Sleep problems in childhood psychiatric disorders: A review of the latest science

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Abstract

Hippocrates flagged the value of sleep for good health. Nonetheless, historically, researchers with an interest in developmental psychopathology have largely ignored a possible role for atypical sleep. Recently, however, there has been a surge of interest in this area, perhaps reflecting increased evidence that disturbed or insufficient sleep can result in poor functioning in numerous domains. This review outlines what is known about sleep in the psychiatric diagnoses most relevant to children and for which associations with sleep are beginning to be understood. There is a description of both concurrent and longitudinal links as well as possible mechanisms underlying associations. Preliminary treatment research is also considered which suggests that treating sleep difficulties may result in improvements in behavioural areas beyond sleep quality. To maximize progress in this field, there now needs to be: 1) greater attention to the assessment of sleep in children; 2) sleep research on a wider range of psychiatric disorders; 3) a greater focus on and examination of mechanisms underlying associations; 4) a clearer consideration of developmental questions; and 5) large-scale well-designed treatment studies. While sleep problems may sometimes be missed by parents and health-care providers and hence constitute a hidden risk for other psychopathologies – knowing about these difficulties creates unique opportunities. The current excitement in this field from experts in diverse areas including developmental psychology, clinical psychology, genetics and neuropsychology should make these opportunities a reality.

Introduction

Parents around the world have witnessed the chaotic sleep patterns of new born babies. As an infant develops, typically sleep patterns consolidate (e.g. Galland et al., 2012) allowing the child to benefit from the multifaceted advantages of sleep on development and functioning (e.g. Gregory et al., 2009a; Touchette et al., 2007; Sadeh et al., 2003). Troubled sleep in children is associated with poorer well-being in family members (Lam et al., 2003; Meltzer & Mindell, 2007) so good sleep in childhood may also bolster family functioning. While many typically functioning children retain or develop certain sleep difficulties as they grow older (Finn Davis et al., 2004; Gregory & O'Connor, 2002), the proportion of those considered to have a sleep problem is particularly high in children with another psychiatric disorder (e.g. Wiggs, 2001; for a review, see Gregory & Sadeh, 2012). This has possible implications for the subsequent development of these children as well as the pressures faced by their families. There have been numerous reviews on sleep and childhood disorders by ourselves (e.g. Gregory & Sadeh, 2012; Barclay & Gregory, 2014; Sadeh et al., 2014) as well as others (e.g. Tesler et al., 2013). Subsequently, this narrative review will focus on the latest science (largely from 2010). We begin with a brief overview of normal sleep physiology and measurement before introducing normal sleep development and pathological sleep in children. The main part of the review focuses on concurrent and longitudinal associations between sleep and a range of disorders listed in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, American Psychiatric Association, 2013) – addressing mechanisms and treatment. The two latter topics are then summarised separately before conclusions are drawn.

What is sleep and how do we assess it?

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Sleep patterns and stages

Sleep is a state which can be distinguished from wakefulness in terms of certain physiological changes including those related to cardiovascular and brain wave activity, posture, mobility, response to stimulation, level of alertness, eyelid movement, respiration and body temperature (see Adair & Bauchner, 1993). Sleep involves alternating patterns of Rapid Eye Movement (REM, sometimes referred to as 'active sleep' in infants) and Non-Rapid Eye Movement (NREM, sometimes referred to 'quiet sleep' in infants). NREM sleep is currently split into three stages. Unsurprisingly, REM sleep is characterised by distinctive eye movements which are not found during NREM sleep. Sleep stages can be distinguished based on brain activity, eye movement, tone of voluntary muscles and heart/ respiratory rate (e.g. Adair & Bauchner, 1993; Carskadon & Dement, 2011).

Sleep-wake regulation

The sleep-wake cycle is hypothesised to be regulated by two core processes (see the 'Two-Process Model', Borbely, 1982). One process is considered 'sleep-dependent' (Process 's') and depends to some extent on the length of time since sleep/ duration of sleep – with a longer period of wakefulness associated with a greater need for sleep. Process 's' is therefore greatest just before sleep and smallest immediately upon waking. The second component is 'sleep-independent' (Process 'c') and focuses on circadian processes which regulate 24-hour rhythmicity. Process 'c' explains why the need for sleep is greater at certain times of the day regardless of when an individual last slept and for how long.

Assessing sleep

Sleep can be measured using a variety of different techniques (Sadeh, 2015, see also **Table 1**). Associations reported with psychiatric difficulties depend in part on the

methodology used to assess sleep (e.g. see section on sleep and depression). While polysomnography (PSG) is often considered the 'gold-standard' method of assessing sleep, it should be noted that subjective reports are not always 'second-best' but provide unique information about the nature of sleep and the mechanisms underlying relationships to daytime functioning. Indeed, when assessing insomnia, the third edition of the International Classification of Sleep Disorders (ICSD-III, American Academy of Sleep Medicine, 2014) emphasises that the routine use of PSG to evaluate this condition is unnecessary – although notes that it can be useful in ruling out other sleep disorders. The degree of correspondence between subjective and objective measures needs to be considered when interpreting results of studies (e.g. Gregory et al., 2011b). Furthermore, discrepancies *within* subjective reports (e.g. between parent- and self-report, see Gregory et al., 2006c) and objective reports (e.g. between actigraphy and PSG, Meltzer et al., 2012) also need to be considered.

Sleep in typically functioning children

During child development sleep-wake patterns undergo dramatic changes. The most prominent changes occur during early childhood and involve the process of sleep consolidation. During the first 6 months, sleep-wake patterns evolve from 5-6 sleep episodes distributed throughout the day and night to more consolidated sleep concentrated during the night-time hours with a diminishing number of daytime sleep episodes (Henderson et al., 2010; Henderson et al., 2011). During this process most infants learn to sleep through the night with minimal disruption. However, difficulties in this process are associated with common complaints of early childhood, namely, excessive and extended night-wakings (Hysing et al., 2014; Wang et al., 2013).

In parallel to sleep consolidation, a major maturational process during the first years of life is related to sleep architecture or the time spent in different stages of sleep. Newborns spend around 50% of their sleep time in active/REM sleep which amounts to around 8 hours

per day (Roffwarg et al., 1966). During the first 2 years of life the proportion of REM sleep diminishes to 20-25% of sleep time, a proportion that is roughly maintained throughout later development (Louis et al., 1997; Roffwarg et al., 1966).

Another prominent developmental phenomenon in sleep patterns is the delay in sleep onset time and the reduction in sleep time starting in preschool years and lasting well into adolescence (Maslowsky & Ozer, 2014; Pesonen et al., 2014; Price et al., 2014; Williams et al., 2013). The delay in sleep onset appears to be associated with puberty and is accelerated during adolescence (Carskadon et al., 1993). This process of a delayed sleep onset and the resultant sleep reduction often leads to insufficient sleep which is very common during adolescence (Carskadon et al., 2004). Importantly, studies have demonstrated a global trend of decreased sleep duration over decades which may suggest that children today are more sleep deprived than children in earlier decades (Matricciani et al., 2012).

Finally, other underlying maturational processes have been documented in regard to the localization, distribution and coherence of brain activity during sleep from early childhood to late adolescence. Indeed, studies have demonstrated that (a) slow wave activity during sleep shifts from posterior to anterior brain regions with maturation (Kurth et al., 2010); (b) the coherence of EEG activity increases with maturation in both the left and right hemispheres (Tarokh et al., 2010); and (c) non-REM slow wave activity decreases during adolescence (Campbell et al., 2011; Feinberg & Campbell, 2010). These phenomena are believed to reflect changes in brain organization and synaptic pruning occurring around the adolescence period (Feinberg & Campbell, 2010).

The maturation of sleep-wake patterns and the structural changes occurring in sleep stages and EEG patterns during sleep suggests that sleep plays a major role in brain development and information processing (Feinberg & Campbell, 2010; Mirmiran & Van Someren, 1993). Therefore, it is unsurprising that poor and insufficient sleep has been linked

to compromised cognitive, emotion and behavior regulation (e.g. Gregory & Sadeh, 2012; Sadeh et al., 2003).

