

Sleep disorders in adult ADHD: a key feature

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Summary

Objectives

Attention deficit hyperactivity disorder (ADHD) is a neuropsychiatric disorder affecting individuals across the life span, and the relationship between ADHD and sleep poses several challenges in clinical practice. As ADHD symptoms overlap with those of sleep disorders, the aim of this paper is to summarise the state of art regarding the relationship between these conditions, in order to provide suggestions for future research and key elements to take into account during the diagnostic assessment of ADHD as well its clinical management.

Methods

We performed a PubMed search for articles published from 2005 to 2016, using the following key words: attention deficit disorder, ADHD, sleep disorders. The literature search was conducted in March 2016. Only articles written in English and providing data on adult population were considered.

Results

We found 773 articles matching keywords. Applying the above-mentioned exclusion criteria, only 30 resulted pertinent to our aim. Other articles from other databases were selected accord-

ing to their importance, and then further filtered according to their capability in answering our research objectives. A total of 35 articles allowed us to identify the most frequently reported sleep disorders in adult ADHD, the potential neurobiological substrates at the basis of the similarities in symptomatology and the most important implications for clinical and research settings.

Conclusions

A poor sleep can worsen ADHD symptomatology, resulting in an increasing risk for accidents and health problems. An increased risk for depression has also been documented. Because of the overlapping symptomatology, the presence of a sleep disorder should be adequately screened during ADHD assessment and during the clinical management of the disorder. The similarities between symptoms of ADHD and those of a sleep disorder suggest certain basic disturbances in a potential common circuitry that require further exploration. The understanding of the causes accounting for the frequent co-occurrence of sleep disorders in people affected by ADHD may help to implement an effective treatment for improving quality of life of these patients.

Key words

ADHD • Attention deficit disorder • Sleep disorders

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurobiological condition with childhood onset characterised by developmentally inadequate symptoms of inattention, impulsivity and hyperactivity causing impairment in several domains (e.g. school, home, social and sentimental relationships, work etc.). For a long time, ADHD has been considered a clinical condition affecting only childhood, but now there is consensus about its frequent persistence over the lifespan.

It is widely known that both children and adults with ADHD may also meet criteria for other psychiatric disorders, and patients with both ADHD and comorbidities may experience greater impairment than people with ADHD alone¹. Mood, anxiety and substance use dis-

orders have been reported as co-occurring conditions of adult ADHD in several study and international surveys, but recently greater attention has been given to sleep disorders. Research data show a prevalence rate of adult ADHD of 3.4%², and up to 83% of adults with ADHD reports sleep complaints³. Adults with ADHD frequently report difficulties in falling asleep, problems in awakening in the morning and may present daytime sleepiness⁴. However, it would be noted that daytime sleepiness, impaired cognitive performance and behavioural problems are usually reported also by patients with sleep disorders⁴.

The relationship between sleep problems and ADHD has been described as extremely complex. In fact, it has been suggested a bidirectional association between sleep dif-

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difficulties and ADHD, so that poor sleep may exacerbate ADHD symptomatology and viceversa ⁵.

Moreover, sleep difficulties, such as restless sleep, bedtime resistance and nocturnal awakenings, have been proposed as a risk factor for the subsequent development of ADHD ⁶: sleep problems in infancy have been found to be associated to attentional and behavioural problems at age 15 ⁷, and short sleep duration was significantly related to increased externalising symptoms ⁸.

Because several studies show how sleep restriction may affect cognition and behaviour in a way that may mimic ADHD ⁸, the intricate nature of such relationship requires an adequate consideration in the diagnostic assessment process for ADHD, in order to avoid an incorrect (or partial) diagnosis.

The relationship between sleep disturbances and ADHD symptoms and its negative impact on functioning have been largely examined in children. With the recognition of the persistence of ADHD in adulthood, research on interaction between sleep and adult ADHD is necessary. The aim of this paper is to provide the state of art regarding:

1. the most reported sleep disorders in adults with ADHD;
2. neurobiological mechanisms underlying the relationship between sleep and ADHD;
3. implications for clinical practice and suggestions for research.

