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Behaviour genetics and sleep: A narrative review of the last decade of quantitative and molecular genetic research in humans

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ABSTRACT

During the last decade quantitative and molecular genetic research on sleep has increased considerably. New behavioural genetics techniques have marked a new era for sleep research. This paper provides a summary of the most important findings from the last ten years, on the genetic and environmental influences on sleep and sleep disorders and their associations with health-related variables (including anxiety and depression) in humans. In this review we present a brief summary of the main methods in behaviour genetic research (such as twin and genome-wide association studies). We then discuss key research findings on: genetic and environmental influences on normal sleep and sleep disorders, as well as on the association between sleep and health variables (highlighting a substantial role for genes in individual differences in sleep and their associations with other variables). We end by discussing future lines of enquiry and drawing conclusions, including those focused on problems and misconceptions associated with research of this type. In this last decade our knowledge about genetic and environmental influences on sleep and its disorders has expanded. Both, twin and genome-wide association studies show that sleep and sleep disorders are substantially influenced by genetic factors and for the very first time multiple specific genetic variants have been associated with sleep traits and disorders.

1. Introduction

Sleep is a non-negotiable biological state, essential for the maintenance of human life [1,2]. The idea that sleep is a luxury or a waste of time (e.g. 'I'll sleep when I'm dead' or 'money never sleeps') has been debunked. It is now widely established that obtaining sufficient sleep is one of the three pillars of a healthy lifestyle along with a healthy diet and exercise [3]. Sleep has received increased attention in the last few decades and there is a rapidly growing field of research on this topic.

There is wide inter-individual variability in sleep and sleep disorders and during the last few decades, researchers have tried to elucidate the causes of variance among individuals. In this regard, twin studies have enabled us to estimate the extent to which these differences are due to genetic or environmental factors. In a seminal meta-analysis, focusing on a vast array of human traits, it was revealed that every single trait was influenced to some extent by genetic factors [4], as are evidently sleep and sleep disorders. If the sleep research field has grown rapidly, the field of behaviour genetics has grown in the same way or faster. Reduction of genotyping costs and the development of new techniques such as genome-wide association studies (GWAS) and polygenic scores (PGS) have marked a new era for genetic research [5,6] and these methods, consequently, have also invigorated the field of sleep research.

Barclay and Gregory in 2013 [7] published a review addressing quantitative genetic research on sleep and discussed the available quantitative genetic research to that date. However, since this review was published the field has undergone substantial change. First, candidate gene studies— hypothesis-driven studies typically focusing on very few genetic variants are now considered to be somewhat outdated when focusing on complex traits and have been replaced by GWAS [5,8]. Second, studies using new techniques such as GWAS have been carried out using very large samples and have yielded remarkable new information about sleep and its disorders. For example, a GWAS by Jansen et al. [9], used a sample of

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Abbreviations

A	additive genetic influences
ADHD	attention deficit hyperactivity disorder
AHI	apnoea-hypopnea index
BMI	body mass index
C	common shared environmental influences
CBCL	child behaviour checklist
D	non-additive genetic influences
DZ	dizygotic
E	non-shared environmental influences
EEG	electroencephalography
GWAS	genome-wide association studies
H^2/h^2	heritability
MZ	monozygotic
ODI	oxygen desaturation index
OSA	obstructive sleep apnoea
PGS	polygenic scores
PRS	polygenic risk scores
PSQI	Pittsburgh sleep quality index
RDI	respiratory disturbance index
rA	additive genetic correlation
rD	dominant genetic correlation
rE	environmental correlation
rG	genetic correlation
REM	rapid eye movement
RLS	restless leg syndrome
SNP	single-nucleotide polymorphism
SWS	slow wave sleep
WASO	wake after sleep onset

Glossary of terms

Additive genetic influence	the sum of allelic effects across all loci
Dizygotic twins	non-identical twins
GWAS	research approach to identify genetic variants associated with a phenotype or disease
Heritability	proportion phenotypic variance that is due to genetic factors
Mendelian randomization	a method that uses genetic variation as a natural experiment to investigate causal relationships
Molecular genetics	branch of genetics that aims to study the architecture and function of genomic structures (genes) at a molecular level
Monozygotic twins	identical twins
Non-shared environmental influences	effects that make family members less alike
Polygenic (risk) scores	score that reflects the genetic propensity for the development of a phenotype
Quantitative genetics	branch of behaviour genetics focused on understanding the aetiology of phenotypes using statistical methods such as twin studies or family studies
Single nucleotide polymorphism (SNP)	a type of genetic variant in which the base letter at a single nucleotide position in the DNA sequence varies across the population
Shared-environmental influences	influences that make twin pairs raised in the same family similar to each other

more than 1.3 million participants, identifying more than 200 genetic loci implicated in insomnia. Third, quantitative research has continued expanding our knowledge about the genetic and environmental influences of sleep and a considerable amount of research using twin designs has been published in this last decade. Finally, different meta-analyses have revealed high heterogeneity among studies when it comes to genetic and environmental estimates on sleep quality, sleep duration and insomnia using twin studies [10–13]. This heterogeneity is likely to reflect differences between samples (e.g. location, cultural habits, time of assessment, sleep measures) and underscores the importance of examining the heritability of sleep traits in samples from different locations with different characteristics. Further research is needed to identify moderators of estimates from behavioural genetic studies.

