both measures have good heritability.

- Individuals with subclinical levels of schizophrenia spectrum symptoms show subtle smooth pursuit and antisaccade impairments, similar in kind to those of patients with schizophrenia.

- Preliminary evidence links SPEM and antisaccade deficits to genetic loci on chromosomes 6p21 and 22q11-q12, respectively.

2.10 Plan of Investigations and Hypotheses

This review has identified a number of gaps in the literature concerning the validity of the SPEM and antisaccade tasks as schizophrenia spectrum endophenotypes. The empirical investigations of this thesis will attempt to fill some of these gaps.

First, before proceeding to address questions concerning the behavioural characteristics of the proposed oculomotor endophenotypes in schizophrenia spectrum populations, a thorough analysis of their reliability is needed. As outlined above, despite reports of good temporal stability of SPEM performance, evidence concerning the antisaccade task

is much less consistent. Thus, one aim of Study I is to investigate the temporal stability of eye movement tasks used in this thesis (Chapter 4). Additionally, reliability characteristics of the methods employed here, such as inter- and intra-rater reliability, as well as internal consistency of performance levels will be considered. Finally, because two sets of eye movement tasks are used in this research, the concurrent validity of these will be addressed. On the basis of the assumed temporal stability of neurocognitive endophenotypes, both SPEM and antisaccade performance is hypothesised to be reliable within and across assessments.

Second, little evidence of eye movement performance of people in their first psychotic episode exists. Study II will aim to replicate and extend the existing findings (Chapter 5). An additional aim will be to explore the relationship between SPEM measures and antisaccade error rate. As outlined above, evidence concerning this relationship is inconsistent but is needed given the possibility of combining these measures in future genetic studies of oculomotor endophenotypes. The main hypothesis of this study is that people in their first episode of psychosis demonstrate SPEM (gain as well as CUS and AS frequency) and antisaccade (error rate) impairments on the background of relatively intact fixation and prosaccade performance.

Third, studies of first-degree relatives have generally indicated good validity of the SPEM and antisaccade tasks as schizophrenia endophenotypes. A sample of siblings discordant for schizophrenia will be examined in Study III in order to replicate and extend this evidence (Chapter 6). The design of Study III will have a number of advantages over previous oculomotor family studies, using tightly matched triplets of patient, sibling and healthy controls and isolating between groups the variable of interest, namely the genetic relatedness to an individual with schizophrenia. Following Study II, the relationship between SPEM performance and antisaccade errors will be examined in the patient, sibling and control groups. The main hypothesis of Study III is that SPEM (gain, CUS and AS) and antisaccade (error rate) impairments will be observed not only in the patient group but also, to a lesser extent, in their healthy siblings; fixation and prosaccade performance is expected to be unimpaired.

Fourth, although previous studies have provided evidence of an association of SPEM and antisaccade performance with schizotypy levels in healthy individuals, the precise relationships of eye movement tasks with specific schizotypal symptom dimensions (e.g. positive or negative schizotypy) are less clear (in particular concerning the antisaccade task). Study IV will address the relationship between eye movement performance and

specific, empirically derived dimensions of schizotypal personality traits (Chapter 7). Additionally, the impact of trait emotionality on the relationship between eye movements and schizotypy will be examined. As outlined above (Section 2.3.5.5.6), there is evidence for an association between trait emotionality and schizotypy; whether trait emotionality accounts for the eye movement deficits seen in individuals with high schizotypy scores is not clear. As in Studies II and III, the relationship between SPEM and antisaccade errors will be addressed. It is hypothesised that individuals with high levels of schizotypy have SPEM (gain, CUS and AS) and antisaccade (error rate) impairments; given the assumed specificity of these endophenotypes to the schizophrenia spectrum, these impairments are hypothesised to be independent of trait emotionality. No relationships between schizotypy and fixation or prosaccade measures are hypothesised.

Fifth, despite a substantial body of knowledge concerning the effects of pharmacological manipulations on eye movements, the effects of anticholinergic drugs in schizophrenia remain unknown. Anticholinergic drugs are often prescribed to schizophrenia patients in order to alleviate extrapyramidal side effects of antipsychotic drug treatment. Due to the role of the cholinergic system in cognition, impairments on neurocognitive tasks may be observed during treatment with anticholinergics. Study V will examine the effects of one widely prescribed anticholinergic compound, procyclidine, on eye movement performance (Chapter 8). The study will address the methodological implications that such a state influence on eye movements might have for the validity of the SPEM and antisaccade measures as schizophrenia endophenotypes. Assuming that measurement of a good endophenotype is resistant to state effects (such as pharmacological treatment), the main hypothesis of this study is that acute administration of procyclidine will not confound the assessment of SPEM and antisaccade function in schizophrenia patients.

Across all studies, therefore, the emphasis lies on the SPEM (gain, CUS and AS) and antisaccade (error rate) measures as schizophrenia spectrum endophenotypes. In order to investigate the specificity of these deficits within the functional domain of oculomotor control, the fixation and prosaccade tasks will also be studied. Following previous arguments (Levy et al 1994; McDowell & Clementz 2001), these tasks are expected to represent oculomotor control conditions; fixation and prosaccade performance in schizophrenia spectrum individuals is thus hypothesised to be relatively unimpaired.

This hypothesised pattern of performance in the schizophrenia spectrum groups will allow the assessment of the discriminant validity of the SPEM and antisaccade deficits.

The empirical studies of this thesis will be reported after a thorough description of the eye movement methods used in these studies (Chapter 3). The findings from Studies I-V will be discussed and integrated in the General Discussion (Chapter 9).

Chapter Three

Eye Movement Methods

3.1 Chapter Overview

This chapter describes the eye movement methods adopted in the present investigations. Wherever possible these methods will be compared to and evaluated against methods employed in previous schizophrenia spectrum studies, as reviewed in Chapter 2. Details of other methods employed in this thesis will be discussed in the relevant experimental chapters (e.g. psychometric questionnaires, Chapter 7; pharmacology, Chapter 8). As different samples were recruited for each of the studies reported in this thesis, the relevant recruitment strategies and sample characteristics will also be outlined in each experimental chapter. Likewise, statistical analyses differ between studies and will be described in detail in the relevant chapters.

3.2 Hardware and Software for Stimulus Presentation

The research reported in this thesis employed two batteries of eye movement tests. When the research for this thesis was begun, a set of eye movement tasks was available in the Section of Cognitive Psychopharmacology, Institute of Psychiatry. This set of eye movement tasks, referred to hereafter as Battery I, had been piloted and used by researchers in this group (Kumari et al 2000). As data collection on Study II had already begun at the beginning of this thesis, and data collection on Study III began shortly thereafter, Battery I was used for these studies (Chapters 5 & 6).

However, during data collection on Studies II and III it was felt that the tasks of Battery I could be improved upon in terms of stimulus properties. To this end, one aim of this thesis was to develop a second set of eye movement tasks suitable for schizophrenia spectrum research. This new set of tests is referred to hereafter as Battery II. A methodological study addressing the relationship and differences between the two batteries was conducted (subsequent to data collection on Studies II and III) and is reported in Chapter 4. Battery II was also used in two further studies reported in this

thesis (Chapters 7 & 8).[16] Hardware specifications as well as stimulus properties of all tasks will be described in detail below.

3.2.1 Battery I

3.2.1.1 Hardware and Laboratory Specifications

Stimuli of Battery I were presented using a commercially available LED array, the AMTech Digital LED Bar 96 (AMTech GmbH, Weinheim, Germany). This LED bar consisted of an aluminium case, 160cm wide, 5cm deep and 5cm high. In this case were mounted, horizontally aligned, approximately 300 diodes of round shape, each of about 5mm in diameter. The LED bar was presented at eye level from participants at a distance of 200cm. The target stimulus (a single LED) thus subtended an amplitude of approximately 0.15°, similar to previous studies (Crawford et al 1998; Curtis et al 2001a; Klein et al 2000c; O'Driscoll et al 1998; Spantekow et al 1999; Sweeney et al 1992a; Thaker et al 1999). A PC was used to run software controlling the LEDs.

Testing took place in a small, quiet room in the Institute of Psychiatry. Lights were dimmed in order to secure optimal recording conditions for the infrared light oculographic equipment. The infrared light recording technique (Sections 2.3.3 and 3.3) demands that ambient infrared light must be eliminated in the recording environment. Participants were seated in a comfortable, height-adjustable office chair. A vertically adjustable chin-rest was attached firmly to a desk in front of participants (Troost et al 1974). Participants were instructed to rest their chins on the chin-rest while resting their arms on the desk, in order to minimise movement artefacts and vestibulo-optokinetic influences and to maximise comfort.

3.2.1.2 Stimulus Properties

The software used to control stimulus presentation for all tasks of Battery I was provided by AMTech GmbH (Weinheim, Germany).

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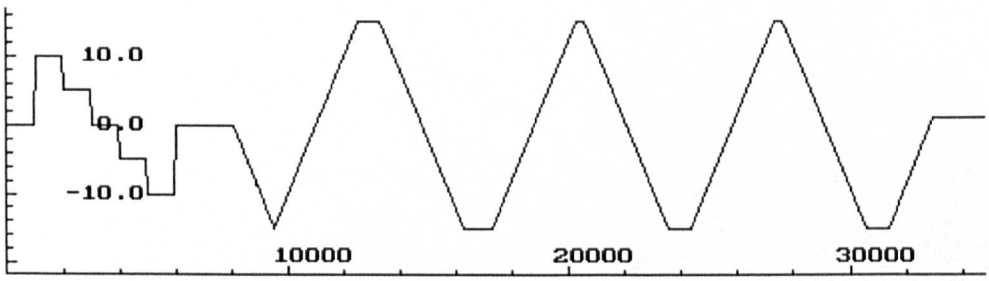
[16] In order to improve the presentation of the experimental chapters in this thesis, the methodological study will be reported first (Chapter 4), followed by the (earlier) studies using Battery I (Chapters 5 & 6) and the (later) studies using Battery II (Chapters 7 & 8).

3.2.1.2.1 SMOOTH PURSUIT TASK

The smooth pursuit eye movement (SPEM) task of Battery I employed a trapezoidal, constant-velocity target waveform. Two different *velocities* were used. The first target moved at a velocity of 10°/s (Figure 3.1) while the second target moved at a velocity of 24°/s (Figure 3.2). Both velocities are comparable to previous studies (Allen 1997; Hutton et al 1998a; Iacono & Koenig 1983; Levin et al 1982a; O'Driscoll et al 1998; Roitman et al 1997).

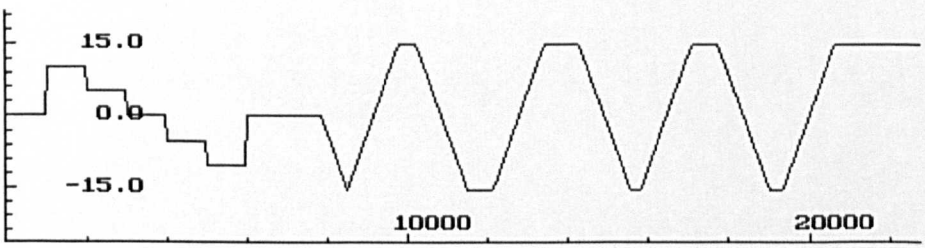
Figure 3.1: Smooth Pursuit Block at 10°/s (Battery I)



Legend: x-axis, time (ms); y-axis, degree of visual angle

Two blocks were run at each velocity. A block of the 10°/s target consisted of 6.5 half-cycles; a block of 24°/s target consisted of 7 half-cycles. Therefore, the 10°/s SPEM task consisted of 13 half-cycles and the 24°/s SPEM task consisted of 14 half-cycles. In both tasks, the target moved horizontally between ±15°, in accord with previous studies (Litman et al 1991; Nkam et al 2001; Ross et al 1999c).

Figure 3.2: Smooth Pursuit Block at 24°/s (Battery I)



Legend: x-axis, time (ms); y-axis, degree of visual angle

At each velocity, the target was initially presented in the central location (0°), from where it moved to the extreme left position (-15°). This first ramp in each block was treated as a practice trial for participants to become familiar with the task and was thus not included in the analysis. The target remained stationary between half-cycles for quasi-random durations between 300ms and 1,000ms.

Instructions to participants were to follow the target, with their eyes, as closely as possible, wherever it moved. Instructions were repeated during the task if necessary. In order to minimise movement artefact, participants were told to keep their head still while only moving their eyes.

A five-point calibration task was carried out immediately before each SPEM block, using target eccentricities of 0°, ±5° and ±10°. This task, calibrating linearly for a horizontal range of 20°, is less than optimal for a SPEM task traversing a range of 30°. Due to practical limitations this was the only calibration task available when the research for this thesis was initiated. It may, however, be argued on two grounds that the SPEM data from Battery I can be used despite this calibration. First, measurement of the frequency of saccades during pursuit is not believed to be influenced by poor calibration (Abel & Ziegler 1988; p. 752). Second, the SPEM gain measure of pursuit accuracy in the current investigations was taken from the middle third section of each half-cycle, thereby minimising effects of poor calibration; these would be expected to be more pronounced for sections of pursuit outside the calibrated range of ±10°.

3.2.1.2.2 Fixation Task

The visual fixation task consisted of the target presented subsequently in three different *locations*. The target was always presented first in the central location (0°), then at -15° and finally at +15°. *Target duration* in each location was 15,000ms. *Instructions* were "to follow the target as closely as possible, wherever it moves". Calibration was based on the central location (0°) as well as the relevant peripheral target eccentricity (±15°).

3.2.1.2.3 Antisaccade Task

The antisaccade task of Battery I is depicted in Figure 3.3. Each block consisted of 8 trials. Each trial began with a central target (0°) presentation for 1,000ms. The target

then moved to a *horizontal peripheral location* (±15°), where it remained for 1,000ms, before moving back to the centre for the next trial.

Figure 3.3: Antisaccade Block of Battery I

Legend: x-axis, time (ms); y-axis, degree of visual angle

Each block used the same, quasi-random sequence of target movements. In Chapters 5 and 6, two blocks were carried out for each participant. In the assessment of the task's reliability and validity in Chapter 4, three blocks each were carried out.

The task *instructions* required participants to fixate the target when in the central location. They were further instructed that, as soon as the target moved to the side, they should look to the exact opposite location. Participants were instructed in detail that they should a) avoid looking towards the peripheral target and b) attempt to match the exact target location on the 'other' side. Participants were asked whether they had understood the task requirements; these were repeated if necessary until it was felt that participants sufficiently understood what was required of them.

In order to familiarise participants with the task requirements, four *practice trials* were carried out which were repeated if necessary. Performance was monitored by the experimenter; participants were provided with verbal feedback during and after the practice trials.

A nine-point calibration task was run between practice trials and the first experimental block, using the central location and ±20°, ±15°, ±10° and ±5°. The target moved from right to left and remained in each location for 1,000ms. A brief gap intervened between the calibration task and the first antisaccade block.

This antisaccade task has a number of disadvantages. First, the number of trials (16 in Chapters 5 and 6; 24 in Chapter 4) was small. While comparable to previous studies (Clementz et al 1994; Curtis et al 2001a; Hutton et al 1998a; Nieman et al 2000), a larger number of trials might ensure more reliable assessment. It has been shown that the number of items (or trials) in a measurement instrument is related positively to the reliability of the instrument (Anastasi & Urbina 1997).

Second, the use of a quasi-random sequence of target presentations might have allowed for procedural, or implicit, learning to occur across repeated presentations of blocks (Corr et al 1997; Kumari et al 1997a). It is possible that this factor influenced between-group comparisons of people with schizophrenia (who have difficulties in procedural learning tasks; Kumari et al 2002) and healthy individuals. However, as only three blocks were used at most, effects of procedural learning were expected to be small.

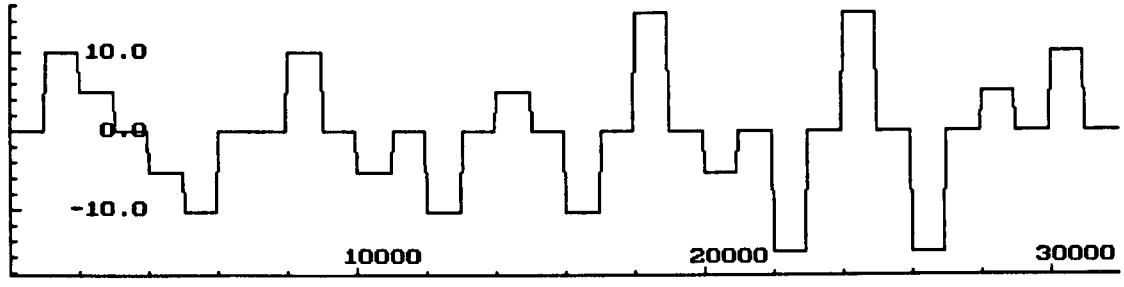
Third, using only one target eccentricity in either half of the visual field increased the spatial predictability of the target movement. Additionally, more than one peripheral target amplitude might be necessary to estimate reliably spatial accuracy on antisaccades.

Fourth, fixed central target durations might have led to temporally predictable peripheral targets. It is unknown how target predictability, which is known to affect saccadic latency on other tasks (Hutton et al 2001b), affected between-group differences on antisaccade error rate.

3.2.1.2.4 PROSACCADE TASK

Battery I provided two prosaccade tasks. The first task (Figure 3.4) was used in Chapters 5 and 6; the second task (Figure 3.5) was used in Chapter 4. Ideally, the same task should have been used in each of these studies, so that the reliability and validity findings of Chapter 4 could be related to the data from Chapters 5 and 6. The first prosaccade task was used as most of the data of Chapter 5 had already been collected, and data collection on the Sibling study (Chapter 6) had been initiated, at the beginning of this thesis. It was, however, felt that the second prosaccade task, which had not been used in these studies, might provide an improvement over the previous task, for reasons outlined below. Therefore, this second task was then employed in the analysis of reliability and validity reported in Chapter 4.

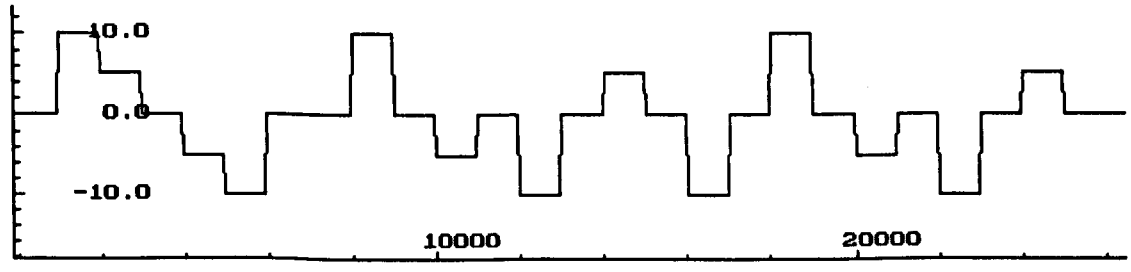
Figure 3.4: Prosaccade Block of Battery I (Chapters 5 & 6)



Legend: x-axis, time (ms); y-axis, degree of visual angle

The first prosaccade task consisted of 12 trials. Each trial began with a 500ms central target presentation. The target then moved to one of three *peripheral locations* (±5°, ±10°, or ±15°) for *durations* of 500ms each. Each target location was used twice, with the sequence of target movement being fixed and quasi-random within each block. Chapter 5 used one block; Chapter 6 used two blocks.

Figure 3.5: Prosaccade Block of Battery I (Chapter 4)



Legend: x-axis, time (ms); y-axis, degree of visual angle

A five-point calibration task was used, presenting the stimulus for 500ms each at 0°, ±5° and ±10°. This calibration task is less than optimal, as it calibrates accurately for a range between ±10°, but less accurately for the ±15° targets. Therefore, measurement of prosaccade gain (but not latency) might have been slightly inaccurate on this task, calling for caution in the interpretation of these data. The second prosaccade tasks circumvented this problem of poor calibration by using peripheral target eccentricities

of ±5° and ±10° and an appropriate five-point calibration (±0°, ±5° and ±10°). The target remained in each location for 500ms. Three blocks of 9 trials each were carried out.

In both tasks, *instructions* to participants were to follow the target, with their eyes, as closely as possible, wherever it moved. Participants were told to keep their head still while only moving their eyes.

These prosaccade tasks suffer two minor weaknesses. First, the number of trials was relatively small. Second, the quasi-random target sequence might be undesirable due to aforementioned possibility of procedural learning effects.

3.2.2 Battery II

Given the apparent weaknesses of Battery I, a second set of stimuli was developed (Battery II). These hardware and software specifications will be described below.

3.2.2.1 Hardware and Laboratory Specifications

A computer screen was chosen for stimulus display to achieve greater flexibility with regard to the manipulation of stimulus properties. The hardware for stimulus presentation consisted of a commercially available PC (Gateway 650), comprising of a midi tower (ATX 200 watt tower case) with a 20-GB 7200RPM hard drive. The computer was a Pentium 3 P600 processor, contained an ATI RAGE 128 16MB graphics card, had 128 MB RAM and was designed to run Microsoft Windows 98. The screen that was used to display stimuli was a 17-inch Gateway EV700 LG monitor. The equipment was chosen to be of sufficient capacity for simultaneous stimulus presentation and data logging. Storage capacity had to be considerable due to the size of the eye movement data files.

The target stimulus consisted of a white dot of circular shape of approximately 3mm in diameter, presented against a black background. As the participant's eyes were at a distance of 57cm from the screen, the target subtended about 0.3° of visual angle, similar to previous studies[17] (Crawford et al 1998; Curtis et al 2001a; Klein et al 2000c; O'Driscoll et al 1998; Spantekow et al 1999; Sweeney et al 1992a; Thaker et al 1999).

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[17] Interestingly, however, Fischer and Weber (1997) demonstrated that differences in stimulus size (0.1°, 0.2°, and 0.4°) have little effect on antisaccade performance.

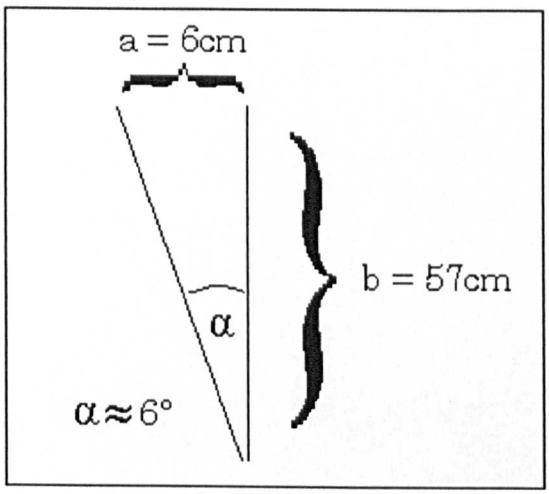
A number of previous studies (Amador et al 1995; Knox 1998; Levin et al 1982a; O'Driscoll et al 1998) have presented stimuli at a distance from participants of 57cm. One reason for using this distance is the ease with which a rough estimate of target amplitudes can be read off from the display. Amplitudes may be calculated using the formula

$$\tan = \frac{a}{b}$$

where a is the distance between two target locations on the display; b is the distance between eye and target display; and α is the amplitude of the angle formed by a and b.

If b=57cm then α (in degrees) will be approximately equal to a (in cm) for short distances of a (Figure 3.6).

Figure 3.6: Relationship Between Target Distance and Amplitude of Visual Angle



A distance of 57cm between eye and monitor was considered acceptable to participants and believed not to strain their eyes unnecessarily, as it is similar to standard reading distances.

The general set-up was identical to that used for Battery I. Experiments took place in the same window-less, light-dimmed, quiet room, using the same chin-rest. The PC monitor was mounted on a small desk in front of participants. Data collection for the study reported in Chapter 7 took place at Goldsmiths College. Hardware and laboratory specifications were identical to those described above.

3.2.2.2 Stimulus Properties

The stimulus properties of the smooth pursuit, fixation and saccadic tasks of Battery II will be outlined in the following sections. The software used to present the stimuli was purpose-written in C++ for Windows.

3.2.2.2.1 Calibration Task

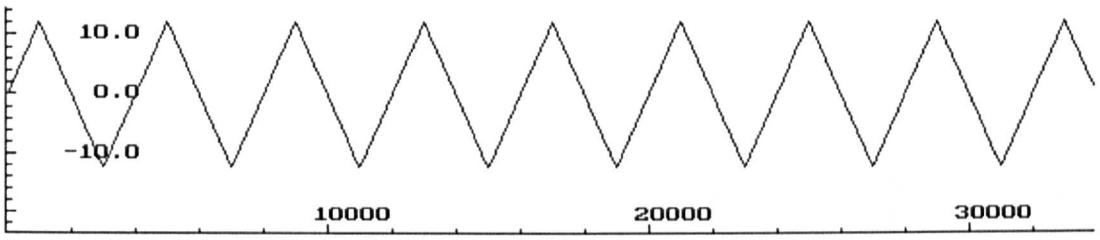
In order to improve the homogeneity of this battery, it was decided to use the same calibration task for all paradigms. At the beginning of each task a three-point calibration task was carried out. This task presented the stimulus first in the central location, then at -12° and finally at +12°. Stimulus *duration* in each location was 1,000ms. *Peripheral target locations* in this calibration task (±12°) were equal to the most eccentric targets used in each task of Battery II, thereby covering the entire range of target movements across tasks. Three-point calibrations have previously been used (Lencer et al 1999, 2000).

In the smooth pursuit, fixation and prosaccade tasks, the calibration task immediately (without gap) preceded the subsequent test. Participants were, therefore, not aware of the transition from calibration to 'actual' eye movement task, as *instructions* were simply to follow the target. In the antisaccade task, the calibration was followed by a break, in which the subsequent task requirements were explained to participants, as well as by the practice trials. Therefore, intervals of up to 1-2 minutes intervened between calibration and antisaccade task. The length of such an interval was deemed not to pose a problem for the accuracy of the calibration, as participants were requested to, and usually did, remain still for that duration. If a participant moved considerably during this gap the task was re-started (including a new calibration).

3.2.2.2.2 Smooth Pursuit Task

The SPEM task employed a triangular waveform (Figure 3.7). *Target velocities* were 12°/s, 24°/s, 36°/s and 48°/s, corresponding to frequencies of 0.25Hz, 0.5Hz, 0.75Hz and 1Hz, respectively.

Figure 3.7: Smooth Pursuit Task of Battery II



Legend: x-axis, time (ms); y-axis, degree of visual angle

The target was initially placed in the central position and then moved horizontally to one side until it reached the ±12° location, where it reversed abruptly and moved to the opposite side. The direction of the first ramp was random (right or left). The first ramp (from the central location to the first eccentric location) was considered practice and was not analysed. It is known that relatively short tracking durations (within a quarter cycle of target onset) are sufficient for predictive pursuit to become established (Leigh & Zee 1999). A total of 16.5 half-cycles were used at each target velocity. Both target excursion and velocities were comparable to previous studies (Allen et al 1990a; Allen 1997; Bell et al 1994; Hutton et al 1998a; Iacono & Koenig 1983; Levin et al 1982a; O'Driscoll et al 1998; Roitman et al 1997; Schwartz et al 1999; Versino et al 1993). Task *instructions* were identical to those of Battery I, requiring participants to keep their eyes on the target wherever it moved.

Although a target velocity of 48°/s may be considered quite fast for successful foveation by the smooth pursuit system (Leigh & Zee 1999), it was decided to include this task. First, previous studies have used similar and faster velocities (Bell et al 1994; Iacono & Koenig 1983; Levin et al 1982a; Schwartz et al 1999; Versino et al 1993). Similarly, Leigh and Zee (1999) suggested using target velocities of 5-50°/s for a comprehensive smooth pursuit system assessment (p. 179). Second, it has been suggested that faster target velocities discriminate better between schizophrenia patients and healthy individuals (Abel et al 1991; Lipton et al 1980a; Pivik 1979b). Finally, the reliability analysis in Chapter 4 indicated good psychometric properties of this task.

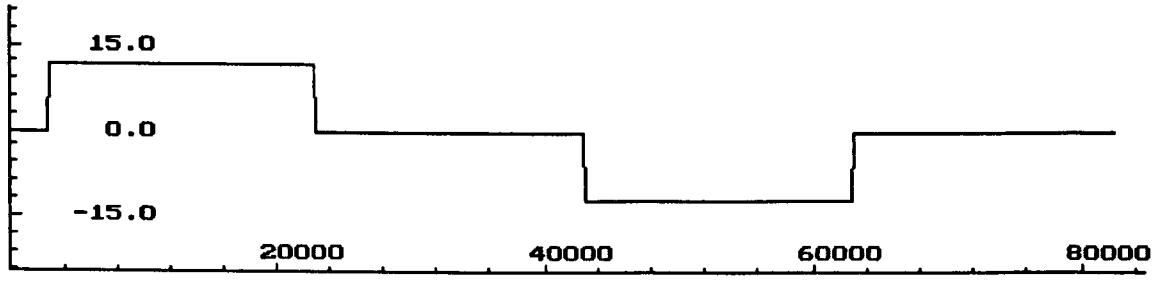
This SPEM task may be considered an improvement over the Battery I task on a number of grounds. First, a slightly larger number of half-cycles (N=16.5 at each

velocity) were used than in Battery I (N=13 and N=14 at the two velocities). Second, the problem of poor calibration encountered in Battery I was circumvented through the use of an appropriate calibration task, covering the entire target range.

3.2.2.2.3 *Fixation Task*

The visual fixation task presented the stationary target stimulus in each of three *locations*. First, after a central presentation of 1,000ms (which served to bring the participant's attention onto the target and was not included in the analysis) the target was moved randomly to either of the two most eccentric target locations (±12°). The target subsequently moved back to the central location, was then presented in the remaining peripheral location and finally moved back to the centre (Figure 3.8). The target *duration* in each location was 20,000ms. *Instructions* were identical to those of Battery I.

Figure 3.8: Fixation Task of Battery II



Legend: x-axis, time (ms); y-axis, degree of visual angle

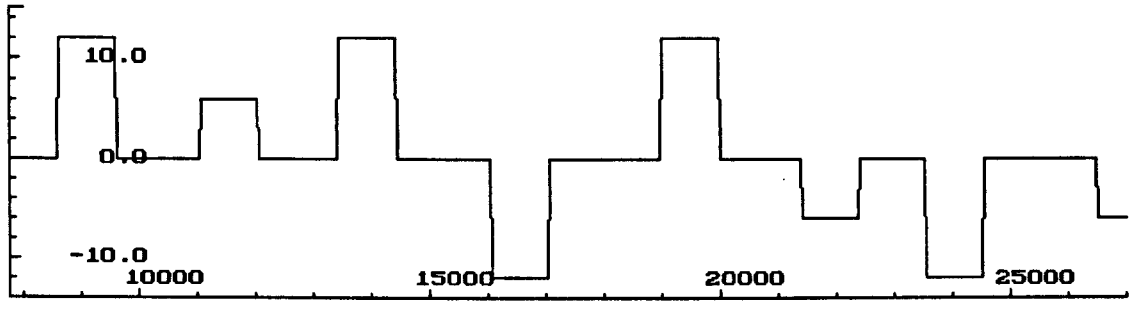
It was chosen to examine fixation of central as well as peripheral targets, as these might require slightly different neural substrates (Kissler & Clementz 1998). Target durations of 20,000ms were deemed sufficient to tax the fixation system (Kissler & Clementz 1998) and were comparable to previous studies (Amador et al 1995; Clementz et al 1994; Gooding et al 2000a; Kissler & Clementz 1998; Rosse et al 1992a).

3.2.2.2.4 *Antisaccade Task*

An antisaccade trial began with the target in the central location for a random *duration* of 1,000-2,000ms. The target was then abruptly moved to one of four *peripheral*

locations (±6° and ±12°) where it remained for 1,000ms. Each peripheral location was used 15 times, resulting in a total of 60 trials. The sequence of peripheral target presentations was random (sampling without replacement). A small sample of antisaccade trials from this task is given in Figure 3.9. Trials were presented in one block without break.

Figure 3.9: Saccadic Trials of Battery II (sample)



Legend: x-axis, time (ms); y-axis, degree of visual angle

Four *practice trials*, using each target location once, were carried out before the experimental trials, and could be repeated if necessary. It was found, however, that most participants required only one session of practice trials.

It has previously been argued that the inter-trial interval in saccadic tasks should be considerably longer than 200ms, which is estimated to be the maximum duration of the refractory period following the completion of a saccade (Stern & Dunham 1990). The current task complied with this requirement.

Varying the duration of the central fixation point in saccadic tasks randomly may be advantageous over using fixed durations as peripheral targets become temporally unpredictable. Previous studies of the antisaccade task have also used quasi-random durations (Clementz et al 1994; Curtis et al 2001a; Karoumi et al 1998b, 2001; Nieman et al 2000; Thaker et al 2000). The temporal characteristics of this task are generally comparable to previous studies.

The number of trials was expected to be appropriate, i.e. providing sufficient between-subject variance without affecting participants' levels of alertness and motivation. The larger number of trials in this task than in Battery I was identical to previous studies

(Brenner et al 2001; Karoumi et al 2001; McDowell et al 1999) and was hoped to improve the task's reliability (Anastasi & Urbina 1997).

Another difference between this task and the Battery I antisaccade task concerned target locations. In order to make target movements spatially less predictable, and to enable the examination of effects of target eccentricity, two locations in either side of the visual field were used. Using more than one target amplitude also allows for a more accurate and reliable assessment of spatial accuracy of saccades. Finally, the task avoided the possibility of procedural learning effects by using a randomised trial sequence.

3.2.2.2.5 PROSACCADE TASK

The *temporal and spatial properties* of the prosaccade task were identical to those of the antisaccade, except for an absence of practice trials. *Instructions* required participants to follow the target as quickly and accurately as possible.

Randomised central target durations have been used in previous prosaccade tasks (Karoumi et al 1998b; Müri et al 1998; Sweeney et al 1997), serving to make the target appearance temporally unpredictable. The number of trials is comparable to previous studies (Clementz et al 1994; Karoumi et al 1998b). Given the larger number of trials, as well as the more accurate calibration, this task was expected to provide an improved assessment of reflexive saccades compared to Battery I.

3.2.2.3 Summary

Battery II provides a homogenous set of tasks for the assessment of oculomotor function in schizophrenia spectrum participants. In developing this battery it was ensured that a number of validity criteria were met. First, the tasks appear to have face validity. Second, content validity was maximised through a comprehensive review of the existing literature on eye movements in schizophrenia. The properties of the stimuli used here are embedded in the existing literature and aim to provide an optimised combination of previous tasks. While care was taken to match previous task characteristics, it has been pointed out that there is no "standard protocol" in the eye movement literature (Klein & Berg 2001; p. 709). Further issues of validity will be discussed in Chapter 4.

Battery II appears to have greater internal homogeneity than Battery I for a number of reasons. First, the same calibration task was used across different paradigms. This was thought to ensure that putative performance differences between tasks, e.g. in saccadic gain between antisaccade and prosaccade tasks, may not be attributable to differences in calibration. Second, horizontal target range was kept identical across tasks (±12°). This is of importance for comparisons across tasks, as target eccentricities have been shown to affect saccadic metrics (McDowell et al 1999; Schreiber et al 1997). Third, the temporal and spatial characteristics of the prosaccade and antisaccade tasks are identical, again facilitating comparisons across tasks.

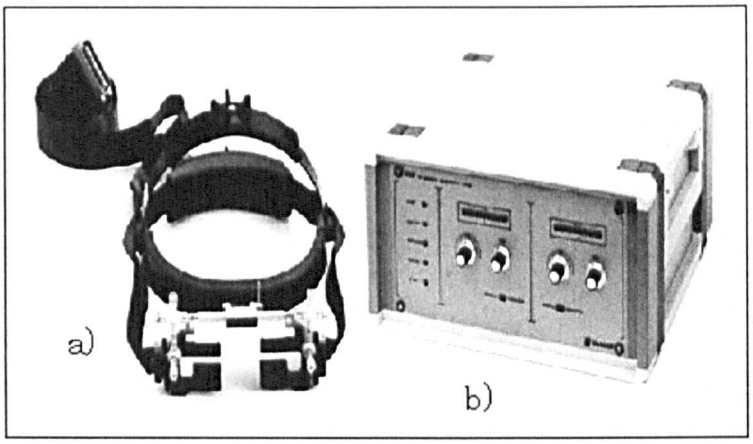
In addition to the improved internal homogeneity, Battery II may be considered an improvement over Battery I for other reasons. First, the number of trials (or half-cycles in the SPEM task) was generally larger, possibly leading to better internal consistency and other reliability criteria (Anastasi & Urbina 1997). Second, Battery II avoided the calibration problems encountered in Battery I. Third, the SPEM task of Battery II used four different velocities, thereby allowing a more detailed analysis of the effects of target velocity on smooth pursuit performance. Finally, saccadic tasks employed sufficient numbers of trials at four peripheral target locations, thereby allowing the assessment of effects of target eccentricity.

3.3 Hardware and Software for Recording Eye Movements

Eye movements were recorded using the IRIS eye-tracker, model 6500 (Skalar Medical BV, Delft, The Netherlands; Reulen et al 1988; Figure 3.10). The IRIS eye-tracker is a system based on the principles of infrared oculography, as outlined above. Some of the hardware specifications are as follows (IRIS 6500 Instruction Manual, Skalar Medical BV; Reulen et al 1988).

Horizontal recordings with the IRIS system may be made within a range of ±30°. Given this limitation, the maximal target range in the current tasks (±15°) is appropriate. The linearity of the system lies within 3% between ±25° of horizontal recordings.

Figure 3.10: IRIS 6500 Eye-tracker and Headset (Skalar Medical BV)



Legend: a = headset; b = eye-tracker

Infrared light is projected onto the participant's eyes using a head-mounted device. This device, which is akin to a light plastic helmet (weight 0.3kg), contains nine infrared light emitting diodes (Siemens BPX 269) and nine infrared light detecting photodiodes (Siemens BPX 69), horizontally aligned in transparent Perspex cases above and below the eyes, respectively. The low weight of the headset guarantees minimised discomfort to the participant. The photodiodes are covered by a black infrared filter to reduce artefacts from ambient light. Each emitter/detector array can be adjusted in three perpendicular directions in order to maximise recording accuracy. The infrared light transducers can be rearranged to record vertical eye movements; however, in the present set-up they are only used for the recording of horizontal eye movements. The emission of infrared light is chopped in order to minimise interference from ambient light, resulting in an improved signal-to-noise ratio. Recording is sensitive to artefacts of eye blinks, head movements and baseline shifts due to excessive tear fluid production.

The IRIS Skalar eye-tracker has been established internationally (mostly in Europe) by a number of laboratories for its use in schizophrenia spectrum research (Allen 1997; Broerse et al 2001b; Crawford et al 1998; Dursun et al 1999; Klein et al 2000c; Knox et al 1999; Krebs et al 2001; Lencer et al 1999; Maruff et al 1998; Nkam et al 2001; Powell et al 2002).

Only horizontal eye movements were recorded in the current investigations. The recording of vertical eye movements was unnecessary, as these are believed to occur only minimally during horizontal eye movement tasks and can be excluded as artefact, or noise, from the data (Leigh & Zee 1999). Moreover, in order to minimise calibration time at the beginning of each test session, recordings were taken from the left eye only. This was possible as the current experiments only required conjugate eye movements; error term due to vergence eye movements with the angles applied in this set-up may be negligible (Leigh & Zee 1999).

Eye position was logged by the eye-tracker and converted from analogue to digital by an analogue-digital (AD) converter card. For Battery I a commercially available AD converter card with a sampling frequency of 500Hz was used (BOT 96 Eye Movement Digitizer, AMTech GmbH, Weinheim, Germany). For Battery II, a purpose-built AD converter was used. This was a 4 channel AD converter with 12 bits resolution per channel and a sampling frequency of 500Hz, i.e. a sample of target and eye position was obtained for every 2ms. This sampling frequency is generally considered adequate for the study of eye movements (Stern & Dunham 1990). Data from the eye-tracker, together with target position, were saved onto the hard disk of a PC for further analysis.

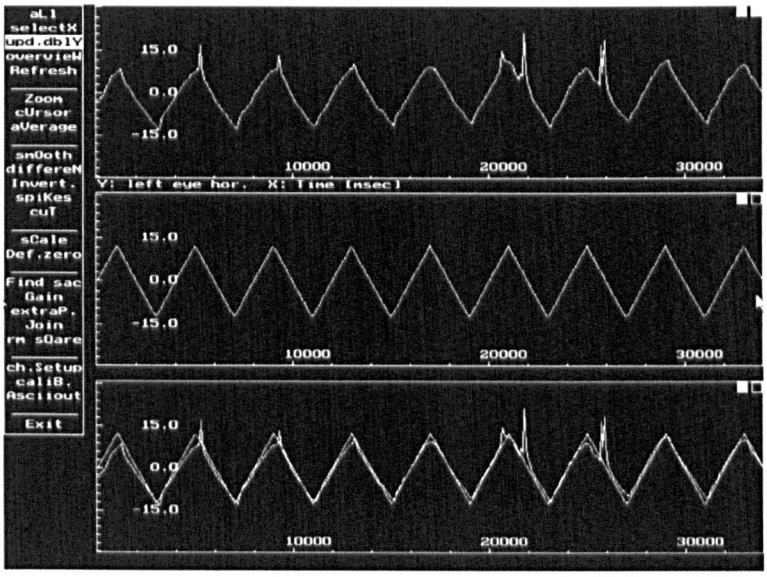
3.4 Eye Movement Data Scoring

The following sections will describe the criteria adopted in this thesis for the analysis of eye movement data from the smooth pursuit, fixation, antisaccade and prosaccade tasks. Before turning to specific criteria, however, the software that is used in the analysis will be described.

3.4.1 Software

Eye movement recordings were analysed using a semi-automated procedure in the EYEMAP software package (Version 2.0; AMTech GmbH, Weinheim, Germany). Semi-automated, or interactive, analyses are believed to be more accurate and reliable than fully automated analyses (Leigh & Zee 1999). EYEMAP allows the analysis of eye movement data from up to eight 'channels' (equivalent to visual presentations of the data in line graphs). Channels of horizontal left eye position, horizontal target position, as well as overlapping target and eye traces were displayed simultaneously (see Figure 3.11 for an example of a smooth pursuit trace from Battery II).

Figure 3.11: Example of an EYEMAP Representation of Eye and Target Trace



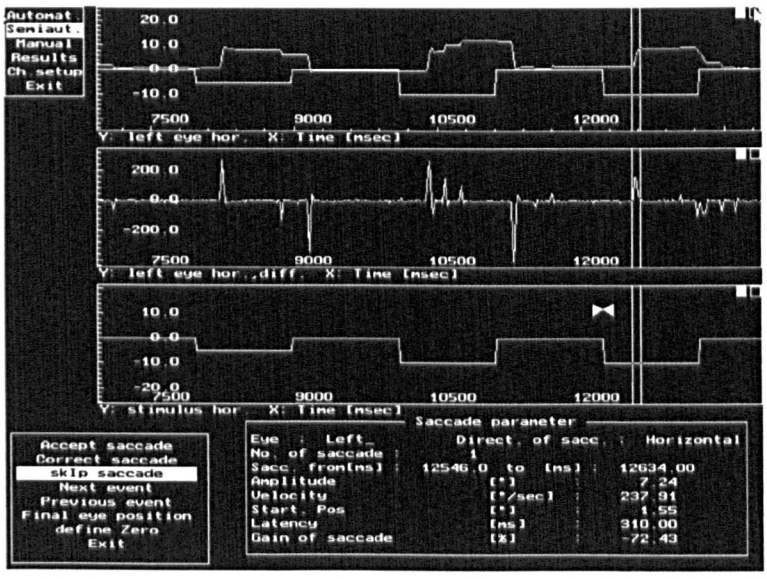
Legend: x-axis, time (ms); y-axis, degree of visual angle

Top: eye channel; middle: target channel; bottom: combined traces in double-window; left: menu bar

Before a data file containing eye movement data can be opened for analysis in EYEMAP a set-up file must be chosen. The set-up file contains information required by the software to access the data file, such as data format, path to data as well as output file, number and kind of channels required and other specifications. Once a data file has been opened, and eye position has been calibrated based on the relevant calibration task, EYEMAP provides a number of options for analysis.