<u>What can go wrong with sleep?</u>

Sleep is a very vulnerable state that can be affected by a variety of medical, physiological, environmental and psychological factors. Every condition leading to physical discomfort or pain (including reflux, milk allergy, atopic dermatitis, headaches and even simple colds) is likely to adversely affect sleep (Brockmann et al., 2014; Camfferman et al., 2013; Chang et al., 2014; Guidetti et al., 2014; Machado et al., 2013). For the main classification of sleep disorders see **Table 2**. Of note, it can be problematic to define certain difficulties (e.g. sleep onset delay) as there may be familial and cultural differences in terms of what constitutes a sleep problem (Wiggs, 2007).

<u>Childhood psychiatric disorders and sleep disturbances</u>

The DSM-5 (American Psychiatric Association, 2013) includes a category of 'sleep-wake disorders'– and also includes sleep disturbances within criteria for other disorders (e.g. a symptom of major depressive disorder can be insomnia or hypersomnia nearly every day). Perhaps what keeps pediatric sleep researchers particularly busy is that when considering the full range of disorders listed in the DSM-5, sleep phenotypes appear to be relevant to most disorders listed. Here we describe the current state of knowledge on associations between sleep and the DSM-5 diagnostic categories most relevant to children and for which associations with sleep are beginning to be understood. Throughout this section we refer to research conducted on both clinical and non-clinical samples. We describe concurrent and longitudinal links between phenotypes and touch upon mechanisms and treatment research.

<u>Neurodevelopmental disorders</u>

Children with neurodevelopmental disorders are more likely than typically developing children to have altered sleep patterns and suffer from sleep problems. This pervasive

comorbidity of disordered sleep has been documented in studies with children suffering from a wide range of disorders including epilepsy (Carotenuto et al., 2014; Pereira et al., 2012), autism (Allik et al., 2006; Cohen et al., 2014; Goodlin-Jones et al., 2008; Hodge et al., 2014; Richdale & Schreck, 2009), Down syndrome (Ashworth et al., 2013; Austeng et al., 2014), Asperger syndrome (Allik et al., 2006; Paavonen et al., 2008), Rett syndrome (Carotenuto et al., 2013), Williams syndrome (Gombos et al., 2011), Angelman syndrome (Miano et al., 2004), Tourette syndrome (Ghosh et al., 2014) and general intellectual disabilities (Wiggs & Stores, 1996).

For example, children diagnosed with autism (and autism spectrum disorders) tend to have more difficulties than others falling asleep and maintaining sleep as well as in experiencing shorter sleep duration (Allik et al., 2006; Hodge et al., 2014; for a meta-analysis see Elrod & Hood, 2015). As with other disorders the aetiology of the associations between autism and sleep disturbances are likely to be complex. One explanation is that sleep problems in children with autism are related to their endogenous melatonin secretion and indeed research has highlighted significantly lower nocturnal 6-sulphatoxymelatonin secretion rate in these children in comparison to controls (Tordjman et al., 2005). Furthermore, the level of melatonin secretion has been negatively correlated with the level of functional impairments. These findings suggest that lower melatonin production is an underlying factor in sleep problems in children with autism. These findings have been challenged by a recent study that found normal endogenous melatonin secretion patterns in children with autism (Goldman et al., 2014). Nonetheless, clinical research suggests that melatonin intake might be a helpful component of intervention for children with autism (Cortesi et al., 2012; Malow et al., 2012). Recent pilot data suggests that genetic variants involved in melatonin metabolism may help to explain why some patients stop responding to melatonin treatment over time (see Braam et al., 2013).

For some disorders, genetic factors lead to development of divergent anatomy that may compromise sleep. For example, in Down syndrome, common anatomical features often lead to mouth breathing and breathing difficulties during sleep (Churchill et al., 2012). Indeed, studies have documented very high prevalence (above 50%) of sleep-disordered breathing and obstructive sleep apnoea (OSA) in children with Down syndrome (Ashworth et al., 2013; Austeng et al., 2014). These sleep-related breathing disorders are associated with severely compromised sleep quality which may have serious developmental consequences.

Extensive research has demonstrated links between sleep and attention deficit hyperactivity disorder (ADHD) in children suggesting that children with ADHD are more likely to be reported as poor and short sleepers and more likely to be diagnosed with OSA and periodic limb movement disorder (PLMS) (Cortese et al., 2009; Sadeh et al., 2006; Sedky et al., 2014). Extensive studies in this area have often led to contradictory or inconclusive results, particularly when objective sleep measures (actigraphy or PSG) are used. However, meta-analyses indicate that, in comparison to controls, children with ADHD are more likely to suffer from periodic limb movements in sleep (Sadeh et al., 2006); and are more likely to have lower sleep efficiency, more sleep stage shifts and higher apnea-hypopnea index (Cortese et al., 2009). Studies have also revealed longitudinal associations between sleep problems and ADHD (e.g. Lycett et al., 2014; Scott et al., 2013). Explanations for the links between ADHD and sleep include the suggestion that sleep disturbance can lead to ADHD. Consistent with this idea, one study of children with ADHD (who were either treated with methylphenidate or placebo) found that sleep efficiency moderated performance on a neuropsychological task (the Continuous Performance Test, which has been found previously to distinguish children with and without ADHD, see Gruber et al., 2007). This study could potentially have implications for treatment – as the children treated with methylphenidate only experienced improved performance on the Continuous Performance Test if their sleep

was poor (as compared to if their sleep was good). Genetic studies have also shed light on the association between sleep and ADHD, with one study suggesting that a functional polymorphism of the catechol-*O*-methyltransferase gene may be involved in risk of poor sleep continuity in those with ADHD (Gruber et al., 2006).

<u>Sleep and schizophrenia spectrum and other psychotic disorders</u>

Much of the literature on sleep and schizophrenia focuses on adults – perhaps because schizophrenia is often considered to develop in late teens/ early adulthood (Sham et al., 1994). In adults, certain sleep patterns appear to characterise those suffering from schizophrenia. For example, those with schizophrenia may show increased sleep onset delay and decreased sleep efficiency (for a meta-analysis, see Chouinard et al., 2004). There is also mixed evidence of atypical sleep architecture such as decreased REM latency (for a review, see Monti & Monti, 2005). Recently, there has been increased interest in the associations between sleep and psychotic experiences in youth, perhaps reflecting more recent knowledge that symptoms of psychosis are likely to appear in early life (e.g. Poulton et al., 2000). In a sample of over 6000 children, previous and concurrent nightmares and sleep terrors predicted psychotic experiences aged 12 (Fisher et al., 2014b). Concurrent associations between sleep phenotypes and psychotic symptoms have also been reported in adolescents – with insomnia, excessive daytime somnolence and probable cataplexy all associated with psychosis – even when controlling for symptoms of depression (Lee et al., 2012) . Furthermore, a prospective study of high-risk adolescents/ young adults, found that sleep disturbances predicted first episodes of psychosis over an 18-month period (Ruhrmann et al., 2010).

It is perhaps unsurprising that sleep disturbances are found in individuals suffering from schizophrenia-related symptoms/ psychotic experiences. Indeed, decades of sleep research links disrupted or disturbed sleep to difficulties in numerous areas of functioning (e.g. see

Roth & Ancoli-Israel, 1999). Of relevance, one study in adults found that participants experiencing one night of sleep deprivation reported psychosis-like symptoms (such as perceptual distortions and disorganised cognition, Petrovsky et al., 2014). The idea that sleep disturbance could cause psychotic experiences has also been considered by others (e.g. Freeman et al., 2012; Freeman et al., 2013). The aetiology of the association between sleep disturbance and symptoms of psychosis can also been considered in other ways – with the possibility that brain abnormalities are important. Indeed, one team found that adolescents at particular high-risk for psychosis had a decreased volume of the bilateral thalamus (a structure involved in sleep) – and that this was associated with the extent of sleep problems reported (Lunsford-Avery et al., 2013). Taking a different etiological perspective, a recent study of 16 year old twins found that genetic factors explained most of the overlap between self-reported sleep disturbance and reports of psychotic experiences (Taylor et al., 2015). Bringing together what is known about genetic and environmental influences as well as brain abnormalities on risk for psychosis a 'neurodevelopmental diathesis-stress conception of sleep dysfunction' has been proposed and needs further testing (Lunsford-Avery & Mittal, 2013).

