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The key role of daytime sleepiness in cognitive functioning of adults with attention deficit hyperactivity disorder

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Abstract

Background. Adults with attention deficit hyperactivity disorder (ADHD) frequently suffer from sleep problems and report high levels of daytime sleepiness compared to neurotypical controls, which has detrimental effect on quality of life.

Methods. We evaluated daytime sleepiness in adults with ADHD compared to neurotypical controls using an observer-rated sleepiness protocol during the Sustained Attention Response Task as well as electroencephalogram (EEG) slowing, a quantitative electroencephalographic measure collected during a short period of wakeful rest.

Results. We found that adults with ADHD were significantly sleepier than neurotypical controls during the cognitive task and that this on-task sleepiness contributed to cognitive performance deficits usually attributed to symptoms of ADHD. EEG slowing predicted severity of ADHD symptoms and diagnostic status, and was also related to daytime sleepiness. Frontal EEG slowing as well as increased frontal delta were especially prominent in adults with ADHD. We have validated and adapted an objective observer-rated measure for assessing on-task sleepiness that will contribute to future sleep research in psychology and psychiatry.

Conclusions. These findings indicate that the cognitive performance deficits routinely attributed to ADHD and often conceptualized as cognitive endophenotypes of ADHD are largely due to on-task sleepiness and not exclusively due to ADHD symptom severity. Daytime sleepiness plays a major role in cognitive functioning of adults with ADHD.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a pervasive neurodevelopmental disorder, which can manifest itself throughout human lifespan and is characterized by symptoms of inattention and hyperactivity/impulsivity. First-line treatment strategy for ADHD comprises psychopharmacological treatments, which can be further optimized with the use of psychosocial interventions. Most adults with ADHD suffer from at least one other psychiatric comorbidity with especially high prevalence of anxiety and mood disorders [1]. In terms of somatic disease, sleep disorders are next to asthma and obesity, one of the best documented comorbidities in adults with ADHD [2].

A total of 50–70% of adults with ADHD experience sleep disorders [3,4]. They also report higher daytime sleepiness [5] and lower sleep quality [6–9] compared to neurotypical controls. These difficulties have a negative influence on quality of life [10] and make management of ADHD and diagnostic differentiation much more challenging, as they result in ADHD-like symptoms [11–13]. However, although verbally reported sleep problems can be robustly linked to ADHD (with effect sizes ranging from medium to very large), there is only very limited evidence from objective sleep measures [14].

Electroencephalogram (EEG) slowing is a consequence of normal daytime sleepiness in healthy, neurotypical adults [15]. It can be used to detect the emergence of fatigue during tasks [16] and can be reversed by consumption of caffeine [17]. EEG slowing is a part of normal development, seen in children, adolescents, and young adults as well as part of normal aging, but can also be indicative of neurodegenerative and neurodevelopmental disorders [18,19]. EEG slowing is also a sign of excessive daytime sleepiness due to hypoxia typical of sleep disorders such as obstructive sleep apnea (OSA) [20,21], where it has been linked with hypoxemic frontal lobe dysfunction and executive function deficits [22,23]. Measured as theta/beta ratio, EEG slowing is a prominent quantitative electroencephalographic marker in ADHD research [24] and considered valuable in predicting response to stimulant medication [25], but not for diagnostic purposes [26]. Multiple

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studies reported EEG slowing in people with ADHD [24,25,27,28] and it has been used a target for neurofeedback treatments in ADHD [29].

Here, we evaluate daytime sleepiness in adults with ADHD compared to neurotypical controls using observer-rated sleepiness [30,31] during the Sustained Attention Response Task (SART); and EEG slowing collected before the cognitive testing session during a short period of wakeful rest with eyes open [20,21,32]. We aim to link sleepiness to ADHD-related cognitive performance deficits to determine the influence of excessive daytime sleepiness on cognitive processing and their relation to symptoms of ADHD. Daytime sleepiness and hypo-arousal are involved in cognitive physiopathology of ADHD [33,34] and are considered to be some of the major research priorities in the field [35].

We hypothesize that: (a) adults with ADHD will exhibit elevated levels of both on-task and at-rest sleepiness compared to neurotypical controls; (b) excessive on-task sleepiness will be linked to cognitive performance deficits; and (c) EEG slowing will differentiate adults with ADHD from neurotypical controls.

Methods

Sample

We used data from the OCEAN clinical trial (Oils and Cognitive Effects in Adult ADHD Neurodevelopment, ClinicalTrials.gov Identifier: NCT01750307). Research ethics approval was granted by the National Research Ethics Service Committee London (reference: 11/LO/1042). In total, 111 English-speaking adults volunteered to participate in the study (60 men, 51 women, mean age 32.4 years, SD 10 years, mean IQ = 110, SD = 13). Among them, 81 diagnosed with ADHD according to the DMS-5 criteria (73 of them with combined-type ADHD) [36] and recruited via South London and Maudsley Adult ADHD Outpatient Service, and 30 non-ADHD controls (see Table 1 for detailed characteristics). Participants were either on stable treatment with ADHD medication (stimulant or nonstimulant medication), or on no medication, and could also be taking a low dose of adjunctive medication for depression or anxiety. Participants had no mental or physical comorbidities; however, as a lifetime history of depression is common in adults with ADHD, only participants with recurrent depression or undergoing a depressive episode were excluded. This resulted in including 14 adults with ADHD additionally taking antidepressants.

