Article

Sleep Disordered Breathing and Risk for ADHD: Review of Supportive Evidence and Proposed Underlying Mechanisms

Journal of Attention Disorders
1–13

DOI: 10.1177/10870547241232313
journals.sagepub.com/home/jad
Sage

Iliyan Ivanov[1], Ben Miraglia[2], Dana Prodanova[3], and Jeffrey H. Newcorn[1]

Abstract

Background: Accumulating evidence suggests that sleep disordered breathing (SDB) is under-recognized in youth and adults with ADHD. SDB may contribute to exacerbating pre-existing ADHD symptoms and may play a role in the development of cognitive deficits that may mimic ADHD symptoms. **Method:** We conducted a focused review of publications on cross-prevalence, overlapping clinical and neurobiological characteristics and possible mechanisms linking SDB and ADHD. **Results**: Exiting studies suggest that co-occurrence of SDB and ADHD is as high as 50%, with frequent overlap of clinical symptoms such as distractibility and inattention. Mechanisms linking these conditions may include hypoxia during sleep, sleep fragmentation and activation of inflammation, all of which may affect brain structure and physiology to produce disturbances in attention. **Conclusions:** The relationship between SDB and ADHD symptoms appear well-supported and suggests that more research is needed to better optimize procedures for SDB assessment in youth being evaluated and/or treated for ADHD. (*J. of Att. Dis. XXXX; XX(X) XX-XX*)

Keywords

ADHD, sleep disorders, sleep disordered breathing

Introductory Commentary

We are submitting this targeted review on sleep disordered breathing (SDB) and ADHD to the special issue in memory of Joseph Biederman. Joe was both a pioneer and champion of ADHD comorbidity. In addition, he was tireless in his pursuit of novel mechanisms driving the disorder. He also had a major interest in disorders that have shared underlying neurobiological mechanisms. This paper addresses all of these critical issues.

Introduction

The relationship between disordered sleep and symptoms of daytime fatigue, low motivation, and impaired cognition have long been recognized. Accordingly, many have suggested a possible link between sleep disorders and ADHD in both children and adults. By some estimates 25% to 50% of children with ADHD experience sleep issues (Wajszilber et al., 2018). Similar to adults, the top three sleep disorders found in children with ADHD are sleep disordered breathing (SDB), obstructive sleep apnea (OSA), and restless legs syndrome. Among these, SDB may have a particularly important role in relation to ADHD for the following reasons: first, there is accumulating evidence suggesting that SDB contributes to both exacerbation of pre-existing ADHD and even producing symptoms that mimic ADHD, and second, SDB seems to be highly prevalent among children with ADHD, and yet it appears to remain largely under-recognized.

This paper provides a focused review of the relationship between sleep disturbances and co-occurring ADHD, with a primary focus on SDB. First, we review literature on the relation between ADHD and current sleep disorder diagnoses such as obstructive sleep apnea (OSA) and restless legs syndrome, which have been extensively studied and described. Next we focus on a highly prevalent but less specifically described syndrome referred to as sleep disturbed breathing (SDB), which includes features such as snoring and sleep fragmentation due to fluctuations in oxygenation during sleep. SDB is not characterized by the full set of

[1]Icahn School of Medicine at Mount Sinai, NY, USA
[2]Private Practice, Mt Kisco, NY, USA
[3]Private Practice, New York, NY, USA

Corresponding Author:
Iliyan Ivanov, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, 1090 Amsterdam Avenue, 16th Floor, Ste F2, New York, NY 10025, USA.
Email: iliyan.ivanov@mssm.edu

symptoms and impairments seen in OSA, and is often under-recognized. Second, we review research that examines the possible mechanisms explaining the relationship between SDB and ADHD, drawing on theories that examine the connection between compromised blood oxygenation and the activation of immune and endocrine responses during sleep. Moreover, we introduce information that specifically examines (i) the available neurophysiological studies, utilizing EEG and neuroimaging, that further explain the possible connection between SDB and cognitive symptoms that may present as inattention and distractibility, thus mimicking ADHD, and (ii) the purported role of mouth breathing in the onset of SDB and related cognitive deficits. Lastly, we discuss directions for future research, some of which have not received much attention but may have potentially important clinical implications - including evaluation and treatment youth with ADHD symptoms.

Methods

This focused review examines selected published studies in the following areas: (1) cross-prevalence of OSA and SDB with ADHD; (2) the purported role of overlapping clinical and neurobiological characteristics that suggest a relationship between SDB and ADHD; and (3) possible mechanisms leading to increasing rates of SDB. As a first step we performed a computerized search to identify all relevant studies in PubMed from January 1980 to September 2022 using the following search terms: "obstructive sleep apnea," "sleep disturbed breathing," "dopamine," "norepinephrine," "neurotransmitters," "stimulant treatment," "ADHD symptoms," "neurocognition." Each of these search terms produced a list of studies that reported on the relationship between SDB/OSA and ADHD and possible underlying mechanisms linking these conditions. Note that this work builds on a series of hypotheses that have not been fully tested and described; hence, we were unable to conduct a meta-analysis or a systematic review. Rather, we conducted a targeted review of selected papers that suggest a possible role of SDB in relation to ADHD clinical presentations.

Prevalence and Co-occurrence of SDB/OSA and ADHD

The association between sleep problems and ADHD has been extensively researched, and the complexities of this relationship have been discussed in relation to potential common underlying neurobiological mechanisms and treatment strategies (Konofal et al., 2010; Owens et al., 2013; Stein et al., 2012). Accumulating evidence shows that disturbed breathing during sleep may start at a very early age—some have suggested that airways centered disorders leading to SDB may start at birth, particularly among premature babies (Huang & Guilleminault, 2012). One report found that in a cohort of 5-year old children ($n = 3,019$) SDB was present in 25% of the children, who were also reported to have significantly higher prevalence of problem behaviors (as per parental reports) including hyperactivity (OR: 2.5; 95% CI: 2.0–3.0), inattention (OR: 2.1; 95% CI: 1.7–2.6), and aggressiveness (OR: 2.1; 95% CI: 1.6–2.6, Gottlieb et al., 2003). One longitudinal study of over 8,000 infants found that 10% to 21% of children aged 6 to 81 months snored (Bonuk, 2012). In the latter study, 4% to 11% of the children were reported to have mouth breathing (Bonuck & Grant, 2012). Additionally, a survey of 20,000 participants in China found that 12% of the children snored (Li et al., 2010). Further, the 2020 National Sleep Foundation survey indicated that 19% of preschool children in the US snored a few times per week, and ~29% of these were reported to have difficulties waking up in the morning (Sleep Foundation, 2020).

Investigations using parental report have shown that a multiplicity of sleep disorders, including SDB, OSA, periodic limb movement disorder (PLMD), enuresis, and delayed sleep phase syndrome, have a high prevalence among youth with ADHD (Chervin et al., 2002; Constantin et al., 2015; Dillon et al., 2007; Johnson & Roth, 2006; O'Brien et al., 2003; Sangal et al., 2005; Sedky et al., 2014; Urbano et al., 2021; Wei et al., 2009). Similarly, elevated rates of hyperactivity, inattention and learning problems have been associated with OSA, restless legs syndrome (RLS), and periodic limb movements (PLMs) (Beebe & Gozal, 2002; Cervenka et al., 2006; Dillon et al., 2007; Lal et al., 2012; Philipsen et al., 2006; Sedky et al., 2014; Wei et al., 2009). One review indicated that attentional deficits are reported in up to 95% of patients with OSA, and OSA prevalence is as high as 20% to 30% in youth diagnosed with ADHD (Urbano et al., 2021). More importantly, untreated OSA has been associated with behavioral problems, growth and developmental delay, cardiovascular dysfunction, insulin resistance (Urbano et al., 2021) as well as obesity, poor academic performance, and disrupted parent-child interactions (Um et al., 2017). One meta-analysis (Sedky et al., 2014) examined data from 18 studies with 1113 children who were further divided into two clinical groups: children with sleep disturbed breathing (SDB; $n = 874$) who also were administered ADHD rating scales, and children diagnosed with ADHD ($n = 239$) who were administered polysomnography (PSG); both groups were compared to controls ($n = 1,405$). This research posed two main questions: (1) Is there a relationship between SDB and ADHD symptomatology and (2) Is there any difference between ADHD symptomatology pre- versus post adenotonsillectomy (AT)? The study results suggested that youth with SDB are at increased risk of presenting with symptoms of ADHD; the reported effect size of 0.57 suggests a medium relationship between SDB and ADHD symptoms. This meta-analysis also found a small to medium ES for improvement in ADHD symptoms following adenotonsillectomy (ES = 0.43). Further, results

from the large, prospective Tucson Children's Assessment of Sleep Apnea Study (TuCASA) of children 6 to 12 years of age (Budhiraja & Quan, 2009; Kaemingk et al., 2003) found an overall ES of 0.31 between respiratory disturbance index (high vs. low) and parent ratings of children's ADHD symptoms, further indicating a relationship between SDB and ADHD symptoms.