Materials and methods

We performed a PubMed search for articles published from 2005 to 2016, using the following key words: attention deficit disorder, ADHD, sleep disorders. The literature search was conducted in March 2016.

The titles and abstracts of identified papers were screened. We excluded all articles not written in English, and not considering the adult population. Articles so filtered were read in full and examined according to their relevance in the field.

Results

We found 773 articles matching keywords. Applying the exclusion criteria before mentioned, only 30 resulted pertinent to our aim. Additional articles from other databases were selected according to their importance and then further filtered according to their capability in answering our research objectives.

Our search of the most recent literature allowed us to identify: the most frequently reported sleep disorders in adult ADHD, the suggested neurobiological substrates at the basis of the similarities in symptomatology and the most important implications for clinical and research settings.

Obstructive sleep apnea (OSA)

Both individuals with ADHD and those suffering from an obstructive sleep apnea complain of daytime inattentiveness and impaired concentration. Attention deficits, poor planning activities, restlessness and irritability are very well documented in these populations, especially in children ⁹. In consideration of previous research ¹⁰ that found the presence of OSA in 5% of subjects affected by relevant symptoms of ADHD, in 26% of people with a mild symptomatology and in 5% of people without the disorder, it has been suggested that the overlap of symptoms between OSA and ADHD may lead patients with OSA to be misdiagnosed as having ADHD ⁹.

In case of co-occurrence of both disorders, higher anxiety levels and a greater deterioration in daytime functions have been described, and the treatment of only OSA was considered of limited efficacy in improving daytime functioning ¹¹.

Restless legs syndrome

Another sleep disorder frequently reported in ADHD population is restless legs syndrome (RLS). RLS is a sensorimotor condition characterised by discomfort and tension in the lower limbs with the urge to move them ¹². Children and adults with RLS have problems falling asleep due to aching, cramping, or tingling leg sensations that cause bedtime resistance until late at night. RLS has been found frequently associated with periodic limb movement disorder (PLMD), which is characterised by periodic and sustained contractions in legs, occurring mainly in non-rapid eye movement (REM) sleep. This interruption of sleep seems to determine irritability, frustration and angry outbursts in the daytime. Growing evidence suggests a link between RLS and PLMD, so that it has been suggested that periodic limb movement may also be a marker for a genotype of RLS ¹³. It is worth noting that in both RLS and PLMD, there is a frequent diagnosis of ADHD in the patient's history ¹². However, much of our knowledge on the relationship between RLS/PLMD and ADHD derives from studies performed on children and adolescents. Up until now there is still a paucity of data regarding the prevalence of RLS and PLMD in the adult population with symptoms of ADHD, and about their impact on quality of life of affected individuals. As a positive association between RLS and the severity of ADHD symptoms has been found in children ⁶, we believe that such conditions need to be adequately investigated in the adult population with a diagnosis with ADHD.

Alterations in circadian rhythms

Adults with ADHD commonly present delayed bedtimes and frequently show a sleep pattern consistent with a de-

layed sleep phase disorder (DSPD)¹⁴. DSPS is a circadian rhythm sleep disorder characterised by a shift in the circadian biological clock for which people fall asleep in the early morning hours. However, their sleep structure seems to be near normal¹⁵. Evidence shows that people with DSPS present a delay in the time of evening in which melatonin levels reach the threshold defined dim-light melatonin onset (DLMO), causing a subsequent delay in the sleep onset¹⁶. Since associations between delayed sleep and symptoms of hyperactivity and impulsivity have been found in both patients and controls¹⁷, a recent study examined the potential associations between other circadian abnormalities, such as alterations in the core body temperature (CBT) and skin temperature with the melatonin profiles in individuals with ADHD and matched controls¹⁸. It was found that individuals with ADHD and DSPS were characterised by large intra-individual day-to-day variability in bedtimes that was not related to the time of melatonin release in the body. Interestingly, dim-light melatonin onset, activity and temperature parameters were all delayed in ADHD + DSPS subjects, and even their profiles were not related to the onset of melatonin release. Moreover, subjects with ADHD and DSPS are characterised by alterations in core and skin temperatures¹⁸. The nature and meaning of such findings require further exploration.

