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Transcranial Oscillatory Direct Current Stimulation During Sleep Improves Declarative Memory Consolidation in Children With Attention-deficit/hyperactivity Disorder to a Level Comparable to Healthy Controls

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ABSTRACT

Background: Slow oscillations (<1 Hz) during slow wave sleep (SWS) promote the consolidation of declarative memory. Children with attention-deficit/hyperactivity disorder (ADHD) have been shown to display deficits in sleep-dependent consolidation of declarative memory supposedly due to dysfunctional slow brain rhythms during SWS.
Objective: Using transcranial oscillating direct current stimulation (toDCS) at 0.75 Hz, we investigated whether an externally triggered increase in slow oscillations during early SWS elevates memory performance in children with ADHD. Methods: 12 children with ADHD underwent a toDCS and a sham condition in a double-blind crossover study design conducted in a sleep laboratory. Memory was tested using a 2D object-location task. In addition, 12 healthy children performed the same memory task in their home environment.
Results: Stimulation enhanced slow oscillation power in children with ADHD and boosted memory performance to the same level as in healthy children.
Conclusion: These data indicate that increasing slow oscillation power during sleep by toDCS can alleviate declarative memory deficits in children with ADHD.

Introduction

With a prevalence of 5–7%, attention-deficit/hyperactivity disorder (ADHD) is one of the most commonly diagnosed childhood disorders [1,2], characterized by the cardinal symptoms of reduced attention, hyperactivity, and impulsiveness [3]. Imaging studies revealed that neuropsychological deficits in ADHD are predominantly caused by dysfunctions in frontal brain regions, the striatum, and the cerebellum [4,5]. Besides the core symptoms, ADHD is often accompanied by memory deficits [6–9], which are likewise caused or at least exacerbated by reduced frontal brain functions (e.g. reduced attention, enhanced distractibility, deficits in buffering information) [10]. At the same time, frontal brain functions are susceptible to sleep deprivation [11–15], and there is a whole body of research linking the often reported sleep problems to neuropsychological deficits in ADHD [16–24].

Sleep does not only restore cognitive capacity but also supports the consolidation in various memory systems in healthy children and adults [25,26]. There is increasing evidence that declarative (i.e. hippocampus-dependent) memory benefits particularly from slow wave sleep (SWS) which is characterized electrophysiologically by slow oscillations (~0.8 Hz) occurring during slow wave activity (.5–5 Hz) [27]. These slow oscillations (SO) originate mainly over frontal brain regions [28–30] and orchestrate hippocampal activity during SWS. Hereby, newly encoded declarative memory

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Table 1
Participant characteristics.

	ADHD	Controls	ADHD vs. controls
	Mean (SD)	Mean (SD)	*P*
Age	12.1 (1.4)	11.9 (1.4)	.678
IQ	105 (7.0)	105 (8.1)	.915
Figural memory	65.4 (24.4)	75.7 (19.4)	.267
Attention problems (CBCL)	68.6 (7.9)	50.4 (1.4)	<.001

SD, standard deviation; CBCL, child behavior checklist.

representations are reactivated, resulting in strengthened memory consolidation during sleep [31]. By using transcranial oscillating direct current stimulation (toDCS) at 0.75 Hz during SWS in young healthy adults, Marshall and colleagues increased SO power, resulting in boosted sleep-dependent consolidation of declarative memory [32,33].

We observed that young patients with ADHD displayed deficits with respect to the sleep-dependent consolidation of declarative memory which was associated with dysfunctional SO activity during early non-rapid eye movement sleep [34]. As recently shown, slow wave activity (SWA, 1–4.5 Hz) during SWS is altered in children suffering from ADHD: while over central positions the SWA was enhanced, it was attenuated by trend over frontal positions [35]. Our previous studies pointed to a reduced frontal brain function as the cause of the impaired memory consolidation during sleep in ADHD [34,36,37]. Therefore, the aim of the present study was to show that an enhancement of frontal SO activity at 0.75 Hz by toDCS during sleep enhances declarative memory consolidation in ADHD to a level comparable to that of healthy controls.

Materials and methods

Twelve male children suffering from ADHD (mean age 12.1 yrs, range 10–14 yrs) and 12 healthy boys (mean age 11.9 yrs, range 9–14 yrs) participated in this study. Patients and controls did not differ with respect to age, IQ, or basic memory skills (all *P*-values >.2; see also Table 1). All children and their parents were interviewed using a German translation of the Revised Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version (K-SADS-PL) [38,39]. A standard questionnaire, the Child Behavior Checklist (CBCL) [40], was filled out by parents to assess any psychiatric symptoms of their children. ADHD patients were excluded, if they displayed any comorbidity apart from oppositional defiant disorder or conduct disorder. Controls were excluded if they displayed any psychiatric abnormalities. Further exclusion criteria for all participants were: below-average intelligence quotient (IQ < 85), as measured by the Culture Fair Intelligence Test 20-Revised Version (CFT 20-R) [41]; profound memory impairment as measured by a figural learning test to assess cerebral dysfunctions (Diagnosticum für Cerebralschädigung, DCS; cut-off score: 16th percentile of the reference sample) [42]; or self-reported sleep-disturbances, as measured by the Sleep-Self-Report questionnaire (SSR, cut-off score: 24).

