An investigation into the role of the motor cortex during early motor learning in adults with Developmental Coordination Disorder

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Declaration

I, Daniel Brady, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:

Date:

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Abstract

Motor learning is a process that continues throughout an individual's lifespan and has a significant impact on their general well-being. The role of the primary motor cortex in motor learning has been well established over the last few decades, with converging streams of evidence reporting electro- and neurophysiological changes during the early stages of learning. However, there is evidence that these changes are not uniform across the general population and that this variability may underlie the differences observed in motor learning ability. At the same time, the literature reports a neurodevelopmental disorder called Developmental Coordination Disorder (DCD) that has a significant negative impact upon motor control and learning. There is little research into the neural correlates of DCD, particularly with adults. As a result, the aim of the research reported in this thesis was to investigate whether the aforementioned variability in the changes occurring in the motor cortex during the early stages of motor learning plays a role in DCD.

The experiments reported examine the neural correlates of the early stages of motor learning in adults with and without DCD. The first experiment described aimed to establish a task that produces changes in motor performance within a single session. The second experiment described was concerned with electrophysiological changes produced by the task. The final experiment examined neurophysiological changes produced by the task. While the motor task was able to successfully produce changes in motor performance; neither of the latter two experiments found motor cortical changes associated with practice of the task.

However, due to methodological challenges reported in these experiments, the conclusions that can be drawn from the results are somewhat limited. The results of these experiments are evaluated and discussed within the context of the broader DCD literature and suggestions for future research directions are made.

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Chapter 1 – General Introduction:

Motor learning and Developmental Coordination Disorder

Outline

Motor learning occurs during all stages of development and into adulthood (e.g. when learning a new skill) and, as will be shown, motor efficacy is important for performing activities of daily living and seems to have a significant impact on general well-being (World Health Organization, 2001).

This chapter will begin by examining motor learning and its neurobiological correlates, eventually focussing on the role of the primary motor cortex (M1) in the early stages of motor learning and how factors affecting motor cortical plasticity may underlie individual differences in motor learning. It will then progress onto outlining Developmental Coordination Disorder (DCD), including the diagnostic criteria, prevalence, and current cognitive and neurobiological hypotheses for mechanisms underlying the problems experienced in DCD. Finally, this chapter will discuss the motor learning problems reported in DCD in the context of the research supporting the involvement of the primary motor cortex in the early stages of motor learning, and outline the primary question that the rest of this thesis will attempt to explore.

Motor learning

Definition and progression of motor learning

Schmidt and Lee (2005) define motor learning as "...a set of processes associated with practice or experience leading to relatively permanent changes in the capacity for movement" (Pg. 302).

As this definition suggests, motor learning is generally considered to be a multi-stage process that occurs over repeated practice sessions (e.g. see Fitts & Posner, 1967; Halsband & Lange, 2006; Schmidt & Lee, 2005), and although the specific number of stages is not agreed upon there is a general consensus of the timeline of processes that occur during the acquisition of a novel skill.

The initial phase of motor learning is characterised by a need for explicit cognitive control of the motor task, individuals need to consider the requirements of the task and plan a motor sequence accordingly, and then consider the sensory information (e.g. performance feedback) provided by that action and adjust the sequence accordingly (Halsband & Lange, 2006). The need for explicit cognitive control during this phase of learning is illustrated by the interference experienced when a secondary task is added. The secondary task adds additional cognitive load and typically has a negative effect on the practiced task both in terms of immediate performance and subsequent retention (Eversheim & Bock, 2001; Passingham, 1996; Rémy, Wenderoth, Lipkens, & Swinnen, 2010; Temprado, Monno, Zanone, & Kelso, 2002; Wu, Kansaku, & Hallett, 2004). In this stage, motor performance is initially poor and highly variable, however as the specific movements needed to successfully perform the task are established rapid improvements in motor performance are observed alongside decreases in movement and performance variability.

Within this initial phase, any improvements made during a practice session are consolidated while the task is not being practiced, allowing for improvements in a practice session to be carried over to future practice sessions. This eventually leads to growing stability in performance of the skill and a shift to the next stage, described below. However, if a secondary motor task is practiced immediately following practice of the primary motor task, consolidation is interrupted and subsequent performance of the primary motor task is negatively affected (Brashers-Krug, Shadmehr, & Bizzi, 1996). Later studies have shown that this window of initial consolidation where the learned motor skill is still subject to

interference closes after approximately 5 to 6 hours (Shadmehr & Brashers-Krug, 1997; Walker, Brakefield, Hobson, & Stickgold, 2003).

As performance of the skill becomes more consistent and the previously observed rapid improvements in performance begin to plateau, the individual enters the middle stage of motor learning. Over the course of the previous stage the most effective way of performing the required action has been established and so in this stage smaller changes to the movement sequence begin to be made over a much longer period of time.

Finally, after extended amounts of practice the skill becomes increasingly automatic, that is: it can be performed with very little cognitive input and other cognitive activities can be performed simultaneously without much interference (Eversheim & Bock, 2001; Passingham, 1996; Rémy et al., 2010; Temprado et al., 2002; Wu et al., 2004). This can be observed in individuals who have extensive practice in a particular motor domain: for example, Beilock, Bertenthal, McCoy, and Carr (2004) found that expert golfers did not experience a decline in performance on a putting task when asked to perform a secondary cognitive task, while novices did. However, at this stage it seems that unconscious control is inescapable, several studies have found that performance is negatively affected when skilled performers are asked to think about the movements they are performing (Beilock, Carr, MacMahon, & Starkes, 2002; Logan & Crump, 2009).

Motor learning paradigms

While examining the current research into motor learning processes and their underlying neurobiology it should be noted that there are two main paradigms used to investigate motor skill learning (Bo & Lee, 2013): The first is motor adaptation, in which participants are required to adapt to disruptions applied while performing a non-novel movement, usually reaching. These disruptions can either be kinematic (i.e. sensory feedback is distorted) or dynamic (i.e. a force field is applied during the movement) in nature. As the name suggests these disruptions force the individual to adapt their movement to

compensate; these compensatory adaptations are eventually incorporated into the original movement as evidenced by the gradual improvement in performance after the disruption is applied and the poorer performance in the original movement once the distortion is removed.

The second of these paradigms is motor sequence learning, in which participants learn a novel action by combining isolated movements to eventually produce a smooth, coherent action after sufficient practice, for example the Serial Reaction Time Task (SRTT; Nissen & Bullemer, 1987). As Hardwick et al. (2013, p. 283) point out, while these are both useful paradigms for examining motor learning and its neural substrates they have different demands: the sensorimotor paradigms have "…greater motor demands and emphasize the learning of novel movement kinematics and dynamics…" while sequential learning tasks, such as the SRTT, have "…relatively minimal motor demands and focus on learning sequential motor behaviour."

Neurobiological models of motor learning

The advent of modern neuroscientific techniques has allowed researchers to examine the neural changes accompanying motor learning. Consequently, it has been established that there are shifts in the areas active at different stages of motor learning that roughly correspond to the aforementioned phases (Floyer-Lea & Matthews, 2005; Halsband & Lange, 2006; Penhune & Steele, 2012). The main brain areas that appear to play a role in motor learning are the primary motor cortex (or M1), the pre-motor cortex, the supplementary motor cortex, the basal ganglia (or striatum), and the cerebellum (Hardwick et al., 2013). Furthermore, there are some areas, such as the parietal and temporal lobes, that are proposed to be involved (Shadmehr & Krakauer, 2008) but there is still uncertainty about whether these areas are a key part of the system or whether they play a more peripheral role.

The evidence gathered thus far has led to models that suggest how these areas interact over the course of motor learning. Doyon et al. (2009) and Penhune and Steele (2012) have each proposed recent models to interpret the current evidence for the differing involvement of distinct neural areas at different stages of motor learning.

The model proposed by Doyon and colleagues suggests that the systems involved in motor sequence learning and motor adaptation differ slightly. Initially both types of learning start off by recruiting areas traditionally associated with motor control and learning, such as the striatum, cerebellum and motor cortical regions. In addition, the prefrontal cortex, parietal cortex and the hippocampus are involved. These structures are involved until the skill has been completely consolidated and can be performed automatically, and then the areas required start to diverge depending on the type of skill being learned. Doyon and colleagues suggest that after extended practice of a novel motor sequence the cerebellum is no longer needed for execution and retention of the skill and so the sequence becomes represented by long-term changes in the cortico-striatal circuit. In contrast, after extended practice of a motor adaptation task the learning is represented by changes in the cortico-cerebellar circuit, and involvement of the striatum is no longer required.

The model proposed by Penhune and Steele focusses specifically on motor sequence learning, and like Doyon and colleagues puts the cerebellum, the striatum and the primary motor cortices at the heart of the model. However, unlike Doyon and colleagues, Penhune and Steele propose that all three structures are continually involved in the process of motor learning, each with their own roles to play. Initially the primary motor cortices and the cerebellum are the primary sites of activity, with the cerebellum providing error correction and M1 providing short term representation of the movement. As practice of the task continues the striatum becomes more involved, contributing to the learning of action sequences and chunking these sequences. The involvement of M1 and the

cerebellum continue alongside the striatum into late stage learning, but their roles shift to long-term movement representation and internal model representation respectively.

The role of the primary motor cortex in the early stages of motor learning

As the primary motor cortex (M1) is the area of the cortex that controls voluntary movement of skeletal muscles, via the descending lateral corticospinal tract, it is unsurprising that there is evidence for its involvement in learning of a new movement. The body is topographically represented on the surface of M1, that is: each muscle is controlled by a specific area on the cortex, as demonstrated by the work of Penfield and Boldrey (1937) who also demonstrated that the somatosensory cortex is similarly organised. These representations are made up of interconnected groups of neurons that have similar inputs and outputs (Keller, 1993) and it is coordinated activation of these groups that produces more complex movements such as reaching (Graziano, 2006). Further, there is evidence that practice of a skill that requires simultaneous coordination of several muscles increases the overlap in the cortical representations of the muscles involved (Tyč & Boyadjian, 2011; Tyč, Boyadjian, & Devanne, 2005).

However, both of the previously described models suggest that the role of M1 in motor learning goes beyond simply generating a final output for movement. The plastic nature of the changes to representation in M1 shows that the area adaptively changes with use and this plasticity may be one of the key biological aspects underpinning the initial stage of motor learning.

Animal research

Animal research has provided strong causal evidence for the involvement of the motor cortex in the initial stages of motor learning. Luft and colleagues were able to block rats' ability to successfully learn a novel reaching task by injecting a protein synthesis inhibitor

into the primary motor cortex (Luft, Buitrago, Ringer, Dichgans, & Schulz, 2004). Injections to the parietal and cerebellar areas produced no effect on learning, suggesting the specific importance of M1. Additionally, they demonstrated that motor learning was only disrupted by protein synthesis inhibition in M1 during the first days of practice and once performance on the task had plateaued (suggesting a transition from the initial stage of learning) injection of protein synthesis inhibitors had no impact on task performance. Wächter et al. (2010) found a similar effect when a protein synthesis inhibitor was injected into the rat's dorsal striatum, suggesting that this area plays a role as well. However, the after-effects of inhibiting protein synthesis in the motor cortex were longer lasting than inhibition in the dorsal striatum; performance was still poorer several days after protein synthesis returned to normal in the motor cortex, whereas performance rapidly improved once protein synthesis in the dorsal striatum resumed.

Kleim et al. (2003) provide a clue as to why disruption of protein synthesis in the motor cortex may have a longer-lasting impact on motor learning. They found that inhibition of protein synthesis produced negative, long-lasting effects on the motor representations of the rats' forelimbs. The representations were significantly smaller both 20 minutes after the initial injection (when inhibition was still active) and four days later (by which time inhibition had stopped); this suggests that ongoing protein synthesis is required to maintain these maps. As well as maintaining already existing motor maps, protein synthesis is also vital for formation of new synapses in the motor cortex, which in turn has been shown to occur during the learning of a novel skill (Greenough, Larson, & Withers, 1985; Kleim et al., 2002; Withers & Greenough, 1989) and is one of the proposed underlying processes behind reorganisation of cortical representations (Kleim et al., 2004).

Further studies in rats have shown that expansions in the motor cortical representations of the forelimb are directly related to changing performance in a reaching task (Molina-Luna, Hertler, Buitrago, & Luft, 2008). The key feature of this study is that performance on the

task was positively correlated with the expansion in the motor cortex, the larger the expansion the greater the improvement on the task. In addition, the expansions were rapid, highly specific to the forelimb area (no changes were observed in other areas, such as the hind-limb or jaw), and returned to baseline levels rapidly without affecting performance of the task once it was learned.

Other research has demonstrated that this process also occurs in primates: Nudo, Milliken, Jenkins, and Merzenich (1996) trained adult squirrel monkeys on motor tasks and found that improvement on these motor tasks was associated with expansion of the representations of the limbs being used as part of the task. They also found that the expansions were very specific depending on the task being practiced: monkeys practicing a task that primary involved use of finger flexion and extension exhibited expansions in the digit representation areas accompanied by reductions in the wrist/forearm area. Conversely, practicing a task that primarily required forearm pronation and supination resulted in expansion of the forearm areas and contraction of the digit areas.

This plasticity of the motor cortex in primates seems to be specific to learning novel motor sequences rather than just repeating familiar movements. Plautz, Milliken, and Nudo (2000) found that the representation for the digits did not expand when the monkeys were presented with a simpler task that only required use of pre-existing motor sequences to complete.

These animal studies clearly demonstrate that the primary motor cortex plays a crucial role during early motor learning in mammals. This begs the question of whether these results can be generalised to humans.

Human research

Currently there is growing evidence that the findings in rats and monkeys are also applicable to human motor learning. In one of the first studies looking at this subject Pascual-Leone et al. (1995) showed that repeated practice of a fine motor skill over the

course of 5 days resulted in specific expansions to the area of the hand representation on the primary motor cortex contralateral to the hand used for practice. This expansion was also accompanied by an increase in the excitability of the specific area being used (i.e. the hand area, but not the leg area), which has also been demonstrated by Ridding and Rothwell (1997). As with the aforementioned primate research, Pascual-Leone and colleagues only found a significant expansion in the representations for the task that required learning, a control condition that consisted of non-directed motor activity showed only limited changes to the hand representations. Similar practice related changes in representation area and excitability have also been demonstrated for the tongue (Svensson, Romaniello, Arendt-Nielsen, & Sessle, 2003; Svensson, Romaniello, Wang, Arendt-Nielsen, & Sessle, 2006) and the leg (Perez, Lungholt, Nyborg, & Nielsen, 2004). These changes in excitability and plasticity have been localized specifically to the primary motor cortex, rather than occurring through changes in other elements of the human motor system such as the muscles or peripheral nerves (Koeneke, Lutz, Herwig, Ziemann, & Jäncke, 2006; Muellbacher, Ziemann, Boroojerdi, Cohen, & Hallett, 2001).

While all of the studies examining the plasticity of M1 mentioned thus far have been conducted over a number of days, Classen and colleagues have demonstrated that transient changes to motor cortical representations can be rapidly induced. They used transcranial magnetic stimulation (TMS) to identify a site on the motor cortex that produced a thumb movement in a specific direction; they then asked participants to practice moving their thumb in the opposite direction for thirty minutes. Stimulating the original site post-practice produced a movement in the practiced direction rather than the original direction, although without practice the movement began to revert back to the original direction after fifteen to twenty minutes (Classen, Liepert, Wise, Hallett, & Cohen, 1998).

One of the key problems with using the aforementioned type of brain stimulation techniques to examine the early stages of motor learning is that generally they only enable the experimenter to look at changes in motor cortical excitability and plasticity at specific time points, for example: between each practice session.

Consequently, such techniques cannot be used to probe the evolution of the primary motor cortex during practice sessions. This is where neuroimaging studies can be used to fill in the gaps, and many have demonstrated the changes in the functional activity of M1 over the course of motor practice (e.g. Albouy et al., 2012; Floyer-Lea & Matthews, 2004; Hazeltine, Grafton, & Ivry, 1997; Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994; Karni et al., 1995; Lacourse, Orr, Cramer, & Cohen, 2005; Landau & D'Esposito, 2006; Steele & Penhune, 2010; Ungerleider, Doyon, & Karni, 2002). As with the previously discussed studies examining changing motor cortical maps during learning, neuroimaging studies of brain activity during motor learning also tend to show a gradual increase in activation of the contralateral M1 during the early stages of motor learning (Hazeltine et al., 1997; Karni et al., 1995; Lohse, Wadden, Boyd, & Hodges, 2014). This gradual increase in activity supports the suggestion that M1 is involved in the early stages of motor learning beyond simply producing the final motor output. However, it should be noted that there are studies that run contrary to this suggestion, reporting a lack of measurable changes in activity (Jenkins et al., 1994) or even decreases in activity (Toni, Schluter, Josephs, Friston, & Passingham, 1999) in motor cortical areas during motor learning.

While studies using fMRI or PET scans to look at evolving wide scale activity in the brain are useful it should be remembered that they provide an indirect measure of neural activity, usually through haemodynamic response. For a more direct measure we have to turn to techniques such as Electroencephalography (EEG) and Magnetoencephalography (MEG), which are able to record the electric and magnetic field directly produced by large scale neural activity. Early work looking at cortical activity during motor learning focussed on a

sub-component of the movement related cortical potentials (MRCP): the Bereitschaftspotential (BP; Shibasaki & Hallett, 2006) or readiness potential (RP). This component is characterised as a negative shift in the electrical activity of the brain that is observed before voluntary movement occurs and is primarily recorded from electrodes placed on the scalp above the primary motor areas. Taylor (1978) examined the BP during execution of a six button sequence learning task and found a steady increase in the size of the BP recorded over the hemisphere contralateral to the responding hand. However, it is not possible to ascertain whether this shift was directly related to learning, repeated motor activity, or changes in the characteristics of the responses (i.e. speed, force, etc) as no control conditions were used. Niemann, Winker, Gerling, Landwehrmeyer, and Jung (1991) found the opposite: a significant reduction in cortical potential size from electrodes over the contralateral motor areas during the course of a motor learning task as compared to a control group who only repeated a simple motor task. It should be noted that this study looked at the entirety of the cortical potential produced, rather than just the BP, and the authors do not report any specifics about changes to the BP, so it is possible there were increases in the BP in line with Taylor's finding, but it is unlikely. Changes to the observed cortical potential are not consistently associated with concomitant changes in behaviour. For example Lang, Beisteiner, Lindinger, and Deecke, (1992) also found a decline in cortical potentials from electrodes placed over the contralateral motor area; however they found no significant change in performance over the course of practice.

More recent electrophysiological studies investigating motor learning have moved away from looking directly at cortical potentials and towards looking at event related synchronisation (ERS) and desynchronisation (ERD) of cortical oscillations. During inactivity there is strong synchronisation in the alpha (8-12 Hz) and beta (18-26 Hz) frequency bands, and just prior to the onset of motor activity the power of these frequency bands begin to decrease (Neuper, Wörtz, & Pfurtscheller, 2006). Research into Brain-Computer interfaces

(BCI) uses the synchronisation and desynchronisation of these frequency bands as a reliable way of detecting motor activity/imagery. A recent study conducted by Pichiorri et al. (2011) investigated how use of a BCI could affect brain plasticity and whether there were any changes in associated neural activity. They found that training to control a cursor on screen using motor imagery was able to alter the properties of the associated motor cortical representations (i.e. area, responsiveness, etc.) similar to the work conducted by Pascual-Leone et al. (1995). In addition the training was able to produce changes in the configuration of the functional network, as identified by decreases in connectivity measures in beta frequency range. Shifts in the beta frequency have been directly tied to changes in performance in a motor sequence learning study by Pollok, Latz, Krause, Butz, and Schnitzler (2014). They found a significant negative correlation between changes in reaction times during a motor sequence learning task and the degree of beta frequency desynchronisation, indicating that greater improvement in performance is associated with greater beta ERD. However, the association between increasing beta ERD and performance improvements over the course of motor practice in not clear cut. Kranczioch, Athanassiou, Shen, Gao, and Sterr (2008) reported that improvements in performance were associated with an increase in alpha ERD. It should be noted that this discrepancy could be due to the use of a different type of motor behaviour (i.e. a 'power-grip tracking task') to look at motor learning. As mentioned previously, differing activity in M1 may represent changes in the properties of the actual movement being performed (i.e. force, timing, speed, etc), rather than a learning component. However, these changes would have to be relatively systematic to be erroneously identified as changes associated with learning.

All of the hitherto outlined human research has provided strong indications that changes in the primary motor cortex occur during the initial stages of motor learning, but evidence suggesting an explicit link to improvements in performance is mixed at best. Fortunately, non-invasive brain stimulation can be used to make this link and has provided evidence

that, like in other animals, the primary motor cortex plays a crucial causal role in the early stages of motor learning in humans. Muellbacher et al., (2002) found that application of low-frequency repetitive transcranial magnetic stimulation (rTMS) to the motor cortex immediately after practice of a unimanual motor task significantly reduced any improvements made during the practice stages. Application of rTMS to the occipital or dorso-lateral pre-frontal cortex had no impact on task performance, and application to the motor cortex after six hours (once the aforementioned window of consolidation had closed) also had no effect on subsequent performance. They also demonstrated that low frequency rTMS significantly reduced the excitability of the primary motor cortex (as determined by assessing the motor threshold) when it was applied, but only had a behavioural impact immediately after practice had finished. Conversely, several studies have demonstrated that by enhancing the excitability of the primary motor cortex using transcranial direct current stimulation (tDCS) motor skill learning can be facilitated (Boggio et al., 2006; Nitsche et al., 2003; Reis et al., 2009).

There is also evidence that the initial excitability of the motor cortex will affect the ability to learn a novel task; Iezzi et al. (2010) found that applying continuous theta-burst stimulation (cTBS) to reduce the excitability of M1 prior to performance of a motor task significantly impaired performance on that task. This impairment manifested more as a delay rather than a complete abolition of motor learning; those in the sham stimulation condition showed a rapid improvement and were able to perform significantly better than those in the active stimulation group; however, this gap in performance was eventually closed. Similarly, Wilkinson, Teo, Obeso, Rothwell, and Jahanshahi (2010) found that inhibition of M1 using cTBS significantly impaired learning of a probabilistic serial reaction time task, whereas cTBS over other areas (specifically the dorsolateral pre-frontal cortex and supplementary motor area) had no effect on learning.

There is, however, evidence that runs contrary to these findings, where lowering the excitability of the motor cortex prior to practicing a novel motor task does not have a negative impact on performance of the task itself, but does impair the subsequent consolidation of the practice (Baraduc, Lang, Rothwell, & Wolpert, 2004; Richardson et al., 2006; Riek, Hinder, & Carson, 2012). It should be noted however that these conflicting studies employ the aforementioned motor adaptation paradigm (rather than procedural motor learning tasks) to investigate motor learning. As mentioned earlier, different neural mechanisms are proposed to underpin these different learning paradigms (Doyon et al., 2009; Hikosaka, Nakamura, Sakai, & Nakahara, 2002) and the conflicting findings may be a reflection of this.

Taken together these results suggest a clear role for the primary motor cortex in the initial stages of motor learning, and the prominent inclusion of M1 in the aforementioned described models of motor learning further support this hypothesis.

Biological mechanisms underlying use dependant plasticity in M1

Given that the primary motor cortex plays a key role during motor learning, and in particular during the early stages of motor learning, what is known about the underlying neurological mechanisms for this learning?

As has been previously discussed, it has been proposed that changes in cortical representations driven by use underlie the role of M1 in motor learning (Sanes & Donoghue, 2000). There is strong evidence from both animal studies (Rioult-Pedotti, Friedman, & Donoghue, 2000; Rioult-Pedotti, Friedman, Hess, & Donoghue, 1998) and research in humans (Ziemann, Ilić, Pauli, Meintzschel, & Ruge, 2004) that this plasticity is driven by long term potentiation (LTP)-like mechanisms, whereby synaptic connections are strengthened through repeated activation. This strengthening of connections primarily occurs horizontally between layers II/III of the motor cortex (Hess & Donoghue, 1994). It should be noted that in these studies plasticity has not been measured directly but is

inferred from LTP occlusion, which is a reduction in the ability of an electrical or magnetic stimulus to induce LTP-like plasticity in the area being stimulated, usually quantified by a reduction in the change in the amplitude of an evoked potential.

It is not fully clear which neurotransmitters may be involved in this LTP-like plasticity but there is research implicating numerous candidates, including: dopamine (Flöel et al., 2005; Korchounov & Ziemann, 2011), Acetylcholine (Ach; Conner, Culberson, & Packowski, 2003; Korchounov & Ziemann, 2011), and Norepinephrine (Korchounov & Ziemann, 2011). Gamma-Aminobutyric acid (GABA) is also thought to be involved in the formation and regulation of motor cortical maps, primarily via inhibitory processes (Jacobs & Donoghue, 1991). This seems to be specific to motor learning as the mean GABA concentration in the primary motor cortex drops during the initial stages of motor learning but not during repetitive movement without a learning aspect (Floyer-Lea, Wylezinska, Kincses, & Matthews, 2006).

Adkins et al. (2006) suggest that the three key processes occurring in the primary motor cortex during motor learning are: Protein synthesis, Synaptogenesis, and Map reorganisation. As previously mentioned, there is strong evidence from animal studies that ongoing protein synthesis is required for motor-cortical plasticity and thus motor learning (Luft et al., 2004), particularly in the initial stages. However it remains to be seen which proteins are key to this plasticity. There is some suggestion that Brain-derived neurotrophic factor (BDNF) has the potential to be one of the proteins that are key to maintaining motor map plasticity, and neural plasticity in general (Kleim et al., 2003). This idea is supported by evidence that there is a single nucleotide polymorphism within the gene for BDNF (val66met) that results in reduced BDNF release (Egan et al., 2003). There is evidence that this reduced expression has a detrimental effect on motor cortical plasticity (Cirillo, Hughes, Ridding, Thomas, & Semmler, 2012; Kleim et al., 2006) and motor learning (McHughen et al., 2010). These results also correspond to the work by Missitzi and

colleagues who have found a strong genetic contribution (approx. 68-70% of hereditability) to motor cortical excitability (Missitzi et al., 2010) and motor learning (Missitzi et al., 2013). However, there is also research showing that there is no correlation between the val66met polymorphism, motor cortical plasticity, and motor learning (Li Voti et al., 2011). Again, the discrepancy between these studies may be due to different paradigms being used to assess motor learning.

Despite this indication that there is a strong genetic component to motor learning and motor cortical excitability, according to the studies conducted by Missitzi and colleagues, there is approximately 30% of variability that must be accounted for by environmental factors. One potential factor may be regular motor activity: Rosenkranz, Williamon, and Rothwell (2007) found enhanced motor cortical excitability and plasticity in musicians when compared to non-musicians, while Cirillo, Lavender, Ridding, and Semmler (2009) found that individuals who engage in regular physical activity also have higher cortical excitability than more sedentary individuals. These findings should be considered carefully however, as it is not clear whether there is a causal link between these factors, or indeed what the direction of causality may be: it may simply be that those with a higher degree of motor cortical plasticity are more likely to engage in physical activity. Other environmental factors that seem to negatively affect motor cortical plasticity include premature birth (Pitcher et al., 2012) and old-age (Rogasch, Dartnall, Cirillo, Nordstrom, & Semmler, 2009).

Individual variability in motor learning

Alongside these individual differences in the plasticity of the primary motor cortex it has long been acknowledged that there is variability between individuals in terms of their motor performance and learning ability (Ackerman & Cianciolo, 2000; Frensch & Miner, 1994). Indeed, Ackerman has proposed that different cognitive factors play a role at the different stages of motor learning. Inter-individual variability in the initial stage is primarily influenced by differences in general ability (i.e. information processing skills); the middle

stage is more influenced by variability in perceptual-speed ability; while the late, more automatic stage is primarily affected by differences in psychomotor ability. (For a more comprehensive overview of the research into this area see Boyle & Ackerman, 2004 or Schmidt & Lee, 2005.)

While it is recognised that this inter-individual variability in motor learning exists there is little research that has directly examined the relationship between individual differences in motor cortical plasticity and motor learning. There have, however, been a few studies that suggest there may be a connection between the two.

Hluštík et al. (2004) had participants practice a simple motor sequence learning task daily for three weeks and scanned the participants using fMRI on a weekly basis. They found that there was a positive correlation between the performance on the task during a particular session and the degree of M1 activation during the same session. Indicating that during learning there may be increasing recruitment of M1 which contributes to performance improvements. However, this result only gives a partial indication of a relationship between individual changes in motor cortical activity and motor learning as it was obtained from pooling all the data for participants over a three-week training task. Hluštík and colleagues did not report looking at within-subject changes of performance on the motor task and activation in M1, and whether the degree of improvement in motor performance was correlated to the degree of activation in M1.

Tomassini et al. (2011) used MRI to look for the structural (grey and white matter density) and functional (BOLD response) changes associated with individual differences across the whole brain. Alongside a multitude of other areas, including the left pre-supplementary motor area and sensorimotor cortex, they found that functional activity in the left primary motor cortex positively correlated to the change in motor performance over the course of the task, while the key structural areas associated with individual learning scores were primarily located bilaterally in the cerebellum. While this study does suggest that M1 is

indeed a key area in the early stages of motor learning and, as previously indicated, that there is a relationship between the degree of learning that occurs and the changes in M1 activation, it only provides correlational evidence of this relationship. Additionally, given the wide range of other regions where activity correlates with performance in this study it is difficult to interpret the result.

As previously mentioned there is evidence suggesting that GABA plays a key role during motor learning (Floyer-Lea et al., 2006), and more recent work has indicated that the responsiveness od an individual's GABA system correlates with differences in their early motor learning (Stagg, Bachtiar, & Johansen-Berg, 2011). Stagg and colleagues used anodal tDCS to test the responsiveness of the GABA system in their participants, using magnetic resonance spectroscopy (MRS) to quantify changes in GABA concentration before and after stimulation. Subsequently the same participants practiced the SRTT while in an fMRI scanner. They found that the degree of responsiveness of the GABA system was positively correlated with changes in reaction times (i.e. greater reductions in GABA concentrations were associated with greater improvement in the motor task) and negatively correlated with changes in M1 activation during the task (i.e. greater reductions in GABA were associated with increases in M1 activity).

The most notable of these studies is the aforementioned work undertaken by Missitzi and colleagues (Missitzi et al., 2010, 2013) who have used twin studies to look at genetic contributions towards motor control, learning and motor cortical plasticity. Their initial study (Missitzi et al., 2010) compared the cortical plasticity and excitability of dizygotic and monozygotic twins, which suggested that the hereditability of motor cortical plasticity is around 68%. They later expanded on this study by looking at motor control and learning (again using monozygotic and dizygotic twins), finding that the hereditability for these were 68% and 70% respectively (Missitzi et al., 2013). They also looked at the correlation between the changes in plasticity (from the earlier study) and the learning related

performance changes, finding a significant, albeit weak, correlation. Although weak, thus far this is the strongest evidence for a direct link between motor learning and motor cortical plasticity.

At this stage it is worth emphasising that despite the key role the primary motor cortex plays in motor learning, particularly during the early stages, all of the current models of motor learning (Doyon et al., 2009; Hikosaka et al., 2002; Penhune & Steele, 2012) consider the motor cortex to be part of a diffuse network that at the very least includes the basal ganglia and the cerebellum. Additionally, the research conducted by Tomassini et al. (2011) clearly suggests that other parts of the system also contribute to inter-individual variability in motor learning.

When taken together all of the research discussed thus far suggests that changes in motor-cortical representations are a crucial component of early motor learning. As an individual commences learning a novel motor skill, numerous molecular and cellular mechanisms begin to modify these representations, resulting in measurable changes in area and excitability. Then, once changes in performance plateau the task can be considered to have been successfully encoded, and the motor cortical representations return to their original state. At this stage any interference to the representation, either through practice of another task or alteration of the motor cortex, has little to no impact on performance of the newly acquired skill. Thus, individual variability in the degree of motor cortical plasticity may play a role in the speed at which a novel motor task may be acquired.

Developmental coordination disorder (DCD)

History of the disorder

Within the general population there are a certain proportion of individuals who suffer from motor difficulties that emerge in childhood, significantly interfere with their daily life, and

have no obvious neurological or medical cause (for example: cerebral palsy, muscular dystrophy, apraxia, etc.). Historically many different terms have been used to describe this grouping of symptoms including: 'clumsiness' (Gubbay, 1975; Henderson & Hall, 1982; Losse et al., 1991), 'developmental coordination disorder' (DCD; American Psychiatric Association, 2013; Polatajko, Fox, & Missiuna, 1995), 'developmental dyspraxia' (Cermak, 1985; Denckla, 1984; Dewey, 1995), 'disorder of attention and motor perception' (DAMP; Gillberg, 2003), 'specific developmental disorder of motor function' (SDDMF; World Health Organization, 1992), and 'perceptuo-motor dysfunction' (Laszlo, Bairstow, Bartrip, & Rolfe, 1988b).

Of these terms, the current thesis used developmental co-ordination disorder (DCD) to describe developmental problems of motor learning. This particular term was chosen for several reasons. Firstly, it is a recognised diagnostic term in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013) and thus has a specific set of diagnostic criteria, outlined below, that can be used to identify DCD. Secondly, this is the term primarily used within the research literature since the London consensus (Polatajko et al., 1995), with a recent review demonstrating that 52% of papers describing these problems using the term DCD (Magalhães, Missiuna, & Wong, 2006).

Diagnostic criteria

The DSM-5 (American Psychiatric Association, 2013) defines the diagnosis of DCD as incorporating a spectrum of motor related difficulties, resulting in a decreased ability to learn and perform coordinated motor skills. The specific diagnostic criteria in the DSM-5 are outlined in Table 1.1 below.

The first of these criteria identify the core feature of the disorder described previously: impairments in motor coordination. The second criterion extends this by adding that, like most clinical disorders, the symptomology of the disorder must interfere significantly with activities of daily living, thus having a negative effect on an individual's daily life. The third

criterion seeks to define DCD as a neurodevelopmental disorder by determining that the problems have been present since childhood. The final criterion is included to rule out other possible causes for the motor disturbances experienced by the individual.

Table 1 - Diagnostic criteria for DCD (American Psychiatric Association, 2013)

A	Acquisition and execution of coordinated motor skills are below what would be expected at a given chronologic age and opportunity for skill learning and use; difficulties are manifested as clumsiness (e.g. dropping or bumping into objects) and as slowness and inaccuracy of performance of motor skills (e.g. catching an object, using scissors, handwriting, riding a bike, or participating in sports)
B	The motor skills deficit significantly or persistently interferes with activities of daily living appropriate to the chronologic age (e.g. self-care and self-maintenance) and impacts academic/school productivity, prevocational and vocational activities, leisure, and play
C	The onset of symptoms is in the early developmental period
D	The motor skills deficits cannot be better explained by intellectual disability or visual impairment and are not attributable to a neurologic condition affecting movement (e.g. cerebral palsy, muscular dystrophy, or a degenerative disorder)

Prevalence of DCD

Numerous studies have attempted to calculate the prevalence of DCD and have produced estimates ranging from 1% to 19% (Ganapathy Sankar & Saritha, 2011; Gibbs, Appleton, & Appleton, 2007; Kadesjö & Gillberg, 1999; Lingam, Hunt, Golding, Jongmans, & Emond, 2009; Maeland, 1992; Tsiotra et al., 2006; Wright & Sugden, 1996). Estimating prevalence depends on numerous factors, including: the sample size, the sampling method, the specific diagnostic criteria, and the tools used to quantify these criteria. Because these

factors vary widely between the aforementioned studies, the prevalence rates calculated also vary widely.

The DSM-5 suggests that approximately 5-6% of children are affected by DCD (American Psychiatric Association, 2013). This estimate is supported by a study conducted by Lingam, Hunt, Golding, Jongmans, and Emond (2009), who found that 4.9% of their sample could be considered to have DCD (i.e. meeting the full DSM criteria) or probable DCD (i.e. demonstrating significant impairments in motor ability). This study is generally considered the most reliable estimate of the prevalence of DCD as they tested a large sample size (>6500 children) recruited from the general population using the full DSM diagnostic criteria. Furthermore, DCD is generally considered to be consistently prevalent across a wide range of differing races and socioeconomic backgrounds (Blank, Smits-Engelsman, Polatajko, & Wilson, 2012); although, it should be noted that the majority of research into DCD thus far has been conducted in western societies and so the extent to which this is true remains to be seen.

Currently it is unclear whether there is a gender bias within DCD; like many other neurodevelopmental disorders it has generally been thought that there is a higher prevalence of the disorder among males. This view is supported by several studies reporting that the prevalence among males is at least twice as high than the prevalence among females (Gibbs et al., 2007; Lingam et al., 2009; Maeland, 1992). However, there is other evidence that suggests that the gender distribution is a much closer to 1:1 (Cairney, Hay, Veldhuizen, Missiuna, & Faught, 2010; Foulder-Hughes & Cooke, 2003; Skinner & Piek, 2001).

In an attempt to explain this discrepancy Cairney (2015) suggests it may arise due to the sampling methods used in the aforementioned studies; the studies that suggest a male bias in DCD have generally taken samples taken from clinical referrals (with Lingam et al., 2009 being the notable exception), while those suggesting that there is a more even split

between genders have used samples taken from the general population. He suggests that one explanation for this discrepancy may be due to the co-morbidity between DCD and attention deficit/hyperactivity disorder (ADHD; which will be discussed later on in the chapter). It is fairly well established that males with ADHD are more likely to receive a clinical referral (Biederman et al., 2002; Rucklidge, 2010), and this may lead them to also having their DCD symptoms identified. However further research is required to examine these suggestions.

Primary symptoms of DCD and their effects on activities of daily living

As will be discussed later, the specific presentation of DCD varies from individual to individual, but problems have been observed across the main motor domains. These problems include: difficulties using appropriate grip force (Hill & Wing, 1999), poorer manual dexterity and hand eye coordination (Rodger et al., 2003), atypical walking gait (Deconinck et al., 2006; Woodruff, Bothwell-Myers, Tingley, & Albert, 2002), poorer throwing and catching (Astill & Utley, 2008; Utley & Astill, 2007), a greater reliance on vision for standing balance on one or two legs (Chung & Stoffregen, 2011; Forseth & Sigmundsson, 2003; Wann, Mon-Williams, & Rushton, 1998), more lateral sway (Williams, Fisher, & Tritschler, 1983), poorer body position awareness (Smyth, 1992), atypical muscle activation in both standing balance and in response to perturbations amongst others (Johnston, Burns, Brauer, & Richardson, 2002; Jover, Schmitz, Centelles, Chabrol, & Assaiante, 2010).

The above descriptions may make it appear like these problems are only detectable under lab conditions and have little impact upon the real-world actions, but there are numerous studies that demonstrate that the motor problems listed above have a negative impact on activities of daily living resulting in, for example, poorer handwriting (Henderson & Henderson, 2003; Rodger et al., 2003) and difficulties in self-care (such as dressing, personal hygiene, and eating; Mandich, Polatajko, & Rodger, 2003; Summers, Larkin, &

Dewey, 2008). Indeed, as mentioned previously, difficulties in activities of daily living are part of the DSM-5 diagnostic criteria. As will be discussed later, these problems experienced in activities of daily living may then have a knock on effect, with negative academic, social and psychological impacts.

Subgroups

While there are commonalties in the symptoms observed in individuals with DCD, the disorder does not present as a homogeneous set of symptoms. Consequently there has been the suggestion that there may be distinct clinical subgroups within DCD in which some aspects of motor coordination are poorer while other remain relatively unaffected (Visser, 2003).

Three studies aiming to identify potential subgroups using cluster analysis were published in 1994 (Dewey & Kaplan, 1994; Hoare, 1994; Miyahara, 1994), however each used slightly different tasks to assess motor ability and consequently found different numbers of subgroups with different motor profiles. For example, Dewey and Kaplan (1994) found that performance on their task resulted in 4 groups: Those with motor sequencing deficits; those with deficits in balance, coordination and transitive gestures; those with deficits on all areas; and those with no specific deficits. The study conducted by Miyahara (1994) also found that their participants could also be divided into four subtypes although the performance profiles of the clusters they found did not map onto those found by Dewey and Kaplan (1994). In contrast, Hoare (1994) found that the children in their study could be divided into 5 clusters based on the performance in their motor battery.

Numerous other attempts at identifying specific subtypes of DCD have been made since these initial studies (Green, Chambers, & Sugden, 2008; Lalanne, Falissard, Golse, & Vaivre-Douret, 2012; Macnab, Miller, & Polatajko, 2001; Vaivre-Douret et al., 2011; Vaivre-Douret, Lalanne, & Golse, 2016; Wright & Sugden, 1996) and while there have been some commonalities in their findings (for example, many find a cluster of participants who have

deficits in all motor domains) generally there is little overlap in the number and characteristics of the identified subgroups.

The fact that few of these studies agree is unsurprising given that they have included different domains in the analysis and have used different methods to quantify performance in each of these domains. This point is illustrated well by Macnab et al. (2001) who used measures of motor ability that were either the same or assessed similar domains as the measures used by Hoare (1994); the cluster analysis produced the same number of clusters with very similar motor profiles, demonstrating that when the same or similar measure are used results can be replicated. Obviously it is debatable which of the measures used in these studies, if any, tap into a given domain best and thus produce the most accurate clusters of subgroup within the disorder. However, ascertaining whether subtypes do exist within DCD and, if so, how they are characterised and what measures can be used to distinguish them is an important endeavour as it will have an impact on the research conducted into the disorder, as different subtypes may have different aetiologies, and potential interventions, as these can be specifically targeted to the needs of the individual.

Comorbidities

An additional complication in examining and quantifying the profile of DCD lies in the observation that there is an above expected prevalence of motor problems alongside other neurodevelopmental disorders. Indeed, a number of studies have estimated this co-occurrence is approximately 40% (Lingam et al., 2010; Pieters et al., 2012). Not all incidences of motor impairments are or can be specifically diagnosed as DCD; however a number of studies look directly at the prevalence of DCD or DCD-like symptomologies in other neurodevelopmental disorders.

The most commonly identified of these co-morbid neurodevelopmental disorders is Attention Deficit/Hyperactivity Disorder (ADHD), with a number of studies showing that between 35-50% of children who fulfil the diagnostic criteria for DCD also demonstrate

high levels of ADHD symptomology or vice-versa (Dewey, Kaplan, Crawford, & Wilson, 2002; Kaplan, Crawford, Cantell, Kooistra, & Dewey, 2006; Piek, Pitcher, & Hay, 1999). DCD-like symptomology also frequently co-occurs with Specific Language Impairment (SLI; Finlay & McPhillips, 2013; Flapper & Schoemaker, 2013; Hill, 1998), developmental reading disabilities (i.e. dyslexia; Fawcett, Nicolson, & Dean, 1996; Nicolson et al., 1999), and Autism Spectrum Disorders (ASD; Green et al., 2002, 2009)

The reasons for the high degree of overlap amongst neurodevelopmental disorders are still being debated, however four mechanisms for these comorbidities have been suggested (Kaplan et al., 2006). Firstly, they could be co-incidental with two distinct aetiologies; Secondly, they could be casually directly related, with one of the disorders leading to the other; Thirdly, they could be causally indirectly related, with both disorders being caused by an underlying aetiology; Finally, they could be cognitive sub-types, with each disorder being caused by unrelated aetiologies but with the co-occurrence being caused by a third aetiology. While there is currently not much evidence to support one of these mechanisms over the others, ascertaining why there is such a high degree of comorbidity between these developmental disorders is an important goal for research into atypical development particularly when attempting to uncover the potential causes of such problems. Especially as this understanding can then potentially be applied in the form of tailored interventions and support for each subgroup.

DCD beyond childhood

Up until relatively recently DCD has been considered a disorder of childhood with individuals 'growing out' of the disorder, with little to no impact in adolescence or adulthood (Fox & Lent, 1996; Sellers, 1995). This is especially evident when looking at research conducted into the disorder, the majority of which is focussed on children (Kirby, Sugden, Beveridge, & Edwards, 2008). However, there is evidence that while a proportion

of children diagnosed with the disorder do indeed 'grow out' of the disorder, there are also many that experience difficulties in adolescence and adulthood.

A longitudinal study conducted by Cantell, Smyth, and Ahonen (1994) tested a group of children using a battery of various different task (including motor tasks) and identified children that experienced significant motor problems. They retested all of the children with these problems after 10 years and found that just under half still had poorer motor skills than age-matched controls. They then followed this up by showing that these individuals still showed problems at the age of 17 and that performance at earlier time points predicted continued motor difficulties (Cantell, Smyth, & Ahonen, 2003). These results support similar findings from a number of other studies that the disorder can continue well into adolescence (Geuze & Borger, 1993; Losse et al., 1991).

Further evidence that motor difficulties also persist into adulthood is provided by Cousins and Smyth (2003) who found that a group of adults that had previously been diagnosed with DCD or who had reported difficulties consistent with DCD performed much poorer on a motor battery than a control group. This particular study is revealing as individuals from a wide age range (19-63 years) participated, demonstrating that the disorder can continue to have an impact well beyond early adulthood. However, there is little research into if and how DCD may change into adulthood; Purcell, Scott-Roberts, and Kirby (2015) have suggested that while motor problems still exist in adults with DCD they are not the primarily reported area of concern. However, this is a small scale study, with only 16 participants, and further research would be needed to examine how widely this applies to adults with DCD.

Part of the difficulty in conducting research into adulthood DCD is the lack of a standardised test to identify motor problems. A variety of approaches are used in an attempt to get around this problem including adapting tasks from the MABC2, self-report questionnaires, and childhood diagnoses of DCD (Hands, Licari, & Piek, 2015), however

none of these are appropriate on their own. This problem is addressed further and a potential solution is suggested in Chapter 3; however, a standardised test would be a major improvement, particularly when trying to make cross-study comparisons.

Secondary consequences of DCD

As well as the aforementioned primary motor problems there is a large body of research indicating that children diagnosed with DCD are more likely to experience a wide range of educational, psychological, social, and health issues. These issues are not considered to be core symptoms of DCD but are thought to be the indirect social and environmental consequences of motor problems (Cummins, Piek, & Dyck, 2005). While it is beyond the scope of the current thesis to give a complete review of all the identified secondary problems associated with DCD, a relatively brief summary will be given to demonstrate that the primary problems experienced in DCD can have consequences that extend well beyond the motor domain and have an impact throughout the lifespan.

In the educational domain DCD has a direct impact on hand-writing and general written communication, with between 70 and 90 percent of children with DCD displaying problems in these areas (Miller, Missiuna, Macnab, Malloy-Miller, & Polatajko, 2001). These difficulties in handwriting and written communication seem to have a knock on effect on more general educational attainment with other research demonstrating that perceptions of scholastic competence in children with DCD is lower than their peers (Watson & Knott, 2006). Children with motor impairments have poorer educational performance and outcomes (Rasmussen & Gillberg, 2000; Wocadlo & Rieger, 2008; although it should be noted that the children discussed in these studies did also present co-morbidities (e.g. ADHD) that may confound this finding). This impact on general achievement may then lead to negative consequences observed in other psychosocial domians.