Neurobiology of sleep and ADHD: suggested overlap in SNC systems and neurotransmission

It is worth to note that notwithstanding the great interest in sleep disorders affecting ADHD individuals, their impact on the severity of ADHD symptomatology and management of the disorder, the underlying mechanisms explaining such frequent overlapping conditions have not been clarified.

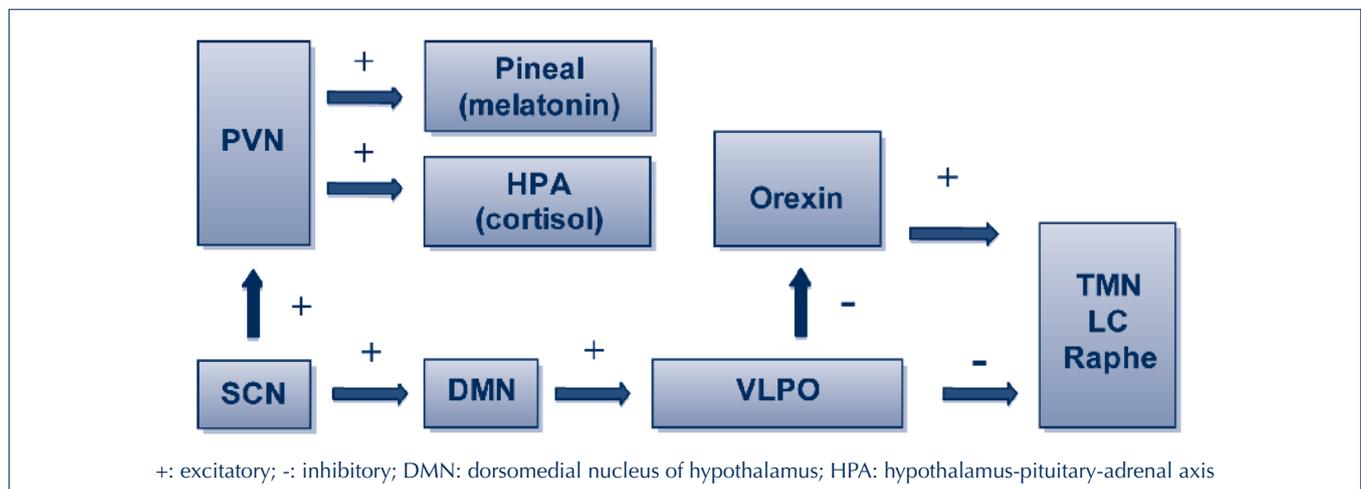
Data regarding the neuroanatomy of ADHD emphasise the role of a dysfunction in dorsolateral prefrontal (DLPFC) and dorsal anterior cingulate cortices (dACC), which are implicated in the neural circuitry underlying executive functioning. Other abnormalities have been found in the inferior parietal cortex and corticostriatal system¹⁹. Indeed, growing evidence from neuroimaging studies in the ADHD population shows the presence of alterations in the cortico-striatal network at the basis of the deficits in motor control, causing excessive moving or talking in subjects affected by the disorder¹⁹.

Sleep deprivation seems to affect the functional connectivity of prefrontal cortical areas²⁰, as well connectivity with subcortical areas²¹, with a reduction in functional connectivity between the thalamus and frontal and temporal gyri.

