Brain Stimulation 15 (2022) 1565–1566

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Closed-loop transcranial alternating current stimulation of slow wave oscillations during sleep reduces declarative learning the next day

Modulating sleep with brain stimulation to alter memory performance can provide valuable insight into how sleep contributes to memory. Slow wave oscillations (SWO) in the EEG are the major marker of slow wave sleep (SWS) and an important contributor to memory consolidation [1]. However, little is known regarding SWS's effects on learning post-sleep. Here we investigated the relationship between SWS and post-sleep learning by modulating SWO with closed-loop transcranial alternating current stimulation (CL-tACS) with an aim toward affecting learning capacity for object location associations.

The data reported here were collected as part of a larger project using stimulation to enhance memory consolidation [2], where inclusion/exclusion criteria are reported. Thirty-six participants (mean age = 20.67 years, SD = 2.93, 22 female) were recruited and assigned to either sham (21 participants) or verum (15 participants) conditions in a between-subjects, sham-controlled, randomized single-blind design. Signed informed consent was obtained from all participants, and the study was approved by the Chesapeake Institutional Review Board.

Upon arrival, polysomnographic (PSG) setup was performed. Lights out occurred at approximately 22:30, and participants slept uninterrupted for up to 8 hours, during which time CL-tACS was delivered to match the phase and frequency of the dominant SWO. Our closed-loop algorithm for electrical augmentation of SWOs first detected their presence. A virtual channel was computed by averaging 13 frontocentral EEG channels (Cz, FC1, FC2, CP1, CP2, Fz, C4, Pz, C3, F3, F4, P3, P4 in the 10–20 system) to determine the overall synchronous activity of EEG recorded during sleep. The algorithm then applied a Fast Fourier Transform (FFT) to determine power spectrum. Stimulation was planned when the ratio of SWO band (0.5–1.2 Hz) power was more than 20% of the total cumulative power from 0.1 to 250 Hz. A sine wave was then fit to the dominant frequency in the SWO band with the amplitude, offset, and phase parameter values optimized to the filtered virtual channel. The sine wave was then projected into the future, identifying the temporal targets that would synchronize brain stimulation to the predicted endogenous signal, and the correct time point to communicate with the hardware to initiate the stimulation was determined. TACS was applied for 5 cycles at the detected SWO frequency over bilateral frontal electrodes (F3 and F4) at 1.5 mA/hemisphere with bilateral temporal/mastoid returns. See Ref. [2] for additional details regarding stimulation parameters, EEG acquisition, PSG acquisition, discussion of sleep metrics, and the timeline of events for the overarching study.

Upon waking, participants completed the encoding phase and immediate test phase of a novel object location memory (OLM) task. A delayed test was also administered after participants returned to the laboratory that evening. This task was based on [3] and created to test hippocampally-dependent spatial memory at multiple time points. Participants were presented with a 5 × 5 matrix of black and white line drawn objects, randomly selected from a larger set of object stimuli, for 30 s (Fig. 1a). The encoding image was then removed, and a mask was presented for 1 s consisting of a black background and white centered crosshair. Eleven randomly selected objects within the matrix switched locations making a new test matrix, which was used for the immediate and delayed tests. Participants were instructed to select the objects that changed location from encoding image to test image.

Neither age, gender, nor measures of total sleep time, time awake after sleep onset, or sleep efficiency were significantly different between stimulation conditions, suggesting length and quality of sleep were not adversely affected by the stimulation protocol. A 2 × 2 repeated measures ANOVA comparing group (verum, sham) by time (immediate test, delayed test) was run to investigate the effect of stimulation on the immediate retrieval of object locations (F1 accuracy). Results suggest a significant main effect of time ($F_{1,34} = 49.155$, $p < 0.001$) where F1 accuracy at immediate test was significantly higher ($M = 0.721$, $SE = 0.024$) than delayed test ($M = 0.542$, $SE = 0.028$), indicating object location retrieval decreased as a function of time. The main effect of stimulation was significant ($F_{1,34} = 5.310$, $p = 0.027$, $\eta^2 = 0.135$; Fig. 1b), where sham ($M = 0.683$, $SE = 0.029$) outperformed verum ($M = 0.580$, $SE = 0.034$), with the η^2 effect size indicating stimulation condition accounted for 13.5% of variance between groups. The interaction effect was not significant, indicating forgetting was similar between stimulation conditions. Planned simple contrasts revealed that verum stimulation significantly reduced F1 accuracy on the immediate test by 12.9% ($p = 0.042$), while the reduction in F1 accuracy of 17.8% on the delayed test was a trend effect only ($p = 0.064$).