For example, within the social domian: social isolation, decreased peer interaction, social immaturity, and reduced ability to establish peer relationships have all been observed in

children with DCD (Miyahara & Piek, 2006; Schoemaker & Kalverboer, 1994; Skinner & Piek, 2001; Smyth & Anderson, 2000)

Moreover, in the psychological domain there are a number of studies that have identified anxious and depressive symptoms in groups of children with DCD (Piek et al., 2007; Pratt & Hill, 2011; Sigurdsson, Van Os, & Fombonne, 2002), as well as low self-perception (Cantell et al., 1994) and emotional and behavioural difficulties (Green, Baird, & Sugden, 2006).

Finally, there is strong evidence that children with DCD have poorer perception of their own motor capabilities and thus tend to prefer a sedentary lifestyle (Wocadlo & Rieger, 2008), which can result in more general health problems such as increased risk of obesity (Cairney et al., 2005) and coronary vascular disease (Faught, Hay, Cairney, & Flouris, 2005).

As with the core symptoms of DCD the secondary issues often continue into adulthood, and there is evidence that adults with DCD report more symptoms of depression and anxiety than their peers, as well as reporting poorer quality of life satisfaction (Hill & Brown, 2013; Hill, Brown, & Sorgardt, 2011; Kirby, Williams, Thomas, & Hill, 2013). Additionally, there is some evidence that individuals with DCD are at greater risk of personality disorders, alcohol abuse, and criminal offending (Rasmussen & Gillberg, 2000); although, as mentioned previously, this specific study looked at individuals who also had co-morbid ADHD which is likely to also play a role in these outcomes. Interestingly, qualitative work by Fitzpatrick and Watkinson (2003) has provided a link between individual experiences of DCD in childhood and how the sufferer perceives those experiences when they reach adulthood.

Cognitive explanations of DCD

A number of different cognitive explanations have been proposed to explain the motor difficulties experienced by individuals with DCD, and these are broadly divided into two broad domains: deficits in motor programming and deficits in perception. This section will

briefly outline some of the current explanations and the supporting evidence behind these theories.

Given that DCD is primarily a disorder of motor coordination and control, it is reasonable to assume that underlying problems may be found in aspects of motor programming. Generally, within motor programming explanations of DCD there are three main hypotheses: Response selection problems, problems in force timing and control, and motor planning problems.

Response selection: A common observation in studies that require motor responses as part of their design is that individuals with DCD typically respond slower and their response times will be more variable than healthy control participants (Henderson, Rose, & Henderson, 1992; Kagerer et al., 2004; Lejeune et al., 2013). This observation has led to the suggestion that individuals with DCD may have problems with mapping the correct response for a particular stimulus (Henderson et al., 1992). A number of studies have used tasks which require increasingly more complex response patterns (Missiuna, 1994; Van Dellen & Geuze, 1988), and have reported that children with DCD show increased response selection times as the response complexity increases.

Difficulties in response selection have also been explored using pre-cuing paradigms, where information indicating which type of response will be required is given in the form of a cue before the appearance of a target. This type of task typically produces faster reaction times as it allows the appropriate response to be selected before a response is required. Van Dellen and Geuze (1990; 1988) reported that while children with DCD do benefit from the pre-cue (showing a similar decrease in response selection time as control children), they still display slower reaction and movement times.

Mon-Williams and colleagues have also used pre-cuing paradigms to look at response selection in children with DCD (Mon-Williams et al., 2005; Pettit et al., 2008). However,

they adapted the traditional pre-cuing paradigm to allow manipulation of the size of the response space, by using the cue to provide differing levels of information. Their findings show that constraining the response space by providing more information decreases the time taken to respond to the stimuli in both children with DCD and healthy controls. Nevertheless, the children with DCD responded slower and made significantly more error than controls for all levels of information provided.

Overall these results seem to indicate that while response selection in individuals with DCD is subject to the same effects as neurotypical individuals (e.g. pre-cueing), distinct deficits in stimulus response compatibility remain.

Motor planning: An alternative way of explaining the slower and more variable responses observed within DCD is through deficits in motor planning, and there are a number of sources that support this explanation. One way of examining motor planning is through the comparison of imagined sequences of movements with real movement sequences; for normal motor planning there is a strong correlation between the time needed to complete either of these (Decety, 1996). Maruff, Wilson, Trebilcock, and Currie (1999) examined if this held true in children with DCD, and found that not only did children with DCD take longer to perform the same sequences but they did not display the linear correlation between real and imagined movement time seen in the control children. These problems in motor imagery in individuals with DCD have also been demonstrated by a number of other studies in both children and adulthood (Fuelscher, Williams, Enticott, & Hyde, 2015; Hyde et al., 2014; Lewis, Vance, Maruff, Wilson, & Cairney, 2008; Noten, Wilson, Ruddock, & Steenbergen, 2014; Williams et al., 2011; Williams, Thomas, Maruff, & Wilson, 2008; Wilson, Maruff, Ives, & Currie, 2001).

An alternative way of looking at motor planning is through the use of end-state comfort paradigms. Briefly, end-state comfort describes the effect whereby during a multi-

sequence action an individual will select a less comfortable initial grip if that allows them to end the action in a comfortable position (Adams, Ferguson, Lust, Steenbergen, & Smits-Engelsman, 2016). Generally, planning for end-state comfort improves over the course of development (Jongbloed-Pereboom, Nijhuis-van der Sanden, Saraber-Schiphorst, Crajé, & Steenbergen, 2013; Stöckel, Hughes, & Schack, 2012), however there are a number of studies that indicate that children with DCD tend to favour initial comfort over end-state comfort (Adams et al., 2016; Fuelscher, Williams, Wilmut, Enticott, & Hyde, 2016; van Swieten et al., 2010; Wilmut & Byrne, 2014). Wilmut and Byrne also demonstrated that while adults with DCD can match typically developing adults on shorter sequences there is a rapid deterioration in performance as the length of the sequences increase.

Timing and Force Control: In order to perform accurate and skilful movements a precise level of timing and force control is required, and problems in either of these domains would in the poorer coordination observed in DCD. It is unsurprising then that there are numerous studies reporting difficulties in both timing and force control.

Williams, Woollacott, and Ivry (1992) examined timing control in children with DCD and healthy controls using a tapping continuation task, where participants had to tap along to a tone and continue tapping when the tone stopped. The children with DCD were more variable in maintaining a set rate of tapping and in accurately judging time intervals than the control participants. These difficulties in timing are well established in the DCD literature, with a number of other studies reporting similar findings (de Castelnau, Albaret, Chaix, & Zanone, 2007; Geuze & Kalverboer, 1987, 1994; Henderson et al., 1992; Hill & Wing, 1999).

When gripping a small object (e.g. cup or glass) and making a vertical movement (either upwards or downwards) there are microscopic adjustments of grip force towards the beginning and end of the movement. In upward movements, grip force briefly increases as

acceleration begins, while in downwards movement grip force increases during deceleration. Two case studies reported by Hill and Wing (1998, 1999) sought to investigate these microscopic adjustments of grip force in individuals with coordination difficulties. In both of these case studies they reported an earlier onset of the increase in grip force than in the typically developing control; in the first study it only occurred during the downward movements, while in the second it occurred during both upward and downward movements. Pereira, Landgren, Gillberg, and Forssberg (2001) reported similar findings in a larger group of participants with DCD, and a number of other studies have reported force control deficits on children with DCD (Oliveira, Shim, Loss, Petersen, & Clark, 2006; Smits-Engelsman, Westenberg, & Duysens, 2003, 2008).

However, it must be remembered that the motor system is inextricably linked with perceptual systems, and there has been the proposal that deficits in perceptual processing may underlie the problems observed in those with DCD. Three areas have been suggested: problems in visual perception, problems in kinaesthetic perception, and internal modelling deficits.

Visual perception: Difficulties in visual perception have been reported in the DCD literature since the 1980's and are not attributable to oculomotor or ophthalmic problems (Mon-Williams, Pascal, & Wann, 1994). Work by Charles Hulme and colleagues (1982; 1984; 1987b, 1988) provided the first evidence for problems in visual perception amongst children with DCD, demonstrating that these children had difficulties with estimating size consistency and discrimination of line length, area, slope, and spatial positioning (Lord & Hulme, 1987b). However, more recent findings from Schoemaker et al. (2001) have questioned these conclusions somewhat by showing that some of the visual perception

problems identified by Hulme and colleagues disappear when the motor component of the task is removed.

Nonetheless, a meta-analysis of the research into information processing abilities in DCD conducted by Wilson and McKenzie (1998) showed that visual-spatial processing was one of the most impaired areas, and the problems were apparent even when the tasks did not include a motor component. Two further studies conducted by Wilson and colleagues provide additional evidence for problems in visual perception (Wilson & Maruff, 1999; Wilson, Maruff, & McKenzie, 1997) using a cuing paradigm similar to the Posner (1980) paradigm. In this paradigm the children were instructed to fixate on a central point and respond to a target present in the periphery. A cue was presented prior to the target and for 80% of trials it would direct attention to the target and for the remaining 20% it would direct attention away from the target. Their results showed that children with DCD took longer to respond than controls but their responses to the invalid cue trials were particularly slow, suggesting that children with DCD have difficulty disengaging and shifting their attention from the invalid location.

As with the studies conducted by Hulme et al., these cuing tasks require a manual response and consequently it becomes difficult to disentangle the aforementioned response selection issues from problems in visuospatial attention from just the behavioural data. Neurophysiological data, on the other hand, can provide an insight into which processes are occurring abnormally; Tsai, Pan, Cherng, Hsu, and Chiu (2009) conducted an ERP study using the same cuing task as employed by Wilson and colleagues. They found similar behavioural results as Wilson et al., but were also able to identify differences between the DCD and control children in ERPs associated with visuospatial attention (i.e. N1 and P3 in particular), indicating that the children with DCD are slower at target identification. Although it should be noted that Tsai and colleagues also highlight that the children with

DCD have poorer cognitive-to-motor transfer speed, as indicated by the elongated interval between N2 and the motor response.

Kinaesthetic perception: The ability to know the position of one's body in space and how it is moving is essential for motor control; indeed, it is a key element in current models of motor control (Shadmehr & Krakauer, 2008; Wolpert, Diedrichsen, & Flanagan, 2011). Within these models kinaesthetic perception (usually included as part of proprioception or afferent sensory information) is part of a feed-forward loop and is checked against the predicted sensory consequences of a movement in order to rapidly check and improve the movement in question. Disruption of this process can result in poorer motor control (e.g. Miall, Christensen, Cain, & Stanley, 2007).

Thus, it has been proposed that the motor problems in DCD may actually stem from deficits in kinaesthetic perception as movements made are based on poor or incorrect information and Laszlo and Bairstow developed the Kinaesthetic Sensitivity Test (KST; 1985) to assess this hypothesis. Briefly, the KST consist of two parts: A test of kinaesthetic acuity and a test of kinaesthetic perception and memory. The kinaesthetic acuity test requires the participant to discriminate the position of the left and right hands after one has been passively moved by the experimenter, with the aim of determining the participant's ability to perceive their body position in the absence of vision.

The test of kinaesthetic perception and memory requires the participant to integrate kinaesthetic and visual information to identify the original orientation of an object they have felt without vision, but which has subsequently had its position altered by the experimenter. This aims to test more complex kinaesthetic processes in order to complement the acuity test, and thus provide a complete picture of kinaesthetic ability in an individual.

However the evidence for problems in kinaesthetic perception is mixed at best; while several studies have shown that children with DCD perform worse on the KST than healthy controls (Laszlo, Bairstow, Bartrip, & Rolfe, 1988a; Piek & Coleman-Carman, 1995), there are others that have not been able to replicate these findings (Hoare & Larkin, 1991; Lord & Hulme, 1987a). Further research is needed to clarify the role of kinaesthetic perception in DCD.

Internal modelling deficit: Related to kinaesthetic perception is the suggestion of an internal model deficit. In the aforementioned forward models of motor control: while a movement is undertaken kinaesthetic information is compared against the predicted sensory outcomes of that movement in order to update and correct the movement plan. These predicted sensory outcomes are produced by an internal model based on the copy of the motor command that it receives, and if the predicted outcomes are poor or noisy the result is much same as when kinaesthetic feedback is poor. This has led to the suggestion that individuals with DCD have a reduced ability to develop and update internal models (Gabbard & Bobbio, 2011; Wilson, Ruddock, Smits-Engelsman, Polatajko, & Blank, 2012), which then requires more time to build and modify action representations.

Evidence for this suggestion comes from two main areas: Studies looking at online control of movement and motor imagery studies. The evidence for motor imagery problems in DCD has been discussed previously with regards action planning, however there is the suggestion that ability to accurately imagine performing an action plays a role in its prediction (Gabbard & Bobbio, 2011). Thus, the difficulties in motor imagery for individuals with DCD may also suggest problems in the internal models of action.

Rapid on-line motor control is the process by which the trajectory of a movement is continuously updated in order to correct for unexpected changes in the target or the environment. A number of studies conducted by Hyde and colleagues utilised the double-

step reaching paradigm in order to assess rapid on-line control of movements in DCD (Fuelscher, Williams, & Hyde, 2015; Hyde & Wilson, 2011a, 2011b, 2013; Ruddock et al., 2014). Their work shows that children with DCD are slower to initiate movements, have longer movement times, and are more prone to make errors when the target they are reaching for changes. Furthermore, kinematic analysis of the reaching movements found that children with DCD were slower to initiate corrections when the target changed mid-movement. These findings led Hyde and colleagues to conclude that impaired predictive control plays a role in DCD.

It is unlikely that one of these above explanations alone can account for all the difficulties observed in individuals with DCD, particularly as several of these explanations overlap. Recently there has been the suggestion by Vaivre-Douret et al. (2016) that the two broad cognitive explanations (i.e. problems in motor programming versus problems in perception) may both be correct, with each accounting for a specific subgroup within the disorder. Although, as stated previously, more research into subtypes within DCD is needed before this suggestion can be examined in detail.

Neural explanations of DCD

The current understanding of the neural correlates of DCD is somewhat limited, but what is known has been derived from two distinct sources. Firstly, from the use of neuropsychological tests; these are test that are used with individuals with brain injury and are typically used to identify the location and extent of a neural insult. Secondly, from the use of neuroimaging techniques like fMRI and EEG; which can be used to examine brain function in a more direct fashion. The majority of our understanding comes from the former source, as currently there is very little published neuroimaging research into DCD.

Based on the evidence available thus far the main neural correlates thought to be implicated in DCD are: the cerebellum, the parietal lobe, and the basal ganglia (Bo & Lee,

2013), although a number of others have been suggested. The evidence for these are outlined briefly below.

Cerebellar involvement: Studies reporting the results of damage to the cerebellum in animals (Gramsbergen, 2003) and humans (Ivry, 2003; Manto et al., 2012) have demonstrated that the cerebellum plays a key role in a number of aspects of motor coordination, including: timing, postural control and visuomotor adaptation. Thus, the involvement of the cerebellum in the disorder has primarily been inferred from a number of behavioural deficits observed in DCD that are typically associated with disruption of normal cerebellar function. These include: postural control deficits (Geuze, 2003, 2005, 2010; Johnston et al., 2002; Wann et al., 1998), timing deficits (Rosenblum & Regev, 2013), online control deficits (Hyde & Wilson, 2011a, 2013), visuomotor adaptation deficits (Cantin, Polatajko, Thach, & Jaglal, 2007; Kagerer et al., 2004; Kagerer, Contreras-Vidal, Bo, & Clark, 2006).

There is also more direct evidence from neuroimaging research: Zwicker, Missiuna, Harris, and Boyd (2011) found reduced activation in areas of the cerebellum during a trail tracing task. Even though this finding aligns with the previous studies, it should be noted that the sample size of this study was fairly small (7 children with DCD and 7 controls) and no behavioural differences between the groups were observed on the trail tracing task.

Parietal cortex involvement: As with the cerebellum, the involvement of the parietal cortex was initially inferred from behavioural deficits observed within individuals with DCD, specifically the aforementioned problems in visuospatial processing (Wilson & McKenzie, 1998) and motor imagery (Wilson et al., 2001).

However, recent neuroimaging evidence has provided support for the role of the parietal cortex in the disorder. Kashiwagi, Iwaki, Narumi, Tamai, and Suzuki (2009) used fMRI to

investigate neural activation of children with DCD and control children while they performed a simple visuomotor task (controlling a cursor on screen using a joystick to track a target). Behaviourally they found that, compared to the control group, the DCD group showed significantly greater distances from the cursor than the control group, indicating they were less able to stay on target, and significantly greater changes in velocity, indicating that they found it significantly more difficult to smoothly manipulate the cursor. These behavioural differences observed in the DCD group were accompanied by lower levels of activation in the left inferior and superior parietal lobes, as well as the left post-central gyrus. Zwicker et al. (2011) observed similar findings using the aforementioned trail drawing task: They found significantly lower activation of the inferior parietal lobules bilaterally.

Work by Querne et al. (2008) also provides support for this hypothesis; however, they suggest that the problems are caused by atypical patterns of connectivity in attentional networks, and show that when undertaking a go/no-go task children with DCD display increased functional connectivity between a network primarily consisting of the middle frontal cortex, the anterior cingulate cortex, and the inferior parietal lobe and decreased functional connectivity between the striatum and the inferior parietal lobe.

Basal Ganglia involvement: As previously discussed, the basal ganglia is a key part of the motor learning networks in the brain (Doyon et al., 2009; Penhune & Steele, 2012), consequently it has been suggested that it may play a role in DCD. The evidence that supports this hypothesis comes from studies indicating problems in force-control, which is typically associated with the basal ganglia, (Pitcher, Piek, & Barrett, 2002; Smits-Engelsman et al., 2008) and from neurological assessments indicating basal ganglia dysfunction (Lundy-Ekman, Ivry, Keele, & Woollacott, 1991).

However, the evidence for this hypothesis is weak since procedural motor learning (also associated with the basal ganglia) appears to be unaffected in DCD and there is no neuroimaging evidence to support it.

Involvement of other areas: There have been suggestions of the involvement of multiple other areas including the corpus callosum (Zwicker, Missiuna, & Boyd, 2009), frontal areas (Gomez & Sirigu, 2015), and the anterior cingulate (Bo & Lee, 2013), but the evidence to support the involvement of these areas is limited due to the aforementioned lack of neuroimaging research in DCD.

Motor learning in DCD

As previously mentioned, there are two paradigms broadly used to examine motor learning: adaptation paradigms and procedural learning paradigms. While the focus of the current thesis is the latter, both will be briefly discussed here to give a complete account of the current understanding of motor learning in DCD.

Unfortunately, despite the fact motor learning deficits are considered one of the core symptoms of the disorder, there have only been a few studies examining it in DCD. On the adaptation side, two studies by Kagerer and colleagues have revealed that children with DCD have problems in visuomotor adaptation tasks (Kagerer et al., 2004, 2006). When visual feedback on the task was rotated by 45 degrees the children in the DCD group were less affected by the distortion and did not produce any of the after-effects of the rotation that are typically observed. This was extended in the 2006 paper in which they found that children with DCD would adapt to a visuomotor rotation, but only when the rotation was large (60 degrees) and abrupt. This supports the notion that motor learning in DCD is impaired, and Kargerer and colleagues suggest that this is due to a deficit in updating the internal model.

Conversely, Cantin, Polatajko, Thach, and Jaglal (2007) found that at the group level children with DCD were able to successfully adapt to gaze shift in a prism adaptation study, however the results are difficult to interpret as there were substantial variation between individual participants. These findings may also be explained in the light of Kagerer et al. (2006), in that successful adaptation to the prism adaptation task may not have occurred if the gaze shift had been smaller.

In contrast to motor adaptation, the research into procedural motor learning has suggested that this is relatively intact in individuals with DCD. An early study conducted by Wilson, Maruff, and Lum (2003) seemingly provided initial evidence showing equivalent performance between children with DCD and control children on a procedural learning task (the serial reaction time task, SRTT). However, as Gheysen, Van Waelvelde, & Fias (2011) noted, there are a number of flaws in the study, including statistical misinterpretation, small sample size, and methodological errors that make that interpretation problematic. Hence, Gheysen and colleagues replicated the original study making adjustments to correct the flaws. Having done this, while they found that the children with DCD did show a gradual improvement on the task (as measured by a gradual decrease in reaction time), they did not show evidence of motor sequence learning as the children with DCD did not show the characteristic decrease in reaction time in the control block. However, this conclusion is somewhat weakened as an equivalent number of children in both the DCD group and the control group developed explicit awareness of the underlying pattern in the SRTT, suggesting a degree of learning.

Lejeune, Catale, Willems, and Meulemans (2013) questioned whether this result was due to impaired motor sequence learning, instead suggesting that deficits observed by Gheysen and colleagues may have been the result of difficulties with the specific perceptuomotor demands of the task used. They tested this suggestion by using a modified version of the SRTT designed by Gabriel, Stefaniak, Maillart, Schmitz, and Meulemans (2012) which used a

touch screen display to both present stimuli and record responses (rather than a screen and separate button box), minimising the perceptuomotor demands of the task. Lejeune and colleagues found no difference between the DCD and control children, providing evidence that procedural learning is unaffected in children with DCD. Lejeune and colleagues have observed similar results (Lejeune et al., 2013; Lejeune, Wansard, Geurten, & Meulemans, 2015). However, it should be noted that the above studies utilised the SRTT which, as discussed in the next chapter, does not fully conform to the previously described stages of motor learning and is more suited to looking at procedural learning in general.

Biotteau and colleagues utilised a self-paced finger-tapping task in order to assess motor learning in groups of children with DCD or dyslexia (Biotteau, Chaix, & Albaret, 2015). They found that while all of the groups of children were able to improve on the task, indicating motor learning is intact, they also observed that the DCD group still showed difficulties in motor learning.

Taken together these findings indicate that while the cognitive processes underlying procedural learning appear to be intact in DCD, there are still difficulties in the integration of these process with motor aspects and thus motor learning is impacted.

The current thesis

The role of this thesis

Despite the previously outlined body of evidence from the motor learning literature indicating that the primary motor cortex plays a key role involved in the acquisition of new motor skills, particularly in the early stages, it is surprising that there is no suggestion in the DCD literature that the primary motor cortex may contribute to the difficulties observed.

A potential explanation for this absence may lie in the history of the disorder: As discussed earlier, prior to the London consensus the disorder was referred to by a number of

different terms, including dyspraxia. The term dyspraxia is derived from the adult neuropsychology literature and is linked to the term apraxia (Henderson & Henderson, 2003; Hill, 2005), which is typically defined as "an acquired disorder of movement affecting gestures and controlled movements in the absence of paresis (paralysis of limbs) or other muscular disorder that may prevent basic motor movements" (Page 375, Andrewes, 2009). Apraxia is not a singular disorder and may be caused by damage to a number of different areas in the brain; however, it is most commonly associated with damage to the left frontal lobe, left parietal lobe and occasionally the basal ganglia (Goldenberg, 2009). Due to the similarities in both symptomologies and deficits observed from neuropsychological tests, albeit with reduced severity in DCD, links were drawn between the two conditions and there was suggestion that DCD may be caused by minimal brain damage/dysfunction (Gubbay, Ellis, Walton, & Court, 1965; Pincus & Glaser, 1966). This is in contrast to the effects of damage to the primary motor cortex, which usually results in some degree of paresis (Nudo, 2003) and thus does not reflect the symptoms seen in cases of DCD.

Consensus on DCD has shifted away from this neuropsychological approach, and it is currently viewed from a neurodevelopmental perspective. That is: deficits in behaviour are thought to be caused by an atypical neural development trajectory rather than due to underlying damage of the brain (Gilger & Kaplan, 2001). However, despite this shift there has been little research published looking at the role motor related areas not associated with apraxia may play in the disorder.

Given the previously discussed role that the plasticity of the primary motor cortex plays in early motor learning and the possibility that variation in motor cortical plasticity could influence the speed of learning, it is possible that the primary motor cortex could play a role in some of the motor difficulties experienced by individuals with DCD. The motor cortical plasticity of individuals with DCD could fall toward the lower end of the spectrum and this may be a rate-limiting step in development of new motor skills.

Thus, the primary aim of this thesis is to run a preliminary investigation exploring the role of the motor cortex in DCD. More specifically this thesis will be attempting to answer the following research question:

Do the aforementioned motor cortical changes associated with the early stages motor learning in typically developing individuals occur at a slower rate in individuals with DCD?

The structure of this thesis

In order to address the question stated above, this thesis will develop along the following path:

The specifics of the task used to investigate motor learning are particularly important within this type of research. Thus, chapter two will briefly explore the motor learning tasks used in the previous literature and discuss reasons for using a novel task. Additionally, chapter two will contain a brief discussion of the problems associated with the commonly used approaches for analysing reaction times and the potential solutions to these problems. Finally, chapter two will report and discuss the results of an experiment to test whether the novel task developed is able to successfully produce learning in a neurotypical population.

Chapter three will be used to discuss the recruitment of adults with and without DCD and how expected differences between the groups (in motor coordination, for example) can be quantified and tested. Chapter three will end with an outline of the battery of tests used within this thesis.

While there are a wide range of different neuroscientific techniques that could be used to explore the current research question, this thesis will focus on using just two: electroencephalography (EEG) and transcranial magnetic stimulation (TMS). Chapters four and six will be used to discuss the methodological aspects of EEG and TMS respectively. Each of these chapters will begin by providing a brief outline the principles behind the

technique in question, before moving onto discuss why that specific technique was chosen to address the research question and detailing the specifics of how it was used and analysed in this thesis.

Chapter five will begin by reiterating the evidence supporting electrophysiological changes in the brain associated with motor learning, before moving onto reporting and discussing the results of an experiment designed to assess these electrophysiological changes over the course of a motor learning tasks in neurotypical adults and adults with DCD.

Similarly, chapter seven will begin with a discussion of previous research that has explored neurophysiological changes associated with motor learning. It will then move onto reporting and discussing the results of an experiment using TMS to examine changes in motor-cortical excitability over the course of a motor learning task in neurotypical adults and adults with DCD.

Finally, chapter eight will reiterate the results of the experiments conducted within this thesis and discuss them in the light of the literature outlined in this chapter. This chapter will then examine challenges encountered while conducting the experiments described in chapters five and seven. Before finally suggesting potential future directions in which research into DCD generally and, more specifically, the neural basis of DCD could proceed.

Chapter 2 – Designing and testing a novel motor learning task

Abstract

In order to successfully examine the early stage of motor learning a suitable task is required. This chapter begins with a brief discussion about the most commonly used sequential motor learning task: the serial reaction time task (SRTT), with a focus on whether it would fit the aims of the thesis. Upon concluding that the SRTT is not suitable the chapter then moves on to discussing factors that need to be considered when designing a new task. Finally, the problems associated with the use of standard summary measures to describe reaction time distributions and potential alternative approaches are considered.

An experiment was conducted to examine the efficacy of the new task in producing motor learning and how suitable an Ex-Gaussian distribution-fitting approach was for examining reaction time data. The experiment consisted of 38 participants divided into the two conditions of the motor task.

The results indicated that distribution-fitting was a suitable approach for use with these data, and that the new motor learning task was successfully able to produce motor learning. These results are discussed taking into account how the task will be utilised in later studies, and slight modifications for these studies are suggested.

Introduction

As discussed in the previous chapter, there are two main motor learning paradigms used within the literature: Procedural motor learning, where participants learn a new motor sequence or mapping through repeated practice of a task; and sensorimotor adaptation, where an already established motor skill (i.e. reaching) is performed while perturbations are added, forcing modifications to that skill.

Of these two options, a procedural learning paradigm was considered to be the better for addressing the aims of the current thesis. This selection was based on three reasons: Firstly, changes in performance in the initial stages of learning a novel skill are easily identifiable as they tend to be relatively rapid. Secondly, as the skill is novel initial skill level does not need to be accounted for before training begins. Finally, as described in the introductory chapter, procedural motor learning produces measurable changes in the primary motor cortex. Thus this type of task is the better option to answer the questions about the involvement of the primary motor cortex in the early stages of motor learning that were posed in the previous chapter.

The Serial Reaction Time Task

The most commonly used procedural learning task is the Serial Reaction Time Task (SRTT; Nissen & Bullemer, 1987). This task typically consists of a stimulus presented on screen in one of four positions, and the participant has to respond by pressing a button that corresponds to that position. Performance, in the form of accuracy and reaction time, is measured over the course of several blocks. Unbeknownst to the participant there is a pattern underlying the stimulus position that is repeated over the course of a block. Typically, as participants practice the task they implicitly (and sometimes explicitly) pick up on this pattern and consequentially their performance begins to improve, as demonstrated by a drop in the mean reaction time for each block. This improvement is underlined by the inclusion of a control block somewhere in the middle of the experiment. This control block is superficially the same as the other blocks but lacks the underlying pattern; as a consequence performance for this block is typically reduced to pre-learning levels.

Despite being a widely used task it was felt that the SRTT was not the appropriate choice to answer the questions addressed in this thesis. This is partly because there is debate in the literature about whether the learning that occurs in the SRTT can be disassociated from

specific motor responses, or whether a motor component is required for motor learning to occur (e.g. Dennis, Howard, & Howard, 2006; Robertson, 2007).

In addition, the SRTT primarily produces sequential learning behaviour, which would typically occur later in real-world motor learning. For example: When learning to play the piano an individual would begin by learning which particular action produces a specific note, and then once this mapping was reasonably well-established they would begin to string sequences of notes together. The learning occurring in the SRTT reflects the later aspect of this example. While, in contrast, the aim of this thesis is to to examine the initial stages of motor learning, where automatic associations between stimuli and responses are being formed, and the task needs to reflect that.

More fundamentally, the inclusion of the pattern underlying stimulus presentation in the SRTT produces motor learning that runs counter to the models of motor learning outlined in the previous chapter. That is, practice of the SRTT results in implicit learning of the pattern, that may also eventually result in explicit awareness; whereas, the aforementioned models of motor learning state that when learning a novel task individuals start with an explicit knowledge of the skill they wish to perform which, with practice, then develops into implicit and automatic performance of the skill.

This point may be illustrated by returning to the piano playing example: for novices there are limited implicit associations between notes presented on a piece of sheet music and the action required to produce these notes on the piano. Thus explicit cognitive control is required to link the note seen with the action required to produce that note. Practice strengthens the association between the note and the action until, eventually, there is minimal cognitive input and there is a more automatic association between the notes presented and the actions required to produce those. With further practice this builds into sequence learning, where links between the notes begin forming.

Given these concerns, it was decided that a new task needed to be developed for use in this thesis. This task would retain certain general features of the SRTT (e.g. the linking of a visual stimulus to a specific motor response) but also needed to ensure that the development of stimulus-response associations leading to automatized responses were emphasised.

Designing a novel motor task

In an attempt to make the new task as realistic as possible it was primarily based on the exercises used to teach touch typing. These generally require the participant to place their fingers in the 'home' position (highlighted green in Figure 1) and correctly respond to letters presented on screen, without looking at their hands of the keyboard. However, as there are more than than thirty-six keys across eight fingers, touch-typing tasks have too many potential stimuli and response options to produce the rapid improvements in performance required to examine the initial stages of motor learning within a single practice session, so a simplified version of this type of task was developed.

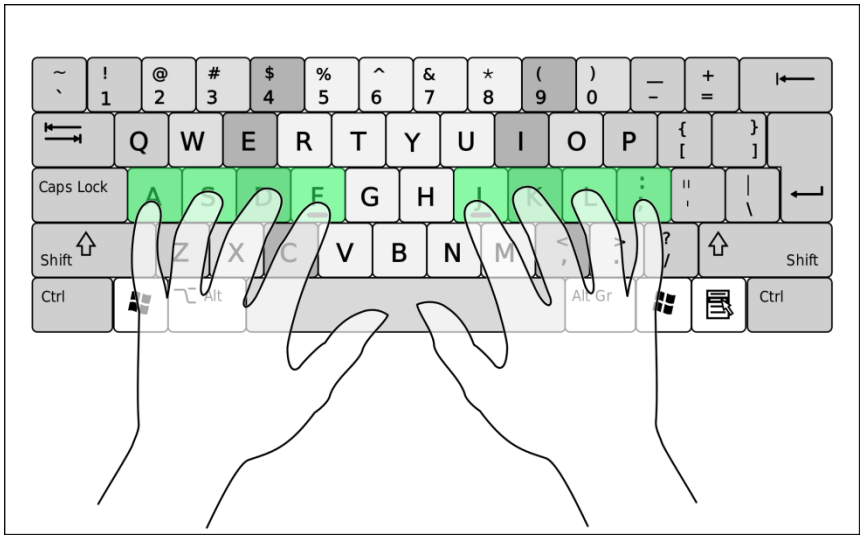

Figure 1 - Finger positions for touch typing.

This simplified version reduced the number of stimulus and response options by limiting responses to the numerical keypad. Additionally, participants only responded with their right index finger, further reducing the potential response options. The numerical keypad

was chosen over a grouping of nine keys on the main, alphanumeric part of the keyboard as the layout is reasonably well known and follows a logical order, allowing for initial success through explicit knowledge; but it is infrequently used by most individuals, allowing for improvement with practice as the responses become increasingly automatic.

The task was designed so that participants began with their right index finger placed on the five key, ensuring that responses for all trials began in the same place. Then a numerical stimulus was presented on screen (1-9, excluding 5) and participants were asked to respond by pressing the corresponding numerical key as quickly and accurately as possible. This design is illustrated overleaf in Figure 2. Participants completed multiple blocks of these trials and performance for each block was quantified using the methods described later in this chapter. The specific number of trials and blocks varied slightly depending on the particular experiment, full details are given in the methods section of the corresponding chapter.

In order to demonstrate that any changes in performance observed for the task described above (henceforth termed the experimental condition) are attributable to motor learning a control condition is required. This control condition must replicate the movement aspects of the experimental condition, whilst omitting the learning component. In order to achieve this trial in the control condition followed the same structure as the experimental condition, but participants were presented with a letter 'G' to indicate they should respond with whichever key they wanted to. This design is also illustrated in Figure 2.

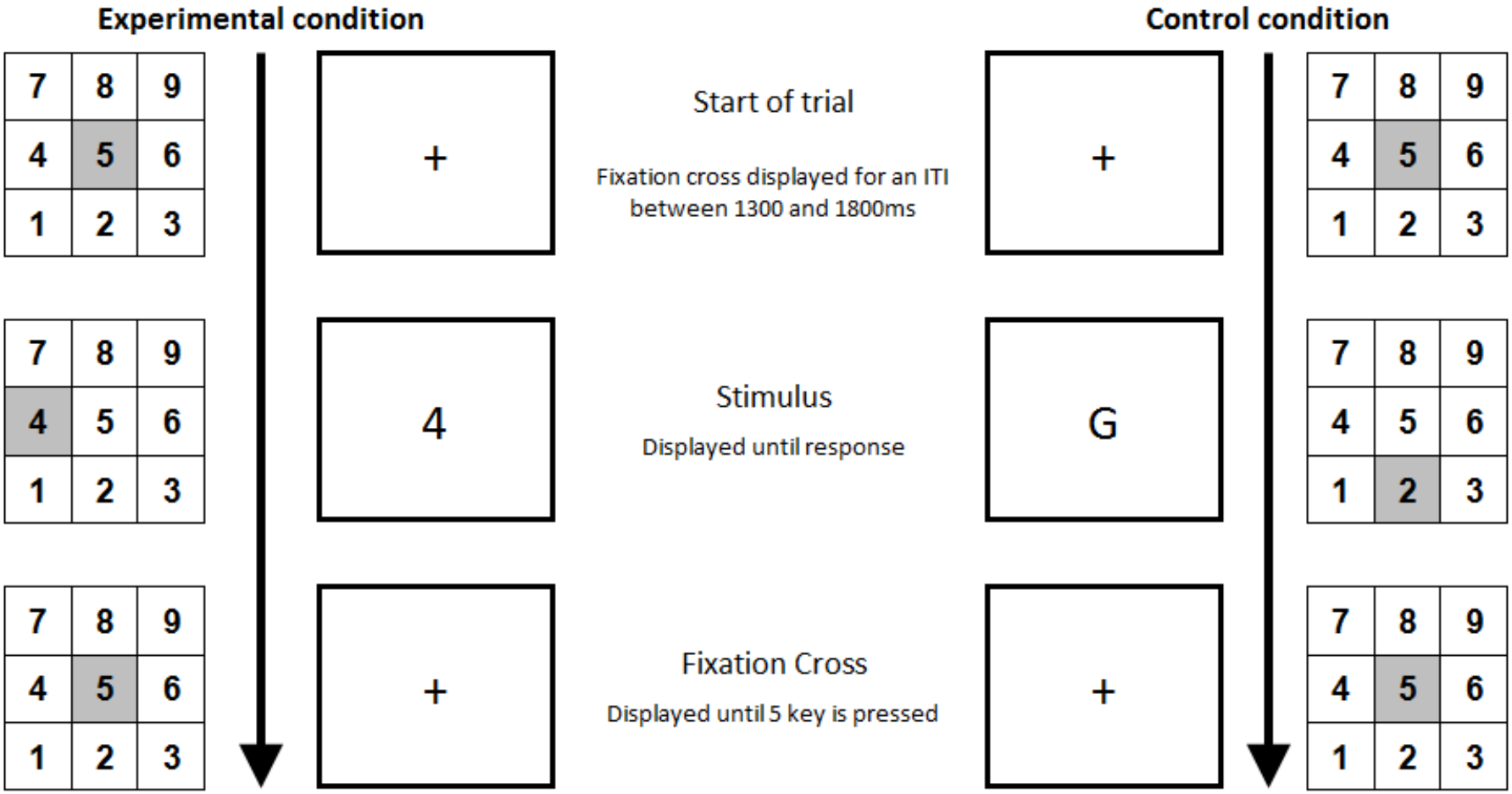

Figure 2 – Structure of a trial for each condition.

Methodological considerations concerning the analysis of reaction time

Most experiments examining reaction time as an indicator of performance will employ the mean and standard deviation in order to summarise the reaction time distribution recorded for each participant or block during statistical analysis. For data with a Gaussian (or normal) distribution the mean and standard deviation are reliable and well accepted ways of summarising the data collected, as the shape of the distribution can be reconstructed from these two statistics.

However, reaction time data are not normally distributed; instead they are usually positively-skewed (see Figure 3). This is primarily due to there being a lower limit on how fast an individual can react to a stimulus (usually between 100-200ms) but no upper limit on how slow they can react. This skew means that the mean and standard deviation do not represent the distribution well, as both are sensitive to extreme values and the shape of the distribution cannot be reconstructed from these two details alone.

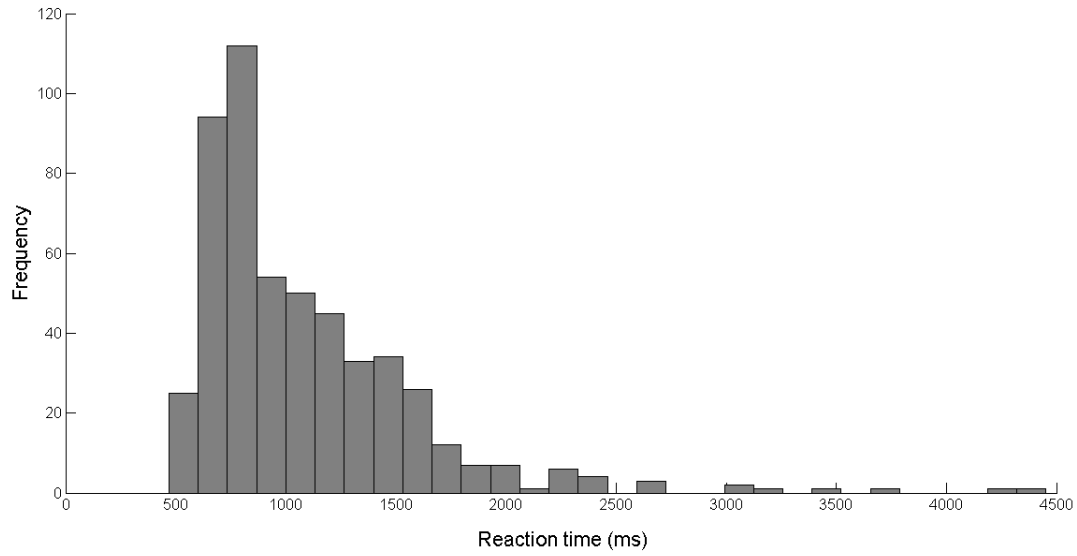

Figure 3 - Example reaction time distribution.

The problems skew in reaction time distributions cause are further highlighted in Figure 4 below, where cases of extreme values within the data are examined. Typically, for Gaussian distributions, extreme values are dealt with by applying a specific cut-off and either

trimming (removing the values that fall beyond this cut-off) or winsorizing (setting the values beyond the cut-offs to equal the cut-off value) the distribution. The cut-off normally selected is any value that falls beyond two standard deviations from the mean as, due to the relationship between the shape of the distribution, the mean and the standard deviation, the values that fall outside of this cut-off represent less than five percent of the total distribution. However, the same logic cannot apply for non-normal distributions: the shape of the distribution is asymmetrical and the mean and standard deviation are skewed by outliers, so using a cut-off of two standard deviations from the mean will not necessarily remove the extreme 5% of the data, and it is unlikely to remove equal amounts of the data from each end of the distribution. Equally problematically, even if applying a two standard deviation cut-off does manage to remove the extreme 5% of the data the resulting distribution will still be asymmetrical, with the majority of the distribution falling to the left of the mean.

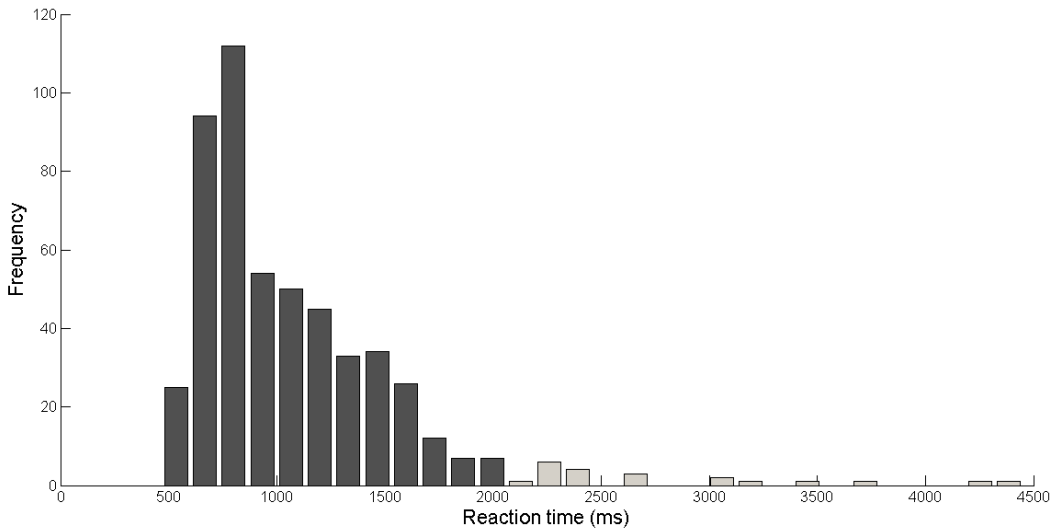

Figure 4 - Example reaction time distribution with outliers greyed out.

There are a number of ways around the problems caused by the non-normal distribution of reaction time data. One of these is to use the median as the measure of central tendency and the median absolute deviation (MAD) as the measure of variability instead of the mean

and standard deviation respectively. However, despite being more robust to outliers than the mean and standard deviation, the median and MAD are sensitive to the number of samples (or trials) in a distribution and thus are not advisable for tasks where there may be uneven numbers of trials included in the analysis (Miller, 1988).

Another way of dealing with this problem is to transform the data (typically with a log or inverse transformation) to make the distribution Gaussian (Balota, Aschenbrenner, & Yap, 2013). This is a popular solution to the problem of non-normal distributions in reaction times and usually works well. However, this approach presents problems in interpreting the transformed data, Lo and Andrews (2015) point out that the shift from a linear to a non-linear scale can hide potential interactions between groups and/or conditions that may be of interest.

The solution chosen for the current thesis is to fit an 'ex-Gaussian' distribution to the reaction time data collected. The ex-Gaussian is a convolution of a Gaussian distribution and an exponential distribution, is summarised by three values, and when plotted exhibits the positive skew associated with reaction time distributions. The three statistics that represent the shape of the distribution are μ (mu), σ (sigma), and τ (tau): μ and σ represent the mean and standard deviation of the Gaussian component of the distribution, while τ represents both the mean and standard deviation of the exponential component of the distribution (see Figure 5below for a graphical illustration of the distribution). It is generally considered that μ mainly reflects average performance, while σ reflects variability in performance, and τ reflects extremes in performance (i.e. the frequency and magnitude of very slow responses).

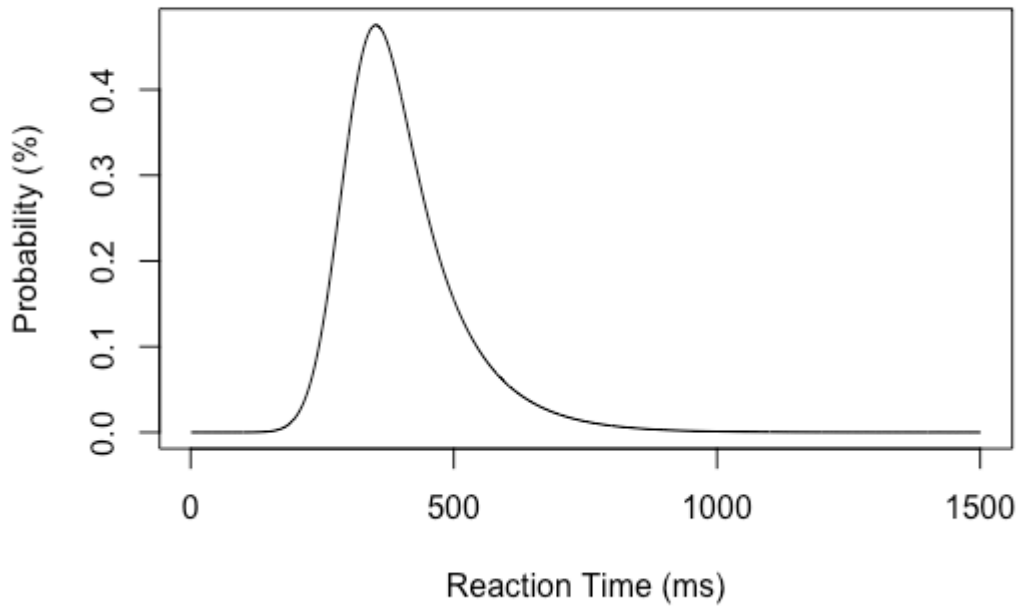

Figure 5 - Example Ex-Gaussian distribution (Mu = 300, Sigma = 50, Tau = 100).