The observation that both ADHD and SDB have their onset in early childhood raises the question of whether the two conditions share underlying mechanisms or risk factors. For instance, some have hypothesized that the high prevalence of snoring and sleep problems in a subgroup of children with ADHD suggests a causative role of SDB in the development of ADHD symptoms (Chervin et al., 1997; O'Brien et al., 2004). One longitudinal study of 11,000 children followed for 6 years found that participants with SDB were 50% more likely to be diagnosed and treated for ADD/ADHD (Bonuck & Grant, 2012). A report from the American Sleep Apnea Association suggested that as many as 25% of children diagnosed with ADHD may actually have symptoms of OSA. Others have suggested that sleep problems associated with SDB/OSA should be more routinely investigated in the assessment of children with ADHD (Golan et al., 2004, Sedky et al., 2014), and that ruling out OSA as a possible etiology for apparent ADHD symptoms could improve differential diagnosis of ADHD (Yarlagadda et al., 2013).

Taken together, the existing epidemiologic and clinical reports show concordance in findings of high cross-prevalence between sleep disorders, particularly in youth, and the presence of ADHD or ADHD symptoms. Further, studies that document improvement of ADHD symptoms following surgical interventions provide indirect confirmation of the link between these conditions. Note that the methods of diagnosing both sleep disturbances and ADHD varied across studies. For the majority of the studies (with the exception of one report by Dillon et al. (2007) that used structured interviews), ADHD symptoms were assessed by parent, teacher, clinician ratings, or self-reports on validated ADHD questionnaires – but a formal diagnosis was not made. Similarly, the presence of sleep disturbances was predominantly determined via parental reports on sleep questionnaires, though a few studies conducted more rigorous assessment using polysomnography (e.g., Dillon et al., 2007; Surman et al., 2006).

Differences in assessment methods which result in imprecise diagnoses (Hvolby, 2015) highlight the importance of distinguishing between OSA and SDB. OSA is a specific sleep disorder diagnosed by polysomnography, which is infrequently occurring in children. In contrast, SDB is much more common, but also more challenging to identify accurately, as it mainly relies on parental reports. One pilot study in adults suggests that polysomnography can document objective evidence for breathing related disorders in some adults with ADHD (Surman et al., 2006); no comparable research on the potential utility of polysomnography in children with ADHD is currently available. Existing reports show that approximately 70% of children with SDB are also diagnosed with primary snoring (Biggs et al., 2014). Prior assumptions that primary snoring is a benign feature of SDB have been challenged by research by O'Brien et al. (2004), showing a significant association between snoring and behavioral deficits in some children. It has also been suggested that SDB involves a switch from nasal to oral breathing, ineffective oxygen exchange, reduction of blood carbon dioxide and nitric oxide levels, and disturbances in sleep architecture, and that these SDB-related physiological abnormalities have negative effects on neurocognition (Pizza et al., 2010; Sano et al., 2013). Therefore, SDB can either worsen existing ADHD symptoms or even play a causative role in the development of ADHD-like symptoms. Related to these hypotheses is the question: what possible brain related mechanisms may underlie the frequent co-occurrence of ADHD and SDB/OSA?

Hypothesized Mechanisms for the Association of SDB/OSA and ADHD

Research examining the relationship between SDB/OSA and ADHD has resulted in the elaboration of different theoretical models. Several studies have examined the hypothesis that fluctuating levels of hypoxia and hypercapnia during the night hours may affect brain functions related to attention and working memory. Hypoxemia, in particular, has been found to strongly contribute to poor performance on some attentional tests among patients with OSA (Bucks et al., 2013; Shpirer et al., 2012). The proposed rationale for this association is that hypoxia/hypercapnia may lead to oxidative stress, with increased release of free radicals and inflammatory cytokines such as C-reactive protein, interleukin-6 and tumor necrotizing factor alpha. Increased levels of these neurochemicals can in turn induce systemic inflammation and oxidative damage causing endothelial dysfunction (Kheirandish-Gozal & Gozal, 2019; Unnikrishnan et al., 2015). This may subsequently lead to a disruption of the blood brain barrier through alterations in the permeability of small vessels. Accordingly, the genes regulating tumor necrosis factor-alpha, C-reactive protein, interleukin-6 (IL-6) have been proposed as candidate genes for susceptibility to the inflammatory effects of nighttime hypoxia/hypercapnia (Gozal et al., 2012). In this model, individuals with SDB/OSA, who also have a particular genetic profile, might be more likely to develop ADHD-like symptoms, possibly related to the effects of night-time hypoxia/hypercapnia on inflammation. This proposed mechanism linking SDB/OSA and ADHD remains theoretical; more research is needed to test this hypothesis.

Another model posits that SDB/OSA frequently leads to sleep fragmentation and micro-awakenings during nighttime, which along with hypoxia may cause fatigue, exhaustion and excessive daytime sleepiness (Lal et al., 2021). One study (Djonlagic et al., 2012) found that sleep fragmentation due to OSA can negatively affect learning during a motor sequence learning task. This has led some to suggest that minimizing arousals during sleep may be essential for optimal memory consolidation. Further, children with sleep fragmentation may experience daytime sleepiness that is in turn associated with behavioral dysregulation, altered neurocognitive functions involving the prefrontal cortex (e.g., attention, working memory, and other executive functions) and may have a direct impact on mood, leading to affective symptoms (e.g., irritability, decreased positive mood) associated with ADHD (Fallone et al., 2002). In short, sleep problems may mimic ADHD symptomatology, may exacerbate existing ADHD symptoms and may by themselves be associated with or exacerbated by ADHD (Owens, 2005).

Other research has examined possible abnormalities in brain anatomy and physiology in individuals with SDB/OSA and comorbid ADHD (see Table 1). Several studies have utilized EEG to examine patterns of neural activation in central and temporal brain areas in association with impaired neurocognitive performance on an oddball attention task (Barnes et al., 2012), as well as altered P300 measures in association with deficits in sustained attention and learning capacity in patients with OSA (Henriques-Filho et al., 2013). These findings provide preliminary evidence of associations between neurophysiological dysfunctions, attentional processes and OSA. One structural magnetic resonance imaging (MRI) study reported regional gray matter reduction in the bilateral parahippocampus and right superior frontal and left middle temporal gyri in patients with OSA (Weng et al., 2014). Further, one systematic review documented altered resting state activation, and in particular, significant deficits in spontaneous activation in the default mode network (DMN) areas in OSA (Khazaie et al., 2017). In addition, two studies on the effect of total or partial sleep deprivation on functional connectivity found that sleep deprivation reduced resting functional connectivity within the DMN and between the DMN and its anticorrelated network, further suggesting that reduced brain functional connectivity may be a precursor to behavioral impairments from sleep loss (De Havas et al., 2012; Sämann et al., 2010).