For analysis of all saccadic tasks as well the saccadic analysis of smooth pursuit and fixation data, EYEMAP searches the eye movement data trace for certain predefined changes in position and velocity assumed to reflect saccades. The criteria used for the detection of saccades will be discussed below (Section 3.4.2.2).

Figure 3.12: Example of an Interactive Saccade Analysis in EYEMAP



Legend: x-axis, time (ms); y-axis, degree of visual angle

The semi-automated saccadic analysis option in EYEMAP was used (Figure 3.12). In this analysis the software places two vertical cursors over each successive change in the eye movement trace assumed to be a saccade based on predefined criteria, starting at the beginning of the trace (0ms). The rater then decides for each such event whether to accept it as a saccade or to reject it (as artefact or eye-blink). If an event is accepted as saccade, the rater is required to label it appropriately. This is done by choosing one of a number of saccade labels from a menu. The saccadic labels have to be specified in a separate file and in the current analyses included: reflexive saccade, antisaccade, antisaccade error, antisaccade corrective saccade, anticipatory saccade, square-wave jerk, back-up saccade, catch-up saccade and other.

The results of a saccadic analysis are stored in a tab-delimited (*.dat) output file. This file contains the saccadic label and metrics of each event that has been accepted. These data were then further analysed as follows. Output files were opened in Microsoft Excel 2000 and copied into template files designed to extract relevant information. Template files differed between different types of eye movement paradigms.

The metrics from the antisaccade and prosaccade tasks relevant to the current investigations (primary saccade gain, latency and antisaccade error rate) were extracted

from saccadic events by a number of Excel formulae stored in the template file. Saccadic events that were utilized for the calculation of saccadic metrics were defined according to criteria outlined below (minimum latency to target, direction, type). Saccades that did not meet these criteria were omitted from this calculation. Average measures for each participant (across saccades) were then copied into SPSS for statistical analysis. Saccades from the SPEM and fixation tasks were counted for frequency; metrics were not further analysed.

In the assessment of smooth pursuit gain the rater manually places a 100ms cursor over sections of pursuit in the 'eye channel' (see Section 3.4.2.1). The software stores gain scores for all sections and writes these into an output file. The SPEM gain output file is opened in Microsoft Excel 2000; each participant's average gain score is extracted and then transferred into SPSS for further analyses. Different gain scores were calculated for different velocities.

The EYEMAP software package was purpose-designed for the analysis of eye movement data from clinical populations and has been validated by different laboratories in a number of studies of eye movements in schizophrenia spectrum samples (e.g. Dursun et al 1999; Hutton et al 2000; Lencer et al 1999; MacCabe et al 2002; Mahlberg et al 2001; Straube et al 1999).

3.4.2 Scoring Criteria

Following the discussion of previous approaches to the analysis of oculomotor data it is clear that criteria for identifying eye movement parameters have to be chosen and justified carefully, as there does not appear to be one single, and universally valid, scoring procedure for any of the tasks discussed here. As with the temporal and spatial characteristics of stimulus presentation in the experimental paradigms it appears that a number of different, equally valid, approaches exist. Scoring criteria were identical across batteries.

3.4.2.1 Smooth Pursuit Task

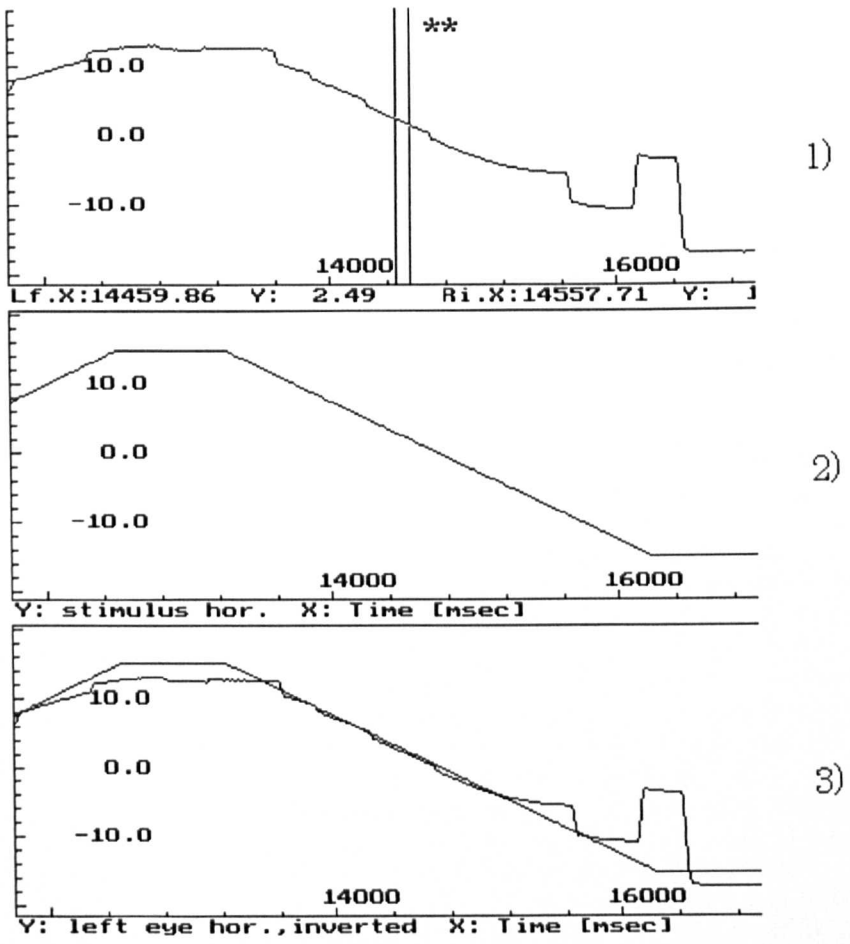
Given the controversies surrounding SPEM analysis, it was decided to employ a comprehensive battery of quantitative measures. Scoring criteria were based on previous studies and were chosen to provide a feasible (in terms of technical and

temporal restrictions) and valid analysis of SPEM performance. Scoring criteria were identical across studies and batteries.

The key variables were gain and the frequency of anticipatory and catch-up saccades. Back-up saccades and square-wave jerks were also observed, but occurred infrequently and were not included in the statistical analyses. Previous studies have repeatedly shown that these measures are not consistently impaired in schizophrenia spectrum samples (Clementz et al 1990; Iacono & Koenig 1983; Lencer et al 1999; Radant & Hommer 1992). Global qualitative (Benitez 1970; Shagass et al 1974) or quantitative (Iacono & Lykken 1979a, 1979b; Lindsey et al 1978) measures were not employed. While these have been shown to provide valid and reliable overall descriptions of smooth pursuit dysfunction in schizophrenia, specific measures were considered to be more informative regarding the precise nature of pursuit dysfunction (Abel & Ziegler 1988; Leigh & Zee 1999; Ross et al 1998c).

SPEM *gain* was measured following previous studies (Gooding et al 2000b; Hutton et al 1998a, 2001a; O'Driscoll et al 1999; Siever et al 1994). Initially, SPEM data was smoothed twice using a 5-point averaging filter. This procedure averaged five consecutive eye position data points, thereby reducing noise in the recordings. For gain analysis in EYEMAP, a cursor covering a time window of 100ms was placed onto sections of steady-state pursuit, not including saccades or eye-blinks, in the middle third of each half-cycle (Figure 3.13). Pursuit gain was calculated by EYEMAP for each window, dividing eye velocity by target velocity and multiplying the result by 100. A participant's pursuit gain was thus evaluated for each half-cycle of pursuit and then averaged across half-cycles for each velocity. The middle third section of each half-cycle was chosen (Hutton et al 2000, 2001a; O'Driscoll et al 1999) as pursuit may slow in anticipation of target reversals and in order to overcome problems of calibration on the Battery I tasks.

Figure 3.13: Example of Smooth Pursuit Gain Analysis



Legend: x-axis, time (ms); y-axis, degree of visual angle

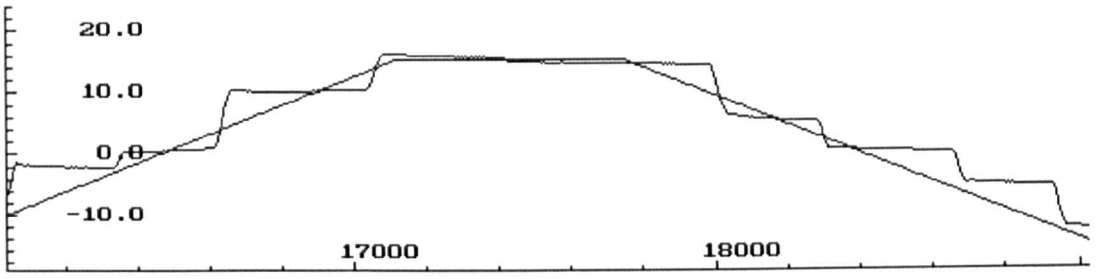
** 100ms window cursor for gain analysis

1) eye channel; 2) target channel; 3) joint representation of eye and target

Measures of pursuit gain were not taken for half-cycles which consisted entirely of saccades (Figure 3.14). Such saccadic, or 'cogwheel' pursuit (Levin 1983; Troost et al 1974), occurred infrequently and was deemed unsuitable for the analysis of the pursuit system (Levin et al 1982a). As Levy et al (1994) argued, "average gain calculations that include epochs with AS, in which gain is reduced to or near zero, should not be included in an assessment of the integrity of the pursuit system because the eye is *not*

engaged in pursuit" (p. 49; italics in original). Saccades were also not included if they occurred within the peripheral fixation period of the trapezoidal target in Battery I.

Figure 3.14: Example of Saccadic Pursuit

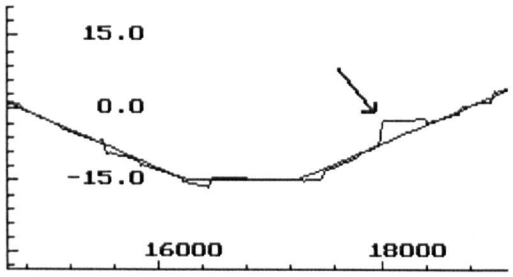


Legend: x-axis, time (ms); y-axis, degree of visual angle

The automatic detection of saccades during pursuit was based on criteria of minimum amplitude (1.5°) and minimum velocity (30°/s), similar to previous investigations (Abel et al 1991; Cegalis et al 1983; Cegalis & Sweeney 1979; Hutton et al 2001a; Matsue et al 1986; Mialet & Pichot 1981; Ross et al 1999c). Once a saccade was identified by EYEMAP, it was classified by the rater according to visual appearance into the categories of anticipatory saccade (AS), catch-up saccade (CUS), back-up saccade (BUS), square-wave jerk (SWJ), or other (if it did not fit any of these criteria).

Anticipatory saccades were defined as saccades in target direction that took the eye ahead of the target (Figure 3.15). AS were typically followed by slowing or cessation of pursuit for the target to 'catch up' with the eye. Observations were also made of AS which were followed by a second saccade in opposite target direction, returning the eye to the target (Figure 3.15). These could be distinguished from SWJ, as pursuit typically slowed, or cessated, during the intersaccadic interval. It is a hallmark feature of SWJ that pursuit continues between saccades (see below). The second saccade, returning the eye to the target following an AS, was classified as BUS.

Figure 3.15: Example of an Anticipatory Saccade (Arrow) during Smooth Pursuit, with Subsequent Back-up Saccade

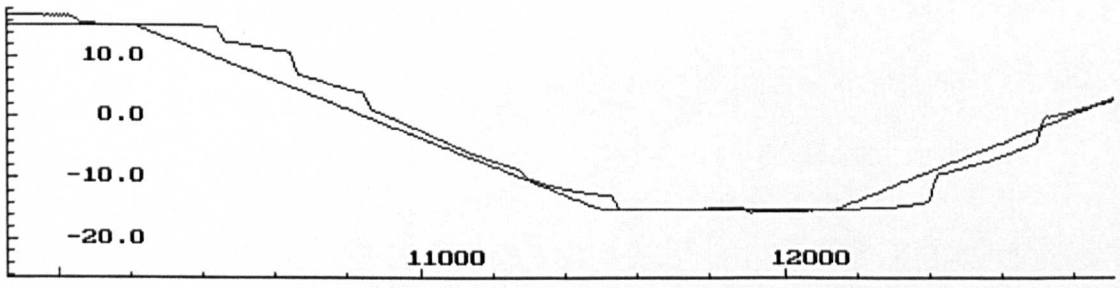


Legend: x-axis, time (ms); y-axis, degree of visual angle

Following Ross et al (1999c) it was decided to include anticipatory saccades with a small minimum amplitude criterion (1.5°). This amplitude criterion, smaller than suggested by others (Whicker et al 1985), was believed to maximise patient-control separations (Ross et al 1999c).

Catch-up saccades were defined as saccades in target direction that served to reduce position error, i.e. to bring the eye closer to the target (Abel et al 1991; Flechtner et al 1997; Levy et al 2000). CUS always began with the eye behind the target. A CUS of perfect accuracy would, therefore, end on the target. Frequently, however, CUS moved the target close to, but slightly off the target, either behind or ahead of it (Figure 3.16).

Figure 3.16: Example of Catch-up Saccades during Smooth Pursuit

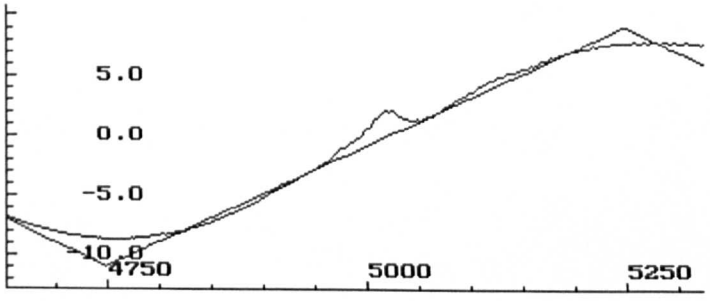


Legend: x-axis, time (ms); y-axis, degree of visual angle

An important criterion for the classification of anticipatory and catch-up saccades was the increase or decrease in position error (Abel et al 1991; Flechtner et al 1997; Levy et al 2000). While not quantified, such a change could be observed visually. If a saccade initiated behind the target and ended ahead of it, it was classified as an AS if more than half of the amplitude served to move the eye ahead of the target. If more than half of the amplitude was spent behind the target, i.e. reducing position error, the saccade was considered a CUS (Clementz et al 1990; Ross et al 1999a).

Back-up saccades were defined as saccades that were executed in direction opposite to target movement (Figure 3.17; Flechtner et al 1997; Lencer et al 2000). Like CUS they were corrective, i.e. served to reduce position error. BUS could be identified relatively unambiguously, usually occurring after segments of hypermetric gain (Figure 3.17) or a large anticipatory saccade (Figure 3.15).

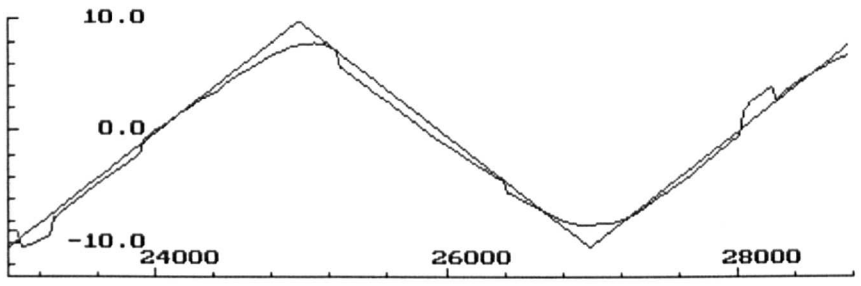
Figure 3.17: Example of a Back-up Saccade during Smooth Pursuit



Legend: x-axis, time (ms); y-axis, degree of visual angle

Square-wave jerks were defined as a complex of two saccades of roughly similar size (Figure 3.18). These saccades were performed in opposite directions, with the first saccade moving the eye ahead, i.e. in target direction, and the second saccade bringing the eye back to the target, i.e. in opposite direction. Typically, these saccades were separated by 50-500ms, although a precise evaluation of inter-saccadic duration was not carried out. Importantly, pursuit typically continues during the pair of saccades in SWJ (Leigh & Zee 1999; Ross et al 2001); this feature served to distinguish them from AS.

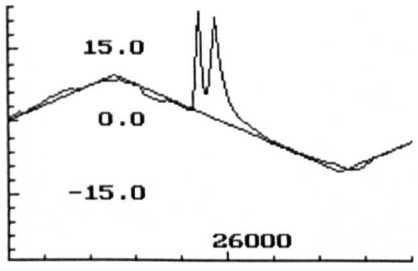
Figure 3.18: Example of a Square-wave Jerk during Smooth Pursuit



Legend: x-axis, time (ms); y-axis, degree of visual angle

Eye-blinks also occurred during pursuit and could in most cases be identified unambiguously (Figure 3.19). Eye-blinks were not counted or included in further analyses.

Figure 3.19: Example of an Eye-blink during Smooth Pursuit



Legend: x-axis, time (ms); y-axis, degree of visual angle

Frequencies were calculated for all types of saccades. First, the number of saccades in each category was established. Then, this number was divided by the duration of each block of pursuit (in seconds), yielding the frequency of saccades per second.

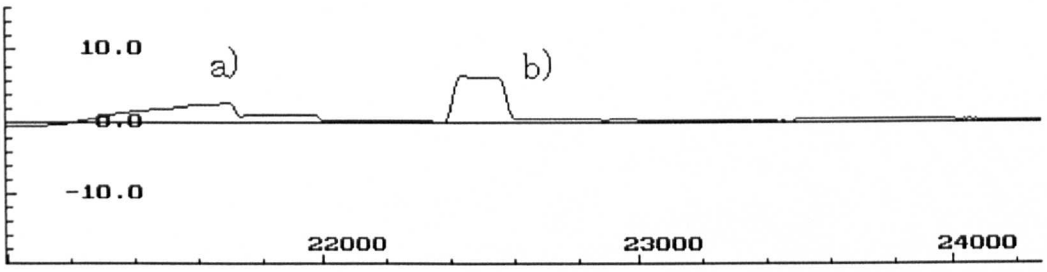
3.4.2.2 Fixation Task

The measure of visual fixation performance was the frequency of saccades. This measure was based on previous studies (Curtis et al 2001b; Gooding et al 2000a, 2000b; Kissler & Clementz 1998; Levin et al 1982a; Mialet & Pichot 1981; Silverman & Gaarder 1967) and was believed to provide a reliable assessment of the integrity of the

fixation system (Leigh & Zee 1999), aiming to yield more accurate information than qualitative ratings (Amador et al 1995; Rosse et al 1992a).

Criteria for the automatic detection of saccades in EYEMAP were as in Section 3.4.2.1. The number of saccades during fixation was counted and divided by the time (in seconds) of task duration. Eye-blinks were not counted or included in analyses. A number of different types of saccades were typically observed during fixation. These were similar to those occurring during smooth pursuit and have been described elsewhere (Kissler & Clementz 1998; Leigh & Zee 1999; Levin et al 1982a).

Figure 3.20: Saccades Occurring during Fixation



Legend: x-axis, time (ms); y-axis, degree of visual angle

a = BUS after period of drift; b = SWJ

SWJ (Figure 3.20) were defined as in Section 3.4.2.1, following Kissler and Clementz (Kissler & Clementz 1998) and Leigh and Zee (1999). During fixation the eye occasionally drifts off the target and subsequently restores eye position through a corrective *BUS* (Leigh & Zee 1999) (Figure 3.20). The third category of saccades that were observed regularly consisted of *saccades away from the target.* These were either followed by a slow drift back towards the target or a second saccade. Only if the second saccade was not part of a SWJ it was counted as a separate saccade. Saccades were then added (irrespective of subtype) for the calculation of saccadic frequency.

3.4.2.3 Antisaccade Task

The antisaccade performance measures used in the present research were chosen to be in agreement with those of previous studies (Section 2.5.3), assessing reaction time (latency), accuracy (gain), direction errors (error rate) and correction rate.

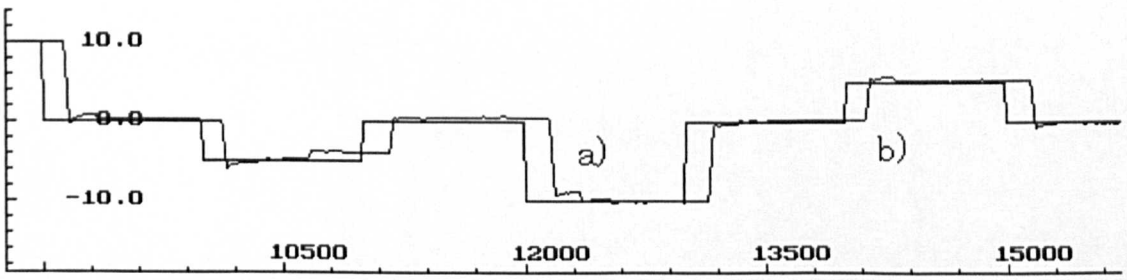
Detection of saccades was based on criteria of minimum amplitude (1.5°), minimum velocity (30°/s) and minimum latency to target (100ms) (Broerse et al 2001b; Crawford et al 1998; Gooding 1999; Katsanis et al 1997; Klein et al 2000c; McDowell et al 1999; Nieman et al 2000). Antisaccade trials were excluded from the analysis if an eye-blink occurred immediately before, during, or after target presentation, or if the participant failed to initiate a saccade. Eye-blinks were identified quite clearly in the current IRO records, although a combination of vertical and horizontal recordings would have been advantageous in a more reliable detection of eye-blinks (Troost et al 1974).

Antisaccade *error rate*, *correction rate*, *latency* and primary saccade *gain* were measured precisely as described in Section 3.4.1.3.1. *Velocity* was not calculated, as it was not considered an important schizophrenia spectrum endophenotype.

3.4.2.4 *Prosaccade Task*

In agreement with previous studies, prosaccade performance was measured using primary saccade *gain* and *latency*. These measures were calculated as described in Section 3.4.1.3.2. Criteria for detection of saccades (minimum amplitude=1.5°; minimum latency=100ms; minimum velocity=30°/s) resembled previous studies of similar populations. Eye-blink trials were excluded. Human primary prosaccade gain is often slightly *hypo*metric, i.e. undershoots the target (Bötzel et al 1993), although *hyper*metric, or overshooting, saccades were also observed (Figure 3.21).

Figure 3.21: Example of Prosaccades



Legend: x-axis, time (ms); y-axis, degree of visual angle

a = *hypo*metric primary saccade; b = *hyper*metric primary saccade

Saccadic velocity was not investigated in order to focus the discussion of this thesis on the key measures, the putative endophenotypes of SPEM performance and antisaccade error rate.

Chapter Four

Study I – Reliability and Concurrent Validity of Eye Movement Measures

4.1 Chapter Overview

This chapter examines a number of issues relating to the reliability and concurrent validity of the eye movement paradigms employed in this thesis. In order to draw firm conclusions regarding effects on oculomotor function of psychotic illness, genetic liability to schizophrenia, schizotypal personality traits and pharmacological manipulation, the reliability and validity of the methods should first be established. Reliability is defined as the extent to which measurement is free of error (relating to human rater bias, technical faults, variability over time, etc.); validity is defined as the extent to which the measurement captures the property it purports to capture.

A potential source of error in the assessment of eye movements concerns the effects of rater, or scorer, variability. To this end, Section 4.2 reports on the intra- and inter-rater reliability of the scoring procedures used for oculomotor data in the studies reported in this thesis. As outlined in Chapter 3, due to practical reasons, two oculomotor batteries – differing in stimulus display specifications, but not recording or scoring techniques – were used in the work reported here. The second point of attention, therefore, concerns the concurrent validity of these two sets of measures, i.e. the relationship of Battery II to Battery I (Section 4.3). Section 4.4 addresses another aspect of reliability, i.e. internal consistency, reporting Cronbach's coefficient alpha for each oculomotor measure. Finally, an important requirement of a putative biological marker in psychiatry research is its temporal stability, or test-retest reliability. To establish the temporal stability of the proposed oculomotor endophenotypes, the current eye movement batteries were subjected to follow-up assessment in a sample of healthy individuals over an interval of several weeks. The reliabilities of these measures and performance changes over time are described in Section 4.5.

4.2 Intra- and Inter-rater Reliability of Scoring Procedures

4.2.1 Introduction

Good intra- and inter-rater reliabilities are important properties of any assessment tool (Anastasi & Urbina 1997; Rust & Golombok 1999). With fully automated scoring procedures, as they may be used in psychophysiological and psychophysical studies, the involvement of the human rater is minimal and unlikely to introduce variability into the data. Therefore, intra-rater reliability is assumed to be perfect, indicating that two analyses of the same dataset by the same rater would produce identical results on both occasions. Likewise, agreement between two (or more) raters, called inter-rater reliability, would be expected to be perfect under these circumstances.

In the field of eye movement research, a number of different scoring routines have been developed to analyse raw data, ranging from purely manual/visual (Benitez 1970; Rosse et al 1992a; Shagass et al 1974) to fully automated (Powell et al 2002). As described in Chapter 3, eye movement data scoring in the research reported here is carried out using the software package EYEMAP. Analysis in EYEMAP is semi-automated and interactive, thereby possibly generating error due to examiner variance. Therefore, less than perfect reliabilities may be expected.

Both saccadic analysis (of smooth pursuit, fixation, antisaccade and prosaccade paradigms) and smooth pursuit eye movement (SPEM) gain analysis involve subjective decisions by the human rater. In the saccadic analysis the rater accepts (and subsequently classifies), rejects (as eye-blink or artefact), or manually adjusts a saccade captured by automated routines in the software. In SPEM gain the rater manually places a cursor onto a trace of pursuit in each half-cycle.

These small subjective elements are utilised in the interactive analysis procedure in order to maximise scoring accuracy; however, they allow for human error, thereby possibly reducing reliability.

4.2.1.1 Aims

The present study aimed to establish the intra- and inter-rater reliabilities of the eye movement scoring procedures used in this thesis, by subjecting SPEM, fixation and

saccadic variables to repeated EYEMAP analysis by the same rater, as well as the fixation, antisaccade and prosaccade tasks to analysis by two raters.[18] Given the relatively small subjective element of the semi-automated scoring procedures, and the precision of the operational criteria outlined in Chapter 3, correlation coefficients were hypothesised to be high (>0.8).

4.2.2 Method

4.2.2.1 Participants

For intra-rater reliability, eye movement data of twelve participants (7 males, 5 females; mean age=28.33 years; SD=6.27) was used. Data of these participants was drawn from the study of siblings discordant for schizophrenia (Chapter 6). Four schizophrenia patients, four participants from the sibling group (not related to the patients in this sample) and four healthy controls were chosen quasi-randomly from the entire sample for inclusion in the re-analysis. For inter-rater reliability, eye movement data of ten participants (5 males, 5 females; mean age=34.70, SD=12.26) was used. This sample of four patients and six controls was drawn quasi-randomly from an unrelated study not reported in this thesis but using identical task specifications as those described in Chapter 3.

4.2.2.2 Eye Movement Assessment

Participants for the analysis of intra-rater reliability were tested on oculomotor Battery I; participants for inter-rater reliability were tested on Battery II (Chapter 3). For intra-rater reliability, SPEM, fixation, prosaccade and antisaccade data were re-analysed 1-2 weeks after first analysis. Identical scoring procedures and software settings were used on both occasions. The dependent oculomotor variables were as described in Chapter 3 and included SPEM gain and frequency of anticipatory (AS) and catch-up saccades (CUS) at each velocity; frequency of saccades during fixation; antisaccade gain, latency and error rate; and prosaccade gain and latency. For inter-rater reliability, frequency of saccades during fixation; antisaccade gain, latency and error rate; and prosaccade gain and latency were measured using identical EYEMAP settings by the author of the thesis

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[18] Due to practical limitations it was not possible to determine inter-rater reliability on SPEM measures.

and a placement student trained in EYEMAP analysis by the author, based on the criteria outlined in Chapter 3.

As some error concerning the correct discrimination between AS and CUS during smooth pursuit was expected due to similarity in appearance (Ross et al 2001; also cf. Chapter 3), the frequencies of these two types of saccades were subsequently added into a combined saccadic frequency measure at each velocity (not including square-wave jerks and back-up saccades). This measure was expected to produce slightly better agreement than either of the individual measures.

4.2.2.3 Statistical Analysis

In order to assess the consistency of the scoring procedure (by the same rater over two occasions, or by two raters), intraclass correlations (ICC) were computed between pairs of variables (e.g. antisaccade error rate at Scoring I and antisaccade error rate at Scoring II; Bartko 1991). As Bartko (1991) pointed out, ICC is the appropriate statistical method for assessing agreement (between raters, or within one rater over time) in reliability analysis. Correlations (Pearson or Spearman) fail to take account of systematic differences between raters (or over time), or within-subject variance. Therefore, if all subjects obtain the same score on two occasions (or from two raters), both (Pearson or Spearman) correlation and ICC will indicate unity, i.e. perfect association and agreement, respectively (r=1; ICC=1). However, if scores differ systematically (over time or between raters), ICC will be a more realistic estimate of agreement, i.e. of within-subjects variance (over time or between raters). The data in Table 4.1 illustrate this example. This dataset represents two assessments (at two time points, or by two raters) of a given behaviour in five participants (Var1 and Var2). Pearson or Spearman correlations between the two variables in the original dataset (N=5; participants a1-a5, until the dotted line) result in coefficients of 1, indicating perfect association (between-subject variance). ICC between the two variables in this dataset, however, is –0.06, indicating poor agreement (over time or between raters). Generally, ICC tend to be somewhat lower than Pearson or Spearman correlations, and may be considerably lower if within-subjects variance is large.

Table 4.1: Example of Spreadsheet Prepared for Intraclass Correlation

Subject	Var1	Var2
a1	1.00	4.00
a2	2.00	5.00
a3	3.00	6.00
a4	4.00	7.00
a5	5.00	8.00
a1	4.00	1.00
a2	5.00	2.00
a3	6.00	3.00
a4	7.00	4.00
a5	8.00	5.00

In order to calculate intraclass correlations the dataset was prepared in the following way (see Table 4.1; Dunn 1989). For any given variable, data from Scoring I was replicated in the corresponding column of that variable at Scoring II by copying these data below the data points from Scoring II (in the same order). Likewise, for the same variable the data points from Scoring II were copied below the data points in the corresponding variable at Scoring I. This procedure yields a 'doubled-up' data file with twice the original sample size. ICC were then computed using Pearson's correlation coefficients between the pair of variables. Coefficients were tested for statistical significance based on the original sample size N. Although exact p-values are stated throughout the thesis, testing for significance (two-tailed) of ICC based on a Pearson's r table (Gravetter & Wallnau 1996) means that significance is given only relative to the nearest landmark (i.e. < or > 0.01, 0.02, 0.05 and 0.10). In order to provide an estimate of how Pearson and ICC coefficients differ in this dataset both coefficients are reported. All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS), Release 10.0.7 (SPSS Inc., Chicago, Ill).

4.2.3 Results

4.2.3.1 Correlations between Scoring I and Scoring II

As can be seen from Table 4.2, all Pearson correlations and ICC were of considerable magnitude and highly significant. Pearson correlations and ICC were the same or very similar for most variables, and Pearson coefficients were never smaller than ICC.

Table 4.2: Pearson and Intraclass Correlations for Intra-rater Reliability of Battery I

	Pearson	**Intraclass**
SPEM gain 10°/s (%)	r=0.85; p<0.001	r=0.82; p<0.01
SPEM gain 24°/s (%)	r=0.89; p<0.001	r=0.82; p<0.01
Anticipatory saccades 10°/s (N/sec)	r=0.95; p<0.001	r=0.92; p<0.01
Anticipatory saccades 24°/s (N/sec)	r=0.89; p<0.001	r=0.86; p<0.01
Catch-up saccades 10°/s (N/sec)	r=0.97; p<0.001	r=0.97; p<0.01
Catch-up saccades 24°/s (N/sec)	r=0.98; p<0.001	r=0.96; p<0.01
Saccades total 10°/s (N/sec)	r=0.99; p<0.001	r=0.99; p<0.01
Saccades total 24° (N/sec)	r=0.98; p<0.001	r=0.98; p<0.01
Fixation (N saccades/sec)	r=0.98; p<0.001	r=0.90; p<0.01
Antisaccade gain (%)	r=0.93; p<0.001	r=0.92; p<0.01
Antisaccade latency (ms)	r=0.92; p<0.001	r=0.89; p<0.01
Antisaccade error rate (%)	r=0.94; p<0.001	r=0.93; p<0.01
Prosaccade gain (%)	r=0.91; p<0.001	r=0.91; p<0.01
Prosaccade latency (ms)	r=0.91; p<0.001	r=0.91; p<0.01

For frequencies of saccades during SPEM, all ICC≥0.86. As expected, agreement for combined frequencies of saccades (adding AS and CUS) at the two velocities was better (ICC=0.99 and ICC=0.98) than for AS and CUS considered separately. ICC for SPEM gain were slightly lower (r=0.82), but still highly significant. ICC for fixation as well as prosaccade and antisaccade variables were all highly significant and ≥0.89.

4.2.3.2 Correlations between Rater 1 and Rater 2

Pearson and intraclass correlations are given in Table 4.3. Inter-rater reliabilities for all variables were high, with ICC ranging from 0.77 to 0.98 and Pearson correlations ranging from 0.86 to 0.99. As above, Pearson correlations tended to be larger than ICC.

Table 4.3: Pearson and Intraclass Correlations for Inter-rater Reliability of Battery II

	Pearson	**Intraclass**
Fixation (N saccades/sec)	r=0.86; p=0.003	r=0.83; p<0.01
Antisaccade gain (%)	r=0.89; p=0.001	r=0.85; p<0.01
Antisaccade latency (ms)	r=0.97; p<0.001	r=0.94; p<0.01
Antisaccade error rate (%)	r=0.99; p<0.001	r=0.98; p<0.01
Prosaccade gain (%)	r=0.96; p<0.001	r=0.95; p<0.01
Prosaccade latency (ms)	r=0.91; p<0.001	r=0.77; p<0.01

4.2.4 Discussion

These findings show that the current eye movement scoring procedures have high intra- and inter-rater reliability, comparable to those of previous quantitative (Clementz et al 1990; Sweeney et al 1994b) and qualitative (O'Driscoll et al 1998; Rosse et al 1992a; Siever et al 1994; Spohn et al 1988) assessments of SPEM and fixation data as well as those of standardised neuropsychological tests used in schizophrenia research (Heaton et al 1993). Both types of reliability are important and necessary, but not sufficient, criteria in the process of establishing the validity of the current methods. As the EYEMAP scoring procedures are identical across eye movement batteries, intra-rater reliability coefficients of Battery I are assumed to generalise to Battery II and inter-rater reliability coefficients of Battery II are assumed to generalise to Battery I.

Identification of saccades (including antisaccade and prosaccade paradigms, as well as saccades occurring during smooth pursuit and fixation) and saccadic metrics (of the antisaccade and prosaccade tasks) was highly reliable (all ICC≥0.86). As expected, adding the frequencies of AS and CUS during pursuit into a combined saccadic frequency measure improved agreement. This indicates that some variability occurred between assessments in the identification of these two types of saccades, but that the overall quantification of saccades during SPEM was highly consistent. Variability in the identification of AS and CUS may stem from the fact that these two types of saccades are sometimes difficult to distinguish (see Chapter 3). Error term remaining in the analysis of the combined measure may stem from the incorrect inclusion of eye-blinks or artefacts (Calkins et al 2001), the rejection of saccades as artefacts or eye-blinks, or the incorrect categorisation of square-wave jerks.

SPEM gain measures had slightly lower intra-rater reliabilities, indicating the presence of greater examiner variance. This variability may be inherent in the choice of SPEM gain analysis method in this thesis. SPEM gain was evaluated using a 100ms window for each half-cycle of pursuit. Although placement of this window by the examiner was restricted to sections of clear pursuit in the middle third of each half-cycle, there was some scope for subjective choice and variability, thereby reducing scorer reliability.

An additional point of concern is that of the SPEM calibration task. As described in Chapter 3, a five-point calibration with target eccentricities of 0°, ±5° and ±10° was used. However, the range of target movement in the SPEM task was between ±15°. This might have led to poor calibration of SPEM data, especially data points exceeding ±10°.

While the gain measure was taken from the middle third of each half-cycle (between stimulus eccentricities of ±5°), it remains a possibility that poor calibration may have introduced additional error term, thereby adversely affecting the intra-rater agreement. Any effects of poor calibration should affect the SPEM gain measure more than the frequency of saccades during pursuit (Abel & Ziegler 1988).

Inter-rater agreement was generally very good. This indicates that error due to the subjective component of interactive EYEMAP analysis may be kept to a minimum if strict operational criteria are used. Establishing the consistency of scoring across two individuals from the same laboratory of course does not preclude the possibility of systematic error in the approach adopted. Further validation through scoring by experienced raters from an unrelated laboratory is required. Finally, due to practical limitations, SPEM data were not subjected to inter-rater analysis. Given the high intra-rater reliabilities of these variables the SPEM scoring procedures may be expected to be of acceptable validity; however, further analysis is required.

To conclude, interactive scoring procedures in EYEMAP have high intra- and inter-rater reliabilities, indicating that scoring is highly consistent over time within the same rater as well as across raters. High intra- and inter-rater reliabilities are necessary, albeit not sufficient, criteria for the validity of the scoring methods used in this thesis.

4.3 Concurrent Validity of the Oculomotor Test Batteries

4.3.1 Introduction

An important criterion in the development of a psychological measurement instrument is its concurrent validity (Anastasi & Urbina 1997; Rust & Golombok 1999). Concurrent validity is defined as the extent to which a new measurement tool is similar to, i.e. correlates with, an existing, conceptually related tool.

Factors leading to less than perfect concurrent validity ($r<1$) principally concern content sampling. Although a novel instrument may be partly based on, or developed out of, an existing instrument, it is almost certainly an aim of the researcher to provide an improvement over the existing tool. Therefore, deliberate differences in content (i.e. questionnaire items, stimulus specifications, etc.) are introduced, thought to improve the statistical or theoretical properties of the instrument. These factors may reduce the correlation between the two measures. In fact, it is argued that an extremely high

correlation between two measures (e.g. r>0.9) may indicate the redundancy of one of them (Anastasi & Urbina 1997; Rust & Golombok 1999).

There are reports confirming the concurrent validity of eye movement tasks across different stimulus display methods. Studies of smooth pursuit and saccadic eye movements in schizophrenia have employed different ways of displaying target stimuli, including pendulum, cathode ray oscilloscope (CRO), laser projector, light emitting diodes and video and computer monitors (Chapter 3). Shagass et al (1974) were the first to establish that SPEM dysfunction in schizophrenia could be observed using different ways of displaying target stimuli, with correlations between pendulum and CRO tracking ranging between r=0.51 and r=0.66. Levin et al (1981b) used a traditional pendulum device as well as an electronically driven rear-projection target. The correlation for SPEM performance between the two displays was r=0.91 (p=0.001).

In addition to correlations for performance measures across different display types, it is important to establish whether average performance levels are comparable. Smooth pursuit performance is affected by a number of stimulus properties, such as target velocity (Leigh & Zee 1999), attentional salience of the stimulus (Sweeney et al 1994b) and physical background of the target display (Hutton et al 2000). However, using comparable target velocities, Levin et al (1981b) observed that there were no significant differences in SPEM performance across the pendulum and rear-projection methods. These findings indicate that mere hardware specifications (unlike changes in the 'cognitive' properties of the stimulus) are unlikely to affect smooth pursuit performance, or to lead to the observation of pursuit dysfunction in the schizophrenia patient group.

Little is known regarding the differences or correlations between saccadic and fixation performance measures across different stimulus display methods. Given the findings from SPEM studies it may be reasonable to expect moderate to high correlations between saccadic metrics across different stimulus displays. Again, performance *differences* may be observed depending on factors known to influence performance, such as presence or absence of a temporal gap between central and peripheral target, the amplitude of the peripheral target, or semantic properties of the stimulus (Klein et al 2000c; McDowell et al 1999; Paus 1991).

4.3.1.1 Aims

The present study had the following aims. 1) To establish the correspondence between the two oculomotor batteries used here. It was hypothesised that corresponding

performance measures from the two display methods would be correlated with each other. 2) To examine performance differences between the two batteries. No *a priori* hypotheses were formulated.

4.3.2 Method

4.3.2.1 Participants

Thirty participants (19 males, 11 females; age range 19-44 years, mean=27.17, SD=6.88) underwent assessment. Participants were recruited from amongst staff and students at Goldsmiths College and the Institute of Psychiatry. All participants were free of major psychiatric disorder by self-report. All participants provided written consent after the study details had been fully explained to them. The study was approved by the Ethics Committee of the Department of Psychology, Goldsmiths College, University of London.

4.3.2.2 Eye Movement Assessment

Participants underwent assessment on Battery I and Battery II. Order of administration was counterbalanced, such that 13 participants were tested on Battery I first and Battery II second and 17 participants were tested in the opposite order.

The oculomotor variables that were used in this analysis were SPEM gain and anticipatory saccade (AS) and catch-up saccade (CUS) frequency at each velocity; frequency of saccades during fixation; antisaccade error rate, gain and latency; and prosaccade gain and latency. In order to provide additional information on how performance measures were related across studies, SPEM gain and frequencies of saccades during pursuit were averaged across target velocities.

One participant's SPEM data from Battery II at 0.25Hz and one participant's SPEM data from Battery II at 0.75Hz were unusable due to fatigue. One participant's fixation data from Battery II was unavailable because of data storage error and one participant's fixation data from Battery II was unusable due to fatigue.

4.3.2.3 Statistical Analysis

Skewness of all oculomotor variables was assessed. Variables were transformed using square or square root transformations if skewness values were less than –1 or exceeded

1, respectively. All statistical analyses reported below were carried out using SPSS Release 10.0.7 (SPSS Inc., Chicago, Ill).

4.3.2.3.1 Effects of Age and Sex

Pearson correlations were carried out between age and oculomotor variables. Males and females were compared on oculomotor performance using multivariate analysis of variance (MANOVA); separate analyses were carried out for Battery I and II.

4.3.2.3.2 Intercorrelations between Oculomotor Measures from Batteries I and II

For SPEM variables, Pearson correlations were carried out between batteries on averaged measures of gain, AS frequency and CUS frequency. Further, as each battery used a SPEM stimulus velocity of 24°/s, Pearson correlations were carried out between gain, AS frequency and CUS frequency at this velocity. For visual fixation and saccadic variables, Pearson correlations were carried out for corresponding variables across batteries.

4.3.2.3.3 Differences between Oculomotor Measures from Batteries I and II

Repeated-measures t-tests were carried out between corresponding saccadic and fixation variables in order to assess differences between stimulus displays. For SPEM variables, t-tests were carried out comparing SPEM gain, AS and CUS at 24°/s across batteries. Averaged SPEM measures were not included in the repeated-measures analysis, as the average target velocities of the two batteries did not correspond.