Cortese et al. (2008)¹² suggested disruptions in dopaminergic neurotransmission as a common brain dysfunction

at the basis of comorbid RLS and ADHD. Altered dopaminergic neurotransmission in people with ADHD has been found in the mid-brain, frontal and pre-frontal areas, whereas dopamine deficiency has been proposed in RLS²². As Owens suggested (2009)⁸, taking into account the interrelations between brain areas implicated in both ADHD and sleep disorders, it is very likely that disruption in one system may adversely affect the other. This consideration is not trivial, particularly for pharmacological management of adult ADHD. Dopamine is implicated in sleep disturbance, whereas noradrenaline plays a role in arousal. Acting by the synaptic release of dopamine and noradrenaline and by blocking their reuptake, stimulants have been considered a potential cause of insomnia and have been found to increase sleep-onset latency by more than 3-fold in children on treatment with methylphenidate, in respect with those on atomoxetine²³. However, data on adults show that methylphenidate has beneficial effects on sleep in adults with ADHD²⁴.

The findings regarding the absence of differences in sleep architecture between subjects with ADHD and controls²⁵, and of similar melatonin levels, activity and temperature parameters in people with and without ADHD¹⁸, demonstrate how challenging clarification of the intricate relationship between ADHD and sleep may be. The master clock of the circadian rhythms is housed in the suprachiasmatic nucleus of the anterior hypothalamus (SCN), a genetically based clock, which is reset by the day light cycle. The SCN drives other circadian rhythms such as that of melatonin and cortisol, a process mediated by the paraventricular nucleus at the tuberal hypothalamus (PVN). Another key brain structure for the sleep circuitry is the ventrolateral preoptic nucleus (VLPO), the neurons of which inhibit such neurons in the posterior hypothalamus as histaminergic neurons of the tuberomammillary nucleus (TMN), orexin neurons in the lateral hypothalamic area, glutamatergic neurons in the supramammillary region, serotonergic neurons at the mesencephalic raphe and noradrenergic neurons at the locus coeruleus (LC) that promote wakefulness^{26,27} as summarised in Figure 1. Sleep circadian rhythm disruption (SCRD) is a common dimension in severe psychiatric disorders such as bipolar disorder, schizophrenia and major depression, where 80% of patients report sleep abnormalities. Although ADHD has been associated with sleep abnormalities, the nature of the association between sleep and the pathophysiology of ADHD has not been clarified at a mechanistic level. At a circuitry level of explanation, there are a few studies in ADHD indicating that the circadian clock circuitry may be affected within the domains of melatonin, cortisol and consequently the HPA axis as well as dopamine (see Review by Coogan et al., 2016)²⁸. Furthermore, another vulnerable node of the circadian circuitry

**FIGURE 1.**

Diagrammatic representation of sleep circuitry. The suprachiasmatic nucleus (SCN) drives other circadian rhythms such as that of melatonin and cortisol, a process mediated by the paraventricular nucleus at the tuberal hypothalamus (PVN). Another key brain structure for the sleep circuitry is the ventrolateral preoptic nucleus (VLPO), the neurons of which inhibit such neurons in the posterior hypothalamus as histaminergic neurons of the tuberomammillary nucleus (TMN), orexin neurons in the lateral hypothalamic area, glutamatergic neurons in the supramammillary region, serotonergic neurons at the mesencephalic raphe and noradrenergic neurons at the locus coeruleus (LC) that promote wakefulness (from Saper, 2013; Rihel and Schier, 2013, mod.)^{26,27}.

in ADHD may be the noradrenergic system housed at the locus coeruleus in the midbrain.

Exploring the potential involvement of such brain circuits in adult ADHD is of great value, also considering evidence emerged from a recent study describing excessive daytime sleepiness in adults with ADHD associated to a great vulnerability to accidents, with the authors indicating the implication of dysregulation of waking system as more important than the typical lacking of attention of ADHD subjects in such adverse events²⁹.