Clinical and cognitive measures

ADHD symptom severity was measured using the Conners' Adult ADHD Rating Scales (CAARS) [37], a self-report 18-item scale assessing the level of inattention and hyperactivity/impulsivity consistent with the DSM-5 criteria for adult ADHD [36]. Two subtests (vocabulary and matrix reasoning) of The Wechsler Abbreviated Scale of Intelligence II (WASI-II) [38] were used to measure IQ. Participants with IQ below 80 were excluded from the study. Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI) [39], a 19-item questionnaire with high validity and reliability in retrospective self-assessment of disturbed sleep quality over the last month, including the ensuing daytime dysfunction [40]. PSQI broadly assess both quantitative (sleep latency, number of awakenings) and qualitative (restlessness, functioning) aspects of sleep.

Cognitive function was measured using the SART and the Cued Continuous Performance Task with flankers (CPT-OX). See Supplementary Material for details of these experimental paradigms. ADHD participants did not take any stimulant medication for at least 48 h prior to cognitive performance test sessions. We recorded commission errors (failure to correctly withhold following a no-go target) and omission errors (OEs) (failure to correctly respond to a go target); as well reaction time variability calculated as the standard deviation (SD) of reaction times.

To evaluate on-task sleepiness during SART, we used video recordings from the cognitive testing sessions and an observer-rated sleepiness assessment protocol [30,31]. It is a well-established, low-cost, and reliable method of rating sleepiness and that has often been used in studies carried out while the participant is driving a car, which requires vigilance and sustained attention. Participants' sleepiness was evaluated during the three blocks of the SART on a continuous scale from 0 to 100 and divided into six categories with detailed behavioral descriptions (ranging from "not drowsy" to "extremely drowsy"). A Behavior and Mannerism Checklist [30] was additionally provided to support quantitative evaluation. Please refer to the Supplementary Material for a detailed description of the Observer-Rated Drowsiness Scale and the Behavior and Mannerism Checklist.

Table 1. Background, clinical and cognitive variables of the study sample

Gender	Participants with ADHD		Controls			
	N = 81	44 males (54%)	*N* = 30	16 males (53%)		
	Mean	SD	Mean	SD	*t*	*p* value
Age (years)	33.5	10.3	29.5	8.8	1.90	0.06
IQ	109.4	13.7	111.7	11.4	−0.83	0.41
ADHD symptom severity	65.2	15.7	14.8	9.8	20.22	<0.001
Sleep quality (PSQI)	14.1	6.8	7.2	4.6	5.10	<0.001
SART commission errors	46.8	17.5	27.9	15.4	5.13	<0.001
SART omission errors	3.8	4.3	1.1	1.5	3.78	<0.001
SART reaction time variability	87.2	60.7	56.3	18.8	4.02	<0.001
CPT-OX commission errors	7.9	14.9	1.1	1.4	5.11	<0.001
CPT-OX omission errors	2.1	2.6	0.4	0.8	4.01	<0.001
CPT-OX reaction time variability	142.1	65.2	103.9	73.9	2.59	0.01

Abbreviations: CPT-OX, Cued Continuous Performance Task with flankers; PSQI, Pittsburgh Sleep Quality Index; SART, Sustained Attention Response Task.

EEG data from the resting-state eyes-open baseline condition was used for this analysis. EEG slowing was calculated as a ratio of the slow frequency bands (delta + theta) to the fast frequency bands (alpha + beta) for each scalp region as well as across regions. This spectral calculation of EEG slowing ensures that the ratio stays sensitive to both simultaneous changes across bands as well as in any individual frequency [32]. See Supplementary Material for details of EEG recording, pre-processing, and statistical analysis.

Analysis and Results

Observer-rated sleepiness

A main effect of time was found and showed a statistically significant difference in mean on-task sleepiness at the three different time points, $F(1.65, 155.50) = 15.018$, $p < 0.001$, partial $\eta^2 = 0.138$. Bonferroni-corrected pairwise comparisons between the time points revealed that participants became gradually sleepier as showed by statistically significant $t2 - t1$ difference (0.119; 95% confidence intervals [CI] 0.050–0.188, $p < 0.001$) and $t3 - t1$ difference (0.148; 95% CI 0.064–0.232, $p < 0.001$).

A main effect of group was also identified and showed a statistically significant difference in mean sleepiness scores between adult ADHD and the control group, $F(1, 94) = 12.274$, $p = 0.001$, partial $\eta^2 = 0.115$. Bonferroni-corrected pairwise comparisons between groups revealed that participants with ADHD were on average much sleepier than neurotypical participants (mean difference = 0.40; 95% CI 0.173–0.627, $p = 0.001$). There was no statistically significant interaction between group and sleepiness, $F(2, 188) = 1.643$, $p = 0.19$, partial $\eta^2 = 0.017$. See Figure 1 for a graphical representation of these results.

As most study participants were not visibly sleepy during the cognitive testing procedure and because the reliability of the observer-rated sleepiness tool is higher at the higher levels of sleepiness, we created an additional group for participants falling into the "at least slightly sleepy" category. See Supplementary Material for details, including analysis of cognitive variables controlled for IQ.

To investigate whether the sleepy group and the ADHD group differ on relevant clinical scales, we compared mean ADHD symptom severity and sleep quality (as measured by PSQI) in the two groups. The analysis showed that sleep quality is slightly lower in the sleepy group (14.03 ± 8.52) compared to the ADHD group (12.88 ± 5.82) and that the ADHD group has a slightly higher ADHD symptom severity (63.64 ± 15.79) than the sleepy group (60.64 ± 24.91), but none of these results were statistically significant.

To further verify whether sleepiness has a detrimental effect on cognitive performance over and beyond ADHD symptoms, we re-analyzed the rate of OEs in the SART task using ADHD symptom severity as a covariate in the model. The result remained statistically significant $F(2, 95) = 7.817$, $p = 0.001$, partial $\eta^2 = 0.141$; although the adjusted values have changed with the highest error rate still in the sleepy group (OE = 4.88; standard error [SE] = 0.67; 95% CI 3.55–6.22), followed by the neurotypical group (OE = 3.28; SE = 1.04; 95% CI 1.22–5.34), followed by the ADHD group (OE = 1.61; SE = 0.59; 95% CI 0.45–2.78).

