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Cross-hemispheric Alternating Current Stimulation During a Nap Disrupts Slow Wave Activity and Associated Memory Consolidation

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ABSTRACT

Background: Slow Wave Activity (SWA), the low frequency (<4 Hz) oscillations that characterize Slow Wave Sleep (SWS) are thought to relate causally to declarative memory consolidation during nocturnal sleep. Evidence is conflicting relating SWA to memory consolidation during nap however.
Objective/hypothesis: We applied transcranial alternating current stimulation (tACS) – which, with a cross-hemispheric electrode montage (F3 and F4 – International 10:20 EEG system), is able to disrupt brain oscillations–to determine if disruption of low frequency oscillation generation during afternoon nap is causally related to disruption in declarative memory consolidation.
Methods: Eight human subjects each participated in stimulation and sham nap sessions. A verbal paired associate learning (PAL) task measured memory changes. During each nap period, five 5-min stimulation (0.75 Hz cross-hemispheric frontal tACS) or sham intervals were applied with 1-min post-stimulation intervals (PSI's). Spectral EEG power for Slow (0.7–0.8 Hz), Delta (1.0–4.0 Hz), Theta (4.0–8.0 Hz), Alpha (8.0–12.0 Hz), and Spindle-range (12.0–14.0) frequencies was analyzed during the 1-min preceding the onset of stimulation and the 1-min PSI's.
Results: As hypothesized, power reduction due to stimulation positively correlated with reduction in word-pair recall post-nap specifically for Slow ($P < 0.0022$) and Delta ($P < 0.037$) frequency bands.
Conclusions: These results provide preliminary evidence suggesting a causal and specific role of SWA in declarative memory consolidation during nap.

Introduction

Memory consolidation is a process whereby new memories are integrated into a pre-existing stable network of long-term associations [1]. Consolidation is strongest during 'off-line' periods when there is no interference from new encoding-such as during sleep [2–4]. Several studies report the importance of slow wave sleep (SWS) in the consolidation of declarative, consciously accessible memories [5–7]. It is believed that during SWS, slow oscillations temporally coordinate hippocampal and thalamic brain activity during the depolarizing up-state of the oscillation. This hippocampal-neocortical dialog is thought to underly the transfer of information between brain structures and their memory systems [8,9].

Most studies investigating sleep and declarative memory have focused on effects of a full night of sleep rather than an afternoon nap. Afternoon naps occur under reduced homeostatic sleep pressure and less advanced circadian phase relative to early nocturnal sleep, both of which are known to influence sleep's electrophysiological profile [10]. Thus it is unclear whether results from full night sleep studies generalize to afternoon nap. Only a small number of published studies have investigated whether a daytime nap is sufficient for declarative memory consolidation. One study opposes [11], whilst four studies support this notion. Of those in support, two found consolidation related to SWS [12,13] and two report no correlation [14,15]. Our study aimed to clarify this relationship.

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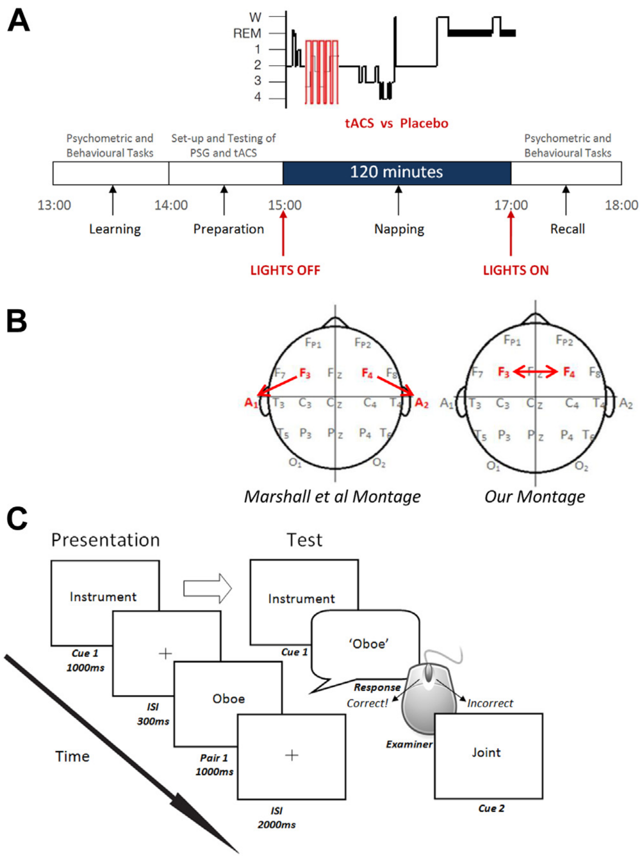

Figure 1. Experimental set up. A, Experimental design. B, Electrode montage. C, PAL task protocol: Following initial presentation and testing (as shown in the diagram) if subjects scored > 30% correct, they progressed to the preparation stage (see Fig. 1A). If however, they scored <30% correct then they were presented the word list again at twice the presentation speed. Following representation they were again tested without feedback, as before. No subjects failed to score 30% following the second presentation.