All participants had normal or corrected-to-normal vision. Patients met the criteria for ADHD according to DSM IV–TR [3]; four suffered from the inattentive type and another eight from the combined type. Three patients with ADHD additionally exhibited an oppositional defiant disorder (ODD) and another two were additionally diagnosed with conduct disorder. According to self-reports all participants were free of any neurological, immunological, or endocrinological disease. Parental reports revealed no significant sleep problems in their children, and no healthy participant took any medication. ADHD patients only took methylphenidate but discontinued medication 48 h (approximately twelve half-lives) prior to each experimental condition. According to self-reports none of them needed daytime naps.

All participating children and their parents gave written informed consent and were reimbursed with a voucher for their participation. The study was approved by the ethics committee of the medical faculty of the University of Kiel and followed the ethical standards of the Helsinki Declaration. The ethic committee, however, recommended not applying toDCS in healthy children, and we followed their advice.

Memory task

Declarative memory was assessed by a computer version of the well-known card game “Concentration” or “Memory” (created with E-Prime 2.1, Psychology Software Tools, USA) which consisted of a configuration of 15 card pairs (6 columns, 5 rows; motives were cartoon animals and everyday items). In the beginning of the encoding session, one pair after the other was displayed faceup by the computer for 2 s and then facedown again. Participants were instructed to memorize as many card locations as possible. After all pairs were shown faceup once, the procedure was repeated a second time. Then, one card (cue) of a pair was shown faceup by the computer and participants were asked to choose the corresponding second card (target) by using the computer mouse. If the decision was correct, a green checkmark appeared on the chosen position, and the next card was turned over by the computer. If the choice was wrong, then a red X appeared on the chosen card and the card’s correct location was displayed. This encoding procedure was repeated until participants made at least nine correct choices (60%). During the retrieval sessions, participants were presented with the same configuration; one cue card was displayed faceup and the target card had to be found using the computer mouse. After all 15 cue cards were presented once, the retrieval session was finished. Two sets of pictures with different positions were used, and their usage was counterbalanced over the experimental conditions. Although healthy children were confronted with only one experimental condition, half of them were confronted with the test material at the end of the diagnostic session. We did this in order to induce a comparable session effect in healthy controls as it might have been for patients. Dependent data were the percent of correctly identified positions. Memory performance was calculated as the difference between correctly identified card locations (in %) in the last round during the encoding phase (baseline) and the retrieval phase in the next morning (in %).

Transcranial oscillating direct current stimulation in ADHD

According to Marshall and colleagues, we employed the following toDCS protocol: two Ag/AgCl sintered skin electrodes (13 mm outer diameter; 8 mm inner diameter: 0.503 cm^2 contact area) were applied bilaterally at frontolateral locations (F3 and F4 of the international 10:20 system, see also Fig. 1). Two further electrodes of the same kind were used as ipsilateral references, one placed at the left and one placed at right mastoid (M1 and M2). While frontal electrodes were affixed by adhesive EC2 paste (Grass, USA), mastoid electrodes were filled with chloride, abrasive electrolyte paste and affixed by adhesive washers (Easycap, Germany). The resistance of all electrodes was below 5 kΩ. Anodal toDCS (i.e., positive polarity at both frontal sites) was applied by two battery-driven constant-current stimulators (neuroconn, Germany). Both stimulators (one for the left and one for the right hemisphere, F3-M1, F4-M2) were synchronized by a common trigger. The current strength of each anodal electrode ranged from 0 to 250 μA at a frequency of 0.75 Hz. The monophasic stimulation was sinusoidal, and the maximum current density per anodal electrode was 0.497 mA/cm^2 (250 μA/0.503 cm^2). Stimulation started 4 min after