Additionally, we run correlations within the ADHD group alone to explore the relationship between observer-rated sleepiness as a continuous variable and the cognitive measures. We did this with and without covarying ADHD symptom severity and IQ. OEs in the SART were strongly correlated with the sleepiness level, $r(66) = 0.49$, $p < 0.001$, and the strength of this correlation was independent of ADHD symptom severity, $r(66) = 0.45$, $p < 0.001$, or IQ $r(66) = 0.44$, $p < 0.001$. Table 2 shows the details on the other cognitive measures.

The multiple regression model statistically significantly predicted OEs in the SART, $F(3, 64) = 4.201$, $p = 0.009$. R^2 for the overall model was 16.5% with an adjusted R^2 of 12.5%, a small effect size. Only observer-rated sleepiness added statistically significantly to the prediction, $p = 0.004$. Regression coefficients and SEs are presented in Table 3.

EEG slowing

The main effect of group, $F(1,100) = 9.016$, $p = 0.003$, $\eta^2 = 0.083$, as well as location, $F(2,200) = 3.184$, $p < 0.001$, $\eta^2 = 0.097$, and no significant interaction, $F(2,200) = 2.610$, $p = 0.076$, $\eta^2 = 0.25$, were identified. EEG slowing in all regions was higher in the ADHD versus neurotypical group and was highest in the frontal region in the ADHD group (3.00 ± 1.64), see Figure 2 for details.

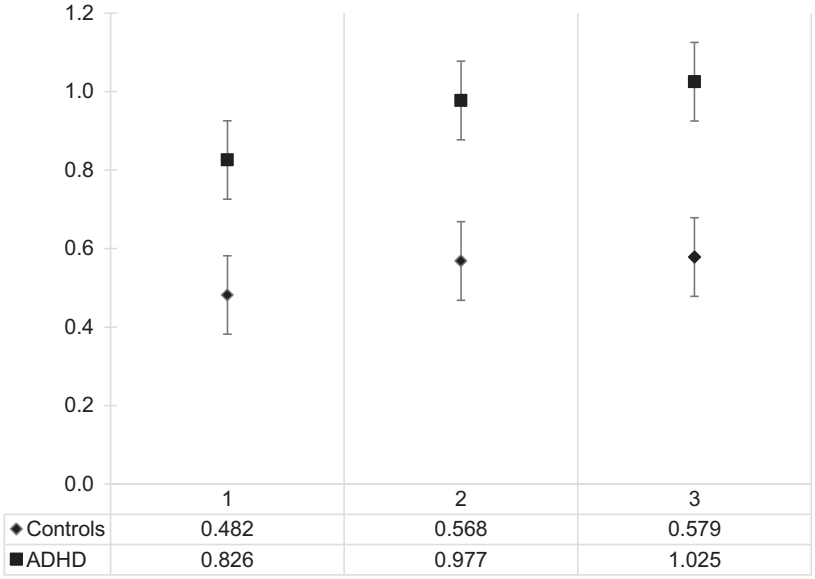

Figure 1. On-task sleepiness (log-transformed) in the adult ADHD and neurotypical group across the three time points. *t*1 is the 5th minute of the Sustained Attention Response Task, *t*2 the 10th, and *t*3 the 15th minute. Abbreviation: ADHD, attention deficit hyperactivity disorder.

Prominently, frontal delta was almost twice as high in the ADHD group (1.04 ± 0.43) than in the neurotypical group (0.53 ± 0.62) and statistically significant at Bonferroni-corrected $\alpha = 0.004$, $t(103) = 4.597$, $p = 0.000012$ (see Figure 2 for details).

Table 2. Correlation coefficients between observer-rated sleepiness and cognitive measures

	Observer-rated sleepiness	Covarying for ADHD symptom severity	Covarying for IQ
SART commission errors	0.14 (0.249)	0.15 (0.210)	0.12 (0.322)
SART omission errors	0.49 (0.001)*	0.45 (0.001)*	0.44 (0.001)*
SART reaction time variability	0.25 (0.042)*	0.17 (0.172)	0.21 (0.086)
CPT-OX commission errors	0.22 (0.066)	0.09 (0.492)	0.13 (0.283)
CPT-OX omission errors	0.11 (0.356)	0.12 (0.083)	0.25 (0.039)*
CPT-OX reaction time variability	0.27 (0.024)*	0.24 (0.037)*	0.28 (0.024)*

All correlations reported as coefficient (*p*-value).
Abbreviations: CPT-OX, Cued Continuous Performance Task with flankers; SART, Sustained Attention Response Task.
*$p < 0.05$.

Table 3. Summary of multiple regression analysis for omission errors in the SART task

Variable	*B*	SE_B	β	Sig.
Intercept	−0.940	2.565		0.715
Sleepiness	2.763	0.918	0.357	0.004
EEG slowing	0.015	0.316	0.005	0.962
ADHD symptom severity	0.036	0.036	0.119	0.320

Abbreviations: *B*, unstandardized regression coefficient; SART, Sustained Attention Response Task; SE_B, standard error of the coefficient; β, standardized coefficient.

EEG slowing was 0.95 (95% CI 0.51–1.39) higher in the ADHD group (2.67 ± 1.56) than in the neurotypical group ($1.72 \pm .64$). This difference was statistically significant, $t(92.314) = 4.343$, $p < 0.001$.

