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PROCEEDINGS #11: REPLAY OF ENDOGENOUS SLEEP RHYTHMS TO PRODUCE SLEEPINESS

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1. Abstract

Varying modes of non-invasive electrical stimulation techniques have been investigated to induce endogenous sleep-like states (historically called Electrosleep). These include transcranial pulsed current stimulation (tPCS) such as Cranial Electrical Stimulation, transcranial direct current stimulation (tDCS), and transcranial alternating current stimulation (tACS) such as 10 Hz sinusoidal stimulation. Prior efforts used synthetic (simple) waveforms selected to modulate excitability (e.g. tDCS) or reproduce a single predominant frequency of endogenous neuronal rhythms of sleep induction (e.g. 10 Hz). To examine the effects of electrical stimulation with a complete spectrum sleep-related endogenous neural activity, we designed and applied an endogenous sleep-derived stimulation waveform to subjects while assessing a range subjective performance and objective physiological data. We hypothesized that a stimulation with complex high-bandwidth waveform reflecting endogenous sleep-associated neuronal activity patterns (transcranial Endogenous Sleep-Derived; tESD) would be more effective, than synthetic frequency-specific waveforms such at tACS, in supporting the transition to sleepiness. The basis for the transcranial Endogenous Sleep-Derived (tESD) waveform was acquired during a resting, sleepy-state EEG session. Data were examined for markers of sleepiness and corresponding segments were extracted, compressed, and scaled to produce a current signal. Stimulation was applied through a custom, high-bandwidth current-control stimulator. Subjects were supine in a light and sound attenuated environment. Using HD bipolar montage (AF7, AF8) with a maximal current amplitude of 0.5 mA over 10 minutes. tESD was also simulated in a computational model. Physiology (EEG, ECG, respiration, EOG, EMG) and behavior (questionnaires, reaction time) was assessed before, during (only for physiology), and after stimulation. Each subject underwent tESD, 10 Hz tACS, and a no-stimulation (non-interventional) sessions in a counterbalanced manner with at least 24 hours between each session. tESD polarized the frontal lobe. Changes in the no-stimulation condition confirms the testing environment was conducive to a wakefulness–sleep transition. Preliminary data indicate an enhanced shift in physiological measures in directions consistent with a relaxed and sleepy state with tESD compared to tACS and no-stimulation conditions. Behavioral data indicate a delay in reactions times post stimulation and subjective sleepiness reports indicate higher sleepiness post stimulation. tESD was well tolerated and blinding was effective. tESD aims to “replay” the endogenous neuronal signature of sleep. Neurophysiological (EEG), physiological (heart rate, respiration) and behavioral (simple reaction time, PVT) indicate that tESD, directed to frontal brain regions, that are associated with top-down thalamo-cortical sleep control mechanisms, accelerated wakefulness–sleep transition in subjects in a baseline relaxed state.

2. Introduction

Varying modes of non-invasive electrical stimulation techniques have been investigated to induce endogenous sleep-like states (historically called electrosleep[1]). These include transcranial pulsed current stimulation (tPCS) such as Cranial Electrical Stimulation, transcranial direct current stimulation (tDCS), and transcranial alternating current stimulation (tACS) such as 10 Hz sinusoidal stimulation. Systematic reviews have showed that prior studies used synthetic (simplified) pattern of transcranial electrical stimulation (tES), such as an arbitrary waveform (e.g. pulse trains, tDCS) or sinusoidal stimulation (tACS) in order to replicate an endogenous frequency of neural sleep signatures (e.g. delta activity) [2, 3]. In the present ongoing pilot study, our aim was to replay endogenous sleep rhythms to promote sleepiness and enhance the spontaneous wakefulness–sleep transition. We hypothesized a higher effectiveness of inducing a sleep like state with current derived from endogenous neural activity as compared to tACS. We believe that a complex, large bandwidth, waveform derived from endogenous sleep activity (transcranial Endogenous Sleep-Derived; tESD) would entrain neural activity towards a sleepiness state.

