Quantitative genetic research on sleep: A review of normal sleep, sleep disturbances and associated emotional, behavioural, and health-related difficulties

Nicola L. Barclay

Northumbria Centre for Sleep Research, Department of Psychology, School of Life Sciences, Northumbria University, Newcastle upon Tyne, NE1 8ST, U.K. Tel: +44 (0)191 227 4163; email: nicola.barclay@northumbria.ac.uk

Alice M. Gregory

Department of Psychology, Goldsmiths, University of London, U.K.

Tel: +44 (0)20 7919 7959; email: a.gregory@gold.ac.uk

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Corresponding author: Nicola Barclay

Abstract

Over the past 50 years, well over 100 twin studies have focussed on understanding factors contributing to variability in normal sleep-wake characteristics and sleep disturbances. Whilst we have gained a great deal from these studies, there is still much to be learnt. Twin studies can be used in multiple ways to answer questions beyond simply estimating heritability. This paper provides a comprehensive review of some of the most important findings from twin studies relating to sleep to date, with a focus on studies investigating genetic and environmental influences contributing to i) objective and subjective measures of normal sleep characteristics (e.g. sleep stage organisation, sleep quality); as well as sleep disturbances and disorders such as dyssomnias (e.g. insomnia, narcolepsy) and parasomnias (e.g. sleepwalking, bruxism); ii) the persistence of sleep problems from childhood to adulthood, and the possibility that the aetiological influences on sleep change with age; iii) the associations between sleep disturbances, emotional, behavioural and health-related problems; and iv) processes of gene-environment correlation and interaction. We highlight avenues for further research, emphasising the need to further consider the aetiology of longitudinal associations between sleep disturbances and psychopathology; the genetic and environmental overlap between sleep and numerous phenotypes; and processes of gene-environment interplay and epigenetics.

Keywords: Environment, Genetic, Heritability, Insomnia, Polysomnography, Sleep, Twins

Abbreviations	
Abbreviation	**Full text**
A	Additive genetic influence
C	Common (shared) environmental influence
CBCL	Child Behaviour Checklist
CSHQ	Children's Sleep Habits Questionnaire
D	Dominance (non-additive) genetic influence
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders – Fourth edition
DZ	Dizygotic
E	Nonshared Environmental influence
EEG	Electroencephalogram
ICSD	International Classification of Sleep Disorders
MZ	Monozygotic
PSG	Polysomnography
rA	Additive genetic correlation
rC	Common (shared) environmental correlation
rD	Dominance (non-additive) genetic correlation
rE	Nonshared Environmental correlation
REM	Rapid eye movement sleep
SWS	Slow-wave sleep

Introduction

There is wide inter-individual variability in sleep – in terms of both normal sleep characteristics such as sleep stage organisation, sleep timing and sleep quality; and sleep disorders such as insomnia, narcolepsy and circadian rhythm sleep disorders, to name a few.[1] The Diagnostic and Statistical Manual for Mental Disorders IV (DSM-IV)[2] and The International Classification of Sleep Disorders (2nd edition) (ICSD-2)[3] together describe numerous sleep disorders prevalent in the general population. It is likely that this variation in sleep between individuals is accounted for by a host of genetic and environmental factors. One method for investigating the extent to which variation in a trait (phenotype) is accounted for by genetic and environmental factors is to conduct research using twins. Twin studies allow us to estimate the relative proportion of genetic and environmental influences accounting for the variation in a trait in the population. In the field of sleep research there are an abundance of twin studies investigating the aetiology of a multitude of sleep phenotypes. Investigation of the contribution of genes and environments to both normal sleep phenotypes as well as clinically diagnosable sleep disorders informs us about the possible mechanisms involved in their occurrence, and has the potential to inform the development of treatment programmes for sleep disorders. Knowledge of the aetiology of sleep phenotypes also has the potential to inform nosology (the classification of disease).

The purpose of this review is to provide an overview of some of the most important findings from twin studies in relation to sleep. The review begins by describing the twin method and illustrates how twin studies go beyond simply estimating heritability. Second, it addresses questions which have been raised by twin studies investigating variation in sleep characteristics in the normal range, as well as clinically diagnosable sleep disorders in childhood and adulthood. Third, it addresses the stability of the aetiological influences of sleep phenotypes during development, and fourth, the possible comorbidity between sleep

disturbances, emotional, behavioural and health-related problems. Fifth, it considers processes of gene-environment interplay, including gene-environment correlation (rGE) and interaction (GxE). rGE is found when genetic effects influence exposure to specific environments (e.g. genetic influence on the tendency to consume caffeine). GxE refers to genotype dependent sensitivity to high risk environments (e.g. genetic influences on a trait vary as a function of some measured environmental stressor). Sixth, keys findings from areas of research other than quantitative genetics are presented which have informed us about specific genetic and environmental influences on sleep; and finally avenues for future research into the aetiology of sleep are suggested.

The Twin Method

Twin studies can be used to make assumptions about the aetiology of a trait by comparing identical (monozygotic: MZ) twin pairs who share 100% of their genetic make-up, and non-identical (dizygotic: DZ) twin pairs who share on average half of their segregating genes, on a particular trait of interest (for example sleep quality measured separately in each twin). Using this method it is possible to estimate the relative proportion of three sources of variance: additive genetic influences (A, the "adding up" of genes to influence behaviour); shared environmental influences (C, environmental influences which act to make family members similar); and nonshared environmental influences (E, environmental influences which act to make family members different).[4] Whether the familial influences on a trait are genetic or environmental in origin is indicated by the MZ:DZ ratio of the within twin pair correlations on that trait. In addition to the standard 'ACE' models, it is also possible to model genetic effects that function in a dominant manner. Dominance refers to the *interaction* of genes at a locus. The sum of all genetic influences, including both additive and dominant effects, is often referred to as "broad-sense heritability".

Despite the increasing number of molecular genetic studies aimed at identifying specific genetic variants associated with numerous sleep phenotypes (see Gregory and Franken[1] for a review), twin studies provide us with a wealth of additional information. First, quantitative genetic designs tell us just as much about the environment as they do about genetics. Second, twin studies can inform us not only about the aetiological influences on one phenotype, but can address issues of comorbidity by informing us about the extent to which the aetiological influences account for associations between multiple phenotypes, and the extent to which the genetic and environmental factors on one phenotype are correlated with those influencing another. Such information has the potential to guide molecular genetic studies aimed at identifying specific genes. For example, significant genetic covariation between traits suggests that genes known to influence one phenotype may be worthy candidates for exploration with regards to the associated phenotypes. Third, twin studies allow us to examine the heterogeneity of a disorder by estimating heritability in subtypes (e.g. individual subtypes of insomnia); or in sub-populations (e.g. between the sexes). For example, finding distinct genetic effects for a disorder in different sub-populations could suggest that different biological mechanisms are at play. Fourth, multivariate genetic analyses can test the stability of the aetiological influences on a phenotype by examining the extent of overlap in these influences over time. Longitudinal analyses would thus inform us as to whether genetic/environmental factors for a particular phenotype are constant across the life-span, or whether new factors come into play at certain developmental time-points (e.g. during puberty). Finally, twin studies allow us to investigate not only the additive effects of genetic and environmental influences on traits, but can unravel the complex interplay between these influences through processes of rGE and GxE. Extensive research has investigated gene-environment interplay for a number of emotional and behavioural traits[5], including sleep[6], discussed later in this review.