In their paper arguing the merits of the ex-Gaussian distribution analysis Balota, Yap, Cortese, and Watson (2008) show that the mean reaction time typically used within the reaction time literature is the algebraic sum of the μ and τ statistics, and that the mean of a reaction time distribution can remain the same despite the fact that μ and τ statistics, and therefore the overall shape of the distribution, has changed. The ex-Gaussian approach has also been used to successfully identify intra-individual variability in atypically developing populations that classical measures of reaction time are not able to pick up (Gmehlin et al., 2014; Gooch, Snowling, & Hulme, 2012).

Quantifying motor learning

Motor learning is difficult to measure directly, however changes in performance of a task are frequently used as an analogue for motor learning. Typically, performance is assessed by examining the accuracy or reaction time for a particular block, and in the current task reaction time was used as the primary measure of performance (see section above). However, during choice based tasks accuracy and reaction time interact to produce what is termed the 'speed-accuracy trade-off'; that is: as the overall accuracy increases participants

tend to respond slower and vice versa (Heitz, 2014). In order to account for this and ensure that changes in task performance were primarily expressed though changes in reaction time, participants were asked to focus on responding as accurately as possible throughout the experimental condition of the task.

During the experimental condition of this task it was expected that the stimulus-response associations would gradually improve, leading to increasingly automatic responses and faster reaction times as a result. In contrast, as there is no association to be learned, it was expected that there would be very little difference in performance between the control blocks.

In order to examine whether these improved associations extended beyond the task described above into an unpractised task a secondary, sequence response task was also included in the initial test. This sequence response task (described fully in the methods section below) consisted of a typing out a string of five numbers presented as accurately and quickly as possible, again using a numerical keypad and the right index finger. If the motor learning task was able to improve the mapping for the numerical keypad in the experimental condition but not the control condition then it was expected that this learning would also produce condition specific improvements in the sequence response task.

Hypotheses

Given the rationale outlined above it was hypothesised that if the task was able to successfully able to produce motor learning then there would be a significant decrease in average reaction times and reaction time variability in the experimental condition of the motor learning task, while there would be no significant change in the control condition. However, given the additional cognitive involvement in the experimental condition of the motor learning task it was expected that the responses for the control condition would be significantly quicker than those for the experimental condition.

As participants were instructed to be as accurate as possible in their responses it was hypothesised that there would be no significant difference between the accuracy scores in the experimental blocks; thus ensuring that reaction time is the main indicator of performance in the task.

Finally, for the sequence learning task it was expected that there would be a significant decrease in reaction times in the post-task condition, but this would be more pronounced for those who had just completed the experimental condition of the motor learning task.

Methods

Participants

38 participants were recruited from an undergraduate population. All participants reported that they were right handed and did not have a diagnosis of any neurodevelopmental or other disorder. The mean age of the sample recruited was 19.91 (±1.76) years and it consisted of thirty-five females and three males.

Materials

The experiment was run on a Windows XP machine using MATLAB (version 7.11.0), with Psychtoolbox (Version 3.0.9) installed, to display the stimuli and record the responses and reaction times for each of the tasks. For both tasks the stimuli were presented in the centre of the screen in a black, size-24 font on a white background and viewed at a distance of 950mm. Responses were collected using a numerical keypad connected to the computer via USB port.

Tasks

Two tasks were used as part of this experiment and are each outlined below. All participants had their right hand covered by a box throughout the experiment to prevent them looking at their hand and the keypad while responding. Participants placed their left hand in a comfortable position on their lap.

Sequence response task: The sequence response task was administered once before the motor learning task and once afterwards (see Figure 6 below). During this task participants were initially presented with a fixation cross. After two seconds the fixation cross was replaced by a string of five digits on screen. Participants were instructed to respond by typing out the sequence as accurately and rapidly as possible on the keypad. They were instructed to only use their right index finger to type the sequence and their right hand was

covered with a box for the entirety of the task. Once five numbers had been typed the stimulus disappeared and was replaced by a fixation cross for a further 1 second. To ensure that all participants understood the task they were given five practice trials with accuracy feedback prior to the first block.

Twenty unique strings of numbers were used for this task, one for each trial. The digits used were between 1 and 9 and were equally distributed across the sequences. The post-task trials displayed the reversed number strings from the pre-task trials (i.e. pre-task sequence: 15849, post-task sequence: 94851).

Motor learning task: This task consisted of 520 trials in total over 5 block (104 per block).

Written instructions were initially presented on-screen to all participants reiterating what they had to do during the task. Participants were allowed to read the instructions at their own pace and once they were finished they moved onto the experiment proper.

The structure of each trial has already been described above and illustrated in Figure 2, but will be reiterated here for the sake of clarity:

Participants were initially presented with a fixation cross. This fixation was displayed for a randomised time selected from a predetermined range so as to introduce some jitter in the inter-trial intervals (ITI). In the current experiment the ITI was between 1300-1800 milliseconds.

This was followed by a stimulus displayed on screen until the participant responded. As described previously, the stimulus presented differed between the two conditions: Participants in the control condition were presented with a 'G' and instructed to respond as rapidly as possible by pressing a key of their choice with their right index finger. Whereas participants in the experimental condition were presented with a numeral from one to nine, excluding five, and instructed to respond by pressing the corresponding key with their right index finger. Participants in the experimental condition were asked to respond as rapidly as possible while also ensuring that they maintained a high degree of accuracy.

All participants ended each trial by pressing the '5' key and keeping their finger there in preparation for the next trial.

Design

This study had a mixed design, and consisted of two parts:

The first part was associated with the sequence response task and consisted of two independent variables: When the task was run, which had two levels (i.e. before or after the motor learning task; the within participant variable), and the assigned group, which had two levels (either experimental or control group; the between participant variable). Three dependent variables were measured for this part of the study: Reaction time, accuracy for individual numbers (overall accuracy), and accuracy for whole sequences (sequence accuracy).

The second part was associated with the motor learning task and also consisted of two independent variables: The block number (i.e. how much practice the participant has had; the within participant variable), which had five levels, and the assigned group, which had two levels (either experimental or control group; the between participant variable). Reaction time was taken as a dependent variable for both groups. Response accuracy was measured as an additional dependant variable for the experimental group.

Procedure

Before starting the study the researcher briefly outlined the study to the participant, before giving them a standard consent form *(See Appendix A)* to read and sign. Once the participant was sitting comfortably at the computer the experimenter briefly outlined the specifics of the experiment; explaining that it would begin with a block of the sequence response task, followed the by the motor learning task, and finally a second block of the sequence response task. The tasks were then administered in the order illustrated in Figure 6. During the break prior to each task the experimenter reminded the participant what that

task entailed, emphasising the need for high degrees of accuracy (except for the control condition of the motor learning task) while still responding as rapidly as possible. Once the participant had finished the tasks they were debriefed and allowed to ask any questions they had about the study.

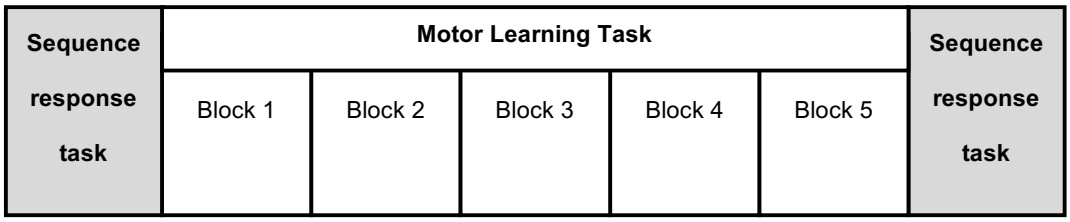

Figure 6 - Order of task administration for this experiment.

Ethics

The experimenter outlined the experiment in full prior to signing of the consent form, and the right of the participant to withdraw at any time without having to give a reason was emphasised both verbally and in the consent form. Additionally, participants were informed that all the data collected, in both paper and electronic format, would be associated with a participant number only, and contained no information that could be used to identify a specific individual. Finally, participants were informed that they had the right to withdraw their data at any time after the completion of the experiment, and were given contact details for the researcher and their unique participant number to do this.

Ethical approval for this project was obtained from the Goldsmiths Psychology Department Ethics Board.

Data analysis

The data for both experiments were imported into MATLAB (Version 7.11.0) for distribution analysis or cleaning and then analysed in IBM SPSS Statistics (Version 22).

Sequence response task processing

The number of trials collected for this task were too low to implement the previously described distribution-fitting method, thus a more traditional approach was used:

1. The mean sequence accuracy was calculated and the reaction times for incorrect trials were removed.
2. Reaction times were log-transformed and any outliers (defined as a trial with a reaction time more than 2 standard deviations from the mean) were removed.
3. The mean reaction time was then recalculated.
4. The mean overall accuracy for each block was calculated by comparing the sequence entered to the sequence displayed and assigning a score (out of 5) for each trial, the mean was calculated from these scores.

Motor learning task processing

As discussed in the introduction a distribution-fitting approach was considered a more appropriate method for looking at performance in each block, more details are outlined below. To ensure the appropriateness of using the summary statistics generated by the fitted Ex-Gaussian distribution it tested against the actual data using a chi-squared goodness of fit test. If the distribution generated significantly differed from the data, then that data was not used in the analysis. The results of the goodness of fit test were visualised in order to ensure that poorly fitted distributions were not related to a specific participant or block. Additionally, if more than 20% of the distributions failed this test then a more traditional approach outlined below was taken with all the data.

In order to examine the efficacy of the Ex-Gaussian fit compared to a normal distribution, the normal distribution generated using the mean and standard deviation for each block was also submitted to a chi-squared goodness of fit test.

Prior to submitting the data to either of the approaches outlined below anticipatory trials (those with a reaction time of <100ms) and incorrect trials (in the experimental group) were removed.

Distribution fitting approach: Fitting of an Ex-Gaussian distribution to the observed data was attempted using a MATLAB toolbox designed by Lacouture and Cousineau (2008). This toolbox uses maximum likelihood estimation approach in order to achieve an optimal fit Outlining the specifics of the maximum likelihood approach to distribution fitting is beyond the scope of this thesis; for more details of this specific implementation consult Lacouture and Cousineau (2008) and for a more general overview of reaction time distribution fitting see Van Zandt (2000).

Traditional analysis approach: The following steps were undertaken as part of the traditional analysis approach:

1. Reaction times were log-transformed and the mean and standard deviation reaction time for each block was calculated.
2. Outliers were classified as any reaction time 2 standard deviations from the mean and were removed.
3. The mean and standard deviation reaction times were recalculated for each block.
4. For participants in the experimental group the mean accuracy for each block was also calculated.

Statistical analysis

Separate analyses were conducted on each of the two tasks, and are outlined below:

Sequence response task: Mixed 2 x 2 ANOVAs were conducted for each dependent variable of the sequence response task (i.e. Mean reaction time, Overall accuracy, and Sequence accuracy). As previously stated, each independent variable had two levels for the within participants factor (pre- or post- task) and two levels for the between participants factor (control or experimental group).

Motor learning task: A repeated measures ANOVA was run on the accuracy scores for the experimental block to ensure that there was no statistically significant change over the course of the experiment.

In addition, separate repeated measures ANOVAs were conducted on the data from each condition of the motor learning task to identify whether there were changes in the average reaction time (the mean or μ), the variability (the standard deviation or σ), and (if possible) the extreme responses (τ) over the course of the experiment. As previously stated, each independent variable had five levels for the within subjects factor (block number).

Results

One participant (P26) from the experimental group was excluded from the analyses, as they had poor accuracy scores throughout both tasks. Thus, the final analysis included 37 participants, who were divided as shown in Table **2** below. An independent samples t-test revealed no significant differences between the age distribution of the two groups (t (35) = 0.5, p = 0.79).

Table 2 - Summary of group divisions for the task analysis

	Number	Sex (F:M)	Mean Age in years (Standard Deviation)
Experimental Group	18	16:2	20.00 (0.75)
Control Group	19	18:1	19.68 (1.77)

Sequence response task

Summaries for each of the dependent measures divided by group and time point are displayed in Table 3 below.

Table 3 - Summary of the sequence response task dependent variables

Measure	Group	Mean pre-task (SD)	Mean post-task (SD)
Sequence response accuracy (%)	Control	81.84 (22.37)	80.26 (16.54)
	Experimental	89.17 (11.66)	91.76 (6.11)
Overall accuracy (%)	Control	91.10 (12.28)	92.89 (7.02)
	Experimental	96.44 (4.60)	96.94 (2.11)
Reaction Time (log10 ms)	Control	3.67 (0.16)	3.58 (0.16)
	Experimental	3.64 (0.17)	3.53 (0.16)

The results of the mixed ANOVAs (time of task completion vs group) performed on the sequence response task data are summarised in Table **4** below.

The tests revealed that there was no main effect of practicing the motor learning task or interaction between groups for either the sequence accuracy or the overall accuracy. There was, however, a significant effect of practicing the motor learning task on reaction time, indicated by a reduction in the mean reaction time from the pre-test administration to the post-test administration (as illustrated in Table **3**). However, there was no interaction, indicating that the change occurred for both experimental and control groups.

Table 4 - Summary of repeated measure ANOVAs for the sequence response task

		Degrees of freedom	*F*-value	*p*-value
Sequence response accuracy	Main effect	1, 34	<0.01	0.96
	Interaction	1, 34	1.10	0.30
Overall response accuracy	Main effect	1, 34	0.14	0.71
	Interaction	1, 34	0.01	0.94
Reaction Time	Main effect	1, 34	82.47	<0.01
	Interaction	1, 34	0.36	0.55

Motor learning task

Ex-Gaussian distribution fitting: The results of the fitting approach are displayed in Figure 7 below. As shown, the Ex-Gaussian distributions fit 97% (87/90) of the blocks in the experimental condition, whereas the normal distribution only fit 24% (22/90). Therefore, the summary variables generated for the Ex-Gaussian distribution (μ, σ and τ) were used in the statistical analysis.

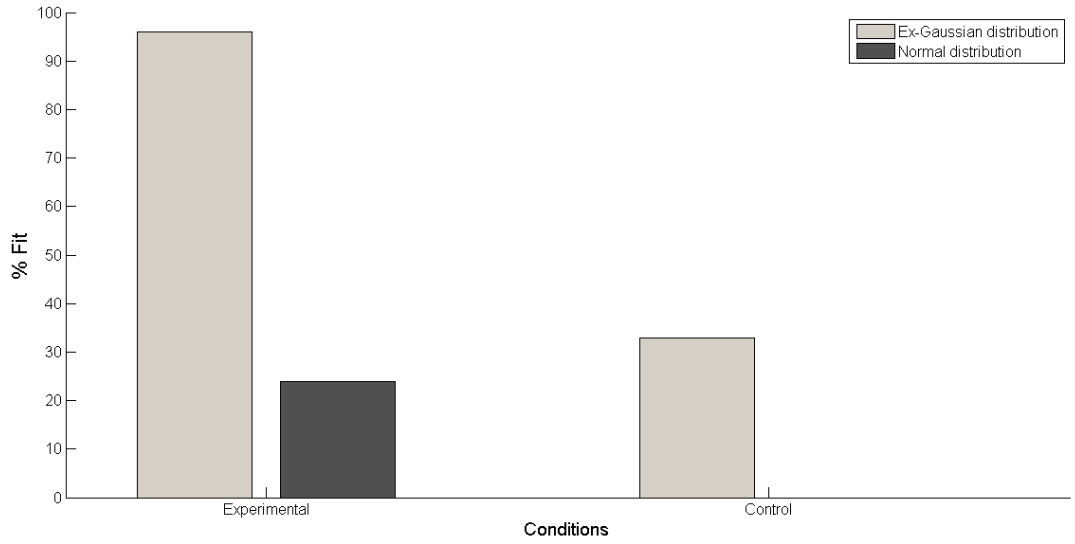

Figure 7 – Percentage of blocks that fit an Ex-Gaussian distribution versus a normal distribution

However, the Ex-Gaussian distributions only fit 33% (31/95) of the blocks in the control condition. While this was still better than the fit of the normal distribution (0%) it was not good enough to use the Ex-Gaussian summary statistics. As a result, the previously outlined traditional measures of reaction time were used. To allow for some comparison of the two conditions, traditional measures of reaction times were also produced for the experimental conditions.

Experimental condition

Accuracy: The repeated measures ANOVA on the accuracy scores revealed that there were no significant changes in accuracy over the course of the experiment, F (4,68) = 1.45, p = 0.23. The mean accuracy score for each block is illustrated in Figure 8.

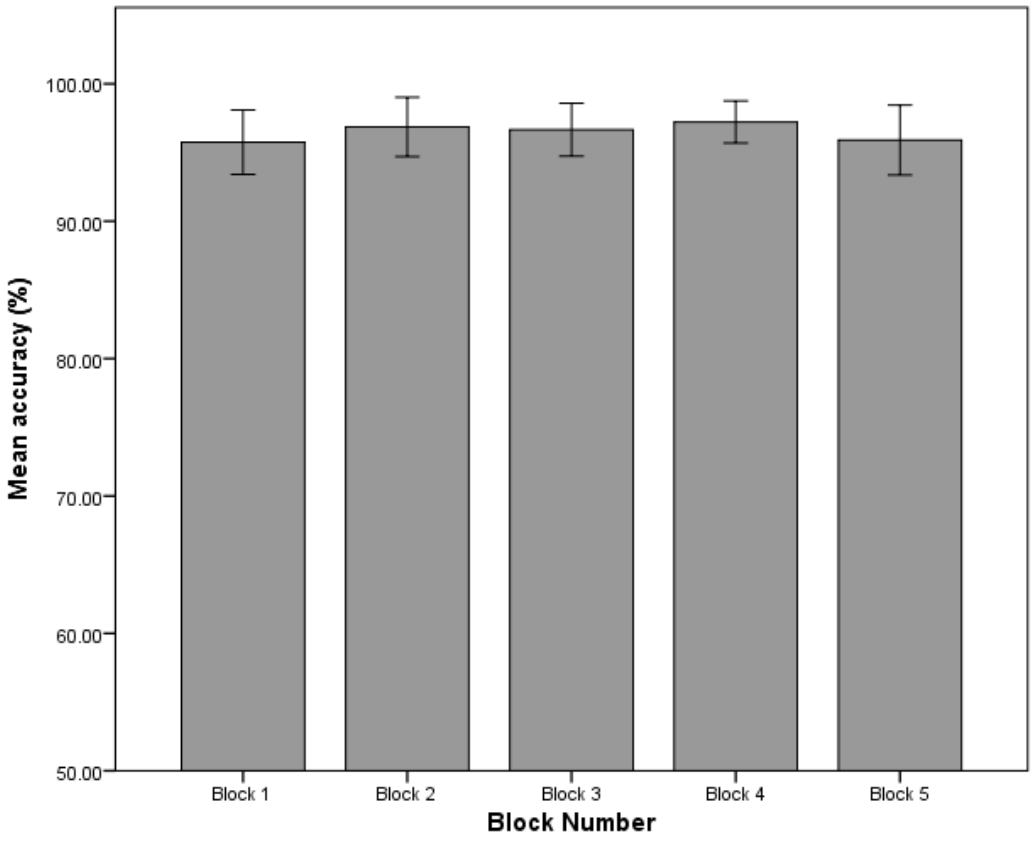

Figure 8 – Plot illustrating the mean accuracy scores for each block in the motor learning task (Error bars: ±2 Standard error)

Changes in μ: Mauchly's test of sphericity was violated for the repeated measures ANOVA ($\chi 2$ (9) = 39.17, $p < 0.01$), so the Greenhouse-Geisser correction was used ($\varepsilon = 0.52$).

The ANOVA revealed that there was a statistically significant main effect of block on μ (F (2.07, 28.94) = 5.50, p = 0.01). As illustrated in Figure 9 there was a reduction in μ over time.

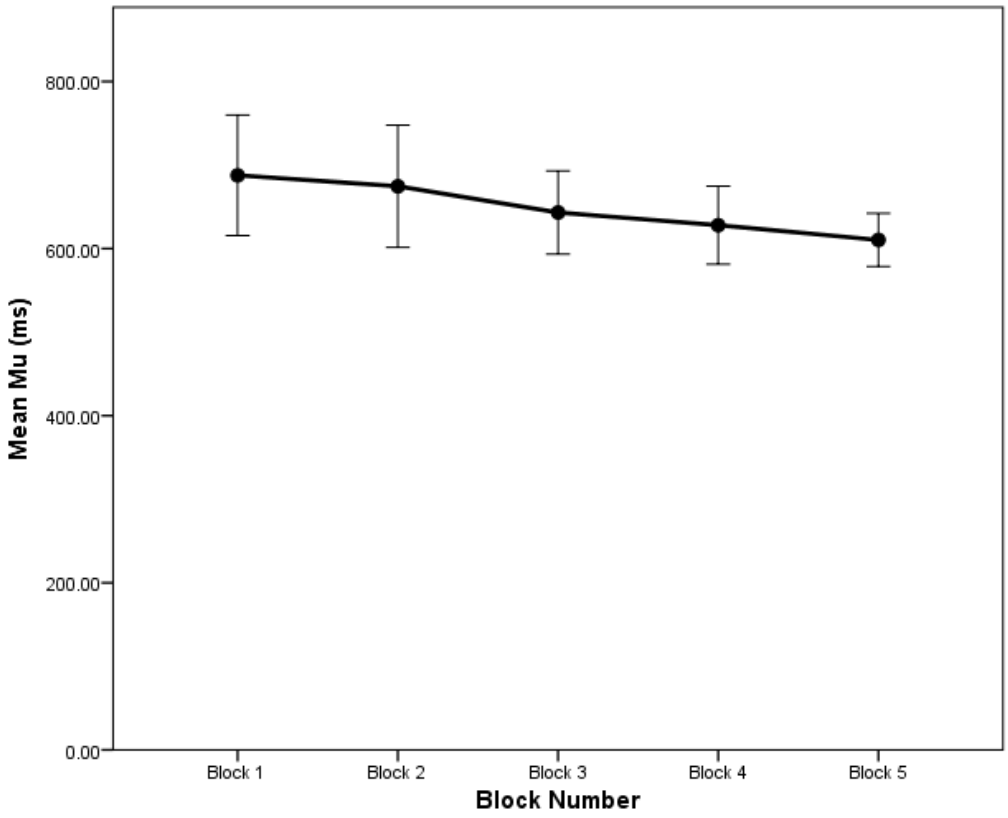

Figure 9 – Plot illustrating changes in the Mu component of the reaction time distribution across the experimental blocks (Error bars: ±2 Standard error)

Changes in σ: Mauchly's test of sphericity was not violated for the repeated measures ANOVA ($\chi 2$ (9) = 13.15, p = 0.16), so no correction was used.

The ANOVA revealed that there was a statistically significant main effect of block on σ (F (4, 56) = 3.80, p = 0.01). As illustrated in Figure 10, there was also a reduction in σ over time, and while there was an increase in σ in the final block it was still lower than in the starting block.

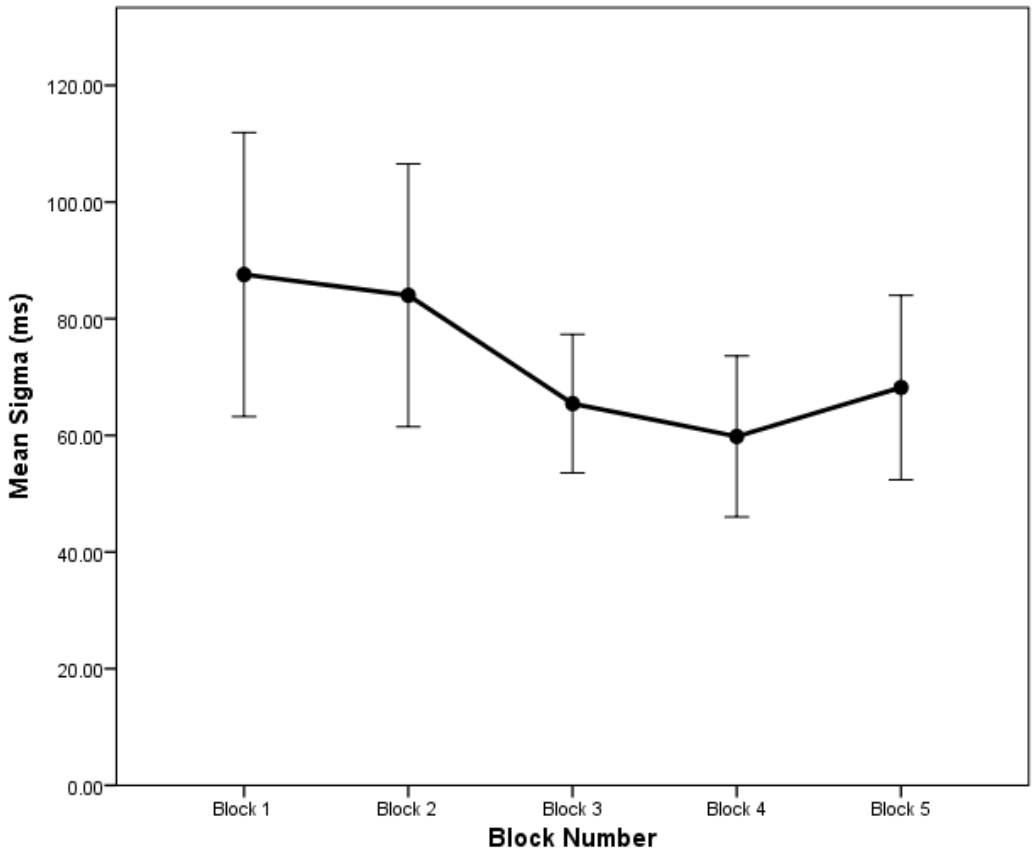

Figure 10 - Plot illustrating changes in the Sigma component of the reaction time distribution across the experimental blocks (Error bars: ±2 Standard error)

Changes in τ: Mauchly's test of sphericity was violated for the repeated measures ANOVA ($\chi 2$ (9) = 17.62, p = 0.04), so the Greenhouse-Geisser correction was used (ε = 0.59).

The ANOVA revealed that there was no statistically significant main effect of block on τ in the experimental condition (F (2.37, 33.19) = 3.01, p = 0.06). However, as illustrated in Figure 11 there was an overall downward trend in τ over time.

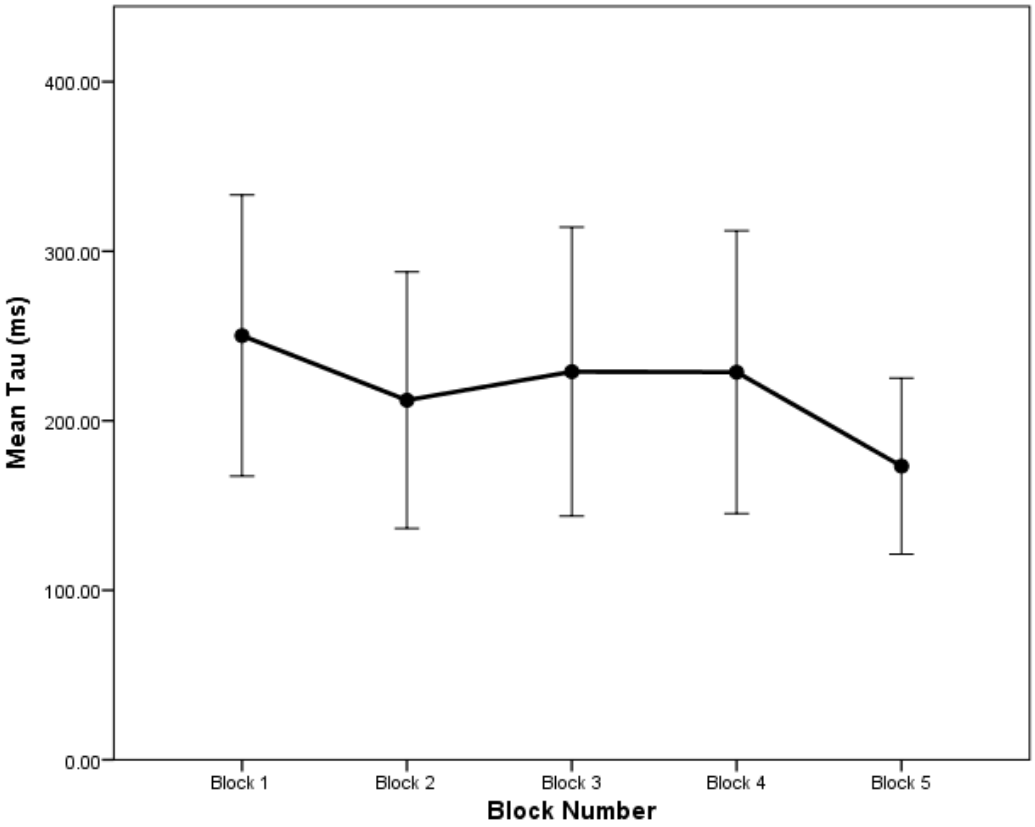

Figure 11 - Plot illustrating changes in the Sigma component of the reaction time distribution across the experimental blocks (Error bars: ±2 Standard error)

Control Condition

Changes in reaction time: Mauchly's test of sphericity was not violated for the repeated measures ANOVA ($\chi 2$ (9) = 7.15, p = 0.62). This ANOVA revealed that there was no statistically significant main effect of block on mean reaction time in the control block (F (4, 72) = 0.32, p = 0.87).

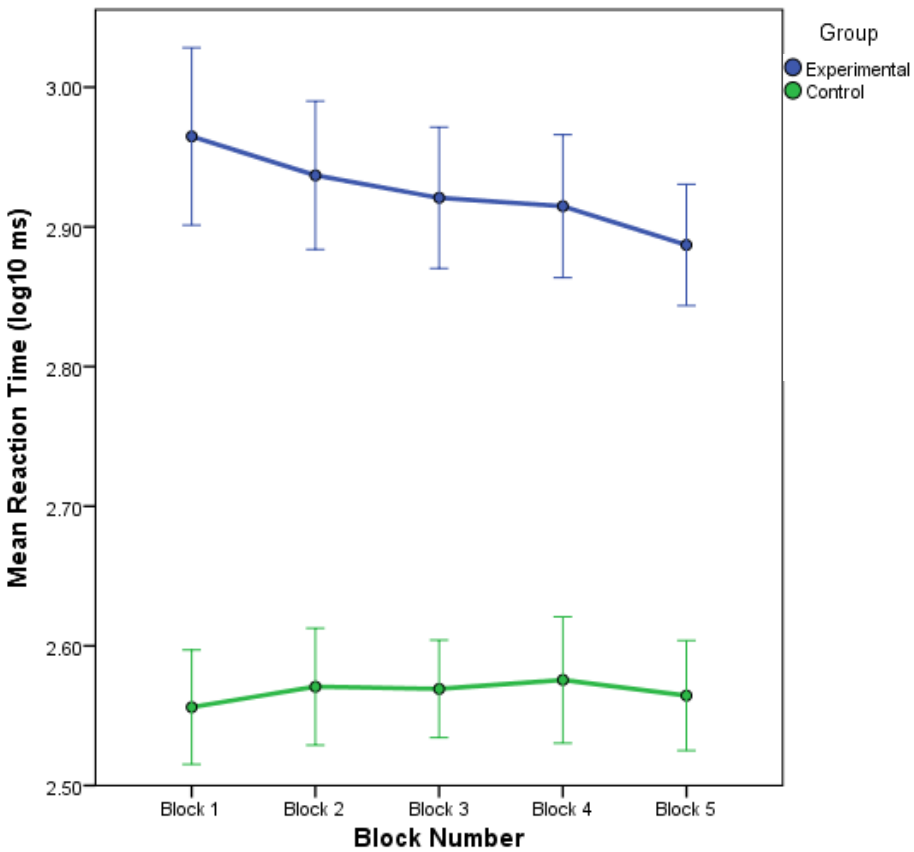

Figure 12 - Graph illustrating the mean reaction times for each block in the motor learning task (Error bars: ±2 Standard error)

Changes in reaction time variability: Mauchly's test of sphericity was violated for the repeated measures ANOVA ($\chi 2$ (9) = 35.87, p < 0.01), so the Greenhouse-Geisser correction was used (ε = 0.44). The repeated measures ANOVA revealed that there was no significant main effect of block on reaction time variability in the control condition (F (1.78, 31.96) = 0.17, p = 0.82).

Discussion

The aim of this experiment was to test the newly designed motor learning task to see if it was able to produce changes in performance indicating motor learning. The changes in performance were assessed directly by examining reaction time statistics for each block of the task, and indirectly by examine whether changes in performance were transferable to another task.

The hypotheses for this study were as follows: Firstly, there would be a condition specific decrease in the mean reaction times for the motor learning task. Secondly, there would be no significant difference between the mean accuracy scores for each of the blocks in the experimental condition of the motor learning task. Finally, there would be a condition specific decrease in reaction times for the sequence response task.

Hypotheses one and two were supported by the results of the experiment, while hypothesis three was not. The remainder of this chapter will be spent discussing the implications for these results before presenting a conclusion.

Hypothesis 1: There would be a condition specific decrease in the reaction times for the motor learning task.

As the task was designed to produce motor learning it was expected that the participants who undertook the experimental condition would improve on the task while those in the control condition would not. The results back up this hypothesis and Figure 9displays the changing performance in the groups clearly. The experimental condition produced a gradual decrease in both the mean response time and the variability of response times over the course of the five blocks. In addition, there was no significant change in either of these measures for the control condition.

This result on its own is not sufficient to demonstrate that the task produces motor learning; the decrease in reaction time could be accompanied by a concurrent decrease in

accuracy. However, the fact that the second hypothesis has also been accepted indicates that the changes in reaction time are due to learning.

As predicted, it was observed that there was a large disparity between the reaction times for the experimental and control conditions. However, it is unknown whether the extra time required for the experimental condition came from an increased response selection period or movement period. It is likely that it is from the former rather than the latter, as the participants in the control group were able to prepare their responses prior to the go signal, but the results do not give a direct indication of this. Given that this task is going to be used to investigate adults with DCD and the literature suggests that both movement time and response selection time is affected in DCD (e.g. Henderson et al., 1992), it is important to ascertain which of these changes more over the course of the task. Consequently the task should be modified so that the response selection period and the movement period can be easily identified. This can be achieved by asking the participants to hold down the '5' key at the start of each trial, rather than just starting from there. When the participant lifts their finger to respond this can be taken as the end of response selection period and the time between this and the actual response can be taken as the movement period, this is illustrated in Figure 13 below.

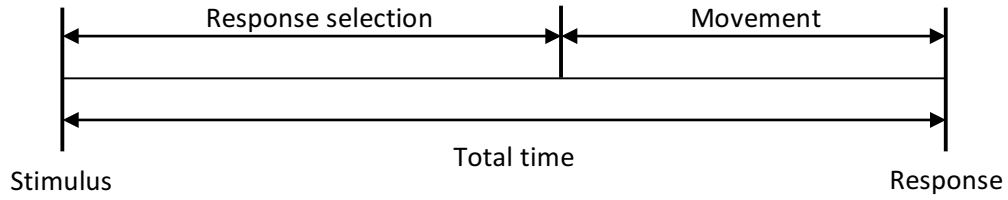

Figure 13 - Partitioning the total response time (TT) into response selection time (RT) and movement time (MT).

Hypothesis 2: There would be no significant difference between the mean accuracy scores for each of the blocks in the experimental condition of the motor learning task

As mentioned in the introduction to this chapter, the accuracy of a task needs to remain stable while the reaction time changes (or vice versa) to demonstrate that the task is having an effect on performance. If this is not the case then the participants are sacrificing performance in one domain (e.g. accuracy) to improve performance in the other (e.g. speed). Hypothesis 2 was formulated in conjunction with hypothesis 1 in order to confirm that changes in performance detected in the task can be attributed to learning and not the speed-accuracy trade off. As mentioned previously and illustrated in Figure 8, the stability in response accuracy supports the notion that the changes in performance in the task can be attributed to motor learning.

Hypothesis 3: There would be a condition specific decrease in reaction times for the sequence response task.

This hypothesis was not supported by the results of the experiment. There was a decrease in the reaction time in the post-task condition but there was no interaction between the two groups. This suggests that just having ongoing exposure to the numerical keypad is enough to produce a shift in reaction time and the learning of the keypad occurring in the experimental condition does not transfer to the sequence response task. Given extended exposure to the motor learning task until, for example, performance began to plateau, may have provided some benefit to the sequence response task, but this is beyond the scope of the current thesis. Needless to say, the sequence response task cannot be used to examine the effects of the motor learning task.

While the design used in the current experiment has been successful, it requires some further modification in order to make it feasible for the later experiments described in this

thesis. One of these modifications: the partitioning of the response has already been described. However, further modification will be required in order to account for the difficulty recruiting adults with DCD. While the between-subject design used in the described experiment was suitable for the current experiment, it requires too many participants (at least 20) to be successfully run with a difficult to recruit population, such as adults with DCD. In order to reduce the number of participants required for the future studies the task was redesigned to have a within-subjects design. This was achieved by amalgamating the control and experimental conditions so that the experiment began and ended with a control block with multiple experimental blocks in between; this design is illustrated in Figure 14.

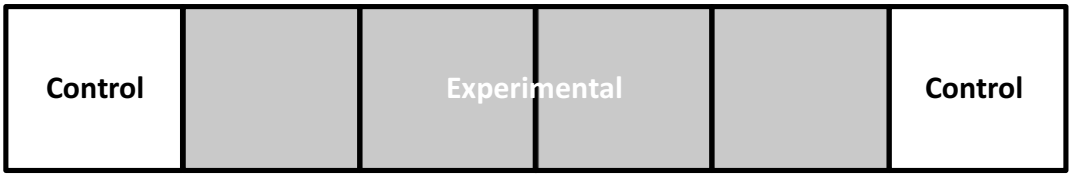

Figure 14 - Block order for within-subjects variant of the motor learning task

In conclusion, the motor learning task designed for use with DCD participants in the rest of this thesis was able to successfully produce motor learning in healthy adults, as measured by a decrease in reaction time. It will, as discussed, need some modifications to reduce the number of participants required and produce data on the distinction between the response selection and movement periods when an individual reacts. Thus the task can be used for the further studies included in this thesis. However, while the motor learning task produces an improvement in performance for the sequence learning task, it is a general improvement suggesting that the change is more to do with exposure to the numerical keypad rather than the task itself.

Chapter 3 – Methodology for assessment of DCD

Outline

Given that the aim of the current thesis is to investigate differences in early motor learning between typically and atypically developing individuals, a method for quantifying the differences in motor ability between the groups is required, in addition to the previously described motor learning task.

This primary purpose of the current chapter is to describe the methodology employed to distinguish between the neurotypical adults and the adults diagnosed with developmental coordination disorder (DCD). It will begin by giving the specific inclusion criteria of the populations being investigated and how they were recruited, before moving onto describing the particular assessments used to ensure the samples are consistent with the outlined populations.

Participant selection and recruitment

To investigate the questions outlined in the previous chapter this thesis drew on two populations: Neurotypical adults (that is, adults with no specific neurological or neurodevelopmental condition) and adults with a diagnosis of DCD or one of the synonymous conditions discussed in the introductory chapter.

General recruitment criteria

The general recruitment criteria for both groups were as follows: Participants recruited had normal or corrected to normal vision, were right handed, and were aged between 18 – 35 years old. An age upper limit of 35 years was set primarily because there is debate in the literature with regards the extent of the deterioration (if any) in neural plasticity of older adults (e.g. Freitas et al., 2011; Oliviero et al., 2006; Ren, Wu, Chan, & Yan, 2013; Smith,

Sale, Higgins, Wittert, & Pitcher, 2011), which could produce confounds in the results of the experiments described here. In addition, there is also research indicating that there may be changes in motor related EEG activity associated with aging (Labyt et al., 2004; Roggeveen, Prime, & Ward, 2007)

Participant recruitment

Individuals diagnosed with DCD were recruited through distribution of recruitment emails. These were primarily distributed through the disability services departments of higher education institutions within a 50 mile radius of London. Additionally, information about the study, with contact details for the primary researcher, was posted on several online resources (e.g. forums, social network groups, etc.) set up for individuals with DCD.

Neurotypical individuals were recruited from the general population, with most coming from the student population of London universities. These individuals were used as an age-matched control group for the DCD participants.

As outlined in the introductory chapter, there are a number of criteria that individuals have to fulfil to meet a diagnosis of DCD in childhood (see Table 1). However, given that there is a lack of assessment criteria for adults the following criteria were used to differentiate the DCD group:

1. Individuals needed to show continued coordination difficulties
2. Individuals needed a profile of motor difficulty and general ability comparable with DSM diagnostic criteria
3. Individuals should not have a profile of deficits that were beyond the scope of a motor coordination disorder and suggested an alternate diagnosis.

Evidence of on-going motor difficulties was assessed quantitatively using the modified motor battery and the Adult DCD checklist (ADC), both described below. The second criterion was assessed using a combination of tests: The ADC was used to determine

whether any motor disturbance significantly interfered with activities of daily living and began in childhood, while a set of sub-tests from the Wechsler Adult Intelligence Scale (Wechsler, 1997) to demonstrate that all participants fell within the normal range for intellectual ability. Finally, the third criterion was assessed based on a previous diagnosis of DCD or one of the previously described synonymous conditions at any age, as any alternate diagnosis should be ruled out before a diagnosis of DCD can be given.

Additionally, all participants were screened for Attention Deficit Hyperactivity Disorder (ADHD) initially using the ADHD self-report scale (ADHD SRS) and then later The Conners' Adult ADHD rating scale (CARRS). ADHD is a condition that is associated with increased distractibility and impulsiveness, and is reported to affect 3-5% of the global population (American Psychiatric Association, 2013) although, as noted in the introductory chapter, the prevalence amongst those diagnosed with DCD has been reported to be up to 50% (Dewey et al., 2002). The assessment was used to quantify the ADHD symptomology displayed within the recruited samples, ensuring that any differences found between the groups can be attributed to DCD rather than ADHD.

Participant assessment

Background assessment of participants

Background information about each participant was collected using a short questionnaire. This background information included basic information, such as their date of birth, sex, and handedness, as well as more detailed information on their educational attainments, diagnoses (if any), and medication (again, if any). Participants were asked to complete the Edinburgh handedness inventory (Oldfield, 1971) when they came in to participate in the study.

Motor Assessments for DCD

Motor ability was initially assessed with the Adult DCD Checklist (Kirby, Edwards, Sugden, & Rosenblum, 2010) which was included with the information pack sent out to potential participants. This was followed up by a series of motor assessments for the individuals who were invited in to participate in the experiments; the aim of these assessments was to quantify the difference in motor ability between the neurotypical and DCD groups.

The full list of the assessments used is summarized in Table 5 and each is described in full below.

Adult DCD Checklist

The Adult DCD Checklist (ADC) is a self-report questionnaire designed by Kirby et al. (2010) as a comparatively quick and reliable means of determining whether an adult could be classified with DCD without a formal diagnosis. It is based on three subscales: The first relates to difficulties that the individual experienced as a child enabling a history of childhood difficulties which can then be distinguished from acquired problems in adulthood. The second and third subscales relate to current difficulties that the individual considers are affecting their performance. While the second subscale focuses on the influence of DCD on the individual's perception of their performance, the third relates to current feelings about their performance as reflected upon by others.

The checklist is a consists of forty questions (ten in the first section, ten in the second section and twenty in the final section), which participants respond to using a four-point Lickert scale consisting of the answers: 'Never', 'Sometimes', ' Frequently', and 'Always' (scored 0 to 3 respectively). The original authors classified individuals attaining a score of 56+ as at risk and those attaining score of 65+ as having probable DCD.

Modified Motor Assessment

The Adult DCD Checklist was followed up with a battery of motor assessments as a more in-depth way of examining participants' motor ability. The majority of these assessments were sub-tests taken from the Upper Age Band (for ages 11 to 16 years) of the Movement Assessment Battery for Children 2nd edition (MABC2; Henderson, Sugden, & Barnett, 2007) as these have previously been demonstrated to be effective for differentiating adults with DCD (Cousins & Smyth, 2003). Additionally, several other assessments not part of the MABC2 that had also been shown to be able to differentiate adults with and without DCD were included (e.g. Finger-Thumb Opposition, Clap-Catch Task).

Each of the motor assessments used were first verbally explained and then physically demonstrated to ensure participants were aware of what they had to do prior to their attempt. Participants were also given a chance to practice the task; enabling the experimenter to be sure that they fully understood the instructions. A full description of each assessment (including how they were scored or quantified) is given below. All timings for the timed tasks were recorded in milliseconds.

Manual Dexterity tasks

The following tasks were used to assess the manual dexterity for each participant. Each task was repeated until two successful trials were recorded and the best of these trials was used for analysis. Unless otherwise stated each of these tasks tested the preferred and non-preferred hand separately, beginning with the preferred hand.

Table 5 - Summary of assessments used as part of this thesis

Demographic questionnaire:

Personal Information (e.g. Age, Sex, etc)

Diagnosis information

Adult DCD Checklist (Kirby et al., 2010)

Adult ADHD Self Report Scale (ASRS-v1.1; Kessler et al., 2005)

Motor Assessments:

Manual Dexterity:

Peg Turning Task (MABC2)

Peg Placement Task (MABC2)

Triangle Construction Task (MABC2)

Drawing Trail Task (MABC2)

Finger Thumb Opposition Task (PANESS-R; Denckla, 1973)

Ball Skills:

Catching with One Hand Task (MABC2)

Ball Aiming Task (MABC2)

Clap-Catch Task (Gubbay, 1975)

Balance:

Static Balance Task (MABC2)

Dynamic Balance Task (MABC2)

Zig-Zag Hopping Task (MABC2)

Wechsler Adult Intelligence Scale: (Wechsler, 1997)

Verbal Assessments:

Vocabulary

Similarities

Performance Assessments:

Picture completion

Matrix reasoning

Block design

Edinburgh handedness inventory (Oldfield, 1971)

Conners' Adult ADHD rating scale – Self-report: Short (CARRS-S:S; Conners, Erhardt, & Sparrow, 1999)

Peg Placement Task: The participant was provided with a pegboard and 12 pegs placed next to the board on the side corresponding to the unused hand. The aim of the task was to place all of the pegs (one at a time using only a single hand) into the pegboard as rapidly as possible. Participants were given a brief practice period for each hand where they were asked to pick up and place four of the pegs. Timing began when the first peg was picked up and finished when the final peg was inserted. If the participants dropped a peg out of reach, used both hands, or picked up more than one peg during the course of a trial it was considered a fail and restarted.