Sleep and Bipolar and Related disorders

Atypical sleep in bipolar disorder is a feature of both manic episodes (where there appears to be a decreased sleep requirement) and depressive episodes (where insomnia or hypersomnia may be present) (DSM-5, American Psychiatric Association, 2013). Research on sleep and pediatric bipolar disorder has been well-reviewed elsewhere (Harvey et al., 2006; Harvey, 2009; Staton, 2008). Briefly, focusing on pediatric populations with mania there is evidence of a decreased need for sleep (for a meta-analysis of characteristics of mania in youth, see Kowatch et al., 2005). Those with bipolar disorder may also have a high prevalence of insomnia symptoms (Faedda et al., 2004; Lofthouse et al., 2007), as well as

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hypersomnia (e.g. Parker et al., 2006). There are other ways in which sleep may differ in children and adolescents with bipolar disorder as compared to others. For example, in one study, adolescents who had recently experienced mania awoke more frequently at night as compared to matched controls (Roybal et al., 2011). Youth with bipolar disorder may also experience a high prevalence of parasomnias (Faedda et al., 2004) and enuresis (Baroni et al., 2012) – although these latter studies did not include comparison groups – so it is difficult to draw clear conclusions. It seems likely that circadian abnormalities are important in bipolar disorder – and research is needed to further understand this in youth (Harvey et al., 2006; Harvey, 2009).

While few pediatric sleep studies have distinguished subtypes of bipolar disorder – one report compared reports of sleep disturbances in those with bipolar disorder type I and those with bipolar disorder not otherwise specified (Baroni et al., 2012). No differences were reported between the groups in terms of sleep difficulties.

While most pediatric studies of sleep and associated difficulties have focused on *concurrent associations*, it is important to understand *longitudinal associations* between phenotypes as this can potentially facilitate prevention and treatment of disorders. A longitudinal study on this topic reported that sleep disturbances were associated with both manic and depressive symptoms over a 2 year period (Lunsford-Avery et al., 2012). As sleep disturbances may be a prodrome for the early onset of bipolar spectrum disorders, it becomes particularly important to understand how to treat these difficulties and one large-scale internet-based study asked parents of children with early-onset bipolar spectrum disorders to provide feedback on the treatments they had been given to aid their children's sleep (Lofthouse et al., 2010). Whereas some treatments were reported to be helpful (e.g. 54% of parents considered atypical antipsychotics to help their children's sleep), others were not (e.g. stimulants were considered by just 3% to be helpful and by 35% to be harmful). Moving on

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from describing sleep abnormalities in pediatric bipolar disorder a next step is to focus more heavily on understanding the mechanisms underlying these associations and to use this information to improve outcome for youth at high risk of bipolar disorder.

<u>Sleep and depressive disorders</u>

Previous reviews have addressed the associations between sleep and depression in children and adolescents (Ivanenko et al., 2005; Lofthouse et al., 2009). To summarise previous findings, it appears that children and adolescents with high levels of depression symptoms (or major depressive disorder [MDD]) report sleep disturbances, perhaps most notably insomnia (e.g. Puig-Antich et al., 1982; Liu et al., 2007; Sivertsen et al., 2014; Urrila et al., 2012). Despite this focus, there is also evidence of an association between depression and obstructive sleep apnoea in children and a recent meta-analyses revealed a medium association between the two and that there was improvement of depression symptoms following adenotonsillectomy (Yilmaz et al., 2013).

Importantly, studies have also revealed that sleep disturbances (including insomnia and hypersomnia) may be an important indicator of depression severity (e.g. Liu et al., 2007) and suicidal thoughts (e.g. see Urrila et al., 2012). While depression is likely to play a role in the association between sleep and suicidality, it has also been proposed that nightmares may be an independent predictor of suicidality in youth (for a review, see Liu & Buysse, 2005).

Associations between sleep and depression appear stronger in adolescents as compared to children (for a meta-analysis of the associations between sleep and depression in adolescence, see Lovato & Gradisar, 2014). For example, in a study of 175 non-clinical children and adolescents the correlation between a composite of different sleep problems and symptoms of depression was smaller in children ($r = .26$) as compared to adolescents ($r = .58$) (Alfano et al., 2009). Furthermore, in a clinical study of MDD, hypersomnia was less

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frequently reported in children (16%) than in adolescents (34%) (Ryan et al., 1987). These differences may in part reflect developmental changes in terms of the CNS and hormonally (see Lofthouse et al., 2009) – and it makes sense that sleep in children is largely protected given the likely vital role it plays for development, particularly in the young.

As flagged at the outset of this review, associations reported are often partially dependent on the methodology used to assess sleep – and whereas subjective reports of sleep problems are commonly flagged in youth with depression, objective differences obtained using PSG data are less consistent. For example, certain reports do not find objective differences in the sleep of youth with depression as compared to controls (e.g. Bertocci et al., 2005; Dahl et al., 1990; Puig-Antich et al., 1982). Nonetheless, some studies do report objective sleep differences between those with MDD and without. For example, short REM latency (time from sleep onset until first REM period) which has been considered a biological marker for depression (Kupfer, 1976), has been found in both depressed children (Arana-Lechuga et al., 2008; Emslie et al., 1990) and adolescents (Lahmeyer et al., 1983). It has been proposed (see Lofthouse et al., 2009) that the discrepancy between subjective and objective reports of sleep in depressed patients could be due a negative perception of sleep caused by negative depression-related cognitions– although it was also noted that this explanation does not easily explain the fact that both subjective and objective differences in sleep are found in adults suffering from depression (who presumably may also suffer from depression-related negative cognitions). Perhaps, as proposed elsewhere (Lofthouse et al., 2009), children suffering from depression do indeed experience - or have a susceptibility towards - objective sleep differences, but that most sleep studies are not sensitive enough to identify these differences.

Adding to what is known about concurrent associations, multiple studies have now addressed longitudinal associations between these phenotypes, using different

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conceptualisations of sleep disturbance and depression and focusing on different time-periods - reporting mixed results. For example, some studies in childhood and adolescents have found that sleep disturbances can predict later depression symptoms or disorders (Gregory et al., 2009b; Roane & Taylor, 2008; Roberts & Duong, 2013). A recent study on this topic examined parent-reported sleep difficulties in a large sample of 5-year olds (Greene et al., 2015). These children were followed up over 30 years – and when the participants were aged 34 years they were asked if they had been treated for depression in the past year. After adjusting for a number of potential cofounds (including maternal depression and sleep), severe, but not modest sleeping difficulties at 5 years were significant predictors of age 34 depression (Greene et al., 2015). Other studies have failed to show that earlier sleep problems predict later depression (e.g. Gregory et al., 2005; Johnson et al., 2000). Furthermore, a recent study investigated sleep disturbances (including self-reports of insomnia, hypersomnia, nightmares, sleep-rhythm disturbances and non-restorative sleep) in a sample of adolescents with MDD followed up over one year (Urrila et al., 2014). Contrary to expectations, sleep problems at baseline were not associated with poorer clinical outcome.

There is some support for the converse association - that depression symptoms in childhood/ adolescence predict later sleep difficulties (for a longitudinal reciprocal relationship between insomnia and depression, see Roberts & Duong, 2013). Investigating the developmental history of adults with insomnia, an epidemiological study reported that after controlling for concurrent diagnoses (depression, Generalised Anxiety Disorder [GAD], Post Traumatic Stress Disorder [PTSD], fear/ phobias, alcohol/cannabis/ hard drug dependence), adults who had a developmental history of anxiety and depression (i.e. who experienced these disorders at childhood, adolescence and young adulthood) and who had a family history of these disorders were at risk for later insomnia (Goldman-Mellor et al., 2014). In contrast, other disorders/ difficulties experienced during development (including alcohol and drug

dependence and externalising problems) did not appear to predict later insomnia. Of note, there have also been studies finding that earlier depression scores do not predict later sleep problems (e.g. Gregory et al., 2009b).