ANOVA models investigating the effect of CL-tACS on sleep showed no significant difference in SWS ratio (number of 30 sec EEG epochs scored as SWS/total sleep epochs; $p = 0.904$), or SWS events identified by the algorithm (sham events were marked by the algorithm but not stimulated; $p = 0.579$). Regression models using SWS ratio to predict F1 accuracy showed SWS ratio was a significant predictor at immediate (ß = −0.446, F(1,18) = 4.466, p = 0.049) and delayed tests (ß = −0.495, F(1,18) = 5.845, p = 0.026) for the sham group, while significantly predicting performance for the delayed test (ß = −0.624, F(1,12) = 7.670, p = 0.017) but not the immediate test (ß = −0.421, F(1,12) = 2.588, p = 0.134) for the verum group. As SWS ratio was a significant predictor of performance, a 2 × 2 repeated measures ANCOVA was run, similar to the ANOVA indicated above, with the addition of SWS ratio as a covariate. Results indicate no main effect of time (F(1,31) = 1.121, p = 0.298) when controlling for

https://doi.org/10.1016/j.brs.2022.12.002

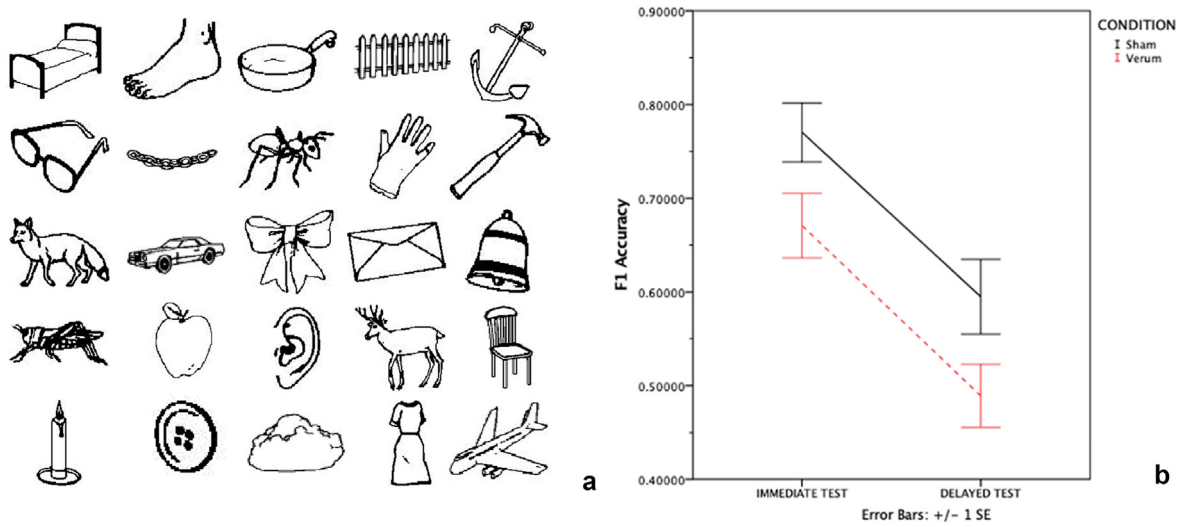

Fig. 1. A) Example encoding image used in the study. Eleven of the 25 objects changed location for testing. B) OLM F1 accuracy scores for immediate and delayed tests. Stimulation resulted in a significant decrease in retrieval performance at the immediate test and a marginal decrease at the delayed test. Forgetting across time was not significantly different between stimulation groups.