Peg Turning Task: Twelve pegs, each with two different coloured ends (red and green), were placed in a pegboard so that one colour was consistently showing. Participants used a single hand pick up each of the pegs and replace them in the board so that the opposite colour was showing, with the aim of inverting all the pegs as rapidly as possible. Participants were given a brief practice period for each hand where they were asked to invert four of the pegs. Timing of this task started from when the first peg was picked up and ceased when the final peg was placed into the board. As with the previous task, if the participants dropped a peg or used both hands during the course of a trial it was considered a fail and restarted.

Triangle Construction Task: The 9 components (3 bars, 3 nuts, & 3 bolts) used for this task were placed in front of the participant, and a complete model was placed above the components. The participant was asked to construct the triangle as fast as possible; any order of construction is acceptable as long as the final model is the same as the example. Participants were given a brief practice period where they joined two sides of the triangle. Timing of the task began when both hands left the desk-top and was stopped when the participant screwed the last nut onto the final bolt. If 2 sides were joined in wrong

arrangement, any of the items were rested on table or body, or any items were dropped the trial was considered a fail and restarted. As this was a bimanual task it was not repeated for each hand.

Trail-drawing Task: Age Band 3 drawing trails from the MABC2 were used along with a fine tipped pen. Using their preferred hand participants had to draw a continuous line from the starting point on the left to the ending point on the right while keeping within the boundaries of the trail. The trials were considered fails and restarted if the drawing direction was reversed, if the pen left the paper, or if the participants turned the paper more than 45 degrees away from the starting position. Both the number of errors and time taken for the successful trials was recorded.

Finger Thumb Opposition Task: This task was taken from a neurological motor assessment battery (Denckla, 1973) by Cousins and Smyth (2003) who demonstrated that adults with DCD perform significantly poorer on this task compared to neurotypical controls.

The aim of this task is to touch the thumb with each finger, starting with the index finger and moving in order to the little finger before restarting at the index. This sequence was repeated 5 times and was completed as rapidly as possible. The participant was given a brief practice period consisting of one cycle of the task with each hand before the recorded trials.

Ball Skills

The following tasks were used to assess the throwing and catching ability of each participant. Each of these tasks was performed only once and the score from this single trial was used for analysis.

Catching with One Hand Task: A line was marked 2 meters away from a bare wall and participants were instructed to stand behind this line and throw a tennis ball at the wall, catching the returning ball with the same hand. Participants were given five practice throws for each hand. Ten recorded throws with the preferred hand were performed with the number of successful catches recorded; this was then repeated for the non-preferred hand. The participant throw the ball from behind the line, the ball must be caught before it hits the ground, and it cannot be trapped against the body or in clothing for a catch to be considered successful.

Ball Aiming Task: A circular target (25cm in diameter) was placed on a wall with the lower edge at approximately the same height as the forehead of each participant. Participants were asked to stand behind a line 2.5 meters away from the wall and use their preferred throwing method (either underarm or overarm) to hit the target with a tennis ball. Each participant was allowed five practice throws followed by ten recorded throws and was given a score based on the number of hits they managed. The ball did not have to be caught on the return and this task was performed with each hand.

Clap-Catch Task: This task is not part of the MABC2 and was proposed for use in assessing motor difficulties in children by (Gubbay, 1975). It has, however, been demonstrated to be effective in differentiating adults with and without DCD (Cousins & Smyth, 2003).

For this task participants were instructed to throw a ball in the air and catch it with the same hand; while the ball was in the air they had to perform a number of hand claps. Participants were allowed a practice throw with each hand with a single hand clap before the recorded trials. The first trial used a single hand clap and the number increased by one for each successfully completed trial. There were four trials in total and the highest number

of claps successfully completed was recorded (with a maximum of four). Each hand was tested only once, starting with the preferred hand.

Balance

The following tasks were used to assess the balance of each of the participants. Each of the tasks was repeated twice and the better of the two scores was used for analysis. If a ceiling score was achieved for the first trial this was taken as the score and the task was not repeated.

Static Balance Task: Participants were instructed to balance 'heel to toe' on the MABC2 Balance Board. They were given a 15 second practice trial before the recorded trials. Timing commenced when the correct balance posture was achieved and ended either after thirty seconds had elapsed or when an error occurred. Errors include: lifting a foot, touching the floor with a foot, or touching the base of the board with the sides of the shoes.

Dynamic balance Task: A 4.5 meter straight line was marked out on the floor using tape. Participants were asked to walk backwards (heel to toe) along the line for 15 steps or until they reach the end of the line, whichever came first. Participants were given a practice trial consisting of 5 steps along the line. A score out of 15 was given based on the number of successful consecutive steps made; a full score of 15 was given if they reached the end of the line. To be considered successful, steps had to be made without stepping off the line, regaining balance by touching opposite foot to the floor, or leaving a large space between the heel and toe when planting the foot.

Zig-Zag Hopping: Six floor tiles from the MABC2 materials were placed on the floor in a zig-zag formation. Participants stood on a single leg on the first tile and had to perform 5 consecutive hops diagonally from one tile to the next until they reached the end.

Participants were given a practice trial with each leg consisting of 2 hops. Trials were considered fails if they hopped outside the area of the mats, hopped twice on a mat, let the raised foot touch the floor, stepped on any mat before the end, or lost balance on the end mat. The task was repeated for each leg and scored based on the number of consecutive successful hops.

Other assessments

In addition to the motor assessments each participant completed assessments of their intelligence and ADHD symptomology. The specifics of these assessments are described below:

Wechsler Adult Intelligence Scale – Third Edition (WAIS-III)

Two verbal and three performance sub-tests from the WAIS-III were used to ensure that intelligence was within the normal range. The sub-tests used were vocabulary, similarities, picture completion, block design, and matrix reasoning. Participants received a raw score for each of these sub-tests and standardised scores (referred to as scaled scores) were calculated for each participant based on their raw score and age. The scaled scores calculated were based on a normal distribution of scores within the entire population and consequently had a fixed mean score of ten with a standard deviation of one and a half; accordingly, participants who received a scaled score of seven or less (which is two standard deviations below the mean) for any of the sub-scales were not included in the study.

Adult ADHD Self-Report Scale (ASR*S-*v1.1) screener

The ASRS is a self-report scale consisting of 18 questions. It is used to ascertain the frequency with which respondents experienced symptomology consistent with the DSM diagnostic criteria for ADHD in the six month period prior to testing. The ASRS screener is a

(Kessler et al., 2005).short form version of the ASRS which performs equally well for clinical screening purposes

It consists of six questions taken from the ASRS to which participants respond using a five-point Lickert scale consisting of the answers: 'Never', 'Rarely', 'Sometimes', 'Often', and 'Very often'. The six questions are listed in Table 6.

Table 6 - ASRS screener questions.

1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?
2. How often do you have difficulty getting things done in order when you have to do a task that requires organisation?
3. How often do you have problems remembering appointments or obligations?
4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?
5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?
6. How often do you feel overly active and compelled to do things, like you were driven by a motor?

Four or more positive responses (classified as an answer of 'Sometimes', 'Often', or 'Very Often' for questions 1-3 and 'Often' or 'Very Often' for questions 4-6) are highly indicative of ADHD symptomology consistent with the DSM-IV diagnostic criteria.

Conners' Adult ADHD Rating Scales – Self Report: Short Version (CAARS-S:S)

The Conners' Adult ADHD Rating Scales (CAARS) are a group of scales that are designed to evaluate ADHD symptomology in adults. There are multiple different versions available, but for this study the short version of the self-report scale was chosen. This consists of a 26 items, to which participants respond on a four-point Likert scale consisting of the answers: 'Not at all, Never', 'Just a little, once in a while', 'Pretty much, often', and 'Very much, very frequently'. It measures ADHD symptomology across four subscales: 'Inattention/Memory

problems', 'Hyperactivity/Restlessness', 'Impulsivity/Emotional Liability', and 'Problems with self-concept', as well as giving a general index of ADHD symptomology. The raw scores produced by the CAARS – S:S are scaled based on the age and sex of the participant, these scaled scores can then be used to determine in which percentile a participant falls within for each of the subscales and the ADHD index.

The CAARS-S:S was administered alongside the ASRS to give a better idea of the extent (if any) of ADHD symptomology in the samples, as it provides a much finer grain of detail (in terms of both the range of scores and the specific profile of symptomology for each participant) than the ASRS.

As previously discussed, in addition to the methods described above, the studies in this thesis also used electroencephalography (EEG) and transcranial magnetic stimulation (TMS) to assess whether there were any electrophysiological or neurophysiological changes associated with performance changes on the behavioural task. A general outline of each of these methods and the specifics of the analyses used for each experiment will be presented in chapters four and six, preceding the chapters reporting the studies utilising these methods.

Chapter 4 – Introduction to EEG Methodology

Outline

Electroencephalography (EEG) is an electrophysiological technique developed in the first decades of the 20th century to measure the electrical activity produced by the brain. The first experiment to use EEG to collect a signal from the human brain was performed in 1924 by Hans Berger (Haas, 2003). He used two electrodes placed on the scalp and amplified the difference signal to produce a waveform that represented the changes in electrical activity of the brain over time.

Since that initial recording EEG has been used clinically and more recently has become a key technique within the field of cognitive neuroscience. It is particularly useful as it allows cognitive neuroscientists to associate the electrical activity produced by the brain with specific cognitive processes, with the aim of identifying the neural correlates associated with the cognitive process.

The current chapter aims to give the reader an understanding of EEG and how it was used in the current thesis. It will begin by discussing what is understood about the source of the signal being recorded by EEG. However, from a cognitive neuroscientific perspective raw EEG recordings are not very informative on their own for looking at the neural correlates of cognition, and so the chapter will then move on to discuss the steps taken to prepare the data for analysis and the different ways of analysing the recorded data. Finally, the chapter will discuss the use of EEG to investigate the questions posed in this thesis.

The EEG signal

It is the electrochemical nature of the neural and muscular tissue that allows activity to be recorded from them. This electrochemical activity consists of the movement of charged

particles into and out of these tissues in order to pass on information. Within the brain there are two processes occurring that involve this movement of ions: Post-synaptic potentials (PSPs) and action potentials (APs). It is the former that is being recorded via EEG.

Post-synaptic potentials

Post-synaptic potentials are generated when neurotransmitters released from a pre-synaptic neuron (or neurons) bind with receptors on the post-synaptic (or dendritic) cell membrane. This causes ion channels in the dendritic cell membrane to open allowing specific ions to flow into and out of the cell. While at rest neurons are polarized and maintain a charge of -70 mV and from here, depending on the specific ion channels activated, the cell membrane can either become depolarized or hyperpolarized. If the ion channels allow negative ions out and positive ions in then the charge becomes more positive and the membrane depolarizes, this is called an excitatory post-synaptic potential. If, however, the ion channels allow negative ions in and positive ions out then the charge becomes more negative and the cell membrane hyperpolarizes, this is known as an inhibitory post-synaptic potential. The movement of ions in and out of the dendrites also changes the charge around the dendrites compared to the rest of the neuron, generating a dipole and an electric field.

Typically, a post-synaptic neuron will receive inputs from multiple neurons, if the post-synaptic potentials generated by these inputs occur close enough in space and time they can sum to depolarize the cell membrane to -55mV, the firing threshold. At this threshold voltage-activated ion channels in the cell membrane open, allowing further depolarization of the cell and causing the chain reaction of depolarizations along the length of the axon that make up an action potential.

As previously stated, the neural activity detected by EEG reflects post-synaptic potentials rather than action potentials. This is because the PSPs occur in the grey matter of the brain (where the neurons connect to one another) which is, for the most part, located nearer the

scalp on the cortex; whereas the axons are typically located in the white matter, which is located deeper in the brain. In addition to this, when compared to action potentials, PSPs are slower and more likely to occur in synchrony. This synchrony is vital as the voltages generated by the post-synaptic potential of an individual neuron is still far too small to be detected at the scalp, it is however possible for the voltages generated by individual neurons to sum to produce a larger, detectable signal. Nonetheless, certain conditions are needed for the voltages produced by the post-synaptic potentials in individual neurons sum and produce a detectable EEG signal.

Firstly, the post-synaptic potentials must occur at approximately the same time (temporal alignment) in a sufficient quantity of neurons, usually numbering in the millions. Secondly, the dipoles produced by these potentials must be also spatially aligned. Groups of neurons that are not oriented in the same direction will produce individual dipoles that cancel one another out, resulting in no overall dipole and hence no signal. Similarly, if the types of potential, excitatory or inhibitory, are mixed then the opposing charges will cancel each other out, again resulting in no overall signal. Thus, a group of neurons numbering in the tens of thousands (at least) all with a similar orientation and all receiving the same type of input at approximately the same time will produce a summed dipole that can be detected by a recording electrode placed on the scalp.

All neurons in the brain contribute to the EEG signal, but the bulk of it is thought to be generated by the cortical pyramidal neurons as they fulfil all of the aforementioned criteria. However, it is certainly possible, although more difficult, to detect signals from other non-cortical areas.

Volume conduction

The process by which the summation of post-synaptic potentials on the cortex translates to a detectable signal at the scalp is called volume conduction. When a dipole is present in a conductive medium, in this case the brain and surrounding cerebrospinal fluid, the current

does not just flow between the two poles; it spreads out through that medium following the path of least electrical resistance until it reaches a surface, where it can be detected.

However, it should be noted that due to a number of factors a signal recorded at an electrode placed on the scalp does not necessarily reflect neural activity occurring directly under the site of that electrode; indeed, it is possible that signals generated at a point in the brain would be detected at a distant part of the scalp. This is partly due to volume conduction, as the signal spreads out in all directions from the source. The spreading of the signal is compounded as the current passes through different tissues in the head, particularly the skull, as each has a different conductivity which further distorts the signal, 'blurring' it.

Finally, the folding of the human cortex complicates this situation further as it means the orientations of the dipoles are not uniformly aligned in relation to the scalp. The overall orientation of a number of differently oriented dipoles can be calculated by averaging the orientation of the individual dipoles to produce an equivalent current dipole (ECD), but the ECD generated may not be oriented perpendicular to the scalp (as it would be if the brain were smooth) and thus the signal produced can be projected at an angle.

Source localisation

Given all the information about dipole source generation it would be relatively straightforward to estimate how the signal produced would be spread out over the scalp, this is called the forward problem. However, with EEG recordings the reverse is true: the distribution of a signal across the scalp is available but given this information it is incredibly difficult to localize where this signal was generated. This is called the inverse problem, and occurs because there are an infinite number of solutions to which dipole configurations would produce the recorded signal.

This problem can be partially resolved by applying logical constraints to reduce the number of possible solutions, for example by excluding solutions that place the dipole generator

outside of the head. However, despite this partial resolution, it should be recognized that EEG has a very poor spatial resolution with regard to the ability to determine which brain regions contribute to the measured signal when compared to other neuroscientific techniques.

EEG acquisition

As noted previously an EEG waveform can be recorded from just two electrodes, however modern systems tend to use 32, 64 or 128 electrode sites distributed across the scalp to provide the best possible spatial coverage, the most common system of electrode placement is based on the international 10-20 system (Luck, 2014) and Figure 15 displays a 64 electrode layout. Each electrode site records the difference in electrical potential between its position on the scalp and the ground electrode.

The EEG data in the reported experiments were recorded using a Biosemi Active two system. A 64 Ag/AgCl electrode set-up was used with the electrodes mounted on an elastic cap and positioned on the head according to the international 10-20 system. A sampling rate of 2048 Hz with a 24 bit analogue-to-digital conversion resolution was used for all EEG experiments.

The primary objective during the collection of EEG data is to ensure that the data initially collected are as free from artefacts as possible; while there are techniques that can be used post-recording to remove some of the artefacts they are not fool-proof and are not substitute for clean raw data. In this section potential sources of artefactual contamination and the steps that were taken to reduce their impact will be discussed.

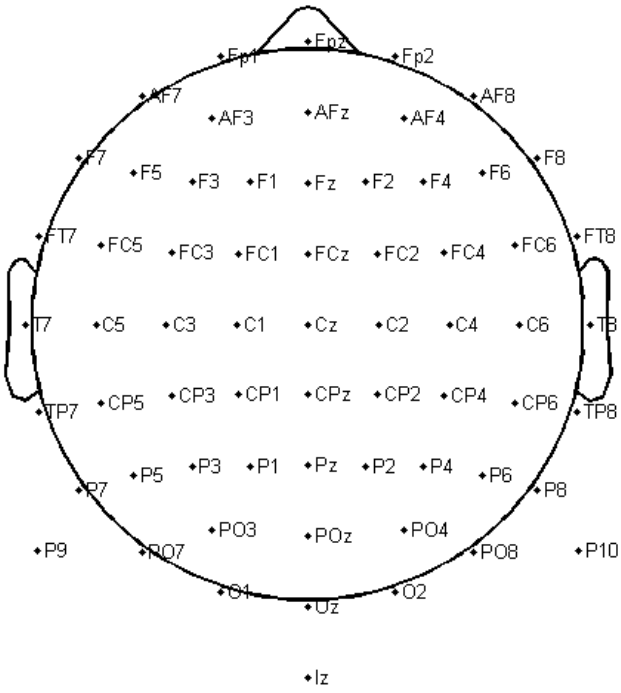

Figure 15 - 64-electrode layout using the international 10-20 system

Reference electrodes

The electrodes placed on the scalp will pick up activity from the brain, but will also pick up signal from a number of other sources, both internal (e.g. skin potentials) and external (e.g. line noise). Some of these extraneous signals can be removed post-recording using techniques such as filtering (which will be discussed later) but others would be practically impossible to remove using these post-recording techniques without also altering the signal of interest. Instead this extraneous activity is removed by subtracting either the mathematical average of all scalp electrodes or the signal collected from a reference electrode (or electrodes) from the signal picked up by each electrode on the scalp, leaving a waveform that is relatively pure measure of brain activity for each of the scalp electrodes.

This makes the placement for reference electrodes important as they are one of the key factors in collecting clean data. The most important feature of a reference site is that it should remain relatively isolated from brain activity whilst still being subject to the same internal and external sources of noise as the scalp electrodes. The most common sites are

on the earlobes, the tip of the nose, and the mastoids (the bony protrusion just behind the ear), and as each site offers its own advantages and disadvantages there is no site that is completely agreed upon. Thus, the choice of reference method and reference electrode location is often based on conventions adopted in the specific research area and requirements dictated by the data analysis employed. For all of the reported EEG experiments external Ag/AgCl electrodes were placed on the earlobes as references.

Ocular artefacts

Another potential source of interference comes from the eyes, specifically through eye movements and blinks. The retina acts as a dipole source and consequently as a participant blinks or moves their eyes it produces changes in potential that are large enough to be picked up by the frontal electrodes and contaminate the EEG recording. In some cases, these movements and blinks can occur systematically throughout the experiment (e.g. after stimulus presentation) and can obscure the neural signal, especially as the potentials produced by eye movements and blinks are many times larger than the signal being recorded from the brain.

When trying to isolate this source of noise the starting point is the experiment itself: what can be done to reduce the number of ocular artefacts that occur at critical times during the experiment? One way of reducing the amount of eye movements during a trial is the inclusion of a fixation cross as part of the experiment; instructing the participant to focus on it while it is on screen will reduce the amount participant's eyes wander during critical points of the recording. The experiment should also be built with the understanding that it is unrealistic to expect the participants not to blink at all throughout the recording session. Hence a specific period where the participant is able to blink freely without contaminating the data should be included and the participant should be instructed that they are free to blink during this time if required.

Even though using these principles when designing an experiment will drastically reduce the frequency of ocular artefacts that appear in a recording, it is inevitable that some artefacts will still appear in a recording. Consequently, it is important that a measure of the ocular artefacts be taken so they can be easily identified in the recording. It is possible to do this by placing electrodes on the face around the eyes in a technique called electrooculography (EOG). As will be discussed in the pre-processing section of this chapter, it is also possible to use the EEG and EOG data recorded to disentangle some of the ocular artefacts from the signal using computational methods such as independent component analysis (ICA).

Four external Ag/AgCl electrodes were used to record the EOG from participants: two for the horizontal EOG measures (one placed on the outer canthus of each eye) and two for the vertical EOG measures (one placed above the left eye and one below).

Other sources of noise

In addition to ocular artefacts the EEG can also pick up signal from muscular sources. As discussed in the TMS methodology chapter, electrical potentials can also be recorded from the muscles (EMG) and these are typically stronger than the EEG signal. Such EMG signals can be difficult to remove (depending on frequency of EMG signal) so it is best to minimise them as much as possible through practical means, for example: ensuring the participant is as comfortable as possible to minimise fidgeting and strain during the recording. Again, making it clear to participants when the crucial parts of the recording are will reduce the frequency of artefacts during those periods.

One of the final considerations is how to minimise external sources of noise. The environment is awash with various types of electromagnetic signal (e.g. wi-fi, mobile signal, radio waves, and 50 or 60 Hz line noise) and in much the same way TMS is able to induce activity in the brain, these signals will produce small currents in the EEG recording equipment. Normally these induced currents would be undetectable; however, because

neural activity requires amplification to be measureable, the induced noise is also amplified, contaminating the recording.

There are several ways this external noise can be mitigated: Firstly, how the EEG system is designed can reduce this. The current system used is an active system, which pre-amplifies the signal recorded at the electrode, significantly reducing the strength of any induced noise when the signal is further amplified later. Secondly, conducting the recording in a room free of electrical equipment and surrounded by a Faraday cage will also significantly reduce the contamination of the signal. The EEG experiments reported in the following chapters were conducted in a shielded room.

Pre-Proccessing

As previously mentioned, once the raw EEG data has been collected there are multiple different ways to analyze it. However, as the previous section implied the EEG recording equipment records all electrical activity regardless of source, thus before any analyses can be undertaken, a series of pre-processing steps must be undertaken to isolate the neural signal from the rest of the recorded activity. A complete pipeline of the pre-processing steps is displayed in Figure 16 below, and each of the steps will be explained briefly.

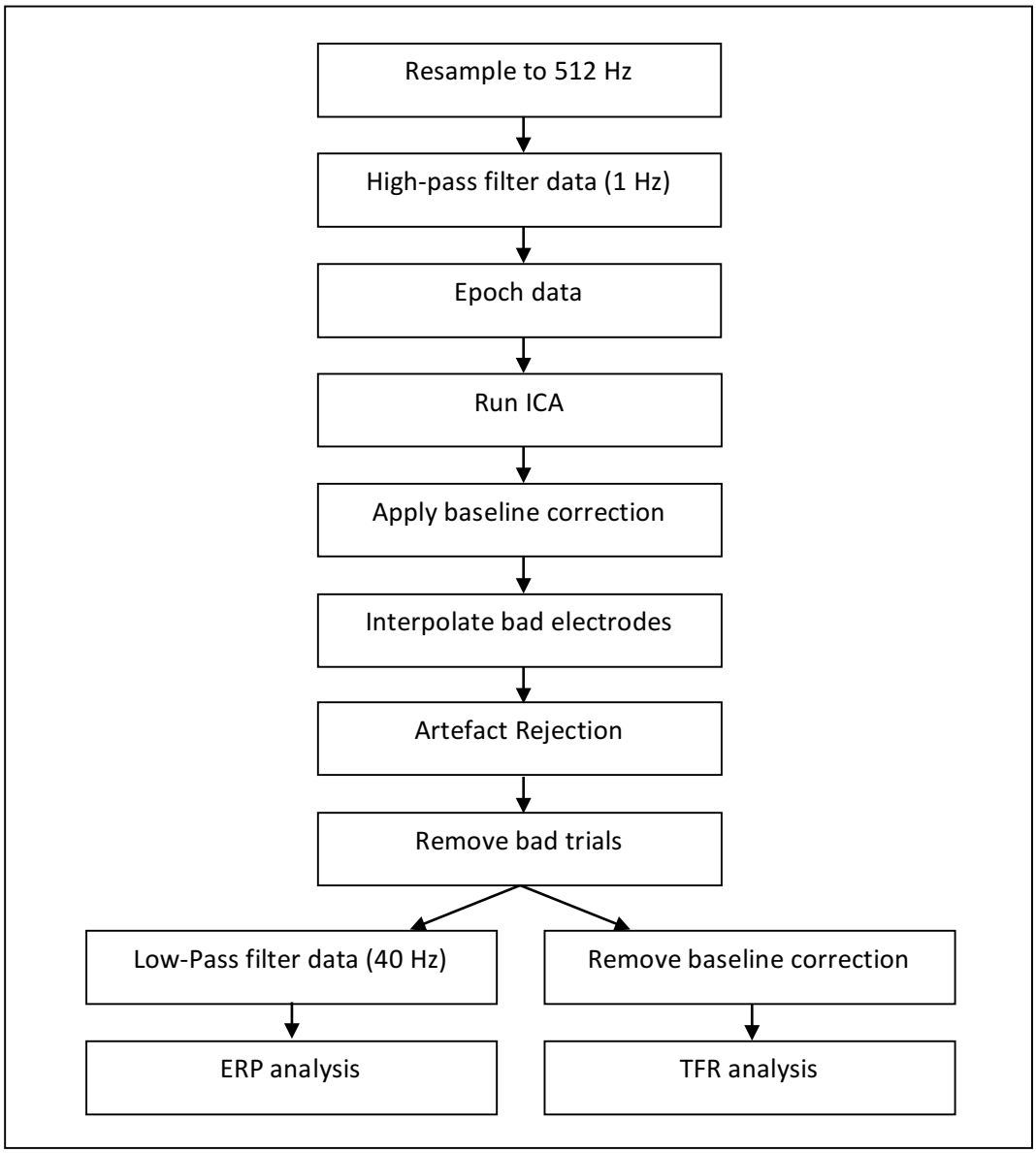

Figure 16 - Schematic of pre-processing steps used on the EEG data

Resampling

As previously mentioned, the data were recorded with a sample rate of 2048 Hz. While a higher sample rate does improve the temporal resolution for the data collected, and allow higher frequency ranges to be investigated in the analyses there are diminishing returns past a sample rate of around 500 Hz. Higher sample rates also increase the amount of storage space and computational time needed to process the data, thus the data were resampled at 512 Hz.

Filtering

The aforementioned subtraction of the reference waveform from each electrode will remove a lot of the noise from the recording. However, even after subtraction of the reference channels the EEG recording will still contain frequencies that fall outside of the range of interest for EEG research. These will affect the overall shape of the raw EEG waveform, potentially obscuring the neural signal amongst extraneous signals. This is remedied by applying filters to the data to remove specific frequency bands, thus reducing the impact of these frequencies on the data and giving a clearer indication of the neural activity accompanying a cognitive event.

However, as the above statements imply, filtering will alter the recorded EEG signal as the waveforms of particular frequencies that make up the original recording are being removed during filtering. Thus deciding the cut-off points for filtering becomes a balance between making the signal as clean as possible and minimizing the distortion to the EEG waveform. This is a particular problem for ERP analyses as the waveform itself is being analysed, and so distortions caused by filtering may impact upon the outcome of these analyses.

For the current pre-processing step, the data were filtered using a 1Hz high-pass filter to remove low frequency activity. Activity below 1Hz is generally considered to occur because of extraneous factors, for example: changes in skin potentials caused by sweating, and thus is not of interest for EEG analyses.

A 40 Hz low-pass filter was applied to the data prior to ERP analysis, but not for TFR analysis. This is because there are frequencies of interest above 40 Hz (e.g. high and low gamma) that can be examined using a frequency-analysis approach but these frequencies do not meaningfully contribute to the ERPs generated, instead they just make the waveforms generated noisier.

Epoching data

Continuous EEG data has its uses (e.g. in clinical practice) but generally in cognitive neuroscience an experiment is run where a number of stimuli occur repeatedly and the averaged neural response time-locked to that stimulus is examined. To get this information from the continuous EEG data it needs to be split into separate waveforms representing individual trials in a process called epoching. This is achieved by placing a marker in the EEG data during recording that indicates when a particular event (e.g. stimulus presentation) occurred. During pre-processing epochs are created around these markers, thus the activity in each epoch is a representation of the activity occurring before or after a particular event. In the current thesis there are two different types of epochs used: stimulus-locked and response-locked. As the name implies the stimulus-locked epochs are created around a marker indicating when a stimulus has occurred, this allows the activity immediately following presentation of the stimulus to be investigated. Similarly the response-locked epochs are locked to a marker indicting when a response occurred, these generally enable investigation of the activity leading up to a response execution, as is the case in the current thesis, but they can also be used to look at activity following execution of a response.

Independent component analysis

Filtering the data will remove some of the artefactual aspects of the recorded waveform, but it can only do so much. If there are artefacts that fall within a similar frequency range

to the neural signal being investigated the artefacts cannot be filtered out without affecting the neural signal.

This is the case for eye-movements and blinks: as the eye moves or blinks the associated potentials are picked up by frontal electrodes and contaminate the EEG signal. As discussed earlier, while it is important to try and minimize the number of blinks and eye movements that occur during crucial parts of an EEG recording is not feasible to completely prevent these events from occurring.

To save the data for trials that have been contaminated with blinks or eye-movements that would otherwise be discarded, independent component analysis (ICA) can be used to remove specific components of the EEG waveform. ICA is a computational technique that is able to separate a signal into its additive subcomponents; these can then be topographically plotted on a map of the scalp to identify artefactual components. ICA allows identification of eye-movement and blink artefacts as they have a distinctive profile (e.g. dominance in the extreme frontal regions when plotted topographically). The primary advantage of ICA over other methods of removing artefacts is that the components can be computed back into an EEG waveform minus the artefactual components, allowing for more of the data to be saved. It is possible to remove EMG, EOG and ECG artefacts from EEG data using ICA but it is most reliable for EOG artefacts, consequently it will only be used for the identification and correction of eye-movements and blinks in the reported experiments. It is possible to identify the artefactual eye-blink component by running the ICA on the data recorded from the scalp electrodes; however, to improve identification of the artefactual component a channel containing the vertical EOG (the difference wave between the two VEOG electrodes) was also included in the ICA.

Baseline correction

Baseline correction is a key step for ERP analyses as a way to account for differences in the vertical offset between trials, usually caused by drifts in the EEG recording. If unaccounted

for these drifts would result in more heterogeneity in ERP amplitudes across trials and individuals, producing ERP waveforms that are unrepresentative of the brain activity involved in the task. As mentioned previously, high-pass filtering is used to remove some of these drifts; however, it is a very coarse tool and so baseline correction is used to adjust the vertical offset on a trial by trial basis. This is achieved by calculating the average voltage over a specific time window in each trial and then subtracting that average voltage from the trial waveform. The most important part of this procedure is the selection of the time window used and while the choice of window can vary depending on the specific of the experiments being run; generally, a 200ms pre-stimulus time window is used. Pre-stimulus time windows are generally considered optimal as it is assumed they are representative of the overall drift in the EEG while containing little to no task related activity (as the stimulus has not been presented yet). There is no concrete consensus on how long the baseline period should be, but Luck (2014) suggests that a window of less than 100ms is too short, a window of above 100ms is acceptable, and a baseline period of 200ms or above is ideal. Thus this was the time window used for baseline correction of the stimulus locked epochs in the reported experiments.

Choosing a time window for baseline correction is a relatively straightforward process for stimulus-locked epochs; however, it can be more difficult for response-locked epochs. This is primarily because the time period preceding the response will contain activity related to the response; this activity may differ between experimental conditions and thus when the baseline is subtracted from the trial it may produce an erroneous result (i.e. a false positive or a false negative). For the purpose of the response locked-epochs in the reported experiments the baseline generated for the stimulus-locked epochs was also subtracted for the response-locked epochs.

Typically baseline correction for ERP analyses is applied immediately after epoching; however there is evidence that identification of ICA components is more reliable of the

data included has not been baseline corrected (Groppe, Makeig, & Kutas, 2009), thus the epochs were baseline corrected using the aforementioned time windows after artefactual components identified by the ICA were removed.

Confusingly, TFR analyses also include a step called baseline correction, although this has a different purpose, method, and occurs at a different time to the baseline correction described above. This type of baseline correction will be discussed in the section on TFR analysis below.

Interpolating bad electrodes

In an ideal recording each electrode would have an excellent connection to the scalp and produce a clear recording of the activity picked up at that site and, as stated in the EEG methodology section, as much should be done as is possible to ensure this is the case. Unfortunately, this is not always possible and it is likely that one or more channels will be either absent (due to a damaged electrode) or overwhelmingly noisy (due to a poor connection). In these cases, it is possible to attempt to reconstruct the waveform that may have been collected at that electrode. This is a technique called interpolation and it uses data from the surrounding electrodes to reconstruct the data from a missing or bad channel. There are multiple methods to interpolate a missing channel but the most common is spherical linear interpolation, this is what was used in this thesis.

This process must be performed after the ICA has been completed as one of the key assumptions made about the data prior to the ICA is that the data recorded at each electrode is independent; interpolation before the ICA would violate this assumption as the signal at the interpolated electrode would strongly correlate with the surrounding electrodes (as it is reconstructed from these electrodes).

Artefact rejection

Despite all of the methods described above used to remove artefacts in the data as possible there will still always be a few instances of epochs where artefacts remain. Obviously, these epochs are unrepresentative of the neural activity occurring during a trial and so leaving them in would alter the final results, and so these are removed before final analysis occurs. Generally this is achieved by using an automated process to mark any trial that breaks a specific rule (in the case of the current pipeline: an amplitude of ±80 mV), then visually inspecting the data to select any epochs with artefacts that the rule may have not picked up on, then rejecting all of the selected epochs.

Removing bad trials

The last step in the pipeline before the EEG data are analysed is to remove the 'bad' trials. The purpose of this step is to remove trails which would not be considered to have neural activity representative of the task being investigated. Firstly, trials where the reaction time was less than 100ms were deemed anticipatory and removed. Secondly, trials where the response was incorrect were also removed.

It would also be usual in this step to remove trials with a response time greater than two standard deviations from the mean. However, the distribution-fitting approach used with the behavioural data collected in this thesis makes this step challenging. A distribution based cut-off of 85% was used to identify and remove outlying trials. Although please refer to the following chapter for further explanation of the challenge in combining these approaches and the solution proposed.

Data Analysis

Once all of the pre-processing steps have been completed the data from the EEG recording should be much more representative of the neural activity than the raw EEG recording.

However, this activity originates from a multitude of different sources in the brain and consists of a mixture of activity that is related to the task and activity that is unrelated. Obviously a cognitive neuroscientist is primarily interested in the task related activity, as this represents the neural correlates of cognition. Thus this section of the chapter will outline two methods used to separate the task related activity from the task unrelated activity.

Event Related Potentials

An event related potential (ERP) methodology uses two principles, time-locking and averaging, to distinguish the task-relevant activity from the task-irrelevant activity.

When performing a task, it can be assumed that activity relating to the task should occur at approximately the same time every time the task is performed, in other words the task-related activity is time locked to the task. In contrast, the task-irrelevant activity is assumed to occur at the same time as the task relevant activity but is not time-locked to the task, and thus is essentially randomly distributed throughout the trials. Consequently, when a number of trial epochs are averaged together the time-locked task-relevant activity will remain in the averaged waveform, while the task-irrelevant activity cancels itself out.

ERP components are generally named according to the direction of the voltage shift (either positive or negative) and either their timing relative to the event onset or the order in which they occur (usually expressed as a number). So, for example, there is an ERP component consisting of a positive shift in the waveform recorded from the parieto-occipital regions approximately 200ms after a stimulus is presented; this component is typically referred to as the P200, reflecting its positive shift and timing, or the P2 (also reflecting its positive shift and the fact it is the second positive peak from stimulus onset.

The main properties of ERPs that are examined are the amplitude of the ERP and the latency. The amplitude of an ERP is the degree of deviation from zero (measured in uV) and

the latency is when an aspect (e.g. the peak) of the component occurred (measured in ms) relative to the time-locking event.

ERPs examined in this thesis

Given the aim of this thesis is to look at the changes in motor cortical activity during the early stages of motor learning, the primary ERPs being examined in the following experimental chapters will be the Lateralized Readiness Potentials.

Lateralized Readiness Potential (LRP): Prior to a unimanual response a slow negative shift in voltage can be recorded from the electrodes placed over the motor areas; this is known as the Bereitschaftspotential (BP) or Readiness Potential (RP). As movement onset approaches the BP becomes more prominent over the electrodes contralateral to the responding hand, this is the Lateralized readiness potential. Typically, the LRP is isolated using a double subtraction technique: activity is recorded while participants respond unimanually with either their left or right hand, then activity for the contralateral electrode is subtracted from the ipsilateral electrode for each type of response to produce a difference wave for each hand. Finally, the two difference waves are subtracted from one another to produce the LRP waveform (this method can be represented by the equation: LRP = RHR(C3-C4)-LHR(C3-C4); de Jong, Wierda, Mulder, & Mulder, 1988). This method cancels out any of the other lateralised components that may occur at the same time as the motor response. The double subtraction method was not possible in the reported experiment as only the right hand was used for responses. Thus, a single subtraction method was used for the analyses (i.e. LRP = RHR(C3-C4)). The experimental design minimised the lateralisation of non-motor components (e.g. the stimulus was presented on the midline to reduce the lateralisation of ERPs associated with early visual processing).

As mentioned earlier in the chapter, the fact that an ERP component is recorded from the electrodes above a particular brain region does not mean that that brain region is the

source of the component. However, there is evidence that the primary motor cortex is the source of the LRP: intracranial recordings in animals have demonstrated a similar negative shift prior to response execution (Gemba & Sasaki, 1990; Riehle & Requin, 1989). Similarly, MEG recordings (which are not subject to the aforementioned signal distortion problems as EEG) demonstrate a similar lateralised negative shift prior to movement onset originating from the sensorimotor areas (Okada, Williamson, & Kaufman, 1982). A final piece of evidence for the LRP originating from the primary motor cortex is paradoxical lateralisation. This is the name given to the reversal in polarity when responses are given by foot instead of hand, and is thought to be caused by the location of the foot and hand areas on the primary motor cortex (Brunia, 1980). The hand areas lie on the cortex parallel to the scalp, thus produce the previously described negative shift in the recording electrodes over the contralateral hemisphere; whereas, the foot areas lie in the median longitudinal fissure, with the outer cortical surface facing the ipsilateral hemisphere. Thus when the foot motor area is activated prior to movement the negative pole of the dipole produced is facing the electrodes over the ipsilateral hemisphere.

As will be discussed in more detail in the following chapter, there is evidence for changes in of LRP properties with age (Roggeveen et al., 2007), movement disorders (e.g. Parkinson's disease; Praamstra, Meyer, Cools, Horstink, & Stegeman, 1996) and motor learning (Eimer, Goschke, Schlaghecken, & Stürmer, 1996).

However, simply using ERPs to examine the data may limit the conclusions that can be drawn about the neural correlates of this task. This is because the task-related activity must be phase-locked within each trial to produce a clearly identifiable in the waveform after averaging. If the activity for different trials is out of phase, the non-phase locked activity will be cancelled out during averaging and the information present in the waveform is lost. One way around this is to also examine the time-frequency representation (TFR) for the trials.

Time-frequency analyses

This methodology is based on the aforementioned fact that all waveforms can be described by the summation of sine waves with regular frequencies. Consequently, any complex waveform, including the recorded EEG waveform, can be decomposed into a spectrum of regular frequencies with specific amplitudes and phases using a Fourier transform. This principle can be extended further by examining the contribution of different frequencies to the recorded waveform at specific time points, producing a time-frequency representation of the signal. This allows changes in the signal over time, in response to a stimulus, or in preparation for an action to be examined.

One of the clearest examples of changes in oscillatory power in response to a stimulus was noted by Hans Berger in his original experiments with EEG: An 8-12 Hz oscillation that is present when an individual is in a relaxed state, and increases in power when their eyes are closed. He termed this 'Alpha' activity and since then a range of other frequency bands that occur in EEG recordings have been identified and categorised.

The primary frequency bands are defined by logarithmically increasing centre frequencies and frequency widths, and the most typically associated with cognitive activity include: delta (2-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (15-30 Hz), lower gamma (30-70 Hz), and upper gamma (80-150 Hz). Although, there are no solid boundaries between these bands and so the ranges may be reported differently, for example: Beta band activity has been reported as low as 13 Hz and up to 35 Hz (Androulidakis et al., 2007). In addition, some of the frequency bands listed may be subdivided (e.g. the 10-12 Hz Mu band or the 13-15 Hz sensorimotor rhythm) and there is activity that fall outside of the bands listed above (e.g. the 150-600 Hz omega band).

As previously mentioned, the primary source of the EEG waveform is thought to be the summation of post-synaptic potentials for large groups of neurons located in the cortex. These post-synaptic potentials are driven by external inputs (from other groups of

neurons), and consequently when these external inputs occur at regular intervals the shifts in post-synaptic potentials are picked up as oscillations. As the number of neurons receiving these inputs increases the amplitude of the signal increases, and thus the spectral power increases. The increase and decrease of spectral power indicates the respective synchronisation and de-synchronisation of the groups of neurons contributing to these oscillations.

Changes in power in these bands of activity have been related to various types of cognitive function. For example, an overall decrease in alpha power has been associated with increasing attentional demand, alertness and task load and there is evidence that theta power increases during memory tasks, particularly during encoding (For reviews of the type of cognitive activity associated with different frequency bands see: Schnitzler & Gross, 2005; Ward, 2003).

Once the EEG data have been pre-processed there are multiple ways of decomposing a signal into a time-frequency representation. Some of the more common methods used include: Complex Mortlet Wavelet analysis; which uses multiple sine waves with Gaussian tapers to determine the contribution of a frequency to a time point in the signal, Filter-Hilbert; which involves band-pass filtering the signal between specific frequencies and then applying a Hilbert transform to the filtered signals, and Short-Time fast Fourier transform (FFT); which performs multiple Fourier transformations on short time windows along the length of the signal. Each of these methods have their own strengths and weaknesses and will produce subtly different time-frequency representations based on those, however it is beyond the scope of the current thesis to go into specifics. The TFR analyses reported in the following experiments used the complex Mortlet Wavelet method to produce the time frequency representations.

Once a time-frequency representation has been produced for the signal, a baseline correction must be applied to it. This is different to the baseline correction mentioned in

relation to the ERP analyses as drift in the EEG recording is less problematic for Time-Frequency analyses. When the EEG signal is decomposed into the different frequency bands it is important to ascertain whether the power of those frequency bands during performance of a task deviate from a resting brain activity, and, if so, by how much. This is usually achieved by looking at the time-frequency content of the pre-stimulus EEG activity and then using it to normalise the activity in the rest of the epoch.

Neural oscillations examined in this thesis

As with the ERP analysis, given that the primary aim of this thesis is to examine changes in neural activity associated with the early stages of motor learning, oscillatory activity associated with motor preparation was examined in the following experimental chapters. Spectral power changes associated with motor preparation occur in three frequency bands: Alpha, Beta and Gamma, however this thesis will only focus on the former two.

Changes in both alpha- and beta- band activity have been observed during a wide variety of motor learning tasks (Boonstra, Daffertshofer, Breakspear, & Beek, 2007; Pollok et al., 2014; Zhu et al., 2010; Zhuang et al., 1997). and while there is evidence of correlation between these two bands (Carlqvist, Nikulin, Strömberg, & Brismar, 2005) there are differences in their time course before movement onset that suggest that they are independent (Neuper & Pfurtscheller, 2001; Neuper et al., 2006). This distinction between the two bands is further supported by the lack of coherence between the alpha band and EMG activation (van Ede & Maris, 2013) and the lack of somatotopic specificity in alpha band changes (Nierula, Hohlefeld, Curio, & Nikulin, 2013), both of which are present in motor-related beta band activity. As a result, these bands were treated as distinct.

Alpha spectral power: While at rest alpha activity is synchronised, and as motor preparation, or motor imagery, begins alpha activity begins to desynchronise resulting in a drop in power. Post-movement levels of alpha synchrony rebound, temporarily exceeding

pre-movement levels. Some papers refer to mu activity instead of alpha, but as mentioned previously the mu band is just a narrower band of activity within the alpha band.

Beta spectral power: Similarly, to alpha activity, beta activity is synchronised while there is no movement, desynchronises when motor preparation or imagery occurs, and resynchronises when the preparation, action or imagery has finished. However, unlike alpha activity, beta activity also re-synchronises when limbs action has ceased but muscles are still engaged (e.g. maintaining grip on an object), consequently it has been suggested that beta synchrony be involved in maintaining states in actions. This hypothesis was supported by a study by Pogosyan, Gaynor, Eusebio and Brown (2009) where applying beta band electrical stimulation slowed voluntary movement.

As with alpha and mu frequency bands, some papers refer to the sensorimotor rhythm instead of beta activity but, again, the sensorimotor rhythm is a narrower band of activity within the beta spectrum.

The following chapter will describe precisely how this EEG set-up was used as part of an experiment to examine the electrophysiological correlates of the early stages of motor learning in adults with and without DCD. In addition, it will present the results of the experiment and discuss their relevance with regards current understanding of the neural basis of motor learning.

Chapter 5 – Electrophysiological correlates of the early stages of motor learning in adults with and without DCD

Abstract

It is well understood that voluntary movements are accompanied by specific patterns of neural activity. These patterns of activity change as movement become increasingly automatized during motor learning. What is not as well understood is how these patterns of neural activity relate to individual differences in the early stages of motor learning; in particular, whether there are differences in these patterns of neural activity among individuals with developmental coordination disorder (DCD). Thus the aim of this study was to investigate the neural correlates of early motor learning in adults with and without DCD using electroencephalography (EEG).

Twenty-four participants (twelve control and twelve DCD) undertook a novel motor learning task while EEG activity was recorded. The motor-related electrophysiological activity recorded was then analysed using an event-related potential and a time-frequency representation approach. The study found that motor performance improved in the control group, but not in the DCD group. However, no change in motor-related electrophysiological activity was observed for either group over the course of the task.

These results are discussed with regards the specific methodologies employed in the study, and then considered in the light of the previous study establishing the motor learning task and the wider literature on both motor learning and DCD.

Introduction

As discussed in the previous chapter, there is a specific profile of neural activity that occurs in the moments leading up to the execution of a unimanual movement: If examined using

an event-related potential approach there is the slow negative shift (termed the readiness potential; RP) that begins several hundred milliseconds before movement onset and slowly builds until onset is reached. Alternatively, if a time-frequency approach is used there is an event-related desynchronisation (ERD) in alpha and beta band activity prior to movement onset.

Given the differing progression of activity produced by these two approaches (i.e. the readiness potential becomes increasingly lateralised, while the opposite occurs for the ERD) it is fairly clear that they are not measuring the same processes. Nonetheless, both are of interest for researchers looking at the neural correlates of motor learning and have led to the question: does activity in either of these measures change as motor learning progresses?