Aetiology of the Variability in Normal Sleep Characteristics

Results from studies using objective methods

The topography of the sleep electroencephalogram (EEG) varies between individuals.[7] Studies which examine patterns of brain activity during sleep typically use polysomnography (PSG) to assess indices of sleep architecture such as sleep stage organisation, the EEG power spectra of sleep, as well as variables related to the timing, latency, length, and efficiency of sleep. Zung and Wilson performed one of the first twin studies investigating sleep using EEG in a small group of MZ twins.[8] The authors observed almost complete concordance between MZ twins in the temporal order of sleep stages, suggesting a possible familial (either genetic or shared environmental) component to sleep stage organisation. However, data from DZ twins is necessary in order to speculate about the possibility of genetic effects. Other studies have more specifically shown that the amount of time spent in sleep stages 2, 4 and delta wave sleep (also known as slow-wave sleep [SWS]),and REM (rapid eye movement) sleep density, appear to have a strong genetic component (indicated by greater similarity between MZ as compared to DZ twins) in samples of 26 pairs of MZ and DZ twins.[9, 10] Likewise, in a sample of 4 MZ and 3 DZ twin pairs genetic influences appeared to be important for the REM period, interval and cycle length.[11] In studies using data from a limited number of MZ twins only, MZ twin concordance was observed for the temporal pattern of rapid eye movements[12], and the amount of REM sleep per night in newborn twins[13], suggesting possible familial effects. Furthermore, in a sample of 14 MZ and 14 DZ young adult twin pairs, the proportion of REM sleep per night appeared to be due to genetic factors.[14] In addition, a study of 35 MZ and 14 DZ twin pairs suggested genetic effects on the overall EEG spectral composition of non-REM sleep.[15] One study found this to be one of the most heritable human traits, with heritability estimates greater than 95%, in a sample of 10 MZ and 10 DZ twin pairs.[16] However, in a sample of 26 pairs of MZ

and DZ adult twins aged 20-36 years, genetic influences on the amount of stage 1 and REM sleep appeared to be confounded by non-genetic factors such as cohabitational status.[10] PSG has also been used as an objective method of measuring sleep characteristics such as sleep latency, total sleep time (also referred to as sleep length/duration) and sleep efficiency. One study of 14 MZ and 14 DZ young adult twin pairs, found a pattern of twin correlations consistent with a role of genetic influences on these objectively measured phenotypes.[14]

Twin studies have also been used to determine the aetiology of chronobiological markers, indexed by neuroendocrine patterns of hormones such as cortisol. In the first twin study to investigate the 24-hour profile of plasma cortisol, Linkowski and colleagues determined that genetic factors were important for the timing of the nocturnal nadir (a robust marker of circadian rhythmicity) as well as the proportion of overall temporal variability of cortisol pulsatility in a sample of 11 MZ and 10 DZ twin pairs.[17] In contrast, environmental factors appeared to contribute to the 24-hour mean cortisol secretion and the timing of the morning acrophase (peak). In line with this, in a sample of 50 MZ and 52 DZ twin pairs, Wust and colleagues found that the mean increase in plasma cortisol after awakening, and the overall area under the curve of the cortisol awakening response, was accounted for by genetic factors (accounting for 40% and 48% of the variability in these phenotypes, respectively).[18] Nonshared environmental influences were also a major contributor to these variables related to the cortisol awakening response.

Whilst the studies reviewed thus far provide insight into the aetiology of various aspects of the sleep electroencephalogram, as well as other objectively defined sleep phenotypes, crucial to the interpretation of these results is the consideration of the sample sizes and consequent power of these studies. The findings presented above are largely based on small numbers of twin pairs and thus require replication in much larger samples before

definitive conclusions can be drawn as to the relative contribution of genetic and environmental influences on these various phenotypes.

Results from studies using subjective methods

Twin studies investigating subjectively defined sleep characteristics are more abundant than those using objective methods. This is perhaps due to the ease of collecting subjective reports of sleep characteristics compared to assessing objective data which can be costly and time consuming - especially in the large samples required to investigate the contribution of genetic and environmental factors. Much of the research on sleep using subjective measures allows for the analysis of much larger samples, and hence greater power to parse the variance into genetic and environmental contributions. Hence, it may be more appropriate to place greater emphasis on studies using large samples utilising subjective measures. However, it should of course be noted that there are often discrepancies between data collected from objective vs. subjective sleep measures. For example, individuals with insomnia may significantly overestimate their sleep onset latency and underestimate the quantity and quality of their sleep compared to objective data[19], and so the extent to which quantitative genetic studies focusing on sleep assessed subjectively are relevant to objectively assessed sleep (and vice versa) is somewhat limited.

In a sample of 127 MZ and 187 DZ 18-month old twin pairs sleep duration was largely determined by shared environmental factors.[20] In line with this, in a sample of 100 MZ and 199 DZ school aged twin pairs, Gregory and colleagues reported that child-reported sleep duration was largely influenced by the shared and nonshared environment with no influence of genetics.[21] Contrastingly, in the same study Gregory and colleagues reported substantial genetic effects on childhood sleep duration when reported by the children's parents. In line with child-reported data, one of the earliest twin studies on sleep in childhood and adolescence (using data from 77 MZ and 76 DZ twin pairs) reported no genetic effects on

sleep duration in 6-8 year olds, and only modest effects in 16-18 year olds.[22] This latter finding chimes well with the notion that there are developmental changes in the extent to which genes and environments influence *sleep duration* (with genetic influences becoming more important with increasing age). Indeed, in a sample of 2238 MZ and 4545 DZ young adult twin pairs, Partinen and colleagues found that genetic influence on sleep duration appeared to be smaller in those aged 18-24 years compared to those aged 25+ years.[23] Furthermore, both MZ and DZ twin correlations were higher in twins living together compared to those living apart – suggesting a role for the shared environment on sleep duration. This finding has been reflected in our own research using data from the G1219 study - a UK population based study of 420 MZ and 773 DZ young adult twins, as well as 363 siblings. We found no evidence for genetic influence on sleep duration, whereas shared and most importantly nonshared environmental influences accounted for the observed variation.[24] A possible explanation for this lack of genetic effect on sleep duration in young adults could be that, unlike many aspects of sleep, sleep duration may be largely under voluntary control. Thus, the impact of genes may be attenuated, particularly in young adults when there are social pressures to stay out late and sleep in late. This set of findings particularly highlights that studies assessing sleep-wake characteristics in children can not necessarily be extrapolated to adult populations, and vice versa. This is perhaps unsurprising given that sleep changes dramatically across the life-span.[25] Accordingly, interpretations of the findings should be limited to the age group (and indeed the population) under study.