The purpose of this review is to examine some of the most important findings from quantitative and molecular genetic research in humans published over the last decade. This provides an overview of the current state of genetic research on sleep and presents a discussion of how this knowledge and new techniques (e.g., PGS) might be applied in clinical practice. We acknowledge that studies using animals have provided valuable information about the aetiology of sleep [14] and for example, have helped to identify genetic variants in humans related to extreme early or late chronotypes or variants that lead to a short sleep phenotype [15]. However, the focus of this review is on quantitative and molecular genetic studies (classical twin studies and GWA studies) in humans. In this review we cover: a) research methods in genetic research; b) genetic and environmental influences on normal sleep and sleep disorders; c) genetic and environmental influences on the association between sleep (and sleep disorders) and health-related variables (especially depression and anxiety which are two of the most studied co-occurring conditions in relation to sleep); d) future directions and conclusions. For ease of presentation, twin studies are presented first and GWA studies next. There are no specific subsections for different stages of the life-span (e.g. paediatric, adult samples) since some of the studies include a wide age range or address the progression from one developmental stage to another.

2. Research methods

One of the key concepts in behaviour genetics is 'heritability' often represented as h^2 (narrow sense heritability – including additive genetic influences exclusively) or H^2 (broad sense heritability – which also includes non-additive genetic influences). Heritability can be defined as the proportion of phenotypic variance that is due to genetic factors [16]. Nonetheless, this is a complex concept which is often misunderstood [17]. For example, heritability is often misunderstood as the likelihood of a phenotype (e.g. insomnia) being passed to the next generation [18]. It is important to note that genes, but not phenotypes, are passed on to the next generation [17]. Heritability can be estimated using both twin data and DNA analyses.

2.1. Twin studies

The classical twin design makes use of the difference between monozygotic (MZ) twins (who share 100% of their DNA) and dizygotic (DZ) twins (who share on average 50% of their segregating

DNA). The comparison between both types of twins allows for the disentanglement of genetic and environmental influences on a variable [16,19]. A larger resemblance of MZ twins as compared to DZ twins suggests genetic influences on the trait under study. On one hand, genetic influences can be divided into those that are additive (A; the sum of allelic effects across all loci) and non-additive (D; the effects of genetic dominance). On the other hand, environmental contributions are shared (C; influences that make twin pairs raised in the same family similar to each other, e.g. socioeconomic status, childhood diet or peer influences shared by both adolescent twins) and non-shared (E, effects that make family members less alike, e.g. accidents, differential parental treatment, differential prenatal exposure – this component includes error) [20,21].

Twin studies can also be used to study genetic and environmental influences on the association between two (or more) phenotypes [22]. In multivariate models we can decompose the variance in order to understand the extent to which phenotypic correlation between two traits is accounted for by genetic and environmental factors. The proportion explained by genetic factors is called bivariate heritability (the same logic applies for the other components). In this model we can also estimate the aetiological correlations which inform us of the extent to which the latent factors (A, C, D and E) correlate across two traits, these correlations are usually represented as follows: rA, rG, rC, rD and rE [23].

There are other twin designs such as: sex-limitation models — which can be used to examine whether the distribution of the variance differs for males and females [24]; common pathway models— a multivariate model in which the covariation between a group of variables is controlled by a single phenotypic latent factor. A special case of the common pathway model is the independent pathway model where the relationship between variables is controlled by genetic and environmental common latent factors [25,26]. Causation has also been address using twin designs by examining the direction of causation models [22,27]. In this regard, twin studies are not only useful for quantifying the genetic and environmental influences on one or more phenotypes but also for studying the association between two traits controlling for genetic and early shared environmental factors. This is possible as MZ are perfectly matched regarding their genetic background and also shared environment. Therefore, the twin design can be considered a 'natural experiment' [28,29]. In addition to these common twin models other designs can be employed, but a deeper review of twin methods is beyond the scope of this article.

2.2. Genome-wide association studies

Twin studies are not able to identify specific genetic variants. Towards this endeavour the 'candidate gene' approach aimed to identify specific genes that might have a role in the phenotype under study. However, in this last decade this hypothesis-driven approach has been questioned — mainly because most of the finding from candidate genes could not be replicated [30,31] and the field has moved to the 'hypothesis free' approach of GWAS using large samples [5].

GWAS aim to identify associations between genotypes and phenotypes. This approach consists of a series of regressions, one per genetic variant (single-nucleotide polymorphism; SNP), to test the association of each SNP and the studied phenotype [5,32]. Genotyping is typically conducted using microarrays for common variants although other methods such as exome-wide studies that use sequencing techniques also include rare variants [32].

Methodological considerations when using GWAS include dealing with population stratification. Ancestry is usually taken into account by using principal components as covariates. Furthermore, as this method consists of running one regression per SNP, around 1 million (the international HapMap project and other studies have shown that this is approximately the number of independent genetic variants) tests are performed so this must be corrected using Bonferroni. Therefore, the significance threshold must be changed from 0.05 to 5×10^{-8}. A more restrictive threshold can be used as well (5×10^{-9}). GWAS can also provide information which can allow us to estimate the heritability of a trait (SNP-based heritability). Note that SNP-based heritability only includes the variance explained by additive effects from a subset of genetic variants since it tests the effect of each SNP but not the interactions between them. This means that heritability estimate is often lower than twin study derived heritability (which can include non-additive effects and additional types of genetic variation). Other explanations for the different estimates include that SNP methods fail to capture the influence of many common variants of very small effect and also of rare variants with large effects [32–35]. As the significance threshold is very restrictive large sample sizes are required in order to identify variants of small effect. Minimal phenotyping may be a cost-effective way to increase power [32]. However, this is by no means a trivial issue, especially in the field of sleep where conclusions can vary depending on whether measurement is subjective or objective.

