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Feasibility of home-based automated transcranial electrical stimulation during slow wave sleep☆

Dear Editor,

Interest in the modulation of slow wave activity (SWA) during non-rapid eye movement (NREM) sleep is rapidly increasing because of the important role NREM sleep plays in regulating neural plasticity and consolidating memories [1]. A growing number of studies support that transcranial electrical stimulation (tES) is able to modulate SWA, and that these changes are associated with enhanced declarative memory consolidation [2]. Notably, studies utilizing tES during sleep have thus far relied on conventional sleep labs with trained sleep technicians to monitor electroencephalographic (EEG) activity and accurately time activation of tES during specific sleep stages. An automated, at-home closed-loop tES system could accelerate sleep-based tES research studies and would enable longitudinal treatment trials. Here we report on our development of such a system along with preliminary feasibility testing results.

Twelve healthy adults were consented under protocol guidelines approved by the Colorado Multiple Institutional Review Board. Subjects received training in the use of the tES device and hardware (Fig. 1A) prior to their home single, overnight test. A StarStim 8 device (Neuroelectrics, Inc.) was used for EEG recording and tES delivery via Neuroelectrics Instrument Controller (NIC, V.2.0). Subjects received training for proper self-application of EEG and tES electrodes, as well as initiation of closed-loop custom MATLAB (V.R2016b Mathworks, Natick, Massachusetts, USA) scripts. Subjects were taught how to place a small amount (~0.5 cc) of electrode cream (Signacreme®, Parker Laboratories) into the base of the silver/silver chloride electrodes (3.14cm^2 surface of cream contact) prior to application, and trained to properly fill the remainder of the electrode reservoir (~1 cc total) via a curved syringe after the placing the pre-mounted electrode cap on their heads. They then self-initiated the automated system in their homes, prior to falling asleep. To detect SWA, data were processed in 30 second epochs and a zero-crossing analysis identified pairs between 0.25 and 1.0 seconds with a peak amplitude greater than 37.5 μV as slow waves per American Academy of Sleep Medicine (AASM) guidelines [3]. A threshold of 10% or greater SWA per 30 second epoch in frontal channels was used to identify stable stage N2 or N3 sleep for timing of tES.

Upon identification of sufficient SWA, 5 minutes of transcranial alternating current stimulation (tACS) at 0.75 Hz with a peak amplitude of 1 mA was delivered, followed by a 100 second post-stimulation pause to record EEG data. After each pause the system initiated another loop of EEG analysis to time subsequent tACS with a maximum limit of 30 minutes total tACS each night.

Data analysis included manual staging in accordance with the AASM manual [3] (Fig. 1B), as well as spectral analysis (Fig. 1C). For multitaper spectral analysis, EEG data was imported to FieldTrip [4] and epoched into 30 seconds segments with 85% overlap with estimates between 0.5 Hz and 30 Hz in 0.1 Hz steps. Twenty-nine tapers were used and the frequency smoothing was ± 0.5 Hz. Sensitivity and specificity values for automated detection of slow wave sleep for the population level were calculated using a logistic generalized estimating equation (GEE), with an exchangeable correlation on the subject. For the "typical subject," sensitivity and specificity values were calculated using a logistic generalized mixed model with a random subject effect. Variances were estimated with empirical methods.

Our automated system correctly identified SWA (during N2 or N3 sleep) with a sensitivity of 17% and specificity of 89% across subjects, and tACS activated during slow wave sleep with a specificity of 89%. Notably, sensitivity values ranged from 0% to 57%, correlating to quality of EEG recordings. Two of the subjects did not have any correct SWA identifications due to suboptimal electrode recording, though these subjects were still included in the sensitivity and specificity analyses. There were no significant adverse effects, although two subjects woke during stimulation and one subject removed the equipment during the night due to discomfort and difficulties sleeping. Two subjects repeated the experiment due to failures in electrode contact quality with insufficient impedance values on their initial attempt, and one subject had their data removed from analysis due to repeated technical issues with electrode contact quality. Our automated safety mechanisms detected a super-threshold impedance value within the electrical stimulation device when there was poor electrode contact, and stimulation was aborted appropriately in each case. Compliance and uniformity of the at-home procedures was also ensured by review of the stimulation log files, which did not contain any irregularities.

The safety of home-based tES has been established in several recent reports [5–9], and we formulated strict standards for this study consistent with guidelines of recent tES recommendations [10]. In agreement with Carvalho et al. [7] and Hyvärinen et al. [9], our safety mechanisms were designed to maintain subject safety without the need for real-time supervision of tES activation. These mechanisms included: thorough training of staff and participants, assurance that participants could follow the