4.3.3 Results

A number of variables were skewed and were transformed accordingly, normalising all distributions (-1<skewness<1). However, results of analyses using *untransformed* variables are reported below, as these were very similar to those using transformed variables, with the exception of frequency of saccades during fixation, as noted below. Descriptive statistics of oculomotor measures are given in Table 4.4. These are generally comparable to performance data reported in previous studies of healthy individuals. Average antisaccade correction rates for Battery I (100%) and Battery II (99.36%; SD=2.09) were very high, indicating that participants were willing and able to follow instructions and perform the task (McDowell & Clementz 1997).

Table 4.4: Descriptive Statistics of Oculomotor Variables from Batteries I & II, Pearson Correlations for Concurrent Validity, and Repeated Measures t-tests (N=30)

	Battery I		**Battery II**		**Pearson**	**t-test**
	Mean	**SD**	**Mean**	**SD**		
SPEM gain 10°/s (%)	103.39	7.96	-	-	-	-
SPEM gain 12°/s (%)	-	-	99.02	8.17	-	-
SPEM gain 24°/s (%)	98.11	8.11	96.41	11.04	r=0.25; *p*=0.18	t=0.78; df=29; *p*=0.44
SPEM gain 36°/s (%)	-	-	89.05	12.88	-	-
SPEM gain 48°/s (%)	-	-	68.82	17.26	-	-
SPEM gain average (%)	100.75	6.60	88.03	9.92	r=0.17; *p*=0.36	-
Anticipatory saccades 10°/s (N/sec)	0.16	0.18	-	-	-	-
Anticipatory saccades 12°/s (N/sec)	-	-	0.15	0.19	-	-
Anticipatory saccades 24°/s (N/sec)	0.50	0.34	0.43	0.31	r=0.63; p<0.001	t=1.21; df=29; *p*=0.24
Anticipatory saccades 36°/s (N/sec)	-	-	0.56	0.36	-	-
Anticipatory saccades 48°/s (N/sec)	-	-	0.44	0.33	-	-
Anticipatory saccades total (N/sec)	0.27	0.21	0.31	0.20	r=0.72; *p*<0.001	-
Catch-up saccades 10°/s (N/sec)	0.11	0.10	-	-	-	-
Catch-up saccades 12°/s (N/sec)	-	-	0.30	0.10	-	-
Catch-up saccades 24°/s (N/sec)	0.74	0.37	1.01	0.38	r=0.45; *p*=0.01	t=-3.73; df=29; *p*=0.001
Catch-up saccades 36°/s (N/sec)	-	-	1.76	0.69	-	-
Catch-up saccades 48°/s (N/sec)	-	-	2.32	0.71	-	-
Catch-up saccades total (N/sec)	0.31	0.13	0.93	0.26	r=0.37; *p*=0.04	-
Fixation (N saccades/sec)	0.030	0.05	0.02	0.04	r=0.41; *p*=0.03 †	t=0.85; df=27; *p*=0.40
Antisaccade gain (%)	-92.34	21.84	-111.68	36.44	r=0.39; *p*=0.03	t=3.06; df=29; *p*=0.005
Antisaccade latency (ms)	279.78	34.13	288.63	36.43	r=0.32; *p*=0.09	t=-1.10; df=29; *p*=0.28
Antisaccade error rate (%)	14.65	11.87	21.89	14.61	r=0.49; *p*=0.007	t=-2.85; df=29; *p*=0.008
Prosaccade gain (%)	103.34	9.11	100.43	11.38	r=0.29; *p*=0.13	t=1.64; df=29; *p*=0.11
Prosaccade latency (ms)	174.30	15.09	189.53	25.00	r=0.36; *p*=0.05	t=-3.95; df=29; *p*<0.001

Legend:
† transformed variables: r=0.32 (*p*=0.10)

4.3.3.1 Effects of Age and Sex

For Battery I, age was correlated significantly with prosaccade gain (r=-0.37; p=0.045). For Battery II, age was correlated significantly with antisaccade gain (r=0.41; p=0.03), antisaccade latency (r=0.42; p=0.02), prosaccade gain (r=-0.48; p=0.07) and CUS frequency at 36°/s (r=0.44; p=0.02) and at trend level with SPEM gain at 48°/s (r=-0.35; p=0.06). No other correlations were significant (all r<0.31; all p>0.10).

For Battery II, females had longer prosaccade latency (F[1,26]=4.29; p=0.049). For Battery II, males had higher antisaccade error rate (F[1,26]=4.73; p=0.04). No other analyses were significant (all p>0.06).

Analyses of age and sex indicate that effects on oculomotor performance were very small and inconsistent. These variables are thus not further considered in the following analyses of Chapter 4.

4.3.3.2 Intercorrelations between Oculomotor Measures from Batteries I and II

Pearson correlation coefficients and levels of statistical significance for pairs of related variables are presented in Table 4.4. Correlations between SPEM gain measures (at 24°/s and averaged) across batteries did not attain statistical significance (both p>0.18). Correlations between AS frequencies across tasks were significant for the 24°/s target (r=0.63; p<0.001) and averaged velocities (r=0.72; p<0.001). Rates of CUS were significantly correlated across batteries for the 24°/s target (r=0.45; p=0.01) as well as averaged velocities (r=0.37; p=0.04). Frequency of saccades per second during visual fixation were significantly correlated across batteries (r=0.41; p=0.03). However, as noted above, frequencies of saccades during fixation from both batteries were positively skewed (Battery I: 2.12; Battery II: 1.74). The correlation across tasks using transformed variables was slightly lower and failed to reach statistical significance (r=0.32; p=0.10).

For antisaccade gain and error rate as well as prosaccade latency, correlations across batteries were significant (all p<0.05). There was a trend for a correlation between antisaccade latencies (r=0.32; p=0.09). Prosaccade gain was not significantly correlated (r=0.29; p=0.13). Inspection of the scatter plot, however, indicated that there was a

general pattern of a positive association between the two variables in the presence of a single case falling outside this pattern. Spearman rank correlation[19] was rho=0.39 (p=0.03). Pearson correlation excluding this case was r=0.35 (p=0.06), further confirming the outlier status and disproportionate influence on the result of this participant.

4.3.3.3 Differences between Oculomotor Measures from Batteries I and II

The results of repeated measures t-tests between pairs of variables across tasks are summarised in Table 4.4. Fixation performance, SPEM gain at 24°/s and AS rate at 24°/s did not differ across batteries (all p>0.24). Battery II elicited significantly more CUS during pursuit at 24°/s than Battery I (t=-3.73; df=29; p=0.001).

There were no differences between batteries for antisaccade latency and prosaccade gain. Performance on Battery II was characterised by higher antisaccade error rate (t=-2.85; df=29; p=0.008), larger antisaccade gain (t=3.06; df=29; p=0.005) and longer prosaccade latency (t=-3.95; df=29; p<0.001).

4.3.4 Discussion

4.3.4.1 Key Findings

The key findings from this study are as follows. 1) SPEM (frequency of saccades), fixation and saccadic eye movement performance measures were largely correlated across Batteries I and II; smooth pursuit gain and prosaccade gain were not significantly correlated. This finding indicates that the two target displays largely correspond in their measurement of oculomotor function in healthy individuals, furnishing evidence of the tests' concurrent validity. 2) Specific differences across tasks were obtained, primarily for saccadic variables. Possible explanations for these differences will be put forward below.

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[19] Parametric tests, such as Pearson correlation, have low power if a variable's distribution departs from normality (Tabachnick & Fidell 2001).

4.3.4.2 Intercorrelations between Batteries

Validation is an important step in the development of a novel measurement instrument. The set of oculomotor tasks specifically developed for research reported in this thesis (Battery II) meets a number of validity criteria. First, the stimulus display and eye movement recording methods have high face validity, as their purpose of eliciting and recording eye movements is unmistakable and the tasks were generally found to be acceptable to participants. Second, content validity was ensured by making the stimulus properties comparable to previously published tasks through an extensive review of the literature (see Chapter 3). Finally, this study provides evidence of concurrent validity, i.e. the correspondence of the new set of tasks (Battery II) with an existing one (Battery I).

Rates of AS and CUS were correlated significantly across batteries. This correlation, which also includes error term from the brief temporal gap between tasks (see Section 4.5) and examiner variance (see Section 4.2), suggests that individual differences in the control of these saccades are not strongly influenced by the physical properties of the two stimulus displays used here. This assumption is further bolstered by the lack of differences in AS rate between the two tasks, although the reason for an increased CUS rate in Battery II is unclear. The reliable identification of AS is particularly important given the role of this measure as a putative schizophrenia endophenotype (Ross et al 1998e, 1999b, 1999c, 2001).

SPEM gain scores were not significantly correlated across display methods, posing a problem for the validity of this task. One possible source of error might be the slightly lower intra-rater reliability of the SPEM gain measure (Section 4.2). Additionally, poor calibration may partly account for the low correlations. Of the SPEM measures used here, gain is more likely to be affected by problems with calibration than saccades during pursuit (Abel & Ziegler 1988). Another possibility is, as before, the limited width of the window used in the SPEM gain analysis (100ms). This factor might have lowered the reliability of SPEM gain assessment. The possibility remains that systematic differences in stimulus properties between the two tasks adversely affected the correlation. However, this possibility may be discounted for the following reasons. First, there were no differences in SPEM gain for the 24°/s target across display methods. Second, systematic differences between tasks may occur without affecting the (Pearson) correlation (Bartko 1991).

Despite the relative infrequency of saccades during fixation, this measure was comparable across tasks; rates of saccades were correlated and did not differ between display methods. However, using transformed variables somewhat lowered the correlation between the two, probably due to the skewed distributions of the variables, as most participants emitted only very few saccades during fixation.

Saccadic performance measures, with the exception of prosaccade gain, were also correlated across display methods. The correlation for prosaccade gain between tasks was in the expected direction, approached statistical significance after exclusion of an outlier and was significant using an ordinal level correlation, which is less sensitive to the effects of outliers.

4.3.4.3 Differences between Batteries

Significant differences between batteries were obtained for prosaccade latency, antisaccade gain and antisaccade error rate. These are discussed in the following.

Battery II was associated with significantly longer prosaccade latency and non-significantly longer antisaccade latency than Battery I. The reason for this may have been the duration of central fixation target presentation, which varied randomly between 1,000ms and 2,000ms in the saccade tasks of Battery II, but was fixed at 500ms and 1,000ms in the pro- and antisaccade tasks, respectively, of Battery I. Quasi-random variation in central fixation point duration means that peripheral target presentation is temporally unpredictable. Temporally predictable targets have been shown to lead to faster latency than temporally unpredictable targets (Zahn et al 1998). Indeed, the fastest saccadic latencies are obtained when target presentation is both *temporally and spatially* predictable (Hutton et al 2001a; Karoumi et al 1998b). The present findings are compatible with these effects.

Battery II was also associated with a higher antisaccade error rate. One possible explanation for this finding is the greater variability in target locations in Battery II. In this task the target appeared in two possible locations on either side of the central fixation point, whereas in the antisaccade task of Battery I only one location was used on either side. As participants were instructed to perform eye movements in opposite direction and *equal distance to* the peripheral target, it is possible that some errors occurred during attempts to encode target location in order to execute spatially accurate antisaccades. Greater choice in target locations would, therefore, require

increased covert attentional processing and might be associated with a greater probability to commit errors.

Another possible explanation for the difference in antisaccade error rate comes from a study by McDowell et al (1999). These researchers reported greater statistical separation between schizophrenia patients and healthy participants for a far (±16°) than a near (±8°) antisaccade target. It was found that healthy individuals made more reflexive errors when the antisaccade target was presented closer to the central fixation point. In the current study the antisaccade task of Battery II used target eccentricities of ±6° and ±12° while the Battery I task used ±15° targets. It may be hypothesised that target occurrences closer to the central fixation point led to greater average error rate in the Battery II antisaccade task.

Finally, while antisaccade gain scores were correlated across stimulus displays, differences were observed between tasks. The Battery I antisaccade task led to slightly hypometric antisaccades and the Battery II task led to slightly hypermetric antisaccades. It is more common for a primary saccade to slightly undershoot the target (Leigh & Zee 1999). The reason for the slight overshoot in the Battery II task is unclear, but may reflect spatial inaccuracies due to greater variability in stimulus locations.

4.3.4.4 Conclusions

To conclude, the two oculomotor batteries employed here demonstrated reasonable concurrent validity for measures of SPEM saccadic frequency, fixation and saccadic performance. Correlations for SPEM gain across tasks, however, were disappointing, pointing to low correspondence of the two batteries for this measure. Specific performance differences between methods occurred. The antisaccade task of Battery II was shown to be more difficult than that of Battery I (as indexed by higher error rate and slightly longer latency). Increased prosaccade (and, non-significantly, antisaccade) latency of Battery II might be due to characteristics of stimulus durations.

4.4 Internal Consistency of Eye Movement Performance

4.4.1 Introduction

An important reliability criterion is an instrument's internal consistency (Anastasi & Urbina 1997; Rust & Golombok 1999). Internal consistency is a measure of the

reliability of content sampling, or homogeneity of items. A test consisting of a set of highly homogenous items (in terms of content, difficulty, or format) will be associated with consistent within-test performance. A heterogeneous selection of items, however, may pose a threat to internal consistency, leading to variable performance across items within the same test.

Only one previous study on internal consistency of SPEM performance could be identified (Cegalis & Sweeney 1979); these authors reported high consistencies of saccadic frequency and spatial error for different intervals of smooth pursuit tracking. No further reports of internal consistencies of eye movement variables could be identified through performing a comprehensive literature search of the *Medline* and *PsycINFO* databases, reading of relevant publications and consulting an eye movement mailing list (http://www.jiscmail.ac.uk/lists/EYE-MOVEMENT.html).

Stimulus properties of oculomotor paradigms used here do not vary within one assessment, with the exception of randomised central target presentation in the saccadic tasks of Battery II. Therefore, high internal consistency may be expected. However, variability of human performance over time, due to effects of fatigue, motivation and learning, may affect the internal consistency of oculomotor paradigms. Additionally, these effects may lead to systematic improvement or deterioration in performance within a test session.

4.4.1.1 Aims

The aims of this study were, therefore, as follows. 1) To assess the internal consistency of the current eye movement paradigms by calculating Cronbach's coefficient alpha (Cronbach 1951). 2) To examine whether there were any significant within-session changes in performance levels, using consecutive time segments of performance within each task.

4.4.2 Method

4.4.2.1 Participants and Eye Movement Data Scoring

Eye movement data of participants from study 4.3 (N=30) was used in this analysis.

4.4.2.2 Statistical Analysis

All statistical analyses were carried out using SPSS Release 10.0.7 (SPSS Inc., Chicago, Ill). Oculomotor variables were assessed for normality of distributions and transformed accordingly if positively (skewness>1) or negatively (skewness<-1) skewed. Transforming variables did not noticeably affect internal consistencies or within-session changes; therefore, results reported below are based on untransformed variables.

4.4.2.2.1 Internal Consistency

Cronbach's coefficient alpha (Cronbach 1951) was used as an estimate of internal consistency (cf. Lund et al 1995). Coefficient alpha is the most appropriate measure of internal consistency for scales (or tests) with items that depart from a binary response format (e.g. 1=correct; 0=incorrect) (Anastasi & Urbina 1997).

In order to compute Cronbach's alpha, sub-scores for SPEM and saccadic performance measures were calculated. Data at the item level (i.e. one SPEM half-cycle, one saccade trial) could not be used for the following reasons: First, regarding SPEM gain, due to eye-blinks or other artefacts, gain measures could occasionally not be obtained for individual half-cycles. Second, AS and CUS during smooth pursuit and saccades during fixation do not occur as a function of fixed trials, vary in frequency between people and can, therefore, not be used in an analysis at the item level. Third, similar problems of missing trials prevented the use of single trial data on the saccadic tasks.

Therefore, sub-scores were obtained for segments (time sections) of pursuit or saccadic eye movement recordings. For Battery I, each of the two blocks of SPEM traces at each velocity was divided into two equally long sections. Gain and frequencies of AS and CUS were obtained for the resulting four subsections at each velocity. For the antisaccade task, each of the three blocks of 8 trials was divided into two equally long sections. Likewise, regarding the prosaccade task, each of the three blocks of 12 trials was divided into two equally long sections. Both antisaccade and prosaccade tasks, therefore, yielded six segments each. Saccadic metrics were then obtained for each segment. For visual fixation, internal consistency was calculated for three segments consisting of the central as well as the two peripheral target presentations.

For Battery II, SPEM traces for each velocity were divided into four sections of equal temporal duration each. Gain and frequencies of AS and CUS were then obtained for each section at each velocity. For antisaccade and prosaccade tasks, four sections of

equal duration were obtained each. Saccadic metrics were then obtained for each section. For visual fixation, internal consistency was calculated for four segments consisting of the two peripheral and two central target presentations.

Cronbach's coefficient alpha was thus calculated for each variable on the basis of the scores from three to six time segments. Larger alpha coefficients indicate better internal consistency, i.e. higher intercorrelations between subscores. Cronbach's alpha has been shown to increase with the number of items in the scale (Anastasi & Urbina 1997). Therefore, it may be criticised that failing to use individual item (or trial) data might adversely affect the internal consistencies reported here. However, using segments of performance data as 'items' is believed to be a robust approach, as each segment already represents an average performance score of a number of trials. That this segmentation does indeed provide an appropriate, and robust, item pool for computing Cronbach's coefficient alpha will briefly be demonstrated using a dataset of psychophysical data collected and published by the author (Ettinger & Corr 2001).

Data from a psychophysical decision task were collected, consisting of 200 identical trials per participant. Each trial required the participant to make a decision (as to the occurrence of a stimulus) and was scored as 1 ('correct') or 0 ('wrong'). Data were gathered amongst 57 participants (mean number of correct trials=140.19; SD=16.74). Cronbach's alpha for this scale of 200 items at the item level was 0.85; for 20 segments of 10 consecutive trials each it was 0.86; and for 4 segments of 50 consecutive trials each Cronbach's alpha was 0.87. This finding demonstrates that truncating multi-trial performance data into segments of consecutive trials does not present a severe threat to the assessment of internal consistency using Cronbach's coefficient alpha.

4.4.2.2.2 Within-session Changes

In order to examine whether performance levels changed over sections of consecutive trials, repeated measures analyses of variance (ANOVA) were carried out for each variable. Due to the large number of analyses statistical significance was considered at the level of $p<0.01$ and statistical trends were considered at the level of $0.05>p\geq0.01$.

4.4.3 Results

4.4.3.1 Internal Consistency

Cronbach's alpha for SPEM and saccadic variables of both Batteries I and II are given in Table 4.5. As can be seen, most coefficients were high, indicating good internal consistency. Coefficients were larger than 0.70 for all but two variables of Battery I, with five coefficients ≥ 0.80. Cronbach's alpha for antisaccade error rate of Battery I was relatively low (0.57). When this analysis of error rate was rerun combining consecutive pairs of segments to yield three performance scores, coefficient alpha increased to 0.65.

All but three coefficients for variables from Battery II indicated very high internal consistency (alpha≥0.73). Coefficients for AS at 48°/s and CUS at 12°/s were 0.43 and 0.34, respectively. Coefficients for fixation data from both batteries were moderate.

4.4.3.2 Within-session Changes

For Battery I, there was a trend for a linear improvement in SPEM gain scores at 24°/s ($F[3,87]=2.95$; $p=0.04$). There was a significant linear reduction in CUS frequency at 24°/s ($F[3,87]=27.34$; $p<0.001$). There was a trend for a significant change in AS frequency at 24°/s over time, with greatest frequencies observed in the first and third segments ($F[3,87]=27.34$; $p<0.001$). Within-subjects contrasts revealed that this was not a linear ($F[1,29]=0.61$; $p=0.44$) but a cubic effect ($F[1,29]=9.32$; $p=0.005$).

A trend for a significant change in antisaccade gain over time was observed, with smallest gain scores observed for segments 3-5 ($F[5,125=2.60$; $p=0.03$). Within-subjects contrasts indicated that this was not a linear ($F[1,25]=0.11$; $p=0.74$) but a quadratic effect ($F[1,25]=6.68$; $p=0.02$). There was a significant linear reduction in prosaccade latency over time ($F[5,115]=6.64$; $p<0.001$).

For Battery II, CUS frequency at 12°/s dropped significantly and linearly over time ($F[3,84]=6.09$; $p=0.001$). There was a trend for a linear reduction of CUS frequency at 36°/s ($F[3,81]=3.39$; $p=0.02$). AS frequency at 36°/s increased significantly and linearly ($F[3,83]=8.48$; $p<0.001$). There were no other within-session performance changes for Battery II.

Table 4.5: Cronbach's Coefficient Alpha and ANOVA for Within-session Changes on SPEM and Saccadic Variables from Batteries I & II

	Cronbach's alpha		**Repeated measures ANOVA**	
	Battery I	**Battery II**	**Battery I**	**Battery II**
SPEM gain 10°/s (%)	0.71	-	F[3,81]=1.18; p=0.32	-
SPEM gain 12°/s (%)	-	0.83	-	F[3,84]=0.20; p=0.89
SPEM gain 24°/s (%)	0.77	0.85	F[3,87]=2.95; p=0.04	F[3,84]=0.54; p=0.65
SPEM gain 36°/s (%)	-	0.85	-	F[3,81]=0.13; p=0.94
SPEM gain 48°/s (%)	-	0.88	-	F[3,84]=1.63; p=0.19
Anticipatory saccades 10°/s (N/sec)	0.88	-	F[3,84]=1.34; p=0.27	-
Anticipatory saccades 12°/s (N/sec)	-	0.88	-	F[3,84]=2.01; p=0.12
Anticipatory saccades 24°/s (N/sec)	0.80	0.80	F[3,87]=3.84; p=0.01	F[3,84]=1.62; p=0.19
Anticipatory saccades 36°/s (N/sec)	-	0.73	-	F[3,81]=8.30; p<0.001
Anticipatory saccades 48°/s (N/sec)	-	0.43	-	F[3,84]=1.24; p=0.30
Catch-up saccades 10°/s (N/sec)	0.74	-	F[3,84]=0.12; p=0.95	-
Catch-up saccades 12°/s (N/sec)	-	0.34	-	F[3,84]=6.32; p=0.001
Catch-up saccades 24°/s (N/sec)	0.76	0.76	F[3,87]=27.34; p<0.001	F[3,84]=1.13; p=0.34
Catch-up saccades 36°/s (N/sec)	-	0.85	-	F[3,81]=3.30; p=0.03
Catch-up saccades 48°/s (N/sec)	-	0.82	-	F[3,84]=2.34; p=0.08
Fixation (N saccades/sec)	0.60	0.45	F[2,58]=0.60; p=0.55	F[3,84]=0.95; p=0.42
Antisaccade gain (%)	0.94	0.94	F[5,125]=2.60; p=0.03	F[3,87]=0.03; p=0.99
Antisaccade latency (ms)	0.80	0.85	F[5,125]=1.64; p=0.15	F[3,87]=0.71; p=0.55
Antisaccade error rate (%)	0.57	0.87	F[5,135]=0.61; p=0.69	F[3,87]=0.77; p=0.52
Prosaccade gain (%)	0.71	0.91	F[5,115]=0.81; p=0.55	F[3,87]=1.82; p=0.15
Prosaccade latency (ms)	0.82	0.89	F[5,115]=6.64; p<0.001	F[3,87]=0.44; p=0.73

4.4.4 Discussion

4.4.4.1 Key Findings

This study has the following findings. 1) Internal consistencies of oculomotor variables investigated in this thesis were generally very good. With a few exceptions, coefficients were larger than 0.70. 2) Some within-session changes in performance levels were observed; however, these were fairly inconsistent.

4.4.4.2 Internal Consistency

This is the first study to thoroughly investigate the internal consistency of a comprehensive set of oculomotor tasks used in schizophrenia spectrum research. Most of the key measures demonstrated very good internal consistency. Internal consistencies for both fixation tasks were relatively low, probably due to the small number of saccades occurring during fixation in this healthy sample. Possibly the greatest challenge to the validity of endophenotypic markers in this thesis is the slightly disappointing coefficient alpha for antisaccade error rate of Battery I.

The reason for this low reliability might lie in the stimulus properties of the Battery I antisaccade task. As this task involves only three blocks of a total of 24 trials, each time segment in the reliability analysis included a maximum of only four trials. This means that for each segment only four different error scores (25, 50, 75 and 100%) may have occurred. Due to missed trials (e.g. eye-blinks) other values were in fact also observed (e.g. 33.33 or 66.67%), however the overall between-subject variation of scores was small. This statistical problem, rather than the neurophysiological correlates of antisaccade performance *per se*, probably led to the task's unsatisfactory internal consistency. Evidence for this hypothesis comes from the finding that antisaccade error rate from Battery II was highly consistent. Additionally, combing the six time sections of the Battery I task into three consecutive segments, thereby allowing for greater within-segment variability of scores, improved Cronbach's alpha to 0.65.

Internal consistencies reported here are largely comparable to those reported by Cegalis and Sweeney (1979) and those of neuropsychological (Wechsler 1981; Wechsler 1987), clinical (Moniz-Cook et al 2001) and psychometric schizotypy (Eysenck & Eysenck 1991; Vollema & van den Bosch 1995) measures used in schizophrenia spectrum research, although highly homogenous tests tend to possess better reliabilities (Nelson

1991). Lund et al (1995) reported Cronbach's alpha coefficients for EEG power spectra; these were somewhat higher than the current reliabilities, with most coefficients above 0.9.

Internal consistency of psychophysiological measures is a non-trivial matter. Most assessments of brain function using psychological or psychophysiological tasks rely on obtaining and subsequently averaging multiple performance samples (e.g. trials). Calculating averages is often necessary for further statistical analysis. However, the validity of this approach assumes that measures of brain function obtained across an extended period of time, or several trials, are consistent. With a few exceptions (Lund et al 1995) this consistency has not been demonstrated. The present study demonstrates consistent oculomotor control and a relative absence of consistent significant within-session practice effects in healthy individuals (with the exception of some improvement on the SPEM task), thereby validating the subsequent averaging of performance data for each participant. The absence of significant within-session deterioration of performance is of importance given the influence of fatigue or loss of motivation, which may ensue after a large number of trials. This finding suggests that tasks from both batteries were of acceptable length for healthy individuals. The extent to which these reliability findings generalise to schizophrenia patients remains to be investigated.

4.4.4.3 Within-session Changes

Some within-session changes were observed. These were fairly patchy, but appeared to be most consistent for SPEM. Improvements in smooth pursuit performance were observed for SPEM gain and CUS frequency, consistent with the notion that the eye requires some time to optimally follow a moving target (Leigh & Zee 1999). However, an increase in AS frequency over time was also observed at one velocity; the reason for this is unclear. Additionally, there was some evidence for faster reaction times of prosaccades over time in Battery I, pointing to effects of learning. As the order of stimulus presentation of a Battery I prosaccade block is quasi-random but employs fixed inter-stimulus durations and three blocks of identical trials were presented, this pattern of learning is compatible with effects of procedural learning commonly observed on psychomotor tasks with such characteristics (Corr et al 1997; Kumari et al 1997a; Kumari et al 2002). The spatial and temporal random sequence of target movements on the Battery II task is most likely to have prevented this effect. Interestingly, no significant linear within-session changes in antisaccade performance were obtained (see Section 4.4 for between-session effects).

4.4.4.4 Conclusions

To conclude, the current oculomotor test batteries demonstrate good internal consistency. Antisaccade error rate of Battery I showed slightly disappointing reliability, most likely due to the small number of trials. Internal consistencies of Battery II were equal to or higher than those of Battery I, but never lower. Within-session practice effects were inconsistent across tasks and batteries, but point to small improvements in smooth pursuit performance, as indexed by increases in gain and reductions in CUS frequency over time.

4.5 Test-retest Reliability of Oculomotor Measures in Healthy Individuals

4.5.1 Introduction

An important characteristic of a putative endophenotype is its trait, rather than state, nature (Clementz 1998; Leboyer et al 1998; Ott 1991). Accordingly, a number of studies have investigated the temporal stability of eye movement performance in samples of healthy individuals as well as people with schizophrenia. As outlined above (Section 2.3.5.5.2), previous research indicates that both global and specific SPEM measures are relatively stable in schizophrenia patients and healthy controls over time intervals ranging from one week to two years, with correlation coefficients between about 0.5 and 0.9 (Campion et al 1992; Gooding et al 1994; Holzman et al 1973; Iacono & Lykken 1981; Rea et al 1989; Roy-Byrne et al 1995; Schlenker & Cohen 1995; Yee et al 1998).

There are relatively few studies of the temporal stability of saccadic eye movements. Good reliabilities of prosaccade velocity, accuracy, latency, as well as amplitude-duration and amplitude-peak velocity relationships have been observed (Iacono & Lykken 1979a; Versino et al 1993; Wilson et al 1993). Even fewer studies have addressed the antisaccade task, with two studies failing to show significant test-retest reliability (Klein & Berg 2001; Roy-Byrne et al 1995) and one study (Thaker et al 1989a) reporting test-retest reliabilities for antisaccade latency and error rate of $r>0.75$ periods from one week to one year.

These studies suggest that the duration of interval between test and retest is not systematically related to the magnitude of reliability coefficients. Therefore, any error

term that reduces the reliability of performance is unlikely to be accumulating over time (at least over periods of up to 1-2 years). Less than perfect test-retest reliability is, therefore, likely to be due to two separate sources of variance: error of measurement (methods) and effects of state measures on the neural circuitry of oculomotor control.

First, an individual's observed score on a behavioural (psychometric or psychophysiological) measure is assumed to reflect their true score plus error of measurement (Anastasi & Urbina 1997; Rust & Golombok 1999). Thus, to the extent that an individual's score on an eye movement task is invariant to state-related changes in the neural system of oculomotor control, less than perfect reliability will reflect error of measurement, which, in the case of oculomotor research, stems from eye movement recording (Reulen et al 1988) and data scoring (Section 4.1).

Second, however, a number of state variables are known to affect eye movement performance, thereby reducing reliability, irrespective of error associated with methodological issues. These variables include time of day (Roy-Byrne et al 1995; Schalen et al 1984), fatigue (Bahill & Stark 1975; Schalen et al 1984), caffeine intake (Litman et al 1989), smoking (Olincy et al 1998; Powell et al 2002; Thaker et al 1991), states of influenza or cold (Smith et al 1999) and motivational factors (Duka & Lupp 1997).

Another topic with relevance to studies investigating the temporal stability of oculomotor performance concerns that of practice effects. Significant practice effects on cognitive tests have been demonstrated in healthy individuals (Lezak 1983; Wechsler 1981; Wechsler 1987). These improvements in performance from first to second assessment (usually over periods of several days or weeks) are likely to be due to effects of learning, but might also reflect reduced anxiety levels due to increased familiarity with the task and laboratory setting. Healthy people generally do not show significant improvements on SPEM measures at retest (Campion et al 1992; Gooding et al 1994; Versino et al 1993). Regarding the antisaccade error rate, however, there is some evidence of practice effects (Green et al 2000; Klein et al 2002).

4.5.1.1 Aims

The present study had the following aims. 1) To investigate the temporal stability of the oculomotor Batteries I and II in a sample of healthy individuals over a period of about two months. Based on previous studies, moderate to good reliabilities were hypothesised. 2) To assess whether performance levels changed over time. Given

previous reports, no improvements on SPEM measures, but reductions in antisaccade error rate were hypothesised.

4.5.2 Method

4.5.2.1 Participants

The sample comprised a subgroup of the participants of study 4.3. Participants of study 4.3 had been informed in advance and agreed that they would be contacted for retest. Due to practical reasons (e.g. unwillingness or unavailability of participants), however, only twenty of these participants could be followed up. The sample consisted of fourteen males and six females. Ages ranged between 19-43 years (mean=26.15, SD=6.48). Participants repeated oculomotor assessments of study 4.2, with an average test-retest interval of 58.35 days (SD=19.40; range=38-105 days).

Participants who volunteered for retest did not differ from other participants on sex (χ^2=1.15; p=0.28), age (F[1,27]=2.51; p=0.13), or any oculomotor variables (all F<4.09; p>0.05), with the exception of lower saccadic frequency during fixation on Battery II (F[1,27]=5.73; p=0.03). It is thus assumed that the subsample used in the retest analysis did not differ consistently from participants who could not be recruited for retest.

4.5.2.2 Eye Movement Assessment

Batteries I and II were administered at assessment I and assessment II. Order of testing was counterbalanced as described in Section 4.3. Additionally, participants who were tested in order 1 at assessment I were tested in order 2 at assessment II and vice versa. Three participants were not tested on Battery I at follow-up due to limitations of time. One participant's SPEM data for Battery I was not available due to data storage error.

4.5.2.3 Statistical Analysis

All statistical analyses were carried out using SPSS Release 10.0.7 (SPSS Inc., Chicago, Ill). Skewness was assessed for all oculomotor variables. If variables were positively (>1) or negatively (<-1) skewed, variables were transformed accordingly.

4.5.2.3.1 TEST-RETEST RELIABILITY

In order to assess the test-retest reliability of oculomotor measures, intraclass correlations (ICC) were used (Bartko 1991; Roy-Byrne et al 1995). The data file was prepared as described above (Section 4.1). ICC were then computed using Pearson's correlation coefficients and tested for statistical significance based on the original sample size N. In order to provide an estimate of the differences in magnitude between the ICC and Pearson correlations, and to allow comparisons with previous studies (Campion et al 1992; Gooding et al 1994; Klein & Berg 2001; Schlenker & Cohen 1995), both coefficients are reported here.

Interestingly, Klein and Berg (2001) imply that Pearson's correlation coefficient is a more appropriate measure of test-retest stability of psychophysiological measure, as ICC assumes that "identical scores are obtained during the first and second measurement" (p. 706). This appears to be not so much an assumption, but a strength, of ICC, as it is sensitive to departures from this assumption. Therefore, ICC is believed to be the better measure of test-retest reliability (Bartko 1991).

4.5.2.3.2 BETWEEN-SESSION CHANGES

In order to probe for effects of repeated exposure on eye movement performance, repeated measures t-tests were calculated between pairs of oculomotor variables across assessments (Rosmark et al 1999). Due to the large number of analyses statistical significance for all below analyses was considered at the level of $p<0.01$ and statistical trends were considered at the level of $0.05>p\geq0.01$.

4.5.3 Results

A number of variables were positively or negatively skewed; transformations normalised distributions of all variables. As results based on untransformed variables were very similar to those of transformed variables, except where stated (Battery I antisaccade error rate), those from untransformed data are reported below.

Table 4.6 summarises descriptive statistics for oculomotor variables of Battery I from both assessments, Pearson correlations and ICC for each variable and the results of the repeated measures t-tests for each variable. Table 4.7 represents the same information for Battery II.

Table 4.6: Descriptive Statistics for Battery I at Assessments I & II, Pearson and Intraclass Correlations for Test-retest Reliability and t-tests for Between-session Changes (N=20)

	Assessment I		**Assessment II**		**Pearson**	**ICC**	**t-test**
	Mean	**SD**	**Mean**	**SD**			
SPEM gain 10°/s (%)	104.58	8.16	105.71	7.51	r=-0.06; p=0.81	r=-0.06; p>0.10	t=0.09; df=16; p=0.93
SPEM gain 24°/s (%)	98.27	8.23	99.83	6.52	r=0.29; p=0.27	r=0.28; p>0.10	t=-0.29; df=16; p=0.78
SPEM gain average (%)	101.42	6.98	102.77	6.13	r=0.06; p=0.83	r=0.06; p>0.10	t=-0.09; df=16; p=0.93
Anticipatory saccades 10°/s (N/sec)	0.12	0.19	0.12	0.14	r=0.46; p=0.07	r=0.43; p<0.10	t=-0.07; df=16; p=0.95
Anticipatory saccades 24°/s (N/sec)	0.43	0.32	0.45	0.27	r=0.55; p=0.02	r=0.53; p<0.05	t=-0.23; df=16; p=0.82
Anticipatory saccades total (N/sec)	0.22	0.21	0.23	0.17	r=0.51; p=0.04	r=0.49; p<0.05	t=-0.15; df=16; p=0.88
Catch-up saccades 10°/s (N/sec)	0.10	0.08	0.10	0.11	r=0.30; p=0.25	r=0.28; p>0.10	t=0.33; df=16; p=0.75
Catch-up saccades 24°/s (N/sec)	0.82	0.38	0.73	0.47	r=0.52; p=0.03	r=0.50; p<0.05	t=0.58; df=16; p=0.57
Catch-up saccades total (N/sec)	0.33	0.12	0.30	0.16	r=0.72; p=0.001	r=0.69; p<0.01	t=0.92; df=16; p=0.37
Fixation (N saccades/sec)	0.03	0.05	0.02	0.03	r=0.23; p=0.35	r=0.17; p>0.10	t=1.08; df=17; p=0.29
Antisaccade gain (%)	-91.19	17.57	-93.33	17.79	r=0.69; p=0.001	r=0.68; p<0.01	t=0.85; df=17; p=0.41
Antisaccade latency (ms)	277.41	39.11	267.33	29.49	r=0.71; p=0.001	r=0.63; p<0.01	t=1.76; df=17; p=0.10
Antisaccade error rate (%)	15.31	13.44	7.80	7.43	r=0.30; p=0.22 †	r=0.15; p>0.10 ‡	t=2.35; df=17; p=0.03
Prosaccade gain (%)	104.31	7.34	100.63	9.47	r=0.06; p=0.81	r=0.01; p>0.10	t=1.28; df=17; p=0.22
Prosaccade latency (ms)	175.93	16.35	179.72	21.05	r=0.76; p<0.001	r=0.72; p<0.01	t=-1.13; df=17; p=0.28

Legend:
† transformed variables: r=0.46 (p=0.06)
‡ transformed variables: ICC=0.35 (p=0.04)

Table 4.7: Descriptive Statistics for Battery II at Assessments I & II, Pearson and Intraclass Correlations for Test-retest Reliability and t-tests for Between-session Changes (N=20)

	Assessment I		**Assessment II**		**Pearson**	**ICC**	**t-test**
	Mean	**SD**	**Mean**	**SD**			
SPEM gain 12°/s (%)	98.47	8.29	95.69	9.00	r=0.09; p=0.71	r=0.06; p>0.10	t=1.10; df=18; p=0.29
SPEM gain 24°/s (%)	95.28	10.85	96.30	11.23	r=0.32; p=0.17	r=0.32; p>0.10	t=-0.35; df=19; p=0.73
SPEM gain 36°/s (%)	90.09	8.99	89.16	11.45	r=0.79; p<0.001	r=0.76; p<0.01	t=0.60; df=18; p=0.56
SPEM gain 48°/s (%)	72.65	15.98	71.57	14.14	r=0.69; p<0.001	r=0.68; p<0.01	t=0.40; df=19; p=0.69
SPEM gain average (%)	88.68	8.88	88.18	8.00	r=0.69; p<0.001	r=0.69; p<0.01	t=0.33; df=19; p=0.74
Anticipatory saccades 12°/s (N/sec)	0.14	0.21	0.14	0.19	r=0.93; p<0.001	r=0.92; p<0.01	t=0.45; df=18; p=0.66
Anticipatory saccades 24°/s (N/sec)	0.41	0.31	0.41	0.39	r=0.67; p=0.001	r=0.66; p<0.01	t=0.50; df=19; p=0.96
Anticipatory saccades 36°/s (N/sec)	0.63	0.37	0.51	0.33	r=0.80; p<0.001	r=0.75; p<0.01	t=1.95; df=18; p=0.07
Anticipatory saccades 48°/s (N/sec)	0.49	0.36	0.42	0.37	r=0.58; p=0.007	r=0.57; p<0.01	t=0.98; df=19; p=0.34
Anticipatory saccades total (N/sec)	0.32	0.21	0.30	0.22	r=0.88; p<0.001	r=0.87; p<0.01	t=0.78; df=19; p=0.44
Catch-up saccades 12°/s (N/sec)	0.28	0.09	0.26	0.15	r=0.42; p=0.07	r=0.36; p>0.10	t=1.60; df=18; p=0.13
Catch-up saccades 24°/s (N/sec)	1.02	0.40	0.98	0.26	r=0.65; p=0.002	r=0.59; p<0.01	t=0.53; df=19; p=0.60
Catch-up saccades 36°/s (N/sec)	1.84	0.68	1.73	0.68	r=0.63; p=0.004	r=0.63; p<0.01	t=0.60; df=18; p=0.60
Catch-up saccades 48°/s (N/sec)	2.39	0.75	2.59	0.74	r=0.58; p=0.007	r=0.55; p<0.01	t=-1.28; df=19; p=0.22
Catch-up saccades total (N/sec)	0.94	0.27	0.95	0.26	r=0.70; p=0.001	r=0.70; p<0.01	t=-0.21; df=19; p=0.84
Fixation (N saccades/sec)	0.009	0.02	0.003	0.008	r=0.74; p=0.01	r=0.45; p<0.10	t=1.46; df=16; p=0.16
Antisaccade gain (%)	-119.82	41.27	-98.59	29.05	r=0.50; p=0.02	r=0.35; p>0.10	t=-2.59; df=19; p=0.02
Antisaccade latency (ms)	284.15	32.47	277.39	26.94	r=0.69; p=0.001	r=0.65; p<0.01	t=1.25; df=19; p=0.23
Antisaccade error rate (%)	20.76	15.52	15.75	10.90	r=0.91; p<0.001	r=0.79; p<0.01	t=3.16; df=19; p=0.005
Prosaccade gain (%)	101.33	7.39	97.92	7.58	r=0.60; p=0.005	r=0.52; p<0.01	t=2.28; df=19; p=0.04
Prosaccade latency (ms)	184.95	16.99	189.30	18.48	r=0.76; p<0.001	r=0.73; p<0.01	t=-1.59; df=19; p=0.13

4.5.3.1 Test-retest Reliability

For all variables, Pearson correlations were the same or larger than ICC, but never smaller. For Battery I, significant or trend level ICC (and Pearson) were obtained for AS at 24°/s and total AS, CUS at 24°/s and total CUS, antisaccade gain and prosaccade and antisaccade latency.

SPEM gain, CUS at 10°/s, frequency of saccades during fixation, antisaccade error rate and prosaccade gain were not stable over time, although the direction of coefficients was as expected. As mentioned above, antisaccade error rate was positively skewed; using the transformed variable yielded a Pearson correlation of r=0.46 (p=0.06) and ICC=0.35 (p=0.04).

For Battery II, all but four ICC and all but three Pearson correlations were significant or reached trend level. Non-significant ICC and Pearson correlations were obtained for SPEM gain at 12°/s and 24°/s, CUS frequency at 12°/s (which approached trend level for Pearson correlation), frequency of saccades during fixation (which was significant for Pearson correlation) and antisaccade gain (which reached trend level for Pearson correlation).

4.5.3.2 Between-session Changes

For variables in Battery I, only antisaccade error rate changed at trend level (t=2.35; df=17; p=0.03). Participants tended to make fewer errors at assessment II (7.80%) than at assessment I (15.31%). Participants also made slightly faster latency antisaccades at assessment II, however this did not reach statistical significance (t=1.76; df=17; p=0.10). No other variables differed significantly over time (all p>0.22).