2.3. Polygenic scores

GWAS are a powerful tool for research, they inform us about the association between millions of genetic variants and a phenotype. Moreover, they allow us to calculate PGS (also referred to as polygenic risk scores [PRS] when referring to an undesirable outcome). PGS are composed of weighted sums of the effect of multiple genetic variants previously identified in GWAS. They function as predictors of the relative risk that an individual has to developing characteristics, disorders, or diseases based on their genetic material. In other words, they provide an estimate of the genetic liability to a phenotype at individual level [36,37]. Heritability provides the upper limit for the genetic predictive value of PGS.

2.4. Mendelian randomization

The gold standard method of testing causality is randomized controlled trials but those are not always possible due to ethical or practical reasons. In this regard, Mendelian randomization studies use genetic variation as instrumental variables. Researchers examine whether a genetic variant (i.e. a SNP) that is associated with the exposure of interest (often a modifiable variable) is also associated with the outcome (e.g. disease) under investigation [38].

So far, the reader could have the impression that molecular genetic methods are replacing twin studies. However, this is not the case. Instead, these methods are complementary. For example, twin studies can be used to estimate the magnitude of genetic and environmental influences. GWAS studies allow us to identify which specific genetic variants are important in explaining the aetiology of a trait/disorder [5]. Furthermore, genotyping is often incorporated into twin and family studies [5,39–41]. Both methods allow us to estimate the heritability of a trait. However, the heritability obtained using the classical twin design is usually higher than SNP-based heritability. This has been referred to as the 'missing heritability' issue [34]. These discrepancies can be due to: SNP methods failing to capture a large number of common variants with small effects as well as rare variants with large effects. Alternatively, heritability estimated in twin and family studies may include specific effects, such as gene-environment correlation, not captured by the SNP-based method [35]. It is also possible that twin studies overestimate heritability due to methodological issues (e.g.

violations of equal environments assumption or assortative mating) [42].

Overall, we have briefly described the main method used in behaviour genetics and in later sections we will describe the main findings in sleep using genetically informative designs. These past ten years of research have brought us numerous studies that have undoubtedly expanded our knowledge and have important applications not only in basic research but also for clinical practice (e.g. PGS). However, much research remains to be done and many unknowns must be solved regarding the role of genetic and environmental factors on sleep and sleep disorders and their associations with health-related variables.

3. Genetic and environmental influences on normal sleep and sleep disorders

Most twin studies have found that sleep characteristics and sleep disorders are markedly influenced by genetic factors [10–13]. GWAS studies have also consistently found significant genetic influences – but to a lesser extent than twin studies [9,43]. In this section we will review studies addressing the genetic and environmental influences on normal sleep characteristics and sleep disorders.

3.1. Normal sleep

3.1.1. Twin studies

There have been several studies that have estimated the role of genetic factors on sleep using objective methods (e.g. polysomnography or actigraphy). Recent studies have investigated the aetiology of normal sleep. For example, a study using a sample of 49 adult twin pairs suggested that genetic factors influence the EEG spectral composition of NREM sleep [44]. A series of studies were conducted in 50–60 adolescent twins (the number varied depending on the study). Heritability estimates ranged from 1 to 57% depending on the frequency band and sleep stage in EEG topography [45]. Using data from EEG, heritability estimates ranging from 32% to 72% were found for sleep latency, sleep efficiency, rapid eye movement (REM) sleep latency, slow wave sleep (SWS) and wake after sleep onset (WASO). However, genetic factors showed no influence or a negligible impact on time in stage 1, stage 2, REM sleep and total sleep time [46]. The heritability of sleep phenotypes was also studied using an accelerometer device. Sleep timing and duration appeared to be significantly more heritable during free days as compared to school days whereas sleep efficiency and sleep latency were highly heritable (>60%) regardless the day of measurement. Furthermore, WASO was strongly influenced by shared environmental factors in a sample of adolescent twins [47]. In a further study using actigraphy in a sample of twins who were children, a high heritability estimate was found for objective sleep duration (h^2 ~ 70%) [48]. In another study using a sample of 12-years old twins it was found that sleep parameters (i.e. total sleep time, WASO, sleep onset latency, sleep efficiency and sleep fragmentation) assessed using a wrist actigraph were highly influenced by genetic factors, ranging from 52 to 83%, whereas sleep start time and sleep end time was substantially influenced by shared environmental factors (67% and 86% respectively) [49]. Another study in a sample of twins aged 16–40 years old (mean age = 21.7; N = 95 twin pairs) found that several actigraphy-assessed traits were substantially (h^2> 40%) influenced by genetic factors (e.g. total sleep time: 49%; sleep efficiency: 58–88% or mean duration of sleep episodes: 44%) and for most variables the best fit was provided by an AE model [50]. Another study conducted in an adult population from Spain (mean age = 51 years old; N = 53 twin pairs) using several objective measures from a wrist device found heritability estimates between 61% and 65%, for daytime sleep duration and night-time sleep duration [51]. Self-reported siesta was also found to be heritable (65%). The heritability of sleep duration has been estimated in different studies and has been estimated to be 31% and 63% heritable using a single question from American adult twins and European adolescents/young adult twins respectively [52,53]. Moreover, several studies have also estimated the heritability of sleep duration using questions from the Pittsburgh Sleep Quality Index (PSQI) [54]. In adults the role of genetic factors was estimated at 29% in twins from USA, 30% in Spanish twins; and 27% in men and 29% in women in a sample of Chinese twins [55–57]. There are also studies that did not find genetic influences on sleep duration in young adults from UK using the PSQI [58] or adults (mean age = 31 years old) from the Netherlands assessing sleep duration using a single question [59]. In both studies a significant proportion of the variance was explained by shared environmental factors (26% and 23% respectively). Using questions from the child behaviour checklist (CBCL), the heritability for 'Sleep less than most kids' and 'Sleep more than most kids' has been estimated at 85% and 89% respectively [60]. Finally, a recent study has also found a substantial influence of genetic factors on the homeostatic response to sleep deprivation measured by polysomnography [61].