Twin studies using subjective measures have also focussed on indices of circadian rhythmicity such as diurnal preference (or related concepts such as chronotype and/or 'morningness-eveningness'). Diurnal preference typically refers to one's preference towards morningness or eveningness (see Kerkhof[26] for a review of the morningness-eveningness dimension in relation to circadian rhythmicity). The morningness-eveningness dimension

exhibits wide inter-individual variation,[26] and considerable attention has been paid to understanding its aetiology. In a sample of reared together (205 MZ twin pairs) and reared apart (55 MZ and 50 DZ twin pairs) adult twins and their spouses, Hur, Bouchard and Lykken were the first to report on the morningness-eveningness dimension in a twin sample.[27] The authors determined that 54%, 3% and 43% of variance in the phenotype was attributable to additive genetic influences, age and nonshared environmental influences, respectively. There was no evidence for effects of the current shared environment, indicated by the dissimilarity in diurnal preference between spouses. Similar overall estimates of genetic (in terms of "broad-sense heritability") and environmental influences have been found in large samples of adolescent, young adult and older adult twins.[28-30] Vink and colleagues[31] investigated the heritability of morningness-eveningness in separate samples of adolescent (627 MZ and 973 DZ twin pairs; mean age 17 years) and adult (61 MZ and 63 DZ twin pairs; mean age 48 years) twins. Similar heritability estimates (in terms of "broad-sense heritability") were derived from the two samples (44% and 47% for the younger and older samples, respectively), however, the genetic correlation between samples (rA =.50) suggested that somewhat different genes influence diurnal preference in adolescence and middle-age. Thus, twin studies investigating diurnal preference have determined that i) different genetic effects may be influencing this phenotype (i.e. functioning additively and non-additively), and ii) different genes may be important across the lifespan. Indeed, a study of a polymorphism in the clock gene *PER3,* found that the association between genotype and diurnal preference was age dependent.[32] Further twin studies are required to investigate the heritability of diurnal preference in children, and whether different genes contribute to the phenotype during childhood as compared to adulthood.

Research on diurnal preference has also centred on understanding its association with other sleep phenotypes, such as sleep quality. Our own research from the G1219 study found

a positive association between a tendency for eveningness and poor sleep quality.[29] Furthermore, the association was largely accounted for by genetic factors (94%), and there was substantial overlap in the genetic factors influencing these phenotypes. Findings such as these have the potential to inform molecular genetic studies since the substantial overlap in the genetic influences on these phenotypes suggests that similar candidate genes should be sought in relation to explaining individual differences in both diurnal preference and sleep quality.

The heritability of subjective sleep quality itself has been the focus of numerous twin studies. Partinen and colleagues were the first to report on the heritability of subjective sleep quality in a sample of 2238 MZ and 4545 DZ young adult twin pairs from the Finnish Twin Cohort, estimating heritability at 44%.[23] Almost identical findings have been reported by ourselves in young adult twins.[24, 29] Heath and colleagues assessed subjective sleep quality in 4 age cohorts ranging from age 17-88 years (from a total of 3810 MZ and DZ twin pairs), and reported heritability estimates ranging from 33% to 46% on subjective sleep quality.[33] Understanding variability in quantitative dimensions such as sleep quality has the potential to inform us about clinical sleep disorders. Assuming the sleep quality distribution represents a continuum of symptom severity, extreme poor sleepers may be directly comparable to individuals suffering from insomnia. This assumption needs to be empirically tested. Explicit investigation of the aetiology of sleep difficulties and sleep disorders has been the focus of many studies, and is the focus of the following section.

Aetiology of Sleep Difficulties and Primary Sleep Disorders

Sleep problems are common in children, adolescents and adults.[34, 35] The accumulating evidence that the magnitude of genetic and environmental factors on numerous phenotypes varies across the lifespan[e.g. see 4] highlights the importance of considering age-dependent effects in relation to sleep problems. In this section we present important findings

from quantitative genetic research in relation to sleep difficulties and primary sleep disorders in childhood and adulthood separately. Furthermore, we differentiate two main categories of sleep disturbances as outlined by the DSM-IV[2] and the ICSD-2[3], dyssomnias and parasomnias.

Children

Dyssomnias

In children, quantitative genetic research on sleep disturbances and disorders has tended to focus on 'sleep problems' (often tapping into sleep duration, latency, night waking, nightmares and disordered breathing) as a whole rather than differentiating specific dyssomnias.[e.g. 36] In a sample of 3-year old twins (446 MZ and 912 DZ twin pairs), Van den Oord and colleagues found that genetic influences accounted for 61% of variance in sleep problems assessed by the Child Behaviour Checklist (CBCL), with the remaining variance due to the nonshared environment.[37] Gregory and colleagues reported similar heritability estimates on composite measures of dyssomnias in 100 MZ and 199 DZ 8-year old twin pairs (using dyssomnia-type items from the Children's Sleep Habits Questionnaire (CSHQ)).[36] Using data collected from the same twins at age 10 years, Gregory and colleagues reported on the aetiology of the longitudinal associations between sleep problems (tapping into the parasomnias and dyssomnias outlined above) across time.[38] Longitudinal studies such as this can inform us about the stability of the genetic and environmental influences on traits. Forty-six percent of the genetic influences on sleep problems at age 8 years were shared with those influencing sleep problems at age 10 years. Whilst this demonstrates the stability of genes influencing sleep problems, it also suggests that new genetic factors come into play with increasing age. In combination, these studies demonstrate that certain sleep problems in childhood appear to be largely influenced by genes. However, a recent study focussing on sleep problems assessed by the CBCL in 270 MZ and 246 adolescent twins, found that the

majority of variance was explained by shared environmental factors (42%).[39] The authors suggest that the effect of the shared environment on subjective sleep phenotypes appears to exhibit an inverse u-shaped pattern – being largely non-existent in young children, school-age children and adults, yet having a substantial effect in adolescence. This suggestion is somewhat contrary to research focusing on other phenotypes which suggests that the shared environment becomes less important with development.[4]

Parasomnias

Twin studies of parasomnias are more common than those of dyssomnias in children, and include studies investigating composite measures of parasomnias as well as specific problems. For example, Gregory and colleagues reported that genetic influences accounted for 50% of variance in an overall measure of parasomnias (tapping into behaviours such as teeth grinding and sleep talking), in 100 MZ and 199 DZ twin pairs.[36] Comparing this heritability estimate to that obtained for dyssomnias (71%), it appears that different types of sleep problems may have different aetiological profiles. Indeed, when assessing the degree of overlap in the aetiological influences on parasomnias and dyssomnias, Gregory reported substantial shared genetic influences between parasomnias and dyssomnias, yet largely unique nonshared environmental factors. This suggests that the expression of one type of disorder over the other may be largely due to environmental differences. This highlights the importance of addressing specific problems rather than using an overall measure of 'sleep problems' wherever possible, in order to understand the mechanisms underlying parasomnias and dyssomnias.