A number of functional MRI studies have investigated the effects of acute, total or partial sleep deprivation on brain activation during performance on a broad range of neurocognitive tasks, including arithmetic calculation (Drummond et al., 1999), attention (Chee et al., 2011; Czisch et al., 2012; Jackson et al., 2011; Kong et al., 2012; Lim et al., 2010; Muto et al., 2012), decision making (Libedinsky et al., 2011; Venkatraman et al., 2011), emotional processing (Yoo et al., 2007), inhibitory control (Y. M. L. Chuah et al., 2006; L. Y. Chuah et al., 2010) and working memory tasks (Lim et al., 2007; Lythe et al., 2012). These studies have documented reduced overall activation after total sleep deprivation, and more specifically, reduced frontoparietal activation during lapses on a visual selective attention task (Khazaie et al., 2017). Consistent with this, PET studies of sleep deprivation have reported significant reductions in metabolic rates in the thalamic, parietal, and prefrontal regions after sleep loss, which correlated with declines in cognitive performance and alertness (Thomas et al., 2000, 2003). Finally, one study used arterial spin labeling (ASL) to measure resting cerebral blood flow (CBF) changes after one night of sleep restriction., finding significantly reduced frontoparietal CBF following sleep loss, but only in participants with significant signs of drowsiness (Poudel et al., 2012). The findings that non-drowsy participants maintained normal CBF in the frontoparietal regions and increased CBF in basal forebrain and cingulate regions also suggests a potential neurobiological mechanism to compensate for drowsiness after sleep loss.

There is emerging neurophysiological research examining the effects of mouth breathing (as seen in SDB) versus nasal breathing on brain functions. One study (Zelano et al., 2016) examined the relationship between type of breathing and brain activity indexed by cortical and intracranial EEG, finding that transition from nasal to oral breathing was associated with disorganization of limbic oscillatory synchrony between the prefrontal cortex and the amygdala and hippocampus. Additional findings indicated that the switch from nasal to oral breathing disrupted the emergence of cross-frequency coupling between theta phase and beta amplitude in the prefrontal cortex. The authors hypothesized that nasal breathing drives respiratory phase-locked oscillations and their coupling to higher-frequency rhythms, and may serve as a common "clock" to organize spatiotemporal excitability broadly throughout the brain (Fontanini & Bower, 2006; Ito et al., 2014; Kay, 2005; Moore et al., 2013; Yanovsky et al., 2014). Of note, cognitive performance on selected tasks significantly declined during oral breathing, while nasal breathing selectively enhanced the reaction times on tasks requiring recognition of fearful stimuli and the accuracy of visual object recognition tasks. The novel aspect of these results is the implication that the nasal route of respiration serves as an entry point to limbic brain areas for modulating cognitive function related to emotion discrimination and recognition memory. It has been shown that humans alter their respiratory patterns in response to emotional stimuli (Boiten, 1998) and during cognitive effort and attention tasks (Evans et al., 2009; Huijbers et al., 2014; Vlemincx et al., 2011). Consequently, the above findings suggest that rather than being a passive target of heightened arousal or vigilance, natural nasal breathing may play a role

Table 1. Summary of Neurophysiological Studies Including EEG and Functional Neuroimaging Documenting the Effects of SD on Brain Physiology.

Authors	Title	Design	Results
Barnes et al., Sleep Medicine 2012	Attention in children with obstructive sleep apnea: An event-related potentials study.	28 children (14 OSA/ 14 controls) ages 4 to 8 underwent overnight sleep studies including event-related potentials (ERPs) during oddball attention task.	OSA children exhibited both significantly altered ERP patterns of neural activation and impaired neurocognitive performance compared to controls.
Henriques et al., Sleep Medicine 2013	Obstructive sleep apnea and P300 abnormalities in children with attention deficit.	80 children (49 boys/ 31 girls) ages 6 to 17 with attention problems as per school underwent overnight polysomnography and P300 evoked potential test. Of the 61 children with abnormalities at P300 tests, 26 met both OSA and ADHD dx criteria.19 participants had no altered results and composed the control group	The study provides evidence of the relationship between OSA and abnormal P300 evoked potentials' amplitudes and latencies, suggesting that sleep disturbances might disrupt sustaining attention abilities leading to school complaints of learning capacity.
Sämann et al., MAGMA 2010	Increased sleep pressure reduces resting state functional connectivity.	16 adult volunteers underwent 6-minute echoplanar imaging time series during rested wakefulness (RW) after normal sleep and after Partial Sleep Deprivation (PSD) conditions.	PSD condition was associated with focal reductions of auto-correlation strength in connectivity of the posterior and anterior midline node of the Default Mode Network (DMN) and in the lateral parietal and insular nodes of the Anti-correlated Network (ACN).
De Havas et al., Neuroimage 2012	Sleep deprivation reduces default mode network connectivity and anti-correlation during rest and task performance.	26 adult volunteers underwent fMRI during RW after a normal night of sleep and then after approximately 24hr of total SD.	SD was associated with significant selective reductions in DMN functional connectivity and DMN-ACN anti-correlation, suggesting that SD induces a robust alteration in the intrinsic connectivity within and between these networks.
Drummond et al., Neuroreport 1999	Sleep deprivation-induced reduction in cortical functional response to serial subtraction.	13 adult volunteers underwent fMRI during arithmetic test after a normal night of sleep and a night of SD in order to test whether the prefrontal cortex (PFC) and the parietal lobe arithmetic areas are vulnerable to the effects of SD	SD condition was associated with decreased activation in bilateral PFC, parietal lobes and premotor areas, which correlated with worse test performance.
Chee et al., Neuroimage 2011	Effects of sleep deprivation on cortical activation during directed attention in the absence and presence of visual stimuli.	12 adult volunteers underwent fMRI during attention tasks after a night of normal sleep and a night of SD. Baseline signal elevations evoked by preparatory attention in the absence of visual stimulation were attenuated within right frontal eye field (FEF), right intraparietal sulcus (IPS) and all retinotopically mapped visual areas during SD, indicative of impaired endogenous attention.	SD condition was associated with attenuated activation in the preparatory period prior to stimulus appearance within rFEF, rIPS and all retinotopically mapped visual areas as well as attenuation of stimulus-related activation in higher visual and fronto-parietal cortices.
Lim et al., PLoS One 2010	Sleep deprivation impairs object-selective attention: a view from the ventral visual cortex.	23 adult volunteers underwent fMRI after a normal night of sleep and a night of SD while performing a selective attention task, containing pictures of houses or faces.	SD condition was associated with less accurate detection of target pictures and with a significant decrement in functional connectivity between the parahippocampal place area (PPA) and two cognitive control areas, the left intraparietal sulcus and the left inferior frontal lobe.
Jackson et al. Brain Imaging Behav 2011	The effect of sleep deprivation on BOLD activity elicited by a divided attention task.	12 adult volunteers underwent fMRI after 27hr of SD and after a normal night of sleep while performing a cross-modal divided attention task (visual and auditory).	SD condition was associated with subjects' reports of feeling significantly more sleepy and with a trend toward poorer task performance. SD was also associated with reduced activation in the left superior frontal gyrus, possibly reflecting an attenuation of top-down control mechanisms on the attentional system.

(continued)

Table 1. (continued)