SWS ratio. The covariate SWS ratio was a significant predictor of performance ($F(1,31) = 14.107$, $p = 0.001$). After controlling for SWS ratio, the effect of stimulation condition remained significant ($F(1,31) = 6.364$, $p = 0.017$).

This is the first study we are aware of to investigate post-sleep learning after employing CL-tACS to augment SWO during nocturnal sleep. We found that, while augmentation of SWO during sleep may improve hippocampally-dependent declarative learning acquired before sleep [4], stimulation across the full sleeping period was detrimental to learning of declarative object location information acquired after sleep. These results support a causal role for SWS in hippocampal synaptic plasticity. The decrease in learning after augmentation of SWO during nocturnal sleep, along with reported benefits of stimulation during a 90-min nap [5], suggests a nonlinear relationship between SWS's effect on, and the resulting benefits of, synaptic downscaling, with more stimulation resulting in detrimental after-effects. This is similar in some respects to our previous finding of an inverted U-shaped effect of the number of stimulation events during sleep on material learned before sleep [4]. Future research including the systematic manipulation of quantity, duration, and timing of SWO augmentation throughout the sleep period would further elucidate this relationship. Additionally, the application of augmented SWS to improve consolidation of memories acquired before sleep should also consider its potentially detrimental effects on memories acquired after sleep.

Funding

This material is based upon work supported by the DARPA and the Army Research Office under Contract No. W911NF-16-C-0018. The views, opinions and/or findings expressed are those of the author and should not be interpreted as representing the official views or policies of the Department of Defense or the U.S. Government.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: VPC is a Scientific Consultant for NeuroGeneces, Inc.

References

[1] Diekelmann S, Born J. The memory function of sleep. Nat Rev Neurosci 2010;11(2):114–26. https://doi.org/10.1038/nrn2762.
[2] Ketz N, Jones A, Bryant N, Clark VP, Pilly PK. Closed-loop slow-wave tACS improves sleep dependent long-term memory generalization by modulating endogenous oscillations. J Neurosci 2018;38(33):7314–26. https://doi.org/10.1523/JNEUROSCI.0273-18.2018.
[3] Eals M, Silverman I. The hunter-gatherer theory of spatial sex differences: proximate factors mediating the female advantage in recall of object arrays. Ethol Sociobiol 1994;15(2):95–105. https://doi.org/10.1016/0162-3095(94)90020-5.
[4] Jones AP, Choe J, Bryant NB, Robinson CSH, Ketz NA, Skorheim SW, et al. Dose-dependent effects of closed-loop tACS delivered during slow-wave oscillations on memory consolidation. Front Neurosci 2018;12:867. https://doi.org/10.3389/fnins.2018.00867.
[5] Antonenko D, Diekelmann S, Olsen C, Born J, Mölle M. Napping to renew learning capacity: enhanced encoding after stimulation of sleep slow oscillations. Eur J Neurosci 2013;37(7):1142–51. https://doi.org/10.1111/ejn.12118.

Bradley M. Robert, Aaron P. Jones, Teagan S. Mullins, Michael C.S. Trumbo
Psychology Clinical Neuroscience Center, Dept. Psychology, UNM, Albuquerque, NM, 87131, USA

Nicholas A. Ketz, Michael D. Howard, Praveen K. Pilly
Proficient Autonomy Center, Intelligent Systems Laboratory, HRL Laboratories, Malibu, CA, 90265, USA

Vincent P. Clark*
Psychology Clinical Neuroscience Center, Dept. Psychology, UNM, Albuquerque, NM, 87131, USA

* Corresponding author.
E-mail address: vclark@unm.edu (V.P. Clark).

3 November 2022
Available online 8 December 2022