A significant reduction in antisaccade error rate was found for Battery II (t=3.16; df=19; p=0.005), with average rate dropping from 20.76% to 15.75%. Saccadic performance at assessment II was also characterised by more accurate antisaccade gain (t=-2.59; df=19; p=0.02) and slightly reduced prosaccade gain (t=2.28; df=19; p=0.04). For SPEM and fixation variables of Battery II no comparisons yielded significant changes, although participants made slightly fewer AS at 36°/s at second assessment (t=1.95; df=18; p=0.07).

4.5.4 Discussion

4.5.4.1 Key Findings

The key findings from this study are as follows. 1) With some exceptions, oculomotor performance was stable over time. As Becser et al (1998) pointed out, ICC>0.75 indicate excellent reliability and ICC>0.40 indicate good reliability. 2) Effects of practice were most consistently observed on the antisaccade task, indicated by reduced error rate (both batteries), improved accuracy (Battery II) and slightly faster latency (both batteries) at retest.

4.5.4.2 Test-retest Reliability

Previous studies have pointed to good temporal stability of global quantitative and qualitative, as well as specific, measures of smooth pursuit. This study only partially replicates these findings. Good Pearson correlations and ICC were obtained for frequency of CUS and AS for both batteries, confirming previous reports (Roy-Byrne et al 1995). However, reliabilities for SPEM gain were more variable, with ICC ranging from –0.06 to 0.77. None of the correlations for the three SPEM gain measures of Battery I but three of five SPEM gain measures of Battery II reached statistical significance. The reason why SPEM gain measures for the two slower velocities of Battery II were non-significant might be the fixed width of the window used to measure gain in EYEMAP. The width of this window is 100ms, which represents a smaller proportion of performance within each half-cycle at slower than at faster target velocities. From this it follows that sampling of a greater proportion of data points due to prolonged measurements would lead to more reliable data at the two faster velocities. As target velocities of the SPEM task from Battery I were comparable to the two slower velocities of Battery II, the same reason might explain the low reliabilities of Battery I SPEM gain.

The high reliability for frequency of AS is particularly important given the proposed role of this measure as an inhibitory schizophrenia spectrum endophenotype (Friedman et al 1992a; Rosenberg et al 1997c; Ross et al 1998e, 1999b, 1999c, 2001).

Test-retest reliabilities of saccadic measures were heterogeneous. The key measure in schizophrenia spectrum research, antisaccade error rate, was highly stable over time when assessed with Battery II, but somewhat less reliable when assessed with Battery I. Probably due to the skewed nature of the Battery I error rate distribution (most participants made very few errors), reliability was improved after data transformation.

Given this finding, and the high reliability of antisaccade error rate from Battery II, it may be argued that actual performance on this measure is stable over time and the somewhat lower reliability of Battery I may be due to methodological issues, as discussed in the following.

Battery I used only 24 trials, compared to 60 trials in Battery II. A critical review of the literature (Chapter 3) indicated that 60 trials might be an appropriate number of trials, making assessment sensitive by avoiding bottom and ceiling effects and allowing for sufficient between-subjects variance. Indeed, Maruff et al (1999) argued that "at least 40 antisaccade trials are required to obtain reliable estimates of error rate" (p. 1383). To provide an indication of the difference in variance between the two tasks, at baseline (N=30; Section 4.3) there were 16 different scores for Battery I antisaccade error rate (with five scores 'shared' by two or more participants) and 29 different scores for Battery II antisaccade error rate (with only one score 'shared' by two participants). The skewed distribution of the data and the subsequent improvement in reliability after transformation further underscores the poor statistical properties of the Battery I task. It is, therefore, likely that the low between-subjects target variance (Bartko 1991) of antisaccade error rate in Battery I adversely affected the task's reliability (Anastasi & Urbina 1997).

The reliability of the Battery II antisaccade error rate is the best reliability reported to date for this measure and contrasts with a recent study by Klein and Berg (2001), who reported a non-significant correlation. The reason for Klein and Berg's (2001) failure to obtain significant reliability might lie in the type of antisaccade task they used, the overlap version. In the overlap version of the antisaccade task, the central target remains 'on' when the peripheral target appears. This version of the antisaccade task is associated with lower error rates (Fischer & Weber 1997), thereby arguably reducing between-subjects variability in healthy individuals. A possible implication of this finding is that the non-overlap task might represent a psychometrically improved measure of saccadic inhibition amongst healthy individuals.

Saccadic latency measures were temporally stable. Prosaccade gain of Battery II, but not of Battery I, was stable over time. The reasons for this divergence in reliability are unclear, as both batteries used comparable stimulus eccentricities (±5° and ±10° for Battery I; ±6° and ±12° for Battery II) and adequate calibration procedures. However, the prosaccade task of Battery II had more trials than that of Battery I. Antisaccade gain was stable over time for both batteries.

The use of Pearson correlation and ICC coefficients allowed the comparison between these two measures of association and agreement, respectively (Bartko 1991). As expected, ICC coefficients tended to be lower, thereby providing a more conservative estimate of temporal stability (Mathalon et al 2000). Despite this, ICC coefficients reported here were comparable in magnitude to (Pearson and ICC) coefficients reported in previous studies. The global quantitative and qualitative SPEM measures employed in previous studies of test-retest reliability may be related to the measures in this study, as global measures are likely to reflect pursuit gain and frequency of saccades (Levy et al 2000; Ross et al 1998c).

It is instructive to compare the obtained temporal stability coefficients of oculomotor performance with those reported for other psychophysiological, neuropsychological and personality trait measures used in schizophrenia spectrum research. Mathalon et al (2000) observed ICC for the electrophysiological measure of P300 amplitude of between 0.84 and 0.93. Fein et al (1984) obtained similar coefficients for electroencephalography spectra over 1-3 years. Cadenhead et al (1999) reported somewhat higher ICC for prepulse inhibition, a measure of sensorimotor gating. Most of the coefficients reported by Cadenhead et al (1999) were above 0.80 and many were above 0.90, although very low coefficients (0.12 – 0.31) were also observed. Test-retest reliability coefficients for neuropsychological and psychometric schizotypy tests commonly used in schizophrenia spectrum research tend to be comparable to those obtained for measures of Battery II and slightly higher than those of Battery I (Vollema & van den Bosch 1995; Wechsler 1981; Wechsler 1987), although even higher reliabilities have been reported for more homogenous tests (Nelson 1991; Trenerry et al 1989). Taken together, temporal stabilities of most measures from Battery II and some measures from Battery I are comparable to other tasks used as endophenotypes in schizophrenia spectrum research.

4.5.4.3 Between-session Changes

Regarding the effects of repeated exposure on oculomotor performance, the most systematic changes over time were observed for the antisaccade task. Average antisaccade error rates from both Battery I and II significantly and considerably dropped from assessment I to assessment II. Additionally, there was some evidence for improved accuracy (Battery II) and slightly faster latency (Batteries I and II).

This pattern of practice effects is compatible with previous research (Klein et al 2002). Green et al (2000) demonstrated significant practice effects in healthy participants undergoing multiple assessments of the antisaccade task. Interestingly, the reduction in error rate from first to second assessment observed by Green et al (from 21.1% to 14.5%) is very similar to that observed on Battery II (from 20.8% to 15.8%).

As no within-session practice effects on antisaccade error rate were observed (Section 4.4), it might be argued that between-session improvements are not due to "fast learning gains" (p. 314) akin to priming, but due to slow, time-dependent (skill) learning processes (Hauptmann & Karni 2002). These processes may include effects of memory and motor consolidation (Shadmehr & Holcomb 1997) as well as increased familiarity with the laboratory environment and consequently reduced anxiety levels (DeRosa & Patalano 1991; Lister & Hilakivi 1988).

Lezak (1983) pointed out that practice effects in neuropsychological assessment are observed particularly on tests that "require an unfamiliar or infrequently practiced mode of response" (p. 115). Regarding the antisaccade task, it may be argued that this measure, due to its artificial nature as a laboratory task, is both unfamiliar and infrequently practised, and that these properties make the task particularly susceptible to practice effects. Interestingly, practice effects have also been observed on the Stroop test (Trenerry et al 1989). The Stroop test resembles the antisaccade task in its assessment of the integrity of (prefrontal) inhibitory function and its nature as an unpractised, infrequently used and artificial laboratory procedure. As Ahonniska et al (2001) noted, practice effects are not commonly observed on tests related to steadiness of motor control, perhaps explaining the absence of consistent practice effects on the SPEM and fixation tasks in the present study as well as previous studies.

Practice effects on the antisaccade task have to be taken into consideration in studies using parallel (between-group) designs involving repeated assessments (within-subjects). These designs are commonly used in clinical studies of treatment effects. Rate and magnitude of learning across sessions may vary between groups and, therefore, confound interaction effects of group and treatment. Practice effects on cognitive measures are particularly likely to occur in samples of young or middle aged individuals of high IQ (Ahonniska et al 2001) and schizophrenia patients treated with atypical rather than typical antipsychotics, presumably due to the existence of maximum learning capacities (Harvey et al 2000). These factors need to be considered in longitudinal studies of group comparisons.

4.5.4.4 Conclusions

To conclude, with some exceptions, oculomotor performance in this sample of healthy individuals was stable over time. Measures of Battery II tended to have higher temporal stabilities than those of Battery I. The disappointing test-retest reliabilities of some measures of Battery I were most likely due to methodological problems. Consistent practice effects were observed on the antisaccade task; these may have to be taken into consideration in longitudinal studies.

4.6 Overall Discussion

The oculomotor test batteries used in this thesis were assessed in this chapter on a number of criteria regarding reliability and validity. The conclusions that may be drawn on the basis of these analyses are as follows.

First, the scoring procedures of the current oculomotor tasks show excellent consistency within the same rater as well as across raters. Second, with the exception of prosaccade gain and SPEM gain, eye movement performance scores were correlated across the two display methods, indicating reasonable concurrent validity. The antisaccade task of Battery II was found to be more difficult than that of Battery I and both saccadic tasks of Battery II were associated with slightly longer latencies than those of Battery I. Third, internal consistencies of the current oculomotor tasks were generally high, with the most notable exception of antisaccade error rate from Battery I. Finally, performance on Battery II was stable over time, with the exception of two SPEM gain measures. Temporal stability of performance on Battery I was less consistent, with low reliabilities observed for measures of smooth pursuit gain and prosaccade gain. Consistent improvements between – but not within – sessions were observed on the antisaccade error rate.

These findings suggest that the thesis may progress using the current eye movement tasks to address the effects of psychotic illness, genetic liability, schizotypal personality traits and pharmacological manipulation, on oculomotor function. A number of caveats, however, have to be borne in mind.

First, the two batteries, in particular the saccadic paradigms, are not identical. Therefore, direct comparisons between studies using Battery I (Chapters 5 & 6) and studies using Battery II (Chapters 7 & 8) have to be treated with caution. As pointed out

in Section 4.2, the saccadic tasks of Battery II are associated with longer latencies and the antisaccade task of Battery II may be described as more difficult.

Second, there was some divergence in reliability (internal as well as temporal) between the two batteries. The antisaccade task of Battery II was somewhat more reliable than that of Battery I, both in terms of temporal stability and internal consistency.

Taken together, it may be argued that the development of an oculomotor test battery specifically adapted for research in this thesis (Battery II) was successful, as judged by this investigation of reliability and concurrent validity. Most measures of Battery II were correlated with the established measures of Battery I. Additionally, implementation of specific differences in stimulus specifications may have led to improvements in the statistical properties of these tasks.

Chapter Five

Study II – Eye Movements in First-episode Psychosis

5.1 Chapter Overview

Patients in their first episode of psychosis constitute an important test for the validity of an endophenotypic marker of genetic liability to schizophrenia. The recent onset of illness in this patient group allows one to study the severity of impairment on a marker in the relative absence of the secondary confounds encountered in chronic schizophrenia patients. Given the established reliability of the current eye movement tasks, this chapter investigates eye movements (using Battery I) in a sample of first-episode psychosis patients, in order to explore the extent of impairment of the smooth pursuit and antisaccade tasks compared to healthy controls, as well as the interrelationship between these two measures in the patient and the healthy control samples.

5.2 Introduction

Most studies of eye movement function in schizophrenia have used samples of chronic patients or combinations of first-episode (or recent-onset) and chronic patients. Studying patients in their first episode of schizophrenia, however, has a number of advantages over studying chronic patients. First-episode patients have not experienced prolonged antipsychotic drug treatment, long-term hospitalisation, or functional, social and professional impairment, as it is commonly encountered in chronic schizophrenia. Further, studying patients in their first episode reduces sample heterogeneity with regard to disease stage and illness duration. Finally, it has been argued that there might be detrimental, e.g. neurotoxic, effects on the brain of the illness itself as well as neurodegenerative processes (although this remains controversial; see Weinberger & McClure 2002). Therefore, neurobehavioural abnormalities seen in the first psychotic

episode are often thought to be linked to the primary disease process rather than secondary confounds or the effects of disease chronicity (Copolov et al 2000; Lieberman et al 1993; Lieberman et al 1992; Lieberman et al 2001; Spohn & Strauss 1989; Waring 1995).

From the perspective of research into biological schizophrenia spectrum markers, the observation of deficits in first-episode patients is, therefore, a crucial test of the validity of these measures. Deficits in recent-onset psychosis patients have been observed on a number of proposed endophenotypes, including neuropsychology (Bilder et al 2000; Hoff et al 1992; Hutton et al 1998b; Riley et al 2000; Saykin et al 1994; Sweeney et al 1992a), brain structure (Copolov et al 2000; Ettinger et al 2001; Fannon et al 2000; Hirayasu et al 2001; Lim et al 1996; Sumich et al 2002; Zipursky et al 1998) and psychophysiology (Hirayasu et al 1998; Papageorgiou et al 2001; Salisbury et al 1998).

Previous studies of oculomotor function in first-episode psychosis patients have obtained evidence of smooth pursuit eye movement (SPEM) (Hutton et al 1998a; Iacono et al 1992; Levy et al 1992; Sweeney et al 1992a, 1998a; Yee et al 1998) and antisaccade (Hutton et al 1998a; Nieman et al 2000) deficits. Importantly, deficits have been observed in untreated and never-medicated patients, further supporting the notion that these deficits are intrinsic to the disease process and not due to the effects of antipsychotic drug treatment (Hutton et al 1998a; Sweeney et al 1998a). Taken together, these studies consolidate the validity of the SPEM and antisaccade tasks as possible genetic markers by ruling out the possibility that deviant performance in the schizophrenia patient group is entirely due to secondary confounds listed above.

Two measures that have not been investigated comprehensively in first-episode psychosis patients are those of visual fixation accuracy and antisaccade gain. Hutton et al (2002) found no evidence of increased saccadic frequency during fixation with distractors; this study, however, did not include a simple fixation task. Antisaccade gain was found to be reduced in one study (Nieman et al 2000); Hutton et al (1998a) observed reduced gain only in antipsychotic treated but not drug-naïve patients.

As outlined in Section 2.8, the relationship between SPEM and antisaccade performance in schizophrenia has not been investigated conclusively, with inconsistent evidence to date (Matsue et al 1994b; Nkam et al 2001; Schlenker & Cohen 1995; Sereno & Holzman 1995; Thaker et al 1989c; Tien et al 1996). Only one first-episode

study has combined these tasks; this study did not find a significant relationship (Hutton et al 1998a).

5.2.1 Aims

The aims of the current study were, therefore, as follows. 1) To replicate and extend the findings of oculomotor impairments in first-episode psychosis patients, including a visual fixation task and investigating antisaccade gain. Selective deficits on the SPEM and antisaccade, but not fixation and prosaccade tasks were hypothesised. 2) To investigate the relationship between SPEM measures and antisaccade error rate in the patient and control groups.

5.3 Method

5.3.1 Participants

The patient sample used in this study was part of a larger investigation of first-episode psychosis (Ettinger et al 2001; Fannon et al 2000; Riley et al 2000; Sumich et al 2002; Tennakoon et al 2000). Due to logistic reasons, not all patients recruited into this first-episode study could be tested on eye movements (assessment of which began after the overall study had been initiated).

The patient group consisted of twenty individuals with DSM-IV diagnoses of schizophrenia (N=10), schizophreniform disorder (N=9) or schizoaffective disorder (N=1).[20] Patients were recruited as inpatients or outpatients from a catchment area including inner and outer London. Diagnoses were ascertained by experienced psychiatrists using the Structured Clinical Interview for DSM-IV Axis I Disorders Research Version (SCID-I; First et al 1996b). Patients were matched on the variables of sex, handedness (Oldfield 1971), parental socio-economic status (SES), ethnicity (white vs. other) and age to a group of eighteen healthy control participants, recruited by newspaper advertisement from a similar geographical area. Ethnicity and SES were based on UK standard classifications (Office of Population Censuses and Surveys 1991).

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[20] As there were no differences between the schizophrenia and schizophreniform disorder groups (excluding the patient with schizoaffective disorder) on any demographic, clinical or oculomotor variables (all $p>0.13$), patients were combined for all following analyses into one first-episode psychosis group.

Controls were free of DSM-IV Axis I and II disorders (First et al 1996a). Additionally, controls were required to have no history of schizophrenia in their first-degree relatives, as ascertained using the Family Interview for Genetic Studies (FIGS; Gershon & Guroff 1984).

Exclusion criteria for all participants were substance abuse or dependence, neurological disorder, or a medical condition with possible effects on brain structure and function.

Patients' symptom levels were rated using the Positive and Negative Syndrome Scale (PANSS; Kay et al 1987). This rating scale is based on a semi-structured interview schedule conducted by a psychiatrist and yields a total negative, total positive, general psychopathology and an overall symptom score. Higher PANSS scores indicate greater symptom severity. Ratings were undertaken by experienced research psychiatrists with high inter- and intra-rater (over a period of 1 year) reliability ($r>0.90$). Duration of treatment for treated patients and duration of psychotic illness (calculated from time of onset of first psychotic symptoms, based on patient interview, corroborative history from family members and medical records where available) for all patients was recorded in weeks. Seven patients were treated with typical antipsychotics, four were treated with atypical antipsychotics and nine were medication-naïve. Demographic and clinical data of the two groups are summarised in Table 5.1.

Table 5.1: Demographic and Clinical Characteristics

	Patients (N=20)	**Controls (N=18)**	**Statistical Analysis**
Age (mean [SD] years)	24.90 [6.19]	24.61 [5.00]	t=0.16; df=36; p=0.88
Sex (% males)	80.00%	66.70	χ^2=0.87; df=1; p=0.35
SES (median) *	3.00	2.00	z=-0.64; p=0.57
Handedness (% right-handed)	90.00%	83.30%	χ^2=0.37; df=1; p=0.54
Ethnicity (% white)	65.00%	77.20%	χ^2=0.23; df=1; p=0.63
Age of onset (mean [SD] years)	25.37 [6.55]	-	-
Illness duration (mean [SD] weeks)	7.06 (6.75)	-	-
Treatment duration (mean [SD] weeks)	5.18 [3.52] †	-	-
PANSS neg. symptoms (mean [SD]) **	20.47 [5.83]	-	-
PANSS pos. symptoms (mean [SD])	21.42 [4.93]	-	-
PANSS gen. psych. (mean [SD])	42.89 [7.57]	-	-
PANSS total score (mean [SD])	84.79 [13.87]	-	-

Legend:
* SES, socio-economic status
** PANSS, Positive and Negative Syndrome Scale
† medicated patients only (N=11)

All participants provided written consent after the study details had been fully explained to them. The study was approved by the Ethics Committee of the Bethlem and Maudsley National Health Service Trust.

5.3.2 Eye Movement Assessment

All participants underwent oculomotor assessment of the SPEM, antisaccade and prosaccade tasks of Battery I. The first prosaccade of Battery I (peripheral targets of ±5°, ±10°, or ±15°) was used. In the visual fixation task, only the central fixation target was used consistently throughout this study; data from peripheral trials were discarded due to a large number of unavailable trials (mainly because of fatigue or movement artefacts in the acutely ill first-episode patients). Other oculomotor dependent variables were as described in Chapter 3, including SPEM gain, frequency of anticipatory saccades (AS) and catch-up saccades (CUS); antisaccade gain, latency and error rate; and prosaccade gain and latency.

Due to computer storage errors as well as participant fatigue and movement artefacts there were missing data for SPEM (patients, N=2; controls, N=3), prosaccade (patients, N=4; controls, N=1) and fixation (patients, N=2; controls, N=1).

5.3.3 Statistical Analysis

All statistical analyses reported below were carried out using SPSS Release 10.0.7 (SPSS Inc., Chicago, Ill). Distributions of oculomotor variables were assessed for normality using the skewness index. If positively (skewness>1) or negatively (skewness<-1) skewed, variables were transformed using square root or square transformations, respectively.

5.3.3.1 Effects of Age and Sex

Interactions of sex and group on oculomotor variables were investigated using analysis of variance (ANOVA). Effects of age were examined using Pearson correlations between age and oculomotor variables.

5.3.3.2 Group Comparisons

Due to the large number of missing values, group differences on oculomotor variables were investigated using univariate analysis of variance (ANOVA) with each oculomotor

variable as dependent variable and group (patient, control) as independent variable.[21] Effect sizes of oculomotor variables were calculated according to the formula

$$\frac{(\mu_1 - \mu_2)}{SD_{(pooled)}}$$

where μ_1 = mean of group 1, μ_2 = mean of group 2 and $SD_{(pooled)}$ = pooled standard deviation of the two groups (Cohen 1988). The pooled standard deviation was calculated as follows:

$$\sqrt{\frac{(N_a - 1)SD_a^2 + (N_b - 1)SD_b^2}{N_a + N_b - 2}}$$

where N_a is the sample size of Group A with its SD; and N_b is the sample size of Group B with its SD.

5.3.3.3 Effects of Target Velocity and Velocity-by-Group Interactions for SPEM Variables

In order to investigate effects of target velocity on SPEM variables and velocity-by-group interactions, repeated measures ANOVA were carried out with group (patient, control) as between-subjects factor and velocity (10°/s, 24°/s) as within-subjects factor.

5.3.3.4 Relationship between SPEM Measures and Antisaccade Error Rate

Interrelationships between SPEM variables and antisaccade error rate in the combined group as well as the patient and control groups separately were investigated using Pearson correlations. Error rate was correlated with each SPEM measure at each velocity; additional correlations were carried out between antisaccade error rate and average SPEM measures (across velocities) in order to provide a more detailed and robust investigation of this relationship.

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[21] Multivariate analysis of variance (MANOVA) was additionally carried out in order to explore similarities and differences to univariate ANOVA results. MANOVA yielded an overall effect of group on oculomotor variables ($F[12,15]=3.28$; $p=0.02$). The pattern of between-group differences and significance levels for individual variables were very similar to those observed

5.3.3.5 Associations of Oculomotor Measures with Clinical Variables and Antipsychotic Drug Treatment

Interrelationships between oculomotor and clinical variables (duration of treatment, duration of illness and age of onset) in the patient group were investigated using Pearson correlations. Medicated and unmedicated patients were compared on oculomotor variables using ANOVA. Differential effects of typical and atypical antipsychotic treatment were not investigated due to the small sample sizes of these groups of patients.

5.4 Results

A number of variables were skewed and transformed accordingly, normalising skewness (-1<skewness<1). Using transformed variables yielded virtually identical results to using untransformed variables; therefore, and for reasons of clarity, descriptive statistics and below results are based on raw (untransformed) data.

5.4.1 Effects of Age and Sex

Age was not correlated significantly with any oculomotor variables (all $r<0.21$; all $p>0.25$). Significant sex-by-group interactions were observed for AS at 10°/s ($F[1,32]=4.67$; $p=0.04$) and CUS at 10°/s ($F[1,32]=4.55$; $p=0.04$). Therefore, sex was used as covariate only in analyses involving these variables.

5.4.2 Group Comparisons

Descriptive statistics and effect sizes of oculomotor measures are summarised in Table 5.2. Average rate of correction in the antisaccade task was 100% for controls and 96.93% (SD=9.30) for patients, indicating that participants appeared to be, in principle, willing and able to perform this task (McDowell & Clementz 1997).

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using ANOVA, supporting the validity of using univariate ANOVA in the analysis of between-group differences.

Table 5.2: Descriptive Statistics and Effect Sizes (d) of Oculomotor Measures

	Patients (N=20)	**Controls (N=18)**	**d**
SPEM gain 10°/s *	91.91 (13.52) †	98.42 (6.20) ∫	-0.60
SPEM gain 24°/s	85.38 (16.70) ‡	99.41 (5.48) ∫	-1.09
Anticipatory saccades 10°/s	0.37 (0.33) †	0.15 (0.27) ∫	0.75
Anticipatory saccades 24°/s	0.66 (0.37) †	0.48 (0.34) ∫	0.52
Catch-up saccades 10°/s	0.44 (0.17) †	0.30 (0.15) ∫	0.84
Catch-up saccades 24°/s	0.46 (0.23) †	0.47 (0.13) ∫	-0.02
Fixation saccadic frequency	1.83 (3.33) †	0.06 (0.24) *	0.74
Antisaccade error rate	28.39 (17.67)	14.45 (11.95)	0.92
Antisaccade gain	-90.20 (19.65)	-105.39 (11.22)	0.94
Antisaccade latency	339.05 (116.78)	292.32 (74.82)	0.47
Prosaccade gain	88.84 (11.40) ‡	95.82 (8.50) *	-0.70
Prosaccade latency	180.65 (32.66) ‡	174.00 (28.24) *	0.22

Legend: †N=18; ‡N=16; *N=17; ∫N=15

Significant between-group differences were obtained for SPEM gain at 24°/s ($F[1,31]=9.67$; $p=0.004$), AS at 10°/s ($F[1,31]=4.56$; $p=0.04$), CUS at 10°/s ($F[1,31]=5.73$; $p=0.02$), frequency of saccades during fixation ($F[1,33]=4.80$; $p=0.04$), antisaccade gain ($F[1,36]=8.30$; $p=0.007$), antisaccade error rate ($F[1,36]=7.93$; $p=0.008$) and prosaccade gain ($F[1,31]=4.00$; $p=0.05$). Differences at trend level were observed for SPEM gain at 10°/s ($F[1,31]=2.95$; $p=0.096$). All other comparisons were non-significant (all $p>0.14$).

These differences indicate reduced SPEM gain, increased saccadic frequency during SPEM and fixation, reduced antisaccade and prosaccade gain and increased antisaccade error rate in the patients compared to controls. Using sex as covariate for analyses of AS at 10°/s and CUS at 10°/s did not change the significance of between-group differences.

5.4.3 Effects of Target Velocity and Velocity-by-Group Interactions for SPEM Variables

Repeated measures ANOVA showed that SPEM gain was non-significantly reduced at 24°/s compared to 10°/s ($F[1,31]=2.71$; $p=0.11$). There was a significant group-by-velocity interaction ($F[1,31]=5.00$; $p=0.03$), indicating that patients had more severely reduced gain at the faster than the slower target velocity (see Figure 5.1).

Figure 5.1: Effects of Target Velocity on Smooth Pursuit Gain (by Group)

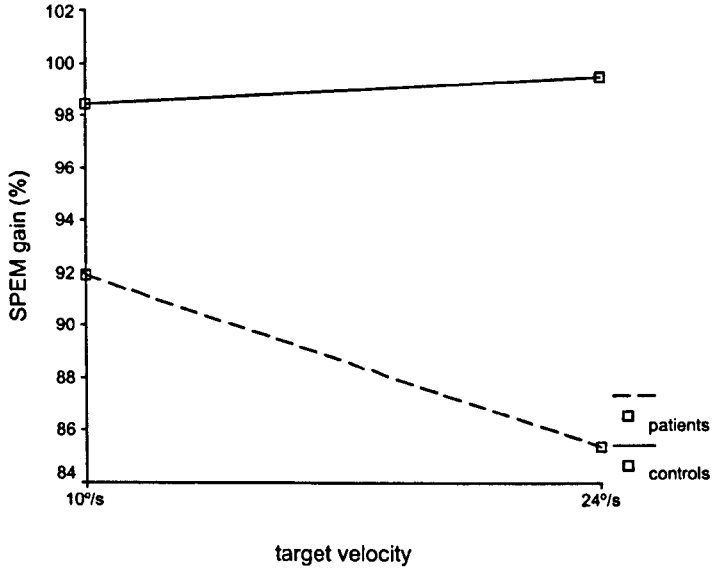


Figure 5.2: Effects of Target Velocity on Anticipatory Saccade Frequency (by Group)

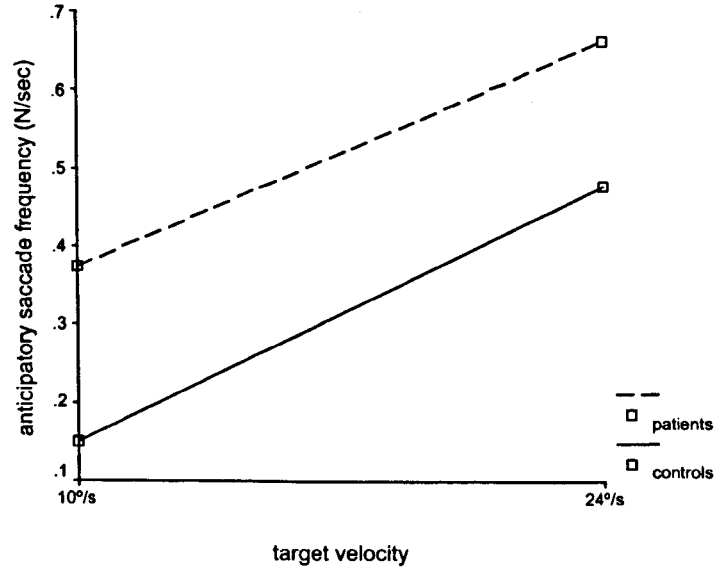
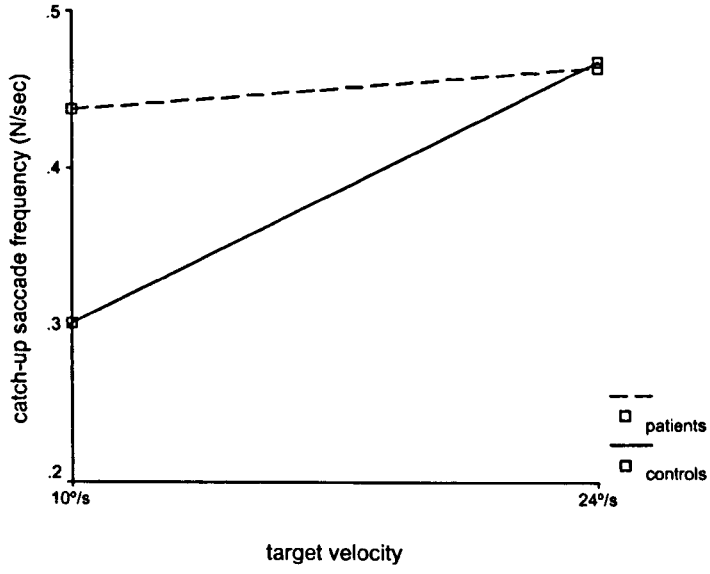


Figure 5.3: Effects of Target Velocity on Catch-up Saccade Frequency (by Group)



There was a significant main effect of velocity on AS frequency ($F[1,31]=58.64$; $p<0.001$), indicating that AS were more frequent at the faster velocity (see Figure 5.2), but no velocity-by-group interaction ($F[1,31]=0.24$; $p=0.63$).

There was a significant main effect of target velocity on CUS frequency ($F[1,31]=7.15$; $p=0.01$) and a trend for a velocity-by-group interaction ($F[1,31]=3.76$; $p=0.06$). This interaction indicates that during slow but not fast velocity SPEM patients had higher CUS rate than controls (see Figure 5.3).

5.4.4 Relationship between SPEM Measures and Antisaccade Error Rate

In the combined group, higher antisaccade error rate was associated with reduced SPEM gain at 10°/s ($r=-0.34$; $p=0.05$), at 24°/s ($r=-0.40$; $p=0.02$) and averaged across velocities ($r=-0.40$; $p=0.02$) as well as increased AS rate at 10°/s ($r=0.53$; $p=0.001$), at 24°/s ($r=0.40$; $p=0.02$) and averaged across velocities ($r=0.49$; $p=0.004$), but not consistently with CUS at 10°/s ($r=0.06$; $p=0.76$), 24°/s ($r=-0.33$; $p=0.06$) or averaged across velocities ($r=-0.18$; $p=0.33$).

In the patient group, higher antisaccade error rate was associated significantly with greater AS frequency at 10°/s (r=0.57; p=0.01) and averaged across velocities (r=0.54; p=0.02), and at trend level with AS frequency at 24°/s (r=0.44; p=0.07), but not with gain or CUS (all p>0.19).

In the control group, antisaccade error rate was correlated at trend level with SPEM gain at 24°/s (r=0.50; p=0.06) and averaged across velocities (r=0.49; p=0.06) but not at 10°/s (r=0.36; p=0.19); antisaccade error rate was also correlated significantly with CUS at 24°/s (r=-0.68; p=0.005) and averaged across velocities (r=-0.62; p=0.01) but not at 24°/s (r=-0.34; p=0.22). These correlations indicated that *better* antisaccade performance was associated with *worse* SPEM performance in the control group. Error rate was not correlated with AS frequency (all p>0.80).

The correlations between antisaccade error rate and AS frequency for the two groups (averaged across velocities) are depicted in Figures 5.4 and 5.5.

Figure 5.4: Relationship between Antisaccade Error Rate and Anticipatory Saccade Frequency (Averaged across Velocities) in the Patient Group

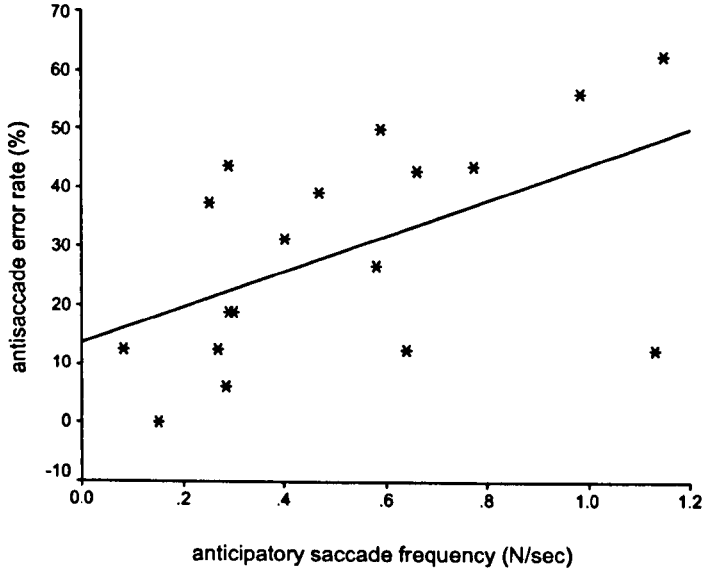
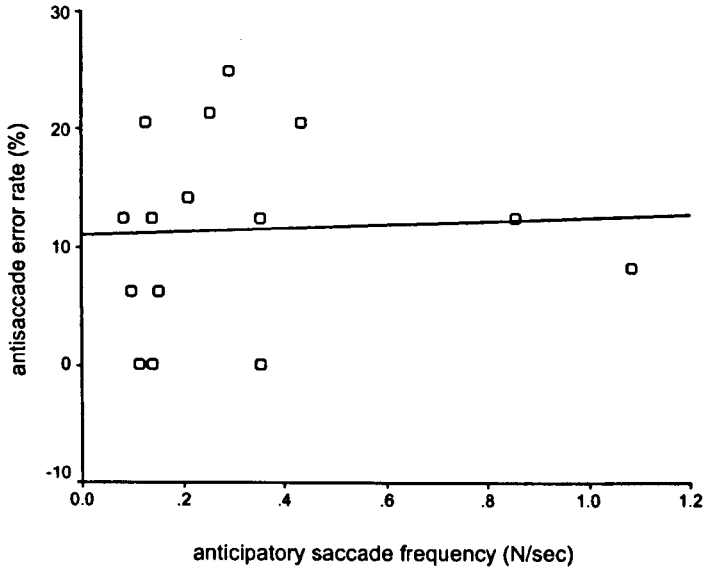


Figure 5.5: Relationship between Antisaccade Error Rate and Anticipatory Saccade Frequency (Averaged across Velocities) in the Control Group



5.4.5 Associations of Oculomotor Measures with Clinical Variables and Antipsychotic Drug Treatment

There was a trend for a correlation between SPEM gain at 10°/s and duration of illness (r=-0.48; p=0.07), indicating that longer duration of illness was associated with reduced SPEM gain, as well as a trend for a correlation between antisaccade latency and duration of treatment (r=0.40; p=0.08), indicating that longer duration of treatment was associated with longer latency. There were no other correlations between oculomotor variables and age of onset (all p>0.20), duration of treatment (all p>0.14), or duration of illness (all p>0.10).

Higher levels of PANSS negative symptoms were associated with increases in antisaccade error rate (r=0.58; p=0.009), reduced SPEM gain at 10°/s (r=-0.52; p=0.03), increased AS frequency at 10°/s (r=0.65; p=0.005) and non-significantly reduced prosaccade gain (r=-0.48; p=0.07). Higher levels of PANSS positive symptoms were associated with increased CUS frequency at 24°/s (r=0.51; p=0.04). Higher levels of PANSS general psychopathology scores were associated with reduced SPEM gain at 10°/s (r=-0.49; p=0.05) and non-significantly increased AS frequency at 10°/s (r=0.47;

p=0.06). Higher PANSS total scores were significantly associated with reduced SPEM gain at 10°/s (r=-0.49; p=0.05), non-significantly increased antisaccade error rate (r=0.40; p=0.09) and non-significantly increased AS frequency at 10°/s (r=0.46; p=0.07). There were no further significant or trend level correlations between PANSS and oculomotor variables (all p>0.10). No significant correlations emerged for prosaccade latency or antisaccade gain when covarying for sex.

Treated and untreated patients did not differ from each other on any oculomotor variables (all p>0.13).

5.5 Discussion

5.5.1 Key Findings

The key findings from this study are as follows. 1) The observation of SPEM and antisaccade impairments in this sample of first-episode psychosis patients replicates and extends previous findings, and points to the presence of oculomotor deficits early in the psychotic disease process. Significant impairments were also observed on visual fixation and antisaccade gain. 2) There were associations between SPEM and antisaccade measures, the most consistent of which was observed between AS frequency and antisaccade error rate.

5.5.2 Oculomotor Abnormalities in First-Episode Psychosis

The replication of smooth pursuit and antisaccade deficits in first-episode psychosis patients is an important piece of evidence in establishing the validity of these oculomotor schizophrenia spectrum endophenotypes. The importance of first-episode studies lies primarily in the fact that these patients are relatively free of secondary confounds, such as prolonged drug treatment, institutionalisation, social isolation and functional impairments, as well as putative toxic effects of the disease process. Eye movement deficits observed in this patient group may, therefore, be argued to be linked to the primary schizophrenic disease process or the genetic predisposition to schizophrenia (Copolov et al 2000; Hutton et al 1998a; Iacono et al 1992; Lieberman et al 1992, 2001; Sweeney et al 1992a; Waring 1995).

The patient group had reduced SPEM gain and increased rates of AS and CUS. Reduced gain and increased CUS frequency confirm previous first-episode studies (Hutton et al

1998a; Sweeney et al 1992a, 1998a). This is the first study to demonstrate increased AS frequency in this patient group.

The group-by-velocity interaction for SPEM gain indicated that patients showed reduced pursuit gain particularly at the faster velocity (Abel et al 1991; Lipton et al 1980a; Pivik 1979b). The group-by-velocity interaction for CUS indicated that patients had increased CUS frequency only at the slower, but not the faster, velocity. A relationship between SPEM gain and CUS frequency has been put forward earlier (Friedman et al 1991). Friedman et al (1991) proposed an analogue of a machine that has two systems, a pursuit and a saccadic correction system. Given slow pursuit and limited tolerance for position error, once a certain threshold has been passed, the saccadic system will execute a CUS to restore gain. This model can explain why segments of low pursuit may be associated with increased numbers of corrective saccades in schizophrenia and other conditions. While data from a number of SPEM studies of schizophrenia patients appear consistent with this hypothesis (Friedman et al 1991; Levy et al 2000; Ross et al 1998c), the present findings are not compatible with this hypothesis. It appears instead that at the slow target velocity patients performed increased rates of CUS despite only moderately impaired SPEM gain (relative to the controls). It is also unclear why there was an increase in AS frequency at the slower (but not the faster) velocity in the patient group.

At the faster target velocity patients displayed reduced gain; however, they failed to produce a corresponding increase in CUS frequency to compensate this reduced gain. As CUS are thought to restore reduced gain (Friedman et al 1991) they are dependent on information concerning position error, i.e. a mismatch of target and eye velocity. This finding suggests that position error detection mechanisms, which may function relatively well at a slower target velocity in this patient sample, were impaired at the faster velocity.

Patients made more saccades away from the target during fixation of a central, stationary target. Studies of visual fixation in schizophrenia have obtained conflicting evidence. While some studies have shown abnormal fixation (Amador et al 1995; Curtis et al 2001b; Silverman & Gaarder 1967) others have found stable fixation (Gooding et al 2000a; Kissler & Clementz 1998). This inconsistency may partly be due to differences in analysis of fixation data as well as sample composition, but challenges the notion that fixation performance is *unimpaired* in schizophrenia.

The patient group also had significantly increased antisaccade error rate. This finding is compatible with previous studies of recent-onset (Hutton et al 1998a; Nieman et al 2000) and chronic schizophrenic patients (Crawford et al 1995a, 1995b; Fukushima et al 1988) and may indicate prefrontal abnormalities (McDowell & Clementz 2001; Müri et al 1998; Roberts et al 1994; Rosse et al 1993). The effect size for error rate of 0.92 may be considered large (Cohen 1988). This confirms that an increase in antisaccade errors robustly characterises the oculomotor performance pattern of patients with schizophrenia and that this deficit is present in the early stages of the disease. As most (96.93%) of antisaccade errors were subsequently corrected by patients, failure to comprehend or lack of compliance with task instructions can be ruled out.

A noteworthy finding was that of reduced antisaccade gain in patients (with a large effect size). While many previous studies of the antisaccade in schizophrenia have not included measures of accuracy, there is evidence of reduced accuracy in schizophrenia patients (Crawford et al 1995a, 1995b; Maruff et al 1998; McDowell et al 1999). Hutton et al (1998a) obtained reduced antisaccade gain in treated but not untreated first-episode patients, suggesting a treatment effect. Antisaccade accuracy is believed to be a measure of sensorimotor coordinate transformations and spatial working memory (Krappmann et al 1998). This process requires the covert encoding of the spatial location of the target and the translation of this sensory signal into a motor output signal, which serves to initiate a saccade to a contralateral location. Sensorimotor coordinate transformations are likely to require prefrontal and parietal cortex integrity (Doricchi et al 1997; Leigh & Zee 1999; Pierrot-Deseilligny et al 1995) and might deserve further attention in the field of schizophrenia research.

Other studies have demonstrated hypometric saccades on other paradigms likely to involve sensorimotor coordinate transformations or spatial working memory, such as the predictive saccade task (Crawford et al 1995b, 1995a; Hommer et al 1991; Hutton et al 2001b; Karoumi et al 1998b; Krebs et al 2001; McDowell et al 1996) or the memory-guided saccade task (Everling et al 1996; Karoumi et al 1998b; McDowell & Clementz 1996; Park & Holzman 1992). Given the role of working memory in the pathophysiology of schizophrenia (Goldman-Rakic 1999; Goldman-Rakic & Selemon 1997), accuracy measures on saccadic tasks (including antisaccade, predictive saccade and memory-guided saccade paradigms) might prove a useful window to studying this process in schizophrenia.

