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Boosting Slow Oscillatory Activity Using tDCS during Early Nocturnal Slow Wave Sleep Does Not Improve Memory Consolidation in Healthy Older Adults

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ABSTRACT

Background: Previous studies have demonstrated an enhancement of hippocampal-dependent declarative memory consolidation, associated slow wave sleep (SWS) and slow wave activity (SWA) after weak slow oscillatory stimulation (so-tDCS) during early non-rapid eye movement sleep (NREM) in young adults. Recent studies in older individuals could not confirm these findings. However, it remained unclear if this difference was due to variations in study protocol or to the age group under study.
Objective/Hypothesis: Here, we asked if so-tDCS promotes neurophysiological events and associated sleep-dependent memory in the visuo-spatial domain in older adults, using a stimulation protocol that closely resembled the one employed in young adults.
Methods: In a randomized, placebo-controlled single-blind (participant) crossover study so-tDCS (0.75 Hz; max. current density 0.522 mA/cm^2) vs. sham stimulation was applied over the frontal cortex of 21 healthy older subjects. Impact of stimulation on frequency band activity (linear mixed models), two declarative and one procedural memory tasks (repeated measures ANOVA) and percentage of sleep stages (comparison of means) was assessed.
Results: so-tDCS, as compared to sham, increased SWA and spindle activity immediately following stimulation, accompanied by significantly impaired visuo-spatial memory consolidation. Furthermore, verbal and procedural memory remained unchanged, while percentage of NREM sleep stage 4 was decreased over the entire night (uncorrected).
Conclusion: so-tDCS increased SWA and spindle activity in older adults, events previously associated with stimulation-induced improved consolidation of declarative memories in young subjects. However, consolidation of visuo-spatial (primary outcome) and verbal memories was not beneficially modulated, possibly due to decline in SWS over the entire night that may have prevented and even reversed immediate beneficial effects of so-tDCS on SWA.

Introduction

Sleep is a critical mediator of memory consolidation [1]. Robust empirical evidence, although mostly obtained from healthy young subjects, demonstrates beneficial effects of nocturnal sleep on subsequent consolidation of hippocampal-dependent declarative memory. Especially slow oscillatory activity (<1 Hz), predominant in slow wave sleep (SWS), and sleep spindles have been implicated in the enhanced consolidation effect [2]. Here, newly acquired, initially labile information may be transferred from the hippocampus to the neocortex, and become integrated into pre-existing memory traces over time by reciprocal hippocampal–neocortical communication mediated by slow oscillations (SO) [3,4]. Cortical EEG-SO reflect synchronized neuronal activity that switches between

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hyperpolarized down-states and depolarized up-states. SO are mainly generated in prefrontal areas [5] and are thought to synchronize neuronal activity in other memory-relevant brain regions, i.e., by grouping top-down hippocampal sharp wave ripples with co-occurring thalamo-cortical spindles to SO up-states [6,7].

Transcranial direct current stimulation is a non-invasive technique known to modulate neuronal excitability and plasticity [8], and is now a widely used tool in cognitive and clinical research [9]. Marshall et al. [10] adopted this method by using a sinusoidally oscillating current (so-tDCS) within the frequency band of SWS (0.7–0.8 Hz) to induce "cortical slow oscillations" during nocturnal sleep in young healthy adults. They demonstrated that exogenous application of so-tDCS improved recall of word-pairs after nocturnal sleep and enhanced SO activity as well as density of frontal slow sleep spindles, but see also Ref. 11 for negative results on sleep physiology and memory consolidation after square-wave oscillating currents in young adults.

Given well-documented age-related changes in sleep parameters, most notably those linked to consolidation, i.e., decrease in SWS, frontal slow wave activity (SWA), number, density and duration of sleep spindles [12,13], the findings of Marshall and colleagues [10,14] open the exciting possibility that so-tDCS could be used to boost SO during SWS and thus to improve associated memory consolidation in older adults. To date only one study [15] has examined this hypothesis for nocturnal stimulation in older subjects. This study failed to show a beneficial effect on memory or sleep parameters, possibly due to their pre-programmed stimulation protocol that did not allow for adaption of stimulation on age-dependent changes in sleep architecture such as higher sleep fragmentation. However, recent findings [16,17] demonstrated that so-tDCS during an afternoon nap increased EEG power in the SWA in older adults and resulted in improved memory consolidation.

Here, we investigate in a randomized, counterbalanced within-subject design whether so-tDCS during early nocturnal non-REM sleep stages (NREM) modulates neurophysiological events previously associated with memory consolidation such as EEG power in SO and sleep spindle frequency band also in older healthy adults and promotes memory consolidation in a visuo-spatial task of which the performance is known to decline with advancing age [12]. For comparison with previous studies, further exploratory analyses were added, assessing the influence of so-tDCS on verbal (word-pair) and procedural (finger-sequence tapping) memory, as well as the impact on the time spent in sleep stages.