Additionally, a statistically significant difference in global EEG slowing between groups was identified when the sleepy group was again separated and included as a third group (see details above), $F(2, 58.648) = 9.226$, $p < 0.001$. Importantly, highest EEG slowing was in the ADHD group (2.81 ± 1.76; 95% CI 2.27–3.35), followed by the sleepy group (2.39 ± 1.29; 95% CI 1.91–2.87), followed by the neurotypical group (1.64 ± 0.62; 95% CI 1.35–1.93). The Games–Howell post-hoc tests revealed a statistically significant difference between sleepy and neurotypical groups (0.75; 95% CI 0.09–1.41, $p = 0.023$) as well as between ADHD and neurotypical group (1.17; 95% CI 0.44–1.90, $p = 0.001$), but not between ADHD and sleepy group (0.42; 95% CI −0.44 to 1.28, $p = 0.473$). Although too small of a group for statistical testing, the four neurotypical controls from the sleepy group for whom EEG slowing data was available showed elevated global slowing (2.11 ± 0.66) compared to others from the neurotypical group (1.64 ± 0.62).

There was a small positive correlation between EEG slowing and ADHD symptom severity, $r(100) = 0.196$, $p = 0.049$, as well as a large positive correlation between EEG slowing and ADHD diagnostic status $r_s(109) = 0.762$, $p < 0.001$. The logistic regression model was statistically significant, $\chi^2(4) = 4.112$, $p = 0.042$. EEG slowing was a statistically significant predictor of ADHD, $p = 0.047$, as well as ADHD symptom severity, $F(1, 100) = 3.978$, $p = 0.049$.

Discussion

Adults with ADHD were much sleepier during the attention task compared to neurotypical controls and they were becoming sleepier as the task progressed. However, they did not get sleepier at a faster rate than neurotypical controls as the task progressed. To investigate whether sleepiness or ADHD plays a larger role in cognitive performance, we created a third group consisting of the sleepiest subjects. This group had the same ADHD symptom severity as the ADHD group. We found that participants in the sleepy group made

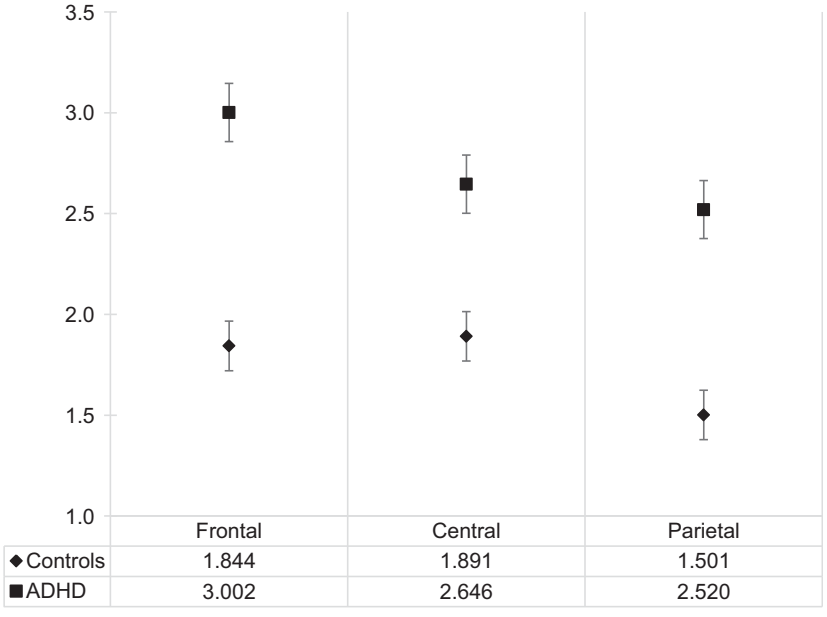

Figure 2. Electroencephalogram slowing in the adult ADHD and neurotypical group across three scalp locations. Abbreviation: ADHD, attention deficit hyperactivity disorder.

more OEs in both cognitive tasks (SART and CPT-OX) and had the highest reaction time variability in the SART compared to the non-sleepy ADHD and neurotypical groups even when we controlled for ADHD symptom severity in the analysis.

These findings indicate that the cognitive performance deficits routinely attributed to ADHD and often conceptualized as cognitive endophenotypes of ADHD, are largely due to on-task sleepiness and not exclusively due to ADHD symptom severity. Among the most established of these cognitive performance deficits associated with ADHD are increased OEs and reaction time variability thought to reflect preparation-vigilance deficits [41]. Here, we show that apart from ADHD symptom severity, these measures are to a significant extent negatively affected by on-task sleepiness. This fits well with some previous findings, where objectively measured sleepiness correlated with OEs but not commission errors in a group of people with narcolepsy [42] or where sleep deprivation in adolescents with ADHD resulted in more OEs [43]. Sleepiness is associated with suboptimal arousal [44] which leads to impairments in cognitive performance [45]. The cognitive-energetic model of ADHD stressed the role of arousal in neurodevelopmental cognitive performance deficits, suggesting that they emerge from reduced energetic states [46]. According to this model the optimization of under-arousal (low energetic state) in ADHD results in reduction of attentional lapses and faster, less variable, and more accurate responses.

Although ADHD participants went through a wash-out phase to ensure elimination of any short-term medication effect, more long-term influence of ADHD medication cannot be excluded. ADHD medication is known to normalize performance measures in people with ADHD [47]; however, data on long-term effects of stimulant medication are limited. Additionally, the only way to ensure that participants were medication free during the testing session would be to assess the blood concentration of ADHD medication, which we considered too burdensome for our study volunteers.