It should be noted, however, that antisaccade accuracy might be partly influenced by task instructions or strategy use. If participants (or the experimenter) emphasise the *inhibition* of reflexive saccades then this might improve the rate of correct antisaccades whilst compromising the accuracy criterion. Conversely, stressing the importance of *spatially accurate* antisaccades may lead to greater recruitment of covert attentional resources necessary to encode the spatial location of the target, and consequently to greater numbers of antisaccade errors.

A limitation of this study is that the present study utilised one antisaccade target amplitude only (±15°). The finding of reduced accuracy must, therefore, be considered preliminary, as assessment of saccadic accuracy may most reliably be achieved by using more than one target amplitude.

Symptom correlates of eye movements in this study partly replicated previous findings. An association between negative symptoms and antisaccade errors as well as SPEM impairments has been reported previously (Crawford et al 1995b; Müller et al 1999; Tien et al 1996), possibly implicating frontal lobe dysfunction (Ross 2000; Wolff & O'Driscoll 1999). No treatment effects were observed, probably due to the short duration of treatment and the relatively small sample sizes of treated and untreated patients. Interestingly, a correlation emerged between SPEM gain at 10°/s and duration of illness, suggesting a small effect of prolonged illness duration on eye movement impairments. This relationship, although of only moderate magnitude and not consistent across tasks, points to the importance of testing patients early in the course of illness.

In order to further elucidate the pathophysiology of schizophrenia and the role of oculomotor deficits in this condition, more research using first-episode patients might be beneficial. Given the already mentioned advantages of first-episode research, as well as the suggested generalisability of findings from this population to other schizophrenia patient groups (Ganguli & Brar 1992), it may be expected that research using this patient group can shed more light on the nature of the association between eye movement abnormalities and the schizophrenia phenotype. Remaining questions concern whether eye movement deficits seen at, or shortly after, onset of illness deteriorate further, remain stable, or improve. It would be of additional interest in this context to investigate whether the patients with schizophrenia and schizophreniform disorder in this study differ in eye movement function at a later stage of the illness.

5.5.3 Relationship between SPEM Measures and Antisaccade Error Rate

Previous studies have provided inconsistent evidence of an association between SPEM and antisaccade error rate (Section 2.8). The present findings suggest an association between antisaccade error rate and SPEM gain in the combined group of patients and controls. However, this relationship was not found in the patient group alone and was reversed in the control group. The inverse association in the control group is very difficult to explain, but could be a chance finding.

The association between frequency of AS during smooth pursuit and antisaccade error rate in the patient group as well as the combined group is intriguing.[22] This statistical relationship between these two putative markers of genetic liability (Clementz 1998; Ross et al 1998e, 1999b; Whicker et al 1985) is consistent with the notion that both measures tap frontal inhibitory oculomotor function (Calkins & Iacono 2000; Friedman et al 1992a; Levin 1984; Müri et al 1998). The key measure of antisaccade performance, the error rate, is a measure of the successful inhibition of reflexive saccadic responses to a prepotent stimulus (Section 2.5.4.2). The occurrence of AS during smooth pursuit may similarly involve breakdown of inhibitory processes, as this type of saccades typically intrudes on otherwise normal pursuit and, unlike CUS, serves no obvious compensatory function.

Inhibitory mechanisms are believed to play an important role in the pathophysiology of schizophrenia (Braff 1993). A recent study (Myles-Worsley et al 1999) combined the antisaccade error rate with an event-related potentials measure of inhibitory function (P50 gating) and demonstrated linkage of this "composite inhibitory phenotype" (p. 544) to a chromosome 22q11-q12 locus in multiple schizophrenia families.

The correlations between antisaccade error rate and SPEM gain as well as AS frequency open up the issue of whether these measures might be profitably combined in genetic schizophrenia spectrum research. Combinations of uncorrelated measures, which are both affected in the patient group, might improve the statistical separation between the patient and control groups (Arolt et al 1998; Robins & Guze 1970; Sponheim et al 2001). The use of multiple neurobehavioural or cognitive measures might also have

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[22] The reason why this relationship was not obtained in the control group could be the relatively low range of antisaccade errors in this group (see Figure 5.5).

advantages over individual measures or diagnostic manuals in identifying clinically and aetiologically homogenous patient groups (Arolt et al 1998; Sponheim et al 2001).

On the other hand, combining conceptually related and statistically correlated neurobehavioural measures might be useful in the development of a composite endophenotype (Myles-Worsley et al 1999), e.g. a combined 'inhibitory' measure of AS frequency and antisaccade error rate. Following Myles-Worsley et al (1999) one could label participants as poor or good performers based not on either but both measures; these labels might then be used in linkage analysis. The moderate magnitude of the correlation between AS frequency and antisaccade error rate prevents complete overlap and redundancy.

However, more research is needed before such a combination of measures may be used as phenotype in schizophrenia linkage studies. First, the correlation has to be replicated using a larger sample. Second, there was no correlation between AS frequency and antisaccade errors in the control group; the reasons for this are unclear, but probably include the reduced range of antisaccade errors in this group (Figure 5.5). Third, it remains to be investigated whether the relationship is also observed in other schizophrenia spectrum populations, such as first-degree relatives of schizophrenia patients, or schizotypal individuals.

5.6 Conclusions

- The present study replicated previous findings of SPEM and antisaccade deficits in first-episode psychosis patients. These deficits are, therefore, thought to be intrinsic to the schizophrenic disease process or the genetic predisposition and not entirely due to secondary, disease-related confounds.
- The finding of reduced antisaccade gain in the patient group may deserve further attention in schizophrenia spectrum research.
- Antisaccade error rate was associated with the frequency of anticipatory saccades during smooth pursuit in patients and in the combined group, pointing to a link between these two putative measures of inhibitory function.

5.7 Limitations

- Due to the acutely ill state of the patient sample and because of technical failures there were a number of missing values on eye movement data.
- The visual fixation task utilised only a central target.
- The sample size is too small to conclusively address the issue of the relationship between SPEM and antisaccade performance and the possible application of a combination of these measures in genetic linkage studies.
- Antisaccade gain was measured using one target amplitude only. Therefore, the finding of reduced gain in the patient group needs to be extended using an antisaccade task with multiple peripheral amplitudes.
- The study was not sufficiently powered to examine treatment effects or clinical correlates in the patient group.

Chapter Six

Study III – Eye Movements in Siblings Discordant for Schizophrenia

6.1 Chapter Overview

Probably one of the best behavioural tests of the validity of a proposed endophenotypic marker is its assessment in unaffected first-degree relatives of members of the patient group under study. Given the observation of smooth pursuit and antisaccade deficits in the crucial group of first-episode psychosis patients, this chapter addresses smooth pursuit and antisaccade performance (using Battery I) in another important schizophrenia spectrum group, namely pairs of full biological siblings discordant for schizophrenia. Following the finding of a relationship between antisaccade error rate and anticipatory saccade frequency during pursuit in Study II (Chapter 5), one focus of this chapter will be on the relationship between smooth pursuit measures and antisaccade error rate.

6.2 Introduction

A considerable number of studies have observed smooth pursuit eye movement (SPEM) and antisaccade deficits in first-degree relatives of schizophrenia patients (Clementz et al 1994; Curtis et al 2001a; Holzman et al 1974; Iacono et al 1992; Katsanis et al 1997; Lencer et al 1999). These observations constitute important evidence of the validity of these measures as schizophrenia endophenotypes. However, a number of questions still remain regarding the precise pattern of behavioural oculomotor performance amongst unaffected first-degree relatives of schizophrenia patients.

First, little is known about the interrelationship between the SPEM and antisaccade measures in first-degree relatives. Previous studies have observed moderate associations (Karoumi et al 2001; Thaker et al 2000). As argued above (Section 2.8), knowledge of a relationship between SPEM and antisaccade measures might be useful

not only in further characterising the behavioural, cognitive and possibly neural correlates of these deficits, but also in the development of an improved oculomotor endophenotype for linkage studies.

A second point of interest in schizophrenia family studies of oculomotor performance concerns the sample composition. Most previous eye movement studies have utilised mixed samples of first-degree relatives, including siblings, offspring and parents, based on the assumption that these relatives all share, on average, 50% of their genes with the proband. However, Ross et al (1998d, 1998e) demonstrated differences in both SPEM and antisaccade performance between parents who were assumed to be likely gene carriers (i.e. with a family history of schizophrenia) and less likely gene carriers (i.e. without a family history of schizophrenia). Therefore, recruiting parents as first-degree relatives increases sample heterogeneity and might lead to sampling bias if both parents of each proband are not included, due to the possibility of differences in willingness to volunteer between likely and less-likely gene carriers. Additionally, given that oculomotor control deteriorates with age (Olincy et al 1997; Ross et al 1999a) a sample of older first-degree relatives might underestimate differences compared to a younger patient group.

A third point of attention concerns the genetic relatedness of the patients and their first-degree relatives, which is likely to lead to correlated performance on biological and behavioural measures (Plomin et al 2000). Therefore, the use of analysis of variance may be inappropriate in the analysis of group differences, as the assumption of independence of observations is violated by the genetic relatedness (Ott 1991). To overcome this problem, a random effects linear regression model has been developed that controls for effects of relatedness in family studies (Rabe-Hesketh et al 2001). Additionally, it may be advantageous to use samples of patients and relatives including only one individual from each family per group. This removes correlations between individuals in the same group, which would lead to a reduction in statistical power.

6.2.1 Aims

Following this overview of the shortcomings of previous oculomotor family studies, the present study had the following aims: 1) To replicate the SPEM and antisaccade deficits observed in unaffected first-degree relatives of schizophrenia patients. Both schizophrenia patients and their siblings were hypothesised to have impaired SPEM and antisaccade, but normal fixation and prosaccade performance relative to a sample

of healthy individuals. 2) To investigate the relationship between SPEM measures and antisaccade error rate in the combined as well as individual groups (patients, relatives, controls). On the basis of the observation in Study II, a relationship between anticipatory saccades during pursuit and antisaccade error rate was hypothesised. 3) To explore whether SPEM and antisaccade performance levels are correlated within family members, thereby justifying the use of statistical techniques taking into account effects of genetic relatedness. It was hypothesised that oculomotor performance levels would be similar, i.e. correlated, within family members.

6.3 Method

6.3.1 Participants

Twenty-four inpatients and outpatients with a DSM-IV diagnosis of schizophrenia (mean age=30.71; SD=5.84; 13 males), 24 of their full siblings (one sibling for every patient) (mean age=28.63; SD=6.41; 7 males) and 24 healthy control participants (mean age=28.50; SD=5.99; 7 males) completed the study. All participants were drawn from similar geographical areas (East, Southeast and Southwest London and West Kent). The non-significantly increased number of males in the patient group when compared to siblings and controls (Pearson x^2=4.27; df=2; p=0.12) was likely due to a higher incidence of schizophrenia amongst younger males (Egan et al 2000; Iacono & Beiser 1992) and a greater willingness of females to participate.

Initially, thirty-four patients underwent preliminary screening for participation in the study; of these, thirty patients consented for their siblings to be contacted (two patients had no eligible siblings and two patients refused for siblings to be contacted). These thirty patients had a total of fifty-three eligible siblings. Siblings were contacted over the telephone for an initial interview with the objective of recruiting only one sibling per patient for the study. A total of twenty-eight patients and twenty-eight of their siblings agreed to come for assessments. However only twenty-four patients and their siblings completed assessments; the remaining patient-sibling pairs did not participate because of logistic problems, e.g. lack of availability or childcare issues (N=3) or because of refusal to take part in the eye movement assessment (N=1).

In each final group, sixteen participants were Caucasian, six were of Afro-Caribbean origin and two were of Asian origin. The study was approved by the Bethlem and

Maudsley Ethical Committee (Research). All participants provided written informed consent after the study procedures had been fully explained to them.

The patients' diagnoses were established by experienced psychiatrists using the Structured Clinical interview for DSM-IV Axis I disorders (SCID I; First et al 1996b). Patients and siblings with a history of alcohol or drug dependence in the last year or a lifetime history of five years of alcohol or drug abuse/dependence, head injury with cognitive sequelae or loss of consciousness exceeding five minutes, epilepsy, history of neurological disorder or medical illness associated with significant neurocognitive impairment were excluded from the study. Patients' duration of illness (defined as duration from first onset of psychotic symptoms) ranged from 2 to 20 years (mean=7.08; SD=5.36; median=5; interquartile range=3-10). Nineteen patients were treated with atypical antipsychotics, four were on typical antipsychotics and one patient was untreated. Additionally, three patients were treated with anticholinergic compounds.

Additionally, siblings had to be within five years of age of the patient, between 16 and 40 years of age (patients between 16 and 45 years of age). Siblings were excluded if they had a DSM-IV Axis I disorder, or Axis II schizotypal personality disorder (SCID II; First et al 1996a).

Healthy controls were recruited through advertisements in the local press and screened according to the same criteria as siblings, with the additional requirement that they did not have a first-degree relative with a history of psychosis. Family history of mental illness was recorded using the Family Interview for Genetic Studies (FIGS; Gershon & Guroff 1984). Controls were individually matched to siblings on age (±5 years), sex, years of education (±2 years), ethnicity and handedness.

Current symptoms of the patients were rated with high reliability using the Positive and Negative Syndrome Scales (PANSS; Kay et al 1987). Schizotypal symptoms were assessed in the siblings and controls with high reliability using the Structured Interview for Schizotypy (SIS; Kendler et al 1989).

6.3.2 Eye Movement Assessment

Eye movements were assessed using Battery I. The first of the two prosaccade tasks (with target eccentricities of ±5°, ±10° and ±15°) was used. Due to computer storage errors smooth pursuit data at both velocities from one patient and one sibling, as well

as smooth pursuit data at 10°/s and prosaccade data from one patient were unavailable.

The oculomotor dependent variables were as described in Chapter 3 and included SPEM gain, frequency of anticipatory saccades (AS) and catch-up saccades (CUS); frequency of saccades during fixation; antisaccade gain, latency and error rate; and prosaccade gain and latency.

6.3.3 Statistical Analysis

The random effects regression model (Section 6.3.3.2) was carried out using Stata Release 7 (Stata Corporation, College Station, TX). All other analyses were carried out using SPSS Release 10.0.7 (SPSS Inc., Chicago, Ill). Distributions of oculomotor variables were assessed for skewness. If variables were positively (>1) or negatively (<-1) skewed, square root or square transformations were applied.

6.3.3.1 Effects of Age and Sex

Sex differences for oculomotor variables were investigated in each group using multivariate analysis of variance (MANOVA). Pearson correlations were obtained between age and oculomotor variables in each group.

6.3.3.2 Group Comparisons and Effects of SPEM Target Velocity

The genetic relatedness between patients and siblings and the likely within-family correlations violate the ANOVA assumption of independent observations. Therefore, group differences on oculomotor variables, age and years of education were analysed using a random effects regression model (Rabe-Hesketh et al 2001). The model uses group membership (patient, sibling, control) as independent variable and each oculomotor variable as dependent variable. A random effect is introduced into the regression equation, which takes on a different value for each patient-sibling-control triplet, thereby allowing for correlations within triplets due to relatedness and individual matching.

Velocity-by-group interactions for SPEM variables were tested using the patient-sibling-control triplets as 'subjects' in repeated measures ANOVAs; group and velocity were used as within-triplet factors.

Effect sizes were calculated according to the formula

$$\frac{(\mu_1 - \mu_2)}{SD_{(diff)}}$$

where μ_1 = mean of group 1, μ_2 = mean of group 2 and $SD_{(diff)}$ = standard deviation of the difference scores (Cohen 1988).

6.3.3.3 Relationship between SPEM Measures and Antisaccade Error Rate

The relationship between SPEM and antisaccade measures was assessed using Pearson correlations. SPEM measures at each velocity as well as averaged measures were used in this analysis. For reasons of clarity, scatter plots between antisaccade error rate and SPEM measures are displayed only for averaged measures; these relationships were mostly very similar to those with SPEM measures at individual velocities.

6.3.3.4 Effects of Relatedness on SPEM and Antisaccade Performance

A cut-off criterion was used to explore effects of relatedness for patients and siblings, i.e. whether siblings of patients with deviant performance also had deviant performance themselves (Crawford et al 1998; Curtis et al 2001a; Iacono et al 1992). Patients were classified as 'impaired' if scores fell more than 1SD below the control group mean for SPEM gain and more than 1SD above the control group mean for SPEM saccadic frequency and antisaccade error rate. Independent samples t-tests were carried out comparing siblings of patients with 'impaired' performance and siblings of patients with less impaired performance on relevant oculomotor measures.

6.3.3.5 Interrelationships between Oculomotor Variables and PANSS, Duration of Illness and SIS; and Effects of Antipsychotic Drug Treatment

MANOVA was used to compare patients on typical and atypical antipsychotics on all oculomotor variables. Pearson correlations were run between all oculomotor variables and PANSS ratings and illness duration in patients and total schizotypy scores in the sibling and control groups.

6.4 Results

Prosaccade latency was still positively skewed after square root transformation and was, therefore, transformed using the natural logarithm. The distribution of the transformed variable was roughly normal (skewness=1.09). Antisaccade latency was heavily skewed (skewness=5.61), due to the presence of an outlier. When this case was excluded the distribution became normal (skewness=0.98). Statistical analyses involving this variable were carried out with and without this case. With the exception of the comparison between patients and siblings results were unaffected by the exclusion of the outlier. Therefore, results based on the entire sample are reported below unless stated otherwise (see Table 6.2). Distributions of other skewed variables were normalised after data transformation. As there were no major differences between results using transformed and untransformed data, for reasons of clarity descriptive statistics and results based on untransformed data are reported below.

Average antisaccade correction rate for patients (79.23%; SD=4.38), siblings (97.10%; SD=4.38) and controls (96.37%; SD=4.58) were similar to those reported previously and suggest that participants understood and were willing and able to follow the task instructions (McDowell & Clementz 1997).

6.4.1 Effects of Age and Sex

Female patients had slightly longer prosaccade latency ($F[1,22]=4.66$; $p=0.04$) than male patients, but no further sex differences emerged (all remaining $p>0.06$). Males and females were, therefore, combined in each group and sex was used as covariate only for prosaccade latency. Groups did not differ in years of education (Wald $\chi^2=2.79$; df=2; $p=0.25$) but differed in age (Wald $\chi^2=15.87$; df=2; $p=0.0004$): patients were significantly older than siblings ($z=-3.34$; $p=0.001$) and controls ($z=-3.34$; $p<0.001$), who did not differ from each other ($z=0.20$; $p=0.84$). Significant correlations between age and oculomotor variables emerged in the patient group with prosaccade latency ($r=0.45$, $p=0.03$) and in the control group with CUS frequency at 10°/s pursuit ($r=-0.55$, $p=0.005$), showing longer prosaccade latency and fewer CUS in older people. Therefore, age was included as a covariate in group comparisons involving these variables.

6.4.2 Group Comparisons and Effects of SPEM Target Velocity

Descriptive statistics and effect sizes for group differences in oculomotor measures are presented in Table 6.1; individual scores for SPEM gain at 10°/s and 24°/s as well as antisaccade error rate are presented in Figures 6.1 and 6.2. Results of the random effects regression group comparisons are summarised in Table 6.2.

There was a trend for a main effect of target velocity on SPEM gain ($F[1,21]=4.08$; $p=0.06$) and a highly significant effect on CUS ($F[1,21]=258.82$; $p<0.001$) and AS frequency ($F[1,21]=67.03$; $p<0.001$), indicating reduced gain and increased saccadic frequency at the faster velocity. There was a trend for a significant velocity-by-group interaction for pursuit gain ($F[2,42]=2.95$; $p=0.06$) but not saccadic frequencies ($F<1.26$; $p>0.29$). The interaction indicated that while patients and controls showed reduced pursuit gain on the faster target, siblings showed no difference between velocities (Figure 6.1).

6.4.3 Relationship between SPEM Measures and Antisaccade Error Rate

In the combined group, antisaccade error rate was correlated with SPEM gain at 10°/s ($r=-0.30$; $p=0.01$) and 24°/s ($r=-0.29$; $p=0.02$) as well as averaged SPEM gain ($r=-0.31$; $p=0.009$). Error rate was correlated with CUS frequency at 10°/s ($r=0.39$; $p=0.001$) and 24°/s ($r=0.38$; $p=0.001$) as well as averaged CUS frequency ($r=0.42$; $p<0.001$) but not AS frequency (all $r<0.18$; all $p>0.15$). Inspection of the scatterplot for the latter relationships indicated the presence of three outliers; after removal of these cases the correlation became significant for AS at 10°/s ($r=0.40$; $p=0.001$) and at 24°/s ($r=0.26$; $p=0.04$) as well as averaged AS ($r=0.38$; $p=0.002$). Spearman correlation including outliers was rho=0.26 ($p=0.03$) for AS at 10°/s, rho=0.21 ($p=0.09$) for AS at 24°/s and rho=0.31 ($p=0.009$) for averaged AS, further supporting the disproportionate influence of outliers in the parametric analyses.

The correlations between antisaccade error rate and AS frequency in the patients were non-significant (all $r<0.18$; all $p>0.42$) arguably due to the existence of three outliers (two of whom were the same as above; see Figure 6.3). After removal of these cases, the correlation approached significance for AS at 10°/s ($r=0.41$; $p=0.08$) as well as averaged AS ($r=0.44$; $p=0.05$) but not at 10°/s ($r=0.34$; $p=0.15$). Spearman rank correlations including outliers were non-significant (all rho<-0.07; all $p>0.75$). The correlations were

not significant in the siblings (all r<-0.24; all p>0.29) (Figure 6.4). In the controls, error rate was correlated significantly with averaged AS (r=0.42; p=0.04) (Figure 6.5) and, at trend level, with AS at 10°/s (r=0.35; p=0.09) and at 24°/s (r=0.38; p=0.07).

Figure 6.1: Smooth Pursuit Gain by Group

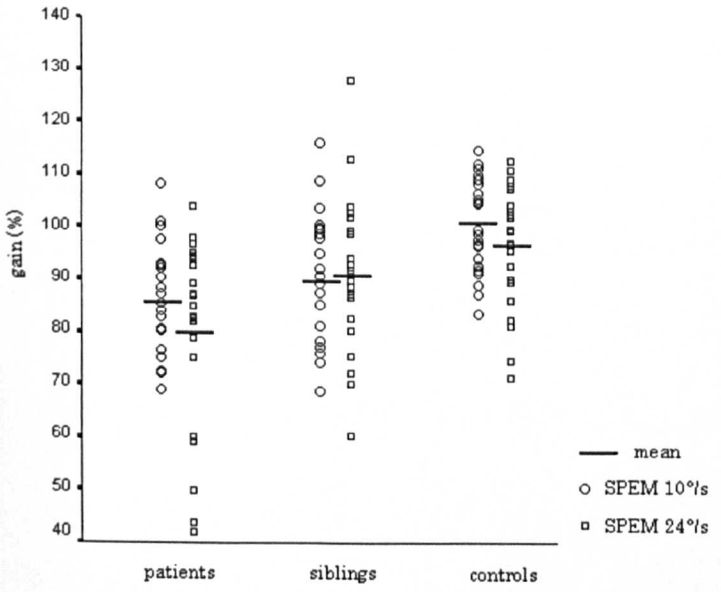


Figure 6.2: Antisaccade Error Rate by Group

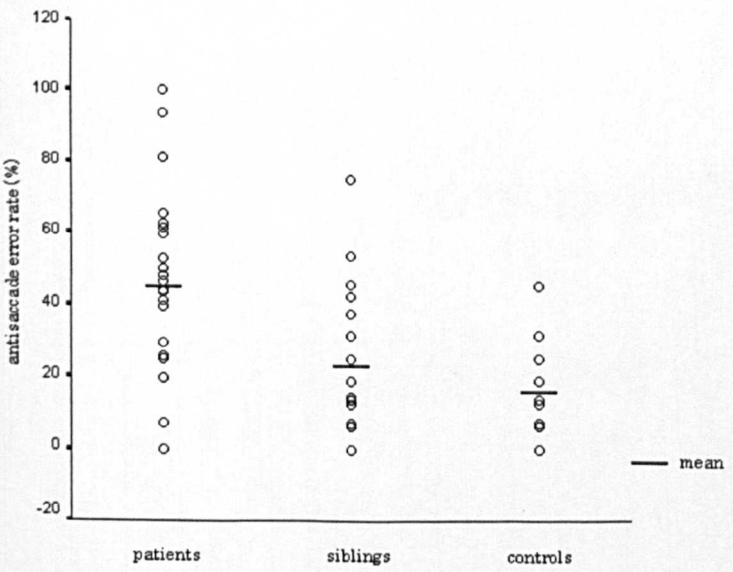


Table 6.1: Descriptive statistics and Effect Sizes of Oculomotor Variables

	Mean (SD)			**Effect Size**		
	P (N=24)	**S (N=24)**	**C (N=24)**	**P – C**	**S – C**	**P – S**
SPEM gain 10°/s	85.90 (10.39) *	89.44 (12.85) †	100.60 (9.07)	-1.15	-0.84	-0.28
SPEM gain 24°/s	79.88 (17.48) †	90.93 (14.81) †	96.72 (11.48)	-0.77	-0.32	-0.54
Anticipatory saccades 10°/s	11.83 (8.04) *	10.48 (6.76) †	6.58 (4.57)	0.53	0.46	0.15
Anticipatory saccades 24°/s	10.96 (5.19) †	9.82 (4.90) †	7.58 (4.27)	0.56	0.36	0.20
Catch-up saccades 10°/s	8.00 (6.26) *	4.35 (4.18) †	1.96 (2.90)	0.87	0.45	0.48
Catch-up saccades 24°/s	17.30 (8.33) †	13.96 (5.25) †	11.79 (4.41)	0.60	0.30	0.37
Fixation saccadic frequency	2.30 (2.57)	3.21 (3.95)	2.00 (2.89)	0.07	0.22	-0.17
Antisaccade gain	-87.75 (31.23)	-85.63 (18.53)	-99.61 (20.33)	0.33	0.59	-0.06
Antisaccade latency	369.53 (215.60)	299.35 (54.99)	282.22 (48.31)	0.41	0.35	0.30
Antisaccade error rate	45.89 (25.09)	24.27 (17.42)	15.04 (11.53)	1.09	0.49	0.73
Prosaccade gain	87.28 (16.61) †	92.40 (14.92)	93.98 (9.84)	-0.40	-0.10	-0.29
Prosaccade latency	200.22 (58.59) †	179.53 (21.65)	181.94 (25.50)	0.29	-0.08	0.33

Legend:
* N=22; † N=23;
P=patients; S=siblings; C=controls

Table 6.2: Results of the Group Comparisons for Oculomotor Variables

	Overall Group Effect		**Patients – Controls**		**Patients – Siblings**		**Siblings – Controls**	
	Wald χ^2 (df=2)	***p***	***z***	***p***	***z***	***p***	***z***	***p***
SPEM gain 10°/s	32.16	<0.0001	5.43	<0.001	1.31	0.19	-4.11	<0.001
SPEM gain 24°/s	25.06	<0.0001	4.92	<0.001	3.37	0.001	-1.53	0.13
Anticipatory saccades 10°/s	8.31	0.02	-2.77	0.06	-0.70	0.48	2.06	0.04
Anticipatory saccades 24°/s	7.43	0.02	-2.66	0.008	-0.82	0.41	1.80	0.07
Catch-up saccades 10°/s †	20.42	<0.0001	-4.49	<0.001	-2.73	0.006	1.78	0.08
Catch-up saccades 24°/s	10.05	0.007	-3.15	0.002	-1.88	0.06	1.22	0.22
Fixation saccadic frequency	1.56	0.46	0.85	0.39	1.22	0.22	0.37	0.73
Antisaccade gain	5.51	0.06	-1.83	0.07	0.33	0.74	2.19	0.03
Antisaccade latency	5.93	0.05	-2.30	0.02	-1.85 *	0.06 *	0.46	0.65
Antisaccade error rate	35.65	<0.0001	-5.82	<0.001	-4.08	<0.001	1.74	0.08
Prosaccade gain	3.73	0.16	1.86	0.06	1.41	0.16	-0.46	0.65
Prosaccade latency ‡	6.28	0.04	-2.08	0.04	-2.32	0.02	-0.25	0.80

Legend:
† with age as covariate
‡ with age and sex as covariates
* after exclusion of outlier: z=-1.58; p=0.12

Figure 6.1: Smooth Pursuit Gain by Group

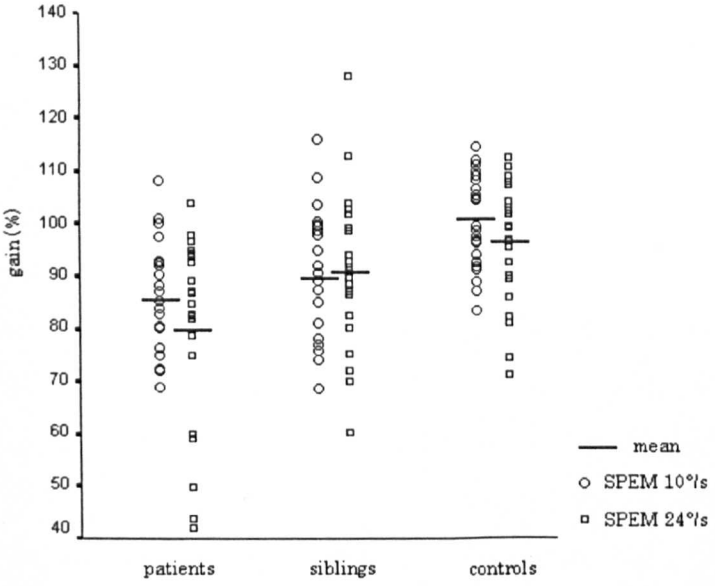


Figure 6.2: Antisaccade Error Rate by Group

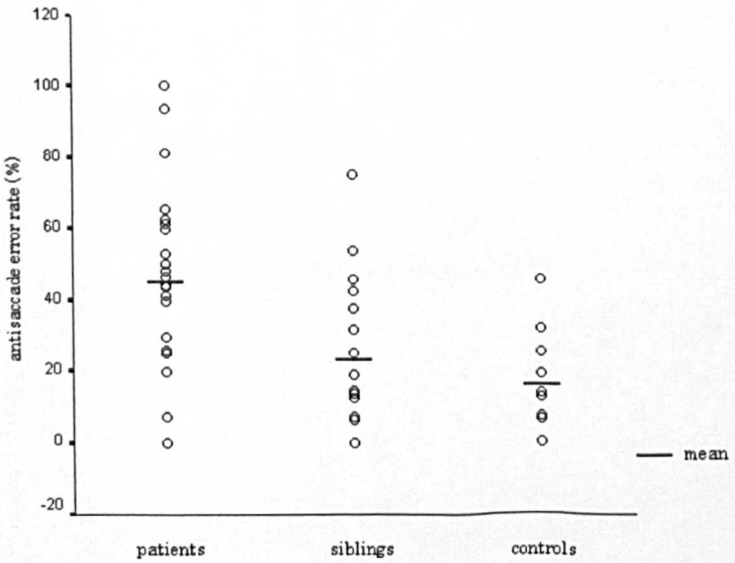


Figure 6.3: Relationship between Antisaccade Error Rate and Anticipatory Saccade Frequency (Averaged across Velocities) in the Patient Group

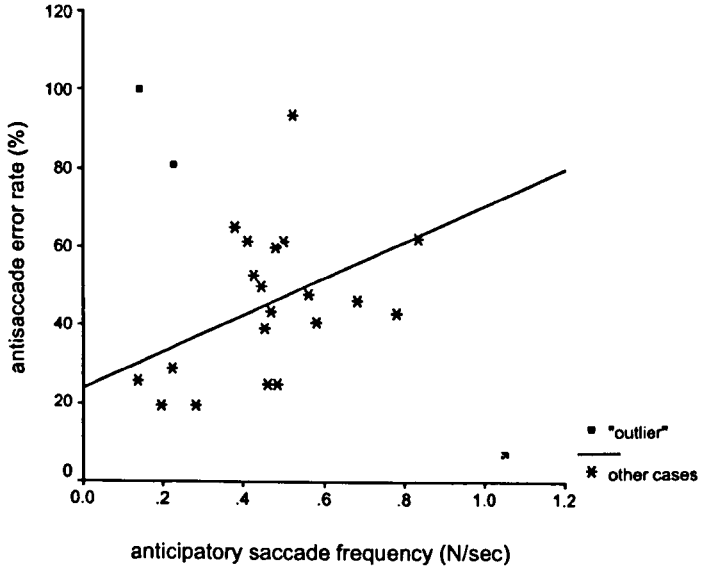


Figure 6.4: Relationship between Antisaccade Error Rate and Anticipatory Saccade Frequency (Averaged across Velocities) in the Sibling Group

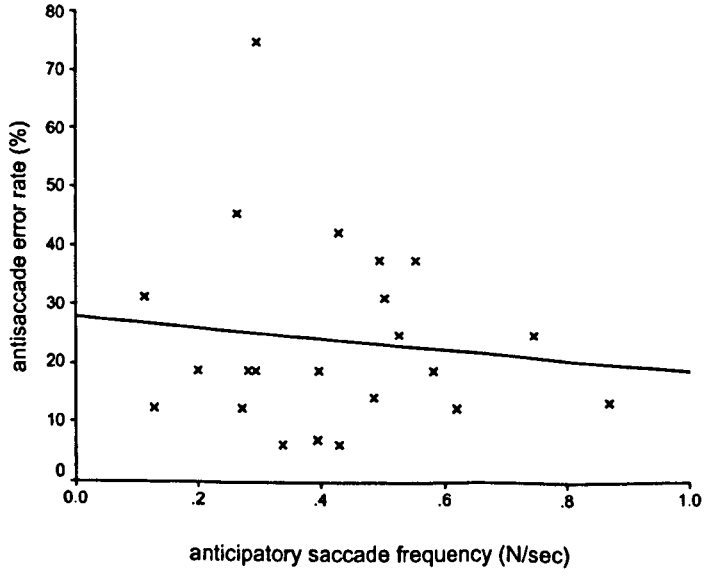
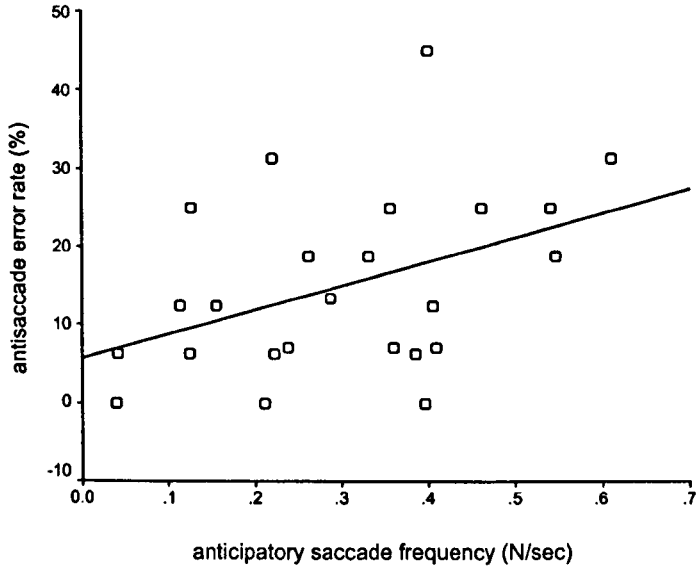
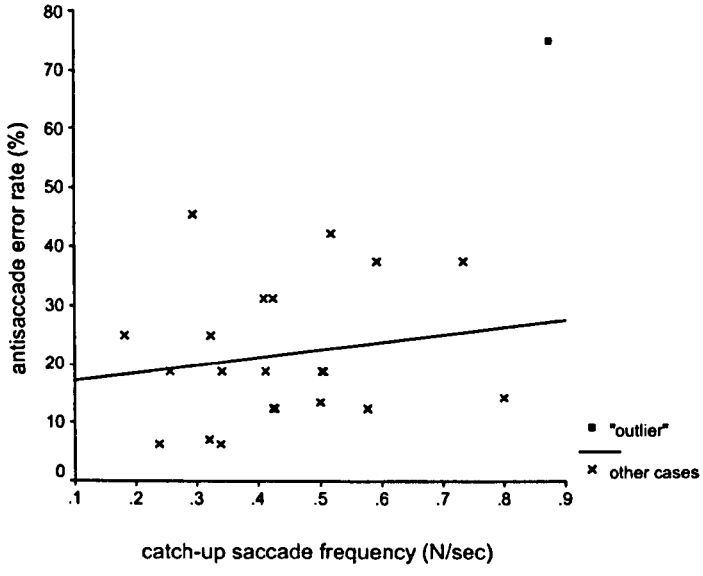


Figure 6.5: Relationship between Antisaccade Error Rate and Anticipatory Saccade Frequency (Averaged across Velocities) in the Control Group



Error rate was significantly correlated with CUS frequency only in the sibling group (10°/s: r=0.45; p=0.03; 24°/s: r=0.37; p=0.09; averaged: r=0.47; p=0.03); after removal of an outlier these correlations became non-significant (all r<0.20; all p>0.38) (Figure 6.6). Correlations between error rate and SPEM gain were not significant at individual group level (all r<-0.21; all p>0.37).

Figure 6.6: Relationship between Antisaccade Error Rate and Catch-up Saccade Frequency (Averaged across Velocities) in the Sibling Group



6.4.4 Effects of Relatedness on SPEM and Antisaccade Performance

Siblings of patients with reduced pursuit gain (N=15) had reduced pursuit gain (t=-2.65; df=20; p=0.02) compared to other siblings (N=7). Siblings of patients with increased AS frequency (N=11) had increased AS frequency (t=2.04; df=20; p=0.05) compared to other siblings (N=11). Siblings of patients with increased CUS frequency (N=10) had similar CUS frequency (t=0.27; df=20; p=0.79) to other siblings (N=12). Siblings of patients with increased antisaccade error rate (N=18) did not differ from other siblings (N=6) on antisaccade error rate (t=1.02; df=22; p=0.32). Samples sizes of less than 24 are due to missing values as described above (Section 6.2.2).

6.4.5 Interrelationships between Oculomotor Variables and PANSS, Duration of Illness and SIS; and Effects of Antipsychotic Drug Treatment

In the patient group, increased positive symptoms were associated with reduced SPEM gain at 24°/s (r=-0.43; p=0.04). Higher levels of general psychopathology were

associated with greater CUS frequency at 10°/s (r=0.65; p=0.001) and at 24°/s (r=0.43; p=0.04) as well as reduced SPEM gain at 24°/s (r=-0.47; p=0.02). Reduced prosaccade gain was associated with increased positive (r=-0.44; p=0.03) and negative (r=-0.44; p=0.03) symptoms. There was a trend for a correlation between saccade frequency during fixation and PANSS general psychopathology score (r=0.39; p=0.06). Duration of illness was correlated with prosaccade latency (r=0.52; p=0.01), indicating that longer duration of illness was associated with longer latency. When this correlation was rerun covarying for age (r=0.33; p=0.13) or age and sex (r=0.34; p=0.13), it became non-significant, suggesting a likely influence of age on this relationship.

No significant correlations between oculomotor measures and total schizotypy score were found in the siblings (all p>0.10) or in the controls (all p>0.10). MANOVA revealed no effect of antipsychotic drug status on oculomotor variables (F[1,21]=1.92; p=0.18). Excluding patients who were treated with anticholinergic drugs did not noticeably affect the pattern of differences between patients and controls as displayed in Table 6.2.

6.5 Discussion

6.5.1 Key Findings

The key findings of this study are as follows. 1) The observation of SPEM and antisaccade deficits in schizophrenia patients and their unaffected siblings largely replicates previous studies. 2) There were correlations between SPEM measures and antisaccade error rate in the combined group as well as in individual groups. The most consistent correlation was that between AS frequency and antisaccade error rate. 3) SPEM measures demonstrated an effect of relatedness, as siblings of 'impaired' patients also displayed somewhat 'impaired' performance. This effect was not statistically significant for antisaccade error rate.

6.5.2 Group Comparisons

The first finding of this study concerns the comparisons between patients, siblings and controls, which largely replicated previous studies. The patient group had significantly reduced smooth pursuit gain (Clementz & McDowell 1994; Ross et al 1988; Sweeney et al 1998a) and increased AS (Ross et al 1999b) and CUS frequency (Radant & Hommer 1992) at both target velocities. On the antisaccade task patients had significant

difficulties suppressing reflexive saccades to the target (Crawford et al 1995a, 1995b; Fukushima et al 1988), increased latency (Fukushima et al 1988; Karoumi et al 1998b) and reduced accuracy (Karoumi et al 1998b; McDowell et al 1999). Patients also had slightly reduced prosaccade gain (Curtis et al 2001a; Nieman et al 2000; Ross et al 1988; Schmid-Burgk et al 1983) and increased prosaccade latency (Mackert & Flechtner 1989). No visual fixation impairments were found (Gooding et al 2000a; Kissler & Clementz 1998; Ross et al 1988).

Siblings performed intermediate, i.e. between patients and controls on most measures. Significant differences between siblings and controls were found on SPEM gain at 10°/s and AS frequency at 10°/s. Siblings also made more AS at 24°/s and CUS at 10°/s, although these comparisons failed to reach statistical significance.

The finding of subtle SPEM deficits in the siblings can be reconciled with previous studies (Clementz et al 1990; Lencer et al 1999), although two studies (Keefe et al 1997; Thaker et al 1998) failed to find reduced pursuit gain in first-degree relatives. The finding of increased AS frequency also agrees with previous studies (Lencer et al 1999; Rosenberg et al 1997c; Ross et al 1998e; Whicker et al 1985). SPEM gain scores of the three groups interacted non-significantly with target velocity, indicating that while patients and controls showed the usual effect of reduced eye tracking accuracy at faster target velocities (Leigh & Zee 1999), siblings showed the opposite pattern.

Siblings had normal prosaccade and visual fixation performance. Despite some previous findings of reduced prosaccade accuracy and fixation impairments in first-degree relatives (Amador et al 1995; Schreiber et al 1995, 1997), the bulk of the literature suggests that these basic eye movements are unimpaired in this population as well as the patient group (Clementz et al 1994; Crawford et al 1998; Curtis et al 2001a, 2001b; Gooding et al 2000a; Karoumi et al 2001; Kissler & Clementz 1998; Ross et al 1988, 1998d; Thaker et al 1996a). Interestingly, however, Rybakowski et al (2001) recently reported an association between fixation (and SPEM) impairments and D3 dopamine receptor gene polymorphism. As SPEM and fixation were correlated in the Rybakowski et al study, and SPEM and fixation are thought to be related at a neurophysiological level (Leigh & Zee 1999), it remains to be investigated further whether fixation performance might not be a useful schizophrenia spectrum measure, perhaps in conjunction with SPEM.

Siblings' performance on the antisaccade task was characterised by reduced accuracy and increased error rate. The observed effect size of 0.49 for the error rate may be described as medium (Cohen 1988) and was very similar to previous studies (Clementz et al 1994; Thaker et al 2000). The relatively small sample size could be the reason why this difference fell short of conventional statistical significance.

A noteworthy finding is that of reduced antisaccade accuracy (Karoumi et al 2001; cf. Chapter 5). Most previous studies of the antisaccade task in first-degree relatives have not included an accuracy measure (Clementz et al 1994; Curtis et al 2001a; Katsanis et al 1997; Thaker et al 2000). While some investigations failed to find differences between relatives and healthy individuals (Crawford et al 1998; McDowell et al 1999), one study showed that a subgroup of relatives (without a family history of schizophrenia) had reduced accuracy (Ross et al 1998d). Other authors have noted reduced antisaccade accuracy in schizophrenia patients (Karoumi et al 1998b; McDowell et al 1999).