Materials and methods

Subjects

Healthy older subjects aged between 50 and 80 years were recruited via advertisements in the local database of Charité University Hospital Berlin, Germany. They were pre-screened by a structured telephone interview for major exclusion criteria (severe untreated medical, neurological and psychiatric diseases, sleep disturbances, contraindications for magnetic resonance imaging (MRI), current intake of medication that affect the central nervous system, and non-native German speakers). Thirty-two eligible subjects then underwent a screening at the laboratory including medical and neurological examination comprising MRI, blood samples and cognitive testing with The Consortium to establish a Registry for Alzheimer's Disease (CERAD [18]) to ensure no subjective or objective memory complaints (CERAD results within 1.5 SD of age/education norms) or cognitive impairments (Mini Mental State Examination [19], exclusion if score <27 points). Psychiatric comorbidity was monitored by Beck's Depression Inventory (BDI [20]) and State Trait Anxiety Inventory (STAI-G X1 [21]). Eight subjects were excluded due to failing the criteria.

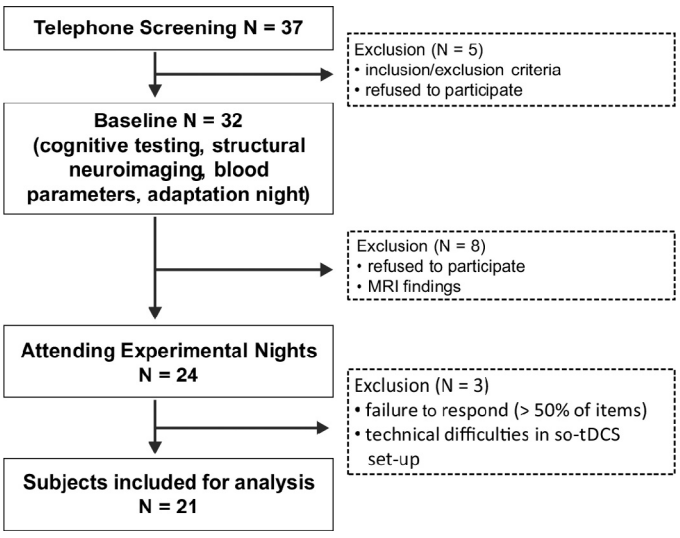

Figure 1. Flow chart of the study. Of 37 volunteers who were screened for inclusion and exclusion criteria, 32 subjects completed baseline sessions including cognitive testing, structural neuroimaging and assessment of blood parameters. Eight participants had to be excluded following baseline visits and before entering sleep sessions because of MRI findings (small strokes in memory-related brain areas) or because they refused to participate. Three subjects had to be excluded due to failure to respond for >50% of items in the visuo-spatial task and technical reasons, leaving 21 subjects for final analysis.

Out of the 24 participants that had entered the main study, including baseline visits and sleep sessions (see also Fig. 1), 3 subjects had to be excluded due to technical problems in so-tDCS set-up or failure to respond for >50% of items in the visuo-spatial task. Thus, 21 subjects remained (11 male; mean age 65 ± 1, mean years of education 17 ± 4) for final analysis. They did not differ from excluded participants in sex, age and education. For sleep stage analyses of the entire night data from two further subjects had to be excluded due to incomplete EEG recordings.

Baseline assessments

In addition, participants underwent a standard neuropsychological test battery assessing verbal memory (German version of Auditory Verbal Learning Test (AVLT [22]), working memory [23], and executive functions (Stroop color-word-test [24]). The affective state at the time of testing was determined by the Positive and Negative Affective Scale (PANAS [25]). Subjective and objective sleep habits were recorded by the German version of Pittsburgh Sleep Quality Index (PSQI [26]), German version of Epworth Sleepiness Scale (ESS [27]), German version of Morningness–Eveningness-Questionnaire (d-MEQ [28]) and the Essener questionnaire on age and sleepiness ("Essener Fragenbogen Alter und Schläfrigkeit" [29]).

Sleep diaries and actigraphy (Actigraph GT3X+, LLC Pensacola, USA) were used to monitor regular sleep–wake-cycles one week prior to each experimental night. To ensure similar conditions between experimental nights (so-tDCS vs. sham), participants were further asked to avoid caffeinated drinks or alcohol during the last 1.5 h before starting each experimental night and to maintain normal sleep duration the night before. Adherence to these instructions was evaluated before starting the experimental night, using a questionnaire which also gathered current wellbeing (yes or no) as well as a subjective rating of sleep quality of the last night (scale ranging from 0 – miserable to 6 – excellent).