Authors	Title	Design	Results
Kong et al., Neuroimage 2012	Functional imaging correlates of impaired distractor suppression following sleep deprivation	22 adult volunteers underwent fMRI after well-reseated and SD conditions while performing an attention task requiring to either attend to pictures of houses or to ignore them (when attending to faces) while viewing superimposed face-house pictures. MR signal enhancement and suppression in the PPA were determined relative to a passive viewing control condition.	SD was associated with lower PPA activation across conditions. Critically SD specifically impaired distractor suppression in selective attention, leaving target enhancement relatively preserved. A post-experiment test of recognition memory showed that attended houses were not significantly better recognized than ignored houses in the SD condition; in contrast, well-rested condition was associated with superior recognition of attended houses.
Czisch et al., Front Neurol 2012	On the need of objective vigilance monitoring: effects of sleep loss on target detection and task-negative activity using combined EEG/ fMRI.	20 adult volunteers underwent simultaneous EEG and fMRI after 36 hr of total sleep deprivation (TSD) vs well-rested night during an acoustic oddball task, with the ability to isolate runs with objective EEG signs of high (SD_{alert}) or reduced (SD_{sleepy}) vigilance.	TSD was associated altered task-negative activity in the right posterior node of the default mode network while in the SD_{alert} condition the task-related activity appears to be sustained by compensatory co-activation of insular regions. In the SD_{sleepy} condition, the task-positive activity was massively impaired, but task-negative activation was showing levels comparable with the control condition after a well-rested night.
Muto et al., J Sleep Res 2012	Influence of acute sleep loss on the neural correlates of alerting, orientating and executive attention components	12 adult volunteers underwent fMRI after TSD and a normal night sleep (RW) while performing the Attention Network Task (ANT).	TSD was associated with a global increase in reaction times, which did not affect specifically any of the three attention effects. Brain responses associated with the alerting effect did not differ between RW and TSD. Higher-order attention components (orientating and conflict effects) were associated with significantly larger thalamic responses during SD than during RW.
Venkatraman et al., J Neuroscience 2011	Sleep deprivation biases the neural mechanisms underlying economic preferences	29 adult volunteers underwent fMRI during a rested wakefulness (RW) and SD conditions while performing three different tasks. First task had six runs of a risky decision-making gambling task, second task was a Counting Stroop task and third, participants watched passively while a subset of modified gambles from the decision runs was resolved to gains and losses during a single outcome run, lasting 7 min.	SDS was associated with reduced activation of bilateral intraparietal sulci, and increased activation in ventro-medial PFC and right thalamus; additionally SD shifted most persons' bias from avoiding loss to pursuing gain. This behavioral change accompanied congruent alterations of activation in brain regions associated with reward anticipation and emotional processing.
Libedinsky et al. Front Behav Neuroscience 2011	Sleep deprivation alters valuation signals in the ventromedial prefrontal cortex	22 adult volunteers underwent fMRI in RW ad SD conditions while performing the Incentive Delay and Economic Exchange tasks.	SD was associated with alteration in decision value signals in ventro-medial PFC. These alterations appear to be accounted by neural changes in processes underlying the valuation of the receipt of social rewards during the Economic Exchange task. These effects of SD on economic preferences were uncorrelated with its effects on vigilance.
Yoo et al., Curr Biology 2007	The human emotional brain without sleep—a prefrontal amygdale disconnect	26 adult volunteers were divided in SD ($n = 14$) and sleep-control ($n = 12$) groups. All participants underwent fMRI scan during emotional stimulus viewing task.	SD condition was associated with an amplified, hyper-limbic response by the human amygdala to negative emotional stimuli under conditions of sleep deprivation. Furthermore, this increased magnitude of limbic activity was associated with a loss of functional connectivity with the medial PFC in the sleep-deprivation group; suggesting a failure of top-down, prefrontal control.
Chuah et al., J Neuroscience 2006	The neural basis of inter-individual variability in inhibitory efficiency after sleep deprivation	27 adult volunteers underwent fMRI scan in SD and RW conditions while performing a Go/No-Go task.	SD was associated with decreased go/no-go task-related activation of the ventral and anterior prefrontal cortex (PFC) bilaterally.

(continued)

Table 1. (continued)

Authors	Title	Design	Results
Lim et al., Sleep 2007	Reproducibility of changes in behavior and f MRI activation associated with sleep deprivation in a working memory task	19 adult volunteers underwent fMRI scans in SD and RW conditions while performing a working memory task.	SD was associated with decreased activation in bilateral parietal regions. The activation decrease in the left parietal region was correlated with changes in in the intra individual variability of reaction times, which was interpreted as the most robust marker of vulnerability in SD.
Chuah et al., Sleep 2010	Sleep deprivation and interference by emotional distracters	24 adult volunteers underwent fMRI in SD and RW conditions while performing a delayed-response working memory task *with 2 distracters;* highly arousing, negative emotional scenes and low-arousing, neutral scenes.	Increased distraction by emotional stimuli following sleep deprivation is accompanied by increases in amygdala activation and reduced functional connectivity between the amygdala and prefrontal cognitive control regions.
Lythe et al., Behav Brain Research 2012	Frontal and parietal activity after sleep deprivation is dependent on task difficulty and can be predicted by the f MRI response after normal sleep	20 adult male volunteers underwent fMRI in SD and RW conditions performing an n-back working memory task.	SD was associated with decreased activation in the right ventrolateral prefrontal cortex during the most difficult working memory load and with increased activation in the right inferior parietal lobe activity during the simplest working memory load.
Thomas et al. J Sleep Res. 2000	Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 hr of sleep deprivation on waking human regional brain activity	17 adult volunteers were scanned during 85 hr of sleep deprivation using positron emission tomography (PET) and (18)Fluorine-2-deoxyglucose ((18)FDG), a marker for regional cerebral metabolic rate for glucose (CMRglu) and neuronal synaptic activity. Subjects were scanned prior to and at 24 hr intervals during the sleep deprivation period, for a total of four scans per subject. During each 30 min (18)FDG uptake, subjects performed a sleep deprivation-sensitive Serial Addition/Subtraction task	SD at 24 hr was associated with significant decrease in global CMRglu, and significant decreases in absolute regional CMRglu in the thalamus and prefrontal and posterior parietal cortices.
Thomas et al., Thalamus Relat Systems 2003	Neural basis of alertness and cognitive performance impairments during sleepiness II. Effects of 48 and 72 hr of sleep deprivation on waking human regional brain activity	17 young, normal, healthy male volunteers were scanned using PET and 18Fluoro-2-deoxyglucose (18FDG) during complex cognitive task.	SD at 48 and 72 hr was associated with absolute and relative regional CMRglu decreased in the prefrontal and parietal cortices and in the thalamus. Compared to 24 hr SD, relative regional CMRglu decreased further in the prefrontal cortex and dorsal thalamus at 48 and 72 hr. Relative regional CMRglu increased in lateral superior occipital cortices, lingual and fusiform gyri, anterior cerebellum, and supplementary and primary motor cortices at 48 and 72 hr SD, indicating a rebound CMRglu activity response from 24 hr SD.
Poudel et al., Sleep 2012	Cerebral perfusion differences between drowsy and non-drowsy individuals following acute sleep restriction	20 adult volunteers underwent arterial spin labeling (ASL) scanning after SD and RW. Participants were also rated for visual signs of drowsiness in the eye-video recorded during the scan.	SD was associated with reduction in CBF in the right-lateralized fronto-parietal attentional network, which was largely driven by participants who showed strong signs of drowsiness in the eye-video after sleep restriction.

OSA = Obstructive sleep apnea; ERPs = event-related potentials; SD = sleep deprivation; RW = rested wakefulness; FEF = frontal eye field; IPS = intraparietal sulcus; PFC = prefrontal cortex; PET = positron emission tomography; CMRglu = cerebral metabolic rate for glucose.

in optimizing information processing in brain areas associated with attention and goal-directed behaviors.

There are several limitations to the human neuroimaging research in this area. Few neuroimaging studies have examined either the time-of-day during which imaging data are obtained, or circadian phase effects of sleep deprivation on brain activation. Also, the available reports are predominantly from adult samples: however, it stands to reason to suggest that these abnormalities in brain functions might also contribute to problems in attention and behavior in children with SDB. Lastly, several imaging techniques used in adults (e.g., PET) are unsuitable for studies in children. Moreover, the potential utility of PET imaging is limited due not only to invasiveness of the procedure, but also the rapid decay of radioactive tracers. The above limitations notwithstanding, there is accumulating evidence that common underlying neurobiological mechanisms may explain the link between SDB/OSA and daytime cognitive symptoms that may either mimic ADHD or exacerbate preexisting ADHD symptomatology.

Taken together, we can conclude that there is a preponderance of evidence to support the notion that SDB is associated with physiological processes, including activation of stress hormones and immunologic responses that produce fluctuations in blood oxygenation during sleep that in turn appears to affect brain regions associated with attention and other executive functions. These effects seem to compromise brain physiology in those regions and cause cognitive deficits consistent with ADHD symptoms. Although the preponderance of findings come from experimental studies in adults (See Table 1) these reports suggest that unrecognized sleep problems in young children may produce deficits misdiagnosed as ADHD.