Before discussing the currently available evidence addressing this question it should be noted that EEG is a less frequently used tool in the examination of motor learning and the associated neural correlates, primarily due to its poorer spatial resolution compared to fMRI. However, this is not so much of a problem as it first appears as there is robust evidence that both the LRP and the ERD of both alpha and beta activity recorded from the central electrodes primarily originate from the motor areas (Ball, Schreiber, Feige, & Wagner, 1999). Thus, the use of EEG to examine motor learning allows the time course of neural activity during motor preparation while a task is being learned to be investigated in fine detail, with a reasonable certainty that the signal is being produced by the areas of interest.

There are two complementary approaches that can be taken to examine the effects of motor-skill learning on motor-related EEG activity. The most popular is the cross-sectional approach whereby two groups of differing motor abilities (typically experts in a particular motor skill and novices) perform a simple motor task and the EEG activity recorded is compared. For example, studies of high-level shooters demonstrate that their movement-

related cortical potentials (MRCPs) are altered compared to unskilled controls, typically with a reduction in the amplitude and onset latency usually taken to indicate more efficient processing (Di Russo, Pitzalis, Aprile, & Spinelli, 2005; Fattapposta et al., 1996). Similar findings have also been observed in elite and novice martial artists (Hatta, Nishihira, Higashiura, Kim, & Kaneda, 2009; Kita, Mori, & Nara, 2001), demonstrating that these changes are associated with motor expertise rather than associated with a particular sport. However, as Wright and colleagues point out many of the tasks used in the previous studies have poor ecological validity, and it Is questionable how well the findings from these simple tasks would scale to more complex motor performance (D. J. Wright, Holmes, Di Russo, Laporto, & Smith, 2012). In order to amend this, they examined the movement-related cortical potentials (MRCPs) in expert guitarists and non-musicians while they played a scale on a guitar. In support of the previous findings, Wright and colleagues found that there were differences in the later components of the MRCP, with smaller amplitude in the negative slope and motor potential components and a later onset for the negative slope for the expert group. These changes in motor related ERPs are typically described as 'increased neural efficiency' where the motor cortex expends less energy or resources to do the same thing; it is unclear whether this is the case although some research has called this into question (e.g. Del Percio et al., 2008).

In a similar vein, there are a number of studies that utilise a cross sectional approach to examine the changes in ERD associated with motor skill acquisition (Hatfield, Haufler, Hung, & Spalding, 2004; Haufler, Spalding, Santa Maria, & Hatfield, 2000; Hillman, Apparies, Janelle, & Hatfield, 2000). These generally show differences in alpha and beta frequency band activity between novices and experts, although there no consensus in the direction of these differences.

While the previously described research indicates that the acquisition of a skill does result in changes to motor-related EEG activity, studies utilising a cross-sectional approach are

not able to indicate at what point in the learning process these changes occur. Instead a longitudinal approach must be taken in order to investigate developments in electrophysiological activity during motor learning. There are a number of studies that have looked at the evolution of motor-related EEG activity during the early stages of skill acquisition. These have been previously discussed in the introductory chapter, but their findings will be reiterated here for the sake of completeness.

One of the earliest of these studies was conducted by Taylor (1978) who asked participants to practice a sequence of button pushes, instructing them to perform the sequence as rapidly as possible without making any error. Over the course of the task he observed a significant reduction in the time taken to perform the sequence, indicating that the sequence was becoming increasingly automatic. This reduction in performance time was accompanied by a gradual increase in RP amplitude. This is somewhat surprising considering that expert motor performance is associated with a reduction in motor related EEG activity; however, this increase in amplitude was followed by a reduction in amplitude at certain electrodes once a plateau in task performance had been reached. The latter finding has been supported by a number of other studies (Lang et al., 1992; Niemann et al., 1991; Wright, Holmes, Di Russo, Loporto, & Smith, 2012). Although the specifics of the findings for each of these studies are slightly different (i.e. some find a difference in onset while others do not, etc.), this may be due to the different types of task that each of these studies have used. Eimer, Goschke, Schlaghecken, and Stürmer (1996) used a serial reaction time-like task to look at the neural correlates of implicit and explicit motor learning. They found comparable results to the previous studies, with a reduction in the onset time of the LRP as participants improved on the task. Although it should be noted that, as discussed in a previous chapter, the SRT task and variations of it are not directly relevant to this thesis as they take a different approach to motor learning. Nonetheless, taken together these studies provide evidence that the electrophysiological differences (as measured by ERPs)

observed between the experts and novices can be observed during the early stages of motor learning.

As mentioned in the introduction, most of the longitudinal research using TFR analyses to examine motor learning comes from the brain-computer interface domain (BCI). Pollok and colleagues used an SRT task while recording neuromagnetic activity using a Magnetoencephalograph (MEG). They found that alpha-ERD significantly decreased over the course of the task and while there was no accompanying decrease in beta-ERD, there was a statistically significant negative correlation between the beta ERD and the reaction times (Pollok et al., 2014). However, while Kranczioch, Athanassiou, Shen, Gao, and Sterr (2008) observed similar decreases in beta-ERD during learning, they found that alpha-ERD increased as the participants learned their task. As mentioned in the introductory chapter, this discrepancy may be related to the differing tasks used.

While there is a general direction to the previous findings of the ERP research described above, the lack of specific consensus makes it difficult to formulate a strong hypothesis about the effects of practice on motor-related ERPs. Nonetheless, given that all of the above studies report some degree of change within the EEG activity it is expected that changes in motor performance on the task will translate to changes in the motor-related ERPs. Similarly, while there is a general direction to the effects of motor learning on ERD, currently the research is somewhat scarce and so a more exploratory approach will be taken when analysing this.

As explored in the introductory chapter, the literature around procedural motor learning in DCD is somewhat contradictory, with some studies showing that motor learning is intact and others showing that it is impaired. Nonetheless, given the design of the motor task used in this thesis and the details of the previous experiments exploring procedural motor learning in DCD, it is expected that the adults with DCD will show impaired learning for this

task. It follows that if there is no change in performance behaviourally then it is also expected that there will be no change in either the LRPs or ERD as the task progresses.

Hypotheses

As discussed, the prior literature suggests that motor learning is associated with changes in the lateralised readiness potential (LRP). Thus, the primary hypotheses for this study is that the control group would show improvement in the experimental blocks of the task, and that this would be accompanied by changes in the properties of the LRP. On the other hand, it was expected there would be no change in motor performance for the DCD group and thus there would also be no change in the properties of the LRP.

As with the previous experiment, participants were instructed to be as accurate as possible in the experimental blocks, thus it was expected that there would be no change in accuracy for either group over the course of the experiment. Additionally, it was expected that there would be no significant change in motor performance for the control blocks for either group.

In addition to these hypotheses, this study will use a cluster-based permutation approach (explained in more detail below) to examine the stimulus-locked ERPs and the time-frequency representations for both the stimulus- and response-locked epochs. As will be expanded on below, this approach will allow the rich dataset to be explored without a-priori hypotheses while also controlling for the chances of finding a false positive.

Methods

Participants

25 participants were recruited for this study. Twelve were 'neurotypical' adults while thirteen had previously received a diagnosis of DCD. All of the participants were right handed and aged between 18 and 35. One of the participants was excluded from the analysis as one of her scores on the WAIS subtests fell below the cut-off outlined in chapter three.

Consequently, the remaining participants formed two groups with each group consisting of ten female and two male participants. There were no significant differences between the two groups in terms of age, handedness or general intelligence measures, see

Table 7 below for details. The two groups did significantly differ in terms of their motor ability (as assessed by the MABC2 and the ADC). In addition, the groups did differ significantly on the ASRS although as there were no differences for the CARRS-S:S this may be due to the limited range of the ASRS.

Materials

As with the previous experiment, the task was run on a Windows XP machine using MATLAB (Version: 7.11.0.584) and Psychtoolbox (Version: 3.0.9) to display the stimuli and record the responses and reaction times for each of the tasks. All stimuli were presented in the centre of the screen in a black, size-24 font on a white background and viewed at a distance of 950mm. Responses were collected using a numerical keypad connected to the computer via USB port.

EEG data were recorded throughout the task on a Windows XP machine using Actiview, and the specifics of how the signal was recorded and initially processed are detailed in the previous chapter.

Table 7 - Summary of participant characteristics for the experiment in chapter five

Measure	Control	DCD	*F* (1, 23)	*p*
Age	27.92 (2.97)	26.58 (3.87)	0.90	0.35
EHI Score	88.67 (15.31)	88.13 (16.55)	0.01	0.93
MABC2 score	103.08 (15.70)	83.33 (22.02)	6.40	**0.02**
ADC score	23.00 (14.12)	89.17 (13.36)	139.00	**<0.01**
ASRS	0.42 (1.44)	4.92 (1.56)	53.64	**<0.01**
CAARS - S:S*	49.75 (9.89)	57.14 (12.02)	2.11	0.16
Vocabulary (WAIS)	13.75 (1.54)	13.92 (2.81)	0.03	0.86
Similarities (WAIS)	14.00 (1.54)	12.50 (3.00)	2.38	0.14
Picture completion (WAIS)	12.08 (2.43)	11.75 (1.82)	0.15	0.71
Block design (WAIS)	13.17 (1.95)	12.00 (3.02)	1.27	0.27
Matrix reasoning (WAIS)	14.33 (1.78)	14.25 (1.96)	0.01	0.91
***Degrees of freedom for this variable are 1, 18**				

Task

The task used for this experiment followed the proposed outline of the task described in the discussion section of chapter two. That is: the original task was converted to a within-subjects design by amalgamating the control and experimental conditions. The block order is illustrated in Figure 14 and the trial order is illustrated in Figure 2.

In addition, responses were modified so that the total response time could be partitioned into the time between stimulus onset and response onset (reaction time) and the time between response onset and response completion (movement time). The reasons for each of these changes are discussed in full in chapter two. In order to account for the reduced number of experimental blocks in the within-subjects version of this task the number of trials per block were increased from 104 to 120.

Finally, in order to allow brain activity to return to baseline before each trial, the inter-trial interval was increased by 500ms to between 1800ms and 2300ms. This adjustment was vital to ensure that EEG activity or rebounds from a previous trial did not contaminate the following trial.

Procedure

Participants began by completing a standard consent form (See Appendix A), followed by the battery of tests outlined in chapter 3. Upon completion of the test battery the experimenter and participant moved to the EEG lab and the electrodes were applied to the participant's head in the positions described in the previous chapter. Participants were then moved into an electromagnetically shielded room to complete the task. Once the participant was sitting comfortably at the computer the experimenter briefly outlined the task, explaining that they would do one control block, followed by four experimental blocks, and then one final control block. The experimenter described how participants should respond in each of the blocks and also emphasised the need for participants to respond as rapidly as possible whilst maintaining a high degree of accuracy. The tasks were then administered in the order described above with breaks taken between the blocks as needed. Once the participant had finished the task they were debriefed and allowed to ask any questions they had about the study.

Ethics

Ethical approval for this project was obtained from the Goldsmiths Psychology Department Ethics Board.

The experimenter outlined the experiment in full prior to signing of the consent form, and the right of the participant to withdraw at any time without having to give a reason was emphasised both verbally and in the consent form. Additionally, participants were informed that all the data collected, in both paper and electronic format, would be

associated with a participant number only, and contained no information that could be used to identify a specific individual. Finally, participants were informed that they had the right to withdraw their data at any time after the completion of the experiment, and were given contact details for the researcher and their unique participant number to do this.

Data analysis

Behavioural Analysis

As with the previous study, a distribution analysis attempted to fit an Ex-Gaussian distribution to the behavioural data on a block by block basis for each participant. The estimated distribution was then compared to the observed data using a chi-squared goodness of fit test. If the estimated distributions fit for over 80% of the blocks then the summary statistics produced by the analysis (Mu, Sigma, and Tau, previously described in chapter two) were used for the statistical analysis. In the case of blocks where the fit of the distribution was poor, the summary statistics for those blocks were not included in the analysis. The success of the fitting procedure across blocks was visualised to ensure that the blocks which did not fit were not from a specific source (i.e. a particular participant or block number). If the estimated distributions fit for less than 80% of the blocks, then the traditional approach described in chapter two was utilised. The variables produced by these approaches (mu, sigma, and tau or log-transformed mean reaction time and standard deviation of reaction time) were analysed using a mixed-design ANOVA.

As discussed previously, the current task was modified so it produced three performance measures see Figure 13 for an illustration): Total response time, the time between stimulus onset and response offset (henceforth called TT); reaction time, the time between stimulus onset and response onset (henceforth called RT); and movement time, the time between response onset and response offset ((henceforth called TT). Thus three mixed-design

ANOVAs were conducted for each of these partitions, each with one between-subjects factor: Group (with two levels: Control and DCD), and one within-subjects factor: Block (with four levels: Block 2 to 5).

EEG analysis

The pre-processing for the EEG analysis for this chapter followed the steps outlined in the previous chapter. However, In order to ensure that the data is appropriate for analysis and that the behavioural and EEG results are comparable, a cut-off was applied to the reaction-time distribution to remove any trial that fell within the final 15% of each reaction time distribution (see Figure 17 for an illustration).

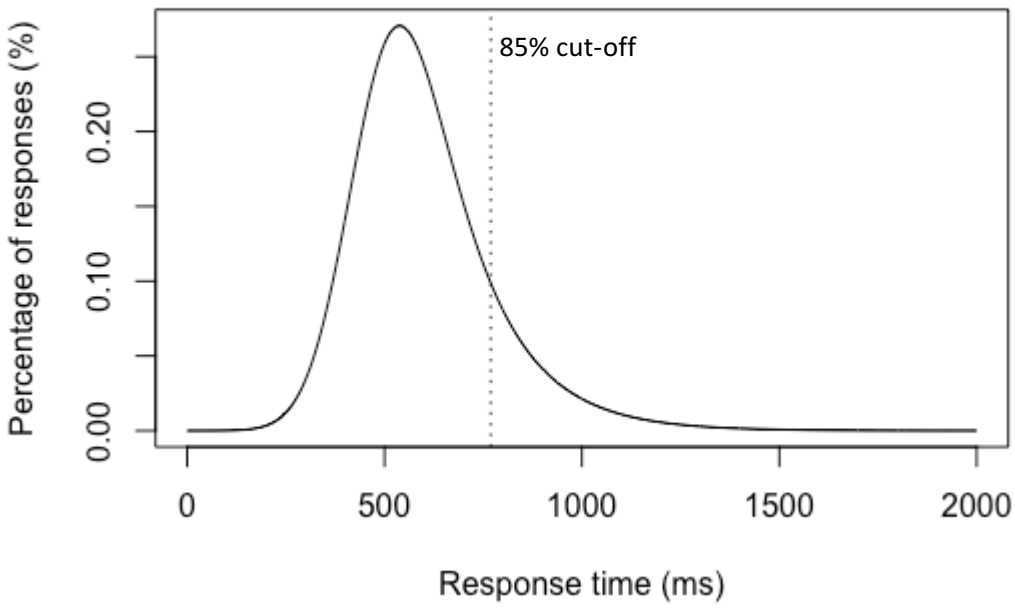

Figure 17 - Cut-off applied to behavioural trials for EEG analyses

This cut-off is required because the EEG activity recorded from trials that fall in the rightward tail of the reaction time distribution do not necessarily follow the same time course as the signal produced by the majority of the other trials, and inclusion of these trials would add noise to the analyses, potentially resulting in an erroneous result during analysis. Normally, these slower trials would be excluded as part of the previously outlined

traditional data cleaning process. While this approach would be an option for the current analysis, using it would make it difficult to draw comparisons between the behavioural and EEG findings in this chapter. The application of a distribution-based cut-off was chosen over a fixed cut-off (e.g. 1000ms) as it allows the cut-off to be tailored on an individual by individual basis, which is essential when looking at samples where group differences are expected, as is the case here. The cut-off was applied to the reaction time distribution rather than the total response time distribution as the primary aim of this experiment was to look at the neural activity preceding response onset.

Event-Related Potential analyses:

Response-locked ERPs: Given the background evidence presented and the hypotheses stated for this experiment the primary ERP of interest was the Lateralised Readiness Potential (LRP). Three measures were used to assess changes in the LRP: The peak amplitude, the peak latency and the onset latency.

While it is relatively easy to assess the peak amplitude simply by inspecting the ERPs for each individual, it can be difficult to quantify the latency measures using this approach. Thus, a jack-knife approach was used for all measures. This approach reduces the variability of individual ERPs by creating a number of grand averages, each with one participant left out (e.g. if there are ten participants in an experiment, then ten grand averages made up of nine individual averages will be created and analysed). The measures being examined (i.e. peak amplitude, onset latency, etc) can then be extracted from these jackknifed ERPs and analysed, with a correction applied to the test statistic to account for the initial loss of variability (for further information on the jackknife procedure consult Luck, 2014 and Kiesel, Miller, Jolicœur, & Brisson, 2008).

The peak amplitude was defined as the largest amplitude (positive or negative) that occurred in the 400ms window prior to the response. The peak latency was defined as the

time in milliseconds that this peak occurred. Finally, onset latency was defined as the time point where the EEG signal reaches 50% of the peak amplitude (for further discussion on reliably identifying onset latency see: Miller, Patterson, & Ulrich (1998) and Kiesel et al. (2008)).

Once the values for each measure were extracted they were statistically analysed using a mixed ANOVA. Each of these ANOVAs had one between-subjects factor: Group (with two levels: Control and DCD), and one within-subjects factor: Block (with four levels: Block 2 to 5).

Stimulus-locked ERPs: No a-priori hypotheses were suggested for the stimulus-locked ERPs, thus a data-driven exploration was undertaken with them. The analysis method selected was cluster-based permutation analysis.

One of the key problems with performing exploratory analyses, particularly with neuroimaging data which consists of a large number of comparisons, is controlling the rate of false positives. For analyses that include a small number of comparisons the Bonferroni correction is a suitable control, however it is far too conservative for the large number of comparisons that are required for exploration of neuroimaging data, and thus may result in false negatives. Cluster-based permutation analysis provides a way of exploring the data while controlling for false positives (see chapters 32 and 33 in Cohen, 2014 for an in-depth discussion on this topic).

Briefly, this method uses permutation testing, whereby the individual samples within a comparison are repeatedly shuffled and compared to produce a probability distribution that comparison. The result of the original comparison can then be placed on that distribution to see if it falls above a particular criterion (usually above the 95^{th} percentile). This then allows clusters of comparisons that are statistically significant and contiguous in time, space, and/or frequency to be identified. The maximum test statistic for each of these clusters is calculated and another permutation test conducted to identify those that are

statistically sufficiently large not to be due to chance (for a more in-depth explanation on cluster-based permutation testing, refer to Cohen, 2014 and Maris & Oostenveld, 2007). As electrophysiological activity related to movement is of interest in this experiment the electrodes analysed will constrained to those positioned over motor related areas, namely: The Fronto-central, Central, and Centro-parietal electrodes, these are highlighted in Figure 18 below. As there were no a-priori hypotheses made about the stimulus-locked data the alpha cut-off was set at the two-tailed level (i.e. 0.025).

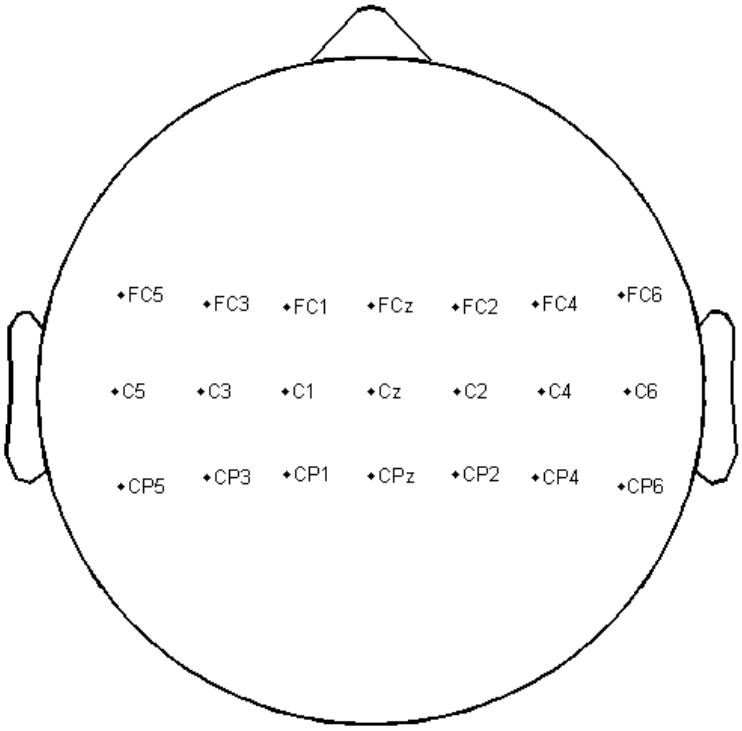

Figure 18 - Channels used in the cluster-based permutation analyses

Initially, separate within-group analyses will be run to ascertain whether there was an effect of learning on the stimulus-locked ERPs. If there are significant changes, then in order to test for an interaction between group and block, the difference between the activity for the first and last blocks of the experimental task will be calculated for each group, and the resulting difference waves will be tested.

Time-frequency analyses

Response- and Stimulus-locked epochs: As with the stimulus-locked ERPs no specific hypotheses were made for the time-frequency representations. Thus exploratory analyses, again using cluster-based permutation tests, were run on the data. As with the stimulus-locked ERPs, there were no a-priori hypotheses made about the direction of the differences within the TFR data and so the alpha cut-off was set at the two tailed level (i.e. 0.025).

For both the response-locked and stimulus-locked epochs all time points (-800 to 100ms and -100 to 800ms respectively) were compared in the cluster analysis, but only the frequencies of interest were analysed, namely: alpha (8-13 Hz) and beta (13-30 Hz). Again, as with the stimulus-locked ERPs, if there were significant changes over the course of the blocks then an interaction was tested by subtracting the activity from the first and last blocks and running a between -groups permutation test.

Results

Behavioural results - Control blocks

As with previous experiments, the success of the distribution fitting approach in the control blocks fell below the 80% cut-off for all reaction time partitions (Success rates: TT = 56%, RT = 63%, MT = 17%). Consequently the traditional approach described in chapter two was utilised to analyse the data. There was no statistically significant change in any of the measures for any of the partitions in the control block. The data for each block and the results of the statistical tests are summarised in Tables 8 and 9 below.

Table 8 – Summary statistics for the control blocks

Partition	Measure	Group	Block 1 (SD)	Block 6 (SD)
TT	Mean	Control	2.68 (0.05)	2.67 (0.06)
		DCD	2.71 (0.11)	2.70 (0.12)
	Variability	Control	0.07 (0.02)	0.07 (0.02)
		DCD	0.08 (0.03)	0.10 (0.05)
RT	Mean	Control	2.47 (0.04)	2.46 (0.05)
		DCD	2.50 (0.05)	2.50 (0.09)
	Variability	Control	0.07 (0.02)	0.08 (0.02)
		DCD	0.08 (0.03)	0.10 (0.05)
MT	Mean	Control	2.22 (0.13)	2.21 (0.11)
		DCD	2.25 (0.21)	2.22 (0.19)
	Variability	Control	0.10 (0.03)	0.09 (0.03)
		DCD	0.10 (0.05)	0.11 (0.07)

Table 9 – Results of the statistical tests for the control blocks

Partition	Measure		Degrees of freedom	*F*-value	*p*-value
TT	Mean	Main effect	1, 22	0.42	0.53
		Interaction	1, 22	0.01	0.92
	Variability	Main effect	1, 22	2.03	0.17
		Interaction	1, 22	1.93	0.18
RT	Mean	Main effect	1, 22	0.13	0.72
		Interaction	1, 22	0.33	0.57
	Variability	Main effect	1, 22	2.50	0.13
		Interaction	1, 22	0.29	0.60
MT	Mean	Main effect	1, 22	1.54	0.23
		Interaction	1, 22	0.33	0.57
	Variability	Main effect	1, 22	0.03	0.86
		Interaction	1, 22	2.26	0.15

Behavioural results - Experimental blocks

<u>*Accuracy:*</u> As shown in figure X below there appeared to be no differences in overall accuracy across blocks and groups. This observation is supported by the results of the mixed ANOVA conducted in the accuracy data: There was no main effect of block (F (3, 66) = 0.07, p = 0.98) and no interaction between block and group (F (3, 66) = 0.73, p = 0.54).

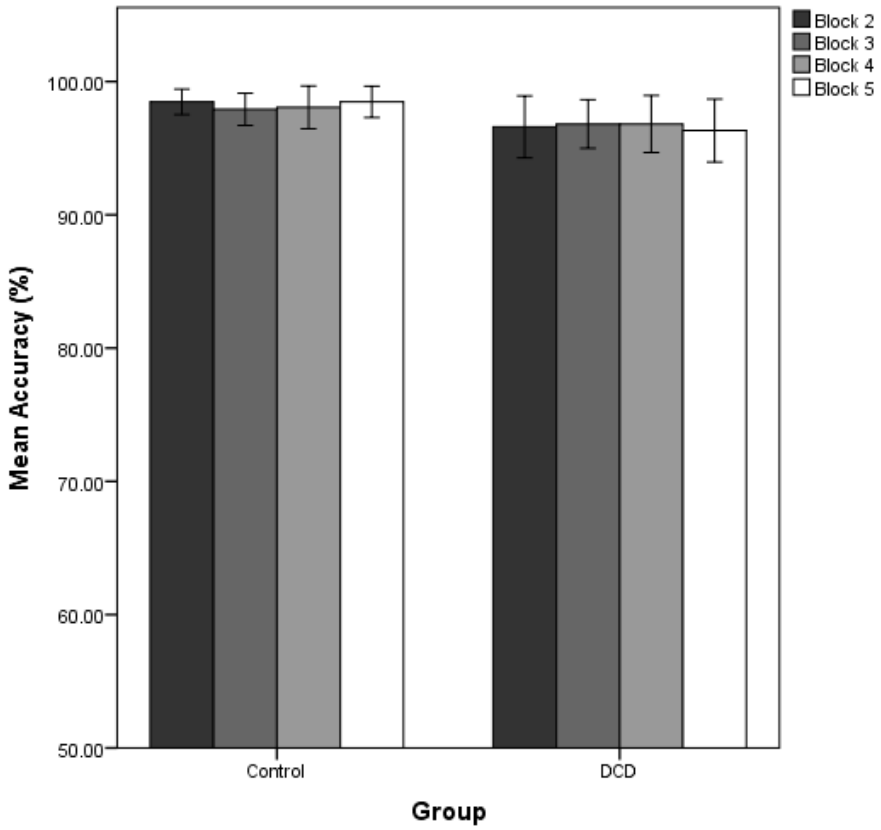

Figure 19 - Plot illustrating changes accuracy across the experimental blocks (Error bars: ±2 Standard error)

Total time: The distribution analysis for TT was able to successfully fit an ex-Gaussian distribution to ninety-three percent of the blocks (89 of 96 blocks), consequently the summary measures (mu, sigma, and tau) for these distributions were used in the statistical analyses. There did not appear to be a specific source (i.e. a specific participant or block number) for the remaining seven blocks with poor fit to the ex-Gaussian, and as a result they were not included in the statistical analysis.

Mu component of TT: As seen in Figure 20 below there appears to be no significant change in the Mu component of TT for either group. This observation is supported by the results of the statistical test.

The data for the Mu component of the TT distribution violate Mauchly's test of sphericity ($\chi^2(5) = 34.68$, $p > 0.01$) consequently the Greenhouse-Geisser correction was applied (ε =

0.45). The mixed ANOVA revealed no main effect for block (F (1.34, 21.50) = 0.14, p = 0.79) and no interaction between block and group (F (1.34, 21.50) = 0.46, p = 0.56).

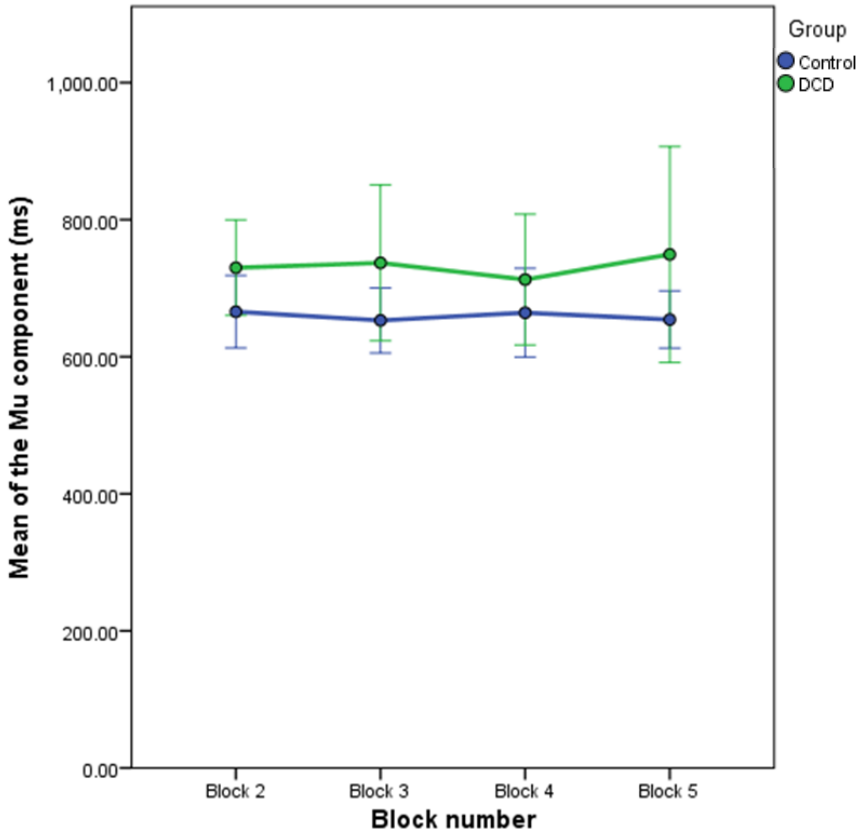

Figure 20 - Plot illustrating changes in the Mu component of the TT distribution across the experimental blocks (Error bars: ±2 Standard error)

Sigma component of TT: As with the Mu component, there appears to be little change in the Sigma component of the TT distribution in either group. However, this component seems to be less stable across blocks for the DCD group, as illustrated in Figure 21. Again this is supported by the statistical analysis.

The data for the Sigma component of the TT distribution violate Mauchly's test of sphericity (χ^2 (5) = 51.13, p > 0.01), consequently the Greenhouse-Geisser correction was applied (ε = 0.39). The mixed ANOVA showed no main effect for block (F (1.16, 18.58) = 0.37, p = 0.59) and no interaction between block and group (F (1.16, 18.58) = 0.57, p = 0.48).

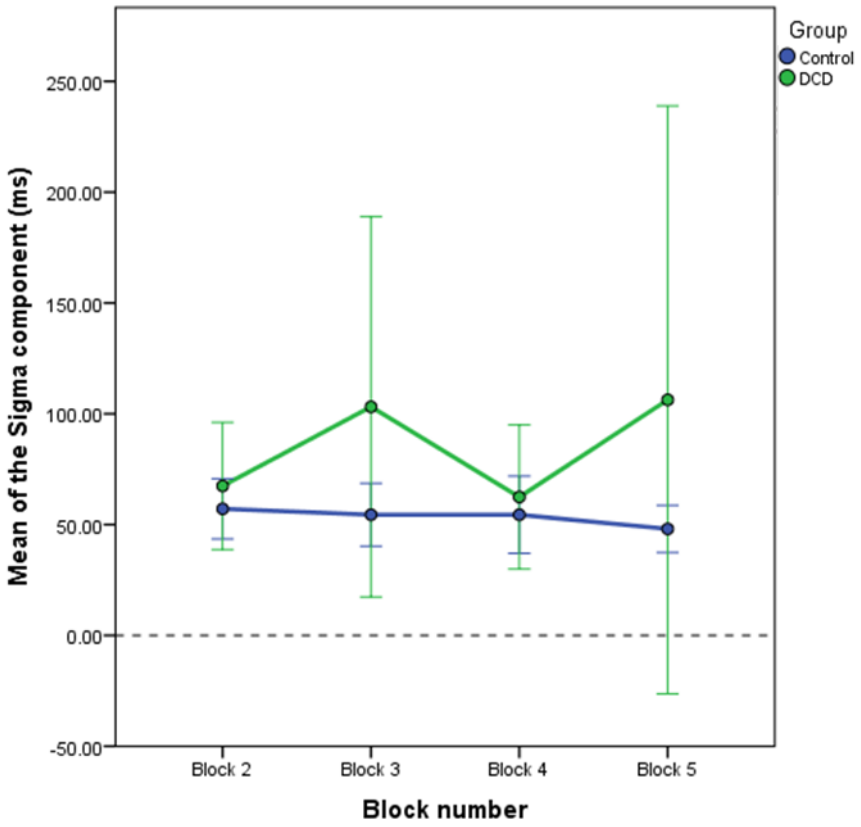

Figure 21 - Plot illustrating changes in the Sigma component of the TT distribution across the experimental blocks (Error bars: ±2 Standard error)

Tau component of TT: The data presented in Figure 22 appears to show a gradual decrease in the mean Tau component of the TT distribution in the control group, and while it looks like there is also a downward trend for the DCD the variability makes the effect somewhat unclear.

The mixed ANOVA partially backs this result up, revealing a statistically significant main effect of block (F (3, 48) = 3.54, p = 0.02), however the interaction between block and group is not statistically significant (F (3, 48) = 0.35, p = 0.79). As shown in Figure 22 this main effect seems mostly to be driven mostly by the control group, and this is confirmed by separate repeated measures ANOVAs conducted for each group: The control group show a statistically significant effect of block (F (3, 24) = 3.48, p = 0.03) while the DCD group do not (F (3, 24) = 1.65, p = 0.20). (NB if a Bonferroni correction were applied here, there would be no significant difference in the main effect of block for the control group.)

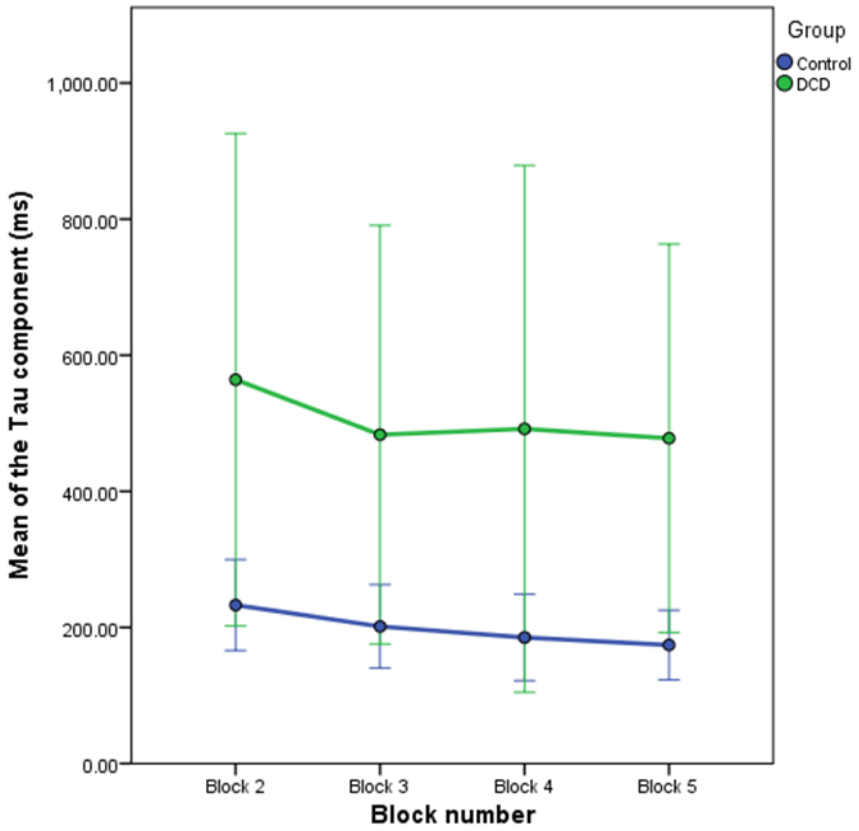

Figure 22 - Plot illustrating changes in the Tau component of the TT distribution across the experimental blocks (Error bars: ±2 Standard error)

Reaction time: The distribution analysis for RT was able to successfully fit an ex-Gaussian distribution to ninety-five percent of the blocks (91 of 96 blocks), consequently the summary measures (mu, sigma, and tau) for these distributions were used in the statistical analyses. The remaining five blocks that the distribution analysis was not able to successfully fit an ex-Gaussian distribution to were not included in the statistical analysis.

Mu component of RT: As with the Mu component of the total time distribution, there appear to be no change in this component for either group over the course of the task (illustrated in Figure 23).

These observations are supported by the results of the statistical analysis. The data for the Mu component of the RT distribution violated Mauchly's test of sphericity (χ^2 (5) = 17.72, p < 0.01), as a result a Greenhouse-Geisser correction was applied (ε = 0.66). The Mixed ANOVA showed no main effect for block (F (1.99, 33.75) = 0.53, p = 0.59) and no interaction between block and group (F (1.99, 33.75) = 0.25, p = 0.78).

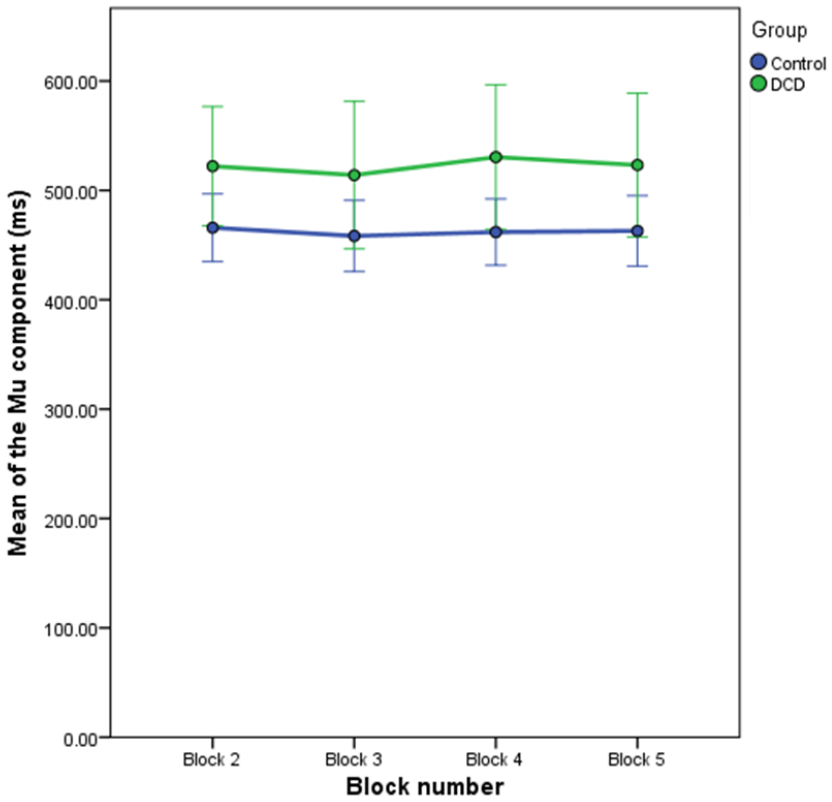

Figure 23 - Plot illustrating changes in the Mu component of the RT distribution across the experimental blocks (Error bars: ±2 Standard error)

Sigma component of RT: Within the Sigma component of RT there appears to be a slight overall decrease for the control group and a slight overall increase accompanied by increasing variability for the DCD group (as illustrated in Figure 24). However, these observations are not supported by the statistical tests.

The data for the Sigma component of the RT distribution violated Mauchly's test of sphericity (χ^2 (5) = 14.32, p = 0.01), as a result a Greenhouse-Geisser correction was applied (ε = 0.63). The Mixed ANOVA showed no main effect for block (F (1.88, 31.89) = 0.08, p = 0.91) and no interaction between block and group (F (1.88, 31.89) = 0.28, p = 0.75).

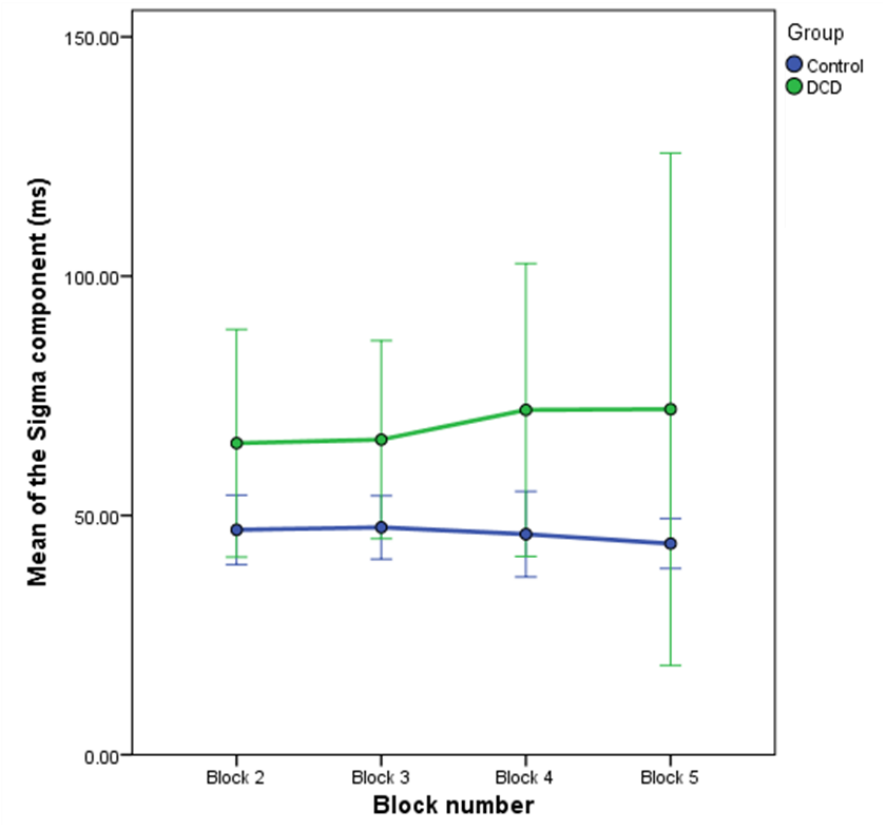

Figure 24 - Plot illustrating changes in the Sigma component of the RT distribution across the experimental blocks (Error bars: ±2 Standard error)

Tau component of RT: As with the TT distribution, there appears to be decrease in the Tau component of the RT distribution for the control block. The mean RT component for the DCD group appears more stable but is much more variable. Figure 25 illustrated the changes in the Tau component of RT.

The data for the Tau component of the RT distribution violated Mauchly's test of sphericity (χ^2 (5) = 20.00, $p < 0.01$), thus a Greenhouse-Geisser correction was applied (ε = 0.58). The mixed ANOVA revealed a statistically significant main effect of block (F (1.73, 29.40) = 3.57, p = 0.05) but no interaction between block and group (F (1.73, 29.40) = 0.79, p = 0.45).

However, when separate repeated measures ANOVAs were conducted for each group neither were statistically significant. (Control group: F (1.42, 14.18) = 3.97, p = 0.06 (Mauchly's test of sphericity violated: χ^2 (5) = 17.61, $p < 0.01$; Greenhouse-Geisser correction applied: ε = 0.47); DCD group: F (3, 21) = 0.90, p = 0.46).

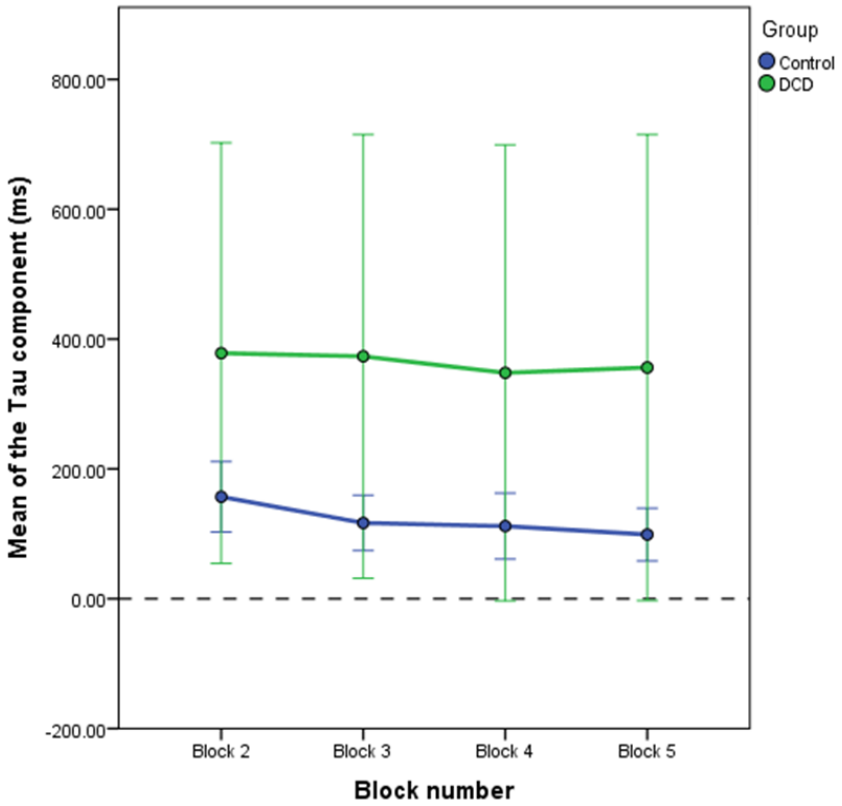

Figure 25 - Plot illustrating changes in the Tau component of the RT distribution across the experimental blocks (Error bars: ±2 Standard error)

Movement time: The distribution analysis for MT was able to successfully fit an ex-Gaussian distribution to only thirty-eight percent of the blocks (36 of 96 blocks). Consequently, a traditional approach was taken for looking at the data.

Mean reaction time for MT: As illustrated in Figure 26 there appears to be a slight decrease in mean movement time for the DCD group, with little to no change in the control group.

The data for the mean reaction time of the MT distribution violated Mauchly's test of sphericity (χ^2 (5) = 14.87, p = 0.01), thus a Greenhouse-Geisser correction was applied (ε = 0.67). The mixed ANOVA revealed a statistically significant main effect of block (F (2.00, 43.90) = 5.32, p = 0.01) but no interaction between block and group (F (2.00, 43.90) = 1.02, p = 0.39).

Separate repeated measures ANOVA were conducted, and revealed that the main effect was driven by the decrease in movement time for the DCD group (Control group: F (3, 33) =

1.25, p = 0.31; DCD group: F (1.74, 19.19) = 4.26, p = 0.03 (Mauchly's test of sphericity violated: χ^2 (5) = 11.59, p = 0.04; Greenhouse-Geisser correction applied: ε = 0.58)).