3. Methods

Our ongoing study was conducted at the City College of New York, CUNY. Eligible subjects ranged in ages between 18 to 45 years old, had no history or diagnosis of neurological or psychiatric disorders, no diagnosed sleep disorders, no diagnosis of heart disease, no pain disorders, and no contraindication to tES.
Prior to conducting our main study, the tESD waveform was derived from a sleep-electroencephalographic (EEG) recording session (Fig 1.A) data segments with markers of sleepiness and signatures were extracted to create a 10 minute bipolar voltage signal was constructed (< 45 Hz filter; amplitude compressed to standard deviations, and scaled to 0.5 mA, modulated with a Tukey window, in order to create a ramp-up and ramp-down; Fig 1.B-C). The study consisted of 3 intervention arms: resting (no stimulation), HD-tESD, and HD-tACS, with >24 hours between sessions. Subjects completed questionnaires and a psychomotor vigilance task (PVT) before and after stimulation. During EEG acquisition subjects were instructed to fixate on a cross in front of them while their eyes were opened (EO) then close their eyes (EC) and relax until they were instructed to open their eyes again and fixate.
All EEG recordings were acquired with an Eego Sports/32-channel Waveguard EEG cap and amplifier, with integrated HD holders (ANT-Neuro). Stimulation dose was HD-bipolar (AF7, AF8) using Ag/AgCl sintered ring electrodes (Soterix Medical Inc.), over 11 minutes (including 30 second ramp up/down), with 0.5 mA peak amplitude. We utilized a custom high-bandwidth current controlled current source for tESD; whereas tACS was applied with a 1X1 tES device (Soterix Medical Inc.).
Data were sampled at 2 kHz, online referenced to CPz. Analysis was conducted using Matlab 2018b and EEGLAB, whereas behavioral measures are analyzed using SPSS Statistics V23 (IBM). Finite element method (FEM) models were parsed with manual segmentation and imaging techniques of ScanIP (Simpleware Ltd, Exeter, UK).

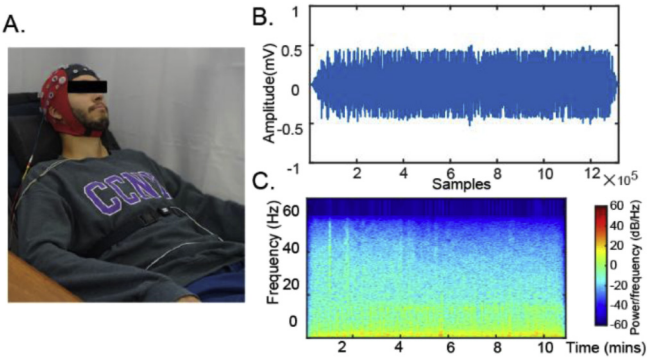

Figure 1. A) SUBJECT RECORDING SET-UP. B) TIME VARYING TESD WAVEFORM USED DURING STIMULATION INTERVENTION. C) SPECTROGRAM OF THE TESD WAVEFORM.

4. Results

Computational head models predict that tESD polarized the frontal pole (Fig 2). Changes in EEG during tESD were localized in frontal regions indicating engagement in the front-thalamo-cortical regions. Alterations observed in the non-stimulation condition confirmed that the testing environment was conducive to a wakefulness–sleep transition, driven by subject isolation and minimized of ambient light/noise. Preliminary data indicate an enhanced shift in physiological measures in directions consistent with a relaxed and sleepy state with tESD compared to tACS and no-stimulation conditions (Fig 3). Behavioral data indicate a delay in reactions

times post stimulation and subjective sleepiness reportings indicate higher sleepiness post stimulation. tESD was well tolerated and blinding was effective (Fig 3.F).

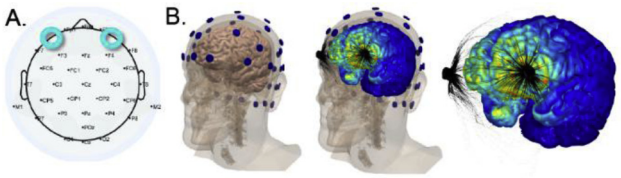

Figure 2. A) EEG CAP LAYOUT WHERE THE RINGS INDICATE THE STIMULATION LOCATION. B) FEM MODELS WITH DIFFERING MODEL LAYERS.