Twin studies assessing specific parasomnias in children have examined problems such as sleepwalking, bruxism, sleeptalking, nightmares, night terrors and enuresis. For example, Bakwin investigated the pairwise concordance for sleepwalking in 199 MZ and 124 DZ twin pairs.[40] Pairwise concordance between MZ twins was six times greater than DZ twins,

suggesting a genetic basis for sleepwalking. In a sample of 1045 MZ and 1899 DZ twin pairs from the Finnish Twin Cohort, concordance between MZ twins was 1.5 times greater than DZ twins in childhood sleepwalking.[41] In the same study, Hublin and colleagues reported on bruxism (a movement disorder characterised by teeth grinding or clenching), sleeptalking and nightmares.[42-44] Genetic influences accounted for roughly half the liability to bruxism and sleeptalking, and 44% of liability to nightmares in childhood.

Other studies of parasomnias have focussed on the aetiology of night terrors and enuresis (bed-wetting) in childhood. In a study of 18-month old (161 MZ and 229 DZ pairs) and 30-month old (140 MZ and 207 DZ pairs) twins, Nguyen and colleagues found that roughly 40% of variance in night terrors was accounted for by genetic factors, with the remainder due to the nonshared environment.[45] Likewise, Abe and colleagues reported a twin study of night terrors in a sample of 61 3-year old and 8-year old MZ and DZ twins, finding greater MZ than DZ twin concordance, suggestive of genetic influence.[46] Enuresis is also common in children but is often only considered problematic if symptoms continue past the age of 5 years.[3] Several twin studies generally concur on the finding that MZ twin correlations are substantially higher than DZ twins - suggesting a hereditary component to enuresis in children.[e.g. 47, 48] Based on such findings, numerous studies have aimed to identify chromosomal loci implicated in enuretic symptoms.[e.g. 49, 50, 51]

Despite these findings, studies assessing subjective childhood sleep problems indicate that there is often a discrepancy between child-reported and parent-reported symptoms. Indeed, results from two independent studies focusing on sleep difficulties in the normal range, suggest that children and adolescents report more frequent sleep problems, and yield higher estimates of the nonshared environment than when these problems are reported on by their parents.[21, 52] This discrepancy between child- and parent-reported symptoms could reflect (i) parents' lack of awareness of their child's sleep patterns; or (ii) the inaccuracy of

children's reports of their sleep - the errors of which may be incorporated into the nonshared environmental component of variance. Thus, it is important to consider the method of assessment when examining sleep problems in children and youth as these discrepancies may lead to differences in the derived heritability estimates as a function of reporter. This highlights the importance of taking a multi-method approach to assessing sleep in children as different measures may be tapping into different aspects of sleep.

Adults

Dyssomnias

In adults, numerous twin studies have investigated specific dyssomnias such as primary insomnia, narcolepsy, obstructive sleep apnoea, sleep disordered breathing, and restless legs syndrome. To our knowledge, there are currently no twin studies specifically addressing heritability of these disorders in children (although we acknowledge that some of these types of symptoms in the normal range may be incorporated into a broad conceptualisation of 'sleep problems', for example[21]). The greater attention to dyssomnias in adulthood compared to childhood is possibly due to their greater prevalence in adults.[3]

Insomnia

Insomnia is characterised by difficulty initiating or maintaining sleep, early morning awakenings, or feeling that the sleep period is non-restorative or unrefreshing.[2] At least some of these symptoms affect around one third of the adult population.[35] Studies of insomnia in population-based and clinical samples have demonstrated increased risk of self-reported insomnia symptoms in individuals with a positive family history of insomnia, reflecting possible genetic and/or shared environmental effects.[53-57] Interestingly, several studies have found this trend to be stronger in individuals with an early age of onset in childhood or adolescence, and that the most frequently afflicted first-degree relatives are mothers.[53-55, 57] This latter finding is perhaps not surprising given the accumulating evidence

of a female predisposition to insomnia.[58] However, this is of particular interest as it sheds light on the possible mode of inheritance (suggesting a possible role for X-linked genes). Such a finding could also reflect the possibility that mothers may be particularly important environmental role models.

Several twin studies have assessed the heritability of insomnia as well as individual insomnia symptoms. McCarren and colleagues investigated specific insomnia symptoms ('trouble falling asleep', 'trouble maintaining sleep', 'waking several times per night', 'early morning awakening' and 'waking up feeling tired and worn out') in a sample of 1605 MZ and 1200 DZ male twin pairs.[59] For a composite measure of insomnia, heritability was estimated at 28% with little influence of the shared environment. When assessing the symptoms individually, however, estimates of heritability differed, ranging from 21% for 'awakening tired or worn out', to 42% for 'trouble staying asleep'. Likewise, using data from the Finnish Twin Cohort on 1554 MZ and 2991 DZ twin pairs, Hublin and colleagues reported heritability of around 46% for an overall measure of insomnia (encompassing difficulty initiating sleep, nocturnal awakening, early morning awakening and non-restorative sleep), whilst heritability of the individual symptoms ranged from 34% (for early morning awakening) to 45% (for nocturnal awakening).[60] Drake and colleagues assessed insomnia symptoms according to DSM-IV-TR criteria in a sample of 988 MZ and 1086 DZ twins, finding heritability estimates of 43% and 55% for males and females, respectively.[61] When breaking the insomnia construct into the individual insomnia symptoms, 'difficulty falling asleep', difficulty staying asleep' and 'nonrefreshing sleep', the authors also noted heterogeneity in the aetiological influences, in line with other studies. Contrastingly, however, whilst genetic factors accounted for around a third of the variability in the latter two symptoms (with the remaining variance due to the nonshared environment), there was no evidence of genetic influences on 'difficulty falling asleep' – highlighting the importance of

both the shared and nonshared environment. Explanations for this discrepancy between studies could be due to sample specific characteristics, such as age or methodological differences. Regardless of these differences, these studies highlight the heterogeneity of aetiological influences on individual insomnia symptoms, suggesting that some symptoms are genetically driven to a greater extent than others.