SDB in Children – A Novel Etiological Perspective

While most of the research on the reciprocal high rates of SDB/OSA in ADHD (and vice versa) has examined mechanisms linking the effects of SDB/OSA to blood oxygenation, sleep disturbances and brain functions, other research has examined the possible contribution of changes in human facial anatomy to SDB. These anatomical changes include underdeveloped mandible and maxilla structure, resulting in narrowing of the nasal cavity and leading to compensatory mouth breathing; the over-reliance on mouth breathing affects both the quality of breathed air and sleep architecture. Abnormalities in the growth of the facial bone structures contribute to compromised airflow through the upper respiratory system via four different mechanisms. First, a narrow and vaulted maxilla results in a smaller nasal cavity, as the maxilla makes up the floor and lateral walls of the nasal cavity. The rising vault and collapsing lateral walls reduce/narrow the nasal cavity and introduce nasal airflow resistance. Second, as the maxilla forms the anterior wall of the nasopharynx, it follows that the underdeveloped maxilla with its lack of forward growth will result in a narrow nasopharynx. Third, the lack of forward maxillary growth forces an under-developed mandible to land behind it during mouth closure. In other words, the maxilla dictates where the mandible can land during mouth closure, which also forces the tongue backwards. The posterior displacement of the tongue results in a narrower oropharynx. Fourth, underdeveloped maxilla and mandible lead to reduced oral cavity volume, resulting in further posterior displacement of the tongue and the narrowing of the oropharynx. Overall, there is evidence that the obstruction of the upper airways is affecting the quality of sleep and contributes to the development of SDB (Kim et al., 2013).

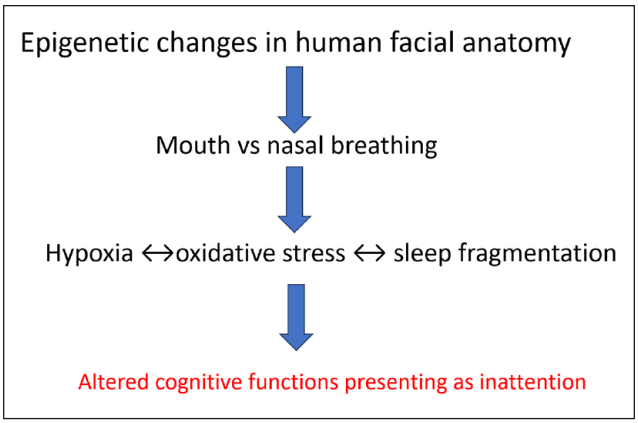

Figure 1. Model for the proposed relationship between epigenetic changes in human facial anatomy possibly leading to the development of compromised breathing and alteration sin attention.

It has also been suggested that environmental factors, such as the introduction of pre-processed soft foods and expanding consumption of refined foods in early life, are related to the etiology of malocclusion in industrialized humans, which could lead to abnormal facial anatomy impacting nasal airflow, and thereby SDB (Ciochon et al., 1997; also see Figure 1). Changes in facial bone anatomy lead to compensatory mouth breathing, which in turn has several clinically relevant consequences (Jefferson, 2010). Mouth breathing causes inflammation and enlargement of the adenoids, thus further worsening airway obstruction. In cases where the adenoids have been removed, mouth breathing may contribute to re-occurrence of the obstruction. Another important consequence of mouth breathing is its effect on the quality of breathed air. As nasal breathing facilitates optimal oxygen absorption by humidifying, filtering and warming up the inhaled air, mouth breathing cannot perform those functions. Further, nasal breathing results in nitric oxide release from the paranasal sinuses into the inhaled air (J. O. Lundberg, 2008). Among its

many functions, nitric oxide has antibacterial, antiviral, antifungal, as well as vasodilation effects (J. O. N. Lundberg & Weitzberg, 1999; Swift et al., 1988; Törnberg et al., 2002). In contrast, mouth breathing does not produce nitric oxide release into the breathed air, which results in a weaker immune response to inhaled pathogens as well as vasoconstriction. Mouth breathing also is excessive and, similar to hyperventilation, may result in lower carbon dioxide (a vasodilator) concentration in the blood, which in addition to the lack of nitric oxide in breathed air may result in increased heart rate and blood pressure (Juliano et al., 2009; Trabalon & Schaal, 2012). Lastly, compensatory mouth breathing is associated with elongation of the face, giving mouth breathers recognizable facial features (Huang & Guilleminault, 2012; Huynh et al., 2013; Jefferson, 2010). While these facial characteristics can be useful to identify individuals with predominant mouth breathing, the development of SDB-related facial characteristics may happen long after the negative physiological and other consequences of abnormal breathing have developed.

Summary and Future Directions

In this focused review, we discussed novel considerations regarding the relationship between SDB and ADHD, emphasizing emerging evidence that, despite being highly prevalent, SDB may remain unrecognized and thus contribute to either exacerbation of already existing ADHD symptoms or the development of symptoms that mimic ADHD (Knight & Dimitriou, 2019). Accumulating evidence on possible neurophysiological mechanisms that may link SDB to the development of ADHD-like symptoms further supports the recommendation that SDB should be considered in the initial assessment of young children exhibiting inattention, daytime fatigue and distractibility. While SDB and ADHD are not mutually exclusive, their comorbidity can influence the severity of each condition. Consequently, there is a need for more targeted assessment of possible sleep disturbances in children evaluated for ADHD. For instance, novel methods for screening for SDB with the use of take-home devices, some currently FDA approved for use in children, can aid in differential diagnosis. This should make screening for sleep problems much more palatable and decrease the need for referral to a sleep lab.

In the context of the above discussion, it is important to consider that treatments for ADHD may be inadequate in cases where ADHD symptoms might be mimicked or exacerbated by unrecognized SDB. Further, while the use of stimulants may be partially effective it may also exacerbate sleep disturbances associated with SDB. It is possible that in some cases, the correction of SDB and associated neurocognitive sequelae may eliminate the need for pharmacotherapy altogether, or require appropriate dose adjustments. Further, novel methods for screening for SDB with the use of take-home devices, some currently FDA-approved for use in children, can facilitate the implementation of procedures for wider use and early detection of SDB without the burden associated with studies conducted in dedicated sleep labs. Lastly, while adenotonsilectomy is considered a gold standard for the treatment of childhood OSA, new techniques for the correction of nasal narrowing and mouth breathing in children with SDB exist that are less invasive and may produce compatible and sustainable results (Ngiam & Cistulli, 2015).

Taken together, there is expanding evidence regarding the relationship between SDB and ADHD symptoms in children, as well as the availability of newly developed methods for early diagnosis and possible non-invasive treatments. These new data necessitate the development of algorithms for comprehensive assessment and more individualized treatments for ADHD in the context of SDB.

Acknowledgments

None

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Iliyan Ivanov – no conflicts. Ben Miraglia – no conflicts. Dana Prodanova – no conflicts. Jeffrey Newcorn – in the last three years J.H.N. was a consultant/advisory board member for Adlon Therapeutics, Cingulate Therapeutics, Corium, Hippo T&C, Ironshore, Lumos, Medice, MindTension, Myriad, NLS, OnDosis, Otsuka, Rhodes, Shire/Takeda, Signant and Supernus; he received research support from Adlon, Otsuka, Shire, Supernus; honoraria for disease state lectures from Otsuka and Shire, and served as a consultant for the US National Football League.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The research for this publication has been supported by R21DA046029 and R21DA045218 grants to Drs. Ivanov and Newcorn from NIDA.

ORCID iD

Iliyan Ivanov https://orcid.org/0000-0003-4340-6695

References

Barnes, M. E., Gozal, D., & Molfese, D. L. (2012). Attention in children with obstructive sleep apnoea: An event-related potentials study. *Sleep Medicine*, *13*(4), 368–377.

Beebe, D. W., & Gozal, D. (2002). Obstructive sleep apnea and the prefrontal cortex: Towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. *Journal of Sleep Research*, *11*(1), 1–16.

Biggs, S. N., Nixon, G. M., & Horne, R. S. (2014). The conundrum of primary snoring in children: What are we missing

in regards to cognitive and behavioural morbidity? *Sleep Medicine Reviews*, *18*(6), 463–475. https://doi.org/10.1016/j.smrv.2014.06.009

Boiten, F. A. (1998). The effects of emotional behaviour on components of the respiratory cycle. *Biological Psychology*, *49*, 29–51. https://doi.org/10.1016/S0301-0511(98)00025-8,pmid:9792483

Bonuck, K., & Grant, R. (2012). Sleep problems and early developmental delay: Implications for early intervention programs. *Intellectual and Developmental Disabilities*, *50*(1), 41–52. https://doi.org/10.1352/1934-9556-50.1.41

Bonuk, K. (2012). Sleep-disordered breathing in a population-based cohort: Behavioral outcomes at 4 and 7 years. *Pediatrics*, *129*(4), e857–e865.