The heritability of sleep quality has also been assessed and several recent publications on this topic have used the PSQI. The heritability of sleep quality was estimated at 42% in adolescents [62], and 43% in young adults [63] and ranged from 34% in Spanish adult twins [56] to 34–36% for American adult twin pairs [55,64].

Research on the heritability of sleep duration and sleep quality was summarized in reviews published in 2020 by our own group [10] and in 2021 by Kocevska et al. [13], These two meta-analyses, with some methodological differences, found a mean heritability of 31–44% for sleep quality and 38–46% for sleep duration. Sex and age were not detected as a significant moderator of sleep quality. However, in the meta-analysis by Kocevska et al. [13], which included a wider age range than the other meta-analysis, age was a significant moderator of the heritability of sleep duration. Shared environmental factors usually had a null or negligible effect on sleep quality or sleep duration from young adulthood onwards which is consistent with the effect of C in other phenotypes which usually decreases with age [65]. In line with this, one study that assessed twins at 15 months found a heritability of 26% and common-shared environmental factors accounted for 66% of the variance for night-time sleep duration [66]. Another study, assessed twins when they were 6, 18, 30 and 48 months old and found heritability estimates for sleep duration ranging from 20% to 58% and common shared environmental factors ranging from 4 to 48% [67]. See Lewis and Gregory [68] for a review of the heritability of sleep and sleep disorders in childhood and adolescence.

The heritability of chronotype has also been estimated. In a study using a sample from the South Korean Twin Registry, the heritability of morningness–eveningness preference was estimated at 45% for a sample including pre-adolescents, adolescents and young adults [69]. Another study of adolescent twins from UK estimated the heritability of diurnal preference at 52% [63]. In adults, the heritability of diurnal preference/morningness-eveningness was estimated at 40–52% in American Twins [70–72] and at 49% in Finnish twins [73]. A recent study also estimated the heritability of chronotype using different questionnaires (i.e. Morningness-Eveningness questionnaire and Munich Chronotype questionnaire) finding similar estimates for both

questionnaires 37% and 32% respectively. This study also found a heritability of 28% for a single question from the Morningness-Eveningness questionnaire enquiring directly about diurnal preference [74].

3.1.2. Genome-wide association studies

A recent review summarized GWA studies of sleep duration [75]. The first GWAS of sleep duration was published by Gottlieb et al. [76], in 2007 using a sample of around 700 participants. In this study only one SNP was associated with sleep duration - not at a genome-wide significance level but reaching a suggestive level of significance ($p = 1.4 \times 10^{-7}$). The first variant (rs11046205; $p = 3.99 \times 10^{-8}$) was identified in 2013 and explained around 5% of the variation in sleep duration [77]. There have also been several studies of limited sample sizes (ranging from 1941 to 4401 participants) that were not able to detect variants at a genome-wide significance level [78–80], although one of these studies found 7 suggestive SNPs [78]. Similarly, no SNPs were found to be significantly associated with sleep duration in a sample of 941 participants using an objective measure of sleep duration [81]. Studies using much larger samples have identified a greater number of genetic variants implicated in sleep duration. For example, Gottlieb and colleagues [82] in a sample of 4771 individuals found 2 independent loci associated with usual sleep duration, the strongest located on chromosome 2. Other studies using samples of more than 100,000 individuals have found 3 and 5 significant variants with a replication in the PAX8 gene [83,84]. More recent studies with yet bigger samples (446,118 and 384,317) have identified 78 and 53 loci associated with self-reported habitual sleep duration (replication in PAX8, VRK2 and SLC6A3) [9,43]. In the aforementioned study by Dashti et al. [43], the 78 loci were also associated with accelerometer-derived sleep duration (e.g. the lead PAX8 genetic variant was associated with a mean of 2.68 min longer objective sleep duration; and 2.44 min longer self-reported sleep duration). Two more studies using accelerometer-based sleep duration also found significant loci (8 and 11; again, with replication in the PAX8 gene). SNP-based heritability for sleep duration has ranged from 8.8 to 19% in different studies [43,85]. There was also one GWAS study of children, highlighting a significant locus at chromosome 11, although this was not replicated in independent studies. SNP-based heritability was estimated at 14% [86].