This is the first paper using video recordings to evaluate on-task sleepiness in ADHD. We have adopted a well-established sleepiness assessment protocol, specifically developed for observer evaluation of naturalistic videos of participant's head and torso during a cognitive task [30]. This systematic protocol adopts a highly reliable scale of sleepiness [31], which is in widespread research use outside psychiatry and resulted in strong inter-rater reliability. We recommend our adopted protocol as a low-cost, reliable tool for assessing on-task sleepiness in psychiatric research.

We also found that global quantitative EEG slowing, as well as EEG slowing in all analyzed scalp regions was higher in adults with ADHD versus neurotypical controls and was highest in the frontal region in the ADHD group. This can be indicative of frontal slowing in ADHD. In terms of individual frequency bands, elevated frontal delta was very prominent in the ADHD group. Contrary to our hypothesis, when the sleepy group was added to the analysis, we found that EEG slowing is greater in the non-sleepy ADHD group than in the sleepy group or in the non-sleepy neurotypical group. Importantly, EEG slowing significantly predicted both ADHD diagnostic status, as well as ADHD symptom severity. Overall, this suggests that EEG slowing is more strongly related to ADHD psychopathology than to normal sleepiness in this group (although data from four neurotypical sleepy subjects showed elevated global slowing).

In a recent latent class analysis study with a large ($N = 620$) sample of children with ADHD, it was found that a sub-group of children with increased delta had a significantly worse cognitive performance relative to all other groups, as measured by OEs in a go/no-go task and reaction-time variability in a spatial working memory task [23]. Elevated delta has also been linked to reduced resting state connectivity in the default-mode network of the brain [48], which is a prominent feature of ADHD [49].

According to the Developmental Origins of Health and Disease Hypothesis (DOHaD) [50,51], our results could be interpreted as a residue of developmentally early ischemic/hypoxic events. According to DOHaD, deficient prenatal blood and oxygen supply results in lowered weight at birth, leading to an enhanced risk of developing ADHD [50,51]. EEG slowing and the elevated frontal delta could perhaps serve as indicators of these altered neurodevelopmental pathways in adults with ADHD.

EEG slowing with elevated frontal delta is also characteristic of people with OSA and can be attributed to the hypoxia apneic patients experience during sleep [20]. A similar delta increase has been found in healthy awake subjects with hypoxia experimentally induced by gas inhalation [52]. Children suffering from OSA-hypopnea syndrome (OSAHS) with comorbid ADHD have a significantly higher hypoxia than children with OSAHS alone [53]. Crucially, converging evidence now exist suggesting that pre- and perinatal hypoxia is a major environmental pathogen for ADHD with the common risk factors associated with ADHD, such as low birth weight, prematurity, obstetric complications, and maternal smoking, all strongly linked to hypoxia-ischemia [50,54]. Animal models suggest that pre-, peri-, or neonatal ischemia-hypoxia results in neurocognitive and behavioral deficits lasting into adulthood [55,56]. Hypoxia results in neuroinflammation which has been linked to ADHD diagnosis and neurocognitive deficits related for ADHD [57,58]. Taken together, this body of evidence gives room for speculation that EEG slowing and the elevated frontal delta in adults with ADHD might be a residue of either developmentally early or sleep-related hypoxic events.

Based on the results presented here and some recently published findings [59], we would like to propose a simple working hypothesis that daytime sleepiness plays a major role in cognitive functioning of adults with ADHD. This will come to no surprise to clinicians, who consistently appreciate sleepiness as an integral part of the disorder [60]. However, the experimental neuro-cognitive literature on adult ADHD leaves an impression that sleepiness is a rather peripheral phenomenon and that the cognitive deficits related to ADHD should be attributed to state-independent neurocognitive deficits.

Sleep plays a key role in restoring brain function responsible for higher-order cognition [61]. Functional neuroimaging studies showed that sleep deprivation reduces global cerebral metabolism, especially in fronto-parietal cortex and thalamus [62,63], as well as reduces the hemodynamic response in the dorsolateral prefrontal cortex and bilateral posterior parietal cortices [64]—regions significantly overlapping with the attentional networks of the brain. Moreover, the extent of such reductions is larger in people with higher susceptibility to sleep deprivation [65]. Therefore, a simple brain mechanism underlying sleep deprivation and the resulting daytime sleepiness in ADHD emerges. As adults with ADHD are more severely sleep deprived compared to neurotypical control subjects [5] and are more vulnerable to sleep deprivation [11], in various neurocognitive tasks, they should manifest larger sleepiness-related reductions in cognitive performance. Many of the cognitive performance deficits might be linearly related to the level of daytime sleepiness.

This circadian-dependent pattern of arousal in ADHD [59] could exacerbate many of the impairments linked with ADHD. For example, sleep deprivation could be exacerbated by educational demand of early morning wakefulness [66], which over time can lead to increased mental health problems [66,67]. Additionally, evening hyperarousal interferes with falling asleep despite high sleep drive [68], leading to a vicious circle of sleep deprivation in

ADHD [69]. This might also explain why morning bright light therapy seems to be promising in ADHD resulting in phase advance in circadian preference and reduction of symptoms [70].

One clear testable prediction of the working hypothesis would be that carefully controlling for sleepiness, time of day and/or individual circadian rhythms, would result in substantial reduction in the neurocognitive deficits in replications of classic ADHD studies. This might possibly lead to identification of specific areas of cognition that are influenced by excessive daytime sleepiness to a different extent, which would enable a more precise specification of the state- and context-independent nature of cognition in adults with ADHD.

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Conflict of Interest. P.A. has received funds for consultancy on behalf of KCL to Shire, Eli-Lilly, and Novartis, regarding the diagnosis and treatment of ADHD; educational/research awards from Shire, Eli-Lilly, Novartis, Vifor Pharma, GW Pharma, and QbTech; speaker at sponsored events for Shire, Eli-Lilly, and Novartis. All funds are used for studies of ADHD. The other authors report no conflicts of interest.