Bucks, R. S., Olaithe, M., & Eastwood, P. (2013). Neurocognitive function in obstructive sleep apnoea: A meta-review. *Respirology*, *18*, 61–70. https://doi.org/10.1111/j.1440-1843.2012.02255.x

Budhiraja, R., & Quan, S. F. (2009). Outcomes from the Tucson Children's assessment of Sleep Apnea Study (TuCASA). *Sleep Medicine Clinics*, *4*(1), 9–18. https://doi.org/10.1016/j.jsmc.2008.11.002

Cervenka, S., Pålhagen, S. E., & Comley, R. A. (2006). Support for dopaminergic hypoactivity in restless legs syndrome: A PET study on d2-receptor binding. *Brain*, *129*(8), 2017–2028.

Chee, M. W., Goh, C. S., Namburi, P., Parimal, S., Seidl, K. N., & Kastner, S. (2011). Effects of sleep deprivation on cortical activation during directed attention in the absence and presence of visual stimuli. *NeuroImage*, *58*, 595–604.

Chervin, R. D., Archbold, K. H., Dillon, J. E., Panahi, P., Pituch, K. J., Dahl, R. E., & Guilleminault, C. (2002). Inattention, hyperactivity, and symptoms of sleep-disordered breathing. *Pediatrics*, *109*(3), 449–456.

Chervin, R. D., Dillon, J. E., Bassetti, C., Ganoczy, D. A., & Pituch, K. J. (1997). Symptoms of sleep disorders, inattention, and hyperactivity in children. *Sleep*, *20*(12), 1185–1192. https://doi.org/10.1093/sleep/20.12.1185

Chuah, L. Y., Dolcos, F., Chen, A. K., Zheng, H., Parimal, S., & Chee, M. W. (2010). Sleep deprivation and interference by emotional distracters. *Sleep*, *33*, 1305–1313.

Chuah, Y. M. L., Venkatraman, V., Dinges, D. F., & Chee, M. W. L. (2006). The neural basis of inter-individual variability in inhibitory efficiency after sleep deprivation. *Journal of Neuroscience*, *26*, 7156–7162.

Ciochon, R. L., Nisbett, R. A., & Corruccini, R. S. (1997). Dietary consistency and craniofacial development related to masticatory function in minipigs. *Journal of Craniofacial Genetics and Developmental Biology*, *17*, 96–102.

Constantin, E., Low, N. C., Dugas, E., Karp, I., & O'Loughlin, J. (2015). Association between childhood sleep-disordered breathing and disruptive behavior disorders in childhood and adolescence. *Behavioral Sleep Medicine*, *13*(6), 442–454.

Czisch, M., Wehrle, R., Harsay, H. A., Wetter, T. C., Holsboer, F., Sämann, P. G., & Drummond, S. P. (2012). On the need of objective vigilance monitoring: Effects of sleep loss on target detection and task-negative activity using combined EEG/fMRI. *Frontiers in Neurology*, *3*, 67.

De Havas, J. A., Parimal, S., Soon, C. S., & Chee, M. W. (2012). Sleep deprivation reduces default mode network connectivity and anti-correlation during rest and task performance. *NeuroImage*, *59*, 1745–1751.

Dillon, J. E., Blunden, S., Ruzicka, D. L., Guire, K. E., Champine, D., Weatherly, R. A., Hodges, E. K., Giordani, B. J., & Chervin, R. D. (2007). DSM-IV diagnoses and obstructive sleep apnea in children before and 1 year after adenotonsillectomy. *Journal of the American Academy of Child and Adolescent Psychiatry*, *46*(11), 1425–1436. https://doi.org/10.1097/chi.0b013e31814b8eb2

Djonlagic, I., Saboisky, J., Carusona, A., Stickgold, R., & Malhotra, A. (2012). Increased sleep fragmentation leads to impaired off-line consolidation of motor memories in humans. *Plos One*, *7*. https://doi.org/10.1371/journal.pone.0034106

Drummond, S. P., Brown, G. G., Stricker, J. L., Buxton, R. B., Wong, E. C., & Gillin, J. C. (1999). Sleep deprivation-induced reduction in cortical functional response to serial subtraction. *Neuroreport*, *10*, 3745–3748.

Evans, K. C., Dougherty, D. D., Schmid, A. M., Scannell, E., McCallister, A., Benson, H., Dusek, J. A., & Lazar, S. W. (2009). Modulation of spontaneous breathing via limbic/paralimbic-bulbar circuitry: An event-related FMRI study. *NeuroImage*, *47*, 961–971. https://doi.org/10.1016/j.neuroimage.2009.05.025

Fallone, G., Owens, J. A., & Deane, J. (2002). Sleepiness in children and adolescents: Clinical implications. *Sleep Medicine Reviews*, *6*, 287–306.

Fontanini, A., & Bower, J. M. (2006). Slow-waves in the olfactory system: An olfactory perspective on cortical rhythms. *Trends in Neurosciences*, *29*, 429–437. https://doi.org/10.1016/j.tins.2006.06.013,pmid:16842864

Golan, N., Shahar, E., Ravid, S., & Pillar, G. (2004). Sleep disorders and daytime sleepiness in children with attention-deficit/hyperactive disorder. *Sleep*, *27*(2), 261–266. https://doi.org/10.1093/sleep/27.2.261

Gottlieb, D. J., Vezina, R. M., Chase, C., Lesko, S. M., Heeren, T. C., Weese-Mayer, D. E., Auerbach, S. H., & Corwin, M. J. (2003). Symptoms of sleep-disordered breathing in 5-year-old children are associated with sleepiness and problem behaviors. *Pediatrics*, *112*(4), 870–877.

Gozal, D., Khalyfa, A., Capdevila, O. S., Kheirandish-Gozal, L., Khalyfa, A. A., & Kim, J. (2012). Cognitive function in prepubertal children with obstructive sleep apnea: A modifying role for NADPH oxidase p22 subunit gene polymorphisms? *Antioxidants & Redox Signaling*, *16*, 171–177. https://doi.org/10.1089/ars.2011.4189

Henriques-Filho, P., Pratesi, R., Gandolfi, L., Nobrega, Y., & Tristao, R. (2013). Obstructive sleep apnea and P300 abnormalities in children with attention deficit. *Sleep Medicine*, *14*(1), e125. https://doi.org/10.1016/j.sleep.2013.11.281

Huang, Y. S., & Guilleminault, C. (2012). Pediatric obstructive sleep apnea and the critical role of oral-facial growth: Evidences. *Frontiers in Neurology*, *3*(3), 184. https://doi.org/10.3389/fneur.2012.00184

Huijbers, W., Pennartz, C. M., Beldzik, E., Domagalik, A., Vinck, M., Hofman, W. F., Cabeza, R., & Daselaar, S. M. (2014). Respiration phase-locks to fast stimulus presentations: Implications for the interpretation of posterior midline "deactivations". *Human Brain Mapping*, *35*, 4932–4943. https://doi.org/10.1002/hbm.22523

Huynh, N., Morton, P., Rompre, P., & Papadakis, A. (2013). Remise C. *American Journal of Orthodontics and Dentofacial Orthopedics*, *140*(6), 762–770.

Hvolby, A. (2015). Associations of sleep disturbance with ADHD: Implications for treatment. *Attention Deficit and Hyperactivity Disorders*, *7*(1), 1–18.

Ito, J., Roy, S., Liu, Y., Cao, Y., Fletcher, M., Lu, L., Boughter, J. D., Grün, S., & Heck, D. H. (2014). Whisker barrel cortex delta oscillations and gamma power in the awake mouse are linked to respiration. *Nature Communications*, *5*, 3572. https://doi.org/10.1038/ncomms4572

Jackson, M. L., Hughes, M. E., Croft, R. J., Howard, M. E., Crewther, D., Kennedy, G. A., Owens, K., Pierce, R. J., O'Donoghue, F. J., & Johnston, P. (2011). The effect of sleep deprivation on BOLD activity elicited by a divided attention task. *Brain Imaging and Behavior*, *5*, 97–108.

Jefferson, Y. (2010). Mouth Breathing: Adverse effects on facial growth, health, academics, and behavior. *General Dentistry*, *58*, 18–25.