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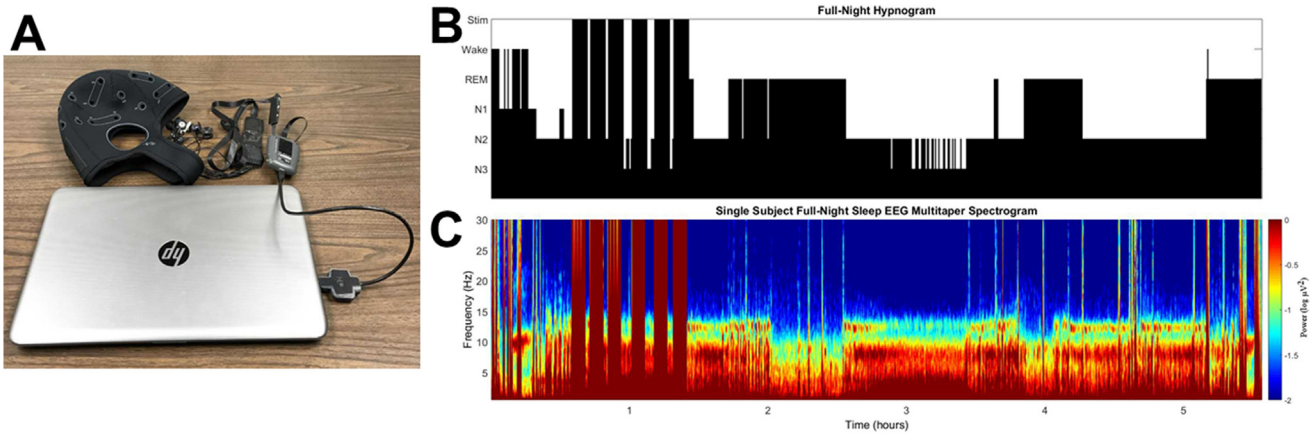

Fig. 1. (A) Equipment setup sent home with subjects, including: neoprene cap, tES/EEG device, cables, electrodes, and a laptop computer. (B) Single subject full-night hypnogram staged manually for stage of sleep. (C) Corresponding multitaper spectrogram from electrode Cz to match the accompanying hypnogram. Note six prominent intervals of EEG artifact corresponding to activation of transcranial electrical stimulation.

protocol, simple and reliable methods of electrode application, strict dose control, monitoring for compliance and adverse events, and procedures for discontinuation under the advisement of an on-call board-certified neurologist who remained available overnight. Additional safeguards were incorporated into the software to ensure predefined limits to stimulation duration and intensity were strictly controlled. The StarStim 8 device limits current intensity with both hardware and software controls. Impedance values are checked prior to and during stimulation and stimulation is aborted in the case of poor contact. In addition to EEG data, log files of all recording and stimulation were generated and reviewed post-recording to ensure proper functioning of equipment and adherence to study protocol.

The application of tES in the familiar environment such as a participant's bedroom has methodological advantages over a sleep lab-based investigation. Furthermore, the requirement of laboratory setting for delivery of tES therapy is a major barrier to conducting longitudinal trials for development of a clinical intervention. Limitations of our study include the relatively low sensitivity of SWA detection in the home environment and occasional issues with electrode contact quality. Further developments in electrode design and refinements in artifact processing will be required to accommodate these technical challenges.

Authorship statement

The authors confirm that they meet the requirements for authorship. An authorship form accompanies the submission of this manuscript.

Conflicts of interest

The authors report no conflicts of interest. A conflict of interest form accompanies the submission of this manuscript.

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References

[1] Raven F, Van der Zee EA, Meerlo P, Havekes R. The role of sleep in regulating structural plasticity and synaptic strength: implications for memory and cognitive function. Sleep Med Rev 2018;39:3–11.
[2] Marshall L, Helgadóttir H, Mölle M, Born J. Boosting slow oscillations during sleep potentiates memory. Nature 2006;444(7119):610.
[3] Berry RB, Brooks R, Gamaldo CE, Harding SM, Marcus C, Vaughn B. The AASM manual for the scoring of sleep and associated events. Rules, Terminology and Technical Specifications, Darien, Illinois. American Academy of Sleep Medicine; 2012.
[4] Oostenveld R, Fries P, Maris E, Schoffelen J-M. FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011;2011:1.
[5] Agarwal S, Pawlak N, Cucca A, Sharma K, Dobbs B, Shaw M, et al. Remotely-supervised transcranial direct current stimulation paired with cognitive training in Parkinson's disease: an open-label study. J Clin Neurosci 2018 Nov;57:51–7. https://doi.org/10.1016/j.jocn.2018.08.037. PMID: 30193898.
[6] Kasschau M, Reisner J, Sherman K, Bikson M, Datta A, Charvet LE. Transcranial direct current stimulation is feasible for remotely supervised home delivery in multiple sclerosis. Neuromodulation: Technol. Neural Interfac. 2016;19(8):824–31.
[7] Carvalho F, Brietzke AP, Gasparin A, dos Santos FP, Vercelino R, Ballester RF, et al. Home-based transcranial direct current stimulation device development: an updated protocol used at home in healthy subjects and fibromyalgia patients. JoVE: JoVE 2018;137.
[8] Van de Winckel A, Carey JR, Bisson TA, Hauschildt EC, Streib CD, Durfee WK. Home-based transcranial direct current stimulation plus tracking training therapy in people with stroke: an open-label feasibility study. J NeuroEng Rehabil 2018;15(1):83.
[9] Hyvärinen P, Mäkitie A, Aarnisalo AA. Self-Administered domiciliary tDCS treatment for tinnitus: a double-blind sham-controlled study. PLoS One 2016;11(4). e0154286.
[10] Charvet LE, Kasschau M, Datta A, Knotkova H, Stevens MC, Alonzo A, et al. Remotely-supervised transcranial direct current stimulation (tDCS) for clinical trials: guidelines for technology and protocols. Front Syst Neurosci 2015;9:26.

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