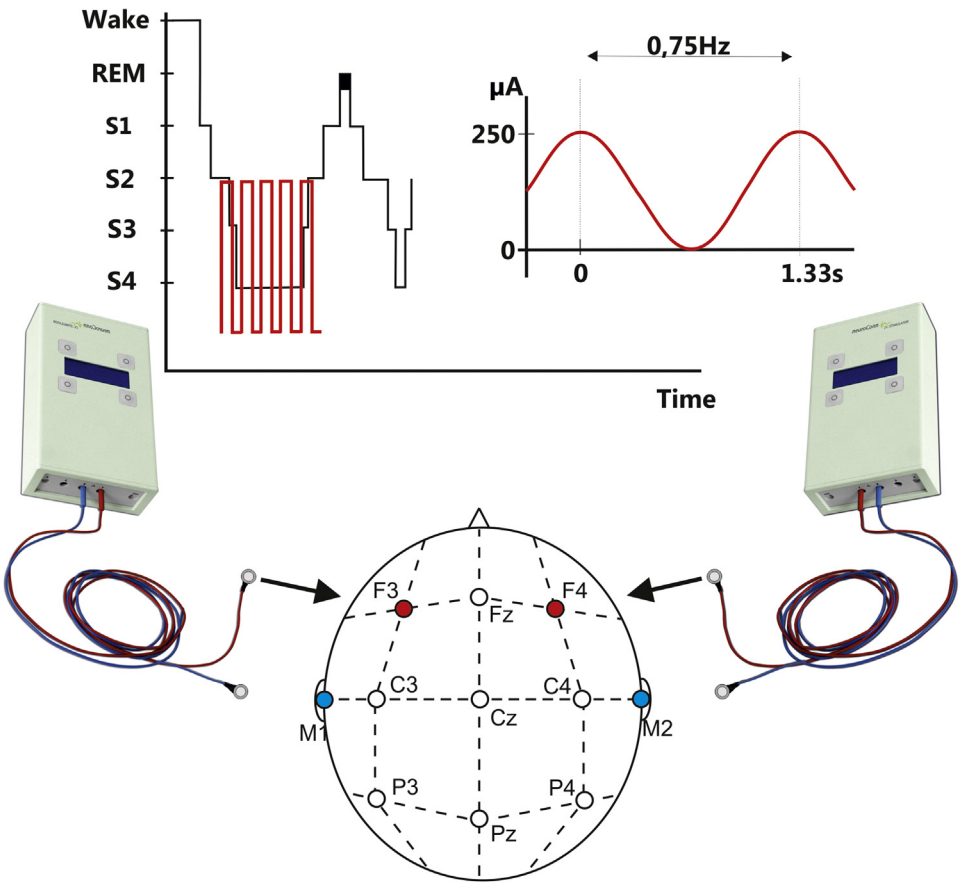

Figure 1. Sinusoidal toDCS of 0.75 Hz started 4 min after patients had entered non-REM sleep stage 2 for the first time (upper panel); stimulation units (5 × 5 min) were separated by 1-min stimulation-free intervals; while anodal electrodes were fixed over F3 and F4 (arrows), cathodal electrodes were placed over ipsilateral mastoids (M1 and M2; lower panel); REM, rapid eye movement.

patients had entered non-REM sleep stage 2 for the first time over a period of 5 × 5 min separated by 1 min intervals free of stimulation. In the sham control session, the electrodes were applied as in the stimulation sessions, but the stimulator remained off. Stimulation was not felt by the participants. After each application, electrodes were cleaned, chlorinated, and the conductivity was checked. If the quality of electrodes was compromised, then they were replaced by new ones; otherwise they were reused. For ethical reasons, toDCS was not applied in the healthy children's group.

Sleep recordings

ADHD patients spent three nights in the sleep laboratory. The first night was used for adaptation and diagnostic purposes. Here a standard polysomnogram (PSG) was recorded using a 16-channel PSG system (Somnomedics, Germany). EEG was recorded at a 256 Hz sampling rate with band-pass filter (0.2–35 Hz) according to the International 10–20 system from Fz, C3, Cz, C4, P3, Pz, P4, Oz and referenced to the tip of the nose with a ground placed at AFz. Diagonal EOG (sampling rate: 256 Hz, band-pass filter: 0.2–10 Hz) was recorded from the lower right and upper left canthi. EMG was recorded from the chin and from the left and right lower legs at 256 Hz with a high-pass filter set to 10 Hz. A thermistor (for monitoring nasal air flow), a nasal air pressure monitor, and a piezoelectric band (for determining thoracic wall motion) were also attached to the patients. During the experimental nights (stimulation and sham), only EEG, EOG, and EMG (chin) were recorded, and the following macro sleep parameters were obtained: time in bed (TIB), sleep onset latency (time in minutes from lights off to the first epoch of sleep stage 2), total sleep time, sleep efficiency (ratio of total sleep time to time in bed), number of awakenings, duration of wakefulness after sleep onset, sleep stages 1–4 and REM sleep (in minutes), and sleep stage change index (number of sleep stage changes per hour of sleep). Sleep stages were visually scored according to standard criteria [43] by a trained rater. Oscillatory EEG activity was obtained and analyzed from Fz, C3, Cz, C4, P3, Pz, P4, and Oz. The fast Fourier transform (FFT) algorithm was performed using Brain Vision Analyzer 2.0.4 (Brain Products, Germany). SO activity (0.6–1.1 Hz) was calculated during the five 1-min intervals after stimulation intervals. Only artifact-free epochs of 8-sec. duration were analyzed, and the truncating error was reduced by a Hanning window. The log-transformed absolute power values for SO were used for further analyzes. To reliably estimate differences in sleep stages and oscillatory activity between nights with stimulation and sham nights, all EEG epochs with distortion caused by toDCS in the stimulation night were correspondingly deleted from the sham night EEG after recording. For this purpose, we marked five intervals (each lasting 5 min) starting 4 min after patients had entered non-REM sleep stage 2. Intervals were separated by a 1-min break. Comparable to the stimulation night, we analyzed SO activity during these 1-min intervals after simulated stimulation.

Healthy controls slept at home. Here, two consecutive nights were used. In the first night, children were familiarized with the EEG recording system by sleeping with a dummy device. The following night was the experimental night where EEG signals from only one position (F4 referenced to M1 with a ground electrode placed at AFz) were recorded by a 3-channel Somnowatch plus system (Somnomedics, Germany). This setup was used to screen for TIB,

sleep onset latency, total sleep time, and non-REM sleep duration in minutes; a more detailed analysis of the EEG data was not possible.

Procedure

ADHD patients

Electrodes were affixed prior to each experimental night at 7 p.m. Thereafter, patients were asked to rate their emotional state using the SAM scales of valence, arousal, and dominance and their current tiredness using a visual analog scale (ranging from 0 "not at all" to 10 "completely exhausted"). Moreover, the subtest digit-span (forward and backward) from the Wechsler Intelligence Scale for Children [44] was conducted to assess the current working memory capacity. At 8 p.m., the memory encoding session took place. After reaching the criterion (at least 60% correctly identified pairs), patients were sent to bed at approximately 9 p.m. After children fell asleep, the investigator left the sleep laboratory. Unknown to the patients and the investigator, either a toDCS or a sham treatment was conducted by a briefed medical doctor. Patients were woken up by the blinded investigator at 7 a.m. After breakfast, patients were asked to rate their emotional state and their current tiredness and to work on the digit-span task before the retrieval session was carried out at 8 a.m. The order of conditions (stimulation/sham; each being conducted at least one week apart) and picture sets were counterbalanced across patients.