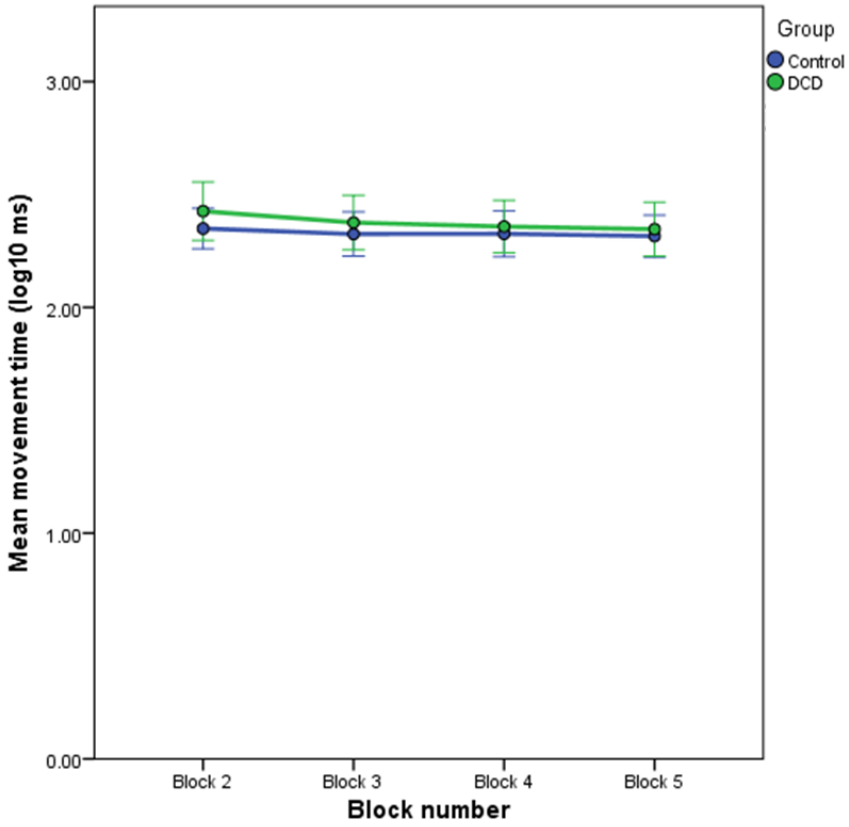

Figure 26 - Plot illustrating changes in the Mean TT across the experimental blocks (Error bars: ±2 Standard error)

Variability in reaction time for MT: There appears to be a substantial reduction in the variability of movement time over the course the task for both blocks (see Figure 27).

This observation is supported by the results of the mixed ANOVA. The data violated Mauchly's test of sphericity (χ^2 (5) = 15.67, p = 0.01), thus a Greenhouse-Geisser correction was applied (ε = 0.72).

The ANOVA revealed a statistically significant main effect of block (F (2.17, 47.69) = 6.62, p < 0.01) but no interaction between block and group (F (2.17, 47.69) = 0.06, p = 0.96).

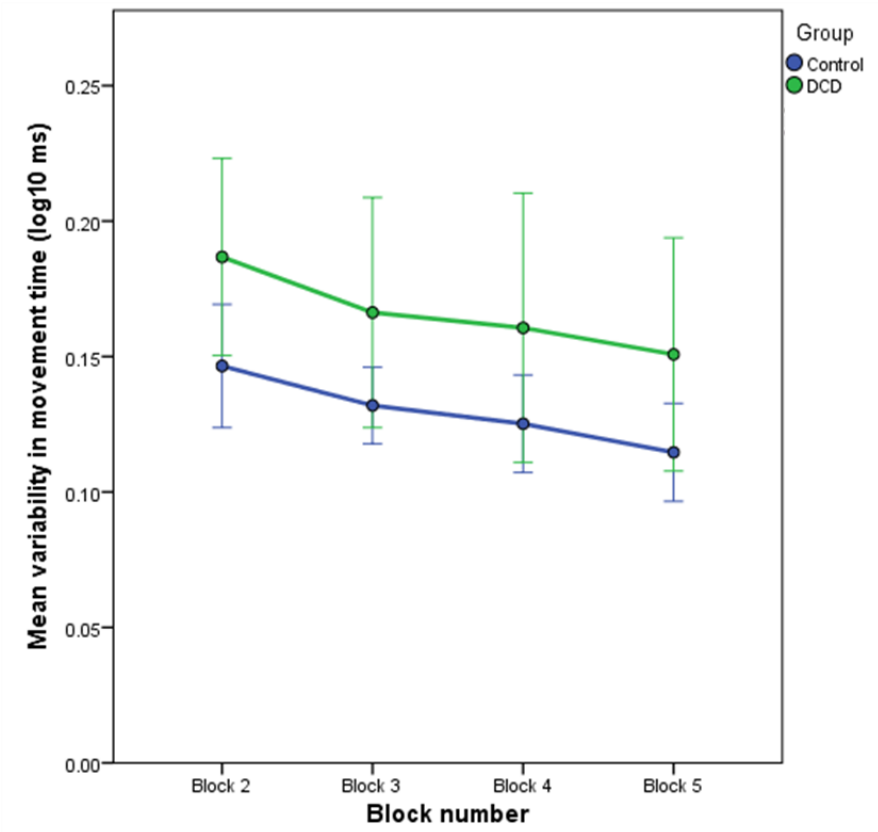

Figure 27 - Plot illustrating changes in the Variability of TT across the experimental blocks (Error bars: ±2 Standard error)

EEG Results

The EEG analyses were conducted as previously described in the methods section. One participant from the DCD group had to be excluded from the EEG analysis as the data recorded were too noisy to be analysed. To ensure parity between the groups a participant from the control group matched for age and sex were also removed from the analysis.

Event-related potentials

Response-locked potentials: As discussed previously, the lateralised readiness potential was examined for possible changes associated with learning. Three measures were examined: The peak amplitude, the peak latency, and the onset latency, each using a mixed-design ANOVA. The grand average for the LRPs divided by group and block are displayed in Figure 31 below. Additionally, the mean for each of the measures analysed are displayed in Figures 28 - 30 below, again these are divided by block and group.

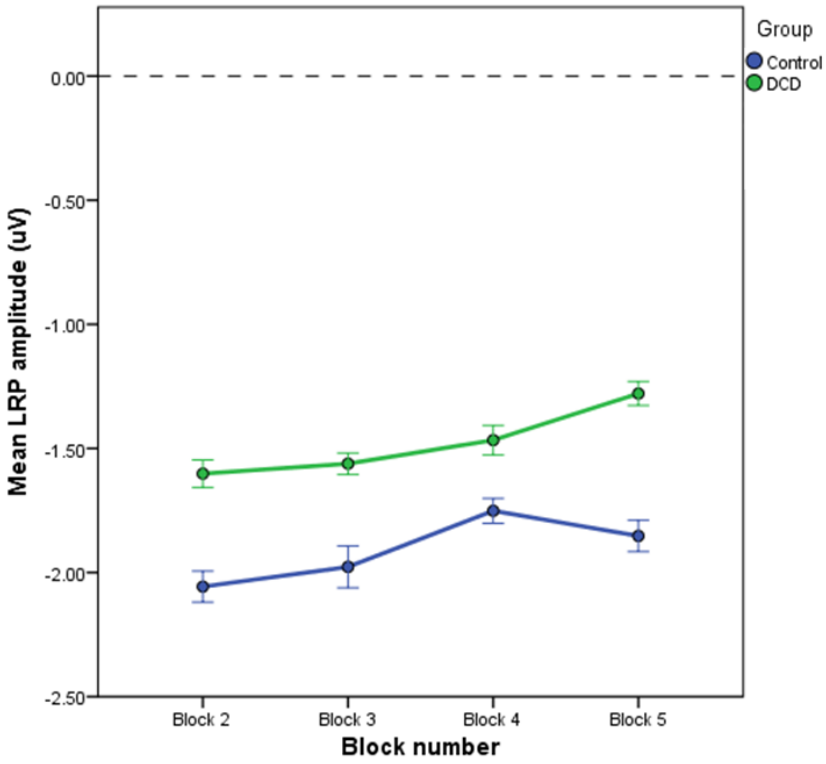

Figure 28 - Plot illustrating the progression of the mean LRP amplitude over the course of the experimental blocks (Error bars: ±2 Standard error)

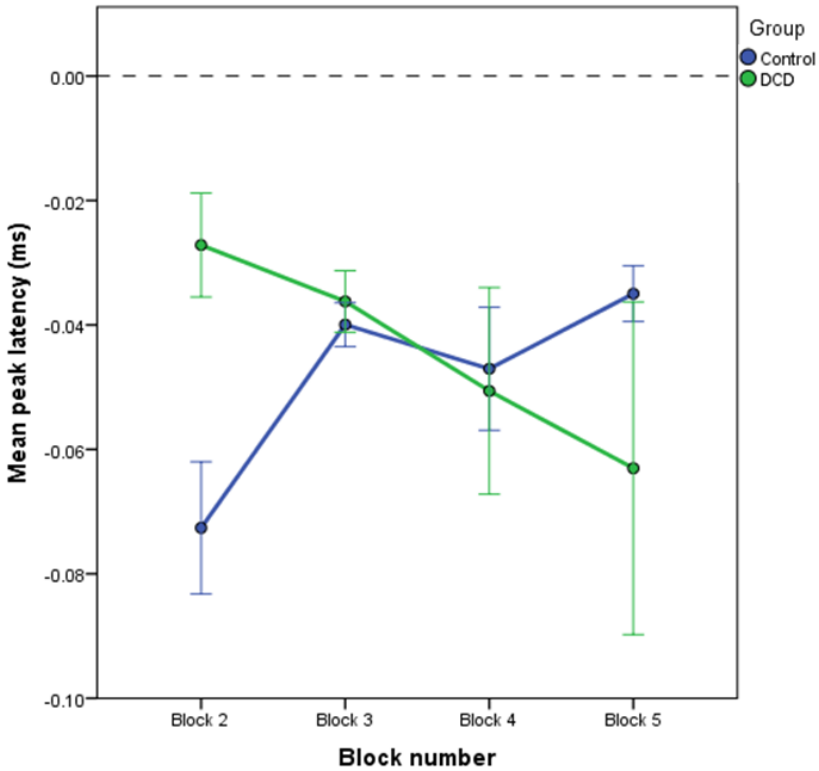

Figure 29 - Plot illustrating the progression of the mean peak LRP latency over the course of the experimental blocks (0 indicates response onset; Error bars: ±2 Standard error)

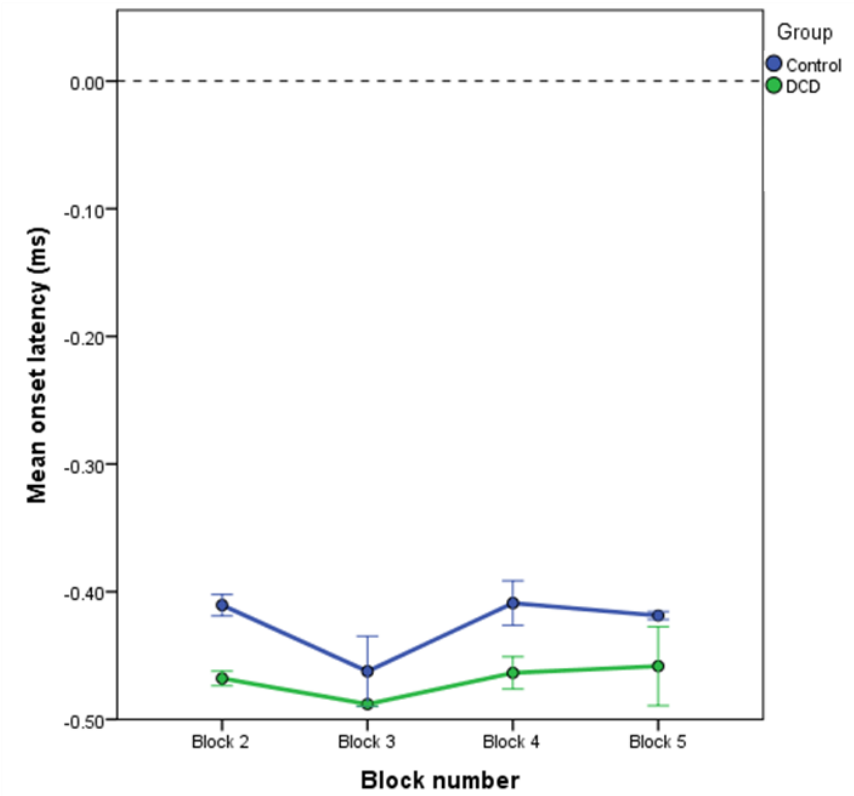

Figure 30 - Plot illustrating the progression of the mean LRP onset latency over the course of the experimental blocks (0 indicates response onset; Error bars: ±2 Standard error)

The grand average LRPs in Figure 31 suggest that there is no change across the groups and there is very little difference between the groups. This observation is supported by the statistical analyses (displayed in Table 10 below). There were no statistically significant main effects of block, and there was no statistically significant interaction for any of the measures.

Table 10 - Results of the mixed ANOVA for the LRP measures

		Uncorrected F (d.f.)	Corrected F	p-value
Peak amplitude	Main effect (Block)	130.91 (3,60)	1.31	0.28
	Interaction (Block x Group)	29.21 (3,60)	0.29	0.83
Peak latency	Main effect (Block)	1.96 (3,60)	0.02	0.99
	Interaction (Block x Group)	14.59 (3,60)	0.15	0.93
Onset latency	Main effect (Block)	8.45 (3,60)	0.08	0.97
	Interaction (Block x Group)	1.30 (3,60)	0.01	0.99

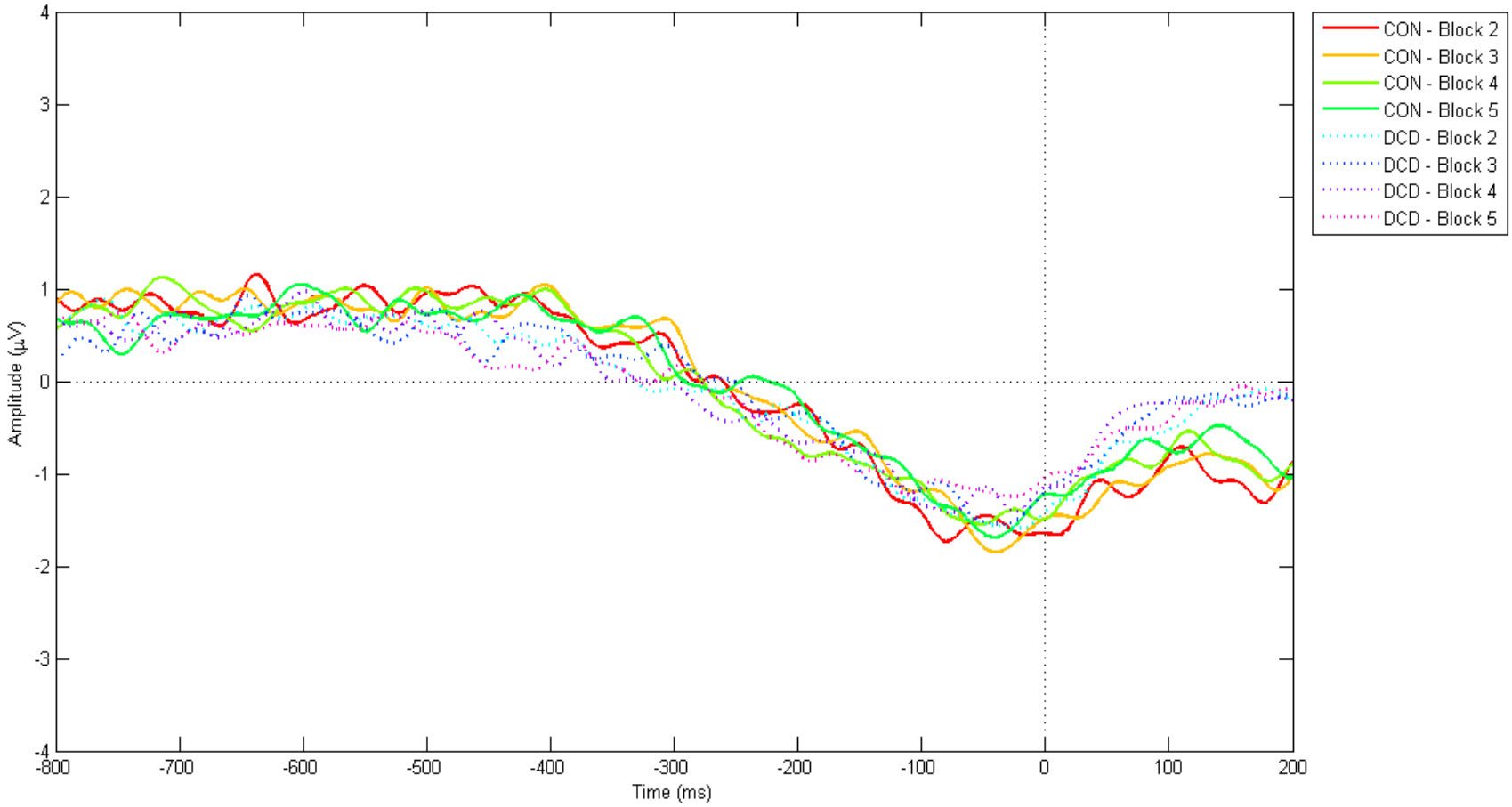

Figure 31 - Grand average LRPs (Electrode: C3 - C4, with 0 indicates response onset)

Stimulus-locked potentials: While the stimulus-locked grand average ERPs displayed in Figure 32 do not appear to show any obvious change for either of the groups over the course of the blocks, there do appear to be a several substantial differences between the overall shapes of the waveforms for each group, particularly around the early (100-300ms) and middle to late (300-600ms) regions.

Unsurprisingly, given that there was no difference in the Mu component of the reaction time distribution, the cluster-based permutation analysis did not reveal any statistically significant clusters of difference between the first and last experimental blocks for either group.

In order to explore the prospective difference in waveforms between the groups that appears in Figure 32, the averaged stimulus-locked ERPs for each block were further averaged together to produce a waveform for each participant representing stimulus locked activity across all blocks, illustrated in Figure 32. These were then explored in a further cluster-based permutation analysis. The results of this analysis did not reveal any statistically significantly different clusters of activity between the groups.

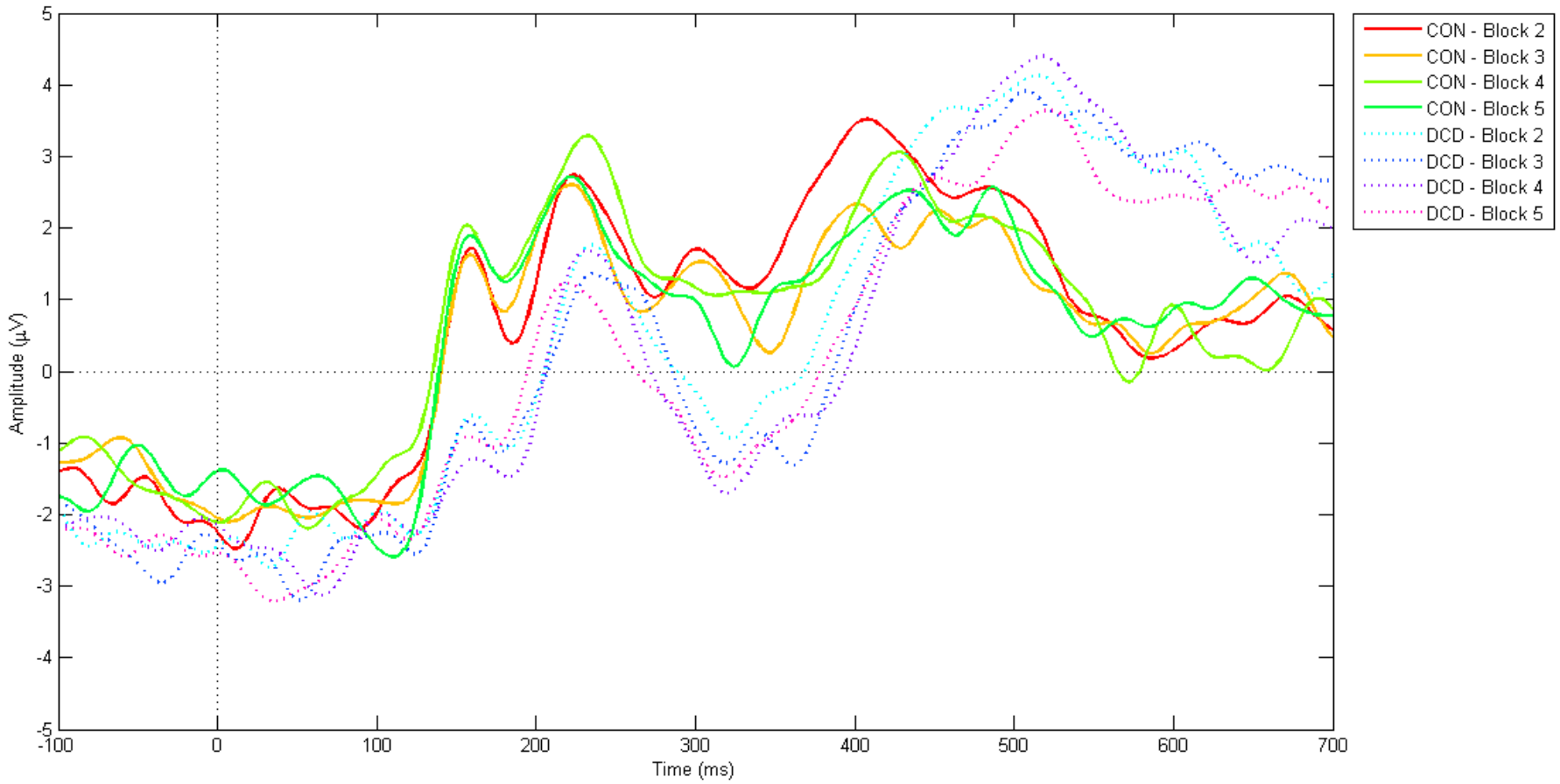

Figure 32 - Grand Average stimulus-locked ERPs (Electrode: Cz, 0 indicates stimulus onset)

Time-frequency analyses

Response-locked TFRs: Head plots for the stimulus-locked Alpha and Beta band activity are displayed below in Figures 33 and 34 below. These plots show very similar patterns of activity between the blocks. Although it appears that beta ERD occurs closer to response onset for the DCD group than for the control group.

The cluster-based permutation analysis between the first and last blocks for the control group identified seven positive clusters. However, none of the p-value for these clusters fell below the 0.025 cut-off, meaning that the clusters identified were not statistically significantly different between the blocks.

Similarly, the analyses for the DCD group revealed three positive and one negative cluster of differences between the first and final experimental blocks; but again the p-values for each of these clusters fell above the 0.025 cut-off. Accordingly, there were no statistically significant differences between the two blocks.

Stimulus locked TFRs: Head plots for the stimulus-locked Alpha and Beta band activity are displayed below in Figures 35 and 36 below. These plots show very similar patterns of activity between the blocks and the groups.

For the control group, the cluster-based permutation analysis between the first and last blocks of the experimental task identified four clusters (three positive and one negative). However, the p-value for each of these clusters did not fall below the 0.025 cut-off, meaning that the clusters identified were not statistically significantly different between the blocks.

Similarly, the analyses for the DCD group revealed one positive and one negative cluster of differences between the first and final experimental blocks, but again their p-values both fell above the 0.025 cut-off. Accordingly, there were no statistically significant differences between the two blocks.

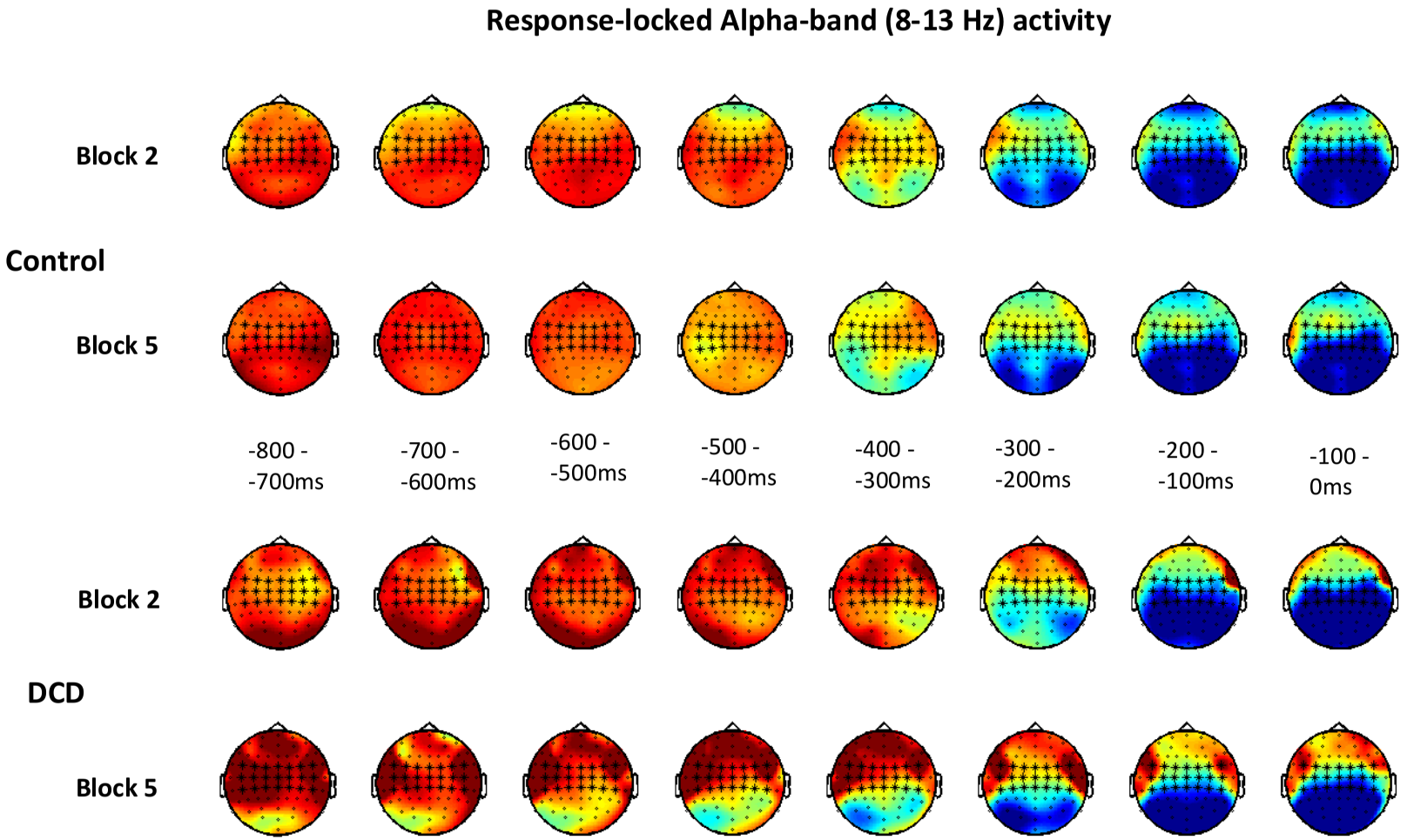

Figure 33 – Head plots illustrating response-locked alpha activity (colours indicate % change from baseline)

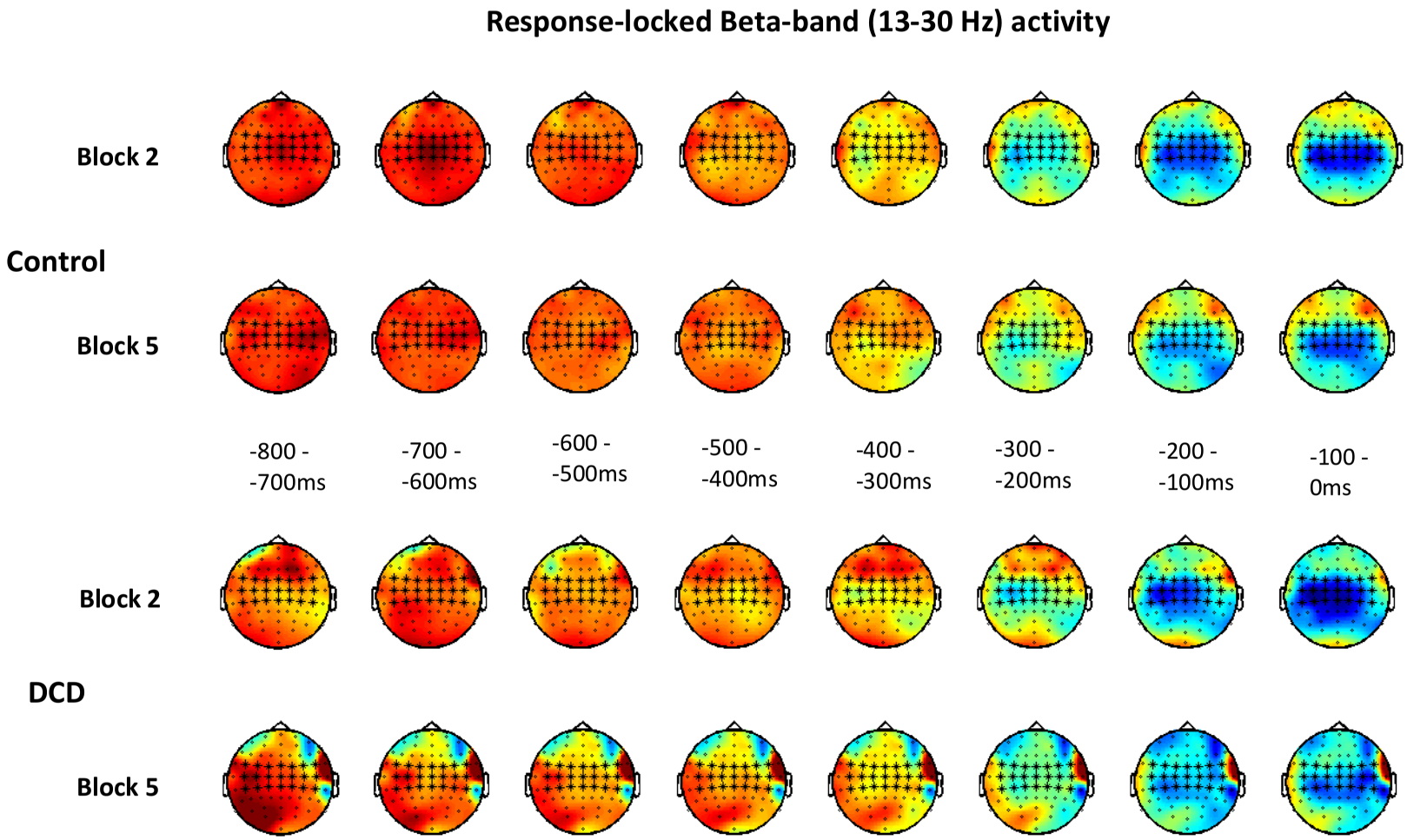

Figure 34 - Head plots illustrating response-locked beta activity (colours indicate % change from baseline)

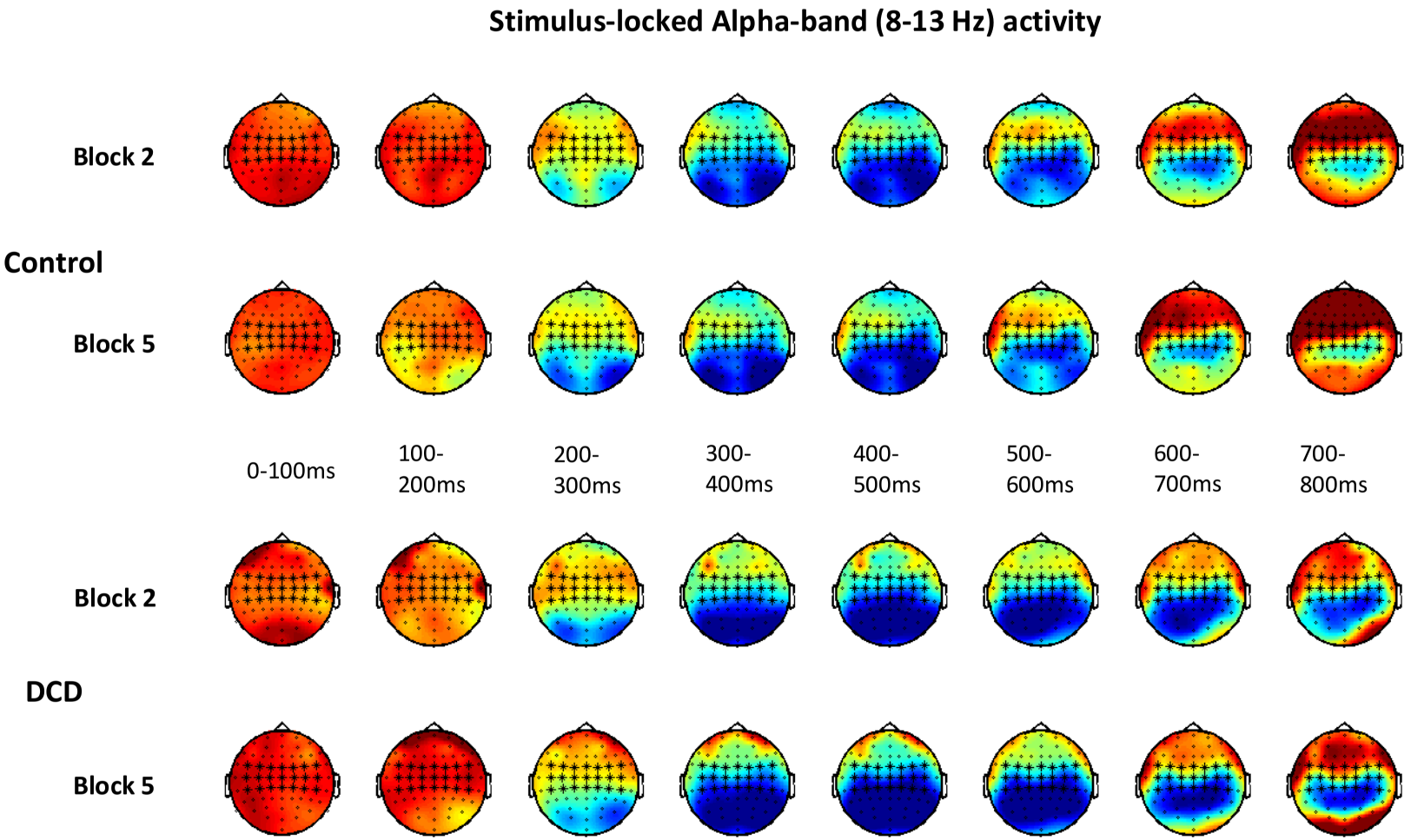

Figure 35 - Head plots illustrating stimulus-locked alpha activity (colours indicate % change from baseline)

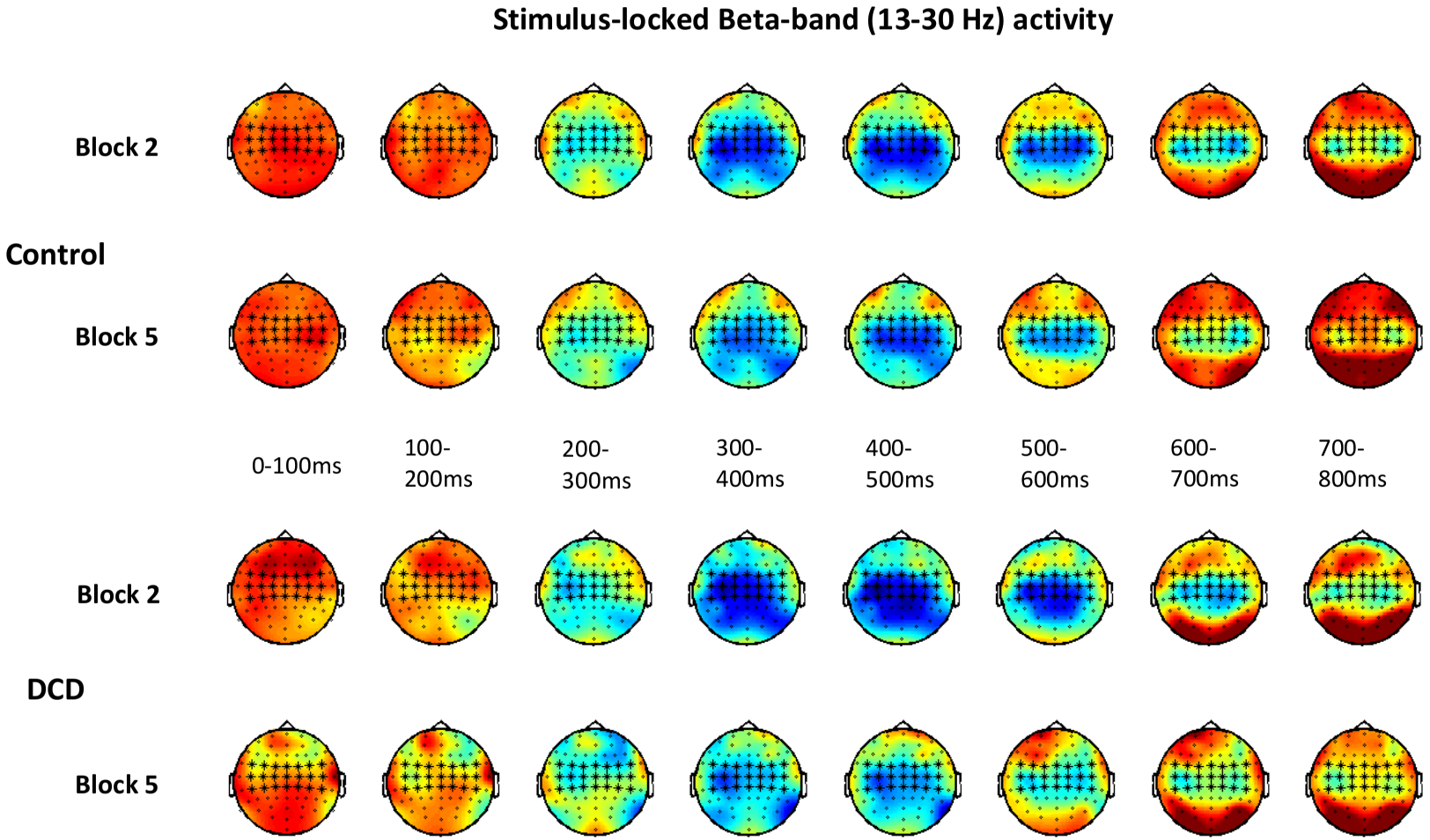

Figure 36 - Head plots illustrating stimulus-locked beta activity (colours indicate % change from baseline)

Discussion

The primary aim of the current chapter was to explore the electrophysiological changes associated with the early stages of motor learning, and examine differences in these changes between individuals with DCD and neurotypical individuals. As such, three hypotheses were tested in this experiment: Firstly, there would be no overall change in performance for the control task in either group. Secondly, there would be an improvement in motor performance for the experimental task, however this improvement would only be observed in the control group, not the DCD group. Finally, these improvements in performance would be accompanied by changes in response-locked EEG activity, again only in the control group. In addition, potential practice related changes and group differences were investigated in the stimulus locked EEG activity using a data-driven, exploratory approach. This section will examine and discuss the results of each of these hypotheses in turn, before discussing how the overarching findings of this experiment fit into the current understanding of early motor learning and DCD.

As expected, there were no changes in the behavioural measures taken during the control blocks for either block and the hypothesis was accepted. As a result, any changes observed for the experimental blocks can be attributed to learning rather than more general changes in reaction time.

The behavioural results from the experimental blocks demonstrate that the control group do indeed show an improvement in performance in the form of a reduction in the number of slower responses within the distribution. As predicted there is no discernable change in the performance of the DCD group over the course of the task. Thus, the second hypothesis can be accepted. However, this result is somewhat difficult to interpret given the results of the experiment in chapter two. This experiment found that performance improved for the experimental task, but this was driven by a reduction in the peak of the reaction time distribution (i.e. the Mu component), whereas the improvements observed in the current

experiment are driven by a reduction in the length of the rightward tail of the distribution (i.e. the Tau component).

The different findings of these two experiments may stem from one of the modifications made to the task. The most obvious change that could have caused the different observations is a change in the initial position of the response finger from simply resting on the starting key to actually holding it down. The additional disengagement required as part of this action may have introduced a limit to how quickly an individual could respond, thus reducing the opportunity for this end of the distribution to decrease further. It is also possible, although less likely, that changing the paradigm from a between-groups design may have played a role in preventing a replication of the findings in experiment two, although it is not immediately clear why this would be the case.

The results of the EEG analyses indicate that there was no reliable change in the response-locked ERP or TFR measures over the course of the task, and that there were no significant differences between the groups, thus the third hypothesis can be rejected. This result is as expected for the DCD group as they did not show a change in performance over the course of the task; however, it is initially surprising that there was no change for the control group given the aforementioned behavioural results. It is somewhat less surprising when the behavioural results are considered alongside the pre-processing steps for the data described in the methods section. As discussed above, the change in performance among the control group was produced by a reduction in the number of trials located in the rightward tail of the distribution. However, to ensure relative homogeneity in the EEG data used in the analysis, trials above the 85^{th} percentile of the RT distribution were not included in the analysis. This effectively removed the rightward tail of the distribution and the trials that drove the change in performance. While it would be interesting to examine the electrophysiological changes for these trials, the analysis approach followed in this thesis does not allow this given that these trials were few in number and heterogeneous in

their timings. In order to study these trials a single-trial analysis approach would need to be taken, which is beyond the scope of the current thesis.

As an aside, it is interesting to note that it is possible this explanation would have been missed had the distribution analysis not been used. As noted by Balota and Yap (2011) the Mu and Tau components of the Ex-Gaussian distribution can be summed to produce the overall mean of the distribution, thus if one of these components change then it would produce a change in the overall mean. Had a more traditional approach to reaction time been utilised, it may have seemed that the results of the experiment in chapter two and the current experiment were comparable (i.e. there is a decrease in the mean reaction time over the course of the task), and would have resulted in the conclusion that the current task is not able to produce electrophysiological changes. Instead a more nuanced conclusion can be drawn from these findings: It is possible that the task produced electrophysiological changes, but given the current methodology it is not possible to conclude one way or the other.

An interesting feature of the LRPs recorded in this study is the distinct lack of a difference between the control and DCD groups in any of the measures; demonstrating that, despite some difference in reaction time between the groups (albeit not statistically significant), neural activity from motor areas in the time immediately before response execution is not statistically different between the groups. This suggests that the slower reaction times are caused by cognitive processes that occur prior to this stage of response execution, and thus slow down the initiation of the processes leading to the final response, as reflected by response-locked ERPs. In further support of this idea is the different ERP waveforms observed in the stimulus-locked epochs, the peak of the N2 component, which occurs around 300ms appears greater in amplitude in the DCD group which, in turn, appears to result in a delayed peak for the P3 component, occurring around 400-500ms (see Figure 32). In the literature both of these components have been associated to processes involved

in response selection and differences in reaction times (Doucet & Stelmack, 1999; Verleger, 1997; Verleger, Jaśkowski, & Wascher, 2005). However, despite the seemingly clear differences observed in the waveforms, the cluster-based permutation analysis revealed no significant differences between the two groups. Thus, while this does suggest a potential avenue of further research, this research would require the use of a paradigm that manipulates these processes directly e.g. by varying the complexity of the responses required and examining the behavioural and neural consequences of doing so. If, as discussed in chapter one, response selection difficulties do play a role in DCD then it would be expected that reaction times for the complex responses would be slower and the suggested N2/P3 differences would be much more pronounced.

In conclusion, the behavioural results for this experiment demonstrate that the control group show improvements in the task indicative of learning, while the DCD group do not. However, whether there is an associated change in electrophysiological processes associated with these improvements remains inconclusive. Nonetheless, the EEG results do suggest potential avenues to further investigate the neural correlates of DCD.

Chapter 6 – Introduction to Non-Invasive brain stimulation Methodology

Outline

Since their development in the 1980s non-invasive brain stimulation (NIBS) techniques have been used to directly explore the connection between the brain and cognition. These techniques have led to the mapping of the muscle representations on the motor cortex, and revealed that the properties of these representations change during the early stages of motor learning. The experiment reported in the following chapter will use a specific technique called transcranial magnetic stimulation (TMS) to explore neurophysiological changes of the primary motor cortex during motor learning. The aim of the current chapter is to give a brief introduction to TMS and the specific methodology used for experiments within this thesis that employ this technique. It will begin by briefly explaining the underling principles behind TMS and the variety of ways it ca be used for research. The chapter will then move on to briefly describe electromyography (EMG) and the production and recording of motor evoked potentials (MEPs). Next, the chapter will then discuss issues of safety and ethics around using TMS. Finally, the chapter will outline the use of TMS to investigate the questions posed in this thesis.

Transcranial magnetic stimulation

Transcranial magnetic stimulation falls within a class of neuroscientific techniques known as non-invasive brain stimulation (NIBS), which also include the various types of transcranial electrical stimulation (TES). These techniques are of particular use to cognitive neuroscientists for two main reasons. Firstly, they allow activity in the brain to be more

directly measured or even influenced; as opposed to neuroimaging techniques (e.g. EEG, fMRI, etc.) that are only able to passively record activity from the brain. Secondly, while techniques to stimulate the brain have existed since the 19th century generally they have required direct access to the cortex which is not feasible in the general population; NIBS techniques are able to stimulate the brain through the skull, negating the need for direct access to the cortex.

The fact that the brain utilises electrochemical principles to communicate information around itself and the rest of the body has been known since at least the 19th century, if not earlier (Walsh & Pascual-Leone, 2003). This fact alongside the principle of electromagnetic induction outlined by Michael Faraday in the early 19th century led to many attempts to stimulate the brain from outside the skull (see Walsh & Pascual-Leone (2003) for a brief history). These early attempts were able to successfully stimulate the visual cortex, producing brief flashes in the visual field of the stimulated participant, which were called phosphenes. However, TMS in its modern incarnation was developed by Barker and colleagues in the mid-1980s when they successfully elicited a hand movement by stimulating the motor cortex with a magnetic pulse (Barker, Jalinous, & Freeston, 1985).

The modern TMS coil consists of a length of wire wound tightly around a core which, when an electric current with large amplitude and a rapid rise time (i.e. a current of up to 8 kiloamperes (kA) reaching its peak amplitude in less than two hundred milliseconds) is passed through the wire, produces a brief magnetic field as per Ampere's law. Due to the rapid rise time of the current, the magnetic field produced is in flux which, via electromagnetic induction, induces an electric field in conductive materials that are in close proximity to the coil, including excitable biological tissues such as the cortex.