Discussion

There is compelling evidence of the interrelation between symptoms of ADHD and disordered sleep. The increasing data show how individuals affected by both ADHD and a chronic sleep disorder are at risk of several health problems, such as mood disorders, obesity and cardiovascular disease, as well as diabetes and metabolic syndrome¹⁶. We believe that the investigation of the interplay between ADHD symptomatology, sleep difficulties and emotional dysregulation in adults with ADHD may provide important information regarding the potential existence of a different adult syndrome that is consistent with ADHD except for childhood onset³⁰⁻³¹. In fact, findings from Moffitt and colleagues (2015)³¹ demonstrated the existence of a substantial number of subjects who received a diagnosis of ADHD in adulthood and did not present signs of the disorder before age 12 years, and

without such neuropsychological deficits characterising those with a childhood onset.

Moreover, it has been pointed out that disrupted sleep in early stages of life can alter brain function by changes in the 5-HT system and in brain structures such as the dorsal striatum, ventral striatum and prefrontal cortex, causing dysfunctions affecting brain development³². Research reports an association between childhood sleeping disturbances and an increased risk for depression at 34 years old³³. In this context, the hypothesis of a common brain system underlying the relationship between ADHD, sleep, mood and emotion regulation finds support in recent data showing an association between depression and ADHD symptoms with a mediating effect on substance use³⁴. Such findings are also in line with previous research reporting sleep problems in ADHD due to comorbidities, such as affective disorders and substance abuse and dependency³⁵.

Because of the evidence regarding the occurrence of sleep problems in adults with ADHD, who frequently report a relevant emotional lability, along with the observation of the paucity of such data collected in adult population, our group is currently involved in a research exploring the clinical impact of sleep disturbances on emotional control and psychosocial impairment in individuals with ADHD, financed by the online crowdfunding platform for ADHD research ADHDFund.com (<http://www.adhdfund.com/en/>).

Not to forget that patients with ADHD have usually a poor

sleep hygiene, sometimes eating at bedtime, or chatting/using social networks until late at night, and we know that circadian clock may be influenced by several factors, such as light exposure, for late sleep timing^{17 18}.

Limitations of our study include the fact that the vast majority of findings differ according to the assessment tools used for evaluating sleep complaints. We know that studies reporting polysomnographic findings do not show consistent results²², and self-reported complaints in adults with ADHD seem to be more related to their frequent nocturnal awakenings, causing a subjective feeling of a poor sleep quality²².

However, there is no doubt about the deleterious impact that sleep deprivation may have on the quality of life of people affected by ADHD. For this reason, we would emphasise the importance of routine screening for the presence of a sleep disorder when assessing adult ADHD or during a follow-up for monitoring treatment response. Such clinical evaluation should take into account the individual's sleep habits, the presence of anxiety or mood disorder and the timing of medication.

A sleep diary and actigraphy may be useful tools for quantifying the variability of sleep patterns, and a polysomnography may be indicated if there are signs of OSA or RLS. Psychoeducation regarding sleep hygiene habits is suggested, and melatonin should also be considered because of its efficacy in reducing sleep onset delay associated or not with stimulant treatment. In light of recent evidence from anatomic and physiologic studies regarding the role of VLPO and its afferents in sleep promotion, further research may help us to define the potential utility of neuromodulation in treating disrupted circuits causing dysfunctional interactions between sleep, circadian and limbic factors, in people affected by ADHD.

Conclusion

ADHD is frequently associated with sleep disorders, and the relationship between such conditions is bidirectional, with several implications for clinical practice. Several studies support that poor sleep can worsen ADHD symptomatology, resulting in an increasing risk for accidents and health problems. Because of the overlapping symptomatology, clinicians should routinely screen for the presence of a sleep disorder when assessing ADHD or vice versa. The bidirectional relationship between ADHD and sleep also need to be considered when choosing for ADHD medications. Further studies should explore underlying neurobiological mechanisms that may account for the frequent co-occurrence of sleep disorders in people affected by ADHD in order to implement effective treatment for improving the quality of life of these patients, and blocking the negative spiral of events deter-

mined by the interaction between poor sleep and ADHD symptomatology.

Conflicts of interest

None.

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