Healthy controls

Comparable to patients, electrodes were affixed in the beginning of the encoding session and children were asked to rate their emotional state and current tiredness using the same instruments as mentioned above. Then, at 8 p.m. the memory encoding phase began, and children were sent to bed after reaching the criterion of 60%. Children were woken up at 7 a.m. by their parents and the retrieval session took place at 8 a.m. To control for possible session effects that might have taken place in ADHD patients, half of the healthy children (randomly chosen) were familiarized with the parallel version of the memory task at the end of the diagnostic session. The other half was naïve to the memory task until the encoding session was conducted.

Statistical analyses

Since only children with ADHD but not healthy children received toDCS employing a full-factorial ANOVA-design was not possible, and the statistical analysis was two-fold: memory performance and control variables (SAM scales, digit-span, alertness ratings) in children with ADHD were analyzed each by a 2 × 2 ANOVA with the within factors STIM (stimulation vs. sham) and SESSION (learning vs. retrieval). To analyze memory performance and control variables between children with and without ADHD, single means were compared using Student's *t*-test for independent samples. Also, the analysis of polysomnographic data was twofold: Due to saturation of the EEG signal during the stimulation, the affected epochs (25 min in total) had to be excluded from the analysis. To estimate differences in sleep stages between stimulation and sham night in ADHD, we deleted the same number of epochs from sham night (see above). SO power during the 5 × 1 minute post-stimulation intervals was analyzed by a 2 × 8 ANOVA with the factors STIM and POSITION (Fz, C3, Cz, C4, P3, Pz, P4, and Oz). To compare sleep architecture in children with ADHD, Student's *t*-tests for dependent samples were used. In order to compare sleep between ADHD patients without stimulation (full data set) and healthy children, Student's *t*-tests for independent samples were used.

While the hypothesis that toDCS elevates sleep-dependent declarative memory performance in ADHD to the same level as in healthy controls was tested one-tailed, all other comparisons were calculated two-tailed. Alpha probability was set to 5%. Descriptive statistics were expressed as mean ± SEM. Data analysis was performed with IBM SPSS for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Declarative memory performance

The analysis of memory performance in children with ADHD revealed a significant interaction between the factors STIM (toDCS vs. sham) and SESSION (learning vs. retrieval) [$F(1,11) = 10.9$, $P = .007$; main effect for SESSION: $F(1,11) = 6.2$, $P = .03$; main effect for STIM: $F(1,11) = 1.0$, $P = .328$]. Subsequent *t*-tests showed that a memory loss over the retention interval was present in the sham condition [baseline: 67.5 ± 1.7; retrieval: 57.3 ± 3.0; $t(11) = 4.3$, $P = .001$] but not in the stimulation condition [baseline: 65.6 ± 1.6; retrieval: 66.2 ± 3.0; $t(11) = .22$, $P = .829$; see also Table 2 and Fig. 2]. These data confirm our hypothesis that sleep-dependent memory consolidation was higher in the stimulation than in the sham condition ($P = .004$, one-tailed).

As assumed, unstimulated children with ADHD displayed worse sleep-dependent memory consolidation than healthy controls [ADHD: −10.2 ± 2.4; controls: −2.3 ± 3.4; $t(22) = 1.9$, $P = .038$, one-tailed]. However after stimulation, the sleep-dependent memory performance did not differ between children with and without ADHD [ADHD: .5 ± 2.6; controls: −2.3 ± 3.4; $t(22) = .6$, $P = .520$]. There were no differences between groups with respect to baseline memory performance ($P > .4$).

Polysomnograhic data

The ANOVA of SO power during post-stimulation intervals in ADHD did not reveal any effects ($P < .09$). However, when the analysis was based only on sleep stage 4 epochs, there was a main effect of STIM, indicating that the SO activity in sleep stage 4 was significantly enhanced after tDCS (157 ± 17.4) compared to the sham condition [134 ± 12.7; $F(1,11) = 7.3$, $P = .02$; see also Fig. 3]. The main effect POSITION [$F(7,77) = 12.8$, $P > .001$] reflects that SO power was not distributed equally over the scalp, however the interaction STIM × POSITION was not significant [$F(7,77) = .49$, $P = .833$]. All macro sleep parameters (TIB, TST, sleep efficiency, and sleep stage durations) did not differ between stimulation and sham night ($P > .3$; see Table S1 in Supplement). Likewise, there were no differences in macro sleep parameters between ADHD during sham night and healthy children ($P > .5$; see Table S1 in Supplement).

Table 2
Results of memory performance.

	ADHD			Controls	Controls vs. sham	Controls vs. stim
	Sham mean (SEM)	Stimulation mean (SEM)	Stim vs. sham *P*	Mean (SEM)	*P*	*P*
Learning	67.5 (1.7)	65.6 (1.6)	.502	68.3 (3.1)	.815	.433
Retrieval	57.4 (3.0)	66.2 (3.0)	.076	66.0 (3.1)	.061	.954
Learning − retrieval	−10.2 (2.4)[a]	0.5 (2.6)	.004[b]	−2.3 (3.4)	.036[b]	.520

SEM, standard error of means; Stim, stimulation.
[a] different from zero ($P = .001$).
[b] one-tailed.