Thus, an electric current can be non-invasively induced in the cortex beneath the coil, which may then produce sites of local depolarisation on neuronal axons leading to the

initiation of action potential and activation of the region stimulated. However, the extent of the activation is dependent on the optimal orientation of both the coil (and therefore the orientation of the induced electric field) and the underlying neurons (Amassian, Eberle, Maccabee, & Cracco, 1992). The effects of stimulation are optimised when the orientation of the electric field is tangential to the axonal cell membrane either due to the field orientation being perpendicular in relation to a straight axon or the axon bending relative to the orientation of the induced field.

The behavioural effects of TMS stimulation depend on a number of different factors, including: The type of coil used, the type of stimulation used, and the site of stimulation. Each of these factors will be briefly discussed here, although for a comprehensive discussion of these factors refer to Wassermann et al. (2008).

Coil type

There are two types of coil commonly used for TMS: the circular coil and the figure-of-eight coil. Because of their differing designs these coils produce different patterns of current flow when applied to the scalp, which in turn produces different effects.

As the name suggests, the circular coil consists of wire wound around a circular core typically 8-15 cm in diameter, for an illustration see Figure 37a. This type of coil produces an evenly distributed electrical field in a circular shape underneath the coil, although it is relatively diffuse in comparison to the figure-of-eight coil. The focality of stimulation with the circular coil can be improved by tilting the coil so that only the edge is in contact with the scalp, but this greatly reduces the efficiency of the stimulation.

The figure-of-eight coil has been shown to provide a much more focal stimulation than the circular coil (Ueno, Tashiro, & Harada, 1988). This is achieved by placing two smaller circular cores side by side to produce a coil shape that looks like a figure of eight (see Figure 37b for an illustration). The wire is wound around the cores in such a way that the current

flows in opposite directions for each of the windings. Thus, when a current is passed through the coil each of the windings produce a magnetic field that converges towards the middle of the coil. When applied to the cortex the induced electrical fields summate at the point where the magnetic fields converge, producing a focal point of maximal intensity just below the centre of the coil. For an excellent illustration of the electromagnetic fields

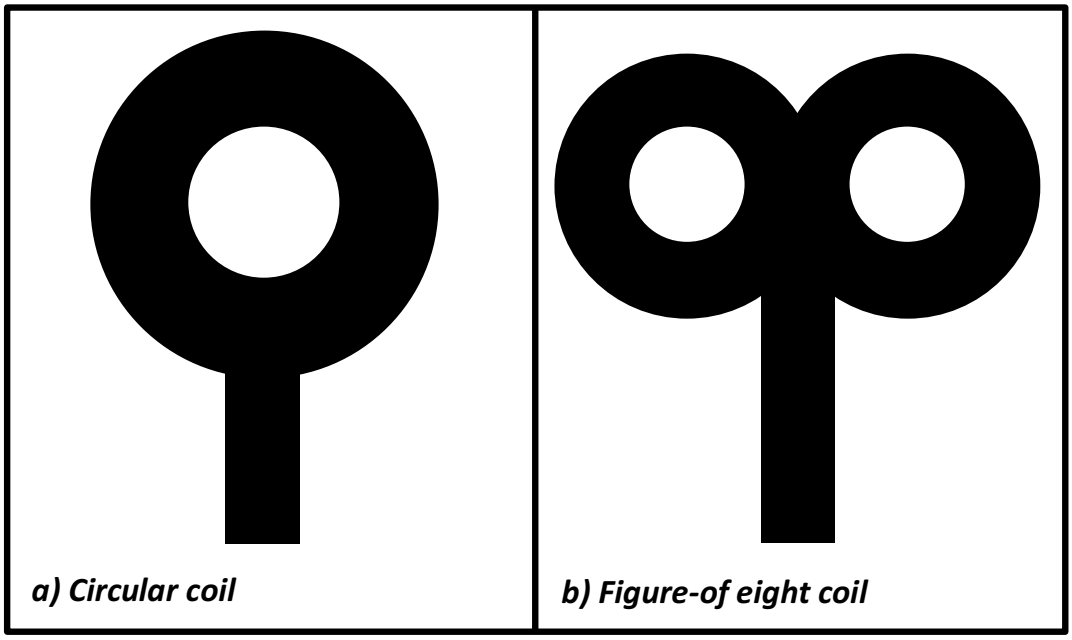

Figure 37 – Commonly used TMS coil designs.

produced by the differing coil shapes refer to the paper by Deng, Lisanby, and Peterchev (2013).

Stimulation type

There are a number of different stimulation types used with in the TMS literature, each with their own effects, nonetheless all generally fall within the repetitive TMS (rTMS) or single-pulse TMS (spTMS) categories.

Repetitive TMS is most commonly used as a virtual lesion paradigm. It uses trains of pulses with a frequency of greater than 1 Hz to stimulate the brain, essentially causing the neurons in the targeted area to activate at random. As a result, this type of stimulation can

introduce noise into processing and temporarily disrupt normal cognitive function if the area being targeted is involved in an aspect of that function. If this stimulation is applied while the participant is performing a task it is termed online stimulation; however, it can also be administered prior to performance of a task to produce effects that outlast the duration of the stimulation (offline stimulation) through long-term potentiation and depression-like mechanisms (Wassermann et al., 2008).

Differing frequencies of rTMS stimulation can produce different effects: 1 Hz repetitive stimulation is generally considered to have inhibitory effects (Chen et al., 1997) and while frequencies greater than 1 Hertz are used, in particular 5 and 10 Hz, it is unclear whether they have excitatory or inhibitory effects. The effects of higher frequency stimulation have been shown to partly depend on the intensity of the pulses, with lower intensities producing inhibition and higher intensities producing excitation (Classen & Stefan, 2008). More recently a type of rTMS known as patterned stimulation has been adopted based around theta-burst stimulation (TBS). TBS involves application of three 50 Hz pulses applied at 200 millisecond intervals, and again differing types of TBS will have differing effects on cortical excitability (see Parkin, Ekhtiari, & Walsh (2015) for more information).

In contrast, single-pulse TMS consists of applying pulses to the cortex at a rate less than 1Hz. This type of stimulation has also been used as part of a virtual lesion paradigm, allowing temporal aspects of processing in particular brain areas to be examined (e.g. Amassian et al., 1989; Dambeck et al., 2006), However, it is now used much less frequently than rTMS due to the challeneges in identifying the specific time points at which the very brief stimulation should be applied. Instead, this method is principally used to produce motor evoked potentials (MEPs) and phosphenes by applying stimulation to the primary motor or primary visual cortices respectively.

Location of stimulation

The location of the stimulation site is possibly the most important factor to consider for any study using NIBS, but this is particularly true for TMS studies.

The strength of the magnetic field produced by the coil falls off rapidly as the distance from the coil increases; this is what makes TMS using the figure-of-eight coil so focal but it also means that the sites that can be stimulated are limited to those close to the scalp (Zangen, Roth, Voller, & Hallett, 2005). This includes: most of the frontal, parietal, and occipital cortices, and parts of the cerebellum. A number of studies have suggested alternative coil designs that could be used to target subcortical and ventral areas of the brain (e.g. Deng, Lisanby, & Peterchev, 2014; Roth, Amir, Levkovitz, & Zangen, 2007; Zangen et al., 2005), however there appears to be a trade-off between focality and depth of stimulation that limits the effectiveness of these coils (Deng et al., 2013).

As has been previously mentioned, there are two sites that produce immediate observable effects in behaviour or a clear percept that can be reported by the participant, namely: the primary motor cortex (M1), which produces muscle activity, and the primary visual cortex, which produces phosphenes (Stewart, Walsh, & Rothwell, 2001). The rest of the cortex can be stimulated but generally does not produce any easily observable overt effects; instead the aforementioned virtual lesion method needs to be employed to determine the effect stimulation of a site is having.

Electromyography

Before motor evoked potentials can be discussed any further a brief outline of electromyography (EMG) must be given. The brain is not the only organ in the body that functions using electrochemical principles; muscles also utilise the flow of ions to produce contractions and, just as with neural activity, the electrical potentials produced by this can

be recorded to quantify muscle activity. This technique is called electromyography (EMG) and relies on exactly the same principles as EEG. The potential between a recording electrode and a ground electrode is measured and the potential between a reference electrode and a ground is subtracted from this. This signal is then amplified and plotted to produce a waveform that represents muscle activity over time.

There are two main types of EMG electrodes used, the first are intramuscular electrodes: these consist of a needle electrode inserted through the skin into the target muscle. These are very similar to the electrodes used for intracranial recordings of neural activity and, much like the intracranial recordings, only provide a very local picture of muscle activity. A less invasive alternative is surface electrodes; these are placed on the skin over the muscle to record the electrical signal and provide a more general view of activity from the target muscle (much like the electrodes placed on the scalp for EEG). Generally, in this set-up the recording electrode is placed on the thickest part of the target muscle (the belly) and, while there are variations, the reference is commonly placed on the tendon of the target muscle.

Motor Evoked potentials

As previously mentioned, when the primary motor cortex is stimulated using a TMS pulse of sufficient intensity it produces muscle activity, and this evoked muscle activity can be measured using EMG. The waveform of the muscle activity recorded by EMG is known as a motor evoked potential (MEP). As M1 consists of a somatotopically organised map of the human body the specific muscle activated depends on which part of M1 is stimulated.

Motor evoked potentials have a number of properties that are of interest to neuroscientists and neurophysiologists; however, the property of most interest in the current thesis is the amplitude of the MEP. More specifically spTMS over the motor cortex will be used to establish the minimum stimulation intensity required to produce

consistently produce MEPs of approximately 100 μV when the target muscle is at rest (Rossini et al., 1994). This minimum stimulation intensity is known as the motor threshold and is a well-established way of determining and quantifying the excitability of the motor cortex (Baykushev, Struppler, Gozmanov, & Mavrov, 2008; Stewart, Walsh, et al., 2001).

Once the optimal stimulation site for producing MEPs for a particular muscle has been established, typically the motor threshold is established by stimulating the cortex at a specific intensity over a number of trials (usually between five and ten) to determine if it produces MEPs with a peak to peak amplitude of 100 μV for approximately 50% of those trials (Stewart, Walsh, et al., 2001). The stimulation intensity is then adjusted accordingly and more trials are run until the specific threshold intensity has been identified. This method is not ideal as it can be fairly time consuming to undertake, instead the experiments described in this thesis used a modified binary search procedure (MOBS) to ascertain individual motor threshold.

MOBS is an adaptive procedure for assessing thresholds developed by Tyrrell and Owens (1988) a brief description will be given below but for a complete explanation refer to Anderson and Johnson (2006) and Tyrrell and Owens (1988). The test range for the MOBS is defined by two boundaries (in the case of the current experiment the upper and lower limits of stimulator output) and the value midway between these two boundaries is used as a stimulus. The boundaries are then updated according to the response to the stimulus: if the stimulus produces a response then the upper limit is lowered to the stimulus value, if not then the lower limit is raised to the stimulus value. The stimulus is then updated and re-tested. If there are consecutive identical responses, then the affected boundary is relaxed by setting to to a previous value. This procedure continues until the responses have reversed (moved from a positive to a negative response, or vice versa) a set number of times, in the case of the current experiment the number of reversals was set at five.

The primary advantage this has over other adaptive staircase techniques used when searching for a threshold is its rapidity, Tyrell and Owens report that the mean number of trials until termination (i.e. an appropriate threshold is found) is between ten and fifteen, while regular staircase methods required more than forty trials to reach termination. It has also been reported that the MOBS procedure performs just as well in reliably determining thresholds as other adaptive methods (Anderson & Johnson, 2006).

Safety and ethics of TMS

As in all experiments, the primary concern in TMS studies is for the health and safety of the participant. It has been noted that TMS can cause 'mild adverse effects', these primarily include: minor discomfort, muscle pain, nausea, and mild headache (Maizey et al., 2013). Maizey et al. report that the overall rate of mild adverse effects across sessions was approximately 5% and 39% of participants who took part in the TMS study reported at least one 'mild adverse effect'. However, they also found that the reported incident rates were higher for initial TMS sessions as opposed to later sessions, and that there was no association between participant characteristics, TMS frequency, or intensity.

Given these findings it seems likely that participants of a TMS study will experience one or more mild adverse effect but there is little that the experimenter can do to prevent it. Regardless, all participants were informed of these potential side effects and asked to tell the experimenter if they experienced discomfort during stimulation including, but not limited to, the aforementioned 'mild adverse effects'. If major discomfort was reported the experimenter stopped stimulation immediately and provided the participant a break, reiterating the participants' right to withdraw from the experiment at any time without having to give a reason why, and only continuing if the participant was happy to proceed.

The most commonly associated 'serious adverse effect' associated with TMS was the small chance of a seizure induced by the stimulation. These are most commonly associated with individuals more susceptible to seizures (e.g. those with a personal or family history of epilepsy) or those taking neuroleptic medication (Stewart, Ellison, Walsh, & Cowey, 2001). As per the safety guidelines outlined by Rossi, Hallett, Rossini, and Pascual-Leone (2009) all participants were screened before testing and participants who were considered susceptible to seizures were not tested. All of the studies involving TMS in this thesis followed the safety guidelines for the use of TMS outlined by Rossi et al., (2009) and were approved by the local ethics committee at Goldsmiths College, University of London.

The use of TMS in this thesis

The aim of the TMS experiment in the current thesis was to determine whether there were significant changes in motor-cortical excitability associated with early motor learning, and whether these changes differed between the DCD and control groups.

Accordingly, the stimulation site of interest was M1, in particular left M1 as participants performed the task with their right hand. The target muscle was the first dorsal interosseous (FDI) as it is relatively easy to isolate using TMS and is involved in the control of the finger used during the task. The initial site of stimulation was at the C3 electrode position in the 10-20 electrode placement system (See Figure 15) but the coil was moved around this site to find the optimal site for producing MEPs in this muscle on a participant by participant basis. The hunting and thresholding procedures both employed single pulse TMS, and a figure-of-eight coil with a wing diameter of 70 mm was used due to the need for high spatial specificity.

The EMG electrodes were Ag/AgCl surface electrodes and were set up so that the recording electrode was placed on the belly of the FDI, the reference was placed on the

tendon and the ground electrode was placed on the back of the hand as illustrated in Figure 38 below. The EMG system used for the MEP experiments in this thesis was a system built in-house; it had a sampling rate of 1800 Hz with 24 bit analogue to digital conversion. The waveform displayed was filtered using a FIR 10 Hz high-pass filter.

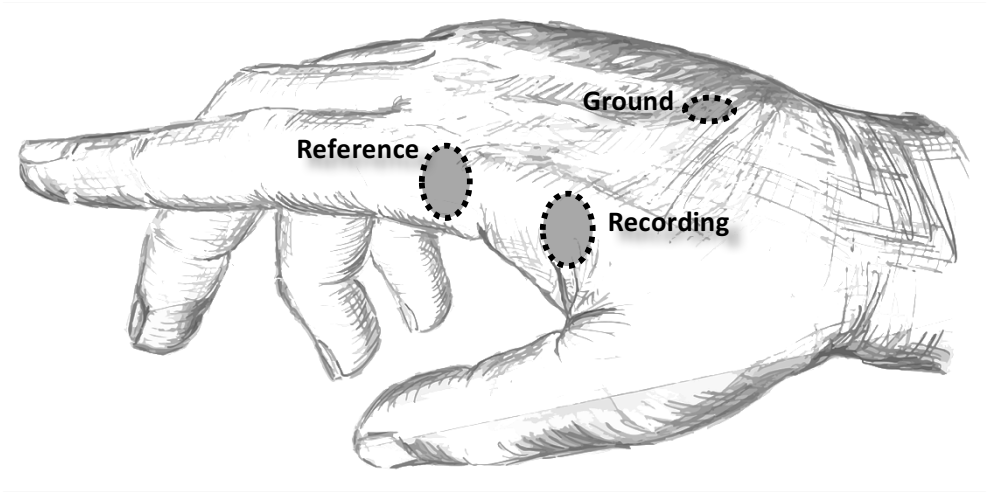

Figure 38 – Positioning of EMG electrodes for measuring MEPs from FDI

The MOBS procedure was implemented so that an MEP below 100uV was considered a 'miss' while a MEP above 100uV was a 'hit', these were entered into the procedure and the stimulation intensity was adjusted accordingly until the threshold was reached.

The following chapter will describe precisely how this TMS set-up was used as part of an experiment to examine the relationship between motor learning and motor cortical excitability in adults with and without DCD. In addition, it will present the results of the experiment and discuss their relevance with regards current understanding of the neural basis of motor learning.

Chapter 7 – Neurophysiological correlates of the early stages of motor learning in adults with and without DCD

Abstract

It has been established that neurophysiological changes in the primary motor cortex, such as increased cortical excitability, are associated with the early stages of motor learning. However, to date there have been no studies examining these changes in individuals with Developmental coordination disorder (DCD). The current study aims to address this in order to examine the role these changes, or lack thereof, play in the motor learning difficulties experienced by individuals with DCD.

Twelve participants (six control and six DCD) undertook a novel motor learning task. At time points through the task the motor cortical threshold of the participants was measured using TMS.

The study found no change in motor performance and no change in motor cortical excitability for either group over the course of the task. However, only limited conclusions can be drawn from this experiment, as a third of the participants recruited did not respond to the TMS, leaving the study statistically underpowered.

These results are discussed in the context of the challenges experiences in this study, as well as the findings of previous studies and the broader literature. Suggestions are made for potential avenues of future research that further explore the neural correlates of DCD, while also addressing the challenges outlined in this study.

Introduction

As discussed in the introductory chapter, it has been established since the early 20th century that the skeletal muscles are mapped onto the primary motor cortex, such that a

particular area of the cortex corresponds to a specific muscle (or action) (Penfield & Boldrey, 1937). More recent research has demonstrated that the cortical representations of the skeletal muscles are not completely fixed: the motor cortex is plastic and these representations will change depending on motor experience, and this plasticity plays a key role in motor learning (Sanes, 2003; Sanes & Donoghue, 2000).

As outlined previously, practice of a novel motor skill results in improvements in performance of said skill, and it also produces changes in motor-cortical properties. Most notably it causes the size of the representation for the area being used to execute the skill to grow. Pascual-Leone and colleagues discovered this by asking participants to practice a one-handed, five note sequence on a piano keyboard for two hours a day over a five day period (Pascual-Leone et al., 1995). Using TMS to map the motor cortex they demonstrated that the cortical motor areas for the muscles used (the long finger flexor and extensor muscles) were enlarged after the practice, and that individuals who just underwent the mapping without practice showed no change. They also demonstrated that while some of this change was due to the increased use of the limb, participants who just used their fingers without practicing a specific sequence did not show the same degree of expansion as the individuals who were practicing a specific sequence.

This growth in the area of the representation of the muscles being used was also accompanied by an increase in the excitability of the same area (Pascual-Leone et al., 1995), which has been successfully replicated a number of times for a number of different muscles (Perez et al., 2004; Ridding & Rothwell, 1997; Svensson et al., 2003, 2006). These practice driven changes in motor-cortical properties have been shown to be a vital component in the early stages of motor learning, as disrupting them has a detrimental impact on improvements made during the initial practice periods (Muellbacher et al., 2002).

These changes do not occur at the same rate for every individual and there are a number of factors that can influence the plasticity of the motor cortex, including: premature birth (J. B. Pitcher, Schneider, et al., 2012), aging (Rogasch et al., 2009), and prior motor expertise (e.g. musicianship; Rosenkranz, Williamon, & Rothwell, 2007). This suggests a potential mechanism to partially explain the different rates of motor learning across the human population: the rate of motor learning in the early stages is limited by how rapidly the motor cortex can change and this may then have an impact on later stages of motor learning. Indeed, Stagg and colleagues have already provided some support for this idea by showing that transcranial direct current stimulation (tDCS) on the motor cortex reduces GABA concentration and the magnitude of the reduction correlates with the degree of motor learning (Stagg et al., 2011).

There are a number of different ways of approaching how to investigate the relationship between motor plasticity and motor learning. The aforementioned study by Pascual-Leone and colleagues utilised a direct approach, whereby they asked participants to practice a task over several days and were able to directly quantify the effect this had on motor cortical properties. In contrast, Stagg and colleagues used a more indirect method whereby they utilised tDCS to alter the properties of the primary motor cortex and then examined whether the responsiveness to tDCS correlated with a measure motor learning. While both options are viable for the current experiment, the former paradigm was chosen over the latter in order to provide a more direct link between motor learning and practice-related brain changes.

The primary aim of the current experiment is to use brain stimulation methods to examine the changes in motor cortical excitability that occur over the course of a motor learning task. As the task used was essentially the same as in chapter 5 the behavioural hypothesis was the same, that is: there will be an improvement in performance in the control group

(as measured by a decrease in reaction time), while there will be no change for the DCD group.

Hypotheses

The prior literature suggests that motor learning is accompanied by an increase in motor cortical excitability, thus it was hypothesised that there would be increases in motor cortical excitability alongside the expected improvements in performance for the control group. Given that, as in previous experiments, the DCD group were not expected to improve on the task it was hypothesised that there would be no change in motor cortical excitability for the DCD group.

As discussed in chapter two, in order to ensure that changes in reaction time reflect actual changes in performance, and not just a shift in the speed-accuracy trade-off, accuracy was also assessed. It was expected that there would be no significant change in accuracy in either group over the course of the experiment.

Finally, as with the experiments in previous chapters, control blocks were included in order to determine whether changes in performance were directly attributable to learning. It was expected that there would be no change in performance or motor cortical excitability in these blocks for either the control or DCD groups.

Methods

Participants

19 participants were recruited for this study. Nine reported a diagnosis of DCD, and the remaining ten were neurotypical controls. All of the participants were right handed and aged between 18 and 35 years.

One of the participants was excluded from the analysis as one of their scores on the WAIS fell below the cut-off outlined in chapter three. Six further participants were excluded as it was not possible to elicit motor evoked potentials from them.

This left twelve participants: six from the control group and six from the DCD group. Each group consisted of 5 female and 1 male participants. There were no significant differences between the two groups in terms of age, handedness, or on any of the WAIS measures, (see

Table 11 below). There were however significant differences in ADHD SRS scores, with the DCD group scoring higher, although this difference was not reflected in the CAARS and may be due to the coarse nature of the ASRS. Additionally there were significant differences between the groups in both measures of motor ability (the MABC2 and the ADC), as expected the DCD group scored significantly worse than the control group

Materials

As with the previous experiments the task was run on a Windows XP machine using MATLAB (Version 7.11.0) and Psychtoolbox (Version 3.0.9) to display the stimuli and record the responses and reaction times for each of the tasks. All stimuli were presented in the centre of the screen in a black, size-24 font on a white background and viewed at a distance of 950mm. Responses were collected using a numerical keypad connected to the computer via USB port.

Table 11 – Summary of participant characteristics for the experiment in chapter seven

Measure	Control	DCD	F (1, 11)	p
Age	28.00 (3.03)	25.67 (4.76)	1.03	0.34
EHI Score	89.00 (13.37)	78.33 (26.85)	0.76	0.40
MABC2 score	102.67 (15.31)	85.33 (10.15)	5.34	**0.04**
ADC score	23.67 (17.28)	91.00 (14.06)	54.82	**<0.01**
ADHD - SRS	0.83 (2.04)	5.50 (0.84)	26.85	**<0.01**
CAARS - S:S	49.33 (12.06)	58.17 (6.43)	2.51	0.15
Vocabulary (WAIS)	13.50 (1.38)	14.50 (2.81)	0.61	0.45
Similarities (WAIS)	14.17 (1.72)	12.17 (2.86)	2.16	0.17
Picture completion (WAIS)	13.00 (2.61)	12.17 (0.75)	0.57	0.47
Block design (WAIS)	12.17 (1.72)	11.33 (2.16)	2.64	0.14
Matrix reasoning (WAIS)	14.00 (1.79)	14.33 (2.16)	0.09	0.78

Task

The task used for this experiment followed the proposed outline of the task described in the discussion section of chapter two. That is: the original task was converted to a within-subjects design by amalgamating the control and experimental conditions. The trial order is illustrated in Figure 2.

In addition, responses were modified so that the total response time could be partitioned into the time between stimulus onset and response onset (reaction time) and the time between response onset and response completion (movement time). The reasons for each of these changes are discussed in full in chapter two.

However, in order to ensure that in terms of the number of trials completed the thresholds between the control blocks and the experimental blocks were comparable, an additional control block was added at the beginning of the experiment, as illustrated in Figure 39

below. Participants undertook 112 trials per block: the total number of trials in the experimental blocks was 448 and the number of control trials was 336.

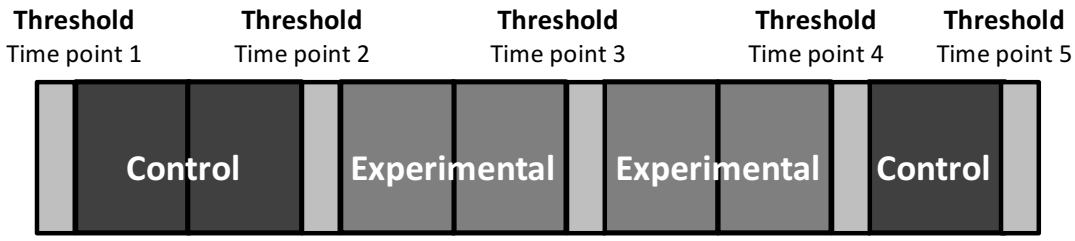

Figure 39 - Amended block order for the experiment in Chapter 7

Procedure

Before starting the study, the researcher briefly outlined the study to the participant, before giving them a standard consent form *(See Appendix A)* to read and sign. The experimenter began by applying the EMG electrodes to the participant's hand in the positions described in the previous chapter. Once a clean signal had been established the experiment began by finding the motor cortex of the participant, and upon establishing a reliable position from which to elicit MEPs the experimenter assessed the participant's initial motor threshold using the procedure outlined in the previous chapter. The participants then undertook the task in the order illustrated in Figure 39. Motor thresholds were taken at specific intervals between the blocks, the thresholding time points are also illustrated in Figure 39 above.

During the breaks between blocks the experimenter reminded the participant what that task entailed, emphasising the need for high degrees of accuracy during the experimental blocks while also responding as rapidly as possible. Once the participant had finished the task they were debriefed and allowed to ask any questions they had about the study.

Ethics

For full details about the specific TMS safety protocols in place please refer to the previous chapter. Ethical approval for this project was obtained from the Goldsmiths Psychology Department Ethics Board.

The experimenter outlined the experiment in full prior to signing of the consent form, and the right of the participant to withdraw at any time without having to give a reason was emphasised both verbally and in the consent form. Additionally, participants were informed that all the data collected, in both paper and electronic format, would be associated with a participant number only, and contained no information that could be used to identify a specific individual. Finally, participants were informed that they had the right to withdraw their data at any time after the completion of the experiment, and were given contact details for the researcher and their unique participant number to do this.

Data analysis

Behavioural analyses

As with the previous experiments, a distribution analysis attempted to fit an Ex-Gaussian distribution to the behavioural data on a block by block basis for each participant. The estimated distribution was then compared to the observed data using a chi-squared goodness of fit test. If the estimated distributions fit for over 80% of the blocks then the summary statistics produced by the analysis (μ (mu), σ (sigma), and τ (tau), previously described in chapter two) were used for the statistical analysis. In the case of blocks where the fit of the distribution was poor, the summary statistics for those blocks were not included in the analysis. If the estimated distributions fit for less than 80% of the blocks, then the traditional approach described in chapter two was utilised.

Based on the modest sizes of the groups included in this study, a non-parametric approach was chosen. Friedman's ANOVA was selected to look at changes in motor learning. Two ANOVAs were conducted to examine changes in motor performance over the course of the task, one for each group. Each of these ANOVAs had one within subject factor: block, with four levels corresponding to each of the experimental blocks.

If either of the analyses demonstrated a statistically significant change in performance a follow up test was conducted to test for an interaction: The difference in performance between the first and last measurements was calculated and then analysed using a Mann-Whitney test.

In addition, separate Friedman's ANOVA were conducted for the control blocks of each group, theses had one within-subject factor: block, with three levels corresponding to the control blocks.

Cortical excitability analyses

As with the analysis of motor performance, a non-parametric approach was taken due to the modest group sizes. Friedman's ANOVA was selected to to look at changes in cortical excitability over the course of the experimental blocks. Separate ANOVAs were conducted for each group and each had a single within-subjects factor: Time point, which consisted of three levels corresponding to time points two, three and four (illustrated in Figure 39).

Again, If either of the previous pairs of analyses demonstrated a statistically significant change in motor cortical excitability, a follow up test was conducted to test for an interaction: The difference in excitability between the first and last measurements was calculated and then analysed using a Mann-Whitney test.

Finally, Wilcoxon tests were used to examine the differences between the motor excitability pre- and post- the control blocks.

Results

Behavioural results - Control blocks

As with previous experiments, In the control blocks the success of the distribution fitting approach fell below the 80% cut-off for all reaction time partitions (Success rates: TT = 58%, RT = 69%, MT = 27%). Consequently the traditional approach described in chapter two was utilised to examine the data. There was no statistically significant change in any of the measures for any of the partitions in the control block. The data for each block and the results of the statistical tests are summarised in Table 12 below.

Table 12 - Summary of performance measures and results of statistical tests for the control blocks

Partition	Measure	Group	Block 1	Block 2	Block 7	X^2	*p* - value
TT	Mean	Control	2.64	2.62	2.61	2.33	0.31
		DCD	2.68	2.70	2.70	1.00	0.61
	Variability	Control	0.06	0.06	0.06	1.00	0.61
		DCD	0.10	0.12	0.10	1.33	0.51
RT	Mean	Control	2.45	2.43	2.42	4.33	0.12
		DCD	2.50	2.50	2.51	1.00	0.61
	Variability	Control	0.06	0.07	0.08	4.33	0.12
		DCD	0.08	0.09	0.08	1.33	0.51
MT	Mean	Control	2.16	2.16	2.15	0.33	0.85
		DCD	2.20	2.22	2.20	0.33	0.85
	Variability	Control	0.08	0.08	0.07	2.33	0.31
		DCD	0.09	0.10	0.15	0.33	0.85

Behavioural results - Experimental blocks:

Accuracy: The accuracy scores for each of the experimental blocks are illustrated in Figure 40 below. The Friedman's ANOVA revealed no significant change for either group: Control group: (X2 (3, N = 6) = 3.1, p = 0.37), DCD Group: (X2 (3, N = 6) = 1.8, p = 0.62).

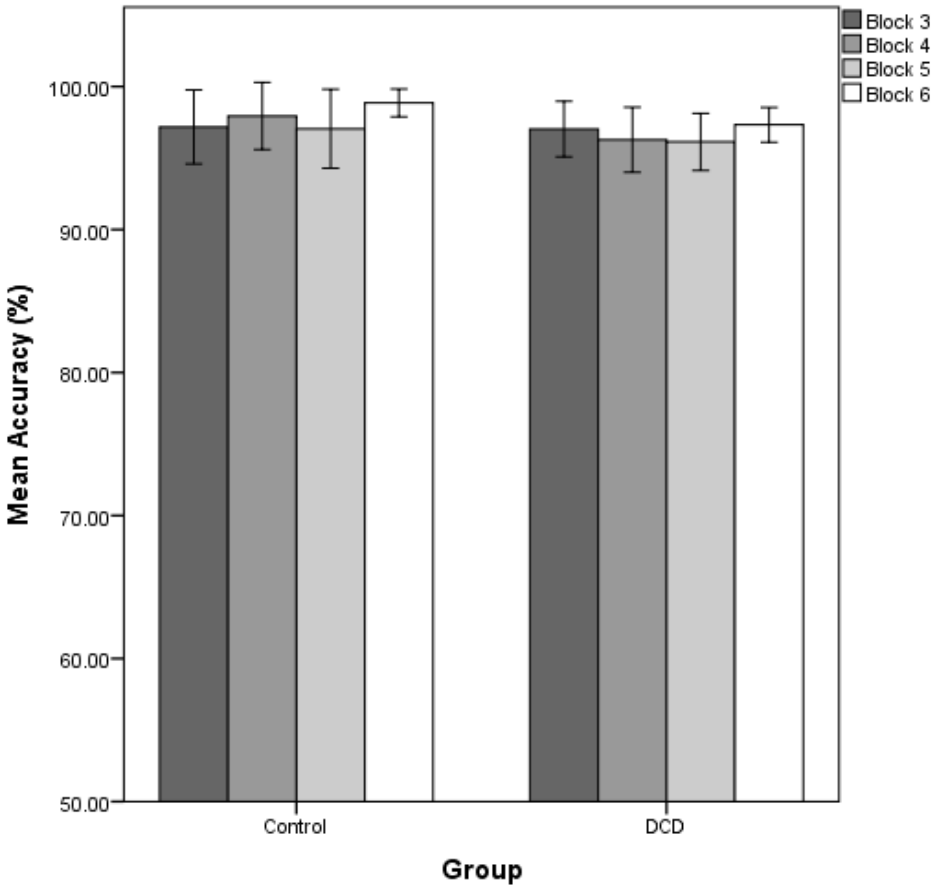

Figure 40 - Accuracy scores for the experimental blocks

Total time: The distribution analysis for TT was able to successfully fit an ex-Gaussian distribution to eighty-five percent of the blocks (41 of 48 blocks); consequently the summary measures (Mu, Sigma, and Tau) for these distributions were used in the statistical analyses. The remaining seven blocks that the distribution analysis was not able to successfully fit an ex-Gaussian distribution were not included in the statistical analysis.

As seen in Figures 41, 42, and 43 below, there does not appear to be any significant change in any of the measures of motor performance in either group for the experimental blocks.

This is backed up by the results of the Friedman's ANOVAs for each of these measures, which are summarised below in Table 13.

Table 13 - Results of the statistical analyses conducted on the TT distributions from the experimental blocks of the task

Measure	Group	χ^2 (d.f. = 3, N = 6)	*p* - value
Mu	Control	6	0.11
	DCD	2.4	0.49
Sigma	Control	1.8	0.62
	DCD	3	0.39
Tau	Control	4.2	0.24
	DCD	2.6	0.46

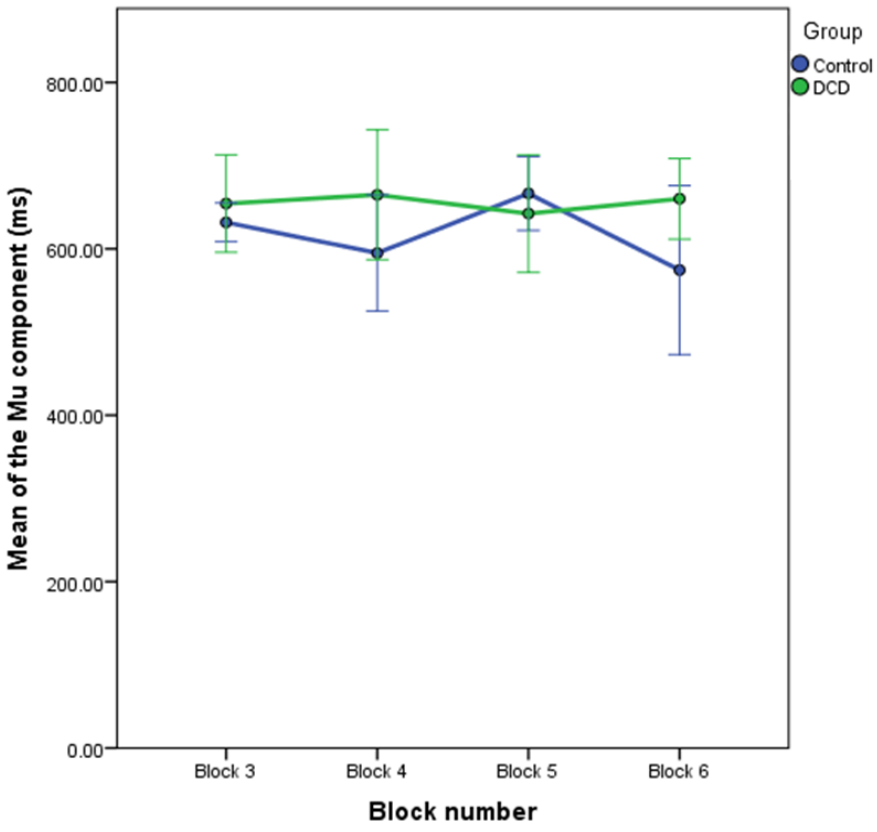

Figure 41 - Plot illustrating changes in the Mu component of the TT distribution across the experimental blocks (Error bars: ±2 Standard error)

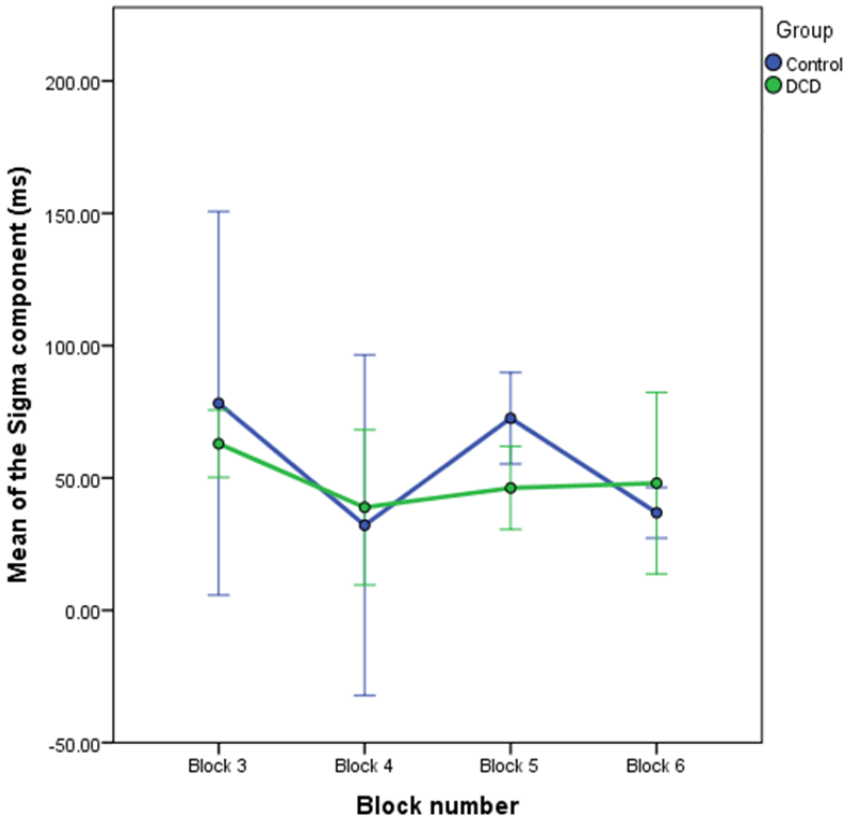

Figure 42 - Plot illustrating changes in the Sigma component of the TT distribution across the experimental blocks (Error bars: ±2 Standard error)

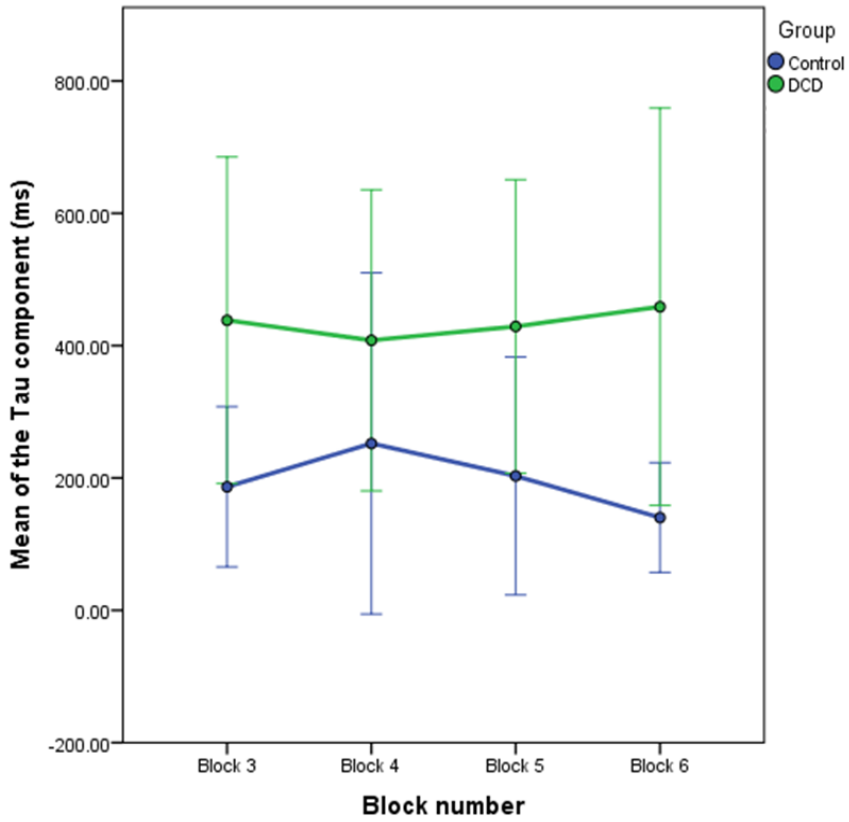

Figure 43 - Plot illustrating changes in the Tau component of the TT distribution across the experimental blocks (Error bars: ±2 Standard error)

Reaction time: The distribution analysis for RT was able to successfully fit an ex-Gaussian distribution to ninety-four percent of the blocks (45 of 48 blocks); consequently, the summary measures of reaction time performance (Mu, Sigma, and Tau) for these distributions were used in the statistical analyses. The remaining three blocks that the distribution analysis was not able to successfully fit an ex-Gaussian distribution were not included in the statistical analysis.

As seen in Figures 45, 44, and 46 below, there does not appear to be any significant change in any of the measures of motor performance in either group for the experimental blocks. For the Mu and Tau components this is backed up by the results of the Friedman's ANOVAs, which are summarised below in Table 14.

However, the statistical analysis did identify a significant change in the Sigma component for the control group. Although it is likely that this result is a false-positive, given the data illustrated in Figure 44 which does not appear to show a particular difference across the blocks beyond the initial decrease in block two.

Table 14 - Results of the statistical analyses conducted on the RT distributions from the experimental blocks of the task

Measure	Group	χ^2 (d.f. = 3, N = 6)	*p* - value
Mu	Control	2	0.56
	DCD	3.5	0.32
Sigma	Control	8.8	0.03
	DCD	6.1	0.11
Tau	Control	1.4	0.71
	DCD	3	0.39

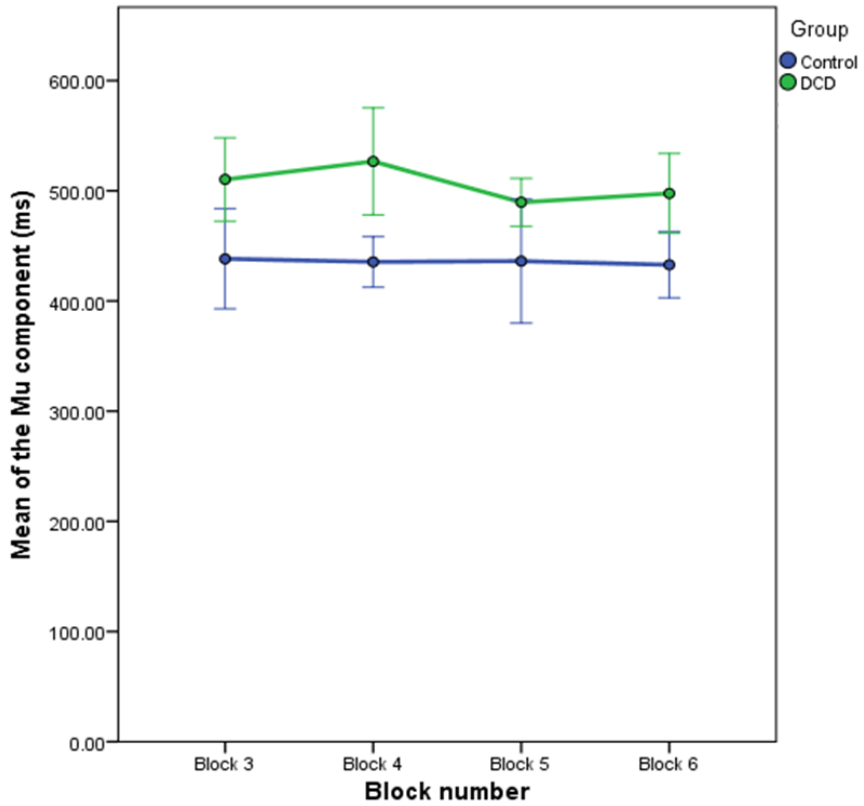

Figure 45 - Plot illustrating changes in the Mu component of the RT distribution across the experimental blocks (Error bars: ±2 Standard error)

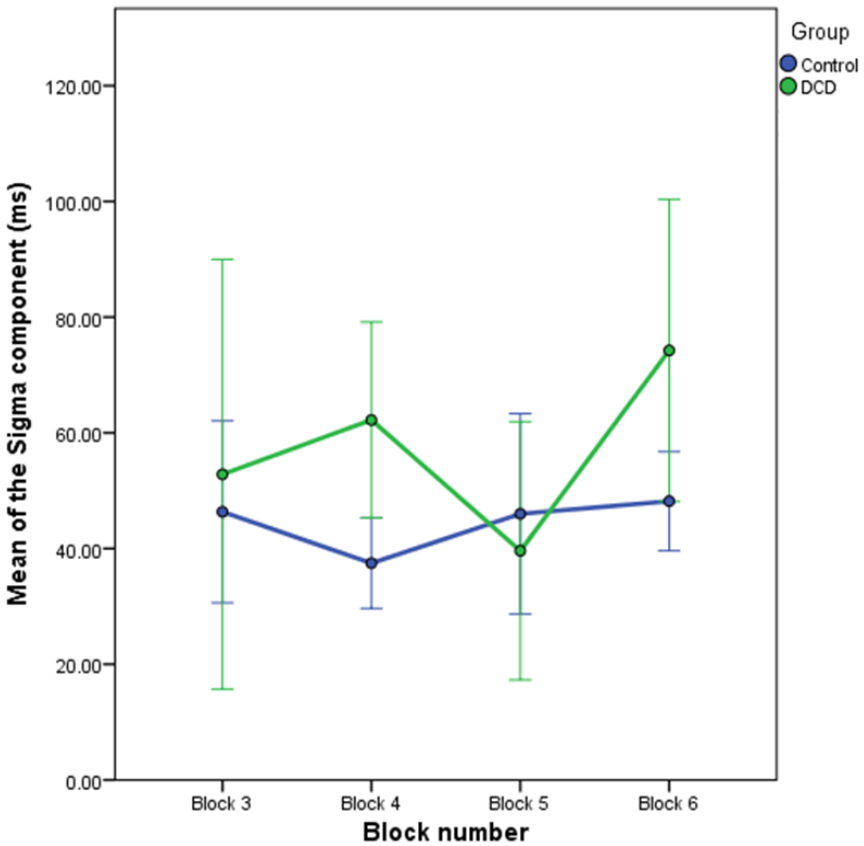

Figure 44 - Plot illustrating changes in the Sigma component of the RT distribution across the experimental blocks (Error bars: ±2 Standard error)

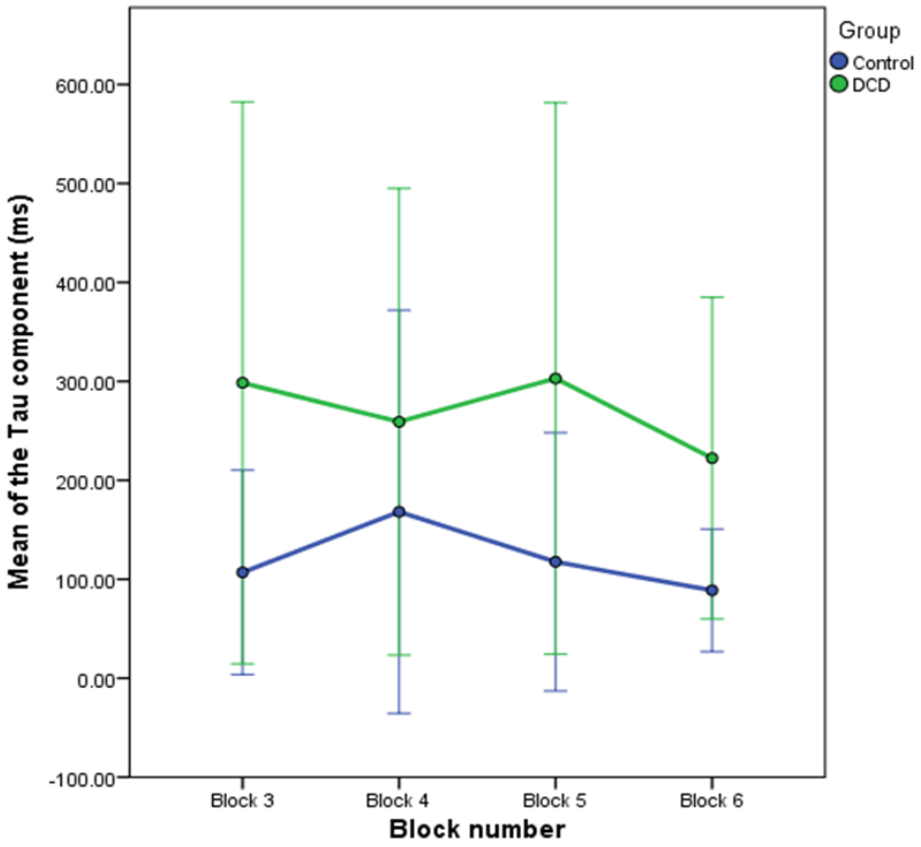

Figure 46 - Plot illustrating changes in the Tau component of the RT distribution across the experimental blocks (Error bars: ±2 Standard error)

Movement time: The distribution analysis for MT was only able to successfully fit an ex-Gaussian distribution to forty percent of the blocks (19 of 48 blocks); consequently the traditional method of examining reaction time, outlined in chapter 2, was used. This approach produces the mean and standard deviation as summary measures of movement time performance, which were used in the statistical analyses.