Although less numerous, there are GWAS studies focused on other sleep phenotypes. For example, sleep quality measured using the PSQI showed a significant SNP based heritability (14.4%) and two loci on chromosomes 2 and 7 were identified [87]. Jones et al. [85], also identified 26 genetic variants associated with sleep quality (21 were associated with the number of nocturnal sleep episodes and 5 were associated with sleep efficiency). Heritability was estimated at 22% and 13% for the number of nocturnal sleep episodes and sleep efficiency respectively. Spada et al. [81], identified two significant hits: one associated with sleep efficiency on weekdays; and one associated with sleep latency. Significant loci have also been identified for napping (123) [88] and chronotype (327) [89] with significant heritability estimates (11.9% and 13.7% respectively).

In summary, the scientific literature points to a substantial role for genetic factors when it comes to normal sleep. Most of the estimates are in the range of 30–50% (as different meta-analyses have also estimated for sleep duration and sleep quality). There are differences across the studies which could be due to methodological variations or sample differences such as age, sex or cultural habits. In the case of age, the effect of C was typically negligible in adult populations but had some effect during infancy/childhood. Estimates from GWAS studies are lower as compared to those from twin studies as expected.

3.2. Sleep disorders

3.2.1. Insomnia

Insomnia is the most prevalent sleep disorder and one of the most common complaints in medical practice. It is characterised by difficulties initiating or maintaining sleep, dissatisfaction with sleep duration or quality and daytime functioning impairments [90]. The heritability of insomnia has been estimated in several twin samples. Recent studies found heritability estimates ranging from 35 to 41% in adolescents [62,91,92], and 28–57% in adults [93–95]. Barclay and colleagues [96] estimated the heritability of insomnia progression during childhood/adolescence and found heritability estimates of 33%, 38%, 14% and 24% for 8 (wave 1), 10 (wave 2), 14 (wave 3) and 15 (wave 4) years olds respectively. In waves 1, 2 and 4 of the study the best fitting model was a DE (non-additive genetic influences and non-shared environmental influences) model, with no additive genetic influences. The prevalence of insomnia is usually greater in females as compared to males [97]. However, that does not necessarily imply that genetic and environmental influences are different for males and females. Nonetheless, some studies have reported different heritability estimates for males and females. For example Drake et al. [98], reported that insomnia was 43% and 55% heritable for males and females respectively and Lind et al. [99], reported that the heritability of a latent insomnia factor was higher in females (59%) than in males (38%). As for sleep quality and duration, two recent meta-analyses (with methodological differences) summarized the relevant literature about the heritability of insomnia and estimated the mean heritability at around 40% [11,12]. In one of these meta-analyses, sex was a significant moderator with a greater heritability for females [12]. These differences could be due to several factors such as menopausal status [100] or a greater likelihood of women suffering from certain chronic health conditions that could increase their risk of sleep difficulties (e.g. osteoporosis, fibromyalgia or back pain [101,102]. Further research is needed to clarify discrepancies among studies and meta-analyses.

Different GWAS studies have attempted to identify the specific genetic variants implicated in insomnia. Byrne et al. [78], using a sample of 2323 participants were not able to identify any SNP at a genome wide significance level. In 2017, using a sample of 113,006 participants three genome-wide significant loci and seven genes were identified [103]. The SNP-based heritability was of 9% for insomnia complaints. However, in 2019 using an unprecedented sample size of 1,331,010 individuals, Jansen et al. [9], found 202 risk loci associated with insomnia and a SNP-based heritability of 7%. The genetic correlation between males and females was very high ($r_g = 0.92$) suggesting no significant role for sex-specific genetic risk factors. Authors from this study have now almost doubled the sample size (2.3 million) for their new work which was recently published and have found 791 independent lead SPNs ((the most significant genes were PTPRD [also associated with RLS] and LSAMP) see Watanabe et al., 2022 supplementary files for more information) and confirmed 190 risk loci and identified 364 novel loci associated with insomnia complaints [104]. Results from this study suggest that insomnia is a genetically heterogeneous disorder which is polygenic and different sub-types are likely. Brain-specific gene expression was also shown in this study and links with habenular, LGN and GABAergic neurons could help to explain the aetiology of insomnia.

Overall, most of the studies found a substantial genetic influence on insomnia symptoms which was confirmed by two recent meta-analysis. However, heritability estimates from GWAS studies are still much lower as compared to those from twin studies. Research so far highlights the role of genetic factors in explaining individual

differences in insomnia and that this disorder is influenced by multiple genes with small effects.

3.2.2. Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is characterised by repetitive episodes of partial or complete upper airway obstruction during sleep [105]. In contrast to insomnia, only a handful of studies have addressed the genetic and environmental influences of OSA. Desai et al. [106], found a heritability estimate of 52% for disruptive snoring. Other studies, (although not using twin designs) reported heritability estimates ranging from 23 to 37% for the Apnoea-Hypopnea Index (AHI) [107,108]. In another study, the heritability of AHI, respiratory disturbance index (RDI) and oxygen desaturation index (ODI) ranged from 69 to 83% in a sample of 71 adult twin pairs from the Hungarian twin registry [109]. However, lower values were found in a sample of 122 male veteran twin pairs (mean age 78 years old) [110]. Airway anatomy has also been shown to be highly influenced by genetic factors [111]. In a recent study, using young adult twins, the heritability of apnoea symptoms was estimated at 40% [112]. Overall, most of the studies point to a moderate role of genetic factors.