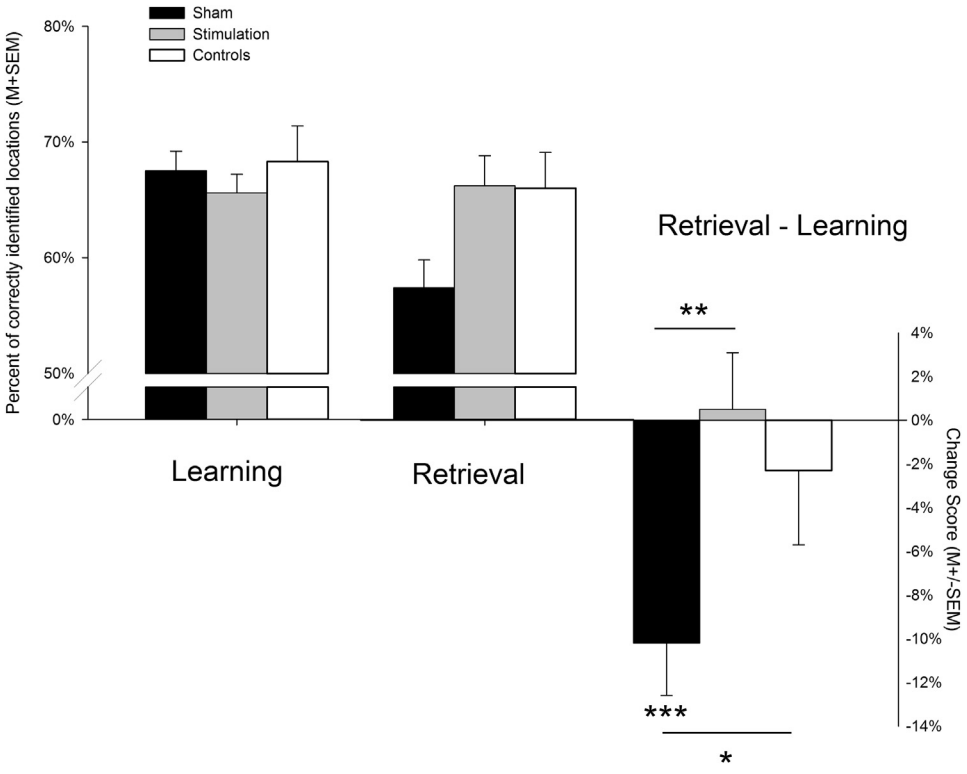

Figure 2. Memory performance; * $P < .036$ (one-tailed); ** $P = .004$ (one-tailed); *** $P = .001$.

Control variables

In children with ADHD, there were no significant main effects or interactions of STIM and SESSION with respect to mood ratings (SAM; $P > .1$) or digit-span performance ($P > .1$; for descriptive information see Table S2 in Supplement). Children with ADHD, in general, felt less alert before encoding compared to the retrieval session [$F(1,11) = 7.3$, $P = .021$], however, neither the main effect for STIM ($P = .6$) nor the interaction STIM × SESSION was significant ($P = .9$). In healthy children, there were no significant differences in mood/tiredness ratings or digit-span performance between encoding and retrieval sessions ($P > .09$). When comparing mood and alertness ratings between children with ADHD and healthy controls no significant differences were found ($P > .05$). The digit-span performance was worse in children with ADHD than in healthy controls in both encoding sessions [stim: $t(22) = 2.2$, $P = .041$; sham: $t(22) = 2.2$, $P = .041$] and by trend during stim retrieval session [stim: $t(22) = 1.8$, $P = .084$; sham: $t(22) = -.84$, $P = .386$].

Discussion

In this study we investigated whether an external enhancement of slow oscillations (SO) by transcranial oscillating direct current stimulation (toDCS) could elevate sleep-dependent memory in children with ADHD to the level of healthy controls. While children

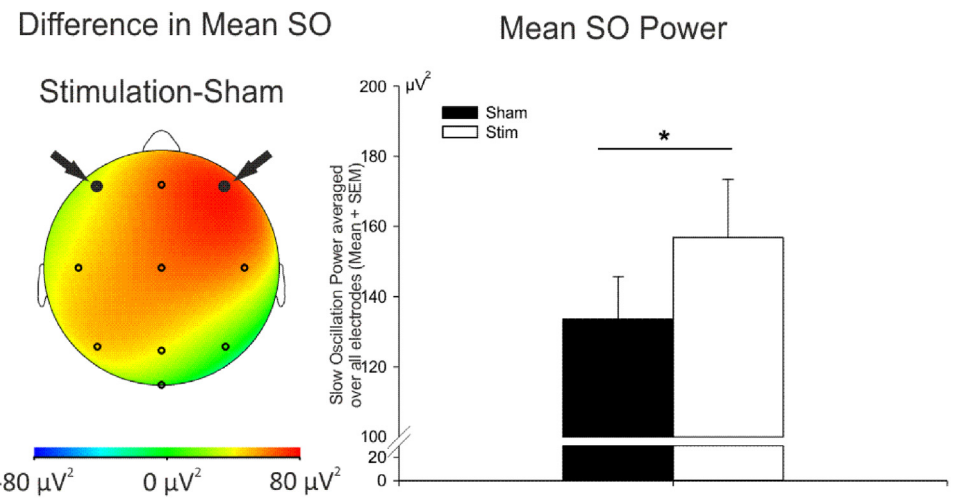

Figure 3. Difference in mean SO power (slow oscillations; 0.6–1.1 Hz) between 1-min intervals after stimulation and comparable intervals during sham night (left panel); arrows indicate location of stimulation; differences in SO power averaged over all electrodes (right panel); Stim, stimulation; * $P = .02$.

with ADHD during sham condition showed worse memory performance than healthy controls, this memory deficit vanished after applying toDCS during sleep.