The majority of studies within this area assess sleep disturbances more generally, rather than focusing on a clinically diagnosable disorder. For example, Heath and colleagues reported that genetic influences accounted for around 33% of the variability in sleep disturbances, in a sample of 3810 MZ and DZ adult twin pairs.[33] In another study, Watson and colleagues estimated the heritability of insomnia (assessed by one question tapping into trouble falling asleep or maintaining sleep) and the association with daytime sleepiness (assessed by one question asking how often one falls asleep during the day against their will) in a community based sample of 1042 MZ and 828 DZ twins. Genetic influences accounted for 57% and 38% of variance in insomnia and daytime sleepiness, respectively, with the remaining source of variance due to the nonshared environment.[62] These findings are in line with the higher heritability estimate for the individual symptom 'trouble staying asleep', as compared to the lower estimate for 'awakening tired and worn out' in the study by McCarren and colleagues. Interestingly, the results of the multivariate analysis by Watson and colleagues largely pointed to the possibility that unique genes were influencing these phenotypes (with only 12% of genetic influences common to both insomnia and daytime sleepiness). Taken together, these findings suggest that perhaps a more accurate method of investigating the heritability of insomnia, and indeed for investigating possible candidate genes involved, is to focus on the individual symptoms underlying the disorder separately rather than relying on an overall 'insomnia' construct.

Narcolepsy

Narcolepsy is characterised by frequent unintentional short naps or lapses into sleep, and periods of REM sleep soon after sleep onset (after around 20 minutes from sleep onset, compared to the more typical 90 minutes observed in the normal population), often coupled with cataplexy.[3] Narcolepsy affects around 0.02%-0.18% of the general population, although prevalence rates rise to 1-2% in first degree relatives of those with narcolepsy - a 10-40 times increased familial risk.[63, 64] Early twin studies report a possible hereditary component to narcolepsy.[e.g. 65] Studies investigating specific genes have identified the human leukocyte antigen (HLA DR2) gene as a genetic marker for narcolepsy.[see 66 for a review] A specific HLA allele is shared by >85% of all individuals with narcolepsy, yet only around 12%-38% of the general population.[63] While this specific allele is clearly important, Pollmächer and colleagues highlight that around 50% of first-degree relatives of individuals with narcolepsy also share the critical gene, yet few of these individuals develop the disorder, suggesting the importance of other genetic and/or environmental influences in its pathogenesis.[67] Indeed, the majority (around two thirds) of MZ twins reported in the literature, are discordant for narcolepsy[see 63, for a review], underscoring the importance of exogenous factors. The vast majority of these twin studies, however, are case studies focussed on one twin pair. Large-scale twin studies of narcolepsy are scarce, reflecting the fact that narcolepsy is a rare condition. Kaprio and colleagues investigated narcolepsy-like symptoms in the Finnish twin cohort, obtaining data on 1322 MZ and 2463 DZ adult twin pairs.[68] Genetic factors accounted for 35% and 39% of variability in narcolepsy-like symptoms for males and females, respectively (assessed by the 11-item Ullanlinna Narcolepsy Scale). Interestingly, when symptom subscales were assessed separately, it appeared that genetic factors were greater for sleepiness symptoms than for cataplexy type symptoms, the latter being largely determined by environmental factors. The authors highlight that the genetic architecture of narcolepsy is complex and may differ depending on the symptom examined. Thus,

narcolepsy appears to have a 'multifactorial aetiology', and although there is evidence for genetics, the disorder is largely influenced by non-genetic factors.[69] Although research has yet to identify specific environmental factors that play a role in the pathogenesis of narcolepsy, epidemiological studies highlight associations with stressful life events, immune responses, body mass index, and suggest the possible importance of adverse environmental exposures in utero and in the first few decades of life.[70] Furthermore, it has been suggested that exposure to neurotoxins may be a likely candidate environmental risk factor for narcolepsy in vulnerable individuals.[for a review, see 70] Given the role of the hypothalamic-hypocretin system in narcolepsy[71], it is possible to speculate that possible environmental factors may be those that have a direct effect on this system.

Obstructive sleep apnoea

Other sleep disorders often result in excessive daytime sleepiness. These include obstructive sleep apnoea (OSA) and associated conditions such as sleep disordered breathing (SDB), snoring, and restless legs syndrome (RLS). OSA affects around 2-4% of the population and is characterised by obstructed airflow during sleep resulting in a brief absence of breathing, a reduction in blood oxygen desaturation and associated difficulties such as sudden awakenings, snoring, sleep fragmentation and excessive daytime sleepiness.[3] Carmelli and colleagues investigated the heritability of self-reported OSA related daytime sleepiness and snoring in a sample of 1560 adult male twin pairs, finding that genetic factors accounted for 40% and 23% of variability in symptoms, respectively.[72] Similarly, in a sample of 1937 adult female twin pairs, Desai and colleagues reported MZ/DZ twin concordance rates which indicated that genetic factors accounted for 48-52% of variance in liability to excessive daytime sleepiness and disruptive snoring.[73] Using objective measures, Carmelli and colleagues also investigated the heritability of a number of physiological measures underlying sleep disordered breathing including respiratory disturbance, oxygen

desaturation, and minimum SaO_2 (available haemoglobin saturated with oxygen) in a sample of 122 older adult male twin pairs.[74] MZ twin concordances were significantly higher than those for DZ twins, and heritability estimates ranged from 10%-37% for the three physiological indices. The authors noted the importance of obesity and nonshared environmental factors in the occurrence of SDB. Relevant environmental factors may include cumulative alcohol and tobacco use.

Restless legs syndrome

Restless legs syndrome (RLS) shows particularly high familial vulnerability. RLS is characterised by an unpleasant sensation and an irresistible urge to move the legs during periods of rest, resulting in disturbed sleep.[3] One study found 10 out of 12 MZ twin pairs concordant for the disorder.[75] Desai and colleagues reported heritability estimates of 54% and 60% for self-reported symptoms of restless legs and leg jerking, respectively.[73] More recent research suggests that the RLS phenotype manifests in two distinct forms: early onset (which the authors defined as occurring before 36 years of age) and delayed onset (occurring after 36 years of age).[76] The authors note that early onset RLS appears to be more severe and highly genetically influenced, whereas late onset appears to occur in individuals with no familial history. To our knowledge, however, no twin studies to date have specifically distinguished between the two forms of RLS although such work would be informative in determining the extent to which the different manifestations of the disorder are aetiologically distinct.

Parasomnias

The most extensive work on parasomnias in adulthood has come from the Finnish Twin Cohort study, and has focused on understanding the causes of variation in adulthood sleepwalking, bruxism, sleeptalking, nightmares and enuresis. The Finnish Twin Cohort covers an extensive number of sleep-related questions in a large sample of adult twins,

including retrospective reports on childhood sleep patterns (a discussion of which is included in the child section above) in the same participants making it possible to assess associations between symptoms longitudinally.

Sleepwalking, sleeptalking, bruxism & nightmares

Using data from 1045 MZ and 1899 DZ adult twin pairs from the Finnish Twin Cohort (aged 33-60 years), Hublin and colleagues reported that sleepwalking persists over time from childhood through adulthood, and rarely presents in adulthood alone.[41] The authors note that overall concordance rates between *adult* MZ twins were 5 times greater than for DZ twins. Genetic effects on sleepwalking accounted for 80% of variance in males compared to 36% in females. This pattern of genetic heterogeneity between the sexes is consistent with the findings in relation to *child* sleepwalking, finding stronger genetic effects in males. Yet several questions remain unanswered. The first is whether genetic effects on sleepwalking are stable across time, or whether distinct genetic effects come into play. The second is the issue of whether the genetic effects on sleepwalking in males are similar to those in females or whether they are qualitatively distinct (i.e. whether different genes are important for males and females). Such questions have been investigated in relation to bruxism, sleeptalking and nightmares using data from the Finnish Twin Cohort.