GWAS using samples ranging from 1074 to 12,550 participant have identified a few loci implicated in sleep apnoea. Cade et al. [113], found two novel loci at genome-level significance for the apnoea–hypopnea index, and for respiratory event duration. Seven additional loci were identified with suggestive significance ($P < 5 \times 10^{-7}$). Another locus (rs12936587 on chromosome 17) was identified in men but not women by Chen et al., [114]. In 2020 Farias-Tempaku [115] identified two significant and 21 suggestive variants associated with OSA. In a preprint, using an unprecedent sample of almost two million individuals, 39 independent genomic loci were robustly associated with sleep apnoea risk. This study also estimated the heritability of sleep apnoea at 10% [116]. As for insomnia, sleep apnoea is substantially influenced by genetic factors. When it comes to sleep apnoea there is much less research as compared to insomnia. However, both disorders are influenced by the effect of multiple genes.

3.2.3. Restless legs syndrome

Restless legs syndrome (RLS) is a relatively prevalent sensorimotor disorder. Using a sample from the St Thomas' UK adult twin registry, the heritability of restless legs and legs jerking was estimated at 54% and 60% respectively [106]. A recent study found a higher concordance for MZ twins as compared to DZ twins but only for painful RLS (and not for painless RLS) [117]. Several GWAS studies have identified different genetic variants (23) associated with RLS and SNP-based heritability has been estimated at 19.6% [118,119].

3.2.4. Narcolepsy

Narcolepsy is an infrequent but very incapacitating chronic sleep disorder that is characterised by sudden attacks of sleep [105]. The low prevalence of narcolepsy makes it difficult to study in twin samples due to the massive sample sizes required in order to afford statistical power. Twin studies point to a multifactorial aetiology whereby non-genetic factors account for a substantial proportion of the variance [120]. The heritability of narcolepsy-like symptoms has been estimated at 35% and 39% for males and females respectively [121].

Other sleep disorders have also been shown to be substantially influenced by genetic factors. Regarding sleepwalking in childhood, 66% and 57% of the variance has been accounted for by genetic factors in males and females respectively; and in adulthood genes explained 80% and 36% of the variance in men and women respectively, using a sample from the Finland twin registry [122]. Using the same sample, for sleep talking, 54% and 51% of the variance was attributable to genetic factors in childhood; and 37% for males and 48% for females in adulthood [123]. In a recent study, the heritability of 'talks or walks' during sleep measured by the CBCL was estimated at 72% [60]. Bruxism is also influenced by genetic factors and in childhood heritability estimates were 49% and 64% for males and females respectively (39% and 53% in adulthood) [124]. Nightmares have also been shown to be genetically influenced, with heritability values ranging from 44 to 73% in children [60,125] and 36–38% in adults with slight differences between men and women [125].

4. Genetic and environmental influences on the association between sleep and its disorders and health-related variables and well-being

4.1. Depression

There is a close relationship between sleep and depression [126]. Several studies have addressed genetic and environmental influences on the association between sleep and depression. Substantial genetic overlap has been found between depression and sleep quality in adolescents (rA = 0.73) [62], young adults, (rA = 0.68) [127] and also in adults (rG = 0.61) [128]. There was also moderate overlap in nonshared environmental factors (rE = 0.27, rE = 0.36 and rE = 0.29 for adolescents, young adults and adults respectively). Depressive symptoms are genetically related to both short sleep duration (rG = 0.28) and long sleep duration (rG = 0.30) [43]. A similar picture can be found when it comes to the overlap between depression and insomnia, with genetic correlations ranging from 0.73 to 0.80 and non-shared environmental correlations ranging from 0.28 to 0.40 in adolescents and young adults [62,91]. Another study found a complete genetic overlap between insomnia and internalizing behaviours [129] and in adults a substantial genetic overlap between insomnia and major depressive disorder was found in males (74%) and females (56%) [130]. Molecular genetic studies have also confirmed the strong overlap between insomnia and depressive symptoms with genetic correlations ranging from 0.42 to 0.64 [9,131]. Other sleep phenotypes have also been shown to have a substantial genetic overlap with depression. These include sleep apnea (rG = 0.60) [112], daytime sleepiness (rA = 0.21) [132] and Morningness-Eveningness (rG = −0.21) [70]. Furthermore, in a Mendelian randomization study, earlier diurnal preference was a significant protective factor against major depressive disorder [133]. A recent publication showed that similar factors could influence both phenotypes — genetic pleiotropy (i.e. same genes influencing different traits) and environmental factors impacting both phenotypes such as stress [134]. However, a causal relationship cannot be ruled out and research is needed to further elucidate the nature of the association.

4.2. Anxiety

Anxiety is also highly correlated with sleep quality [126]. In adolescents, substantial genetic correlations between anxiety and sleep quality have been reported in adolescents (rA = 0.61 for anxiety symptoms and 0.52 for anxiety sensitivity symptoms) [62] and young adults (rA = 0.58) [127]. As for insomnia, genetic correlations of 0.59 and 0.51 were found between insomnia and anxiety symptoms and anxiety sensitivity symptoms in adolescents respectively [62]. In these two studies, non-shared environmental correlations were also significant although of a smaller magnitude. In adults there was a complete genetic overlap between generalized anxiety disorder and insomnia [130]. High genetic overlap

between anxiety and insomnia (rG = 0.56) was also estimated in a GWAS study [9]. Research has revealed a modest nonshared environmental correlation (rE = 0.20) and a non-significant genetic correlation for the overlap between sleep apnoea and anxiety [112]. As for depression shared factors (both genetic and environmental) could be underlying this association - but a causal relationship is also possible [134].