Children and adults suffering from ADHD are known to display long-term memory deficits [9,45] which are often ascribed to deviant encoding rather than to problems during consolidation or retrieval [6]. Studies concerning long-term memory performance, however, often focused on memory encoding and retrieval on the same day, thus neglecting the supporting role of sleep in memory performance. In our previous studies, we controlled for sleep/wake states and observed deficits in sleep-dependent consolidation of long-term declarative memory (picture recognition) in ADHD. Most strikingly, reduced memory performance in ADHD after sleep was linked to SO activity during sleep [34,37].

As shown by Marshall and colleagues, frontally applied anodal toDCS in healthy adults can remarkably improve the sleep-dependent consolidation of declarative memory [32,33]. SO synchronizes hippocampal sharp wave ripple activity and thus fosters the integration of newly encoded hippocampus-related memories into already existing memory networks located in the neocortex [27,31,46]. Children suffering from ADHD are suspected to display less frontal slow wave activity during sleep [35]. Therefore, the external induction of frontal SO by toDCS in our study might have superimposed deficient SO functionality during sleep and thereby normalized sleep-dependent memory consolidation in children with ADHD.

Since the ethic committee did not support the proposal to stimulate healthy children by toDCS, children of the control group performed the experimental tasks at home and also slept in their own bed. This might lead to the concern that experimental sessions were not comparable between the two groups. Indeed, based on the findings that healthy children display worse cognitive performance at home than under laboratory conditions [47], differences between healthy children and children with ADHD in memory performance might have been even underestimated. To ensure that the home environment and laboratory conditions were comparable as much as possible, parents of control children were instructed to provide a quiet, room with an unstimulating workplace and to take care that no disturbing events happened during the sessions. Moreover, by introducing a learning criterion (60% correctly identified pair locations), we made sure that patients and healthy children ended the encoding session on a comparable level of encoded items. In the same way patients and healthy children during sham night did not differ in sleep length, efficiency and architecture, or in self-rated tiredness or mood. Therefore, we doubt that differences in memory performance can be attributed to different experimental conditions.

The therapeutic benefit of brain stimulation by modulating cortical excitability and restoring neuronal networks in psychiatric patients becomes more and more evident [48–50]. For example, in the case of depression the positive effect of tDCS can last for weeks [51]. This, however, might lead to the concern that stimulation did not boost sleep-dependent memory consolidation itself but rather induced a non-specific cognitive enhancement supporting retrieval performance on the next morning. Please note that only memory performances but not the performance on any control variable (mood, alertness, or working memory performance) was affected by the stimulation. Moreover, our stimulation method did not follow the usual tDCS protocols for the treatment of clinical symptoms during daytime as reviewed by [48,49]: a) in comparison to most other studies, we applied DC only in one single stimulation session; b) the applied current strength in our study was significantly lower than in other studies (0.25 mA vs. 1–2 mA); and c) DC stimulation in our study was not constant above 1 mA (or higher) but oscillating, ranging from zero to a maximum of 0.25 mA. In addition, there is evidence that toDCS only at 0.75 Hz (not at 5 Hz) and applied only during sleep leads to an increase of memory consolidation [32,52,53]. In the same way, Mölle and colleagues replicated a comparable memory-boosting effect by using acoustic instead of electrical stimulation: every time an SO wave (<1 Hz) was detected in the sleep EEG signal, a short burst of noise was applied to increase the SO amplitude which resulted in elevated hippocampus-related memory consolidation during sleep [54,55].

It should be mentioned that toDCS might not be suitable to improve declarative memory performance in all populations. While healthy adults [32,33], adults suffering from schizophrenia [56], and children with ADHD benefited from toDCS during sleep, elderly healthy participants did not [57]. Of course, slight differences in stimulation protocol between the studies should be taken into account. However, due to fundamental changes in sleep architecture and sleep regulation with age [58], it seems plausible to assume that the benefit of toDCS may also change with age [57]. However, not only replications of our study outcome are required, but also further studies including other groups of young patients with deficits in declarative memory (e.g. epilepsy [59] or Down's syndrome [60]) are necessary in order to draw a conclusion as to whether or not toDCS can reduce memory deficits until mid-age.

Although using toDCS seems promising to enhance sleep-dependent memory performance in ADHD, its application during sleep still requires sophisticated technical support. A more practical approach, however, comes from the field of sports medicine: intensive physical exercise during the daytime increases endogenous slow wave activity during subsequent sleep [61]. It therefore seems necessary to investigate whether or not an enhancement of endogenous SO (e.g. through physical activity) could improve sleep-dependent memory consolidation in children with ADHD in the same way as toDCS did.

Conclusion

Here, we observed that toDCS during early sleep enhanced slow oscillation power and elevated memory consolidation to the level of healthy controls. These findings are of interest because the first ADHD symptoms usually occur before the age of 7, and the disorder is accompanied by significant school problems often resulting in academic underachievement. Indeed, ADHD symptoms can improve after puberty but gaps in education remain. ADHD drugs improve the ability to encode scholastic knowledge during the daytime but their therapeutic effects vanish toward the evening due to their short half-life. Thus, supporting sleep-dependent memory functions might help to treat childhood ADHD more thoroughly.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.brs.2014.07.036.

References

[1] Willcutt EG. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. Neurotherapeutics 2012;9:490–9.
[2] Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry 2007;164:942–8.

[3] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 2000. DSM IV-TR.