While the literature is clearly mixed, a recent meta-analysis focusing on sleep and depression in adolescents concluded that sleep disturbance appears to predict later depression but not vice versa (Lovato & Gradisar, 2014). A further systematic review of the field (including studies of both childhood and adulthood) concluded that the best evidence suggests a likely bidirectional association between insomnia, anxiety and depression (Alvaro et al., 2013). This review also noted, in line with the aforementioned meta-analysis, that some childhood studies had found that sleep problems predicted later anxiety/ depression but not vice versa (Alvaro et al., 2013).

Possible mechanisms underlying associations between sleep disturbances and depression have been considered from multiple perspectives, including quantitative genetic approaches (for a review see Barclay & Gregory, 2013) and those considering intermediate pathways, including the role of hormones, neural and psychological processes (see Gregory & Sadeh, 2012). To summarise some of the findings concerning mechanisms, there is some indication that shared environmental influences may be important in the associations between sleep disturbances and emotional difficulties in early childhood (Van den Oord et al., 2000) – but that genes are more important in explaining associations in older children and adolescents (Gregory et al., 2006b; Gehrman et al., 2011). Genes may also be important in explaining longitudinal associations between phenotypes within childhood (Gregory et al., 2009b). Specifying these shared genetic effects is a work-in progress, with heroic efforts underway. Understanding of neural processes has also advanced (for an overview of the neuroanatomy of psychopathology, see Hariri, 2015). A recent study of children with obstructive sleep apnoea examined functional neural activation in response to a task which has been associated

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with depression previously (empathy-eliciting scenarios) (Kheirandish-Gozal et al., 2014). Interestingly, apnoea-hypopnea index (a measure of the severity of sleep apnoea) was associated with activity in the left amygdala (a brain region previously associated with response to emotional stimuli) in response to viewing harm versus neutral actions. Specifically, greater severity of sleep apnoea appeared to be associated with reduced amygdala response. A further study (albeit in adults) demonstrated that in those reporting poor sleep (but not in good sleepers), amygdala response to threat-related facial expressions was associated with symptoms of depression (Prather et al., 2013). When sex differences were examined, this pattern of results was found in men and not women. An elegant synthesis of the literature on the importance of sleep in the functioning of the emotional brain has been proposed elsewhere (see Goldstein & Walker, 2014). This includes the proposal that REM abnormalities found in those suffering from depression could result in noradrenaline activity being blunted which could lead to differences in brain functioning, including less top-down control and greater amygdala response to non-salient information.

Given the possibility that sleep disturbances may exacerbate or even cause depression symptoms, there has been a call to incorporate treatment for sleep disturbances in adolescents suffering depression – including the proposal of specific guidelines for treating insomnia in this population (Clarke & Harvey, 2012). An initial study attempting to improve sleep (by extending sleep and providing information about sleep hygiene) in adolescents with chronic sleep reduction, found this initiative to have a positive impact on both sleep length as well as insomnia and depression symptoms (Dewald-Kaufmann et al., 2014).

<u>Sleep and anxiety disorders</u>

Anxiety has been associated with a range of sleep disturbances in youth (for recent reviews see Peterman et al., 2014; Willis & Gregory, 2015). For example, in non-clinical

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samples of children, anxiety symptoms have been associated with both increased bedtime resistance (Gregory & Eley, 2005; Gregory et al., 2006b); as well as nightmares (Gregory & Eley, 2005; Mindell & Barrett, 2002) – although results are mixed and certain sleep disturbances may not be associated with anxiety. For example, in one study, self-reported anxiety in children aged 8 was associated with parent-reported bedtime resistance, but not other aspects of sleep including sleep onset delay, sleep duration, nightwakings or parasomnias (Gregory et al., 2006b) .

In clinical samples, anxious youth have also been found to have sleep disturbances (e.g. Alfano et al., 2007; Alfano et al., 2010; Alfano et al., 2013; Forbes et al., 2008). Focusing on subjectively assessed sleep disturbances, one study found that one or more sleep related problem (including a range of difficulties such as insomnia, nightmares, and long and short sleepers) were reported by 88% of youth aged 6-17 years with an anxiety disorder (Alfano et al., 2007). A very similar proportion (90%) of anxious disordered youth also reported sleep related difficulties in a further study (Chase & Pincus, 2011). In this latter study it was also reported that the number of anxiety disorders was associated with more sleep related problems (Chase & Pincus, 2011). There is also evidence of objective sleep differences in anxious youth – and comparing children and adolescents with: 1) anxiety disorders; 2) MDD and; 3) no history of psychiatric disorder, it was found that those with anxiety had less slow wave sleep than the other groups, and also woke more during the night than the those with MDD (Forbes et al., 2008).

More recent studies have distinguished anxiety subtypes, and a PSG study of children with GAD (who did not have comorbid depression and were unmedicated) revealed increased sleep onset latency and reduced REM latency as compared to controls (Alfano et al., 2013). Studies examining anxiety subtypes have revealed that certain sleep related problems may be more common in certain types of anxiety than others. For example, one study examined

sleep-related problems in youth with different types of anxiety disorders, reporting (amongst other findings) that those with separation anxiety disorder were more likely to experience nightmares and walk/ talk in their sleep; whereas those with social phobia were more likely to experience fatigue than those without (Chase & Pincus, 2011). Of note, patterns vary between samples investigated (Alfano et al., 2009; Gregory & Eley, 2005) – and further research is necessary before conclusions about specificity can be drawn.

Longitudinal studies between sleep disturbances and anxiety have reported that certain early sleep problems (conceptualised in different studies in different ways) can forecast anxiety symptoms or disorders in later childhood (Jansen et al., 2011; Shanahan et al., 2014) and even adulthood (Gregory et al., 2005). As with the depression literature, bidirectional associations have been reported (Shanahan et al., 2014; Kelly & El-Sheikh, 2014), although there is also some evidence that sleep disturbances are more predictive of later anxiety than vice versa (Jansen et al., 2011; for a study combining anxiety/ depression see Gregory & O'Connor, 2002; for a recent review see, Leahy & Gradisar, 2012).

Certain mechanisms underlying associations between sleep disturbances and depression reviewed above, may also be relevant to anxiety (e.g. genes shared with poor sleep quality, anxiety and depression, see Gregory et al., 2011a). Environmental risks may also help to explain the association between sleep disturbance and anxiety. For example, it has been proposed that co-sleeping, which occurs in many homes of anxious children may impair sleep quality and also reinforce levels of anxiety (see Peterman et al., 2014). Of note, a recent study of young infants (aged 2 months and 24 months) found that parental presence at sleep onset but not co-sleeping, predicted anxiety and depression symptoms at 36 months (Jansen et al., 2011). Further research is needed to explore the role of these common familial practices on the associations between sleep quality and anxiety at different developmental stages.

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Genetic and environmental risks exert their effects via various pathways including their impact upon hormones – and cortisol disruption is a sign of hypothalamic-pituitary-adrenal (HPA) axis dysregulation and so may be particularly relevant in the association between sleep disturbance and anxiety. Studies examining presleep cortisol levels in anxious children have reported mixed results (e.g. Alfano et al., 2013; Feder et al., 2004; Forbes et al., 2006). For example, one study found that anxious children (although not adolescents) showed elevated levels of cortisol during the pre-sleep period as compared to those with depression or controls (Forbes et al., 2006). However, a further study of children with GAD and matched controls, reported no differences between pre-sleep cortisol levels between the two groups (Alfano et al., 2013). Higher levels of cortisol during the presleep period may be associated with arousal during the presleep period and subsequent sleep difficulties in anxious children (see Peterman et al., 2014). Indeed, research has reported associations between presleep arousal (particularly cognitive rather than somatic) and symptoms of insomnia in both children and adolescents (Alfano et al., 2010; e.g. Gregory et al., 2008). Alternatively, stress associated with bedtime struggles in anxious children could lead to elevated cortisol levels (Forbes et al., 2006). The associations are likely to be complex and are only just beginning to be understood.