4.3. Behavioural problems

Externalizing behaviours are also linked with sleep disturbances. In children, the relationship between aggression and rule-breaking and several measures of sleep assessed by examining individual CBCL items (i.e. 'sleep less than most kids', 'nightmares", 'overtired'; 'sleep more than most kids', 'talks or walks' and 'trouble sleeping') was assessed [60]. A moderate to strong genetic overlap was found between aggression and all of the sleep items (rG ranging from 0.27 to 0.64); whereas just two genetic correlations were significant for the association between rule-breaking and sleep items (i.e. 'sleep more than most kids' and 'trouble sleeping'). In young adults, Barclay et al. [135], found that 18% of the genetic influences on externalizing behaviours were shared with diurnal preference and sleep quality and an additional 14% were shared with sleep quality alone. Using the same sample, both significant genetic and environmental correlations between symptoms of apnoea and externalizing behaviours (rG = 0.42 and rE = 0.20) were reported [112]. A substantial genetic and environmental overlap was also found between sleep quality and attention deficit hyperactivity disorder (ADHD) (rA = 0.49 and rE = 0.19) [136]. The literature in adults is more scarce than in children since externalizing behaviours are most commonly studied in paediatric samples. However, research examining adults [130] found that genetic influences on alcohol abuse and dependence (18%) and antisocial personality disorder (23%) overlap with insomnia in adults. In young adults, significant genetic correlations were found between insomnia and regular cannabis use (rA = 0.20) [137]. In another study in adults, genetic influences on diurnal preference were also associated with alcohol consumption [71].

4.4. Somatic health related variables

Genetic and environmental influences on the associations between sleep and other variables and disorders have also been addressed in the past decade. For example, a higher body mass index (BMI) has been associated with poor sleep quality even when familial factors are controlled results from this study also suggest the directionality of this association - where poor sleep quality influences BMI rather than the reverse [138]. Pain is another variable that is strongly associated with sleep quality, even when controlling familial factors [139]. Significant genetic (rG = 0.33) and non-shared environmental (rE = 0.19) correlations have been found between sleep quality and low back pain in a sample of adult twin pairs from Spain, suggesting that genetic factors are shared between both phenotypes to some extent [140]. Another study in adults also found significant correlations between sleep quality and pain (rG = 0.69 and rE = 0.21) [128]. In a recent study it was shown that a small (albeit significant) proportion of the variance is shared by back pain (including neck and low back pain) and poor sleep quality [141]. Moderate genetic correlations were also found between sleep quality assessed in the year 1975 and life dissatisfaction assessed 6 years later in 1981 (rG = 0.21 and rG = 0.27 for males and females respectively [142]. Bullying victimisation and sleep disturbances are associated and genetic and environmental factors also underlie this association [143]. An association between sleep quality and loneliness has also been reported in young adults even when controlling for familial factors [144]. Personality has also been shown to have moderate associations with sleep. For example, there were some significant genetic correlations between sleep duration and neuroticism (rG = −0.26) or openness (rG = −0.22) in Croatian twins [52]. Posttraumatic stress disorder and insomnia often co-occur and one study found that a substantial proportion (36–44%) of the phenotypic association between these two phenotypes was accounted for by genetic factors [145]. Genetic and environmental influences also overlap across psychotic-like experiences and sleep disturbances [92]. Molecular genetic studies have also supported some of these links. For example, in a GWAS for insomnia, significant genetic correlations were found between insomnia and subjective well-being (rG = −0.51), longevity (rG = −0.32), BMI (rG = 0.16), coronary artery disease (rG = 0.18) and type 2 diabetes (rG = 0.20) among other variables. In this study significant genetic correlations were also found between sleep duration and subjective well-being (rG = 0.18) and BMI (rG = −0.09) [9]. In summary, significant genetic correlations were found among sleep and most of the somatic health related variables, suggesting that genetic factors implicated in sleep are also playing a role in those variables. The mechanisms underlying these associations are complex and not fully understood yet. Further research is needed to elucidate the aetiology of these complex relationships and interactions.

4.5. Interactions

Although twin studies typically examine genetic and environmental influences separately, they are unlikely to exert their effect independently but instead work in concert. For example, gene-environment correlation refers to the idea that we are more or less likely to be exposed to certain environmental experiences based in part on our genetic propensities. Gene-environment interaction refers to the concept that some people are more sensitive than others to certain environmental experiences based on their genetic propensities. It is also possible to find Gene × age interactions where the role of genetic and environmental influences varies across the life span. In line with this, it was found that genetic influences on diurnal preference are attenuated in middle adulthood (34%) as compared to younger and older adulthood (44%) [72]. The relationship between sleep quality and independent/dependent negative life events was also studied. It was found that poor sleep quality is more strongly associated with dependent negative life events as compared to independent negative life events. Genetic liability was not moderated by dependent negative life events [146]. Another study that examined gene-environment interplay focused on the close relationship between short sleep duration and increased BMI. The team considered sleep as an 'environmental' moderator, it was found that the heritability of body mass index was much higher for individuals who sleep <7 h (h^2 = 70%) as compared to those who sleep ≥9 h (h^2 = 32%) [147]. Another study from this group also found higher genetic contributions to depressive symptoms for those with short or long sleep duration as compared to normal sleep duration [148]. Future research may benefit from incorporating PGS into models of gene-environment interplay [149]. MZ differences studies may also help to increase understanding of the associations between methylation and sleep phenotypes. A study of this type identified methylation differences in MZ twins discordant for diurnal preference [150]. There is also clear evidence of epigenetic alterations following sleep deprivation [151] and future research may benefit from examining these associations further.