Further, we sought to determine if slow wave activity (SWA) – slow oscillatory (0.7–0.8 Hz) and delta activity (1.0–4.0 Hz) – has a causal influence on declarative memory consolidation by measuring memory changes resulting from disruption of SWA. A small number of full night sleep studies have already provided evidence of this causal relation [16–18]. Marshall and colleagues effected an increase in SWA during non-REM (NREM) sleep by using bilateral frontolateral tDCS to intermittent slow-oscillation-like (0.75 Hz) potential fields through the cortex. They enhanced retention of the word-pair associations. Stimulation was only delivered during the first period of NREM sleep with no effect during the remainder of the night. It is reasonable then to hypothesize that manipulation of SWA during an afternoon nap would also affect declarative memory.

We delivered sinusoidal tACS, which is able to entrain [19,20] and also hypothesized to be able to desynchronize [21,22] neuronal oscillations. Oscillations are often generated by two symmetrically located neural generators, one in each hemisphere [23–26], and modeling suggests that cross-hemispheric sinusoidal tACS can disrupt neural functions governed by inter-hemispheric phase synchronization [21]. Because slow oscillations originate predominately in the prefrontal cortex [27], we targeted this area with cross-hemispheric stimulation (see Fig. 1b). We hypothesized that sinusoidal cross-hemispheric frontal tACS would disrupt slow oscillation generation, inhibiting SWA and memory consolidation.

Materials and methods

Participants

Eight subjects (4 female) aged 20–22 (mean 21 ± 0.926) participated in both experimental sessions. All provided written informed consent, and the University College London ethics committee approved all experimental procedures. All participants were fluent English-speaking students enrolled at University College London. Subjects were recruited who reported being capable of afternoon nap and no history of neurological, psychiatric or sleep disorders, drug or alcohol abuse.

Experimental design

Subjects were instructed to avoid caffeine, alcohol, and psychoactive substances for 12 h prior to experimentation. Each subject participated in two sessions: a stimulation session and a sham stimulation (control) session (Fig. 1A). The order of stimulation/sham and of word list version was counterbalanced across the eight subjects, who were naïve to which session they received stimulation.

To control for circadian and homeostatic factors affecting sleep architecture [3], testing always began at 13:00. Two standard psychometric tests (the Weschler Adult Intelligence Scale Digit Span Test and a word fluency task, see *Psychometric tests* in Supplementary Methods) were carried out to assess general retrieval function, wakefulness and working memory. Following these tests, subjects carried out training and pre-nap testing for a Paired Associate Learning (PAL) task (Fig. 1C, see Supplementary Methods), which served as a measure of declarative memory. Then EEG electrodes were attached and polysomnographic recording was set up and tested.

At approximately 15:00, subjects were instructed to nap for a 120-min period in a dark room. To control for effects of sleep inertia, if a subject completed a sleep cycle near the end of the nap opportunity, the subject was woken before they entered a further cycle, and if a subject was in deep (stage 3 or 4) sleep at the 2 h mark, they were not woken until they re-entered light sleep. During stimulation sessions, subjects underwent five stimulation periods, each 5 min in duration, followed by 1-min inter-stimulation intervals that were stimulation free, totaling 25 min of stimulation over a 30 min period. Stimulation always began eight epochs (30 s per epoch) after subjects had entered NREM sleep stage-2 without any transition back to NREM sleep stage-1 or stage-Wake. During sham sessions, no stimulation was delivered during the nap.

Subjects were woken around 17:00 (depending on their sleep cycle), and given a short time to wash and rehydrate before the two psychometric tests were performed again. If a subject scored lower than pre-nap on these tests, they were re-tested until performance equivalent to pre-nap was reached so as to equate cognitive performance pre- and post-nap before assessing memory recall. Following this, subjects were re-tested on the PAL task they had undertaken before the nap.

Polysomnographic (PSG) recording

See Supplementary Methods.

Electrical stimulation

Transcranial alternating current stimulation (tACS) was applied as a 0.75 Hz bipolar sinus wave (550 μA maximum amplitude). A battery operated DC-Stimulator Plus (NeuroConn. Ilmenau, Germany) delivered the current to subjects via two conductive rubber