[4] Hart H, Radua J, Mataix-Cols D, Rubia K. Meta-analysis of fMRI studies of timing in attention-deficit hyperactivity disorder (ADHD). Neurosci Biobehav Rev 2012;36:2248–56.

[5] Cubillo A, Halari R, Smith A, Taylor E, Rubia K. A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with attention deficit hyperactivity disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. Cortex 2012;48:194–215.

[6] Skodzik T, Holling H, Pedersen A. Long-term memory performance in adult ADHD: a meta-analysis. J Atten Disord 2013 Nov 14. Available from: http://jad.sagepub.com/content/early/2013/11/14/1087054713510561.

[7] Krauel K, Duzel E, Hinrichs H, Santel S, Rellum T, Baving L. Impact of emotional salience on episodic memory in attention-deficit/hyperactivity disorder: a functional magnetic resonance imaging study. Biol Psychiatry 2007;61:1370–9.

[8] Prehn-Kristensen A, Krauel K, Hinrichs H, et al. Methylphenidate does not improve interference control during a working memory task in young patients with attention-deficit hyperactivity disorder. Brain Res 2011;1388:56–68.

[9] Rhodes SM, Coghill DR, Matthews K. Neuropsychological functioning in stimulant-naive boys with hyperkinetic disorder. Psychol Med 2005;35:1109–20.

[10] Valera EM, Faraone SV, Biederman J, Poldrack RA, Seidman LJ. Functional neuroanatomy of working memory in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry 2005;57:439–47.

[11] Choo WC, Lee WW, Venkatraman V, Sheu FS, Chee MW. Dissociation of cortical regions modulated by both working memory load and sleep deprivation and by sleep deprivation alone. Neuroimage 2005;25:579–87.

[12] Curcio G, Ferrara M, De Gennaro L. Sleep loss, learning capacity and academic performance. Sleep Med Rev 2006;10:323–37.

[13] Drummond SP, Brown GG, Gillin JC, Stricker JL, Wong EC, Buxton RB. Altered brain response to verbal learning following sleep deprivation. Nature 2000;403:655–7.

[14] Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. Semin Neurol 2005;25:117–29.

[15] Killgore WD. Effects of sleep deprivation on cognition. Prog Brain Res 2010;185:105–29.

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

[17] Cortese S, Konofal E, Yateman N, Mouren MC, Lecendreux M. Sleep and alertness in children with attention-deficit/hyperactivity disorder: a systematic review of the literature. Sleep 2006;29:504–11.

[18] Gruber R, Grizenko N, Schwartz G, Bellingham J, Guzman R, Joober R. Performance on the continuous performance test in children with ADHD is associated with sleep efficiency. Sleep 2007;30:1003–9.

[19] Owens J. Sleep in children with attention deficit/hyperactivity disorder. In: Clete K, editor. Encyclopedia of sleep – assessment, methodology, training, and policies of sleep. 1st ed. Waltham: Academic Press; 2013. p. 625–7.

[20] Schredl M, Alm B, Sobanski E. Sleep quality in adult patients with attention deficit hyperactivity disorder (ADHD). Eur Arch Psychiatry Clin Neurosci 2006;257:164–8.

[21] O'Brien LM, Holbrook CR, Mervis CB, et al. Sleep and neurobehavioral characteristics of 5- to 7-year-old children with parentally reported symptoms of attention-deficit/hyperactivity disorder. Pediatrics 2003;111:554–63.

[22] Cohen-Zion M, Ancoli-Israel S. Sleep in children with attention-deficit hyperactivity disorder (ADHD): a review of naturalistic and stimulant intervention studies. Sleep Med Rev 2004;8:379–402.

[23] O'Brien LM. The neurocognitive effects of sleep disruption in children and adolescents. Child Adolesc Psychiatr Clin N Am 2009;18:813–23.

[24] Kirov R, Brand S. Sleep problems and their effect in ADHD. Expert Rev Neurother 2014;14:287–99.

[25] Diekelmann S, Born J. The memory function of sleep. Nature reviews. Neuroscience 2010;11:114–26.

[26] Wilhelm I, Prehn-Kristensen A, Born J. Sleep-dependent memory consolidation - what can be learnt from children? Neurosci Biobehav Rev 2012;36:1718–28.

[27] Rasch B, Born J. About sleep's role in memory. Physiol Rev 2013;93:681–766.

[28] Van Someren EJ, Van Der Werf YD, Roelfsema PR, Mansvelder HD, da Silva FH. Slow brain oscillations of sleep, resting state, and vigilance. Prog Brain Res 2011;193:3–15.

[29] Massimini M, Huber R, Ferrarelli F, Hill S, Tononi G. The sleep slow oscillation as a traveling wave. J Neurosci 2004;24:6862–70.

[30] Murphy M, Riedner BA, Huber R, Massimini M, Ferrarelli F, Tononi G. Source modeling sleep slow waves. Proc Natl Acad Sci U S A 2009;106:1608–13.

[31] Molle M, Born J. Slow oscillations orchestrating fast oscillations and memory consolidation. Prog Brain Res 2011;193:93–110.

[32] Marshall L, Helgadottir H, Molle M, Born J. Boosting slow oscillations during sleep potentiates memory. Nature 2006;444:610–3.

[33] Marshall L, Mölle M, Hallschmid M, Born J. Transcranial direct current stimulation during sleep improves declarative memory. J Neurosci 2004;24:9985–92.

[34] Prehn-Kristensen A, Goder R, Fischer J, et al. Reduced sleep-associated consolidation of declarative memory in attention-deficit/hyperactivity disorder. Sleep Med 2011;12:672–9.