Johnson, E. O., & Roth, T. (2006). An epidemiologic study of sleep-disordered breathing symptoms among adolescents. *Sleep*, *29*(9), 1135–1142.

Juliano, M. L., Machado, M. A., de Carvalho, L. B., Zancanella, E., Santos, G. M., Do Prado, L. B., & Do Prado, G. F. (2009). Polysomnographic findings are associated with cephalometric measurements in mouth-breathing children. *Journal of Clinical Sleep Medicine*, *5*(6), 554–561.

Kaemingk, K. L., Pasvogel, A. E., Goodwin, J. L., Mulvaney, S. A., Martinez, F., Enright, P. L., Rosen, G. M., Morgan, W. J., Fregosi, R. F., & Quan, S. F. (2003). Learning in children and sleep disordered breathing: Findings of the Tucson Children's assessment of sleep apnea (tuCASA) prospective cohort study. *Journal of the International Neuropsychological Society*, *9*(7), 1016–1026. https://doi.org/10.1017/S1355617703970056

Kay, L. M. (2005). Theta oscillations and sensorimotor performance. *Proceedings of the National Academy of Sciences*, *102*, 3863–3868. https://doi.org/10.1073/pnas.0407920102,pmid:15738424,pmid:15738424

Khazaie, H., Veronese, M., Noori, K., Emamian, F., Zarei, M., Ashkan, K., Leschziner, G. D., Eickhoff, C. R., Eickhoff, S. B., Morrell, M. J., Osorio, R. S., Spiegelhalder, K., Tahmasian, M., & Rosenzweig, I. (2017). Functional reorganization in obstructive sleep apnoea and insomnia: A systematic review of the resting-state fMRI. *Neuroscience and Biobehavioral Reviews*, *77*, 219–231. https://doi.org/10.1016/j.neubiorev.2017.03.013

Kheirandish-Gozal, L., & Gozal, D. (2019). Obstructive sleep apnea and inflammation: Proof of concept based on two illustrative cytokines. *International Journal of Molecular Sciences*, *20*(3), 459. https://doi.org/10.3390/ijms20030459

Kim, H. Y., Jeong, J. I., Dhong, H. J., Sohn, J. H., Hong, S. D., Kim, J. H., Jang, S. Y., Jung, Y. G., & Chung, S. K. (2013). Nasal obstruction and palate-tongue position on sleep-disordered breathing. *Clinical and Experimental Otorhinolaryngology*, *6*(4), 226–230. https://doi.org/10.3342/ceo.2013.6.4.226

Knight, F. L. C., & Dimitriou, D. (2019). Poor sleep has negative implications for children with and without ADHD, but in different ways. *Behavioral Sleep Medicine*, *17*(4), 423–436. https://doi.org/10.1080/15402002.2017.1395335

Kong, D., Soon, C. S., & Chee, M. W. (2012). Functional imaging correlates of impaired distractor suppression following sleep deprivation. *NeuroImage*, *61*, 50–55.

Konofal, E., Lecendreux, M., & Cortese, S. (2010). Sleep and ADHD. *Sleep Medicine*, *11*, 652–658. https://doi.org/10.1016/j.sleep.2010.02.012

Lal, C., Strange, C., & Bachman, D. (2012). Neurocognitive impairment in obstructive sleep apnea. *Chest*, *141*(6), 1601–1610. https://doi.org/10.1378/chest.11-2214

Lal, C., Weaver, T. E., Bae, C. J., & Strohl, K. P. (2021). Excessive daytime sleepiness in obstructive sleep apnea. Mechanisms and clinical management. *Annals of the American Thoracic Society*, *18*(5), 757–768. https://doi.org/10.1513/AnnalsATS.202006-696FR

Libedinsky, C., Smith, D. V., Teng, C. S., Namburi, P., Chen, V. W., Huettel, S. A., & Chee, M. W. (2011). Sleep deprivation alters valuation signals in the ventromedial prefrontal cortex. *Frontiers in Behavioral Neuroscience*, *5*, 70.

Lim, J., Choo, W. C., & Chee, M. W. L. (2007). Reproducibility of changes in behaviour and fMRI activation associated with sleep deprivation in a working memory task. *Sleep*, *30*, 61–70.

Lim, J., Tan, J. C., Parimal, S., Dinges, D. F., & Chee, M. W. (2010). Sleep deprivation impairs object-selective attention: A view from the ventral visual cortex. *Plos One*, *5*.

Li, S., Jin, X., Yan, C., Wu, S., Jiang, F., & Shen, X. (2010). Habitual snoring in school-aged children: Environmental and biological predictors. *Respiratory Research*, *11*, 144.

Lundberg, J. O. (2008). Nitric oxide and the paranasal sinuses. *Anatomical Record*, *291*(11), 1479–1484.

Lundberg, J. O. N., & Weitzberg, E. (1999). Nasal nitric oxide in man. *Thorax*, *54*, 947–952.

Lythe, K. E., Williams, S. C., Anderson, C., Libri, V., & Mehta, M. A. (2012). Frontal and parietal activity after sleep deprivation is dependent on task difficulty and can be predicted by the fMRI response after normal sleep. *Behavioural Brain Research*, *233*, 62–70.

Moore, J. D., Deschênes, M., Furuta, T., Huber, D., Smear, M. C., Demers, M., & Kleinfeld, D. (2013). Hierarchy of orofacial rhythms revealed through whisking and breathing. *Nature*, *497*, 205–210. https://doi.org/10.1038/nature12076

Muto, V., Shaffiile Bourdiec, A., Matarazzo, L., Foret, A., Mascetti, L., Jaspar, M., Vandewalle, G., Phillips, C., Degueldre, C., Balteau, E., Luxen, A., Collette, F., & Maquet, P. (2012). Influence of acute sleep loss on the neural correlates of alerting, orientating and executive attention components. *Journal of Sleep Research*, *21*, 648–658.

Ngiam, J., & Cistulli, P. A. (2015). Dental treatment for paediatric obstructive sleep apnea. *Paediatric Respiratory Reviews*, *16*(3), 174–181. https://doi.org/10.1016/j.prrv.2014.11.002

Owens, J. (2005). The ADHD and sleep conundrum: A review. *Journal of Developmental & Behavioral Pediatrics*, *26*(4), 312–322.

Owens, J., Gruber, R., Brown, T., Corkum, P., Cortese, S., O'Brien, L., Stein, M., & Weiss, M. (2013). Future research directions in sleep and ADHD: Report of a consensus working group. *Journal of Attention Disorders*, *17*, 550–564. https://doi.org/10.1177/1087054712457992

O'Brien, L. M., Holbrook, C. R., Mervis, C. B., Klaus, C. J., Bruner, J. L., Raffield, T. J., Rutherford, J., Mehl, R. C.,

Wang, M., Tuell, A., Hume, B. C., & Gozal, D. (2003). Sleep and neurobehavioral characteristics of 5- to 7-year-old children with parentally reported symptoms of attention-deficit/hyperactivity disorder. *Pediatrics*, *111*(3), 554–563.

O'Brien, L. M., Mervis, C. B., Holbrook, C. R., Bruner, J. L., Klaus, C. J., Rutherford, J., Raffield, T. J., & Gozal, D. (2004). Neurobehavioral implications of habitual snoring in children. *Pediatrics*, *114*(1), 44–49. https://doi.org/10.1542/peds.114.1.44

Philipsen, A., Hornyak, M., & Riemann, D. (2006). Sleep and sleep disorders in adults with attention deficit/hyperactivity disorder. *Sleep Medicine Reviews*, *10*(6), 399–405. https://doi.org/10.1016/j.smrv.2006.05.002

Pizza, F., Biallas, M., Wolf, M., Werth, E., & Bassetti, C. L. (2010). Nocturnal cerebral hemodynamics in snorers and in patients with obstructive sleep apnea: A near-infrared spectroscopy study. *Sleep*, *33*(2), 205–210.

Poudel, G. R., Innes, C. R., & Jones, R. D. (2012). Cerebral perfusion differences between drowsy and nondrowsy individuals after acute sleep restriction. *Sleep*, *35*, 1085–1096.