Regulatory systems are likely to overlap for sleep, arousal and affect (Dahl, 1996). Indeed, disturbed sleep may disrupt prefrontal cortex functioning (Muzur et al., 2002) which plays an important role in emotional processing (e.g. Hariri, 2015). The amygdala is also likely to play an important role in the associations between sleep and emotional regulation – and the neural mechanisms described in the section on sleep and depression above are also likely to be relevant in explaining associations with anxiety (Kahn et al., 2013).

Focusing on psychological processes, a sleep deprivation study in adolescents and adults included a focus on anxiety (and examined catastrophizing, worry, threat appraisal,

likelihood of specific threats occurring amongst other things, Talbot et al., 2010). There was mixed support for the prediction that sleep deprivation results in greater anxiety. For example, participants when sleep deprived (as compared to when rested) reported greater anxiety following catastrophizing and considered the likelihood of catastrophes occurring to be greater. In contrast, sleep deprivation was not associated with greater worries or longer catastrophizing sequences. There were also interesting developmental findings including the discovery that while early adolescents rated their most concerning worry as significantly worse when sleep deprived as compared to when rested – this was not the case for older adolescents and adults. Models integrating explanations at different levels have been proposed – and further work is needed to test different pathways (see Peterman et al., 2014).

Shared mechanisms underlying sleep disturbance and anxiety and insight from treatment literature focusing on adults, suggests that treating anxiety in youth may result in benefits to sleep and vice versa (for a review of the literature see Peterman et al., 2014). While pediatric reports are few, a study of cognitive behavioural therapy (CBT) for behavioural insomnia (which included anxiety reduction techniques) in children aged 7-13 years found that those in the treatment group (as compared to waiting list controls) made significant improvements on a number of sleep phenotypes (e.g. sleep latency, efficiency and wake after sleep onset) as well as for anxiety (total and separation) following treatment and at 6-months follow-up (Paine & Gradisar, 2011). Furthermore, a recent study of 4 children examined the effects of Targeted Behavioural Therapy (which included a component aimed at improving sleep) for GAD on anxiety symptoms as well as sleep at post-treatment and 3 month follow-up – finding some significant improvements for both anxiety and sleep (rated by the children themselves but not their parents) over time (Clementi & Alfano, 2014). While the authors noted that some of their results (such as the large fluctuation in symptoms at

different points during treatment) are difficult to interpret – further study of this topic on a larger scale is underway by different groups (e.g. Clementi & Alfano, 2014).

<u>Sleep and obsessive-compulsive and related disorders</u>

A recent review of sleep and obsessive compulsive disorder (OCD), emphasised that atypical sleep seen in adults suffering from OCD may resemble that of depressed patients (e.g. reduced sleep efficiency, see Paterson et al., 2013) – although there were also differences which are not typically found in depressed populations – e.g. circadian differences (such as delayed sleep phase). While with almost every disorder, there has been less attention to sleep in children as compared to adults – interestingly, the pediatric literature reflects to some extent what has been found in adults. For example, one study compared six unmedicated children aged 7-9 years with OCD but not depression to matched controls (Alfano & Kim, 2011). Those with OCD were also found to have reduced total sleep time as well as longer wake after sleep onset as compared to the control group. Reduced total sleep time was also reported in a study of adolescents suffering from OCD as compared to controls matched for age and sex (Rapoport et al., 1981). This study also highlighted differences in sleep architecture between those with OCD and controls, such as less time spent in NREM sleep in the patient group. Further considering the association, in a child/ adolescent sample, the reported number of sleep-related problems (e.g. experiencing nightmares, being overtired, having trouble sleeping) was associated with the severity of OCD symptomology and cognitive behavioural therapy for OCD, appeared to improve sleep (Storch et al., 2008; see also, Ivarsson & Skarphedinsson, 2015). It has also been shown that sleep problems recorded prior to CBT can predict worse outcome for OCD in children and adolescents following treatment – emphasising the complex associations between sleep and OCD symptoms (Ivarsson & Skarphedinsson, 2015). Explanations for the association between OCD symptomology and sleep disturbances include the suggestion that those suffering OCD are

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more likely to experience pre-sleep arousal (which can interfere with sleep) or may engage in pre-sleep rituals which extend the pre-sleep period (see Ivarsson & Skarphedinsson, 2015). As noted elsewhere, (e.g. Ivarsson & Skarphedinsson, 2015), while these explanations can account for certain sleep related problems (e.g. sleep onset delay) they are perhaps less able to explain others (e.g. short sleep duration). Future work needs to more thoroughly understand the mechanisms underlying these various associations.

Sleep and trauma and stress related disorders

The relevance of sleep to trauma and stressor related disorders is highlighted clearly by reference to sleep in the diagnostic criteria for both posttraumatic stress disorder and acute stress disorder (DSM-5, American Psychiatric Association, 2013). Of all the trauma and stressor related disorders, most sleep research has focused on PTSD. The diagnostic criteria for PTSD includes reference to recurrent distressing dreams related to the trauma and also increased arousal which may be shown by insomnia symptoms or restless sleep (DSM-5, American Psychiatric Association, 2013).

In line with reviews of the literature focusing on PTSD and sleep in children (see Charuvastra & Cloitre, 2009; Kovachy et al., 2013), we include discussion of both exposure to traumatic events and sleep as well as PTSD and sleep. With regards traumatic events, it is clear that exposure to different types of traumatic events can result in sleep disturbances and nightmares. For example, a previous review highlighted mixed evidence that experiencing traumas including child abuse, exposure to war and disaster could lead to sleep problems (Sadeh, 1996). However, there is also some suggestion that certain types of traumas may have a particularly salient impact upon sleep disturbances and/ or sleep-related problems (e.g. Cecil et al., 2015; for a review, see Sadeh, 1996). Sexual abuse is one type of abuse that has been particularly associated with sleep problems – possibly because this type of abuse is

particularly likely to occur at night or in a child's bedroom (Noll et al., 2006). Of note, not all studies have reported this pattern (e.g. Glod et al., 1997; for a study in adults see Germain et al., 2004).

A further question which has been addressed is whether there is a relationship between the extent of the trauma and the severity of the sleep disturbance. Supporting this idea, an association was reported between the severity of childhood maltreatment reported and the frequency of disturbing dreams/ nightmare distress and psychopathology in a retrospective study of female undergraduates (Duval et al., 2013). There is also evidence of an association between the severity of sleep disturbances including sleep quality, insomnia and nightmares, and that of PTSD in adults (see Germain et al., 2004; Pigeon et al., 2013).

Examining the association between trauma and sleep longitudinally has yielded interesting results. For example, a number of studies have now revealed that stress/ trauma, in the form of child abuse (Greenfield et al., 2011) and family conflict (Gregory et al., 2006a) can predict sleep problems (e.g. poor sleep quality and/ or insomnia) in adulthood (for a systematic review see Kajeepeta et al., 2015). Focusing on longitudinal associations between sleep problems and PTSD symptoms specifically, a recent study of 350 adolescent survivors of the Wenchuan Earthquake in China investigated self-report symptoms at 1, 1.5 and 2 years following the disaster (Zhou et al., 2014). All three types of PTSD symptoms (ie the intrusive, avoidance and hyperarousal clusters) predicted sleep problems from 1 to 1.5 years following the earthquake. Conversely, during this time, sleep only predicted the intrusive PTSD symptoms (but not the others). At 1.5 to 2 years following the earthquake, only the avoidance PTSD symptoms (and not the others) predicted sleep problems. Conversely, during this period, sleep problems did not predict any of the PTSD symptom clusters – highlighting a reduction in magnitude of the association between sleep problems and PTSD symptoms over time. Understanding more about sleep following trauma has the potential to be of

prognostic value for the development of PTSD (for a discussion in adults, see Harvey et al., 2003).