[35] Ringli M, Souissi S, Kurth S, Brandeis D, Jenni OG, Huber R. Topography of sleep slow wave activity in children with attention-deficit/hyperactivity disorder. Cortex 2013;49:340–7.

[36] Prehn-Kristensen A, Molzow I, Munz M, et al. Sleep restores daytime deficits in procedural memory in children with attention-deficit/hyperactivity disorder. Res Dev Disabil 2011;32:2480–8.

[37] Prehn-Kristensen A, Munz M, Molzow I, Wilhelm I, Wiesner CD, Baving L. Sleep promotes consolidation of emotional memory in healthy children but not in children with attention-deficit hyperactivity disorder. PLoS One 2013;8:e65098. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3667133/.

[38] Delmo C, Weiffenbach O, Gabriel M, Bölte S, Marchio E, Poustka F. Fragebogen für affektive störungen und schizophrenie für kinder im schulalter (6–18 jahre). 3rd ed. Frankfurt: Klinik für Psychiatrie und Psychotherapie des Kindes- und Jugendalters; 2000.

[39] Kaufman J, Birmaher B, Brent D, et al. Schedule for affective disorders and schizophrenia for school-age children - present and lifetime version (k-sads-pl): Initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997;36:980–8.

[40] Achenbach TM. Manual for the child behavior checklist/4-18 and 1991 profile. Burlington,Vermont: Department of Psychiatry, University of Vermont; 1991.

[41] Weiß RH. Grundintelligenztest skala 2 revision, cft 20-r. Göttingen: Hogrefe; 2006.

[42] Lamberti G, Weidlich S. Dcs - a visual learning and memory test for neuropsychological assessment. 3rd ed. Goettingen: Hogrefe; 1999.

[43] Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages in human subject. Washington DC: US Government Printing Office, National Institute of Health Publication; 1968.

[44] Wechsler D. Wechsler intelligence scale for children – fourth edition (wisc-iv). San Antonio, TX: The Psychological Corporation; 2003.

[45] Cutting LE, Koth CW, Mahone EM, Denckla MB. Evidence for unexpected weaknesses in learning in children with attention-deficit/hyperactivity disorder without reading disabilities. J Learn Disabil 2003;36:259–69.

[46] Born J, Wilhelm I. System consolidation of memory during sleep. Psychol Res 2012;76:192–203.

[47] Raz S, Bar-Haim Y, Sadeh A, Dan O. Reliability and validity of the online continuous performance test among young adults. Assessment 2012;21:108–18.

[48] Kuo MF, Paulus W, Nitsche MA. Therapeutic effects of non-invasive brain stimulation with direct currents (TDCS) in neuropsychiatric diseases. Neuroimage 2014;85(Pt 3):948–60.

[49] Demirtas-Tatlidede A, Vahabzadeh-Hagh AM, Pascual-Leone A. Can noninvasive brain stimulation enhance cognition in neuropsychiatric disorders? Neuropharmacology 2013;64:566–78.

[50] Fregni F, Pascual-Leone A. Technology insight: noninvasive brain stimulation in neurology-perspectives on the therapeutic potential of RTMS and TDCS. Nat Clin Pract Neurol 2007;3:383–93.

[51] Nitsche MA, Boggio PS, Fregni F, Pascual-Leone A. Treatment of depression with transcranial direct current stimulation (TDCS): a review. Exp Neurol 2009;219:14–9.

[52] Kirov R, Weiss C, Siebner HR, Born J, Marshall L. Slow oscillation electrical brain stimulation during waking promotes eeg theta activity and memory encoding. Proc Natl Acad Sci U S a 2009;106:15460–5.

[53] Marshall L, Kirov R, Brade J, Molle M, Born J. Transcranial electrical currents to probe eeg brain rhythms and memory consolidation during sleep in humans. PLoS One 2011;6:e16905. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3038929/.

[54] Ngo HV, Claussen JC, Born J, Molle M. Induction of slow oscillations by rhythmic acoustic stimulation. J Sleep Res 2013;22:22–31.

[55] Ngo HV, Martinetz T, Born J, Molle M. Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. Neuron 2013;78:545–53.

[56] Goder R, Baier PC, Beith B, et al. Effects of transcranial direct current stimulation during sleep on memory performance in patients with schizophrenia. Schizophr Res 2013;144:153–4.

[57] Eggert T, Dorn H, Sauter C, Nitsche MA, Bajbouj M, Danker-Hopfe H. No effects of slow oscillatory transcranial direct current stimulation (TDCS) on sleep-dependent memory consolidation in healthy elderly subjects. Brain Stimul 2013;6:938–45.

[58] Pace-Schott EF, Spencer RM. Age-related changes in the cognitive function of sleep. In: Green AM, Chapman CE, Kalaska JF, Lepore F, editors. Prog brain res. Amsterdam, The Netherlands: Elsevier; 2011. p. 75–89.

[59] Urbain C, Galer S, Van Bogaert P, Peigneux P. Pathophysiology of sleep-dependent memory consolidation processes in children. Int J Psychophysiol 2013;89:273–83.

[60] Lott IT, Dierssen M. Cognitive deficits and associated neurological complications in individuals with Down's syndrome. Lancet Neurol 2010;9:623–33.

[61] Dworak M, Wiater A, Alfer D, Stephan E, Hollmann W, Struder HK. Increased slow wave sleep and reduced stage 2 sleep in children depending on exercise intensity. Sleep Med 2008;9:266–72.