Data Availability Statement. The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Supplementary Materials. To view supplementary material for this article, please visit http://dx.doi.org/10.1192/j.eurpsy.2020.28.

References

[1] Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry. 2006;163(4):716–23. doi: 10.1176/ajp.2006.163.4.716.

[2] Instanes JT, Klungsoyr K, Halmoy A, Fasmer OB, Haavik J. Adult ADHD and comorbid somatic disease: a systematic literature review. J Atten Disord. 2018;22(3):203–28. doi: 10.1177/1087054716669589.

[3] Sobanski E. Psychiatric comorbidity in adults with attention-deficit/hyperactivity disorder (ADHD). Eur Arch Psychiatry Clin Neurosci. 2006;256(Suppl 1):26–31. doi: 10.1007/s00406-006-1004-4.

[4] Yoon SY, Jain U, Shapiro C. Sleep in attention-deficit/hyperactivity disorder in children and adults: past, present, and future. Sleep Med Rev. 2012;16(4):371–88. doi: 10.1016/j.smrv.2011.07.001.

[5] Bjorvatn B, Brevik EJ, Lundervold AJ, Halmoy A, Posserud MB, Instanes JT, et al. Adults with attention deficit hyperactivity disorder report high symptom levels of troubled sleep, restless legs, and cataplexy. Front Psychol. 2017;8:1621. doi: 10.3389/fpsyg.2017.01621.

[6] Boonstra AM, Kooij JJ, Oosterlaan J, Sergeant JA, Buitelaar JK, Van Someren EJ. Hyperactive night and day? Actigraphy studies in adult ADHD: a baseline comparison and the effect of methylphenidate. Sleep. 2007;30(4):433–42.

[7] Schredl M, Alm B, Sobanski E. Sleep quality in adult patients with attention deficit hyperactivity disorder (ADHD). Eur Arch Psychiatry Clin Neurosci. 2007;257(3):164–8. doi: 10.1007/s00406-006-0703-1.

[8] Sobanski E, Schredl M, Kettler N, Alm B. Sleep in adults with attention deficit hyperactivity disorder (ADHD) before and during treatment with methylphenidate: a controlled polysomnographic study. Sleep. 2008;31(3):375–81.

[9] Surman CB, Adamson JJ, Petty C, Biederman J, Kenealy DC, Levine M, et al. Association between attention-deficit/hyperactivity disorder and sleep impairment in adulthood: evidence from a large controlled study. J Clin Psychiatry. 2009;70(11):1523–9. doi: 10.4088/JCP.08m04514.

[10] Um YH, Hong SC, Jeong JH. Sleep problems as predictors in attention-deficit hyperactivity disorder: causal mechanisms, consequences and treatment. Clin Psychopharmacol Neurosci. 2017;15(1):9–18. doi: 10.9758/cpn.2017.15.1.9.

[11] Bioulac S, Micoulaud-Franchi JA, Philip P. Excessive daytime sleepiness in patients with ADHD—diagnostic and management strategies. Curr Psychiatry Rep. 2015;17(8):608. doi: 10.1007/s11920-015-0608-7.

[12] Oosterloo M, Lammers GJ, Overeem S, de Noord I, Kooij JJ. Possible confusion between primary hypersomnia and adult attention-deficit/hyperactivity disorder. Psychiatry Res. 2006;143(2–3):293–7. doi: 10.1016/j.psychres.2006.02.009.

[13] Poirier A, Gendron M, Vriend J, Davidson F, Corkum P. The impact of sleep restriction on daytime movement in typically developing children. ADHD Atten Defic Hyperact Disord. 2016;8(1):53–8. doi: 10.1007/s12402-015-0180-3.

[14] Diaz-Roman A, Mitchell R, Cortese S. Sleep in adults with ADHD: systematic review and meta-analysis of subjective and objective studies. Neurosci Biobehav Rev. 2018;89:61–71. doi: 10.1016/j.neubiorev.2018.02.014.

[15] Santamaria J, Chiappa KH. The EEG of drowsiness in normal adults. J Clin Neurophysiol. 1987;4(4):327–82.

[16] Jap BT, Lal S, Fischer P, Bekiaris E. Using EEG spectral components to assess algorithms for detecting fatigue. Expert Syst Appl. 2009;36(2):2352–9.

[17] Patat A, Rosenzweig P, Enslen M, Trocherie S, Miget N, Bozon MC, et al. Effects of a new slow release formulation of caffeine on EEG, psychomotor and cognitive functions in sleep-deprived subjects. Hum Psychopharmacol. 2000;15(3):153–70. doi: 10.1002/(sici)1099-1077(200004)15:3<153::aid-hup154>3.0.co;2-c.

[18] Britton JW, Frey LC, Hopp J, Korb P, Koubeissi M, Lievens W, et al. Electroencephalography (EEG): an introductory text and atlas of normal and abnormal findings in adults, children, and infants. Chicago, IL: American Epilepsy Society, 2016.

[19] Petit D, Gagnon JF, Fantini ML, Ferini-Strambi L, Montplaisir J. Sleep and quantitative EEG in neurodegenerative disorders. J Psychosom Res. 2004;56(5):487–96. doi: 10.1016/j.jpsychores.2004.02.001.

[20] Morisson F, Decary A, Petit D, Lavigne G, Malo J, Montplaisir J. Daytime sleepiness and EEG spectral analysis in apneic patients before and after treatment with continuous positive airway pressure. Chest. 2001;119(1):45–52.

[21] Morisson F, Lavigne G, Petit D, Nielsen T, Malo J, Montplaisir J. Spectral analysis of wakefulness and REM sleep EEG in patients with sleep apnoea syndrome. Eur Resp J. 1998;11(5):1135–40.