There does not appear to be any systematic change in either the mean movement time or the variability of movement time over the course of the task for either group (as illustrated in figures 48 and 47), and these observations are supported by the results of the Friedman's ANOVAs displayed in Table 15

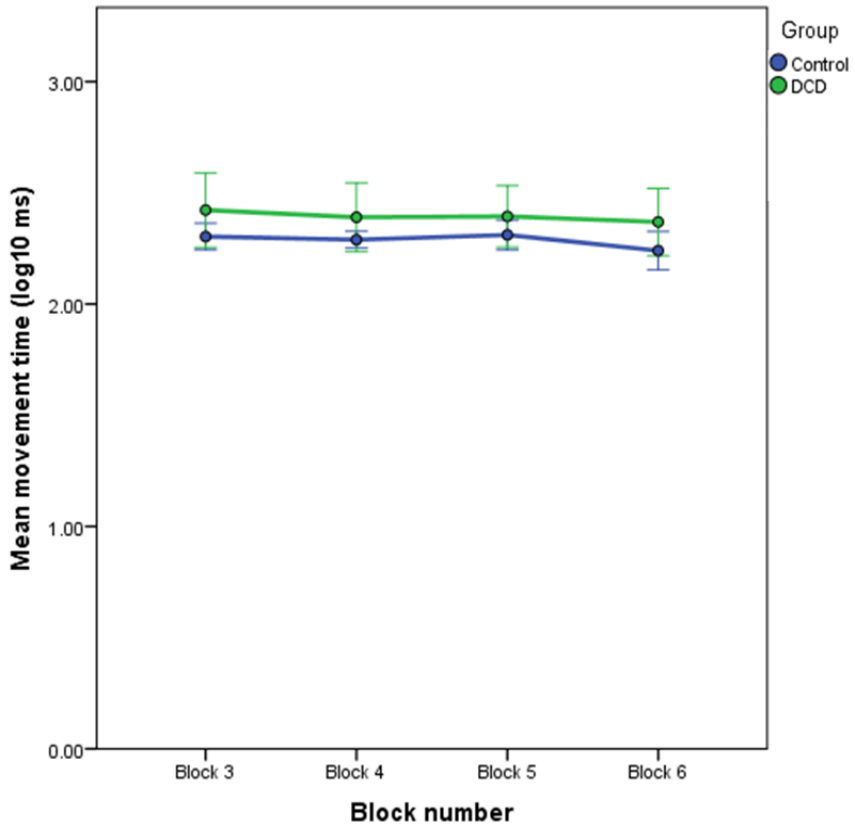

Figure 48 - Plot illustrating changes in the Mean MT across the experimental blocks (Error bars: ±2 Standard error)

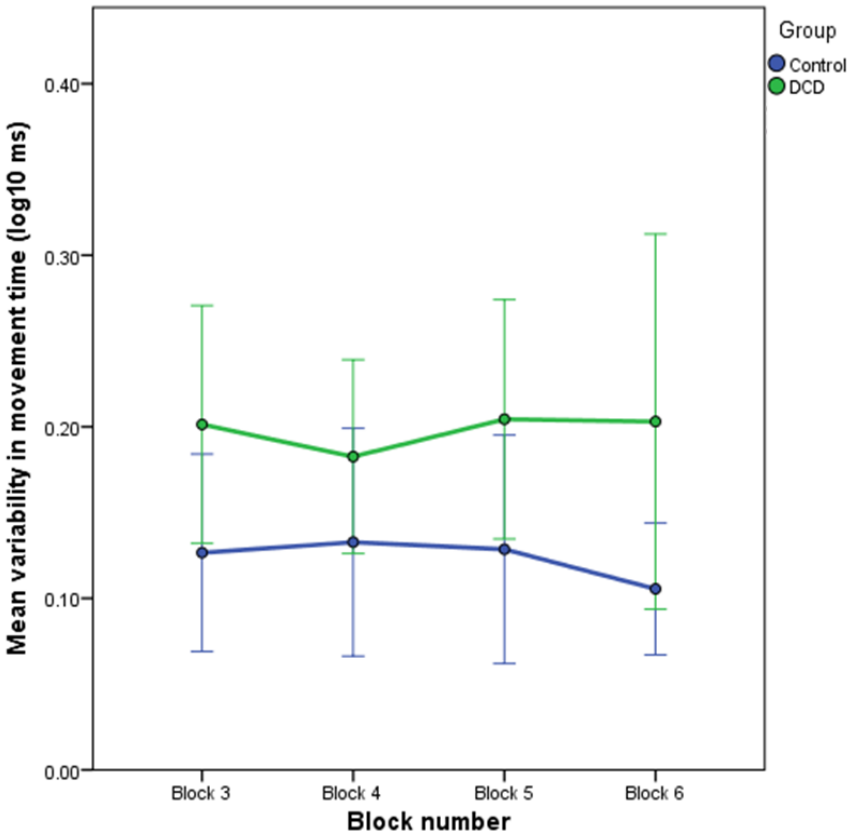

Figure 47 - Plot illustrating changes in the Variability of MT across the experimental blocks (Error bars: ±2 Standard error)

Table 15 - Results of the statistical analyses conducted on the MT measures from the experimental blocks of the task

Measure	Group	χ^2 (d.f. = 3, N = 6)	*p* - value
Mean	Control	1.8	0.62
	DCD	5.0	0.17
Variability	Control	3.0	0.39
	DCD	3.0	0.39

Motor cortical excitability results:

The changes in motor cortical excitability over the course of the task for both groups are displayed in Figure 49 below.

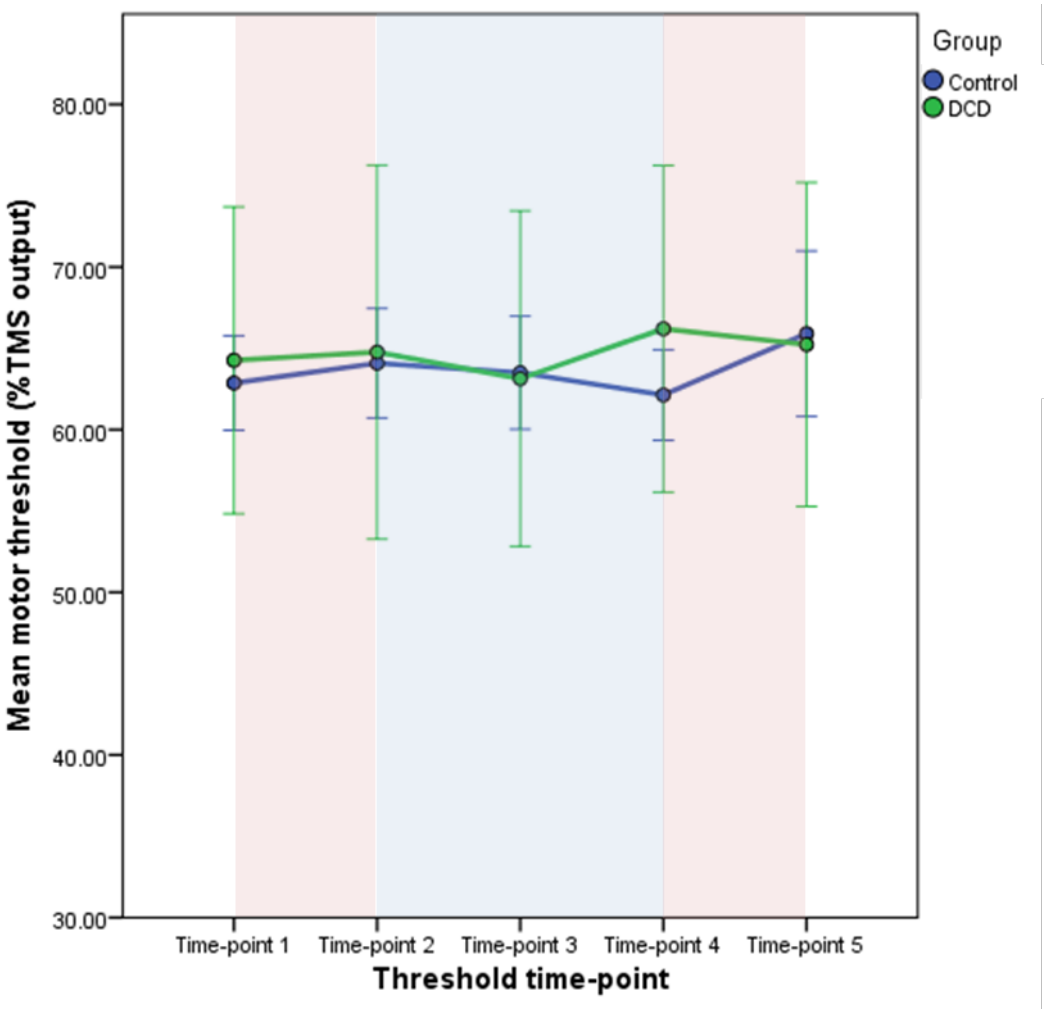

Figure 49 - Changes in mean motor cortical excitability over the course of the task (Control blocks highlighted in red. Experimental blocks highlighted in blue; Error bars: ±2 Standard error)

Control blocks: The Wilcoxon's tests found no significant change in motor cortical excitability for the first control blocks (time point 1 to time point 2) or the final control block (time point 4 to time point 5) for either group, see Table 16 below.

Table 16 - Results of the statistical analyses conducted on the cortical excitability measures for the control blocks.

Group	Time point	Test statistic	*p* - value
Control	1 to 2	Z = -0.84	0.40
	4 to 5	Z = -1.68	0.09
DCD	1 to 2	Z = -0.52	0.60
	4 to 5	Z = -0.94	0.35

Experimental blocks: Similarly, the Friedman's ANOVA used to analyse the experimental blocks also found no significant change in motor cortical excitability for either the control (X^2 (2, N = 6) = 4.53, p = 0.10) or the DCD (X^2 (2, N = 6) = 2.80, p = 0.25) groups.

Discussion

The aim of this experiment was to investigate changes in motor cortical excitability associated with motor learning in adults with and without DCD. The study found no change in motor performance or motor cortical excitability for either group. Although, as expected there was no change in accuracy for the experimental blocks and there was no difference in motor performance or cortical excitability for the control blocks. Explanations for this result and potential future directions for this research are discussed below.

There are several possible explanations for the results observed in this study; although due to the small number of participants included in the analysis interpretation of the results should be approached very carefully. The most obvious explanation is that these results are correct, the motor task is unable to produce motor learning and consequently there were no changes in motor cortical excitability. Alternatively, it may be that the findings of this study represent a false negative, that is: The task is able to produce motor learning and there are associated changes in cortical excitability but these changes are smaller than the statistical power available in this study is able to detect.

The first of these explanations, that there is no significant effect of practice on motor cortical excitability in this study, it is difficult to justify this interpretation from the findings of the current study. This is primarily due to the fact that there are no changes in motor performance, and it is expected that changes in cortical excitability are driven by motor learning. However, as the motor task has been shown to produce learning in both previous experiments it is reasonable to assume that given more statistical power it would do the same in this experiment, whether that would produce the predicted changes in cortical excitability remains to be seen. Further difficulty in accepting this second explanation arises when the less pronounced changes in cortical excitability that Pascual-Leone and colleagues observed for movement repetition are taken into account. Given that during the task participants were using the muscles controlling their right index finger for

approximately an hour, changes in motor cortical excitability produced by the repetitive action of the task would be expected even in the absence of changes in motor performance. Again, it is probable that this is due to a lack of statistical power.

Thus the second of the explanations seems, at least partially, the more likely of the two. With the size of the sample analysed in the current experiment it does not have the statistical power to detect the behavioural changes observed in the previous described experiments, and so is also unlikely to have enough statistical power to detect any changes in motor cortical excitability.

A specific challenge to obtaining larger sample sizes for this study was whether participants' responded to TMS; a reliable motor threshold could only be obtained for two-thirds of the participants tested. Transcranial magnetic stimulation is one of the only methods that is both non-invasive and able to provide a direct way of looking at how the brain changes during the course of a task. Nonetheless, as illustrated by this experiment, some individuals may not respond to the magnetic stimulation of the brain at all. To my knowledge, there are no studies reporting individual differences in susceptibility to TMS. If, however such a sub-group exists then it presents a problem when planning for these types of experiments, as it is unknown what proportion of the planned sample size will not respond to stimulation. It is likely that other studies that may have encountered this problem have simply continued to recruit participants to ensure a large enough sample size (without reporting the participants who did not respond to the stimulation). This option was not feasible here, as this study included a sub-sample of a population who are already challenging to recruit (e.g. adults with DCD).

It should be emphasised that while there is a lack of statistical power it does not automatically follow that the findings for this experiment are a false negative, it may be that even with sufficient statistical power to reproduce the behavioural results from the

previous experiments there would be no statistically significant change in motor cortical excitability with practice.

A further consideration is one of the key differences between the current study and the studies by Pascual-Leone and colleagues: the latter included a consolidation phase. In contrast, in the current study learning is assessed in the same experimental session in which the practice took place. It is apparent from the literature outlined in the introduction that consolidation is an essential component for motor learning. However, it has only been relatively recently that the role sleep plays in this consolidation phase has been elucidated. Walker and colleagues provide one of the most striking examples of the role of sleep in motor consolidation: they asked participants to repeatedly practice a finger tapping sequence on one hand for approximately 10 minutes. Participants were then asked to return later the same day and the following morning to assess how well they could reproduce the learned pattern. Following sleep, participants showed a marked improvement in reproducing the pattern, with a significant reduction in the number of correct sequences they could produce in 30 seconds and a significant reduction in errors (Walker, Brakefield, Seidman, et al., 2003).

Given the role of consolidation in motor learning, it is possible that even though the task used in the current study is able to produce behavioural changes (as demonstrated in previous chapters), any changes in motor cortical properties may not be observable until after a consolidation phase. The absence of a consolidation period may also have contributed to the lack of electrophysiological changes observed in chapter 4. It should be emphasised that the suggestion that a consolidation phase is needed before changes in excitability can be observed is speculative, and another experiment with a sufficient sample size and at least one return session would have to be conducted to test it.

It should also be noted that there is some evidence that individuals with DCD experience more sleep disturbance than controls (Barnett & Wiggs, 2012). This may indicate that

problems in consolidation linked to poorer sleep quality may play a role in the poorer motor ability observed in DCD, however more research would be required to confirm this.

In summary, the current experiment is unable to provide definite conclusions about the relationship between the early stages of motor learning and motor cortical excitability, particularly with respect to DCD. Nonetheless, it has provided an initial exploration into DCD using non-invasive brain stimulation methods that future research can build on. It has also highlighted the need for a better understanding of individual variability in susceptibility to transcranial magnetic stimulation; particularly when using this technique with populations that are challenging to recruit. Both of these latter points will be explored further in the general discussion chapter.

Chapter 8 – General Discussion

Outline

The scientific literature investigating the neural correlates of motor learning has identified a network of regions that play key roles in the motor learning process. As outlined in chapter one, there are lines of converging evidence utilising a number of different neuroscientific techniques that have identified the primary motor cortex as one of these key areas. Furthermore, while it is continuously involved throughout the process to some degree, it is predominantly involved in the early stages of motor learning. However, the changes that the primary motor cortex undergoes during the early stages of motor learning differ across the population due to a number of factors, and these differences may play a role in motor learning ability.

Simultaneously, it is well-established that a proportion of the general population experience significant difficulties in motor coordination and learning that have a negative impact on activities of daily living and wellbeing, have been present since childhood, and do not have a clear medical explanation. The condition, termed developmental coordination disorder (DCD), continues to have negative impact into adulthood, but currently the cognitive and neural underpinnings for this disorder are not well understood.

The aim of the current thesis was to further understanding of potential neural correlates of DCD by exploring the observed motor learning difficulties in light of the current understanding of the neural underpinning of the early stages of motor learning. More specifically, it aimed to establish whether the aforementioned practice-related changes in motor cortical properties and activity may be compromised in individuals with DCD, thus producing the poorer motor learning reported in the literature. In order to achieve this, a

multi-modal approach was taken to provide an initial investigation into the role of the motor cortex during the early stages of learning a novel motor task in adults with DCD.

Chapter two discussed the types of task that have been used previously as part of the motor learning literature and outlined why a novel task is required for the current thesis. It also considered the need to move away from using the mean and standard deviation as summary measures of reaction time, instead shifting to a distribution-fitting approach using the Ex-Gaussian distribution. As part of this chapter an experiment was conducted to test the suitability of the newly-designed task and the distribution analysis approach. Results indicated that the task was successful in producing performance changes within a single session, and that a distribution-fitting approach was more suitable than the traditional approach. This established that the grounding of the task and analysis methods were sound and the approach was applied to the research population of interest.

Chapter three outlined the specific methodology used to ensure that the participants included in the reported studies could be considered to have met the criteria for DCD (or not in the case of the control group). From here, two complementary methods were employed to examine the neural changes associated with early motor learning in adults with and without DCD: electroencephalography (EEG) and transcranial magnetic stimulation (TMS). Specifics for each of these methods were discussed in chapters four and six respectively.

Chapter five describes an experiment that uses EEG to examine the electrophysiological changes associated with the early stages of motor learning. Two analysis approaches were employed to examine the EEG data collected: Event-related potential and the time-frequency representation analyses. These analysis approaches complement one another, allowing for different aspects of the data to be explored. The experiment demonstrated that the control group were able to improve on the task, but the DCD group did not. However, due to factors that are discussed in chapter five, the electrophysiological

correlates of this improvement in performance were inconclusive. There did however appear to be little difference between the groups in the activity immediately preceding response onset, suggesting that the differences leading to delays to reaction time observed in the DCD group occur earlier in processing.

Chapter seven described an experiment that utilises TMS to examine the neurophysiological changes associated with the early stages of motor learning. This experiment found no change in motor performance and no change in motor cortical excitability for either group over the course of the task. However, the conclusions that can be drawn from this experiment are limited as a third of the participants recruited did not respond to the TMS leaving the experiment statistically underpowered.

Where do the findings from this thesis fit into the DCD literature?

The behavioural results of the studies in this thesis indicate that the motor learning deficits observed in children with DCD remain to differing degrees in adulthood. Nonetheless, it is important to note that there are large intra-group differences among the DCD participants in terms of their motor ability (as evidence by the range of scores observed from the MABC2), and this makes it difficult to draw more general conclusions about motor learning in adults with DCD.

It is possible that this variability may be a product of the recruitment process; as discussed in the challenges section below, the criteria used to identify DCD in a higher education setting has a slightly different focus than those used within the research field. This may lead to the wide variability in motor ability and learning amongst participants recruited through universities. Nonetheless, there are a number of studies demonstrating that the trajectory of DCD in adolescence and adulthood is complicated particularly with regards to motor ability (Cantell et al., 1994, 2003; Geuze & Borger, 1993; Losse et al., 1991; Purcell et al., 2015), and the variability found in this thesis may simply be a further expression of that.

Given the inconclusive results from chapters five and seven, it is not possible to ascertain whether the difficulties in motor learning observed here are due to differences in motor cortical activity. However, from the studies reported here there are slight indications that this hypothesis may be incorrect. The foremost of these is the highly similar waveforms observed for the lateralized readiness potential between the groups. Even though the experiment in chapter five was unable to directly link changes in the LRP with motor learning, the lack of significant group differences suggests that the late lateralised preparatory activity associated with the primary motor cortex is unaffected in the DCD group. This is despite the fact that generally the individuals in the DCD group reacted slower than those in the control group, albeit not statistically significantly slower. Indicating that if there are neural correlates associated with deficits in reaction time then they are more likely to occur at an earlier stage of response processing. The data even give a potential, although fairly weak, indication of where that earlier processing deficit may occur, namely in the response selection stages associated with the N2/P3 components.

It should be noted however, that solely assessing a groups' motor ability based on the LRP has limitations. Firstly, as the LRP only measures lateralised activity changes could be more apparent in the non-lateralised response-locked activity. Secondly, while it is a useful starting point for research into the neural correlates of motor learning in DCD there are other approaches that may reveal more. For example, as discussed below, the deficits observed in neurodevelopmental disorder are not caused by a single area (as in brain damage) but an atypical development of the entire system. Thus a connectivity-based approach may reveal subtler differences between the groups.

Challenges encountered during this thesis

As with any research, a number of expected and unexpected challenges were encountered during the course of conducting this thesis. This section of the discussion will outline three

of the most prominent, explore their potential impact on the research, and what action was (or may be) taken to mitigate the impact of these challenges in this or future research. These three challenges were: the lack of standardised motor assessment for adults, combining the reaction-time distribution fitting approach with a standard EEG analysis pipeline, and the variability in responsiveness to TMS.

Lack of standardised motor assessment for adults

The lack of a standardised set of tests for motor ability in adulthood has already been discussed in the introductory chapter, however it will be further explored here taking into account the experiences from this thesis. In order to quantify motor ability in adulthood for experiments presented in this thesis a combination of a self-report measure (the Adult DCD Checklist; Kirby et al., 2010) and a motor battery (the upper age band from the Movement Assessment Battery for Children; Henderson et al., 2007) were used. While successful this approach was not ideal because, as the name suggests, the MABC2 is only standardised for individuals up to the age of sixteen. This means that the tasks used were designed to test motor ability for much younger individuals and may not have been challenging enough to successfully identify difficulties in the adults tested. In addition, while the MABC2 does provide cut-offs to indicate whether an individual has significant motor difficulties, again these are standardised for children and not appropriate to use with adults.

Both of these points are borne out by the data collected. Firstly, of the eighteen adults with DCD tested as part of this thesis, only one fell below the cut-off specified for the upper age band of the MABC2. Secondly, although the motor tests used were successfully able to distinguish between the neurotypical and DCD participants at the group level this finding belies the individual differences within each of the groups. There was a large degree of variation between the two groups, and the degree of overlap was such that if the participants were considered based on the scores of motor ability alone then several individuals in the DCD group could be classified as neurotypical and vice versa.

Furthermore, there were also differing degrees of success in distinguishing the two groups based on particular subtests. For example, the performance for both groups was comparable for the ball skills sub-tests, while it differed significantly for the manual dexterity portion. The scores on the ADC were a much better indicator of whether an individual had a diagnosis of DCD or not, although this is rather unsurprising given that the ADC was specifically designed to identify DCD in adulthood. Unfortunately, the number of participants tested in this thesis was too small to begin to look at the correlation between these two measures, and in view of the difficulty in recruiting participants with DCD a multi-lab approach may be required in order to examine the relationship between the two measures.

The requirement for a valid and reliable measure of motor ability becomes even more important when, as is the case in the current thesis, participants are primarily recruited from a higher education setting. Within this setting it is possible for students to receive a diagnosis of DCD/Dyspraxia from a specific learning difficulties (SpLD) professional. While assessment for this diagnosis does take past and present motor ability into account using a case history and examination of hand-writing. For obvious reasons it is more focussed on the cognitive difficulties the individual experiences that may then feed into academic problems (SpLD Test evaluation committee, 2016). As a result, the diagnosis provided by SpLD professionals does not correspond entirely to the criteria used within the research field. Because of this, having a clear indication of whether or not an individual's motor ability is significantly impaired independently of the need for direct comparison to a control group is vital.

Combining the reaction time distribution fitting approach with EEG processing

In the context of the current research the use of reaction-time distribution fitting presented a further challenge, specifically with regard to integrating it with the EEG processing pipeline.

As outlined in chapter four, both event-related potential and time-frequency analyses utilise time-locked averaging to increase the signal to noise ratio. It is assumed that when performing a task, the associated neural activity will follow approximately the same course while non-task related activity is essentially randomly distributed throughout the recording. Thus, when the waveforms are averaged the task-related activity will remain while the non-task related activity will cancel out. Consequently, as the variability in onset of a particular task-related component increases the ability for these methods to distinguish it from the non-task related activity decreases.

In traditional reaction time analyses this heterogeneity is less of a problem as typically there will be a processing step in the behavioural analysis where trials considered outliers (usually those beyond 2 standard deviations from the mean) are identified, allowing their waveforms to be removed from the EEG analysis. In contrast, because a complete distribution is required for the distribution-fitting approach it does not necessarily include an outlier removal step. As a result, there is the potential to include the more heterogeneous trials found in the rightward tail of the distribution that would decrease the overall signal-to-noise ratio for the analyses. In order to account for this problem a distribution specific cut-off was applied for each RT distribution analysed. The following section will briefly explore the reasoning behind the use of a distribution-specific cut-off, the value that the of was set at, and the consequences of using this approach.

For any given distribution it is possible to calculate how much of that distribution is contained between two points. For example, for data that fit a normal distribution 95% of the observations fall between points two standard deviations from the mean. As a result, it is possible to exclude 5% of the total data by removing data that falls beyond two standard deviations from the mean. Similarly, it is possible to ascertain the value of a data point that corresponds to a particular percentage of the overall distribution by examining the cumulative distribution function (CDF). To illustrate this figure X.X shows the CDF for a

Gaussian distribution with a mean of 500 and a standard deviation of 100, it is possible to use the CDF to determine that the point on the X axis at which 97.5% of the total distribution is accounted for is 700. Using this method, it is possible to only include a specific percentage of a distribution in an analysis for any distribution. This approach was chosen over simply applying a single, monolithic cut-off time for all participants, as the latter would likely skew the analysis given the motor difficulties experienced by DCD group. The cut-off percentage for the EEG analyses was set at 85% as it was felt that this gave the best trade-off between ensuring the relative homogeneity of the EEG signal being analysed, while also ensuring that a sufficient number of trials remained to conduct the analyses. Nevertheless, it is recognised that this figure is somewhat arbitrary given that this is the first known attempt to combine these methods and as a result there is no discussion on how to approach this problem in the literature.

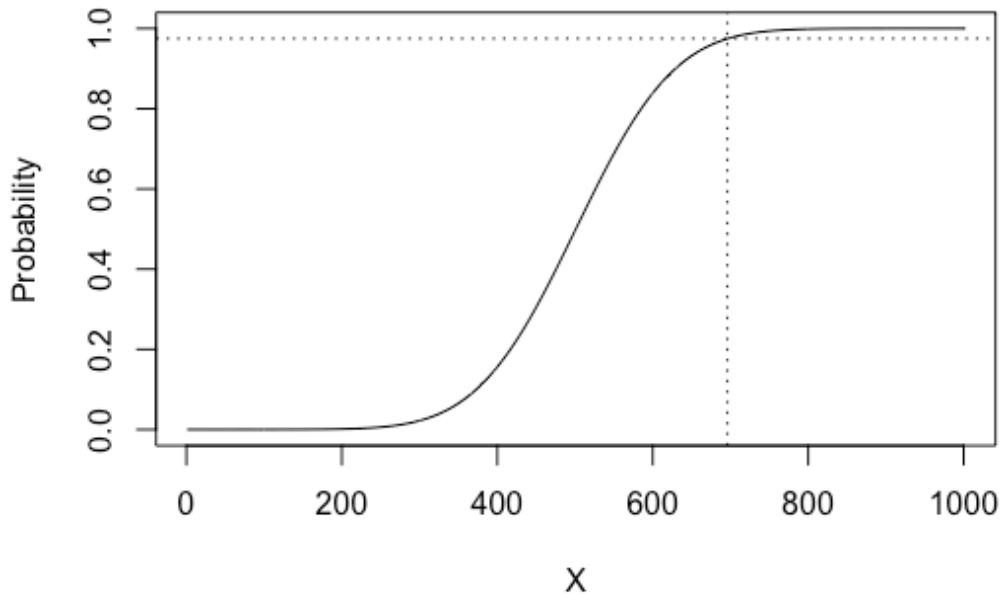

Figure 50 - Example cumulative distribution function (CDF) for a Gaussian distribution

Responsiveness to transcranial magnetic stimulation

One further issue experienced during the course of this thesis is the difficulty eliciting motor evoked potentials (MEPs) in several participants (both controls and DCD). Out of the 18 participants tested for the experiment outlined in chapter seven it was only possible to

elicit MEPs in 12 individuals. Currently, there is nothing in the literature to indicate whether this is an isolated finding or it is a more widespread occurrence that remains unreported.

There are a number of reasons why an individual may not respond to TMS: It may be that these participants have a particularly high motor vertical threshold. Generally, the experimenter did not use a stimulation level beyond 90% of the maximum stimulator output due to the discomfort caused by inadvertent stimulation of the cranial nerves and muscles. Alternatively, the inability to elicit a response in some individuals could be due to limitations inherent to the TMS technology: While the system is able to produce very focal activation on the cortex, the depth this stimulation can reach is limited to a few centimetres (Zangen et al., 2005). If the motor cortex of an individual is structured in such a way that it is not within the reach of stimulation, then it will have little to no effect.

Regardless, these hypotheses are conjecture until there is evidence that this problem is more widespread than just the current study. This could be relatively easily considered as there are numerous labs that use TMS as part of their research methodology and, even if they are not looking at the motor cortex directly, it is standard to use resting motor threshold to calibrate the stimulation intensity for other parts of the brain. Simply gathering the stimulation response rate from a number of these labs throughout the course of testing over a month would give a reasonable indication of whether this problem is more widespread, and if so what proportion of the population is affected.

As mentioned in the discussion section of chapter seven, this variability in response is less of a problem for testing within the neurotypical population as there is ample supply of potential participants. In contrast, it adds further challenge to researching a sample who only make up a small proportion of the population and are not well identified. Having an indication of how many individuals could be expected not to respond to TMS would allow for better planning for future studies using this method with the DCD population.

The future direction of research into DCD

Theoretical considerations

When considering possible future directions for research into DCD, and research attempting to understand the neural underpinnings of the disorder in particular, it is important to consider on what basis avenues of investigation are proposed. As discussed in the introductory chapter, currently DCD is generally considered from a neurodevelopmental rather than a neuropsychological perspective, yet the proposed neural correlates identified so far are still closely tied to those associated with apraxia. Considering that there is an already large and ever-growing body of literature looking at the neural correlates of motor control and learning in the neurotypical population, and that there are several proposed models to account for this literature, it is surprising that there appears to be little direct exploration of this in the DCD literature.

The use of existing theories of motor control and learning in examining DCD would serve a two-fold purpose: Firstly, it would ensure that research in DCD is grounded in the existing literature on motor learning and control and thus would provide clear, testable hypotheses about the cognitive and neural bases of the disorder. However, for reasons discussed below, typically these theories are ineffective at accounting for findings from research into neurodevelopmental disorders, and so the second purpose of using this hypothesis-driven approach would be to update the theories to incorporate the newer findings.

The difficulties observed in neurodevelopmental disorders are either explained using a cognitive neuropsychological approach or disregarded in these models. Briefly, traditionally the cognitive neuropsychological approach consists of three central posits: first, there are distinct modules in the brain that perform specific cognitive processes; second, the organisation of these modules is broadly the same across the general population; finally, these modules and the connections between them cannot be added to, only removed. As a

result, when examining a patient with brain damage it can be inferred that the deficits observed reveal something of the underlying cognitive architecture (Coltheart, 2002). Given the substantial success of this approach in utilising adults with brain damage to gain further understanding of human cognition and neurobiology, attempts have been made to apply it to developmental disorders, such as DCD.

However, the attempts that have been made to utilise this approach to explain the deficits observed in neurodevelopmental disorders have been less successful. A number of developmental researchers, including Karmiloff-Smith (1997, 1998, 2013) and Bishop (1997), have argued that this is because the assumptions made about an adult brain that underlie the neuropsychological approach do not apply to individuals who follow an atypical developmental trajectory. As Karmiloff-Smith states: *"…the brains of … impaired children are not simply normal brains with parts intact and parts damaged. Rather, they develop differently throughout embryogenesis and postnatal brain growth."* (1997, p. 514). Likewise, findings from literature on typical development further challenge the view that the assumptions made by cognitive neuropsychology can also be made about the cognitive and neural architecture of children. A growing body of evidence (See Johnson, 2011 for an overview) has found that during early development the brain is broadly tuned to the environment and as development progresses more specialised modules emerge, indicating that different cognitive and neural architectures exist in different developmental periods.

If theoretical models of motor control and learning aim to provide a framework with multiple levels of description (i.e. explanations from genetic, cellular, cognitive, social, etc levels), as seems to be the case (e.g. the description provided by Sanes & Donoghue, 2000), then incorporating the findings from research into typical and atypical development will be a vital component for disentangling how various levels interact during the development of these processes.

While this is a fairly obvious suggestion in theory, there are a number of practical issues that need to be addressed before significant headway can be made. One particular problem with incorporating DCD into models of motor learning or motor control is the degree of comorbidity with other neurodevelopmental disorders. There appears to be a higher than expected incidence of neurodevelopmental disorders that co-occur, to the point where Kaplan and colleagues (2006) suggest that co-occurring neurodevelopmental disorders may be the rule rather than the exception, as mentioned in the introductory chapter.

This begs the question: is the underlying cause in a case of 'pure' DCD different from a case where DCD co-occurs with another disorder (for example ADHD)? Both cases will exhibit significant motor problems, but is it possible that these motor problems could stem from different sources and simply have a common presentation? This problem is made even more complicated in DCD with the potential of different subgroups within the disorder. As discussed in the introductory chapter, these questions are starting to be considered in both the DCD and wider neurodevelopmental literature. However, a clearer understanding is still required before the results of studies into DCD could be used to inform theories of motor learning or motor control.

Specific suggestions for future research

Bearing the above discussion in mind, one clear target for future investigation is the cerebellum, as it is a key component in models of motor learning and is suggested to be involved in DCD.

It is fairly well established that stimulation of the cerebellum using TMS or tDCS has an inhibitory effect on motor cortical excitability in healthy controls (usually termed cerebellar brain inhibition, CBI; Daskalakis et al., 2004; Galea, Jayaram, Ajagbe, & Celnik, 2009; Hardwick, Lesage, & Miall, 2014). A number of studies that have made use of this finding in order to explore the role of the cerebellum in motor learning, and their methodologies

could easily be adapted to test the DCD population. Of particular note is work conducted by Galea and colleagues (Galea, Vazquez, Pasricha, de Xivry, & Celnik, 2011; Schlerf, Galea, Bastian, & Celnik, 2012) in which they employ non-invasive brain stimulation techniques in order to investigate the role of the cerebellum during visuomotor adaptation. Their results indicate that modulation of cerebellar excitability with anodal tDCS produced faster adaptation to a visuomotor perturbation. Further, there is greater cerebellar involvement during the early stages of an abrupt visuomotor perturbation (versus a gradual perturbation). The use of cerebellar stimulation methods to further explore visuomotor adaptation in DCD seems like a logical next step given that Kagerer and colleagues (2004, 2006) have already demonstrated that children with DCD show difficulties with visuomotor adaptation, generally requiring a large perturbation in order to adapt effectively, as discussed in the introductory chapter.

Conclusions

Ongoing research into the effects of DCD in adulthood and the potential neural underpinnings of the disorder is required in order to better understand the disorder and provide potential interventions to mitigate its primary and secondary impacts on individuals. This thesis has attempted to do both of these things, and while the results of some experiments are inconclusive, overall it has provided insights and potential future directions for research into both DCD in adulthood and the potential neural underpinnings of DCD.

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Appendix A – Standard consent forms used for this thesis

Information and Consent Form – Chapter 2

Participant Name: _____

Ref. Number: _____

This study is being run by Dan Brady (dan.brady@gold.ac.uk) and supervised by Jose Van Velzen (j.vanvelzen@gold.ac.uk) & Elisabeth Hill (e.hill@gold.ac.uk).

In the following experiment you will be asked to do a task which will entail responding to stimuli presented on screen as quickly and accurately as possible.

Participation in this study will take a maximum of 40 minutes. You may cease participation at any time, and no reason will be required. If you do wish to leave, you may request to erase your data.

Your data will be handled confidentially, and will not be passed on to anyone with your name attached.

Please tick the boxes below to indicate that you consent to the procedure

	Yes	No
Are you aware of the maximum duration of the testing session?		
Do you consent to us recording your behavioural responses to experimental stimuli?		
Do you consent to us recording medical details provided by you **strictly confidentially**?		
Do you understand that you will be able to leave at any time?		
Do you understand that you will be free to ask questions pertaining to the procedure at any time?		
Do you understand that your identity will be kept confidential, will not be passed on to anyone not involved in the conduct of this study, and will not appear in any publication?		

There are a few medical details which are required prior to participation. Ticking a 'yes' to these questions does not necessarily mean that you will not be able to take part. Please read the following questions and place a tick in the box to indicate your answer. All information you give here will be treated as confidential.

	Yes	No	Details
Are you currently taking/ have you recently taken any prescription or over-the-counter medications? If yes, please give details.			
Do you have normal or corrected to normal vision?			
Have you been feeling unwell over the last few days? If yes, please give details			
Have you taken any sort of legal or illegal drug in the past 24 hours? If yes, please give details			
Have you consumed alcohol in the past 24 hours? If yes, please give details			

Age:…….. Sex:……. Handedness:……..

Please sign the declaration below to consent to participation in this study subject to the conditions outlined above:

I freely give my consent to participate in this study. I have had the procedure explained to me and my questions have been answered to my satisfaction.

Print name……. E-Mail…….

Sign name……. Date…….

Information and Consent Form – Chapter 5

Participant Name: _____

Ref. Number: _____

This study is being run by Dan Brady (dan.brady@gold.ac.uk) & Xavier Job (ps301xj@gold.ac.uk) and is supervised by Jose Van Velzen (j.vanvelzen@gold.ac.uk) & Elisabeth Hill (e.hill@gold.ac.uk).

The experiment will consist of a series of subtests from the Movement ABC-2 and the Wechsler Adult Intelligence Scale (WAIS). These will then be followed by three EEG experiments: one looking at motor learning, one at reaching and the third at tapping. In total testing will take roughly a day: Max 2 hours for MABC and WAIS and Max 4 Hours for EEG.

You may cease participation at any time, and no reason will be required. If you do wish to leave, you may request to erase your data. Your data will be handled confidentially, and will not be passed on to anyone with your name attached.

Please tick the boxes below to indicate that you consent to the procedure

	Yes	No
Do you consent to you use of adhesive stickers?		
Do you consent to the use of conductive gel?		
Do you consent to us recording your EEG?		
Are you aware of the maximum duration of the testing session?		
Do you consent to us recording your behavioural responses to experimental stimuli?		
Do you consent to us recording medical details provided by you **strictly confidentially**?		
Do you understand that you will be able to leave at any time?		
Do you understand that you will be free to ask questions pertaining to the procedure at any time?		
Do you understand that you will be free to ask questions pertaining to the EEG procedure at any time?		
Do you understand that your identity will be kept confidential, will not be passed on to anyone not involved in the conduct of this study, and will not appear in any publication?		

There are a few medical details which are required prior to participation. Ticking a 'yes' to these questions does not necessarily mean that you will not be able to take part. Please read the following questions and place a tick in the box to indicate your answer. All information you give here will be treated as confidential.

	Yes	No	Details
Are you currently taking/ have you recently taken any prescription or over-the-counter medications? If yes, please give details.			
Have you or a close relative ever suffered from epilepsy?			
Have you had any surgery in which metal items have or may have been placed in your head?			
Do you have any history of allergic reactions to skin products, cosmetics or lotions? If yes, please give details			
Do you have normal or corrected to normal vision?			
Do you have a pacemaker fitted?			
Do you use any other medical electrical device? If yes, please give details			
Have you been feeling unwell over the last few days? If yes, please give details			
Do you suffer from any sort of chronic skin condition (dermatitis, eczema, psoriasis etc)? If yes, please give details			
Do you have any blood clotting disorder, or are you currently taking any drugs which reduce the effectiveness of blood clotting? If yes, please give details			
Have you taken any sort of legal or illegal drug in the past 24 hours? If yes, please give details			
Have you consumed alcohol in the past 24 hours? If yes, please give details			
Have you been diagnosed with any kind of psychiatric disorder? If yes, please give details			
Do you have any family history of psychiatric illness that you know of? If yes, please give details			

Age:…….. Sex:…….. Handedness:……..

Please sign the declaration below to consent to participation in this study subject to the conditions outlined above:

I freely give my consent to participate in this study. I have had the procedure explained to me and my questions have been answered to my satisfaction.

Print name…….. E-Mail……..

Sign name…….. Date……..

Information and Consent Form – Chapter 7

Participant Name: _____

Ref. Number: _____

This study is being run by Dan Brady (Dan.Brady@gold.ac.uk) and supervised by Jose Van Velzen (j.vanvelzen@gold.ac.uk) & Elisabeth Hill (e.hill@gold.ac.uk).

Transcranial magnetic stimulation (TMS) is a technique in which the brain is stimulated using a very brief magnetic field. This results in a variety of outcomes depending on what part of the brain is stimulated. In this study we will be stimulating the visual cortex, which produces phosphenes, and the motor cortex, which produces muscle activity.

We will be measuring muscle activity using an Electromyograph (EMG) which uses electrodes attached to the skin with adhesive stickers and conductive gel to ensure good contact with the electrodes. While these are not harmful, it may cause irritation if the participant suffers from skin allergies and in these cases should not be used.

Participation in this study, including preparation, will take a maximum of 2 hours. You may cease participation at any time, and no reason will be required. If you do wish to leave, you may request to erase your data.

Your data will be handled confidentially, and will not be passed on to anyone with your name attached.

Please tick the boxes below to indicate that you consent to the procedure

	Yes	No
Do you consent to the use of TMS?		
Do you consent to the use of adhesive stickers?		
Do you consent to the use of conductive gel?		
Are you aware of the maximum duration of the recording session?		
Do you consent to us recording your EMG?		
Do you consent to us recording your behavioural responses to experimental stimuli?		
Do you consent to us recording medical details provided by you **strictly confidentially**?		
Do you understand that you will be able to leave at any time?		
Do you understand that you will be free to ask questions pertaining to the procedure at any time?		
Do you understand that your identity will be kept confidential, and not passed on to anyone not involved in the conduct of this study and will not appear in any publication?		

There are a few medical details which are required prior to participation. Ticking a 'yes' to these questions does not necessarily mean that you will not be able to take

part. Please read the following questions and place a tick in the box to indicate your answer. All information you give here will be treated as confidential.

	Yes	No	Details
Are you currently taking/ have you recently taken any prescription or over-the-counter medications? If yes, please give details.			
Have you or a close relative ever suffered from epilepsy?			
Have you had any surgery in which metal items have or may have been placed in your head?			
Do you have any history of allergic reactions to skin products, cosmetics or lotions? If yes, please give details			
Do you have normal or corrected to normal vision?			
Do you have a pacemaker fitted?			
Do you use any other medical electrical device? If yes, please give details			
Have you been feeling unwell over the last few days? If yes, please give details			
Do you suffer from any sort of chronic skin condition (dermatitis, eczema, psoriasis etc)? If yes, please give details			
Do you have any blood clotting disorder, or are you currently taking any drugs which reduce the effectiveness of blood clotting? If yes, please give details			
Have you taken any sort of legal or illegal drug in the past 24 hours? If yes, please give details			
Have you consumed alcohol in the past 24 hours? If yes, please give details			
Have you been diagnosed with any kind of psychiatric disorder? If yes, please give details			
Do you have any family history of psychiatric illness that you know of? If yes, please give details			

Age:…….. Sex:…….. Handedness:……..

Please sign the declaration below to consent to participation in this study subject to the conditions outlined above:

I freely give my consent to participate in this study. I have had the procedure explained to me and my questions have been answered to my satisfaction.

Print name…….. E-Mail……..

Sign name…….. Date……..