Antisaccade accuracy is a measure of sensorimotor coordinate transformations that occur between sensory input and motor output, requiring internal manipulation of spatial information (Krappmann et al 1998). Possible neural substrates for these processes include parietal and prefrontal cortex (Doricchi et al 1997; Leigh & Zee 1999; Pierrot-Deseilligny et al 1995). It remains to be investigated whether saccadic accuracy measures of sensorimotor coordinate transformations may serve as a useful genetic marker in schizophrenia research. The finding of unimpaired prosaccade accuracy of relatives in this and previous studies (Crawford et al 1998; Curtis et al 2001a; Karoumi et al 2001) provides an adequate control condition for the programming and execution of saccadic motor commands in the presence of visual targets.

However, as the present study included only one antisaccade target amplitude (±15°), the finding of reduced accuracy must be considered preliminary and should be replicated in future studies utilising several amplitudes for a more reliable estimation of spatial accuracy. Also, as in Chapter 5 it has to be pointed out that antisaccade accuracy might in part reflect effects of task instructions or strategy use. It is unknown to what extent the participants' emphasis on inhibition of error saccade or antisaccadic accuracy influenced performance and performance differences between groups. Future research is needed to clarify exactly how strategy use may interact with stimulus amplitude to influence antisaccade error rate, latency and accuracy.

6.5.3 Effects of Relatedness

The choice of statistical analysis of between-group differences was based on an important assumption. The genetic relatedness between the patient and sibling pairs violated the assumptions of analysis of variance concerning independence of groups (Egan et al 2000; Ott 1991). In particular, first-degree relatives were expected to attract similar, i.e. statistically correlated, scores across groups (Rabe-Hesketh et al 2001). Evidence of this effect of relatedness was obtained in this study for two of three SPEM measures. Siblings of patients with 'impaired' smooth pursuit gain (defined relative to the control group mean) had themselves reduced gain compared to siblings of patients who performed above the cut-off point. The same pattern was observed for AS frequency. This finding is of interest as it highlights the familial contribution to variance in SPEM gain and AS frequency and underscores the need to consider effects of familial relatedness in the statistical analysis of between-group differences.

Similar findings were obtained previously for SPEM (Iacono et al 1992) and antisaccade performance (Crawford et al 1998) as well as other proposed neurocognitive endophenotypes (Chen et al 1998). No effect of relatedness was obtained for antisaccade error rate in the present investigation, possibly due to the small and unequal sample sizes used in this analysis. The two groups in the Crawford et al study consisted of 19 and 25 participants, whereas in the present study there were 18 siblings of 'impaired' antisaccade patients and only 6 siblings of 'unimpaired' patients. The error rates for these two groups were 26.36% and 18.01%, respectively, compared to a control mean of 15.04%. This difference was, therefore, in the expected direction and might have achieved statistical significance given larger and more equal group sizes.

In the present design it is impossible to dissect this familial contribution to SPEM and antisaccade variance into genetic and non-genetic components. Familial patterns of schizophrenia related phenotypes may not necessarily indicate the operation of genes, but could also reflect non-genetic familial factors, such as viruses, diet, teratogens, or psychosocial factors (Torrey & Yolken 2000). Based on estimated heritabilities of SPEM and antisaccade measures, however, it may be argued that the main source of within-family correlations consists of genetic factors (Katsanis et al 2000; Malone & Iacono 2002).

6.5.4 Relationship between SPEM Measures and Antisaccade Error Rate

A number of correlations were obtained between SPEM and antisaccade variables. In the combined group, SPEM gain and AS and CUS frequency were correlated with antisaccade error rate (after the removal of outliers, or using non-parametric statistics). The only correlation that held across individual groups was that between AS frequency and error rate (in the patient and control groups), supporting the robustness of this relationship.

The association between AS frequency and antisaccade error rate mirrors that of Chapter 5. Previous research has suggested that both tasks may tap (frontal) inhibitory function (Calkins & Iacono 2000; Friedman et al 1992a; Levin 1984; Müri et al 1998). It may be speculated that a combination of AS and error rate might provide an improved composite oculomotor phenotype, given its moderate statistical association in this and the previous sample (Chapter 5). The finding has to be treated with caution, however, due to the relatively small sample sizes and the existence of cases whose scores did not conform to this relationship. This heterogeneity regarding the relationship between these two measures, however, could be compatible with the clinical and biological heterogeneity of schizophrenia and its biological correlates and suggests that a combination of AS and antisaccade errors might identify only a subgroup of individuals (possibly with a certain genotype).

It is also somewhat puzzling that AS and error rate were not correlated significantly in the sibling group. While the absence of this relationship in this crucial schizophrenia spectrum group might represent a disappointing failure of the hypothesis linking AS and error rate, it is a possibility that these measures follow the pattern of a two-hit model proposed by Freedman and colleagues (Waldo et al 2000). These researchers have shown that the deficits of P50 suppression and reduced hippocampal volume co-occur in schizophrenia patients, but are inversely associated in first-degree relatives. While AS and antisaccade errors were not inversely correlated in this sample of first-degree relatives, it remains a possibility that these measures represent two facets of inhibitory control, likely to co-occur in full-blown schizophrenia, but unrelated in first-degree relatives, possibly due to protective mechanisms.

6.5.5 Clinical Considerations

The current sample of relatives may be described as relatively homogeneous as only full biological siblings were used and no more than one sibling from any family was included. Ross et al (1998d, 1998e) have shown that schizophrenic patients' parents with a family history of schizophrenia differed on eye movements from parents without family history. Therefore, including parents into studies of first-degree relatives increases the genetic heterogeneity of the sample, in addition to introducing cohort effects (Egan et al 2000).

Both siblings and controls in the present study were free of DSM-IV Axis I and Axis II schizophrenia spectrum symptoms. These exclusion criteria represent a strength of the design as it allows the isolation of the variable of interest, i.e. the genetic relationship with a schizophrenia patient, in the absence of other, possibly confounding effects of symptoms or treatment. The current findings agree with previous studies (Curtis et al 2001a; Katsanis et al 1997), which have reported that antisaccade deficits in first-degree relatives are not due to the presence of psychiatric symptoms. However, as one study found antisaccade abnormalities only in relatives with schizophrenia spectrum personality symptoms (Thaker et al 2000), and antisaccade performance has been linked to schizotypy levels in healthy individuals (Gooding 1999; O'Driscoll et al 1998), it is possible that the magnitude of the observed differences in error rate in the current study would have been greater if relatives with higher levels of such symptoms had been included. The low levels and small range of sub-clinical schizotypy personality traits in the sibling and control groups might also explain why there were no relationships between eye movement measures and schizotypy scores.

Another feature of the present sample worth discussing is that the majority (87.5%) of siblings came from sporadic schizophrenia families, as established through patient interviews. As there have been previous reports of worse SPEM and antisaccade performance in multiplex compared to simplex schizophrenia family members (McDowell et al 1999; Schwartz et al 1995b) it is possible that the inclusion of more relatives from multiplex families would have provided larger group separations. Interestingly, Ross et al (1998d) observed reduced antisaccade accuracy only in family history negative but not positive relatives, somewhat consistent with the present findings. Regarding SPEM, however, Lencer et al (2000) found equal impairments in familial and non-familial relatives.

No effects of antipsychotic or anticholinergic drug treatment on oculomotor performance were observed. The present study was not designed to investigate the effects of atypical antipsychotic treatment on oculomotor function. There were a number of PANSS symptom correlates of oculomotor measures, in particular those of general psychopathology and positive symptoms.

6.6 Conclusions

- The study confirms that SPEM and antisaccade performance may be useful markers of genetic liability to schizophrenia by demonstrating subtle deficits in a genetically and clinically homogenous sample of siblings of schizophrenia patients.
- Antisaccade gain may prove to be an important oculomotor endophenotype, possibly involving working memory or visuospatial sensorimotor transformation processes.
- AS frequency and antisaccade error rate were correlated in the combined group as well as the patient and control groups (but not in the siblings). Future research will need to establish whether these measures might be profitably combined as a composite inhibitory oculomotor endophenotype in genetic linkage studies.
- The effects of familial relatedness on eye movement performance further underscore the validity of oculomotor measures as endophenotypic markers and highlight the need to use statistical techniques that take into account between-group relatedness.

6.7 Limitations

- The small and unequal sample sizes throw doubt over the findings concerning the effects of relatedness.
- The finding of reduced antisaccade gain in the siblings and patients has to be confirmed using more than one target amplitude before this task can be considered a putative endophenotype.
- Additionally, between-group differences in antisaccade gain may partly reflect differences in strategy use.

- The reasons for the absence of a relationship between AS frequency and antisaccade error rate in the sibling group remain unclear.

Chapter Seven

Study IV – Relationship between Eye Movements and Schizotypy

7.1 Chapter Overview

Given the evidence of impaired smooth pursuit and antisaccade eye movements in first-episode patients as well as healthy siblings of schizophrenia patients, this chapter investigates another population from the schizophrenia spectrum, individuals with high scores on psychometric measures of schizotypy. On the basis of the continuum hypothesis (Claridge 1990), an individual differences approach will be adopted, relating eye movement performance (Battery II) to continuous scores from self-report questionnaires of schizotypal personality traits. The study focuses on the relationship between eye movements and empirically defined schizotypy symptom dimensions, as well as the role of trait emotionality in this relationship. Following the finding of an association between antisaccade error rate and anticipatory saccade frequency in Chapters 5 and 6, this relationship will also be examined.

7.2 Introduction

The hypothesised proximity of schizotypal personality traits and schizotypal personality disorder (SPD) to schizophrenia is thought to be reflected at clinical, biological and genetic levels (Cadenhead & Braff 2002; Cannon et al 2002; Fanous et al 2001; Gruzelier 1996; Gunderson & Siever 1985; van Os et al 2000). Therefore, the role of oculomotor tasks as putative schizophrenia endophenotypes has to be explored in relation to schizotypal personality features. Confirming this assumed proximity, a number of studies have observed a relationship between schizotypal personality traits and smooth pursuit eye movement (SPEM) and antisaccade error rate (Gooding 1999; Gooding et al 2000b; Larrison et al 2000; O'Driscoll et al 1998; Siever et al 1984, 1989), despite some failures to replicate (Klein et al 2000c; Simons & Katkin 1985). Deficits

have also been observed in individuals with SPD (Brenner et al 2001; Keefe et al 1989; Lencz et al 1993; Siever et al 1994).

As noted in Chapter 1, schizotypy is a multifaceted construct, comprising positive, negative and possibly other symptom dimensions (Vollema & van den Bosch 1995). Consequently, some studies have aimed to investigate the relationships between specific schizotypal traits and eye movement performance. The most commonly used traits in these studies were those relating to positive and negative features. As summarised above (Section 2.3.5.5.6), SPEM deficits in SPD patients as well as in healthy individuals tend to be associated more strongly with negative than positive signs and symptoms (Coursey et al 1989; Siever et al 1982, 1989, 1994). This pattern somewhat agrees with findings from schizophrenia studies (Section 2.3.5.3) and suggests a continuum of pathological schizophrenic and SPD symptoms and 'normal' schizotypal traits at clinical and psychophysiological levels. Evidence of clinical correlates of antisaccade errors from studies of schizophrenia and schizotypy is much less consistent, implicating positive as well as negative symptom correlates (Section 2.5.4.3).

No previous study has combined the SPEM and antisaccade tasks with a *comprehensive* set of schizotypy measures, including both positive and negative features. Given the multifactorial nature of schizotypy, it might valuable to empirically derive dimensions of schizotypy from a range of psychometric questionnaires to explore their relationships with oculomotor performance.

A second point of interest concerns the relationship between measures of schizotypy and trait emotionality. A number of studies have demonstrated an association between trait emotionality and schizotypy/schizophrenia (Bentall et al 1989; Braunstein-Bercovitz et al 2002; Catts et al 2000; Eysenck & Barrett 1993; Gurrera et al 2000; Lipp et al 1994; Muntaner et al 1988; O'Driscoll et al 1998; Rust & Chiu 1988; Tien et al 1992a; van den Bosch 1984; Wuthrich & Bates 2001).

Therefore, in order to establish the specificity of relationships between schizotypy/schizophrenia and neurocognitive or behavioural measures, the possibly confounding effects of trait emotionality have to be considered (Raine & Lencz 1995). To establish this specificity is important, if a given endophenotypic marker is assumed to reflect the action of a specific, schizophrenia-related disease gene.

Following this argument, Braunstein-Bercovitz and colleagues (Braunstein-Bercovitz 2000; Braunstein-Bercovitz et al 2002; Braunstein-Bercovitz & Lubow 1998) have

demonstrated that the statistical relationship between schizotypy and one such behavioural measure, latent inhibition (LI), can be accounted for by measures of trait anxiety. LI is a phenomenon in which preexposure of a stimulus slows subsequent learning about that stimulus. The LI paradigm has been widely used in schizophrenia spectrum and pharmacological studies due to its susceptibility to dopaminergic manipulation and its proposed role in the pathophysiology of schizophrenia (Gray et al 1995; Lubow & Gewirtz 1995; Moser et al 2000). Given the proposed attentional underpinnings of this task (Braunstein-Bercovitz et al 2002) and the role of anxiety in attentional processing (Clark & McManus 2002), the lack of specificity of this deficit to schizotypy (and possibly, by extension, to schizophrenia) may not be surprising, yet warrants serious reconsideration of the usefulness of LI as a schizophrenia spectrum marker.

Similarly, Corr et al (2002) recently observed an association between trait emotionality and a psychophysiological measure of sensorimotor gating known to be impaired in schizophrenia, prepulse inhibition (PPI). PPI has been studied as an endophenotype in schizophrenia genetics as well as to elucidate the pathophysiology of schizophrenia and the pharmacology of antipsychotic drugs (Braff et al 2001; Cadenhead & Braff 2002; Kumari 2000; Swerdlow & Geyer 1998). An association between impaired PPI and increased levels of neuroticism might suggest reduced specificity of this measure to schizophrenia spectrum symptoms.

Whether trait emotionality affects the relationship between eye movement performance and schizotypy/schizophrenia has not been explored. O'Driscoll et al (1998) observed that high scorers on the Chapmans' Perceptual Aberration scale (a measure of positive schizotypy) also had higher scores on state measures of anxiety and depression and that there was a correlation between state depression scores and antisaccade errors. Importantly, neither of these measures fully accounted for the relationship between SPEM and antisaccade dysfunction and positive schizotypal traits. O'Driscoll et al's (1998) choice of *state* emotionality measures, however, leaves open the question of whether *trait* emotionality impacts on the relationship between error rate and schizotypy.

7.2.1 Aims

The aims of the present study were, therefore, as follows. 1) To confirm the multifactorial nature of schizotypy. Based on previous evidence, a multivariate factor

structure, possibly comprising positive and negative dimensions, was hypothesised. 2) To investigate the relationships between empirically derived subfactors of schizotypy and eye movements. Higher levels of schizotypy were hypothesised to be related to greater impairments on the SPEM and antisaccade, but not the fixation and prosaccade tasks. Given the evidence from schizophrenia studies, SPEM impairments were hypothesised to be associated with negative symptoms. No clear *a priori* hypotheses could be made regarding the schizotypy dimension correlates of antisaccade errors, due to the inconsistent findings from schizophrenia studies. 3) To investigate whether the relationship between schizotypy and eye movements can be accounted for by trait emotionality. Assuming specificity of oculomotor endophenotypes to the schizophrenia spectrum, trait emotionality was hypothesised to be unrelated to SPEM and antisaccade measures.

7.3 Method

7.3.1 Participants

One-hundred and fifteen participants took part in this study. Participants were recruited from amongst psychology undergraduate students at Goldsmiths College (N=68; 59.1%) and postgraduate students and university staff (N=47; 40.9%). There were 40 (34.8%) males and 75 (65.3%) females. Ages ranged from 18 to 44 (mean=23.88; SD=5.95). All participants provided written informed consent, after the study details had been fully explained to them. The study was approved by the Ethics Committee of the Department of Psychology, Goldsmiths College.

No full psychiatric screening was carried out, in keeping with other investigations of schizotypy in non-clinical samples (Braunstein-Bercovitz 2000; Sharpley & Peters 1999; Suhr & Spitznagel 2001; Wuthrich & Bates 2001). Instead, participants filled in a self-report questionnaire probing for demographic data as well as information on drug use and clinical history. Participants indicated whether they or a family member had a history of mental illness, and if so what kind (open-ended question). The questionnaire also asked for the number of units of alcohol consumed per week, whether participants consumed psychoactive drugs, and if so what kind (open-ended question). No participant had a history of psychosis, as assessed by this questionnaire. Ninety-eight participants (85.2%) denied any psychiatric history, but twelve individuals (10.4%) reported a history of depression and five participants (4.3%) provided no information.

Eighty-seven individuals (75.7%) reported no psychiatric family history, fifteen individuals (13%) reported a family history of depression, one person (0.9%) reported a family history of anxiety disorder, three participants (2.6%) indicated a family history of schizophrenia and nine participants (7.8%) provided no answer. These data were dichotomised for further analyses, yielding groups of individuals with or without any psychiatric history, with or without any family history and with or without a family history of schizophrenia (excluding those who failed to provide an answer).

Sixty-five individuals (56.5%) denied any drug use, twenty-four (20.9%) admitted to cannabis use, one individual (0.9%) used cocaine and nineteen (16.5%) reported using more than one type of drug. Six participants (5.2%) supplied no information. These data were dichotomised to create separate variables of individuals who did or did not use any drugs, did or did not use cannabis and did or did not use more than one type of drug (excluding those who failed to provide an answer).

7.3.2 Eye Movement Assessment

Eye Movement Battery II was used. Prosaccade data from five participants was unusable. SPEM data was unusable for four participants at 12°/ and 48°/s, for six participants at 24°/s and for eight participants at 36°/s. Fixation data was unavailable for nine participants. Reasons for missing data included fatigue or movement artefact, computer storage error and calibration error.

The dependent oculomotor variables were, as before, SPEM gain and frequencies of catch-up saccades (CUS) and anticipatory saccades (AS); frequency of saccades during fixation; antisaccade gain, latency and error rate; and prosaccade gain and latency.

7.3.3 Psychometric Assessment

The choice of psychometric self-report schizotypy questionnaires reflects the well-established observation that in non-psychiatric individuals the expression of schizophrenia/schizotypy traits is attenuated; therefore, less pathological items, such as psychometric questionnaires rather than clinical interviews, should be used (Johns & van Os 2001).

Table 7.1: Sample Items of Psychometric Questionnaires

O-LIFE **UE**	Are your thoughts sometimes so strong that you can almost hear them? Can some people make you aware of them just by thinking about you? Do you sometimes feel that your accidents are caused by mysterious forces?
O-LIFE **IA**	Do you enjoy many different kinds of play and recreation? Are there very few things that you have ever really enjoyed doing? Does it often feel good to massage your muscles when they are tired or sore?
O-LIFE **IN**	Do you often change between intense liking and disliking of the same person? Do you at times have an urge to do something harmful or shocking? Do people who drive carefully annoy you?
O-LIFE **CD**	Are you sometimes so nervous that you are 'blocked'? Do you dread going into a room by yourself where other people have already gathered and are talking? Do you often have difficulties in controlling your thoughts? Are you a person whose mood goes up and down easily?
RISC	I never use a lucky charm. I consider no person or country to be my enemy. Sometimes I get a weird feeling that I am not really here. I have, on occasions, tried to reach the very essence of an object with my mind.
PSQ-80 **AC**	I sometimes jump quickly from one subject to another when speaking. I often ramble on too much when I speak. I frequently find my thoughts are racing.
PSQ-80 **WD**	I prefer to keep to myself. I feel that I cannot get close to people. People sometimes find me aloof and distant.
PSQ-80 **UR**	I am sometimes sure that other people can tell what I am thinking. Sometimes things on the TV or radio have a hidden meaning for me. My sense of smell sometimes becomes unusually strong.
PSQ-80 **SD**	I am never late for anything. I always try my hardest at everything I do. I am not always totally honest.
PSQ-80 **IT**	I spend most of my time in galoshes. I think cars are a form of transport. I have never seen a television set.
EPQ-R **E**	Are you a talkative person? Are you rather lively? Do you often make decisions on the spur of the moment?
EPQ-R **N**	Does your mood often go up and down? Are you an irritable person? Are your feelings easily hurt?
EPQ-R **P**	Do you take much notice of what people think? Should people always respect the law? Do you enjoy hurting people you love?
EPQ-R **L**	Are *all* your habits good and desirable ones? Do you always practice what you preach? Do you always wash before a meal?

For legend see Section 11

Missing data occurred for the Eysenck Personality Questionnaire (N=1), the Rust inventory (N=6) and the Personality Syndrome Questionnaire (N=7). Therefore, factor scores could be calculated for all but nine participants. Sample items of all questionnaire scales are given in Table 7.1.

7.3.3.1 Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE)

The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE; Mason et al 1995) was developed from the Combined Schizotypal Traits Questionnaire (CSTQ; Bentall et al 1989). Factor analysis of the CSTQ yielded four factors, labelled Unusual Experiences, Cognitive Disorganisation, Introvertive Anhedonia and Impulsive Nonconformity. The O-LIFE has 159 items with a binary (YES/NO) response format.

Unusual Experiences (UE; 30 items) has been related to positive schizotypy, containing perceptual, hallucinatory and magical thinking items. *Cognitive Disorganisation* (CD; 24 items) also relates to positive schizotypy, describing cognitive aberrations, manifested in decision-making, attention and concentration difficulties. CD also includes items relating to emotional deficits, such as a sense of purposelessness, moodiness and social anxiety. Items from the Eysenck Personality Questionnaire-Revised (EPQ-R; see Section 7.2.3.4) neuroticism scale are included in CD. *Introvertive Anhedonia* (IA; 27 items) describes social independence, solitude, introversion, reduced experience of pleasure from social interactions and a range of other activities, as well as a dislike of emotional and physical intimacy. IA contains some EPQ-R extraversion items. *Impulsive Nonconformity* (IN; 22 items) bears some resemblance to the Eysencks' (Eysenck & Eysenck 1991) psychoticism scale, containing items relating to disinhibited, impulsive, violent, self-abusive and reckless behaviours. IN includes EPQ-R psychoticism scale items.

UE, CD and IN scores were shown to decrease with age while IA increase with age; males score higher on IA and IN, females score higher on UE and CD (Mason et al 1995). The scale has good reliability characteristics (Burch et al 1998; Mason et al 1995) and is probably one of the most widely used questionnaires in experimental and psychophysiological studies of schizotypal personality (Mason et al 1997; Nunn & Peters 2001; O'Reilly et al 2001; Rawlings & Goldberg 2001; Startup 1999; Steel et al 1996).

In order to reduce statistical overlap (collinearity) between O-LIFE and EPQ-R, items from the EPQ-R E, N and P scales contained in the O-LIFE scales IA, CD and IN, respectively, were excluded from O-LIFE scale scores.

7.3.3.2 Rust Inventory of Schizotypal Cognitions (RISC)

The Rust Inventory of Schizotypal Cognitions (RISC; Rust 1987, 1988, 1989) is a psychometrically constructed, cognitively based, questionnaire of 26 items. Its response format is a four-point forced choice set ("strongly agree", "agree", "disagree", "strongly disagree"). The RISC is a unitary scale (no subscales). Total scores range between 0-78, with higher scores indicating greater incidence of schizotypal cognitions. In order to eliminate an acquiescent response bias, thirteen items are positively and thirteen items are negatively scored. Items were designed so as to be acceptable in content to the general public, i.e. obviously pathological ("mad"; Rust 1988) items were avoided. As an example, the item "Sometimes my thoughts seem so loud I can almost hear them" was preferred over the more pathological "I sometimes hear imaginary voices" (Rust et al 1988).

In contrast to other, related instruments the RISC was developed and standardised to yield approximately normally distributed scores in the general population. The test was developed primarily on students, so can be used easily in the present sample. Validation studies demonstrated an absence of sex differences, but younger individuals tend to have higher scores (Rust et al 1988; Rust 1987, 1988, 1989).

The RISC was validated in acute schizophrenia patients who had higher scores than healthy controls. RISC scores were also correlated with psychiatrist ratings of schizotypal symptoms in chronic schizophrenia patients. Chronic patients had lower RISC scores than acute patients, reflecting the positive rather than negative schizotypal nature of the test (Rust 1987, 1988, 1989). Interestingly, no difference was found between relatives of schizophrenia patients and healthy individuals. Rust (1989) argued that this might reflect the expression of denial or defensiveness of schizophrenia related content in the relatives (see also Catts et al 2000; Claridge et al 1983; Katsanis et al 1990).

Further evidence of validity was obtained through correlational studies, which showed associations between RISC and the Minnesota Counselling Inventory (MCI) in university students, in particular with MCI subscales of emotional stability ($r=0.45$), low mood ($r=0.27$), nonconformity ($r=0.40$) and poor social relations ($r=0.26$) (Rust & Chiu 1988).

Larrison et al (2000) reported the highest correlations between RISC and PSQ subscales with unusual perceptual experiences, constricted affect and odd beliefs/magical thinking. RISC scores were almost uncorrelated (r=0.12) with the Eysencks' psychoticism but significantly correlated (r=0.38) with neuroticism in students (Rust et al 1988). As the RISC was designed at least partly with the aim to provide an improvement over the then predominant measure of psychosis-proneness, the Eysencks' P scale (see Section 7.2.3.4), its low statistical relation with P is not surprising and, according to Rust (1987, 1988, 1989), reflects the independence of the positive schizotypal dimension (RISC) from the psychopathy or (antisocial) personality disorder spectrum (P scale). MacDonald et al (2001) observed correlations between RISC and the Chapman Perceptual Aberration and Magical Ideation scales.

Balogh et al (1991) observed correlations between RISC and subscales of the Chapman scales, such as perceptual aberration, magical ideation, impulsivity-nonconformity and social anhedonia, but not physical anhedonia. Additionally, RISC was correlated with subscales of the widely used clinical assessment tool Minnesota Multiphasic Personality Inventory (MMPI), such as paranoia, psychasthenia, schizophrenia and hypomania. The RISC has been used in experimental schizotypy research (Larrison et al 2000).

7.3.3.3 *Personality Syndrome Questionnaire (PSQ-80)*

The Personality Syndrome Questionnaire (PSQ-80) is based on a three-factor model of schizotypy, originating in psychophysiological observations and mirroring hypothesised syndromes of schizophrenia (Gruzelier 1996, 1999, 2002). The questionnaire contains 78 items, scored using a binary response format (true/false), of three schizotypy measures, relating to the hypothesised Unreality, Withdrawn and Active syndromes. PSQ-80 also contains two validity measures, the Social Desirability and Inattentiveness scales.

The *Unreality* syndrome (UR) scale (24 items) is a measure of positive schizotypy, tapping perceptual anomalies and magical ideation. The *Active* syndrome (AC) scale (18 items) provides a measure of increased mental and physical activation, similar perhaps to certain aspects of thought disorder observed in schizophrenia and mania. The *Withdrawn* syndrome (WD; 25 items) scale is a measure of negative schizotypy, describing social and emotional withdrawal, constricted affect and social anxiety. The *Social Desirability* (SD; 8 items) and *Inattentiveness* (IT; 3 items) scales provide estimates of the honesty and validity of a participant's responses. Elevated scores on

these scales would suggest questionable validity of the data, although no precise cut-off criteria are provided for the exclusion of 'dishonest' or 'inattentive' participants. The PSQ-80 (or previous versions of it) has been used in psychophysiological and experimental studies (Croft et al 2001; Gruzelier & Kaiser 1996; Kaiser & Gruzelier 1999).

7.3.3.4 *Eysenck Personality Questionnaire – Revised (EPQ-R)*

The EPQ-R (Eysenck & Eysenck 1991) is the widely used and well-established psychometric instrument for the assessment of the Eysenckian personality variables of extraversion (E), neuroticism (N) and psychoticism (P). It contains 106 items, which make up the three main scales, a Lie (L) scale and Criminality and Addiction scales. These latter two scales are not utilised in the present investigation. Items are scored using a binary response format (YES/NO). While E, P and L scales have both positively and negatively scored items, all N items are positively scored.

The EPQ-R is the final product of a series of questionnaires, originating in the 1952 Maudsley Medical Questionnaire (MMQ), a brief measure of neuroticism. The extraversion and neuroticism dimensions, which are at the heart of Eysenck's theory, were captured in subsequent versions of the 1959 Maudsley Personality Inventory (MPI), the 1964 Eysenck Personality Inventory (EPI), the 1975 Eysenck Personality Questionnaire (EPQ) and its 1991 revision, the EPQ-R. The psychoticism scale (Eysenck & Eysenck 1976; Eysenck 1992) was first included in the EPQ and considerably revised in the EPQ-R.

Extraversion (23 items) is primarily intended to be a measure of sociability. According to Eysenck and Eysenck (1991), a high-scorer on the E scale is sociable, enjoys and craves social interaction, has many friends, is an optimist and gets bored and restless in situations of solitude and lack of excitement. E, however, also has a second component, relating to impulsivity. This component describes spontaneous and carefree behaviour, lack of planning, control and reliability (Eysenck & Eysenck 1991).

Neuroticism (24 items) is a measure of trait emotionality. High levels of N describe excessive worrying, unstable mood, high reactivity to emotional stimuli, high levels of anxiety and depression and consequent physical symptoms of sleeplessness, pain sensitivity and psychosomatic disorders (Claridge & Davis 2001; Eysenck & Eysenck 1991). Neuroticism and extraversion are amongst the most widely accepted 'normal' personality dimensions (Costa & McCrae 1997).

Psychoticism (32 items) was proposed as a measure of the liability (or diathesis) to disorders from the psychosis spectrum (Eysenck & Eysenck 1976; Eysenck 1992). However, the spectrum of psychosis defined here also includes impulsive, antisocial and criminal tendencies, in short psychopathy-related behaviours (Zuckerman et al 1988). The term tough-mindedness is often used to describe this dimension. Despite a proposed link between psychopathy and psychosis (Corr 2000), items from the P scale have a somewhat different flavour compared to positive schizotypy scales and correlations tend to be moderate (Chapman et al 1982; Raine 1991; Rust 1989). A longitudinal study confirmed the association between P and psychotic-like symptoms and personality disorder, but not an increased rate of psychosis *per se* (Chapman et al 1994a).

The *Lie* scale (21 items) is a measure of social desirability and tendency to 'fake good'. Eysenck and Eysenck (1991) suggested correlating L scores with other measures, excluding high scorers, and then repeating the analyses. In this manner the effects of L can be investigated.

A plethora of experimental, psychometric, biological and psychophysiological studies have used the E, N and P scales (for review see Eysenck & Eysenck 1976, 1991; Eysenck 1992; also see special issue of *Personality and Individual Differences*, 2001, Volume 31, Number 1).

7.3.4 Statistical Analysis

All statistical analyses were carried out using SPSS Release 10.0.7 (SPSS Inc., Chicago, Ill). O-LIFE UE (skewness=1.02) and IA (skewness=1.23), prosaccade latency (skewness=1.09) and AS at 12°/s (skewness=1.35) were slightly positively skewed. Square root transformation normalised skew for all variables (-0.06, 0.57, 0.84 and 0.22, respectively) and yielded results virtually identical to those reported below, which are based on untransformed variables.

7.3.4.1 Effects of Age and Sex

Pearson correlations were carried out between age and oculomotor and psychometric variables. Multivariate analyses of variance (MANOVA) were used comparing males and females on schizotypy questionnaires, saccadic and smooth pursuit and fixation variables.

7.3.4.2 Schizotypy Factor Structure

The Pearson correlation matrix of questionnaire scales was factor analysed using principal components analysis (PCA) with oblique rotation (direct oblimin). Oblique rotation was chosen as it was deemed phenomenologically unlikely that different facets of the schizotypy construct would be statistically unrelated to each other. As Tabachnick and Fidell (2001) pointed out, orthogonal (i.e. uncorrelated) factor solutions "strain reality unless the researcher is convinced that underlying processes are almost independent" (p. 614). Factors[23] were extracted if their eigenvalues exceeded 1. To confirm factorability of the correlation matrix, the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy was used. Bartlett's test of sphericity was not used as it is likely to be significant with large sample sizes even if correlations are zero (Tabachnick & Fidell 2001). KMO indicates the proportion of variance in the variables that are shared, i.e. might be caused by underlying factors. In order to explore the specific role of N (see below), PCA was repeated excluding this variable.

Participants' factor scores were obtained using linear regression of questionnaire scales onto factors. This approach takes into account the loading of each variable onto a factor and produces factor scores with mean=0 and SD=1. Higher scores on a factor reflect higher scores on questionnaire scales loading positively onto that factor. As Tabachnick and Fidell (2001) argue, factor scores are ideally suited for further statistical analyses and may be more reliable than scores on individual variables. Individual questionnaire variables were not used in correlations with oculomotor measures due to the probability of Type I errors with multiple analyses.

7.3.4.3 Relationship between Schizotypy and Eye Movements

Factor scores were then used in multiple regression models as predictor (or independent) variables, with oculomotor measures as dependent variables. Factor scores were entered using the stepwise method (probability to enter set at 0.05). Regression analyses were repeated with N as covariate and factor scores from the PCA excluding N as predictors using the stepwise method. Further regression analyses were carried out with antisaccade error rate as dependent variable, factor scores as

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[23] Following Tabachnick and Fidell (2001), the term factor is used to describe the components from PCA, as the processes underlying the extraction of factors and components are similar, and the term factor is used widely and unambiguously by others in this context.

independent variables and a number of other variables (age, sex, drug and alcohol use, psychiatric history, family history, lie scales) as covariates. Antisaccade error scores were then combined, separately, with SPEM gain, AS, or CUS frequency by averaging z-scores of these variables. For the combination of error rate with SPEM gain, the percentage of *correct* antisaccades (100 – error rate) was used, so that lower scores on both variables indicated greater error. Likewise, SPEM measures were combined with each other, with SPEM gain multiplied by -1 for that purpose. These combined variables were then used as dependent variables in regression models with factor scores as independent variables.

7.3.4.4 Comparisons of Extreme Groups and Relationship between SPEM Measures and Antisaccade Error Rate

Then, t-tests were carried out, comparing factor score top and bottom scorers on eye movements. This analysis was carried out in order to make the results of this study comparable to previous studies (Gooding 1999; Gooding et al 2000b; O'Driscoll et al 1998). Finally, Pearson correlations were carried out between antisaccade error rate and SPEM gain, CUS and AS for each velocity as well as for averaged velocities.

7.4 Results

Descriptive statistics of oculomotor variables are given in Table 7.2 and psychometric questionnaires in Table 7.3. Antisaccade correction rate was high (mean=96.86%; SD=10.59), indicating that participants were, in principle, able and willing to perform the task (McDowell & Clementz 1997).

7.4.1 Effects of Age and Sex

Females had slightly higher antisaccade error rate than males ($F[1,110]=3.67$; $p=0.06$) and reduced pursuit gain at 12°/s ($F[1,98]=3.56$; $p=0.06$), 24°/s ($F[1,98]=7.96$; $p=0.006$), 36°/s ($F[1,98]=13.18$; $p<0.001$) and 48°/s ($F[1,98]=16.46$; $p<0.001$), as well as a higher frequency of CUS at 48°/s ($F[1,98]=5.50$; $p=0.02$).

Males scored higher on EPQ-R P ($F[1,107]=6.31$; $p=0.01$) and females scored higher on EPQ-R N ($F[1,107]=3.49$; $p=0.06$), EPQ-R L ($F[1,107]=6.56$; $p=0.01$), PSQ-80 UR ($F[1,107]=6.40$; $p=0.01$) and PSQ-80 SD ($F[1,107]=4.80$; $p=0.03$).

Table 7.2: Descriptive Statistics of Oculomotor Variables

	Mean	**SD**
SPEM gain 12°/s	95.75	7.75
SPEM gain 24°/s	91.19	10.98
SPEM gain 36°/s	81.63	15.75
SPEM gain 48°/s	63.96	17.40
Anticipatory saccades 12°/s	0.17	0.16
Anticipatory saccades 24°/s	0.50	0.32
Anticipatory saccades 36°/s	0.57	0.33
Anticipatory saccades 48°/s	0.49	0.37
Catch-up saccades 12°/s	0.38	0.13
Catch-up saccades 24°/s	1.13	0.41
Catch-up saccades 36°/s	1.86	0.72
Catch-up saccades 48°/s	2.54	0.79
Fixation saccadic frequency	0.02	0.03
Antisaccade gain	-109.14	33.10
Antisaccade latency	275.48	39.54
Antisaccade error rate	29.23	18.83
Prosaccade gain	98.76	11.33
Prosaccade latency	173.82	22.84

Table 7.3: Descriptive Statistics of Psychometric Questionnaire Scales

	Mean	**SD**
O-LIFE **UE**	7.72	6.70
O-LIFE **IA**	4.35	2.87
O-LIFE **IN**	7.98	3.01
O-LIFE **CD**	7.03	4.48
RISC	32.20	9.17
PSQ-80 **AC**	8.44	3.97
PSQ-80 **WD**	7.86	4.32
PSQ-80 **UR**	7.66	4.92
PSQ-80 **SD**	1.59	1.30
PSQ-80 **IT**	0.12	0.35
EPQ-R **E**	15.57	4.72
EPQ-R **N**	11.83	5.92
EPQ-R **P**	8.14	3.84
EPQ-R **L**	6.35	4.05

For legend see Section 11

Age was not significantly correlated with any oculomotor variables. Older individuals tended to have lower scores on EPQ-R E (r=-0.28; p=0.003), PSQ-80 AC (r=-0.36; p<0.001), PSQ-80 UR (r=-0.26; p=0.008), RISC (r=-0.20; p=0.04), O-LIFE UE (r=-0.30; p=0.001) and IN (r=-0.22; p=0.02).

7.4.2 Schizotypy Factor Structure

The communalities (Table 7.4) represent the squared multiple correlation for each variable using the factors as predictors in linear regression and are, therefore, the proportion of variance accounted for by the factors extracted. All communalities were substantial (>0.62), indicating that variables were accounted for well by the final factor solution. The KMO statistic was 0.82, indicating excellent factorability of the correlation matrix.

Table 7.4: Communalities of Personality Measures

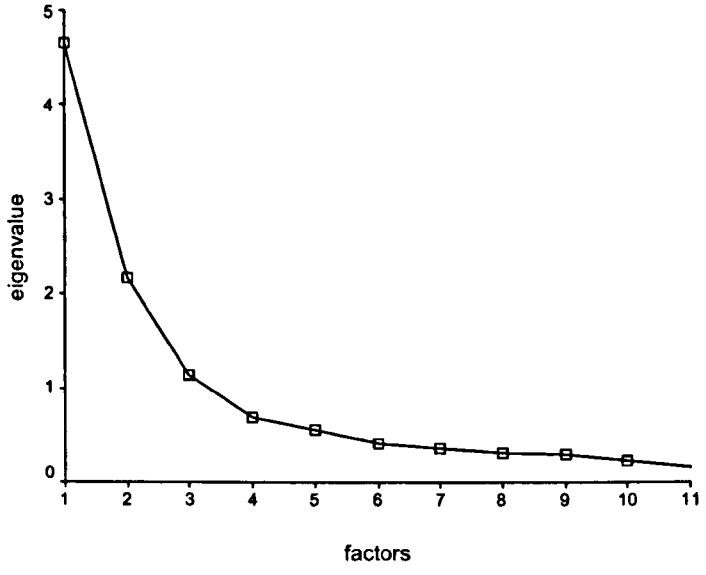
Variable	Communality
O-LIFE **UE**	0.78
O-LIFE **CD**	0.80
O-LIFE **IA**	0.66
O-LIFE **IN**	0.66
EPQ-R **E**	0.78
EPQ-R **N**	0.76
EPQ-R **P**	0.84
RISC	0.62
PSQ-80 **AC**	0.63
PSQ-80 **WD**	0.78
PSQ-80 **UR**	0.70

For legend see Section 11

Three factors were extracted, accounting for 72.44% of the variance (Figure 7.1; Table 7.5). Interpretation of the pattern matrix (Table 7.6) led to the labelling of these factors as Positive Schizotypy (factor 1), Negative Schizotypy (factor 2) and Psychoticism (factor 3). The pattern matrix summarises the unique relationships between factor and variables, uncontaminated by factor intercorrelations and is preferable to the structure matrix, which simply gives the correlation between factor and variable (Tabachnick & Fidell 2001).[24]

[24] In many datasets, including the present one, differences between pattern and structure matrix are small.

Figure 7.1: Scree Plot for Factor Solution



The Positive Schizotypy factor included O-LIFE UE, CD and IN, RISC, PSQ-80 AC and UR and EPQ-R N. This factor was, therefore, made up mainly of positive schizotypal features, such as schizotypal cognitions and experiences (UE, UR, AC, RISC, CD), but also contained items relating to emotional reactivity (N, CD) and impulsiveness (IN). The Negative Schizotypy factor was defined by a positive loading of EPQ-R E and negative loadings of PSQ-80 WD and O-LIFE IA, pointing to an extraversion component. In order to increase the semantic proximity to the schizotypy construct, however, the best label for this factor might be the inverse of extraversion, such as introversion, withdrawal, anhedonia, or negative schizotypy. The Psychoticism factor was defined by EPQ-R P.

Table 7.5: Eigenvalues, Percentages of Variance, and Squared Multiple Correlations of the Three Factors

	Factor		
	1	**2**	**3**
Eigenvalue	4.66	2.17	1.14
Percent of variance	42.36	19.74	10.34
SMC	0.99	0.96	0.71

Legend:
SMC denotes squared multiple correlation of scales onto factor scores

As Tabachnick and Fidell (2001) pointed out, factor loadings in excess of 0.71 may be considered 'excellent', those in excess of 0.63 'very good' and those in excess of 0.55 'good'. As can be seen from Table 7.6, factor loadings were good to excellent, indicating a good description of the factors by the variables. Squared multiple correlations (SMC) of variables onto their respective factor scores confirmed this finding (Table 7.5).

Table 7.6: Factor Structure of Personality Measures (Pattern Matrix)

	Factor		
	1	**2**	**3**
O-LIFE **UE**	0.86	-	-
PSQ-80 **UR**	0.84	-	-
PSQ-80 **AC**	0.80	-	-
O-LIFE **IN**	0.78	-	-
RISC	0.75	-	-
O-LIFE **CD**	0.61	-0.51	-
EPQ-R **N**	0.61	-	-
EPQ-R **E**	-	0.87	-
PSQ-80 **WD**	-	-0.84	-
O-LIFE **IA**	-	-0.70	-
EPQ-R **P**	-	-	0.83

For legend see Section 11

Factor intercorrelations were non-significant between factor 1 and factor 3 (r=0.07; p=0.51) and factor 2 and factor 3 (r=0.03; p=0.75). The correlation between factor 1 and factor 2 approached formal levels of statistical significance (r=-0.18; p=0.06), indicating that higher scores on factor 1 were weakly associated with lower scores on factor 2.

To confirm the stability of the solution, combinations of a variety of extraction (principal components, alpha factoring, principal axis factoring, image factoring) and rotation (varimax and direct oblimin) methods were employed. Identical factor structures were obtained each time, with only small differences in the size of loadings. As Tabachnick and Fidell (2001) argued, if a factor solution from a 'good' dataset is stable then it is likely to be obtained across a number of different methods of extraction and rotation.