Sämann, P. G., Tully, C., Spoormaker, V. I., Wetter, T. C., Holsboer, F., Wehrle, R., & Czisch, M. (2010). Increased sleep pressure reduces resting state functional connectivity. *Magma*, *23*, 375–389.

Sangal, R. B., Owens, J. A., & Sangal, J. (2005). Patients with attention-deficit/hyperactivity disorder without observed apneic episodes in sleep or daytime sleepiness have normal sleep on polysomnography. *Sleep*, *28*(9), 1143–1148.

Sano, M., Sano, S., Oka, N., Yoshino, K., & Kato, T. (2013). Increased oxygen load in the prefrontal cortex from mouth breathing: A vector-based near-infrared spectroscopy study. *Neuroreport*, *24*(17), 935–940.

Sedky, K., Bennett, D. S., & Carvalho, K. S. (2014). Attention deficit hyperactivity disorder and sleep disordered breathing in pediatric populations: A meta-analysis. *Sleep Medicine Reviews*, *18*(4), 349–356.

Shpirer, I., Elizur, A., Shorer, R., Peretz, R. B., Rabey, J. M., & Khaigrekht, M. (2012). Hypoxemia correlates with attentional dysfunction in patients with obstructive sleep apnea. *Schlaf & Atmung*, *16*, 821–827. https://doi.org/10.1007/s11325-011-0582-1

Sleep Foundation. (2020). https://www.sleepfoundation.org/sites/default/files/FINAL%20SOF%202004pdf

Stein, M. A., Weiss, M., & Hlavaty, L. (2012). ADHD treatments, sleep, and sleep problems: Complex associations. *Neurotherapeutics*, *9*, 509–517. https://doi.org/10.1007/s13311-012-0130-0

Surman, C. B. H., Thomas, R. J., Aleardi, M., Pagano, C., & Biederman, J. (2006). Adults with ADHD and sleep complaints: A pilot study identifying sleep-disordered breathing using polysomnography and sleep quality assessment. *Journal of Attention Disorders*, *9*(3), 550–555. https://doi.org/10.1177/1087054705282121

Swift, A. C., Campbell, I. T., & McKown, T. M. (1988). Oronasal obstruction, lung volumes, and arterial oxygenation. *Lancet*, *1*(8577), 73–75.

Thomas, M., Sing, H., & Belenky, G. (2003). Neural basis of alertness and cognitive performance impairments during sleepiness II. Effects of 48 and 72 h of sleep deprivation on waking human regional brain activity. *Thalamus & Related Systems*, *2*, 199–229.

Thomas, M., Sing, H., Belenky, G., Holcomb, H., Mayberg, H., Dannals, R., Wagner, H. Jr, Thorne, D., Popp, K., Rowland, L., Welsh, A., Balwinski, S., & Redmond, D. (2000). Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *Journal of Sleep Research*, *9*, 335–352.

Törnberg, D. C., Marteus, H., Schedin, U., Alving, K., Lundberg, J. O., & Weitzberg, E. (2002). Nasal and oral contribution to inhaled and exhaled nitric oxide: A study in tracheotomized patients. *European Respiratory Journal*, *19*, 859–864. https://doi.org/10.1183/09031936.02.00273502

Trabalon, M., & Schaal, B. (2012). It takes a mouth to eat and a nose to breathe: Abnormal oral respiration affects neonates oral competence and systemic adaptation. *International Journal of Pediatrics*, *2012*, 1–10.

Um, Y. H., Hong, S. C., & Jeong, J. H. (2017). Sleep problems as predictors in attention-deficit hyperactivity disorder: Causal mechanisms, consequences and treatment. *Clinical Psychopharmacology and Neuroscience*, *15*(1), 9–18. https://doi.org/10.9758/cpn.2017.15.1.9

Unnikrishnan, D., Jun, J., & Polotsky, V. (2015). Inflammation in sleep apnea: An update. *Reviews in Endocrine and Metabolic Disorders*, *16*, 25–34. https://doi.org/10.1007/s11154-014-9304-x

Urbano, G. L., Tablizo, B. J., Moufarrej, Y., Tablizo, M. A., Chen, M. L., & Witmans, M. (2021). The link between pediatric obstructive sleep apnea (OSA) and Attention Deficit Hyperactivity Disorder (ADHD). *Children*, *8*(9), 824.

Venkatraman, V., Huettel, S. A., Chuah, L. Y., Payne, J. W., & Chee, M. W. (2011). Sleep deprivation biases the neural mechanisms underlying economic preferences. *Journal of Neuroscience*, *31*, 3712–3718.

Vlemincx, E., Taelman, J., De Peuter, S., Van Diest, I., & Van Den Bergh, O. (2011). Sigh rate and respiratory variability during mental load and sustained attention. *Psychophysiology*, *48*, 117–120. https://doi.org/10.1111/j.1469-8986.2010.01043.x

Wajszilber, D., Santiseban, J. A., & Gruber, R. (2018). Sleep disorders in patients with ADHD: Impact and management challenges. *Nature and Science of Sleep*, *10*, 453–480.

Wei, J. L., Bond, J., Mayo, M. S., Smith, H. J., Reese, M., & Weatherly, R. A. (2009). Improved behavior and sleep after adenotonsillectomy in children with sleep-disordered breathing: Long-term follow-up. *Archives of Otolaryngology: Head and Neck Surgery*, *135*(7), 642–646.

Weng, H. H., Tsai, Y. H., Chen, C. F., Lin, Y. C., Yang, C. T., Tsai, Y. H., & Yang, C. Y. (2014). Mapping gray matter reductions in obstructive sleep apnea: An activation likelihood estimation meta-analysis. *Sleep*, *37*, 167–175.

Yanovsky, Y., Ciatipis, M., Draguhn, A., Tort, A. B., & Brankačk, J. (2014). Slow oscillations in the mouse hippocampus entrained by nasal respiration. *Journal of Neuroscience*, *34*, 5949–5964. https://doi.org/10.1523/JNEUROSCI.5287-13.2014

Yarlagadda, A., Connell, M., Kasaraneni, J., & Clayton, A. (2013). Insomnia and attention deficit hyperactivity disorder in pediatrics: A checklist for parents. *Innovations in Clinical Neuroscience*, *10*(11–12), 19–22.

Yoo, S. S., Gujar, N., Hu, P., Jolesz, F. A., & Walker, M. P. (2007). The human emotional brain without sleep—A prefrontal amygdala disconnect. *Current Biology*, *17*, R877–R878.

Zelano, C., Jiang, H., Zhou, G., Arora, N., Schuele, S., Rosenow, J., & Gottfried, J. A. (2016). Nasal respiration entrains human limbic oscillations and modulates cognitive function. *Journal of Neuroscience*, *36*(49), 12448–12467. https://doi.org/10.1523/JNEUROSCI.2586-16.2016

Author Biographies

Iliyan Ivanov MD is a Professor in the Department of Psychiatry of the Icahn School of Medicine at Mount Sinai and Site Division Chief for Child and Adolescent Psychiatry at Mount Sinai Morningside. His research focuses on using functional imaging, psychophysiological, and computational approaches to investigate brain mechanisms underlying the onset of substance use disorders in youth at risk.

Ben Miraglia DDS graduated from SUNY at Buffalo School of Dental Medicine in 1993. Dr. Miraglia is the VP of GP Clinical Education with CandidPro. He is a co-founder and Chief Clinical Officer at Airway Health Solutions, is a member of the Board of Directors of the American Academy of Physiological Medicine and Dentistry and is a founding member and Chief Clinical Officer at Toothpillow.

Dana Prodanova DDS graduated from NYU College of Dentistry in 2002. Dr. Prodanova is in private practice in Manhattan with over 20 years of clinical experience in the areas of general dentistry with specialization in full oral restoration and upper airways malocclusions and is an active member of Airway Health Solutions and American Academy of Clear Aligners.

Jeffrey H. Newcorn MD is a Professor in the Department of Psychiatry of the Icahn School of Medicine at Mount Sinai and Director of Pediatric Psychopharmacology for the Mount Sinai Health System. Dr. Newcorn is the Director of the Center for Excellence for ADHD and Related Disorders and is an internationally regarded researcher in the areas of ADHD, aggression, descriptive psychopathology of child and adolescent disorders, and child and adolescent psychopharmacology, whose work spans both clinical and translational topics.