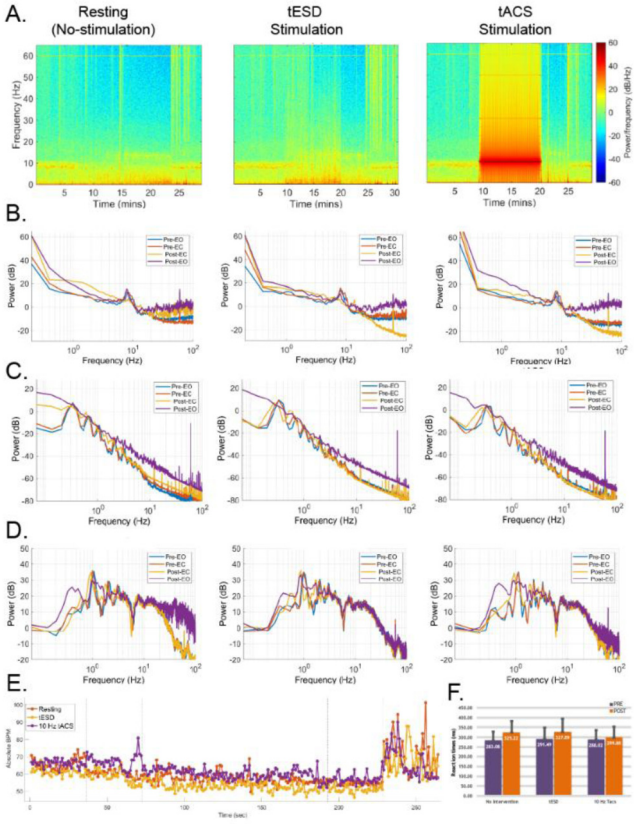

Figure 3. A) EEG SPECTROGRAM COMPUTED FOR F7. B) SPECTRAL CONTENT OF PRE EO, EC, AND POST EO, EC FOR EEG, C) RESPIRATION, D) ECG, E) ECG OVER TIME FOR THE 3 STUDY ARMS. F) PVT RESULTS.

5. Discussion and Conclusion

tESD aims to “replay” the endogenous neuronal signature of sleep. Neurophysiological (EEG), physiological (heart rate, respiration) and behavioral (simple reaction time, PVT) indicate that tESD, directed to frontal brain regions, associated with top-down thalamo-cortical sleep control mechanisms [4, 5], accelerated wakefulness–sleep transition in subjects in a baseline relaxed state.

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PROCEEDINGS #12: INFLUENCE OF INCORPORATING ELECTRODE INFORMATION FROM MR IMAGES: TOWARDS BUILDING MORE REALISTIC FORWARD MODELS

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1. Abstract

Magnetic Resonance Imaging (MRI)-guided models of transcranial electrical stimulation are commonly used to predict cortical current flow. These models can be very accurate as they are based directly on the individual anatomical information. However, less emphasis is placed on replicating exact stimulation electrode information - mainly due to the fact that the scans collected, do not include relevant information. Simulations including in-accurate electrode information will in turn result in in-accurate current flow predictions, thereby hindering any meaningful use. The effect of non-inclusion of exact electrode information is compounded in applications that combine stimulation with MRI. The supine position of the subject and the tight confines of the cage may result in electrode shift, electrode shorting, etc. We propose collecting MRI data including electrode information in such cases and utilizing this information to build more accurate models. We consider two stimulation scenarios (normal and electrode short) to highlight the impact of considering true electrode information.

2. Introduction

Magnetic Resonance Imaging (MRI) - guided computational models for electric stimulation are used to determine brain current flow on an individual basis [1]. These predictions allow analyzing stimulation results or devising strategy for optimal stimulation (avoid specific regions, target specific regions, etc.) for the individual. Since these models are tissue-MRI based, models naturally include the individual anatomical information available [2]. Specifically, these models use the gray scale intensity variation to demarcate different tissue compartments i.e. skin, cerebrospinal fluid, etc. to assign corresponding tissue properties. This approach therefore ensures capturing realistic anatomical details with high accuracy. However, when incorporating individual electrodes for simulating montages, seldom does “true” electrode position- as employed in a session or would be used in a future session is actually considered. The electrodes are typically incorporated based on planned “ideal” approaches like- positioning based on coinciding with the underlying intended gray matter region / TMS hotspot, using automated script following 10-10 electrode placement methodology, based on matching electrode position pictures taken during the session, etc. In such cases, using neuronavigation to document electrode placement and incorporating into the modeling pipeline presents the only viable option to mitigate this aforementioned risk.
In applications that combine stimulation with MR imaging, the potential for electrode shift is compounded. The supine position of the subject and tight confines of the cage presents a challenge to ensure that there is no undue pressure or slippage of the headgear. However, the potential to scan the subject with headgear on, presents an opportunity to image the electrodes and thereby document any electrode deviation. It should be noted that in addition to position, electrode geometry and related contact conditions may also deviate in a session making accurate simulations not possible. This includes cases when electrodes do not make full scalp contact due to non-optimal/non-uniform pressure from headgear, conductive gel/paste/fluid smears from underneath the electrodes