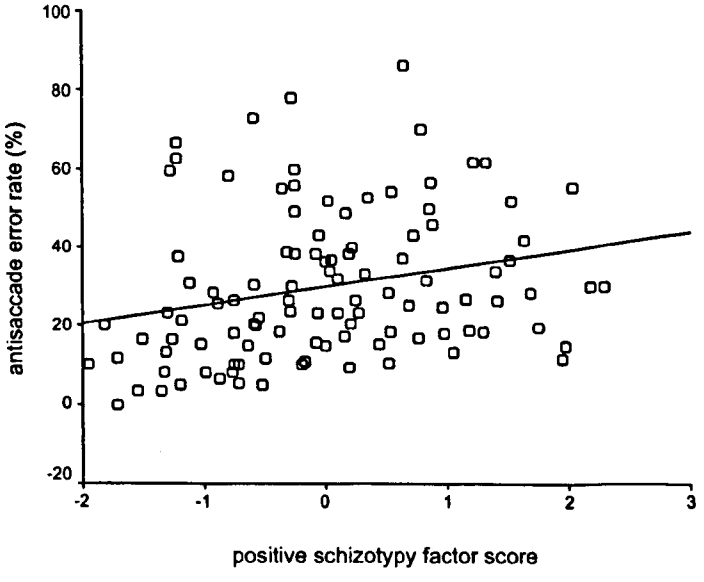
PCA was then repeated excluding N. The factor structure that emerged differed from that described above as P now loaded onto the first factor. Therefore, two factors were extracted (eigenvalues: 4.21, 2.13) accounting for 63.39% of the variance. Otherwise, distribution of variables across factors was identical to the factor solution above, with very similar sizes of loadings.

7.4.3 Relationship between Schizotypy and Eye Movements

Predicting SPEM variables from factor scores yielded a significant model for CUS frequency at 12°/s: $F(1,101)=4.68$; $p=0.03$. Psychoticism factor score was the only variable accepted by the model, resulting in a 4.4% increase in the percentage of variance explained. Higher psychoticism factor scores were associated with greater CUS frequency, with a standardised regression coefficient of 0.21 ($p=0.03$). No other regression models with SPEM variables as DV yielded any significant predictors. Given the sex differences on SPEM gain (Section 7.3.1) regression analyses were carried out for males and females separately using gain as dependent variable and for the combined group using sex as covariate. No significant predictors emerged.

Predicting saccadic variables from factor scores yielded no significant models for antisaccade gain, prosaccade latency and antisaccade latency. Positive schizotypy factor score was the only significant predictor of antisaccade error rate, resulting in a 6.1% increase in variance explained: $F(1,105)=6.85$; $p=0.01$. Higher factor scores were associated with more antisaccade errors (Figure 7.2), with a standardised regression coefficient of 0.25 ($p=0.01$).

Figure 7.2: Relationship between Antisaccade Error Rate and Positive Schizotypy



A significant model was also obtained for prosaccade gain: $F(1,100)=4.46$; $p=0.04$. Psychoticism factor score was the only variable accepted by the model, resulting in a

4.3% increase in variance explained. Higher psychoticism factor scores were associated with reduced prosaccade gain, with a standardised regression coefficient of -0.21 (p=0.04).

The stability of the most interesting of these relationships, that between antisaccade errors and positive schizotypy factor scores, was then explored further. Using the positive schizotypy factor score from the PCA without N in a multiple regression analysis predicting antisaccade error rate from factor scores yielded identical R^2, Beta, F and p values as above. In a second analysis, entering N as covariate explained 2.2% of the variance, indicating a non-significant change from zero: $F(1,104)=1.95$; p=0.17. Positive schizotypy was still accepted into the model, predicting significantly over and above N, with an increase in 4.5% of the variance explained and a standardised coefficient of 0.25 (p=0.03).

Similarly, covarying in separate analyses for age, sex, cannabis use (yes, no), use of any drugs (yes, no), units of alcohol per week, psychiatric history (yes, no), psychiatric family history (yes, no), family history of schizophrenia (yes, no), or EPQ-R L, PSQ-80 SD or IT scales did not alter the relationship between antisaccade error rate and positive schizotypy. Excluding participants with EPQ-R lie scores of 10 or higher (N=25), participants with PSQ-80 social desirability scores of 4 or higher (N=19), or PSQ-80 inattentiveness scores of 2 (N=1) in separate analyses did not affect this finding.

Standardised questionnaire variables from each factor were then averaged to yield an approximation of the factor scores based solely on test scores, i.e. irrespective of factor loadings (E scores were multiplied by –1 for that purpose). The averaged z-score of variables making up the positive factor again emerged as sole significant predictor (Beta=0.23; p=0.02; R^2=0.05), further underscoring the robustness of this finding.

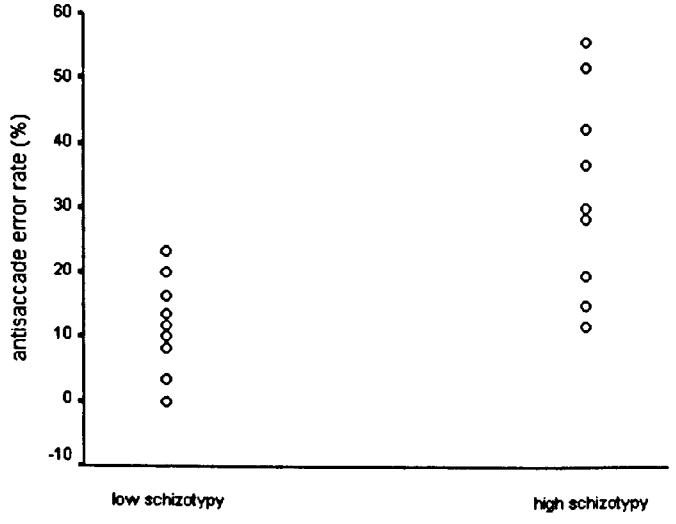
Using the combined smooth pursuit (gain, AS, CUS) performance score as dependent variable yielded no significant psychometric predictor. Similarly, combining antisaccade errors with either SPEM variable or the combined SPEM measure demonstrated no significant relationship.

7.4.4 Comparisons of Extreme Groups

Comparing ten participants with the highest positive schizotypy factor score with ten participants with the lowest score on antisaccade error rate (Figure 7.3) yielded a

significant difference (t=-4.03; df=18; p=0.001); the high scorers had higher average error rate (31.07%) than the low scorers (10.99%).

Figure 7.3: Antisaccade Error Rates for High and Low Positive Schizotypy Groups



7.4.5 Relationship between SPEM Measures and Antisaccade Error Rate

Antisaccade error rate was correlated with SPEM gain at 24°/s (r=-0.32; p=0.001), 36°/s (r=-0.32; p=0.001), 48°/s (r=-0.23; p=0.02) and at averaged velocities (r=-0.30; p=0.001), indicating that higher error rates were associated with reduced SPEM gain, but not at 12°/s (r=0.01; p=0.94). There was a trend for a correlation between error rate and CUS at 12°/s (r=0.18; p=0.06), indicating that higher error rates were associated with more CUS. No other correlations between error rate and CUS or AS were significant (all p>0.13). Covarying for positive schizotypy factor score did not increase the magnitude of the correlations between antisaccade error rate and AS frequency.

7.5 Discussion

7.5.1 Key Findings

The key findings of this study are as follows. 1) A three-dimensional factor structure emerged from schizotypy questionnaires subscales, consisting of positive schizotypy, negative schizotypy and psychoticism. 2) There was a relationship between levels of positive schizotypy and antisaccade error rate; prosaccade gain was correlated with scores from the psychoticism dimension. 3) The relationship between antisaccade error rate and positive schizotypy was not accounted for by individual differences in trait emotionality, suggesting specificity to the schizophrenia spectrum phenotype.

7.5.2 Schizotypy Factor Structure

Consistent with a plethora of previous investigations, the factorial structure of self-report schizotypy scales in this study was not unitary (Vollema & van den Bosch 1995). It is a truism that the factor solution that one obtains depends on the number and kind of variables that are factor analysed (Gould 1981; Stuart et al 1999; Tabachnick & Fidell 2001). As has been noted in the context of schizophrenia syndrome research (Stuart et al 1999), factor analysis does not reveal whether the symptom variables being analysed are a balanced and adequate representation of the syndrome(s) under investigation. For example, if a particular type of symptom (e.g. positive symptoms) is over-represented it will dominate the factor solution. Therefore, comparisons with previous factor analytic studies are only of moderate interest, as the particular combination of items (e.g. questionnaire subscales) is virtually unique to each investigation.

Despite these caveats, the factor structure obtained here somewhat resembled those obtained in previous studies. Lipp et al (1994) found a positive (with high N), a negative (with low E) and a psychoticism/physical anhedonia (with high P) factor; N additionally loaded on the negative factor. Muntaner et al (1988) obtained a positive factor, an impulsivity factor and an introversion factor. In their study, the positive factor was characterised by perceptual aberrations, magical ideation, as well as the O-LIFE and its precursor questionnaire. As in the present study, N loaded on this factor. Impulsivity contained, in addition to P, lie scale and borderline personality scales. The introversion factor included E as well as physical and social anhedonia. Kelley and Coursey (1992)

obtained a general (positive) schizotypy and a physical anhedonia factor; the psychoticism scale was not used. The positive factor observed here resembles that of a previous study (Venables & Rector 2000), as symptoms of delusions and unusual experiences as well as those of cognitive disorganisation loaded on the same factor.

Some studies obtained evidence of negative and psychoticism factors but more than one positive factor, or an additional emotionality factor. Bentall et al (1989) found a positive, a social anxiety/cognitive disorganisation (including N), a negative and a psychoticism factor. Kendler and Hewitt (1992) obtained a positive, neuroticism, nonconformity and a social schizotypy factor. In the development of the O-LIFE questionnaire, Mason et al (1995) observed two factors relating to positive schizotypy (UE and CD), a negative factor (IA) and a psychoticism/impulsivity factor (IN). These studies, therefore, partly match the present solution, with the exception of a unitary positive factor including neuroticism.

Besides this confirmatory evidence, however, a number of studies have obtained schizotypy factor structures considerably departing from the present one (Hewitt & Claridge 1989; Raine & Allbutt 1989; Vollema & van den Bosch 1995). The reasons for this most probably include the choice of questionnaires that were factor analysed, as well as sample issues.

With some discrepancies, therefore, the present factor structure may be reconciled with previous research. In particular, the relationship between N and positive schizotypal items has been observed previously (Bentall et al 1989; Kendler & Hewitt 1992; Lipp et al 1994; Muntaner et al 1988).

As has been pointed out (Johns & van Os 2001; Vollema & van den Bosch 1995), the factor structure of schizotypy bears remarkable resemblance to the syndromes of schizophrenia. While this could be due to artefacts such as item selection (Stuart et al 1999), the possibility of genetic and clinical continuity is intriguing (Fanous et al 2001). The present factor structure resembles the syndromes of schizophrenia in so far as there are distinguishable positive and negative features (Crow 1980a, 1980b). It has been shown, however, that 'positive symptoms' in schizophrenia may represent two independent statistical clusters (Liddle 1987a, 1987b). The current study did not observe two such factors.

The present study was not designed to address comprehensively the factorial nature of schizotypy. To resolve this longstanding issue, larger sample sizes and possibly a larger

number of questionnaire scales should be used. Alternatively, a factor analysis at the item (rather than scale) level of questionnaire data might be instructive. The present study did not factor analyse item level data due to the relatively small sample size. Sex and age effects on trait measures were largely consistent with previous studies (Eysenck & Eysenck 1991; Mason et al 1995; Rust 1989).

7.5.3 Relationship with Eye Movements

The most interesting relationship, in terms of oculomotor schizophrenia spectrum endophenotypes, was that between increased antisaccade errors and increased levels of positive schizotypy. This finding is compatible with previous studies that observed increases in error rate in students scoring high on the Perceptual Aberration (Gooding 1999; O'Driscoll et al 1998), Magical Ideation (Gooding 1999), or RISC (Larrison et al 2000) scales. In contrast to Gooding (1999), however, there was no relationship between negative symptoms and antisaccade error rate.

Klein et al (2000c) failed to find a relationship between schizotypy and antisaccade errors in a student sample. The reason for this might have been, apart from sampling issues, the use of an overall schizotypy score (Schizotypal Personality Questionnaire [SPQ] total score) rather than positive or negative subscores. Vollema and van den Bosch (1995) have pointed to the importance of using schizotypy subscales, as a total score (or global measure) might give "one-sided results" (p. 25) or mask important effects.

Most eye movement studies have used an 'extreme groups' approach to the study of schizotypy, following the medical dichotomy of affected vs. unaffected, by comparing high and low schizotypy scorers on eye movement parameters. However, dichotomising continuous data results in a loss of statistical power (Cohen 1988). It may be desirable to conserve the wide range of individual differences in this measure, which also better reflects the assumed continuous nature of the schizotypy construct (Claridge 1990). The present study achieved this through the use of (normally distributed) factor scores, however, and replicated the association between antisaccade errors and positive schizotypy by demonstrating significantly higher error rate in positive schizotypy high scorers than low scorers.

The observation of a relationship between antisaccade error rate and positive but not negative schizotypal features is intriguing. The schizophrenia literature is inconsistent

with regard to the symptom correlates of antisaccade errors, with findings of associations with positive and negative symptoms, or absence of statistical associations. However, a relationship between antisaccade errors and negative symptoms might have been expected on the basis of previous findings. These findings include (1) the role of the frontal cortex in both antisaccade performance (Everling & Fischer 1998; McDowell & Clementz 2001; Müri et al 1998) and negative symptoms (Carpenter et al 1999), (2) the association between negative symptoms and motor abnormalities in the schizophrenia spectrum (Ross 2000; Wolff & O'Driscoll 1999) and (3) the generally stronger correlation between (frontal) cognitive deficits and negative rather than positive symptoms (Addington et al 1991). A number of explanations may be drawn upon in order to account for the observed finding.

First, it was recently conjectured that although the defining subclinical features in first-degree relatives of schizophrenia patients are *negative* schizotypal symptoms, the hallmark features of schizotypy in healthy individuals without a family history of schizophrenia are *positive* symptoms (Faraone et al 2001). The present results are in agreement with this hypothesis, linking the defining features of schizotypy with a proposed marker of risk for schizophrenia. A replication of the current design using a sample of first-degree relatives would provide a crucial test of the hypothesis of a predominant role of negative symptoms in these individuals.

A second explanation might lie in the nature of the positive and negative schizotypy scales typically used in this type of research. Items from positive scales, probing for unusual perceptions and experiences as well as delusional and magical thinking, generally appear to be more pathological in their content than those of negative scales, relating to social withdrawal and anhedonia (Table 7.1). It is possible, therefore, that high scores on the positive factor index greater subclinical abnormality, i.e. proximity to the schizophrenia spectrum, than high scores on the negative factor. This suggests that positive schizotypal features might be a more sensitive index of schizophrenia-related psychopathology in non-clinical populations (Faraone et al 2001).

Third, if a 'true' relationship existed between antisaccade errors and positive features, it could be masked in studies of schizophrenia patients. Positive symptoms in schizophrenia are known to fluctuate, in particular in the early stages of the illness and with change in antipsychotic medication (Kapur & Remington 2001; Leonard 1997). Given the relative stability of antisaccade performance over time (Chapter 4), a statistical relationship between antisaccade errors and symptom scores could easily be

abolished by low temporal reliability of one of the measures, namely that of symptom severity (Anastasi & Urbina 1997).

In contrast to antisaccade errors, SPEM performance was not consistently associated with schizotypy measures. CUS frequency at 12°/s was associated with psychoticism factor scores. However, this relationship was not observed for CUS frequency at faster velocities, or other SPEM measures at the same or other velocities, indicating that the finding was not consistent and might have been a chance observation due to multiple analyses.

The absence of a consistent relationship between SPEM and schizotypy scores in this sample is somewhat disappointing and unexpected given the previous literature (Gooding et al 2000b; O'Driscoll et al 1998; Siever et al 1984, 1989). The above finding of a relationship between antisaccade errors and schizotypy levels provides important evidence of the validity of the choice of psychometric, sampling and statistical methods used here, suggesting that the failure to obtain a relationship with SPEM may not be attributed to mere methodological weaknesses. This finding contrasts with the studies by O'Driscoll et al (1998) and Gooding (1999; Gooding et al 2000b), who obtained similar patterns of findings for the SPEM and antisaccade tasks in each sample. A possible reason for this lies in the choice of psychometric questionnaire. Previous studies have used the physical and social anhedonia measures from the Chapman scales (Chapman et al 1980; Mishlove & Chapman 1985), which might provide better measures of negative schizotypy.

Reduced prosaccade gain was associated with higher psychoticism scores. This finding, although unexpected and in contrast to previous research (Gooding 1999), might be compatible with the schizophrenia literature. There is evidence, albeit inconsistent, of reduced saccadic gain in schizophrenia patients (Curtis et al 2001a; Schmid-Burgk et al 1983) and first-degree relatives (Schreiber et al 1995, 1997). Given the proposed proximity of psychoticism to schizophrenia, reduced prosaccade gain might be another trait marker of the schizophrenia spectrum, possibly related to dopaminergic processes (Gray et al 1994). The inconsistent evidence of this finding in schizophrenia, first-degree relative and schizotypal samples, however, somewhat weakens this conclusion.

7.5.4 Effects of Trait Emotionality

The most promising of the current findings, the relationship between antisaccade error rate and positive schizotypy, was tested for the influence of trait emotionality using the Eysencks' neuroticism (N) scale. N failed to predict antisaccade errors and covarying for N did not significantly reduce the predictive power of positive schizotypy. This indicates that positive schizotypy scores, in this sample, significantly predicted antisaccade error rate, over and above the contribution of a general index of psychopathology and trait emotionality, or N.

The importance of this finding lies in the assumed specificity of antisaccade deficits to the schizophrenia spectrum. As argued above, neuroticism is a general indicator of psychopathology and associated somatic complaints. Therefore, a strong influence of this variable on antisaccade errors would have undermined the claim of this oculomotor task being a specific schizophrenia spectrum endophenotype. This observation is in accord with O'Driscoll et al's (1998) finding of a lack of significant effect of *state* emotionality on the relationship between antisaccade performance and schizotypy. Given the evidence of a relationship between neuroticism and schizophrenia/schizotypy (Bentall et al 1989; Braunstein-Bercovitz et al 2002; Claridge & Davis 2001; Eysenck & Barrett 1993; Lipp et al 1994; Muntaner et al 1988; O'Driscoll et al 1998; Rust & Chiu 1988; Tien et al 1992a; Wuthrich & Bates 2001), it may be argued that neuroticism and antisaccade impairments represent two independent sources of variance, both associated with the schizophrenia phenotype. The antisaccade endophenotype might, therefore, tap genetic sources independent of affective disturbance. However, given the evidence of an association between schizophrenia and affective disorder at a genetic level (Berrettini 2000a; Maier et al 1999), the observation of antisaccade errors in people with affective disorders (Crawford et al 1995a; Curtis et al 2001a; Gooding & Tallent 2001; Katsanis et al 1997; Sereno & Holzman 1995; Sweeney et al 1998b; Tien et al 1996) and the use of only one self-report measure of trait emotionality in the present study, this evidence of specificity should be considered preliminary.

The Eysencks' N scale is a general measure of trait emotionality, encompassing the two related but dissociable components of anxiety and depression (Claridge & Davis 2001; Eysenck & Eysenck 1991). Future research should replicate the present design, replacing N with separate trait measures of anxiety and depression. Such an investigation might be useful given the link between anxiety and attention and the presumed attentional demands of the antisaccade task (Kristjánsson et al 2001).

O'Driscoll et al (1998) failed to find an effect of *state* anxiety; however, a *trait* measure might be more useful in this context. It is instructive to note that Wuthrich and Bates (2001) failed to obtain a correlation between latent inhibition and neuroticism, suggesting a specific influence of *anxiety* on the relationship between latent inhibition and schizotypy (Braunstein-Bercovitz 2000; Braunstein-Bercovitz et al 2002; Braunstein-Bercovitz & Lubow 1998). Whether a similar effect exists with regard to the antisaccade task remains to be investigated.

7.5.5 Relationship between SPEM Measures and Antisaccade Error Rate

Antisaccade error rate was negatively correlated with SPEM gain, indicating that worse performance on the antisaccade task (higher percentage of errors) was associated with worse performance on the SPEM task (reduced gain). This finding replicates previous schizophrenia spectrum research (Thaker et al 2000). However, the expected relationship between antisaccade errors and anticipatory saccade (AS) frequency (Chapters 5 & 6) was not observed. This negative finding, given the large sample size, represents a disappointing failure of the hypothesis linking the two measures on the basis of their inhibitory requirements (Calkins & Iacono 2000; Friedman et al 1992a; Levin 1984; Müri et al 1998).

A combination of antisaccade error rate and AS frequency (or any SPEM measure) did not result in improved associations with schizotypy levels. This finding is probably due to the lack of correlation between error rate and AS frequency and the absence of consistent correlations between SPEM measures and schizotypy.

The reasons for the failure to replicate the previous findings of an association between antisaccade error rate and AS frequency are unclear. One possibility could be differences in stimulus presentation methods (Battery II in this study; Battery I in Chapters 5 and 6). However, both measures of antisaccade error rate and AS frequency were previously found to be significantly correlated across batteries (Chapter 4). Given the finding of higher error rate on Battery II compared to Battery I, the question arises of whether task difficulty produced spurious correlations in Chapters 5 and 6, possibly through a floor effect on antisaccade error rate. However, inspection of the scatter plots (Chapters 5 & 6) suggested that this was not the case. Additionally, given the better psychometric properties (greater range and variability) of antisaccade scores of Battery

II (Chapter 4), a stronger correlation might have been expected in the present study (Anastasi & Urbina 1997). Sampling issues might have affected the results. The control group of Chapter 6, in which a significant correlation was demonstrated, consisted largely of members of the general public recruited through newspaper advertisements, whereas the present sample consisted largely of university students and staff. This suggests that a restricted range in the more homogenous sample of this study might account for the failure to obtain a correlation. However, the range of antisaccade errors in this study (0%-86.44%) was much greater than that of the control group in Chapter 6 (0%-45%).

It remains to suggest that future studies attempt to address this question in order to clarify whether the relationship between increased antisaccade error rate and AS frequency, which appears attractive at a theoretical level, was a chance finding, or whether the failure to replicate in the present study represents a false negative.

7.6 Conclusions

- The factor structure of schizotypy replicates previous studies, suggesting a positive, a negative and a psychoticism dimension.
- Increased levels of positive schizotypy were related to increased antisaccade errors.
- Increased levels of psychoticism were related to reduced prosaccade gain.
- SPEM performance was not consistently related to schizotypy scores.
- Trait emotionality was not related to antisaccade errors and did not account for the relationship between antisaccade errors and positive schizotypy.
- Antisaccade errors were related to SPEM gain but not anticipatory saccade frequency. Combining error rate with SPEM measures did not result in stronger correlations with schizotypy measures.

7.7 Limitations

- Information regarding the psychiatric history of participants and their first-degree relatives was derived from a self-report questionnaire and was not ascertained through thorough clinical examination.

- The measures of schizotypy employed here were based on self-report, thereby arguably allowing for the presence of bias in responding.
- Trait emotionality was assessed using the very general measure of neuroticism, thus possibly masking or underestimating specific contributions of the anxiety or depression components.
- The proposed continuity between schizotypal features and schizophrenic symptoms is tenuous, given the nature of the positive factor extracted in the present study, which might not mirror schizophrenic symptoms very closely (Fanous et al 2001).
- The relationship between antisaccade errors and schizotypy was of moderate magnitude, suggesting the operation of many other factors in explaining antisaccade variance.

Chapter Eight

Study V – State Influences on Eye Movements: Effects of Procyclidine in Schizophrenia

8.1 Chapter Overview

This chapter examines state effects on eye movements (Battery II) of an anticholinergic drug, procyclidine, which is commonly administered to patients with schizophrenia in the treatment of extrapyramidal side effects. Given the role of the cholinergic system in cognition, and the role of cognitive processes in smooth pursuit and antisaccade eye movements, it is of interest to examine whether performance on these tasks is affected by acute administration of procyclidine. The implications of this putative effect concern both the pharmacology of oculomotor control and the need to consider anticholinergic conjunctive treatment when comparisons are made between schizophrenia patients and healthy individuals.

8.2 Introduction

Procyclidine (1-cyclohexyl-1-phenyl-3-(pyrrolidin-1-yl)-propan-1-ol hydrochloride) is a synthetic anticholinergic agent (Whiteman et al 1985). While previously used in the treatment of Parkinson's disease (Brocks 1999) it is now most commonly administered to schizophrenia patients in order to alleviate antipsychotic-induced side effects (Mindham et al 1977; Spohn & Strauss 1989). The most common side effects of typical antipsychotic drug treatment in schizophrenia are akathisia (restlessness), dystonia (muscle cramps), akinesia (motor slowing), tremor and muscle rigidity (Leonard 1997). Some of these side effects, in particular those with resemblance to Parkinsonian symptoms (e.g. tremor, rigidity), can be treated successfully with anticholinergic drugs, such as procyclidine (Leonard 1997; Spohn & Strauss 1989).

Central cholinergic projections are extremely diffuse. The key pathways arise from cholinergic neurons in the mid- and hindbrain, such as the nucleus basalis

magnocellularis of Meynert, and project on to cortical neurons (Deutch & Roth 1999). Procyclidine primarily antagonises muscarinic (M) receptors M1, M2 and M4, of which M1 and M4 are diffusely distributed throughout the brain; M2 is the heart isoform of the receptor and is not widely found in other organs (Waxham 1999). Procyclidine also acts, less strongly, on N-methyl-D-aspartate (NMDA) glutamine and nicotinic acetylcholine receptors (Whiteman et al 1985).

The neurotransmitter acetylcholine has been implicated in cognition. Both animal and human studies have demonstrated a role of the central cholinergic system in processes of memory, attention and learning (Everitt & Robbins 1997; Francis et al 1999; McGaughy et al 2000). The role of acetylcholine in cognition is also compatible with the cognitive degeneration observed in Alzheimer's disease, a neurological condition with known pathology of basal forebrain cholinergic neurons (Francis et al 1999). Given this evidence, as well as the evidence of cognitive dysfunction in schizophrenia (Sharma & Harvey 2000), it is of particular interest to study the effects of clinical doses of procyclidine on cognition.

Recently, Kumari et al (2001) observed disrupted prepulse inhibition in healthy individuals after administration of 15mg (but not 10mg) of procyclidine. Prepulse inhibition (PPI) is an operational measure of sensorimotor gating that has been shown to be impaired in schizophrenia (Braff et al 2001; Kumari 2000; Swerdlow et al 2000). Zachariah et al (2002) observed impairments on a variety of cognitive tests in healthy individuals after procyclidine administration. Sharma et al (2002) found reduced heart rate and alertness (assessed using the critical flicker fusion threshold paradigm) after 15mg (but not 10mg) of procyclidine in healthy individuals. Taken together, these reports suggest that procyclidine dose-dependently impairs cognitive function and leads to sedation in healthy individuals. Relatedly, Mori et al (2002) observed improvements in schizophrenia patients in memory and psychopathology and increases in regional cerebral blood flow after withdrawal from anticholinergics.

Given the role of the cholinergic system in cognition and the use of anticholinergic drugs such as procyclidine as adjunctive treatment in schizophrenia patients, it is an important question to investigate the effects of anticholinergic agents on neurocognitive endophenotypes, such as the smooth pursuit eye movement (SPEM) and antisaccade tasks, in this patient group. Studies of the cognitive component processes of smooth pursuit and antisaccade performance have suggested that successful task performance relies on recruitment of overt and covert attention (Kristjánsson et al 2001; Roitman et

al 1997; Schwartz et al 2001; Sweeney et al 1994a) and response inhibition and working memory (Mitchell et al 2002; Roberts et al 1994; Stuyven et al 2000), all of which are likely to be at least partly mediated by central cholinergic pathways (McGaughy et al 2000). If deleterious effects of procyclidine on SPEM and antisaccade performance were obtained, statistical differences on these measures between schizophrenia patients taking this drug and unmedicated individuals might be inflated and should be treated with caution (Spohn & Strauss 1989).

8.2.1 Aims

The present study, therefore, had the following aims. 1) To quantify the effects of procyclidine on SPEM and antisaccade performance in a sample of schizophrenia patients using a double-blind placebo-controlled crossover design. 2) Given the observation of practice effects on antisaccades in previous pharmacological studies (Green et al 2000; Klein et al 2002), to investigate further whether oculomotor performance was affected by procyclidine as a function of drug administration order.

8.3 Method

8.3.1 Participants

Fifteen schizophrenia patients were recruited into the study. Two of these refused second assessment, thus leaving a final sample size of thirteen patients (7 males, 6 females; mean age=35.54; SD=11.59). All patients were treated with one of two atypical drugs with low intrinsic anticholinergic properties, risperidone or quetiapine. Five patients were on quetiapine (dose range: 100-300mg daily) and eight were on risperidone (dose range: 2-6mg daily). Patients were not on any anticholinergic medication for at least six months prior to taking part in the study, although six patients had in the past been prescribed procyclidine. All patients were required to have stable symptoms for at least one month before taking part in the study and reported to be free from drug abuse. Diagnoses were established using the Structured Clinical Interview for DSM (First et al 1996b) and current symptoms were rated using the Positive and Negative Syndrome Scale (PANSS; Kay et al 1987).

All patients provided written consent after detailed explanations of the study procedures had been given to them. The study was approved by the Ethics Committee of the Institute of Psychiatry, University of London.

8.3.2 Eye Movement Assessment

Battery II was used in the assessment of eye movements. Antisaccade and fixation data from one patient (on procyclidine) could not be collected due to lack of compliance. Fixation data from one patient (on placebo) was not usable due to data storage error. The dependent oculomotor variables were, as before, SPEM gain and frequencies of catch-up saccades (CUS) and anticipatory saccades (AS); frequency of saccades during fixation; antisaccade gain, latency and error rate; and prosaccade gain and latency.

8.3.3 Drug Dose and Administration

Participants were administered oral 15mg procyclidine or a placebo (200mg ascorbic acid) of identical appearance on two occasions under double-blind conditions. Intervals between assessments ranged between 10-14 days. Participants were quasi-randomly assigned to one of two orders of drug administration: seven participants received procyclidine first and placebo second, six participants were assessed in the reverse order. All patients received placebo or procyclidine between 9.00 and 11.45am (kept constant for each participant within ± 30min across both sessions) to control for effects of time of day on drug metabolism. A dose of 15mg procyclidine was deemed appropriate as it is clinically relevant and has been shown to affect central nervous system processing in healthy individuals in the absence of severe side effects (Kumari et al 2001; Sharma et al 2002; Zachariah et al 2002).

Eye movements were assessed between 4 and 5 hours post drug administration. A self-rating measure of sedation was taken shortly before drug administration and shortly before or after eye movement assessment. This measure consisted of a 100mm visual analogue scale, ranging to "alert" to "drowsy" (Bond & Lader 1974).

8.3.4 Statistical Analysis

Statistical analyses were carried out using SPSS Release 10.0.7 (SPSS Inc., Chicago, Ill). A number of oculomotor variables were slightly skewed. As both positive (<1.63) and negative (>-1.37) skewness values were only moderate and no obvious outliers were

observed, these distributions were not considered to be a significant challenge to the normality assumption of the parametric statistical analyses reported below.

Each SPEM variable (gain, AS, CUS) was analysed using a 2x4x2 repeated measures analysis of variance (ANOVA) with drug (procyclidine, placebo) and velocity (12°/s, 24°/s, 36°/s, 48°/s) as within-subjects factors and order (procyclidine first, placebo first) as between-subjects factor. Each saccadic and fixation variable was analysed using a 2x2 repeated measures ANOVA with drug (procyclidine, placebo) as within-subjects factor and order (procyclidine first, placebo first) as between-subjects factor.

To assess effects of drug on mood state (alertness) at time of eye movement assessment, a 2x2x2 repeated measures ANOVA was carried out with time (baseline, eye movement assessment) and drug (procyclidine, placebo) as within-subjects factors and order (procyclidine first, placebo first) as between-subjects factor.

8.4 Results

Descriptive statistics of oculomotor variables are given in Table 8.1; ANOVA results are given in Table 8.2. Antisaccade correction rates after administration of both procyclidine (mean=92.48; SD=10.56) and placebo (mean=90.43; SD=16.48) were high, indicating that participants were willing and able to follow task instructions (McDowell & Clementz 1997). There were no between-group effects of order (all $p>0.10$), indicating that the quasi-random allocation of participants resulted in two groups matched on eye movement performance levels. For SPEM, there were significant effects of target velocity on gain ($F[3,33]=49.20$; $p<0.001$), CUS ($F[3,33]=107.73$; $p<0.001$) and AS frequency ($F[3,33]=8.90$; $p<0.001$), indicating worse performance at faster velocities (Leigh & Zee 1999). There were no velocity x order (all $p>0.08$) or velocity x order x drug interactions (all $p>0.14$), indicating that drug effects on SPEM variables were similar across velocities.

Table 8.1: Means (SD) of Oculomotor Variables by Condition

	Procyclidine		**Placebo**	
	Procyclidine first (N=7)	Placebo first (N=6)	Procyclidine first (N=7)	Placebo first (N=6)
SPEM gain 12°/s	84.56 (13.51)	93.88 (10.36)	94.99 (11.45)	92.32 (14.84)
SPEM gain 24°/s	75.77 (24.96)	89.73 (10.08)	86.20 (19.14)	82.85 (10.42)
SPEM gain 36°/s	63.93 (26.59)	60.63 (15.65)	67.20 (23.99)	65.83 (12.23)
SPEM gain 48°/s	50.17 (30.15)	45.11 (17.88)	56.85 (26.20)	53.29 (11.87)
Anticipatory saccades 12°/s	0.32 (0.36)	0.36 (0.13)	0.20 (0.17)	0.27 (0.14)
Anticipatory saccades 24°/s	0.35 (0.40)	0.70 (0.27)	0.48 (0.32)	0.30 (0.14)
Anticipatory saccades 36°/s	0.26 (0.15)	0.91 (0.39)	0.49 (0.47)	0.61 (0.24)
Anticipatory saccades 48°/s	0.35 (0.48)	0.63 (0.54)	1.24 (0.46)	0.84 (0.53)
Catch-up saccades 12°/s	0.67 (0.24)	0.41 (0.14)	0.51 (0.47)	0.68 (0.41)
Catch-up saccades 24°/s	1.50 (0.50)	0.96 (0.37)	1.87 (0.65)	1.70 (0.44)
Catch-up saccades 36°/s	1.84 (0.66)	1.44 (0.57)	0.19 (0.27)	0.26 (0.14)
Catch-up saccades 48°/s	2.48 (0.66)	2.18 (0.63)	2.58 (0.74)	2.47 (0.72)
Fixation saccadic frequency	0.09 (0.11)	0.09 (0.09)	0.12 (0.16) *	0.10 (0.14)
Antisaccade gain	-110.86 (32.34) *	-132.24 (45.55)	-101.10 (19.11)	-102.03 (39.42)
Antisaccade latency	399.22 (104.78) *	291.09 (70.70)	389.85 (110.08)	332.86 (70.64)
Antisaccade error rate	56.49 (17.72) *	40.02 (15.42)	43.29 (24.53)	46.99 (17.51)
Prosaccade gain	95.80 (16.55)	96.66 (11.07)	93.10 (11.54)	94.64 (14.73)
Prosaccade latency	236.39 (75.70)	192.43 (28.21)	211.27 (45.70)	204.34 (34.53)

* N=6

8.4.1 Effects of Procyclidine on SPEM and Fixation

SPEM gain was reduced by procyclidine compared to placebo at trend level (Table 8.2); there was no effect of order or order x drug interaction on this variable. AS frequency was increased by procyclidine compared to placebo at trend level. Additionally, there was a drug x order interaction but no effect of order. The interaction indicates that AS frequency was increased by procyclidine if administered second; if procyclidine was administered first, the reverse pattern was observed. There were no significant main or interaction effects on CUS frequency or frequency of saccades during fixation.

8.4.2 Effects of Procyclidine on Antisaccade and Prosaccade

Antisaccade gain scores were increased by procyclidine compared to placebo at trend level (Table 8.2); there was no effect of order or drug x order interaction. There was a significant drug x order interaction on antisaccade latency but no main effects of drug or order; procyclidine was associated with faster latency if administered second. There was a significant drug x order interaction but no main effects of drug or order on antisaccade error rate; procyclidine increased error rate only when administered first.

There was a significant drug x order interaction but no main effects of drug or order on prosaccade latency. Procyclidine was associated with shorter latency when administered second; the reverse pattern was observed when procyclidine was administered first. There were no main or interaction effects on prosaccade gain.

8.4.3 Effects of Procyclidine on Alertness

There were no effects of drug, time or order, or drug x order, drug x time, time x order or drug x time x order interactions on mood ratings (all $p \geq 0.09$).

Table 8.2: Analysis of Variance Results for Effects of Drug, Order and Drug x Order Interactions on Oculomotor Performance

	Effect of Drug			**Effect of Order**			**Effect of Drug x Order**		
	F	df	*p*	F	df	*p*	F	df	*p*
SPEM gain	3.69	1,11	0.08	0.003	1,11	0.96	1.93	1,11	0.19
Anticipatory saccades	4.37	1,11	0.06	2.21	1,11	0.17	7.86	1,11	0.02
Catch-up saccades	0.01	1,11	0.99	2.11	1,11	0.17	0.74	1,11	0.41
Fixation saccadic frequency	0.01	1,9	0.94	1.21	1,9	0.30	0.02	1,9	0.89
Antisaccade gain	4.06	1,10	0.07	0.49	1,10	0.50	0.73	1,10	0.41
Antisaccade latency	0.96	1,10	0.35	2.21	1,10	0.17	6.39	1,10	0.03
Antisaccade error rate	1.29	1,10	0.28	0.15	1,10	0.70	6.06	1,10	0.03
Prosaccade gain	0.40	1,11	0.54	0.03	1,11	0.86	0.01	1,11	0.93
Prosaccade latency	0.54	1,11	0.48	0.90	1,11	0.36	4.28	1,11	0.06

8.5 Discussion

8.5.1 Key Findings

The findings from this study are as follows. 1) Acute administration of procyclidine non-significantly worsened both smooth pursuit and antisaccade performance in patients with schizophrenia, pointing to the importance of considering these drug-related state effects in studies of oculomotor schizophrenia endophenotypes. 2) The effects of procyclidine on some variables were affected by the order in which procyclidine and placebo were administered, suggesting the need to consider order effects in drug administration studies.

8.5.2 Effects of Procyclidine

Procyclidine non-significantly reduced the key smooth pursuit measure of velocity gain. Similarly, procyclidine non-significantly increased AS frequency during pursuit. It is possible that these effects could have reached statistical significance if a larger sample had been used. A possible explanation for the impairments in smooth pursuit performance during procyclidine administration is the role of the cholinergic system in attention (Everitt & Robbins 1997). Previous studies have suggested that successful generation of smooth pursuit eye movements requires attentional processes (Roitman et al 1997; Schwartz et al 2001; Sweeney et al 1994a). A likely consequence of the anatomically non-specific antagonistic action of procyclidine at the M1 and M4 receptors across the entire brain is a reduction in levels of alertness and, possibly, attention (Coull 1998; Sharma et al 2002). The lack of an effect of procyclidine on self-reported alertness/drowsiness suggests that this effect was centrally mediated.

The effect of procyclidine on AS frequency was mediated by order of drug administration. Procyclidine led to an increase in AS frequency when administered second, but the reverse pattern was observed when procyclidine was administered first. The reasons for this interaction are unclear. Importantly, however, the main effects of procyclidine on AS frequency were adverse, leading to a non-significant overall increase.

On the antisaccade task, procyclidine increased antisaccade error rate when administered first. When administered second, procyclidine appeared to have no

significant effect on error rate. To explain this pattern of performance, both placebo and practice effects have to be considered.

It is a possibility that in the group receiving placebo first, performance at first assessment was slightly impaired due to psychological factors, such as the expectancy to receive a performance-impairing compound (Beecher 1959). Participants were aware that they would on one occasion receive a compound that could have detrimental effects on their cognitive function. At second assessment (during procyclidine in this group), practice effects on antisaccade error rate might be expected (Green et al 2000; Klein et al 2002; Chapter 4). Indeed, the overall pattern of *reductions* in error rate from first to second assessment (irrespective of drug administration) in Table 8.1 is compatible with the operation of practice effects. However, participants receiving placebo first would be expected to have experienced only small practice-related reductions in error rate as, at second assessment, procyclidine could be expected to have negatively influenced performance through its anticholinergic action. This hypothesised pattern of effects might explain the observation of a small reduction in error rate from first to second assessment in this group.

In participants receiving procyclidine at first assessment, the same factors (of pharmacological effects and practice) may be drawn upon to explain the observed change in error rate across the two assessments. First, the adverse effects of procyclidine at first assessment (in the possible presence of expectancy effects) might have led to a substantially increased error rate in this group (56.49%), the highest observed in this study. Second, practice effects can be expected to have led to reductions in error rate at second assessment. These expected improvements were likely to have been further strengthened by the absence of performance-impairing pharmacological effects at second assessment. In other words, the reductions in error rate from first to second assessment expected due to the switch from procyclidine to placebo were overlaid by practice effects on this measure.

A notable feature of the current study in the context of practice effects is that all patients were treated with atypical antipsychotic drugs. Previous research has demonstrated that practice effects on cognitive tasks may be observed in patients treated with atypical, but to a lesser extent typical, antipsychotics. This finding is most likely to be due to the effects of atypical antipsychotics on restoring patients' capacity to learn (Harvey et al 2000).

A similar interaction between drug and order of administration, probably due to practice effects, was observed by Klein et al (2002). In their study of individuals with ADHD, methylphenidate improved antisaccade errors only when administered second, with the improvement overlaid by practice effects. When administered first, the operation of practice effects at second assessment probably masked improvements effected by this compound at first assessment. In order to investigate effects of practice more comprehensively, Klein et al (2002) as well as the present study should have included a third group of participants, given placebo on both occasions. In such a design the magnitude of practice effects could have been assessed without the influence of pharmacological agents.

The finding of increased antisaccade error rate due to procyclidine administration accords well with the putative role of a variety of cognitive processes in task performance and the role of the cholinergic system in these processes. Previous studies have shown that successful antisaccade performance requires intact response inhibition and working memory capacities (Mitchell et al 2002; Roberts et al 1994; Stuyven et al 2000). Conversely, animal studies have shown disrupted performance on memory-sensitive tasks after inactivation of cholinergic projections (Everitt & Robbins 1997; McGaughy et al 2000). Antisaccade performance and working memory both involve a cortical network including, but not restricted to, the dorsolateral prefrontal cortex (DLPFC) (Mitchell et al 2002; Müri et al 1998), suggesting that this area might be a possible locus for the action of procyclidine and its effects on task performance. However, neuroanatomic localisation of procyclidine effects on antisaccade errors in this study is made difficult by the widespread nature of central cholinergic projections and the widely distributed occurrence of muscarinic acetylcholine receptors in the human brain.

Procyclidine also led to non-significantly increased, or *hypermetric*, antisaccade gain irrespective of order of administration. Reduced, or *hypometric*, saccadic gain has been observed in schizophrenia patients treated with typical antipsychotic drugs as well as in patients with Parkinson's disease, suggesting a common influence of the parkinsonian effects of dopamine antagonism (Crawford et al 1989, 1995b, 1995a; Hutton et al 1998a). It is a possibility that procyclidine administration led to the opposite pattern of increased saccadic amplitudes in this sample through its antagonist action on Parkinsonian side effects.