Indeed, Hublin and colleagues reported that genetic effects on bruxism, sleeptalking and nightmares were somewhat similar between adult males and females (accounting for 39%, 37% and 36% for bruxism, sleeptalking and nightmares in males; and 53%, 48% and 38% for these parasomnias in females).[42-44] The authors also noted high genetic correlations within these individual parasomnias between childhood and adulthood (ranging from rA = .75-.95) suggesting that substantially similar genetic effects accounted for the parasomnias across time. Nonshared environmental correlations within parasomnias across time were substantial although somewhat lower than genetic correlations (rE = .57-.75), suggesting the

importance of different environmental factors across time. This makes intuitive sense, since the types of factors that may influence childhood nightmares (such as being afraid of the dark) are likely to be different to the types of environmental factors affecting adults (such as life stresses).

Enuresis

To date, studies estimating the heritability of enuresis in adulthood have been underpowered, due in large part to the rarity of the disorder being reported and the small number of concordant twin pairs in the general population. It is likely that the small number of cases of adult enuresis is partly an issue of under-reporting of this potentially embarrassing symptom. Hublin and colleagues reported only one concordant and six discordant MZ twin pairs, and 20 discordant DZ twin pairs in the Finnish Twin Cohort.[47] Although it is likely that genetic influences play a role, sample sizes are too small to calculate the relative proportions of aetiological influences on enuresis in adulthood.

Co-occurrence of parasomnias

As well as looking at the relative contribution of genes and environments to the parasomnias individually, Hublin and colleagues also investigated their co-occurrence. The highest correlations between parasomnias were between sleeptalking with sleepwalking, nightmares, and bruxism in both children and adults (r = .43-.73).[77] There was genetic covariation between sleeptalking and sleepwalking, sleeptalking and bruxism, and between sleeptalking and nightmares (50%, 30% and 26%, respectively). This shows that, not only do these parasomnias co-occur, but that there are shared genetic influences between them. Of course there are also likely to be many unique genetic effects between them given that, when assessing the correlations between parasomnias from childhood to adulthood, the genetic covariation was less than unity. In addition, these studies do not negate the effects of the

environment. Given that the majority of affected twin pairs in the Finnish Twin Cohort were discordant for these parasomnias, environmental factors are likely to be important.

Co-occurrence and Comorbidity

In addition to the co-occurrence of similar types of sleep disorders, certain sleep problems are known to co-occur with emotional, behavioural and health-related problems. Finding that sleep difficulties are co-morbid with other disorders may be useful in identifying individuals at risk for such disorders. Several twin studies have assessed the comorbidity between sleep and other phenotypes in children and adults, as outlined below.

Children

Sleep, behavioural and emotional problems

In a study assessing concurrent associations between a range of sleep problems and behavioural and emotional disorders (including anxiety, depression, conduct, hyperactivity, and aggression) in 446 MZ and 912 DZ 3-year old twin pairs, Van den Oord and colleagues were the first to report that associations between sleep difficulties, behavioural and emotional problems were largely accounted for by shared environmental factors, rather than genetics.[78] However, in an older sample of 100 MZ and 199 DZ 8-year old twin pairs, Gregory and colleagues reported that the association between sleep difficulties and depression symptoms were largely accounted for by genetics.[79] In addition to assessing concurrent associations, Gregory and colleagues investigated the direction and aetiology of associations between sleep problems and depression symptoms longitudinally.[38] Depression symptoms at age 10 years were predicted by prior sleep problems at age 8 years, whilst the converse was not true. This finding sheds light on the mechanisms involved in the association between sleep and psychopathology in children, suggesting that prior sleep problems are a risk factor for the development of depressive symptoms. Thus, this study has the potential to inform the development of prevention and/or intervention strategies for such problems. Furthermore, this

longitudinal association, while of small effect, was largely explained by shared genetic effects. Similarly, in one study investigating the genetic covariation between insomnia symptoms, anxiety and depression in a sample of 689 MZ and 666 DZ 8-16 year old twin pairs, there were substantial genetic effects on insomnia shared with depression and anxiety.[52] The high genetic correlations observed between sleep and depression in these studies suggests that similar genes influence these phenotypes and thus investigation of genetic variants implicated in both sleep and depression may lead to fruitful insights into molecular genetic mechanisms underlying sleep and depression in middle childhood (for example, the serotonin system is a plausible candidate given its role in sleep and depressive phenotypes).

Adults

Sleep disturbances, anxiety and depression

Sleep problems are also often co-morbid with emotional, behavioural and health-related problems in adults, and these associations have been the focus of behavioural genetic research. Evidence of a relationship between sleep problems, anxiety and depression in adults is well established.[e.g. 80] However, there has been great debate within the literature as to the direction of effects between these difficulties.[81] It is likely that associations between them are bidirectional, and evidence has confirmed a role for both genetic and environmental contributions. Our own research from the G1219 study focusing on young adults reported substantial overlap in the genes influencing sleep disturbance and anxiety (rA = .58) and sleep disturbance and depression (rA = .68). Overall, these associations were largely accounted for by genetic factors (58% and 74%, respectively).[82] These findings are in line with the work of Gehrman and colleagues in relation to the overlap in the genetic and environmental influences on insomnia, anxiety and depression in children and adolescents.[52] Evidence also demonstrates genetic overlap between daytime sleepiness and depression

symptoms in a sample of elderly male twins.[83] However, the genetic correlation between daytime sleepiness and depression decreased after accounting for covariates (including activities of daily living, snoring and history of diabetes), suggesting that these factors were in part contributing to the genetic relationship between phenotypes.

As well as investigating associations between sleep and depressive symptoms, studies have tried to identify factors contributing to associations between subjective well-being, life dissatisfaction and sleep. One study reported substantial genetic overlap between subjective well-being and sleep (rA = -.85) in a sample of 8045 twins, suggesting that genes that enhance well-being facilitate sleep.[84] Using a longitudinal design and a sample of 2168 MZ and 4314 DZ twin pairs, a recent study aimed to determine the direction of effects between life dissatisfaction and poor sleep quality.[85] In line with findings in relation to the association between sleep and depression in children (see above[38]), prior sleep problems predicted new onset life dissatisfaction, whilst the converse was not true. However, genetic overlap between life dissatisfaction and sleep quality was small, in contrast to the finding in relation to subjective well-being. These studies highlight the importance of considering associations between sleep and various conceptualisations of life and well-being.