Much of the PTSD literature focuses on subjectively defined sleep problems – and future research is needed to establish whether there are also objective sleep problems in youth with PTSD. This is particularly important as research in adults has revealed that while those suffering PTSD are likely to report sleep disturbances, this is not always verified by objective assessments (see Harvey et al., 2003).

Nonetheless, certain objective measures of sleep have been reported in some adults with PTSD as compared to controls – such as increased REM sleep (see Harvey et al., 2003). In a recent review, it was argued that increased REM is likely to aid recovery following stress (Suchecki et al., 2012). REM abnormality following trauma is noteworthy as nightmares (a criteria of PTSD) are most likely to occur during REM sleep. While objective data of sleep disturbance in children experiencing trauma or with PTSD is sparse, there is some actigraphy data to suggest that children experiencing trauma or who are diagnosed with PTSD are more likely than others to show disturbed sleep (e.g. increased sleep onset latency and nocturnal activity and poorer sleep consolidation, see Sadeh et al., 1995; Glod et al., 1997).

There now needs to be greater attention to understanding the mechanisms underlying associations between trauma, sleep disturbances and PTSD in children. Furthermore, it will be important to understand whether reducing sleep difficulties in those who have experienced trauma has positive implications for long-term outcome. Indeed, in line with the adult literature, it is possible that treating insomnia symptoms and nightmares and could improve PTSD outcome (Krakow et al., 2001b; Krakow et al., 2001a).

Finally, while this section has focused exclusively on trauma and PTSD – it is noteworthy that little is known about sleep in children with other trauma and stressor related

disorders such as reactive attachment disorder and disinhibited social engagement disorder. It is likely that children with such disorders may be particularly susceptible to sleep related problems (e.g. sleep onset delay or a desire to have a parent present at sleep-onset) given what is known about the links between attachment and sleep (e.g. for a review, see Adams et al., 2014) understanding more about these association appears to be a fruitful line of future investigation and holds promise for improving life for these children and their families.

Sleep and feeding and eating disorders

During early childhood, sleep and feeding problems tend to coexist and have some shared predictors such as pre-term birth, family adversity and psychological stress (Schmid et al., 2011; Tauman et al., 2011). Accumulated research has documented that from early ages, short and/or poor sleep is associated with increased body mass index and obesity (Fatima et al., 2015; Miller et al., 2015; Spruyt et al., 2011). Recent research suggest that these relations are mediated by under-regulated eating behaviors (Fisher et al., 2014a; Kruger et al., 2014; Yeh & Brown, 2014). Other physiological mechanisms have been proposed to explain the links between short sleep and excessive weight gain (Markwald et al., 2013).

Considering the metabolic, physiological and psychological links between sleep and eating regulation it is not surprising that eating disorders such as anorexia nervosa and bulimia have also been linked to sleep problems (Bos et al., 2013; Lauer & Krieg, 2004). Furthermore, a NREM-related parasomnia, 'sleep related eating disorder' has been described in the ICSD-III (American Academy of Sleep Medicine, 2014; see also, Howell et al., 2009). This disorder involves involuntary eating following an arousal during sleep.

Sleep and disruptive, impulse control, conduct disorders

Externalizing disorders such as conduct disorder and oppositional-defiant disorder are prevalent disorders that are considered serious risk factors for later psychopathology (Kessler et al., 2012; Loth et al., 2014; Witkiewitz et al., 2013).

Unsurprisingly, research has repeatedly demonstrated that externalizing behavior problems are associated concurrently and longitudinally with poor sleep quality (Armstrong et al., 2014; Kamphuis et al., 2012; Shanahan et al., 2014; Sheridan et al., 2013; Simola et al., 2014) and short sleep duration (Kelly & El-Sheikh, 2014; Scharf et al., 2013). Relationships are likely to be complex, and in a longitudinal study of children aged 5-9 years it was reported that mothers ratings of infant temperamental resistance to control moderated sleep and externalizing behaviour trajectories (with the sleep and externalising trajectories associated only in children who were reported to show high temperamental resistance to control, Goodnight et al., 2007).

In the most recent version of the DSM (DSM-5, American Psychiatric Association, 2013) a distinction has been drawn between those with conduct disorder who do and do not display limited prosocial emotions . Given important distinctions between these two groups (e.g. in terms of affective characteristics, for a review see Frick et al., 2014) we predict that sleep disturbances may also be more characteristic of one group (ie those who do not experience limited prosocial behaviour) as compared to the other (ie those who do experience limited prosocial behaviour) – although future work needs to address this.

As with other associations reported in this review, understanding of the aetiology of the association between sleep quality and externalising behaviours is increasing all the time – and amongst other work, a twin study (albeit of young adults) found that the link between poor sleep and externalising behaviours were largely explained by shared genes (Barclay et al., 2011).

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Sleep and substance use and related addictive and risk-taking behaviors

As discussed, inadequate sleep predicts externalizing behavior problems which are considered major risk factors for the development of risk-taking behaviors, substance abuse and other addictive disorders. Therefore, the concurrent and predictive links between insufficient or poor sleep and domains of risk-taking behaviors and addictions are unsurprising (Conroy & Arnedt, 2014; Digdon & Landry, 2013; Hasler et al., 2014b; Hasler et al., 2012; Hasler et al., 2014a; Telzer et al., 2013; Womack et al., 2013; Wong et al., 2010). Insufficient sleep has been proposed as the underlying mechanism for the association between compromised sleep and addictive behaviors and there has been experimental work on the effects of sleep deprivation on reward brain function (Gujar et al., 2011; Venkatraman et al., 2011).

It is important to note that the links between sleep and addictive behaviors are bi-directional such that sleep deprivation can lead to compromised regulatory capacities leading to substance use or other addictions, and vice versa, addictive behaviors and substances can have adverse influence on sleep (Chan et al., 2013; Do et al., 2013; Lin & Gau, 2013).

Mechanisms

It is difficult to discuss, in general, the mechanisms underlying the diverse relationships between various sleep disturbances and psychopathologies. Indeed, the mechanisms underlying short periods of slow wave sleep in adolescents with anxiety disorders (Forbes et al., 2008) are likely to differ from those underlying the associations between nightmares and psychotic experiences (Fisher et al., 2014b). Given that this review has addressed a diverse range of sleep phenotypes and associated difficulties, possible mechanisms have been briefly discussed throughout. Nonetheless, this section brings together a more general discussion of a handful of explanations of comorbidity (for a more thorough discussion of comorbidity of childhood disorders see Angold et al., 1999).

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Briefly, when considering associations between sleep disturbances and psychiatric disorders it is important to consider nosology. As described in this review, certain sleep disturbances are listed in the diagnostic criteria for various psychiatric disorders (e.g. depression, DSM-5, American Psychiatric Association, 2013). It is important to note that despite sleep disturbance sometimes being considered a symptom of another disorder, there has been a shift away from simply considering sleep disturbances as a symptom of other problems – and 'primary' insomnia was removed from the most recent version of the DSM (DSM-5, American Psychiatric Association, 2013) reflecting the current thinking that insomnia should not be dismissed as secondary to other disorders where comorbidity occurs (for a comprehensive discussion, see Harvey, 2001). Regardless of whether sleep disturbances are considered a symptom of another disorder or a diagnosis in their own right, it remains important to understand co-occurrence.

Other explanations for the associations between sleep disturbances and psychiatric disorders include the suggestion that one disorder causes the other. While causal associations are notoriously difficult to establish (e.g. Hill, 1965) – some research is consistent with the possibility that disrupting sleep could increase vulnerability for certain psychological disorders, including depression. For example, in a neuroimaging study, participants who had been sleep deprived for 35 hours (as compared to non-sleep deprived controls) showed increased amygdala response to negative emotional stimuli and weaker functional connectivity between the medial prefrontal cortex (which plays a role in regulating amygdala functioning) and the amygdala (Yoo et al., 2007). Poorer ability to moderate emotional responses in sleep deprived participants is consistent with the possibility that sleep disturbance could cause certain psychopathologies – including depression.