Effects of procyclidine on saccadic latency were moderated by order of drug administration. Both prosaccade and antisaccade latencies were shorter only when procyclidine was administered second. Conversely, procyclidine led to prolonged latency when administered first. Aizawa et al (1999) observed shortened latency and increased frequency of 'express saccades' (saccades with latencies of less than 120ms) in monkeys after injection of the cholinergic *agonist* nicotine into the superior colliculus, a midbrain region involved in the control of saccades. The finding of prolonged latency after administration of the cholinergic *antagonist* procyclidine under some conditions are compatible with this finding and with observations of the sedative effects of this drug (Sharma et al 2002). However, it remains unclear why prosaccade and antisaccade latencies were shortened by procyclidine under some conditions. Also, comparisons between the present findings and those of Aizawa et al (1999) are tenuous as procyclidine and nicotine act on different acetylcholine receptor subtypes and due to the localised action of nicotine in the Aizawa et al study.

An alternative explanation for these paradoxical effects of procyclidine and placebo on saccadic latency is the operation of practice effects. As Table 8.1 reveals, both antisaccade and prosaccade latencies were consistently shorter at second compared with first assessment. These improvements in performance are similar to those reported by Klein et al (2002) over a comparable time interval (see also Chapter 4).

8.5.3 Implications

The present findings have research as well as clinical implications; both are discussed below.

With regard to schizophrenia research, impaired performance of patients taking procyclidine might lead to inflated between-group differences when compared to groups of unmedicated individuals. Procyclidine treatment might also represent a confound in studies assessing the effects of different types of antipsychotics on oculomotor function. As procyclidine is more likely to be prescribed to patients on typical antipsychotics due to the extrapyramidal side effects of these drugs (Kapur & Remington 2001; Leonard 1997), comparisons with patients on atypical antipsychotics might be selectively affected. Finally, the measures of SPEM gain, AS frequency and antisaccade error rate are particularly promising oculomotor schizophrenia endophenotypes. The present findings suggest that procyclidine treatment might have to be considered as a possible confound in genetic schizophrenia studies using these endophenotypes. In genetic

linkage studies, procyclidine treatment of some but not all patients might lead to the spurious identification of gene carriers (false positives). As Ott (1991) pointed out, false positives may have serious effects in linkage studies, far more than false negatives. Spohn and Strauss (1989) similarly pointed out the methodological implications for experimental psychology and psychophysiology research of anticholinergic treatment in schizophrenia.

Clinically, cognitive dysfunction is a pervasive feature of schizophrenia (Sharma & Harvey 2000), possibly the most debilitating (Friedman et al 1999; Green 2001). Research has highlighted the importance of cognition in psychosocial function of schizophrenia patients (Beiser et al 1994; Katsanis et al 1996; Kurtz et al 2001; Spaulding et al 1999). Adjunctive treatment with anticholinergic agents will have to be evaluated in the light of these cognitive impairments, as it may have further deleterious effects on patients with this disorder.

The second main finding of this study, the interactive effects of drug and order of administration, highlights the need to consider these factors in pharmacological research. Administration of pharmacologically inert placebos may have pronounced effects on cognition and emotion (Beecher 1959). Additionally, practice effects have been demonstrated for some of the eye movement parameters measured here and may have overlaid drug effects. A methodological implication of the present finding is that future pharmacological studies should consider the effects of practice as well as order of drug administration.

The present study has a number of limitations. First, the sample size, although comparable to previous studies, was relatively small. Replication using a larger, independent sample is, therefore, required. However, the fact that even in this small sample effects of procyclidine on oculomotor function were observed indicates they are likely to be clinically meaningful. Second, there was no control group of healthy individuals. While the main focus of this investigation was to examine the effects of a clinical dose of procyclidine on eye movements in schizophrenia patients, who are often prescribed this drug, it might have been valuable to compare performance levels of the patient group to healthy individuals. Third, a group of patients administered placebo on both occasions might have been valuable to study the effects of practice on performance measures. Finally, the extent to which these findings generalise to longitudinal treatment of schizophrenia patients with procyclidine remains open. It has to be investigated how clinically relevant procyclidine treatment over durations of several

weeks or months affects smooth pursuit and antisaccade eye movements in schizophrenia patients.

8.6 Conclusions

- Acute administration of procyclidine non-significantly impaired smooth pursuit and antisaccade performance in schizophrenia patients. This finding points to the importance of considering this drug in studies of oculomotor endophenotypes in samples of schizophrenia patients.
- The effects of procyclidine on a number of variables were mediated by the order in which drug and placebo were administered and were partly overlaid by practice effects. These effects have methodological implications, suggesting the need to consider order and practice in drug administration studies of oculomotor performance.

8.7 Limitations

- The sample size used in the present study, although comparable to previous studies, was small.
- There was no control group of healthy individuals.
- A third group of patient participants given placebo on both occasions would have been desirable in order to investigate practice effects more thoroughly.
- The extent to which these findings generalise to longitudinal treatment of schizophrenia patients with procyclidine remains to be investigated.

Chapter Nine

General Discussion

9.1 Chapter Overview

This chapter will attempt to integrate the findings obtained in the empirical investigations of this thesis and place them into the context of previous research. The research problem, the aims of the thesis and the theoretical underpinnings of the current investigations will first be reviewed. Methodological criticisms and implications will be made. Finally, suggestions for future research in the field of oculomotor schizophrenia spectrum endophenotypes will be made.

9.2 The Endophenotype Approach Revisited

The present thesis investigated the validity and reliability of smooth pursuit and antisaccade deficits as endophenotypes in schizophrenia spectrum research. The endophenotype approach to the study of schizophrenia genetics was argued to circumvent a number of difficulties associated with genetic schizophrenia research, such as the biological and clinical heterogeneity of schizophrenia, the complexity of genetic influence on this condition and methodological problems associated with focussing on the patient group.

An endophenotype was defined as a specific biological or behavioural deficit thought to be a more direct expression of a disease-related gene than the disease phenotype (Section 1.8.1). Endophenotypes were argued to be objective, reliable and phenotypically homogenous deficits. Due to their assumed genetic control, endophenotypes were expected to be observed not only in the schizophrenia patient group but also in clinically unaffected individuals with a genetic predisposition to the illness (schizophrenia spectrum populations). An endophenotype was argued to reflect the action of a disease-related gene, or the action of a gene in linkage disequilibrium with a disease-related gene. Oculomotor endophenotypes, i.e. smooth pursuit eye movement

(SPEM) and antisaccade deficits, were argued to be particularly promising schizophrenia spectrum endophenotypes.

The present thesis aimed to investigate a number of issues concerning the reliability and validity of the SPEM and antisaccade endophenotypes in the schizophrenia spectrum. Specifically, the present thesis addressed some of the key criteria required in the process of establishing the validity of a schizophrenia spectrum endophenotype. These criteria were temporal (and internal) reliability of measurement; observation of the deficit in people in their first-episode of psychosis; observation of the deficit in healthy first-degree relatives of people with schizophrenia; association with schizotypy; and susceptibility to secondary state effects, such as pharmacological treatment. Other important criteria, such as heritability or specificity to schizophrenia, could not be addressed in this thesis due to practical limitations.

The hypotheses that were investigated in this thesis were the following.

- On the basis of the assumed temporal stability of neurocognitive endophenotypes, both SPEM and antisaccade performance levels were hypothesised to be reliable within and across assessments.
- It was hypothesised that people in their first episode of psychosis would demonstrate SPEM and antisaccade impairments.
- SPEM and antisaccade impairments were hypothesised to be observed not only in schizophrenia patients but also in their healthy siblings.
- Individuals with high levels of schizotypy were hypothesised to have impaired SPEM and antisaccade performance. Given the assumed specificity of these endophenotypes to the schizophrenia spectrum, these impairments were further hypothesised to be independent of trait emotionality.
- Assuming robustness and reliability of assessment of a useful endophenotype, possible pharmacological state effects, such as procyclidine administration, were hypothesised not to interfere with SPEM and antisaccade performance.
- Additionally, it was explored (across studies) whether SPEM performance was correlated with antisaccade error rate.
- Finally, following previous studies, the visual fixation and prosaccade tasks were included as oculomotor control conditions in order to demonstrate

specificity across oculomotor functions of the SPEM and antisaccade impairments (discriminant validity). Across all studies, therefore, fixation and prosaccade performance levels were hypothesised to be relatively unimpaired in schizophrenia spectrum individuals.

9.3 Discussion and Evaluation of Findings

9.3.1 Key Findings in Relation to Hypotheses

The key findings from the current thesis in relation to the above hypotheses are as follows. First, SPEM and antisaccade performance was largely stable amongst healthy individuals both within and between assessments over a period of several weeks. Second, SPEM and antisaccade impairments were observed in individuals in their first episode of psychosis. Third, subtle SPEM and antisaccade impairments were observed in the healthy siblings of schizophrenia patients. Fourth, antisaccade (but not SPEM) deficits were observed in individuals with high levels of schizotypy; these deficits were independent of trait emotionality. Fifth, procyclidine disrupted SPEM and antisaccade performance. Sixth, there was inconsistent evidence of an association between SPEM performance and antisaccade error rate; the most consistent relationship concerned the frequency of anticipatory saccades during pursuit and antisaccade errors. Finally, there was inconsistent evidence relating to the visual fixation and prosaccade tasks.

9.3.1.1 Validity of SPEM and Antisaccade Deficits as Schizophrenia Spectrum Endophenotypes

The main findings of studies I-IV largely support the hypothesised validity of the SPEM and antisaccade tasks as schizophrenia spectrum endophenotypes. In agreement with the hypotheses, deficits were observed in a number of crucial samples from the schizophrenia spectrum (with the exception of a failure to observe SPEM deficits in schizotypal individuals). These findings thus provide important evidence of the validity of the SPEM and antisaccade endophenotypes.

Although some of these findings represent replications of previous observations at a general level (e.g. the observation of 'oculomotor performance impairments in first-degree relatives of schizophrenia patients'), a number of novel observations were made.

First, despite previous observations of temporal stability of SPEM performance, Study I is the first investigation to provide detailed evidence of the good temporal stability of the antisaccade error rate. Additionally, Study I represents the first thorough investigation of the internal consistency of oculomotor performance across a number of tasks. The importance of this type of reliability in psychophysiology research has been discussed (Section 4.4.4). Likewise, despite the previous observation of practice effects on antisaccade errors, no study to date has shown that these improvements are due to between-session effects (of motor consolidation, slow learning gains or reduced anxiety) and not due to within-session learning. These practice effects, which were also demonstrated in Study V, have to be taken into consideration in longitudinal studies. Additionally, this pattern of performance changes, and the relative absence of practice effects on the SPEM task, may shed light on the cognitive nature of the antisaccade task. As discussed, practice effects do not occur on all cognitive or motor tasks, but tend to be specific to unpractised and infrequently used tasks.

Second, the investigation of first-episode psychosis patients yielded the first observation of increased anticipatory saccade frequency in this crucial schizophrenia spectrum population, thus confirming the validity of this proposed endophenotype. Additionally, this study was the first to demonstrate visual fixation and antisaccade gain abnormalities in the first episode of psychosis.

Third, Study III made a contribution to the literature of oculomotor family studies beyond replicating the observation of SPEM and antisaccade deficits in first-degree relatives. The design and statistical analysis of this study was unique amongst this literature as it utilised tightly matched triplets of patients, siblings and healthy controls and chose a statistical analysis that acknowledged and accommodated the genetic relatedness between patients and siblings. Additionally, the crucial comparison between the sibling and control groups allowed the isolation of the key variable of interest, the genetic relatedness to someone with schizophrenia. Finally, SPEM (and, non-significantly, antisaccade) performance showed familial patterns. These findings thus represent strong evidence of the validity of the SPEM and antisaccade endophenotypes.

Fourth, Study IV was the first to address the schizotypy correlates of SPEM and antisaccade performance using empirically derived schizotypy dimensions based on psychometric questionnaire subscales. This analysis demonstrated that positive, but not negative, schizotypy was related to antisaccade errors. SPEM performance was not associated with schizotypy; the reasons for this are unclear. An important, and novel,

finding of this study was that the relationship between antisaccade errors and schizotypy was not accounted for by a general measure of trait emotionality and psychopathology. The relationship between antisaccade error rate and schizotypy thus showed specificity to schizophrenia-related traits.

Finally, the observation of adverse effects of procyclidine on SPEM and antisaccade performance represents a methodological challenge to future studies of these oculomotor endophenotypes in people with schizophrenia. State effects of pharmacological treatments, such as procyclidine, will have to be considered in genetic linkage studies involving the SPEM and antisaccade phenotypes in schizophrenia patients. The administration of compounds that interfere with eye movement performance, such as procyclidine, might lead to the false positive detection of 'gene carriers' (if identified on the basis of oculomotor data), which has serious consequences for the investigation of genetic linkage (Ott 1991). Strategies to surround this potential problem in future studies might be 1) the exclusion of patients on anticholinergic drugs or 2) the withdrawal of anticholinergic treatment for a sufficient period of time before oculomotor assessment.

9.3.1.2 *Relationship between SPEM Measures and Antisaccade Error Rate*

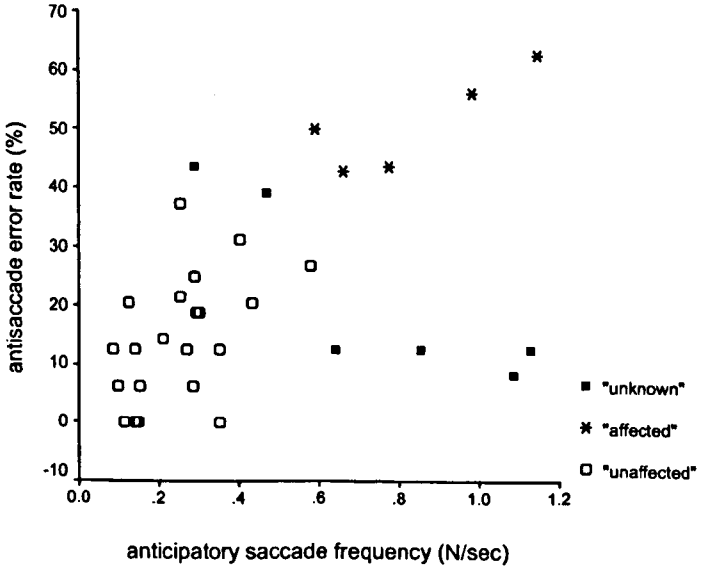
The relationship between SPEM and antisaccade was found to be inconsistent. This inconsistency, ironically, is consistent with previous research, which has provided mixed evidence of a relationship between various measures of smooth pursuit and antisaccade error rate. An *a priori* focus of interest in this thesis concerned the relationship between frequency of anticipatory saccades during pursuit and antisaccade error rate. A meaningful relationship between these two putative measures of inhibitory oculomotor function was indeed observed in two studies; however a later study failed to replicate this observation. Sample characteristics (such as the failure to thoroughly screen for psychiatric illness or drug consumption) might account for the failure to replicate in this study. Antisaccade error rate was, however, correlated with SPEM gain in this sample.

On the basis of the arguments outlined in Section 2.8, a moderate relationship between these two conceptually related measures might have suggested that they can be used with profit as a composite oculomotor endophenotype in linkage studies. Whether or not this does indeed represent a useful approach will have to be tested further, possibly

using linkage studies. These studies might explore the power of a combined oculomotor endophenotype. Participants with 'impaired' performance (e.g. ≥2SD of the mean) on both anticipatory saccade frequency and antisaccade error rate might be labelled 'affected'; participants with impairments on either of the measures might be labelled 'unknown'; and participants with impairments on neither measure might be labelled 'unaffected'. It will then be crucial to determine whether linkage occurs between genetic loci and this composite endophenotype, a single oculomotor endophenotype or the schizophrenia phenotype.

Figure 9.1 illustrates the identification of 'affected' individuals using the antisaccade and anticipatory saccade measures. This illustration is based on the combined patient and control groups from Study II; due to the small sample size a cut-off criterion of 1SD is used here.

Figure 9.1: Illustration of the Identification of 'Affected' Individuals Using a Combination of Antisaccade Error Rate and Anticipatory Saccade Frequency



9.3.1.3 *Visual Fixation and Prosaccade Performance*

The previously held assumption that the visual fixation and prosaccade tasks are unimpaired in schizophrenia spectrum individuals and may thus represent convenient control tasks for oculomotor performance may be challenged on the basis of the present

findings. Prosaccade impairments were observed in patients from studies II (reduced accuracy) and III (reduced accuracy and increased latency). The impairments observed in Study II are unlikely to be due to secondary confounds due to the recent onset of psychosis in this patient group. Additionally, fixation impairments were observed in the first-episode patients of Study II. Finally, prosaccade accuracy was reduced in individuals with high psychoticism scores (Study IV).

These findings, in conjunction with previous research, indicate that the notion of *unimpaired* visual fixation and prosaccade performance in schizophrenia spectrum individuals is untenable. Instead, the present and previous findings suggest that the evidence regarding these tasks is mixed. Given the inconsistencies of findings regarding fixation and prosaccades, however, it would be equally untenable to propose these two measures as particularly promising schizophrenia spectrum endophenotypes (however, see Rybakowski et al 2001). The reason for the inconsistencies in evidence regarding fixation and prosaccade performance is unclear, but sample and task characteristics may play a role (Section 2.6.4.1). It should be pointed out, however, that the prosaccade task of studies II and III suffered some methodological weaknesses, as outlined before (Section 3.2.1.2.4). The findings concerning saccadic accuracy from these studies, but not saccadic accuracy from Study IV or saccadic latency, thus have to be treated with caution.

9.3.2 Additional Findings

In addition to the positive evidence of the reliability and validity of the SPEM and antisaccade endophenotypes, however, a number of other, less expected findings emerged from this research.

9.3.2.1 Between-group Comparisons

A striking feature of the between-group comparisons on SPEM and antisaccade variables between first-episode patients and healthy controls (Study II), between schizophrenia patients as well as their siblings and healthy controls (Study III) and between high and low schizotypy individuals (Study IV) was the overlap in variance within these pairs of groups. This overlap in variance (see, for example, Figures 6.1, 6.2 and 7.3) has a number of implications.

First, there are (in the present as well as in previous studies; see, for example, Figure 2 of Curtis et al 2001a) healthy, unaffected, low-schizotypy individuals with worse oculomotor performance than members of putative schizophrenia spectrum populations. A clear implication of this observation is that it will not be possible to use any single SPEM or antisaccade measure as a diagnostic tool (although a combination of psychophysiological and clinical measures might be more successful; Arolt et al 1998; Robins & Guze 1970). Eye movement deficits are thus not *pathognomic* of schizophrenia.

Second, the observation of differences in group means with overlapping variance suggests that the 'deficits' seen in the schizophrenia spectrum groups are subtle. A similar argument has been made for the observation of structural brain changes in schizophrenia (Wright et al 2000). Indeed, the differences in oculomotor performance between the patient groups and healthy individuals observed in this thesis are comparable to deficits observed on many other neurocognitive measures used in schizophrenia spectrum research.

A variety of explanations might be drawn upon to account for the magnitude of the observed between-group differences. People with schizophrenia or other schizophrenia spectrum characteristics are clearly not *qualitatively* different from healthy, non-schizophrenia spectrum individuals in their performance patterns and average performance levels. Indeed, the 'deficits' seen in the patient group and other spectrum individuals are also observed, to a lesser extent, in healthy non-spectrum controls (e.g. CUS and AS during pursuit, segments of less than perfect pursuit gain and reflexive errors in the antisaccade paradigm).[25]

These performance patterns, in conjunction with the normality of data distributions, which were observed for the vast majority of oculomotor variables in the present research (see Sections 5.4, 6.4, 7.4), have an important implication. It may be argued that several, genetic and non-genetic, factors influence individual and between-group differences in task performance (see also Section 9.5). Normality of distribution is, in statistical terms, typically thought to come about through the combined effects of a number of variables of small-to-moderate effect each as well as random error of

[25] Very few healthy individuals, for instance, make *no* antisaccade errors during an assessment involving more than 20 trials.

measurement (Mood & Graybill 1963); in biological variables these factors are likely to be genetic and non-genetic.

This inferred action of several factors on task performance is consistent with the involvement of several cognitive and neural components in SPEM and antisaccade performance. Although assumed to be phenotypically and biologically more homogenous than the schizophrenia phenotype, it becomes clear from the delineation of their cognitive and neural components (Sections 2.3.5.2 and 2.5.4.2) that the SPEM and antisaccade tasks are, in fact, complex and multivariate tasks (Levy et al 2000; Section 2.3.4). It has been argued that both tasks involve a number of cognitive processes and a widespread network of cortical and subcortical brain structures. This assumed cognitive and neural complexity can be argued to be reflected at the statistical level, such as in approximately normal distributions and overlap in variance between groups.[26]

On the basis of this task heterogeneity and the observed patterns of data distributions and between-group differences it may be speculated that it is unlikely that a single gene can explain all (or a vast majority) of the variance of any oculomotor endophenotype. Consequently, a single gene is unlikely to produce the average 'impairments' in performance that are observed in the schizophrenia spectrum groups. A more likely scenario is that a number of genes influence task performance and underlying neural activity, with each gene having a small but significant contribution. The average performance deficits in schizophrenia spectrum groups may thus be explained by a number of factors, which might differ in severity and frequency between individuals. This complex pattern of effects might be able to explain why some schizophrenia spectrum members show better oculomotor performance than non-spectrum controls.

A first indication for the action of more than one gene in oculomotor performance deficits comes from molecular genetic studies of the SPEM endophenotype. While one study (Arolt et al 1999) showed linkage of SPEM dysfunction to a locus on chromosome 6p21, another study (Rybakowski et al 2001) showed an effect of a gene located on a different chromosome, i.e. chromosome 3q. Unless one or both of the studies represent

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[26] However, error of measurement alone, in the absence of further variables of small-to-moderate effect, can cause statistical normality. Thus, the observation of normal distributions of variables in the current research is merely *consistent with* the operation of multiple causal factors and not necessary evidence of it. More convincing evidence for this assumption comes from the known cognitive, genetic and neural correlates of task performance.

a false positive finding, there are already two promising genetic loci implied in the behavioural SPEM deficit in schizophrenia.

Additional evidence of the action of several genes in SPEM and antisaccade performance comes from biometric model-fitting analyses of data from healthy monozygotic and dizygotic twins (Katsanis et al 2000; Malone & Iacono 2002). These studies (from the same laboratory) have shown that *additive* genetic influences and non-shared environmental factors account for the majority of variance in performance. It is thus likely that the SPEM and antisaccade tasks face similar issues of genetic complexity and phenotypic heterogeneity to the schizophrenia phenotype, albeit to a much lesser extent.

To put these speculations concerning the genetic influence on oculomotor performance into context, a recent study has investigated the effects of a schizophrenia candidate gene, the catechol-*O*-methyltransferase (COMT) gene, on neuropsychological performance (Egan et al 2001b). These researchers found that COMT genotype accounted for 4.1% of variance in WCST performance. The effect of COMT was thus very small but statistically (and theoretically) significant.

The present findings of subtle oculomotor impairments and overlapping variance between schizophrenia spectrum and control groups should be viewed in this context. The effects of schizophrenia spectrum group status on SPEM and antisaccade performance are clearly observable and often reach conventional thresholds of statistical significance, yet are small in overall terms. There is thus likely to be a number of factors accounting for variance in performance.

The latent trait model outlined in Section 2.3.5.5.7 argues that a major gene with pleiotropic effects produces schizophrenia and/or SPEM impairments (Matthysse & Holzman 1987). This model is consistent with the present findings of overlapping variance in SPEM measures between schizophrenia spectrum and control groups, as it postulates that a proportion of schizophrenia spectrum individuals with the SPEM/schizophrenia genotype will not possess the phenotype of SPEM impairments. The normal performance scores of these individuals would thus overlap with those of non-spectrum controls.

While the above speculations are consistent with the action of more than one gene with small-to-moderate effect, a direct test of the latent trait hypothesis was not carried out. Testing for bimodality was not undertaken as the sample sizes used here were deemed

too small to produce reliable results. It thus remains a possibility that a pleiotropic model could account for the overlap in SPEM variance observed between schizophrenia spectrum and control groups. (Bimodality and pleiotropy has not been postulated regarding the antisaccade error rate; this issue requires clarification.)

9.3.2.2 *Antisaccade Gain*

Primary antisaccade accuracy (gain) was found to be impaired in first-episode psychosis and schizophrenia patients as well as in healthy siblings of schizophrenia patients. Although reduced antisaccade gain has been observed in previous studies, the consistency with which these deficits were observed in the present investigations is suggestive. The status of this measure as a putative schizophrenia spectrum endophenotype remains to be further characterised. It is particularly intriguing, however, that one study (Ross et al 1998d) observed reduced antisaccade accuracy in individuals without, but not with, a family history of schizophrenia. This finding might be compatible with the observation of strongly reduced antisaccade gain in the siblings of schizophrenia patients (Study III), most of whom were from simplex schizophrenia families. The antisaccade gain reduction of the first-episode psychosis group suggests that it was not due to the long list of secondary confounds discussed above (Section 2.3.5.5.5).

As outlined before, antisaccade accuracy is likely to be a good measure of sensorimotor coordinate transformation processes and working memory. Sensorimotor coordinate transformations require the encoding of the spatial location of a target and the transformation of this stored information into a motor output in the absence of a physical target. These processes are also likely to be involved in other saccadic paradigms known to be impaired in schizophrenia spectrum individuals, such as the memory-guided and predictive saccade tasks (Section 2.7). The present findings, and the hypothesised prefrontal and parietal neural correlates of antisaccade accuracy, suggest that this measure might be added to the list of potential schizophrenia spectrum endophenotypes of neurocognitive function. Importantly, antisaccade gain meets a number of reliability criteria: antisaccade gain scores in this research had high intra- and inter-rater reliability; were correlated across two stimulus display methods; had high within-session consistency; and had good test-retest reliability (but reaching only trend level using one stimulus display method). Before considering this measure as a schizophrenia spectrum endophenotype, however, a number of caveats must be addressed.

First, the assessment of antisaccade gain in studies II and II is open to methodological criticism. As argued before, only one antisaccade target amplitude was used in each visual hemifield. More reliable assessment of spatial accuracy would have been obtained using more than one amplitude in each hemifield. Future studies should use improved methods, such as those of eye movement Battery II.

Second, there was no relationship between antisaccade gain and schizotypy in Study IV. It remains a possibility that sample characteristics particular to this study were responsible for the failure to observe this relationship; future studies are needed to clarify this issue. However, given the positive evidence of a relationship between schizotypy and antisaccade *error rate*, this finding represents preliminary negative evidence in the attempt to establish antisaccade gain as a useful schizophrenia spectrum endophenotype.

Third, on a methodological note, the effects of procyclidine on antisaccade gain warrant consideration of anticholinergic treatment in future studies of antisaccade accuracy. Given the effects of antipsychotic drug treatment on accuracy of other saccadic measures (Crawford et al 1995a, 1995b), studies of unmedicated schizophrenia patients are needed.

9.3.3 Conclusions

To conclude, the importance of the main findings of the present research lies in providing supportive evidence of the SPEM gain, anticipatory and catch-up saccade and antisaccade error rate measures as schizophrenia spectrum endophenotypes; suggesting the possibility of combining key measures in genetic studies; questioning the notion of unimpaired performance on fixation and prosaccade tasks in the schizophrenia spectrum (and thus the discriminant validity of the SPEM and antisaccade deficits); demonstrating the subtlety of group differences and making implications concerning their neural and behavioural sources; proposing the measure of antisaccade gain as a preliminary schizophrenia spectrum endophenotype; and pointing to an important pharmacological state effect that needs to be taken into consideration in future studies.

Although a formal comparison of the relative effect sizes of SPEM and antisaccade impairments in schizophrenia spectrum individuals was not made, impairments of similar magnitude were observed across the schizophrenia spectrum on both tasks. The

only notable exception to this pattern was the failure to observe a relationship between SPEM and schizotypy. The present findings thus suggest that the SPEM and antisaccade tasks have passed a number of reliability and validity criteria of schizophrenia spectrum endophenotypes at the behavioural level and may thus be studied with profit in molecular genetic schizophrenia spectrum investigations.

9.4 Methodological Criticisms and Implications

The eye movement tasks used in this thesis served to elicit specific oculomotor behaviours in the laboratory. While most types of eye movement under investigation here (SPEM, fixation, and reflexive saccade) may be observed in the natural human environment, the experimental tasks that served to study these behaviours in the laboratory (in this thesis as well as in previous studies) are highly operationalised and somewhat artificial. Additionally, the antisaccade – although physiologically similar to the prosaccade – is unlikely to occur frequently in the natural human habitat. The ecological validity of these measures may, therefore, be questioned (Stern & Dunham 1990).

However, given the specificity of the hypotheses addressed in this thesis, and to increase compatibility with previous research, operationalisation and laboratory-based assessment of eye movements was inevitable, and indeed desirable. It should also be pointed out that the SPEM, fixation and prosaccade tasks are reasonably adequate measures of naturally occurring behaviours. Additionally, the difficulties in ecological validity of the oculomotor tasks used in this thesis are comparable to (or smaller than) some of the even more operationalised, artificial and indirect measures of cognition often used in neuropsychological assessment (Lezak 1983).

Due to practical reasons, two sets of eye movement tasks were used in the research reported here. This fact alone represents a methodological weakness of the current thesis, as differences between tasks made the direct comparison of findings across studies difficult.

The utilisation of two sets of tasks, however, also offered the unique opportunity to compare and contrast these different measures. As argued in the methodological review (Section 3.2.2.3), the tasks that were specifically developed by the author for the research of this thesis were held to possess a number of advantages over the previously used tasks, such as better psychometric properties and greater homogeneity and

compatibility across measures. These advantages were achieved through careful design and selection of criteria on the basis of previous studies. Although it is difficult to isolate specific factors contributing to the better psychometric properties (such as internal and temporal reliability) of the new tasks, reasons are likely to concern the number of trials (or duration of trials in the SPEM task), quasi-randomisation of trials (in the saccade tasks) and adequate calibration.

The optimal number of trials in saccade tasks was discussed by Maruff et al (1999). These authors suggested the use of at least 40 trials in an antisaccade task. The present findings agree with this suggestion, as an antisaccade task with a larger number of trials (N=60) yielded better reliability, probably due to greater between-subject variance, than a task with fewer trials (N=24). As argued in Chapter 4, using a random sequence of target movements in saccade tasks makes the target spatially unpredictable, thus avoiding the confounding effects of procedural motor learning. This feature may also be advantageous, as it isolates the cognitive component of interest in the absence of secondary learning effects. Finally, adequate calibration (over the entire range of target excursions) is, of course, a necessary step in the development of any eye movement task. Future studies would benefit by taking these issues into consideration.

Another methodological criticism that should be made of the current research concerns the measures of schizotypy employed in Study IV. As others have argued (Johns & van Os 2001), psychometric self-report questionnaires are probably the most appropriate measure of schizotypy in non-clinical samples, such as members of the general population or university students. This argument is based on the assumption (and empirical observation) that levels of schizotypal and schizophrenic symptoms are relatively low in these populations compared to people with schizophrenia. Therefore, clinical interview schedules designed to ascertain symptom severity and diagnosis of related disorders in clinical samples (i.e. individuals in a hospital setting) might be insensitive to the small individual differences in schizotypy observed in non-clinical samples.[27] An indication of this effect may be the failure to observe any relationships between SPEM or antisaccade measures and scores on the Structured Interview for Schizotypy (SIS; Kendler et al 1989) amongst healthy controls of Study III. Psychometric

[27] Another advantage of psychometric self-report questionnaires is, of course, the ease with which these can be administered and scored amongst large samples, as was the case in Study IV.

self-report questionnaires are thus designed to provide a 'magnifying glass' for individual differences in schizotypal traits in non-clinical samples (Rust 1987, 1988).

These measures may, however, be criticised on other grounds. First, it is difficult to estimate the truthfulness with which participants provided information given the self-report nature of these scales. It is, in this context, however, important to note that exclusion of participants who attracted high scores on measures of social desirability and truthfulness of responding (e.g. 'lie' scales) did not change the key finding of Study IV, that is the relationship between positive schizotypy and antisaccade error rate. Second, it has been shown by several researchers that assessment of schizotypy with psychometric self-report and clinical measures diverges in the relatives of schizophrenia patients. While first-degree relatives have reliably elevated levels of schizotypal and schizophrenic symptoms as well as increased rates of SPD when assessed using clinical (one-to-one) interview schedules, their scores on psychometric self-report measures of schizotypy are the same or lower than in healthy control groups. This finding has been explained in terms of defensive response bias in first-degree relatives, but nevertheless casts doubt on the validity of these measures. Finally, it has been argued that positive schizotypy in the general population might not be a good reflection of positive schizophrenic symptoms (Fanous et al 2001). It thus remains unclear whether the relationship between positive schizotypy and antisaccade errors observed in Study IV has relevance for research into the clinical symptom correlates of antisaccade performance amongst people with schizophrenia.

9.5 Outlook

The present thesis has identified a number of avenues for future research. First, the observation of good internal consistency of oculomotor performance in healthy individuals needs to be extended to schizophrenia patients and other schizophrenia spectrum groups. Given the generally more variable performance in the patient group, somewhat lower internal consistency may be expected.

Second, despite the relatively established observation of oculomotor deficits in people in their first psychotic episode, longitudinal studies are needed to further chart the course of these deficits. As discussed in Chapter 5, despite the clinical exacerbation often observed in the first few years of the illness, neurocognitive performance appears to remain stable. This putative stability in the early phase contrasts with the evidence of significantly greater impairments in patients with chronic schizophrenia, as established

through cross-sectional studies. Future studies are required facing the logistically difficult task of tracking the change in oculomotor performance over several years of illness, from first episode to chronic schizophrenia.

Third, clarification of the symptom correlates of antisaccade performance is required. As discussed (Chapter 2), the schizophrenic symptom correlates of antisaccade error rate in the patient group are not clear. Similarly, both positive and negative *schizotypal* symptoms have been shown to be associated with elevated antisaccade error rate (Gooding 1999; O'Driscoll et al 1998). The findings from Study IV point to a relationship between antisaccade errors and positive, but not negative symptoms. This relationship might be partly due to the more pathological nature of positive than negative symptoms, but requires clarification.

Relatedly, the theoretically intriguing but methodologically problematic finding of normal or reduced levels of schizotypy in first-degree relatives of schizophrenia patients when assessed with self-administered schizotypy questionnaires has implications for oculomotor schizotypy research. Future studies might use clinical assessments in samples of individuals selected for high and low psychometric self-report scores of schizotypy to confirm the validity of these measures, such as the participants used in the analysis of Section 7.4.4. (The use of clinical interviews in samples as large as that of Study IV is probably impractical.)

Fourth, the deleterious effects of procyclidine on oculomotor function observed in Study V need to be replicated and extended to longitudinal treatment of people with schizophrenia. Additionally, related pharmacological side-treatments used in schizophrenia should be investigated. Only then will it be possible to reliably estimate the potential confound that state effects of such treatments represent in linkage studies involving schizophrenia patients.

Fifth, in addition to the criteria of a valid endophenotype listed in Section 1.8.1, it has been argued that such a deficit should not only precede, but *predict*, the diagnosis of the disease (Gottesman & Erlenmeyer-Kimling 2001; Iacono 1998). No study to date has addressed this question using oculomotor endophenotypes in schizophrenia research. Studies are needed to track high-risk groups, e.g. individuals with elevated scores of schizotypy (cf. Chapman et al 1994b), or off-spring of schizophrenia parents, from adolescence into adulthood, through the period most critical for the development of schizophrenia.

Sixth, as argued in Chapter 1, the ultimate aim of the endophenotype approach is to provide a better, or quantifiable, objective and phenotypically and biologically homogenous phenotype for linkage studies. Clearly, therefore, this is an area where future research is much needed. Preliminary linkage evidence exists, linking SPEM and antisaccade deficits to genetic loci on chromosomes 6p21 and 22q11-q12, respectively (Arolt et al 1999; Myles-Worsley et al 1999). Given the large amount of work at the level of behavioural genetics, such as oculomotor family studies, it is perhaps surprising that more linkage studies of oculomotor endophenotypes have not been carried out.

Seventh, the cognitive and neural complexity of the SPEM and antisaccade tasks has already been discussed. This complexity indicates that the SPEM and antisaccade measures might suffer some of the problems that the endophenotype approach aims to circumvent, such as phenotypic heterogeneity. One strategy around this problem might be to study more closely the cognitive and neural component processes of these measures. This research, exemplified by studies of the motion processing component of SPEM (Chen et al 1999a, 1999b, 1999c), might focus on a cognitive candidate process thought to underlie the performance deficits in the schizophrenia spectrum groups.

Once such a process has been identified, e.g. response inhibition (for antisaccade) or motion processing (for smooth pursuit), it could be assessed using a number of different neurocognitive tasks and might thus be phenotypically more homogenous than each task itself. Utilising several measures of the same function but from different modalities (e.g. eye movements, neuropsychology, electrophysiology, etc.) would have the advantage of partialling out random or nuisance variance due to other cognitive or motivational processes (or error of measurement) unique to each task. An example of this approach is the combination of the antisaccade and P50 sensorimotor gating tasks in an investigation of the component of inhibitory function (Cadenhead et al 2002; Myles-Worsley et al 1999). The exploration in this thesis of the relationship between anticipatory saccades during smooth pursuit and antisaccade errors represents a related approach. It remains to be investigated further whether the combination of these two measures provides a useful assessment of the assumed common component of inhibitory function.

Finally, molecular genetic studies are needed. For example, candidate gene studies investigate genes whose protein products are thought to play a role in the pathophysiology of the disorder under study. A number of schizophrenia candidate genes have been put forward. To date, only one study has investigated the relationship

between such a gene (the D3 dopamine receptor gene) and oculomotor performance (Rybakowski et al 2001). Future candidate gene studies of oculomotor endophenotypes should examine the relationship between genes likely involved not only in schizophrenia, but also eye movement control. One such gene is the COMT gene (Egan et al 2001b). This gene has a common polymorphism resulting in variations of the COMT protein's efficiency of frontal dopamine metabolism. Given the role of frontal lobe dopamine in the pathophysiology and treatment of schizophrenia and the evidence of impairments on frontal lobe tests, such as the WCST, in people with schizophrenia, a recent study examined the effect of COMT genotype on WCST performance (Egan et al 2001b). Additionally, these researchers studied the effects of COMT genotype on prefrontal activation during performance of a working memory task. It was demonstrated that the disease-related COMT genotype (Val-Val homozygosity) was associated with poorer WCST performance and prefrontal neural inefficiency.

A replication and extension of this design to the field of oculomotor endophenotypes might be useful. Specifically, antisaccade error rate has been associated with 1) WCST performance, 2) prefrontal neural activity, 3) dopaminergic manipulation and 4) a chromosomal region including the locus of the COMT gene (22q11-12). It is likely that future studies combining molecular approaches (such as the study of candidate genes) and functional neuroimaging techniques will provide the strictest tests so far of the validity of the proposed oculomotor endophenotypes.

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List of Abbreviations

°/s	Degrees per second
5-HT	5-hydroxytryptamine
AC	Active syndrome scale (PSQ-80)
AD	Analogue-to-Digital (converter card)
ADHD	Attention Deficit/Hyperactivity Disorder
ANOVA	Analysis Of Variance
AS	Anticipatory Saccades
BDI	Beck Depression Inventory
BPRS	Brief Psychiatric Rating Scale
BUS	Back-up Saccades
CBT	Cognitive Behavioural Therapy
CD	Cognitive Disorganisation scale (O-LIFE)
cm	Centimetre
CNV	Contingent Negative Variation
COMT	Catechol-*O*-methyltransferase
CPT	Continuous Performance Test
CRO	Cathode-ray Oscilloscope
CSTQ	Combined Schizotypal Traits Questionnaire
CT	Computed Tomography
CUS	Catch-up Saccades

DA	Dopamine
DLPFC	Dorsolateral Prefrontal Cortex
DRD3	D3 Dopamine Receptor
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Version IV
DV	Dependent Variable
DZ	Dizygotic
E	Extraversion scale (EPQ-R)
EE	Expressed Emotions
EEG	Electroencephalography
EOG	Electrooculography
EPI	Eysenck Personality Inventory
EPQ	Eysenck Personality Questionnaire
EPQ-R	Eysenck Personality Questionnaire – Revised
EPS	Extrapyramidal Side Effects
ETD	Eye-tracking Dysfunction
FEF	Frontal Eye Fields
FIGS	Family Interview for Genetic Studies
fMRI	Functional Magnetic Resonance Imaging
Hz	Hertz
IA	Introvertive Anhedonia scale (O-LIFE)
ICC	Intraclass Correlation
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Version 10

IN	Impulsive Nonconformity scale (O-LIFE)
IQ	Intelligence Quotient
IRO	Infrared Oculography
IT	Inattentiveness scale (PSQ-80)
Kg	Kilogram
KMO	Kaiser-Meyer-Olkin
L	Lie scale (EPQ-R)
LED	Light-Emitting Diode
LI	Latent Inhibition
ln	Natural Logarithm
MANOVA	Multivariate Analysis Of Variance
MCI	Minnesota Counselling Inventory
MMPI	Minnesota Multiphasic Personality Inventory
MMQ	Maudsley Medical Questionnaire
MPI	Maudsley Personality Inventory
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
Ms	Millisecond
MSC	Magnetic Search Coil
MST	Medial Superior Temporal area
MT	Middle Temporal area
MZ	Monozygotic
N	Neuroticism scale (EPQ-R); Number of participants

NAA	N Acetyl-aspartate
NMDA	N-methyl-D-aspartate
NSS	Neurological Soft Signs
OCD	Obsessive-compulsive Disorder
OKR	Optokinetic Reflex
O-LIFE	Oxford-Liverpool Inventory of Feelings and Experiences
P	Psychoticism scale (EPQ-R)
PANSS	Positive and Negative Syndrome Scale
PCA	Principal Components Analysis
PEF	Parietal Eye Fields
PET	Positron Emission Tomography
PKU	Phenylketonuria
PPC	Posterior Parietal Cortex
PPI	Prepulse Inhibition
PSQ-80	Personality Syndrome Questionnaire – 80
rCBF	Regional Cerebral Blood Flow
RISC	Rust Inventory of Schizotypal Cognitions
RMSE	Root Mean Square Error
S/N	Signal-to-Noise Ratio
SANS	Schedule for the Assessment of Negative Symptoms
SC	Superior Colliculus
SCID	Structured Clinical Interview for DSM-IV Axis I Disorders
SD	Social Desirability scale (PSQ-80); standard deviation

SEF	Supplementary Eye Fields
SES	Socio-Economic Status
SIS	Structured Interview for Schizotypy
SMC	Squared Multiple Correlations
SPD	Schizotypal Personality Disorder
SPEM	Smooth Pursuit Eye Movements
SPET	Single Photon Emission Tomography
SPQ	Schizotypal Personality Questionnaire
SPSS	Statistical Package for the Social Sciences
SWJ	Square-wave Jerks
TD	Tardive Dyskinesia
TMT	Trail Making Test
UE	Unusual Experiences scale (O-LIFE)
UR	Unreality syndrome scale (PSQ-80)
V1	Visual Cortex Area 1
VOR	Vestibulo-ocular Reflex
WAIS	Wechsler Adult Intelligence Scales
WCST	Wisconsin Card Sorting Test
WD	Withdrawn syndrome scale (PSQ-80)