Sleep disturbances and health-related factors

Other studies have investigated associations between daytime sleepiness and sleep disturbances with a range of health-related factors, such as snoring, obesity, and caffeine consumption. In one study, Carmelli and colleagues assessed self-reported daytime sleepiness, snoring and BMI in 818 MZ and 742 DZ elderly male twin pairs – finding significant positive associations such that greater daytime sleepiness was associated with snoring and higher BMI.[72] Furthermore, between 72-100% of the phenotypic associations were accounted for by genetic factors with significant genetic correlations between them, yet almost complete environmental specificity. Watson and colleagues assessed associations

between insomnia symptoms, daytime sleepiness and obesity in a sample of 1042 MZ and 828 DZ adult twin pairs aged on average 32 years.[62] The authors noted some common genetic effects between insomnia and obesity (around 10% of the phenotypic correlations were due to common genetic effects). Recently, Watson and colleagues demonstrated that the association between short sleep duration and increased risk for obesity is in large part determined by nonshared environmental factors.[86] This association could be driven by environmental factors contributing to the voluntary control of sleep length. Several lines of evidence suggest that voluntary curtailment of sleep affects metabolic processes which predispose to weight gain.[see 86, for more information]

Studies which have assessed associations between psychostimulants and sleep in genetically informative designs are scarce. One study investigated associations between coffee-attributed sleep disturbance and other types of insomnia in 1799 MZ and 2009 DZ twin pairs.[87] The heritability of coffee-attributed sleep disturbance was in line with that in relation to sleep quality, accounting for around 40% of variance. There were also significant associations between coffee-attributed sleep disturbance and other types of insomnia, yet it appeared that different genetic factors accounted for them. Thus, the effects of caffeine on sleep may operate on a distinct biological pathway to that implicated in general sleep disturbances.

Sleep disturbances and externalising behaviours

Our own research has investigated associations between diurnal preference, sleep quality and externalising behaviours (including behaviours such as aggression and rule breaking) in a sample of young adults from the G1219 study.[88] In this study, evening-types compared to morning-types, and those experiencing poor sleep quality, were more likely to report greater externalising behaviours. These associations were largely accounted for by genetic factors (accounting for ~80% of the phenotypic correlations). There was some

indication of shared genes between the sleep phenotypes and externalising behaviours, yet little evidence for common environmental influences. Although this may suggest a direct path from genes to behaviour (i.e. the genes that influence diurnal preference also influence externalising behaviours), it is possible that these genetic correlations are meditated by intermediate variables. For example, alcohol consumption could be associated with aggressive behaviours, and alcohol may be more likely to be consumed during the evening hours. Thus, individuals with an eveningness preference may consume more alcohol, and consequently exhibit greater alcohol-induced externalising behaviours.

Specifying Genes and Environments

Although the classical twin design does not typically provide information as to which genes or which environmental influences may be contributing to a particular phenotype, twin studies can be used to guide molecular geneticists and epidemiologists as to where to focus their search for specific factors. Identifying specific genes/environments may help to highlight those at risk of sleep difficulties and aid in reducing or ameliorating these symptoms in genetically vulnerable individuals. One particular genetic polymorphism which has received a great deal of attention in the psychiatry field more generally, is located in the transporter region of the serotonin gene (*5HTTLPR*) and consists of either a 'short' or 'long' allele. Typically, the shorter variant has been associated with greater psychopathological symptoms.[e.g. 89, 90] knowledge of the overlap in the genetic influences between sleep disturbances and internalising problems, such as anxiety and depression, suggests that investigating genes associated with these disorders may lead us to identify genes also associated with sleep disturbances such as insomnia. Indeed, two studies to date have found that the 'short' allele conferred greater risk for sleep disturbances, including problems such as insomnia.[91, 92] However, a recent candidate gene study focusing on *5HTTLPR* by our group found that 'long-long' homozygotes experienced poorer sleep quality than carriers of at least

one 'short' allele.[93] It is possible that these discrepant findings are due to differences in sample composition. This highlights the necessity of further research on this gene in clinical and non-clinical populations before we can draw definitive conclusions as to the role of *5HTTLPR* in sleep. Likewise a group of 'clock' genes (including *CLOCK* and *PERIOD*) have repeatedly been investigated in relation to sleep disturbances and circadian phenotypes, although findings to date are inconsistent.[e.g. see 93, 94, 95-98]

Other studies have also investigated genes previously found to be associated with psychopathology in relation to sleep disturbances. For example, one study recently found an association between a polymorphism of the *GRIA3* gene and sleep duration, which has previously been associated with depression.[99] Furthermore, the risk allele of the *CACNA1C* gene, which has previously been associated with bipolar disorder, has been found to be associated with *reduced* risk for insomnia symptoms in individuals with major depression.[100] Such studies highlight the importance of considering phenotypic covariation to maximise the likelihood of identifying molecular genetic variants associated with sleep disturbances.

Identification of environmental factors affecting sleep can be achieved by looking at areas of research other than quantitative genetics. In children, studies have highlighted possible links between sleep problems, family disorganization and maternal depression, to name a few.[101] Family conflict during childhood has also been shown to predict later insomnia in young adulthood.[102] Epidemiological data have identified a host of environmental factors associated with sleep problems in adults including low socioeconomic status, unemployment, low income, negative life events, and negative lifestyle factors such as a lack of exercise, smoking and drinking alcohol.[e.g. 35, 103, 104, 105] However, longitudinal data are required before we can determine the direction of effects. Furthermore, determining whether these 'environmental' influences are indeed environmental in origin is complicated due to the possibility that genetic influences may contribute to these environmental factors

through processes of gene-environment correlation. Our own research using the monozygotic twin differences design has confirmed that associations between several traditionally conceptualised 'environmental' variables are likely to intertwine with genetic factors to influence sleep.[106] More studies of this kind will enable us to understand more about the processes contributing to the associations between the environment and sleep problems.

Gene-Environment Interplay

Although genetic and environmental influences may work independently, research is beginning to acknowledge that these factors work in concert to influence behaviour via processes such as gene-environment correlation and interaction. In the molecular genetic field this work has been highly influential with regards to a range of traits such as depression and anxiety [107, 108], yet research assessing the interplay between genetic and environmental influences focused on sleep is scarce. One molecular genetic investigation of gene-environment interaction in relation to sleep demonstrated that a genetic polymorphism in the transporter region of the serotonin gene (*5HTTLPR*) is associated with poor sleep quality in individuals experiencing chronic stress.[92] Twin studies can also be used to investigate processes of gene-environment correlation and interaction. Our own twin study is one of the only studies to date to investigate these processes in relation to sleep.[6] We focused on understanding the interplay between genes and negative life events on sleep quality, finding that experiencing a greater number of negative life events in the past year was associated with poorer sleep quality. Most interestingly, however, was evidence for a substantial genetic correlation between dependent negative life events (events that are partially dependent on one's behaviour, such as the break-up of a steady relationship) and sleep quality (rA = .62), suggesting that the same genes influence both the phenotype and exposure to the environmental risk – evidence of gene-environment correlation. One explanation for this finding is that poor sleep may have detrimental effects on functioning leading to impaired