4.6. Mechanisms by which genetic and environmental influences impact sleep

Behavioural genetic studies of sleep have also tried to shed light upon the complex pathways by which genetic and environmental factors can impact sleep variables. In research in which one of us (AMG) was involved, there was an attempt to understand more about genetic and environmental influences on some of the cognitive processes associated with insomnia symptoms (e.g. see Harvey, 2002 for a Cognitive Model of Insomnia [152]). Overall, we found strong genetic correlations between pre-sleep arousal and insomnia, suggesting that those with cognitive and/or pre-sleep arousal could also have a vulnerability to insomnia [153]. On the other hand, significant nonshared environmental correlations were found for the links between insomnia and dysfunctional beliefs [154], as well as insomnia and mindfulness [155].

5. Conclusions and future directions

In this review we have summarised the main findings from research focused on behaviour genetics and sleep in humans published during the last 10 years. We note that given the extent of the literature, we have had to be selective in this review – and some valuable papers on this topic have not been included.

Twin studies have expanded our knowledge about genetic and environmental influences on sleep. Although, heritability is a population statistic, heritability estimates for insomnia, sleep duration and sleep quality are largely similar across populations [10–13]. However, results to date must be interpreted with caution since most of the studies have come from Northern Europe and North America and results are not necessarily applicable to other populations who may differ in terms of their sleep (due to factors such as climate or cultural habits). Similarly, GWAS have been performed mainly using populations with European ancestry [32]. One of the most replicated findings from behaviour genetics is that most environmental effects are not shared [65]. This is also applicable to sleep and all the available research indicates that common-shared environmental factors explain a small proportion of the variance and that these influences decrease across the life-span [10–13]. In this last decade numerous genetic variants have been associated with most sleep characteristics and disorders. Nevertheless, these variants have very small effects and SNP based estimates are lower as compared to previous expectancies (i.e heritabily estimates from twin studies). As with other complex traits, sleep is influenced by multiple genes of small effects. New techniques have enabled us to develop polygenic risk scores which inform us about the relative genetic risk of suffering from a sleep disorder (e.g. insomnia). Therefore, for the very first time, there is a tool that allows us to make predictions based on the genetic predisposition about the relative risk of suffering from sleep disorders—although the predictive value is still very limited. This has relevant implications for prevention programs and tailored treatments and future work may also look to investigate the extent to which genetic and environmental influences are important in treatment outcome (see Denis et al., 2017 [156]).

Despite the great advances in behaviour genetics—and specifically sleep, concepts from this discipline are still regularly misunderstood, even by those involved in genetic research [18]. This is important since perceptions about the aetiology of a trait may impact adherence and effectiveness of a treatment [18]. As researchers, we should be cautious about how we communicate and interpret the results from these studies. Additionally, twin and molecular studies have shown the relevant role of genetic factors in explaining sleep and sleep disorders and their relationship with several variables including psychiatric disorders. Therefore, genetic information should be taken into account in observational and experimental research not only as a possible confounder but also as a potential moderator of environmental effects on a trait.

This last decade of genetic sleep research has expanded our knowledge about the aetiology of sleep and sleep disorders. However, there is still much to learn by studying sleep using behaviour genetics techniques. For example, GxE studies could help to expand our knowledge of genetic influences upon certain disorders (e.g. insomnia) interacting with environmental factors (e.g. stressful life events). We need to learn more about the inter-individual variability in response following exposure to a stressor [157]. Whereas previous studies of gene-environmental interplay for sleep phenotypes have largely focused on candidate genes, future studies may benefit from considering the interaction between PRS and environmental risks. Many SNPs have been identified in the case of insomnia but SNP based heritability is still very low as compared to twin studies. Future research should aim to elucidate reasons for this gap. Future studies should also aim to identify further genetic variants implicated in each sleep phenotype – including the role of genetic variants other than SNPs and the role of rare variants. The combination of twin and molecular designs could also help us to disentangle the role of direct parental influences or shared genetics when it comes to sleep disorders [158]. Finally, experimental research should also take advantage of behavioural genetic methods and include genetic information (e.g. PGS) in research designs in order to control for the effect of genetics on sleep traits. Using this information will ultimately help us to develop preventative programs and will increase our changes of ensuring that people are given optimal treatments for their sleep difficulties.

Practice points.

1. New techniques from behaviour genetics have marked a new era for sleep research
2. Twin and genome-wide association studies show that sleep and sleep disorders are substantially influenced by genetic factors
3. These findings have been supported by different meta-analyses
4. Many genetic variants associated with sleep and sleep disorders have been identified in this last decade
5. There is a substantial genetic overlap between sleep/sleep disorders and psychopathology

Research agenda.

1. Further twin studies should be carried out in different populations
2. Further very large-scale GWAS studies are also needed in order to identify further relevant genetic variants implicated in sleep and sleep disorders
3. Basic research should take into account genetic influences as a highly relevant confounder
4. Polygenic risk scores could eventually be used in clinical practice as a preventive tool—although their predictive value is still limited
5. Knowledge from behaviour genetics could help us to pave the way for more accurate treatments

Declaration of competing interest

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