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Brain stimulation during an afternoon nap boosts slow oscillatory activity and memory consolidation in older adults

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ABSTRACT

Sleep-related consolidation of declarative memories, as well as associated neurophysiological events such as slow oscillatory and spindle activity, deteriorate in the course of aging. This process is accelerated in neurodegenerative disease. Transcranial slow oscillatory stimulation (so-tDCS) during sleep has been shown to enhance slow oscillatory brain activity and thereby improve memory consolidation in young subjects. Here, we investigated whether so-tDCS applied to older adults during an afternoon nap exerts similar effects.

Eighteen older human subjects were assessed using visuo-spatial (picture memory, primary, and location memory) and verbal memory tasks before and after a 90-min nap either comprising weak so-tDCS at 0.75 Hz over fronto-central location or sham (no) stimulation in a within-subject design. Electroencephalographic activity was recorded throughout the naps and immediate effects of stimulation on brain activity were evaluated. Here, spectral power within three frequency bands of interest were computed, i.e., slow oscillatory activity, slow spindle and fast spindle activity; in 1-min stimulation-free intervals following 5 stimulation blocks.

So-tDCS significantly increased frontal slow oscillatory activity as well as fast spindle activity, and significantly improved picture memory retention after sleep. Retention in the location memory subtask and in the verbal memory task was not affected. These findings may indicate a novel strategy to counteract cognitive decline in aging in a convenient manner during brief daytime naps.

Introduction

Sleep plays a pivotal role in memory consolidation (for review, see Rasch and Born, 2013). Even short naps of 1–2 h lead to considerable improvements of memory retention performance (Tucker et al., 2006; Van der Helm et al., 2011). There is convergent evidence that the beneficial effects of sleep on declarative memory are associated with characteristic field potential oscillations measured by electroencephalography during non-rapid eye movement (NREM) sleep, such as slow oscillations (SO, <1 Hz; Marshall et al., 2006; Mölle et al., 2009; Diekelmann and Born, 2010) and sleep spindles (8–15 Hz; Gais et al., 2002; Schabus et al., 2004; Tamminen et al., 2011). According to the active system consolidation hypothesis (Born and Wilhelm, 2012; Diekelmann and Born, 2010), newly acquired declarative memories are initially encoded into hippocampal networks during wakefulness. During subsequent sleep, these memory traces are repeatedly activated, accompanied by hippocampal sharp-wave ripples, and gradually transferred to neocortical sites for long-term storage. According to the model, SOs play an important role in this process. They stimulate the redistribution of hippocampal memories toward neocortical sites by temporally grouping spindles with hippocampal sharp-wave ripples (Buzsáki, 1998; Mölle et al., 2002; Steriade, 2006). Previous studies revealed that slow spindles (8–12 Hz) are strongest in the frontal region and fast spindles (12–15 Hz) are mainly distributed over the central and parietal regions (Mölle et al., 2011). Both types of spindles further differ in their circadian and homeostatic regulation, their age-related changes (Doran, 2003), as well as their pharmacological properties (Ayoub et al., 2013). Fast spindles, as compared to slow spindles, have been

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more consistently linked to memory consolidation effects (Rasch and Born, 2013).

A study that specifically induced an increase in endogenous slow oscillation activity by transcranial application of slow oscillatory stimulation (so-tDCS) during NREM sleep improved declarative memory consolidation after a full night of sleep in healthy young subjects (Marshall et al., 2004, 2006). This type of stimulation within the frequency range of slow oscillatory activity (0.7–0.8 Hz) applied during early nocturnal sleep increased frontal SO as well as frontal slow spindle activity and in parallel enhanced the overnight retention of word-pair memories.

In the course of aging, sleep quality, including SO and spindle activity, declines, with associated deterioration in declarative memory consolidation (Backhaus et al., 2007; Mander et al., 2013, 2014). This process is accelerated in Alzheimer's disease (AD, Wang et al., 2011) and its precursor mild cognitive impairment (Westerberg et al., 2012). Therefore, findings of improved sleep parameters by means of so-tDCS might open novel strategies to counteract age-associated detrimental changes. However, previous studies on so-tDCS effects in older adults have yielded inconsistent findings. One study in older adults using so-tDCS during nocturnal sleep could not show an improvement of memory-relevant sleep parameters and overnight retention performance on a word-pair association task (Eggert et al., 2013). Here, small but possibly important differences in stimulation protocol may have prevented beneficial effects. For example, Eggert et al. included a current ramping at the beginning and end of each stimulation interval, which might have prevented entrainment of slow oscillatory activity by the stimulation. Differences in the applied current (0.331 mA/cm^2 vs. 0.517 mA/cm^2) and the type of Ag–AgCl electrodes (non-sintered vs. sintered) as compared to Marshall et al. (2006) may have also affected the stimulation outcome. In addition, their stimulation protocol did not account for changes in sleep characteristics of older adults, such as higher sleep fragmentation. This might be a crucial issue, since so-tDCS effects seem to critically depend on ongoing brain state (Kanai et al., 2008; Kirov et al., 2009; Marshall et al., 2011). A recent study on so-tDCS during an afternoon nap in older subjects, however, was able to demonstrate improvement in word-pair recall, and increase in SO activity (Westerberg et al., 2015). However, this study failed to enhance memory for associative fact-face information, possibly due to differences in underlying cognitive processes (forced-choice vs. yes–no recognition) and associated brain structures. Note also that a forced-choice recognition task, in which the familiarity system is more strongly involved than recollection processes, was employed here (Westerberg et al., 2006), and it is known that the contribution of the hippocampus to familiarity-based decisions is limited (Sauvage et al., 2007; Yonelinas et al., 2005). Therefore, the face-fact recognition task might not have been sensitive to so-tDCS-induced effects on sleep physiology.