decision making, consequently increasing the possibility of experiencing negative stressors. In the same study, we also investigated whether genetic liability to sleep quality was moderated by dependent negative life events. Whilst we found no evidence of an effect, the possibility of gene-environment interaction in relation to sleep remains. Thorough investigation of a wider scope of environmental measures is necessary in order to determine whether this possibility is likely. Given the dearth of twin studies investigating gene-environment interplay in this context, it is essential for future research to address this important issue. Such investigations will shed light on the mechanisms underlying the complex interplay between genetic and environmental influences on sleep. However, it is worthy of note that current discussion within the area of gene-environment interaction in relation to psychiatry more generally emphasises the fact that replication attempts of significant findings from GxE work are often underpowered, resulting in fruitless investigations.[109] Current debate highlights the necessity of strong hypotheses and large sample sizes, in appropriately phenotyped samples, in order to investigate GxE effectively.

Conclusions and Future Directions

As is evident, twin studies allow us to tackle challenging questions regarding the ways in which genetic and environmental influences affect behaviour. Exploiting these techniques has led to new discoveries in the field of sleep research which has advanced our understanding of the factors underlying the physiological processes of sleep, as well as factors implicated in chronic sleep disorders in children and adults. There are numerous on going large-scale twin studies worldwide and research from these existing twin studies will afford us the opportunity to answer many new and challenging questions. Of particular importance, future research from longitudinal twin designs will enable us to investigate the stability of the genetic and environmental influences on many aspects of sleep from young adulthood to old age; the direction of longitudinal associations between sleep and comorbid

phenotypes; and processes of gene-environment interplay with a broad scope of candidate environmental risk factors. In addition, studying MZ twins will enable us to understand more about epigenetic processes in sleep.[for general information focusing on epigenetics see 110]

The ability of twin studies to investigate differences in the genetic and environmental influences between males and females, over developmental periods, and in disorder sub-types should be exploited in order to further understand the heterogeneity in the aetiology of sleep difficulties. Furthermore, behavioural genetic research has the potential to inform nosology. With the emergence of the next edition of the DSM (scheduled for publication in 2013), behavioural genetic research should focus on investigating whether the aetiological profiles of the revised insomnia disorder symptoms (e.g. the inclusion of the criteria of a predominant complaint of dissatisfaction with sleep quantity or quality) support these diagnostic refinements. For example, identifying substantial genetic overlap between the symptoms of insomnia necessary for diagnosis would support the hypothesis that the symptoms are, to some extent, factors contributing to the same underlying condition.

Finally, it is of particular importance to use quantitative genetic methods to investigate endophenotypes. An endophenotype can be described as a "...measurable component unseen by the unaided eye along the pathway between disease and distal genotype..." [(111)] In order to be classified as a potential endophenotype, the trait in question must consistently be evidenced in the phenotype/disorder under study, and be found to be more heritable than the broader disorder.[(111)] Several studies have demonstrated increased beta activity in insomnia patients as compared to controls.[(see 112, for a review)] Beta activity has been shown to be more heritable than insomnia symptoms and so may be a candidate for an endophenotype.[(113, 114)] Furthermore, a recent report from The Netherlands found disturbed intracortical excitability during waking in insomnia patients using Transcranial Magnetic Stimulation (TMS).[(115)] The authors suggest that this pattern of brain activation may be an

endophenotype of insomnia. Investigating the heritability of the candidate endophenotype within the twin design will be one step towards determining whether the trait in question satisfies this criterion. Studying endophenotypes has the potential to facilitate successful identification of genetic polymorphisms associated with sleep disturbances, since investigating the endophenotype may be a more objective method of characterising the insomnia phenotype as compared to relying on subjective reports.

Although twin studies have increased our knowledge of the genetic and environmental underpinnings of sleep over the past 50 years, there is still much to be learnt. With the continuation of existing twin studies, improvements in the methodologies for characterising sleep, and the ever decreasing costs of molecular genetic techniques, the future of sleep research is likely to see fast progress in the understanding of the genetic and environmental factors contributing to this complex behaviour.

Practice Points
Twin studies have been useful in the field of sleep research and have highlighted that:
1. genetic and environmental factors appear to contribute to a number of sleep phenotypes assessed both objectively (using polysomnography) and subjectively (by self-report);
2. child-reported and parent-reported data on sleep do not always converge. In community samples, children consistently report higher rates of sleep disturbances than when such problems are reported on by parents. Thus, studies assessing the aetiology of childhood sleep problems should consider that parents may underestimate the extent of such problems. Differences in reporting may also lead to differences in heritability estimates derived from child- and parent-reported data;
3. in adults, insomnia is heritable and individual insomnia symptoms appear to have distinct aetiological profiles;
4. sleep problems often co-occur with various emotional, behavioural and health-related conditions in childhood and adulthood. These associations appear to be influenced by shared environmental effects in young children but shared genetic effects appear to become more important in mid-childhood and adulthood; nonshared environmental influences are often trait-specific;
5. associations between genotypes and phenotypes are likely to be complicated by processes of gene-environment correlation and interaction.

Research Agenda
1. Further twin studies should investigate the overlap between the genetic factors influencing sleep and a range of phenotypes – finding genetic overlap between phenotypes may facilitate the search for molecular genetic variants associated with sleep;
2. Longitudinal designs will enable us to determine the stability of the genetic and environmental influences on sleep problems across time; the direction of effects between sleep problems and associated phenotypes (such as depression and anxiety); and the degree of stability in the aetiological influences accounting for the phenotypic associations;
3. Further research on the interplay between genetic and environmental influences on sleep is essential, and should focus on a wider range of genetic polymorphisms and 'environmental' factors;
4. Examining the heritability of candidate endophenotypes of sleep disorders such as insomnia may facilitate the search for molecular genetic polymorphisms;
5. The MZ twin differences design should be utilised to tell us more about 'environmental' influences on sleep as well as epigenetic processes.

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Glossary of Terms	
Additive genetic influence	The "adding up" of genes to influence behaviour
Aetiological influences	Genetic and environmental influences underlying a phenotype/disease
Aetiology	The causes of a phenotype/disease
Broad-sense heritability	The sum of all genetic effects – additive and dominant
Dizygotic twins	Non-identical twins
Monozygotic twins	Identical twins
Narrow-sense heritability	Sum of all additive genetic influences
Dominance genetic influence	The "interaction" of genes at a particular locus which influence behaviour
Nonshared environmental influence	Environmental factors unique to each family member which account for their dissimilarity
Nosology	The classification of diseases
Quantitative genetics	The branch of behavioural genetics focused on understanding the aetiology of numerous phenotypes using statistical methods and a special study design – e.g. family studies or twin studies
Shared environmental influence	Family-wide environmental influences which act to make family members similar

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