An alternative view is that shared risks of different types (e.g. genetic, environmental, hormonal, neural and psychological) may underlie associations between sleep disturbances

and other psychopathologies. For example, there is increasing support for the 'generalist genes hypothesis' which proposes that genes may explain the co-occurrence of traits and the persistence of disorders over time – with environmental factors more likely to be time and phenotype specific (e.g. Eley, 1997). Such explanations could explain why those suffering from sleep disturbances are also more likely than others to display signs of other psychopathologies.

Finally, it is possible that for certain sleep and sleep-related problems (e.g. nightmares; sleep onset delay; poor sleep efficiency) the same mechanism (i.e. a general disruption to sleep) could underlie seemingly disparate associations (see Peterman et al., 2014). Nonetheless, explanations should be tailored for specific associations. For example, recent research suggests that impaired cortical processing may explain associations between sleep disordered breathing and behavioural disorders. Indeed, a study found that children with sleep disordered breathing (as compared to controls) had a reduced amplitude of heartbeat evoked potentials during NREM sleep (Immanuel et al., 2014). This suggests that at least one aspect of cortical processing (interoceptive processing) may be impaired in those with sleep disordered breathing as compared to controls. This could help to explain some of the behavioural differences between groups (e.g. in terms of both internalizing and externalizing disorders). Importantly, following adenotonsillectomy group differences in terms of heartbeat evoked potentials did not remain (although interestingly the children originally classified with sleep disordered breathing retained greater behavioural problems as compared to controls, which the authors hypothesise could be due to insufficient time to 'unlearn' these behaviours before testing). Research would need to test explicitly the extent to which the same mechanisms underlie the associations between other sleep disturbances (such as insomnia) and behavioural problems.

Research on prevention and treatment of sleep disorders

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The bad news is that sleep disturbances are very prevalent in infants, children and adolescents. The good news is that there are techniques to help prevent certain sleep problems (such as insomnia) and most sleep problems are responsive to clinical interventions.

Preventing sleep disorders

It may be possible to reduce the chances of insomnia symptoms from developing. For example, one study gave a randomly allocated half of the parents of infants aged 3 months a booklet about the importance of routines and methods which can be used to settle an infant (Kerr et al., 1996). The other half did not receive this information. When parents were asked about their infants sleep aged 9 months, those who had received the booklet (as compared to those who had not received the booklet) were less likely to report difficulties with settling their children to sleep and night wakings.

Sleep hygiene

Sleep hygiene involves ensuring that aspects of lifestyle and the environment are optimal for sleep. For example, a family may be advised that their child should avoid caffeine, have a regular bedtime and ensure that their child falls asleep alone. Good sleep hygiene practices have been found to be associated with good sleep in children from birth to 10 years of age (Mindell et al., 2009). Sleep hygiene (including considering light exposure and sleep schedule) may be important for treating a range of sleep disorders including circadian rhythm sleep-wake disorders (Morgenthaler et al., 2007).

Behavioural interventions

Extensive research has demonstrated that brief behavioral interventions are very effective for pediatric insomnia (Meltzer & Mindell, 2014; Mindell et al., 2006). Most research in this area has been conducted in early childhood where the evidence supporting behavioral interventions is strong – and there is now need for more research in older children and adolescents (Meltzer & Mindell, 2014). Prevention, in the form of early brief online

intervention for parents of infants and toddlers with moderate sleep problems, has been shown to be effective in improving sleep immediately following the intervention (Mindell et al., 2011a) and in a 1-year follow-up (Mindell et al., 2011b). Different behavioural approaches have been developed to address different types of sleep problems. For example, sleep terrors can be treated using scheduled waking whereby a child's sleep pattern is disrupted by waking them fully a short time (e.g. 10-15 minutes) before they are expected to have a sleep terror and then allowing them to return to sleep (Lask, 1988). Over time the sleep terrors should stop and the parents no longer need to engage in this scheduled waking.

Cognitive interventions

Cognitive interventions have also been shown to be effective in children. For example, image rehearsal has been proposed as an effective treatment for nightmares in children (St-Onge et al., 2009; for a meta-analysis, see Hansen et al., 2013). While standard treatments have been constructed with typically developing children in mind, it is important to consider whether modifications are necessary in order to be of optimal value to children suffering from co-occurring disorders. For example, it is possible that standard imagery rehearsal is inappropriate for a child who has intellectual development disorder and is experiencing nightmares.

Pharmacotherapy

Pharmacotherapy is useful for treating sleep disorders of different types. For example, Montelukast (a cysteinyl-leukotriene receptor Antagonist) appears to hold potential to be a successful treatment for OSA in children (Goldbart et al., 2012). Modafinil has also been found to be an effective treatment for excessive daytime sleepiness - which often occurs in the context of narcolepsy (Thorpy, 2015). Circadian rhythm sleep-wake disorders can be treated via pharmacological treatments (such as melatonin, hypnotics and stimulants - for an

expert consensus on this topic see, Morgenthaler et al., 2007; for a meta-analysis of melatonin treatment for delayed sleep phase disorder see van Geijlswijk et al., 2010).

Mechanical applications and surgery

Mechanical applications may also yield benefit and continuous positive airway pressure and dental appliances are used as treatments for OSA (e.g. see Kuhle et al., 2009). The efficacy of surgical (adenotonsillectomy), for OSA has also been repeatedly demonstrated (Chervin et al., 2012; Goldbart et al., 2012; Huang et al., 2014; Kuhle et al., 2009; Marcus et al., 2013). There is some evidence that adenotonsillectomy may improve children's sleep and behaviour although certain issues may remain with aspects of neuropsychological functioning (Giordani et al., 2012). Although adenotonsillectomy has some positive outcomes in improving sleep and related daytime functioning, it has limitations particularly when obesity is involved (Huang et al., 2014). Focusing on ADHD symptoms in particular, a recent meta-analysis revealed that there was a moderate association between ADHD symptoms and sleep disordered breathing and that adenotosillectomy improved ADHD symptoms (Sedky et al., 2014).

The pervasive effects of treatments

As outlined in this review, it is important to note, that in many studies the effects of the sleep interventions manifested beyond sleep, benefitting other behavioral domains such as a child's increased sense of security, lower irritability and reduced crying (Mindell et al., 2006). However, it has also been argued that early infant sleep interventions, during the first 6 months do not lead to persistent or established improvement in infant outcomes (Douglas & Hill, 2013). Addressing sleep disturbances in children may also have a positive impact upon parents - with one study demonstrating that successfully treating the sleep problems experienced by children with severe intellectual disabilities resulted in various, although

differing, advantages for mothers and fathers (with mothers experiencing reduced stress for example, see Wiggs & Stores, 2001).

Because of the bidirectional links between sleep and psychopathology, treating one domain is likely to improve the health status in the other domain or to reduce the risk for developing comorbidity. For example, it has been demonstrated that sleep problems during adolescence often precede and predict the development of depression and that early detection and treatment of sleep problems may reduce the risk for depression (Lovato & Gradisar, 2014). This promising idea needs to be further established by clinical research. Similarly, because insufficient or poor sleep often mimics the symptoms of ADHD and early childhood sleep problems predict later ADHD it has been suggested that treating early childhood sleep problems may reduce the risk for ADHD (Dahl et al., 1991; Owens, 2005). Again, this is yet to be demonstrated in clinical studies.

Discussion

Since we last collaborated on a review of this topic (Gregory & Sadeh, 2012) there has been a long overdue surge of research interest in this area from those with a diverse array of expertise. This increased interest is clearly justified given that comorbidity is an epidemiological reality, with (as outlined in this review) sleep disturbances characteristic of many psychological disorders during childhood. Furthermore, disorders typically start early in life (Kim-Cohen et al., 2003) so it is negligent to ignore the childhood and adolescence period when trying to understand the development of psychopathology. Sleep can be assessed very early in life (even from pre-birth), and has been found to constitute an early risk indicator of later problems (e.g. Jansen et al., 2011). As outlined previously, research to date on this topic has proved fruitful clinically, in suggesting that sleep disturbances may serve as a red flag for the development of a host of other disorders as well as predicting the severity and prognosis of certain associated difficulties.