Given the mixed findings so far, and a focus primarily on verbal information (Barham et al., 2016), additional research is needed to explore the efficacy of so-tDCS in relation to sleep and memory consolidation especially in older adults. Thus, the present study examined the impact of so-tDCS on memory-relevant sleep parameters, similar to previous studies, and for the first time investigated so-tDCS effects on consolidation of memories in a visuo-spatial memory task combing visual (primary) with more complex (location) memory in older adults. These functions are important in everyday life (Bishop et al., 2010; Flöel et al., 2012) and known to decline with advancing age (Hedden and Gabrieli, 2004). Visual recognition memory, in particular, is impaired early in the course of AD (Barbeau et al., 2004) and might thus be a promising target for interventional approaches.

Specifically, we hypothesized that (i) so-tDCS during napping benefits the offline retention performance of visual declarative memory (picture recognition) and that (ii) so-tDCS enhances memory-relevant sleep parameters such as endogenous slow oscillatory and spindle activity relative to sham condition. For comparison with previous studies (Eggert et al., 2013; Westerberg et al., 2015), consolidation of word-pair recall was also assessed, in addition to a procedural control task (Eggert et al., 2013; Göder et al., 2016; Marshall et al., 2006, 2011; Prehn-Kristensen et al., 2014). Here, we hypothesized that location and verbal memory would likewise benefit from so-tDCS during the nap. No modulation, however, was expected for procedural memory, given the absence of so-tDCS effects for procedural memory in previous studies (Marshall et al., 2006, 2011).

Important from a practical point of view, it might be sufficient to apply so-tDCS during a daytime nap (Antonenko et al., 2013; Del Felice et al., 2015; Westerberg et al., 2015), thus avoiding the more inconvenient setup of nocturnal stimulation (i.e., stressful due to testing in the late evening, and unfamiliar environment during nocturnal sleep). Hence, in the present study, stimulation was applied during an afternoon nap. Sleep was monitored following each stimulation block and stimulation was only applied during NREM sleep stage 2, 3, and 4.

Materials and methods

Participants

Healthy older adults aged between 50 and 80 years were recruited via a local database of the Charité University Hospital Berlin, Germany, and 54 underwent a structured telephone interview to clarify major exclusion criteria, including history of severe untreated medical, neurological, and psychiatric diseases; subjective cognitive decline; sleep disorders; cognitive impairment; intake of medication acting primarily on the central nervous system (e.g., antipsychotics, antidepressants, benzodiazepines, or any type of over-the-counter sleep-inducing drugs like valerian); daily consumption of >50 g of alcohol or >10 cigarettes; and not native German speaking.

During baseline visits, eligible subjects underwent a medical and neuropsychological screening comprising magnetic resonance imaging (MRI) of the brain for neuroradiological evaluation (exclusion if brain tumor or previous stroke was detected) and cognitive screening with the Mini-Mental State Examination (exclusion if scores <27 points; Folstein et al., 1975) and the Consortium to establish a Registry for Alzheimer's Disease (CERAD-Plus; www.memoryclinic.ch; exclusion if verbal recall below 1.5 SD of age/education norms). Moreover, psychiatric comorbidity was monitored by Beck's Depression Inventory-II (BDI-II, exclusion if BDI-scores ≥13; Kuehner et al., 2007) and State Trait Anxiety Inventory (STAI- X1, exclusion if STAI-X1 score ≥ 40; Spielberger et al., 1970). Out of 33 participants that had entered the main study including baseline visits and up to three nap sessions, 2 participants had to be excluded due to elevated depression scores (BDI-scores ≥13), 12 subjects due to insufficient sleep (when less than three so-tDCS /sham intervals were possible; which corresponds to ~22 min spent in sleep stage 2 or SWS), and one subject due to severe EEG artifacts, leaving 18 subjects (10 female, mean age 65 ± 1) for final analysis (see Table 1 for baseline characteristics of included subjects). The excluded subjects did not differ in baseline parameters from the 18 subjects except for SEX ($\chi^2_{(1,33)} = 4.33$; $p = 0.037$). More male compared to female participants were excluded.

Baseline assessments

Participants underwent comprehensive neuropsychological testing for assessment of general cognitive status comprising memory performance (German version of Auditory Verbal Learning Test (AVLT; Helmstaedter et al., 2001), working memory (Wechsler, 1997), executive functions (Stroop color-word test; Van der Elst et al., 2006), Trail Making test (TMT) part A and B (Tombaugh, 2004), and attention (AKT; Gatterer, 2008). The affective state at the time of the testing was assessed using the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988). For baseline characteristics, see Table 1.

In addition, subjective and objective sleep habits were assessed using the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 2015), Epworth Sleepiness Scale (ESS; Johns, 1991), the German version of