[22] Bedard MA, Montplaisir J, Richer F, Rouleau I, Malo J. Obstructive sleep apnea syndrome: pathogenesis of neuropsychological deficits. J Clin Exp Neuropsychol. 1991;13(6):950–64. doi: 10.1080/01688639108405110.

[23] Loo SK, McGough JJ, McCracken JT, Smalley SL. Parsing heterogeneity in attention-deficit hyperactivity disorder using EEG-based subgroups. J Child Psychol Psychiatry. 2018;59(3):223–31.

[24] Snyder SM, Hall JR. A meta-analysis of quantitative EEG power associated with attention-deficit hyperactivity disorder. J Clin Neurophysiol. 2006;23(5):440–55. doi: 10.1097/01.wnp.0000221363.12503.78.

[25] Arns M, Conners CK, Kraemer HC. A decade of EEG Theta/Beta Ratio Research in ADHD: a meta-analysis. J Atten Disord. 2013;17(5):374–83. doi: 10.1177/1087054712460087.

[26] Lenartowicz A, Loo SK. Use of EEG to diagnose ADHD. Curr Psychiatry Rep. 2014;16(11):498. doi: 10.1007/s11920-014-0498-0.

[27] Barry RJ, Clarke AR, Johnstone SJ. A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. Clin Neurophysiol. 2003;114(2):171–83.

[28] di Michele F, Prichep L, John ER, Chabot RJ. The neurophysiology of attention-deficit/hyperactivity disorder. Int J Psychophysiol. 2005;58(1):81–93. doi:10.1016/j.ijpsycho.2005.03.011.

[29] Doehnert M, Brandeis D, Straub M, Steinhausen HC, Drechsler R. Slow cortical potential neurofeedback in attention deficit hyperactivity disorder: is there neurophysiological evidence for specific effects? J Neural Transm (Vienna). 2008;115(10):1445–56. doi: 10.1007/s00702-008-0104-x.

[30] Wiegand DM, McClafferty J, McDonald SE, Hanowski RJ. Development and evaluation of a naturalistic observer rating of drowsiness protocol. 2009. [Available at: https://scholar.lib.vt.edu/VTTI/reports/ORD_Final_Report_022509.pdf; accessed date: 11 March 2020].

[31] Wierwille WW, Ellsworth LA. Evaluation of driver drowsiness by trained raters. Accident Anal Prevent. 1994;26(5):571–81.

[32] Petit D, Lorrain D, Gauthier S, Montplaisir J. Regional spectral analysis of the REM sleep EEG in mild to moderate Alzheimer's disease. Neurobiol Aging. 1993;14(2):141–5.

[33] Asherson P, Buitelaar J, Faraone SV, Rohde LA. Adult attention-deficit hyperactivity disorder: key conceptual issues. Lancet Psychiatry. 2016; 3(6):568–78.

[34] Benikos N, Johnstone SJ. Arousal-state modulation in children with AD/HD. Clin Neurophysiol. 2009;120(1):30–40. doi: 10.1016/j.clinph.2008.09.026.

[35] Owens J, Gruber R, Brown T, Corkum P, Cortese S, O'Brien L, et al. Future research directions in sleep and ADHD: report of a consensus working group. J Atten Disord. 2013;17(7):550–64. doi: 10.1177/1087054712457992.

[36] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.

[37] Conners CK, Erhardt D, Sparrow EP. Conners' Adult ADHD Rating Scales (CAARS). North Tonawanda, NY: Multi-Health Systems; 1999.

[38] Wechsler D. WASI-II: Wechsler abbreviated scale of intelligence: San Antonio, TX: Psychological Corporation; 2011.

[39] Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193–213.

[40] Carpenter JS, Andrykowski MA. Psychometric evaluation of the Pittsburgh Sleep Quality Index. J Psychosom Res. 1998;45(1):5–13.

[41] Cheung CH, Rijsdijk F, McLoughlin G, Brandeis D, Banaschewski T, Asherson P, et al. Cognitive and neurophysiological markers of ADHD persistence and remission. Br J Psychiatry. 2016;208(6):548–55. doi: 10.1192/bjp.bp.114.145185.

[42] Van Schie MK, Thijs RD, Fronczek R, Middelkoop HA, Lammers GJ, Van Dijk JG. Sustained attention to response task (SART) shows impaired vigilance in a spectrum of disorders of excessive daytime sleepiness. J Sleep Res. 2012;21(4):390–5. doi: 10.1111/j.1365-2869.2011.00979.x.

[43] Velez-Galarraga R, Guillen-Grima F, Crespo-Eguilaz N, Sanchez-Carpintero R. Prevalence of sleep disorders and their relationship with core symptoms of inattention and hyperactivity in children with attention-deficit/hyperactivity disorder. Eur J Paediatr Neurol. 2016;20(6):925–37. doi: 10.1016/j.ejpn.2016.07.004.

[44] Jackson M, Van Dongen H. Cognitive effects of sleepiness. In Thorpy M, Billiard M, editors. Sleepiness: causes, consequences, disorders and treatment. New York, NY: Cambridge University Press; 2011. p. 72–81.

[45] Yerkes RM, Dodson JD. The relation of strength of stimulus to rapidity of habit-formation. J Comp Neurol Psychol. 1908;18(5):459–82.

[46] Sergeant J. The cognitive-energetic model: an empirical approach to attention-deficit hyperactivity disorder. Neurosci Biobehav Rev. 2000;24(1):7–12.

[47] Skirrow C, McLoughlin G, Banaschewski T, Brandeis D, Kuntsi J, Asherson P. Normalisation of frontal theta activity following methylphenidate treatment in adult attention-deficit/hyperactivity disorder. Eur Neuropsychopharmacol. 2015;25(1):85–94. doi: 10.1016/j.euroneuro.2014.09.015.