Despite our excitement regarding the growth of this research field, there are five areas that should be further considered in future investigation. The first concerns the measurement of sleep. Our review highlights that associations between phenotypes can vary by measurement (e.g. see section on sleep and depression). Indeed, associations may differ depending on whether scales are parent or self-rated or whether objective measurements of sleep are made. This underscores the importance of using multiple methods to assess sleep. Previously, perhaps reflecting the historical neglect of sleep, researchers have used items available from other measures in order to develop their own sleep scale – even referred to as a 'Frankenscale' (Peterman et al., 2014). While this approach has allowed important questions to be asked there are obvious limitations associated with using these scales and future work needs to focus on more widely validated measures which precisely measure the phenotype under investigation and include a focus on the severity and duration of a difficulty.

The second area that we would like to highlight for further study, concerns the array of disorders under investigation. Whereas understanding concerning sleep and depression in youth is becoming more sophisticated all the time, it seems that knowledge about the associations between sleep and certain other phenotypes lags behind. For example, within neurodevelopmental disorders there is strong understanding of the links between sleep and certain disorders (e.g. ADHD) – but not others. For example, almost nothing is known about possible links between sleep and developmental co-ordination disorders, although this appears to be a line of fruitful enquiry (Barnett & Wiggs, 2012). Similarly, within trauma and stress related disorders, there is a good understanding of the associations between sleep and PTSD – but less is known in relation to reactive attachment disorder and disinhibited social engagement disorder. While further investigation of these under-researched areas will likely prove beneficial – researchers also need to carefully consider comorbidity between disorders

– to acknowledge the possibility that a comorbid phenotype (e.g. anxiety) could drive other associations.

The third area to consider in future investigation concerns the mechanisms underlying associations. Most of the research to date describes associations without much attempt to explain them. Perhaps a fruitful next step within this area could be to consider sleep restriction as an environmental stressor (as in previous work focused on depression symptoms, Carskadon et al., 2012) in gene-environment interaction models of symptoms of other phenotypes. Indeed, it may be sleep disturbances trigger symptoms of other disorders in those who are at greatest genetic risk. Given the recent surge of interest from researchers specialising in genetics, neuroscience, cognitive psychology as well as other disciplines, we hope, and think it likely, that in future reviews of this topic, the descriptions of mechanisms underlying associations will constitute a much more substantial component.

The fourth point to address in future research concerns developmental questions. Much of what we know about sleep in children lags behind what is known in adults. For example, most neuroscience research on the links between sleep and emotion has focused on adults (see Goldstein & Walker, 2014). While the adult literature can often provide a useful starting point from which to ask questions concerning the association between sleep and other phenotypes in children – it is important to keep in mind developmental differences in the manifestations of sleep disturbances as well as the underlying processes (e.g. the maturity of cognitive skills; life events experienced). Furthermore, sleep in children in particular must be considered in the family context, given that parents are likely to have control over bedtime routines and the sleep environment (see special edition of Journal of Family Research, with an introduction by Dahl & El-Sheikh, 2007). Taking the field forward, it may also be valuable to investigate associations over sensitive periods. For example, one study investigating sleep and symptoms of anxiety and depression focused on the transition to

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University (Doane et al., 2015). Other stages that may be worth focusing on further include the transition to primary and secondary school, and in adults, becoming parents for the first time. Finally, whereas age is often used as a crude index of development, it may be worthwhile considering this from different perspectives (e.g. pubertal development, see Noone et al., 2014).

The fifth area to emphasise for future research is the need to focus on treatment studies – and in particular well-designed randomized controlled trials (RCTs) given that current treatment guidelines and recommendations in this area are often based on expert consensus rather than empirical evidence from well-conducted RCTs (see Bruni et al., 2015; Cortese et al., 2013). It is becoming increasingly clear that treating sleep disturbances may prevent or improve associated difficulties and vice versa (see section on treatment). The effects of tailoring treatments based on whether or not a child with a disorder has comorbid sleep disturbances should also be investigated. Large scale studies of this type should become easier to conduct given continuous development of online treatments for sleep disturbances which can be disseminated widely (e.g. Mindell et al., 2011a).

We hope we have justified why it is fruitful to learn more about sleep in children and adolescents suffering from other disorders - and we believe this knowledge has clinical value. Indeed, parents and youth themselves may find it easier to discuss their sleep as compared to other difficulties – and discussing sleep may provide a starting point from which to build rapport with a health provider. Conversely, we note that sleep problems – such as short sleep, often constitute an 'invisible risk' (Carli et al., 2014) – which must not be ignored. Since the days of Hippocrates, the value of sleep for good health has been discussed (see Suchecki et al., 2012) - but perhaps only now are paediatric researchers really waking up to this.

Key Bullet Sentences

- It is becoming increasingly apparent that sleep disturbances in childhood are associated with and predictive of a wide range of psychopathologies - although certain associations are underexplored.

- Longitudinal links between phenotypes suggest that sleep disturbances may represent a 'red flag' for later difficulties – although they may also be missed by parents and clinicians hence constituting an 'invisible risk'.

- There is a recent surge in excitement around the field of pediatric sleep from researchers with diverse expertise (including genetics, neuroscience, cognitive psychology) so future reviews should provide a greater understanding of mechanisms underlying associations.

- There needs to be further well-conducted randomized controlled trials in order to establish the very best treatments for children of different ages and with comorbid difficulties of various types.

- Treatment studies need to further establish the extent to which treating sleep disturbances in children has positive effects on other developmental domains (e.g., psychopathology) beyond the direct effects on sleep.

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Table 1. Common methods used to assess sleep

Method of assessment	Details	Further comments
Polysomnography (PSG)	Physiological information (e.g. brain activity and eye-movement) is used to draw inferences about sleep stages	Often considered the 'gold-standard' for assessing sleep, but sometimes considered infeasible for large-scale studies
Actigraphy	A watch-like device measures movement from which inferences can be drawn about sleep/ wake	The role of actigraphy in sleep medicine is discussed elsewhere (Sadeh & Acebo, 2002)
Sleep diaries	Typically completed in the morning and comprises self (or rater) report of variables including sleep timing and quality the night before	For a consensus sleep diary, see elsewhere (Carney et al., 2012)
Questionnaires	Questions about sleep are completed by children themselves (or by a rater such as their parents)	For a discussion of pediatric sleep questionnaires, see elsewhere (Spruyt & Gozal, 2011)
Smartphone applications	These utilise high quality sensors (e.g. those detecting movement and sound) to draw inferences about aspects of sleep (e.g. sleep apnoea)	These techniques are often not validated (see Behar et al., 2013)

Table 2. Six main categories of sleep disorders

Category	Description
Insomnia	- Persistent sleep difficulty
	- Adequate opportunity for sleep
	- Daytime impairment
	- E.g. Chronic Insomnia Disorder
Sleep Related Breathing Disorders	- Abnormal respiration during sleep
	- E.g. Obstructive Sleep Apnea (OSA)
Central Disorders of Hypersomnolence	- Excessive sleepiness
	- Not caused by poor sleep or circadian rhythm misalignment
	- E.g. Narcolepsy
Circadian Rhythm Sleep-Wake Disorders	- Misalignment of timing of sleep-wake propensity and the external environment
	- E.g. Delayed Sleep-Wake Phase Disorder
Parasomnias	- Physical events/ experiences during sleep (or transition to/ from sleep)
	- E.g. Sleep Terrors
Sleep Related Movement Disorders	- Characterised by movements that prevent or disrupt sleep
	- E.g. Restless Legs Syndrome

Note. Categories are proposed in and defined by ICSD-3 (American Academy of Sleep

Medicine, 2014)