[48] Luchinger R, Michels L, Martin E, Brandeis D. Brain state regulation during normal development: intrinsic activity fluctuations in simultaneous EEG-fMRI. Neuroimage. 2012;60(2):1426–39. doi: 10.1016/j.neuroimage.2012.01.031.

[49] Posner J, Park C, Wang Z. Connecting the dots: a review of resting connectivity MRI studies in attention-deficit/hyperactivity disorder. Neuropsychol Rev. 2014;24(1):3–15.

[50] Smith TF, Schmidt-Kastner R, McGeary JE, Kaczorowski JA, Knopik VS. Pre- and perinatal ischemia-hypoxia, the ischemia-hypoxia response pathway, and ADHD risk. Behav Genet. 2016;46(3):467–77. doi: 10.1007/s10519-016-9784-4.

[51] Wadhwa PD, Buss C, Entringer S, Swanson JM. Developmental origins of health and disease: brief history of the approach and current focus on epigenetic mechanisms. Semin Reprod Med. 2009;27(5):358–68. doi: 10.1055/s-0029-1237424.

[52] Saletu B, Grunberger J, Anderer P, Linzmayer L, Konig P. On the cerebroprotective effects of caroverine, a calcium-channel blocker and antiglutamatergic drug: double-blind, placebo-controlled, EEG mapping and psychometric studies under hypoxia. Br J Clin Pharmacol. 1996;41(2):89–99.

[53] Wu J, Gu M, Chen S, Chen W, Ni K, Xu H, et al. Factors related to pediatric obstructive sleep apnea-hypopnea syndrome in children with attention deficit hyperactivity disorder in different age groups. Medicine (Baltimore). 2017;96(42):e8281. doi: 10.1097/md.0000000000008281.

[54] Zhu T, Gan J, Huang J, Li Y, Qu Y, Mu D. Association between perinatal hypoxic-ischemic conditions and attention-deficit/hyperactivity disorder: a meta-analysis. J Child Neurol. 2016;31(10):1235–44. doi: 10.1177/0883073816650039.

[55] Miguel PM, Schuch CP, Rojas JJ, Carletti JV, Deckmann I, Martinato LH, et al. Neonatal hypoxia-ischemia induces attention-deficit hyperactivity disorder-like behavior in rats. Behav Neurosci. 2015;129(3):309–20. doi: 10.1037/bne0000063.

[56] Rehn A, Van Den Buuse M, Copolo D, Briscoe T, Lambert G, Rees S. An animal model of chronic placental insufficiency: relevance to neurodevelopmental disorders including schizophrenia. Neuroscience. 2004;129(2): 381–91.

[57] Oades RD. An exploration of the associations of pregnancy and perinatal features with cytokines and tryptophan/kynurenine metabolism in children with attention-deficit hyperactivity disorder (ADHD). ADHD Atten Defic Hyperact Disord. 2011;3(4):301–18.

[58] Oades RD, Myint A-M, Dauvermann MR, Schimmelmann BG, Schwarz MJ. Attention-deficit hyperactivity disorder (ADHD) and glial integrity: an exploration of associations of cytokines and kynurenine metabolites with symptoms and attention. Behav Brain Funct. 2010;6(1):32.

[59] Bijlenga D, Vollebregt MA, Kooij JJS, Arns M. The role of the circadian system in the etiology and pathophysiology of ADHD: time to redefine ADHD? Atten Defic Hyperact Disord. 2019;11(1):5–19. doi: 10.1007/s12402-018-0271-z.

[60] Bioulac S, Philip P. From Japan to Europe: the importance to assess excessive daytime sleepiness in adults with ADHD symptoms. Sleep Med. 2017;37:221. doi: 10.1016/j.sleep.2017.06.008.

[61] Nofzinger EA. Functional neuroimaging of sleep. Semin Neurol. 2005; 25(1): 9–18. doi: 10.1055/s-2005-867070.

[62] Thomas M, Sing H, Belenky G, Holcomb H, Mayberg H, Dannals R, et al. Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. J Sleep Res. 2000;9(4):335–52.

[63] Thomas M, Sing H, Belenky G, Holcomb H, Mayberg H, Dannals R, et al. 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 Relat Syst. 2003;2(3):199–229.

[64] Mu Q, Nahas Z, Johnson KA, Yamanaka K, Mishory A, Koola J, et al. Decreased cortical response to verbal working memory following sleep deprivation. Sleep. 2005;28(1):55–67. doi: 10.1093/sleep/28.1.55.

[65] Mu Q, Mishory A, Johnson KA, Nahas Z, Kozel FA, Yamanaka K, et al. Decreased brain activation during a working memory task at rested baseline is associated with vulnerability to sleep deprivation. Sleep. 2005; 28(4):433–46. doi: 10.1093/sleep/28.4.433.

[66] Roberts RE, Roberts CR, Duong HT. Sleepless in adolescence: prospective data on sleep deprivation, health and functioning. J Adolesc. 2009;32(5): 1045–57.

[67] Altevogt BM, Colten HR. Sleep disorders and sleep deprivation: an unmet public health problem. Washington, DC: National Academies Press; 2006.

[68] Cluydts R, De Valck E, Verstraeten E, Theys P. Daytime sleepiness and its evaluation. Sleep Med Rev. 2002;6(2):83–96.

[69] Brown TE, McMullen WJ. Attention deficit disorders and sleep/arousal disturbance. Ann N Y Acad Sci. 2001;931(1):271–86.

[70] Rybak YE, McNeely HE, Mackenzie BE, Jain UR, Levitan RD. An open trial of light therapy in adult attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2006;67(10):1527–35.