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Automated selective disruption of slow wave sleep

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HIGHLIGHTS

- Easy-to-use tool that effectively and specifically reduces slow wave sleep.
- Normal sleep architecture is preserved.
- Identified settings are effective in a middle-aged population but can be adjusted for each individual.

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ABSTRACT

Background: Slow wave sleep (SWS) plays an important role in neurophysiologic restoration. Experimentally testing the effect of SWS disruption previously required highly time-intensive and subjective methods. Our goal was to develop an automated and objective protocol to reduce SWS without affecting sleep architecture.
New method: We developed a custom Matlab™ protocol to calculate electroencephalogram spectral power every 10 s live during a polysomnogram, exclude artifact, and, if measurements met criteria for SWS, deliver increasingly louder tones through earphones. Middle-aged healthy volunteers (n = 10) each underwent 2 polysomnograms, one with the SWS disruption protocol and one with sham condition.
Results: The SWS disruption protocol reduced SWS compared to sham condition, as measured by spectral power in the delta (0.5–4 Hz) band, particularly in the 0.5–2 Hz range (mean 20% decrease). A compensatory increase in the proportion of total spectral power in the theta (4–8 Hz) and alpha (8–12 Hz) bands was seen, but otherwise normal sleep features were preserved. N3 sleep decreased from 20 ± 34 to 3 ± 6 min, otherwise there were no significant changes in total sleep time, sleep efficiency, or other macrostructural sleep characteristics.
Comparison with existing method: This novel SWS disruption protocol produces specific reductions in delta band power similar to existing methods, but has the advantage of being automated, such that SWS disruption can be performed easily in a highly standardized and operator-independent manner.
Conclusion: This automated SWS disruption protocol effectively reduces SWS without impacting overall sleep architecture.

1. Introduction

Slow wave sleep (SWS) is characterized by high-amplitude delta frequency range (0.5–4 Hz) electroencephalogram (EEG) waves, signifying synchronous relative quiescence of cortical neurons (Nir et al., 2011). SWS represents the deepest part of non rapid eye movement (NREM) sleep, and day-to-day variations in cortical activity and preceding sleep affect the distribution and amplitude of SWS at night (Ferrara et al., 1999; Huber et al., 2006; Pugin

Abbreviations: EDF, European Data Format; EEG, electroencephalogram; NREM, non rapid eye movement; REM, rapid eye movement sleep; SWS, slow wave sleep.

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et al., 2015). SWS plays a key role in synaptic downscaling and other processes that underlie plasticity and memory consolidation (Tononi and Cirelli, 2006; Tononi and Cirelli, 2014) and has been hypothesized to be important in neurophysiologic restoration. SWS is linked with lower amyloid-β (Aβ) levels likely due to decreased synaptically driven Aβ release (Kang et al., 2009) as well as to an increased rate of glymphatic metabolite clearance in the brain, such as clearance of amyloid proteins (Xie et al., 2013). In turn, neurodegenerative amyloid plaques inhibit both the amount of NREM sleep (Roh et al., 2012) and the normal propagation of slow waves (Mander et al., 2015). Given the tight interaction between SWS and neurological physiology from the biochemical to the behavioral levels, many groups have sought to experimentally disrupt or enhance SWS in humans (Landsness et al., 2009; Ngo et al., 2013; Santostasi et al., 2016). Prior methods of SWS disruption have typically relied on highly-trained individuals subjectively interpreting EEG in real time, and delivering auditory or other stimuli to cause arousals out of deep NREM sleep. Therefore, these existing methods are highly subject to inter-operator variability in EEG scoring, selection of stimuli, and delivery of stimuli. Our aim was to develop an automated and operator-independent SWS disruption protocol, using on-line spectral power analysis and auditory tones, to reduce specifically SWS without affecting sleep architecture in healthy middle-aged participants.

2. Methods

2.1. Participants

We recruited 11 healthy participants aged 45–65 years from a community-based research participant registry in Saint Louis, Missouri, USA. One participant was lost to follow-up prior to completing the study; therefore 10 participants were included in the final analysis. Participants had no comorbidities, took no neuro-active medications, and were cognitively normal (Mini Mental Status Examination score ≥27/30). Participants had regular sleep schedules with bedtime between 8PM-12AM and wake time between 4AM-8AM, confirmed by ≥5 days of actigraphy immediately prior to polysomnograms. Participants did not have obstructive sleep apnea or periodic limb movement disorder, as defined as an apnea-hypopnea index ≥5 or periodic limb movement index ≥15, during a screening unattended polysomnogram. This study was approved by the Washington University Human Research Protection Office. Written, informed consent was obtained from all participants.

2.2. Sleep studies

The first four participants each underwent two trial polysomnograms, at least one week apart. The trial polysomnograms were used to test and refine the SWS disruption protocol parameters. All ten participants then underwent two protocol polysomnograms with the final parameters. Four participants therefore underwent a total of four polysomnograms, with only the last two included in this analysis. The SWS disruption protocol was used for one polysomnogram, and a sham protocol used for the other; the order was random and participants were blinded to the condition. Sham protocol consisted of identical set up including earphones, but no noises were delivered through the earphones during the night. Standard polysomnogram channels were used, including frontal (F3, F4), central (C3, C4), and occipital (O1, O2) parasagittal electrodes referenced to the opposite mastoid (M1, M2) electrodes (Iber et al., 2007). EEG data were acquired at 200 Hz and recorded to a MK3 TrackIt™ (Lifelines Neurodiagnostic Systems, Illinois, USA) device in European Data Format (EDF). A registered sleep technologist, blinded to the condition, performed sleep staging on 30-s epochs using standard criteria (Iber et al., 2007). Additionally, the technologist scored movement or arousal artifact for each 10-s mini-epoch of sleep. Following polysomnograms, participants completed a questionnaire asking "Do you recall being woken during the night because of the noises through the earphones?", and "If yes, how many times do you think you woke up because of the noises?"

2.3. Development of the SWS disruption protocol

A live, automated protocol to disrupt SWS was developed in Matlab™ (Fig. 1). Every 10 s, or mini-epoch, the protocol accessed the EDF file, extracted the most recent EEG data, and calculated spectral power for the delta (0.5–4 Hz) and the alpha (8–12 Hz) bands from the F4-M1 electrode using a fast Fourier transform function over the most recent 10.24 s (2048 samples). While SWS often is calculated by the amount of N3 (NREM stage 3) sleep, due to decreasing EEG amplitude with age, many adults have little to no sleep that meets scoring thresholds for N3 (Van Cauter et al., 2000). Therefore, spectral power in the delta band—or "delta power"—serves as a more appropriate and continuous measure of SWS. The F4 electrode was chosen rather than an average of multiple electrodes because SWS is most prominent in the frontal electrodes (Finelli et al., 2001), to reduce computing requirements, and to enable adding this protocol to a standard polysomnogram montage which shows F4, C4, and O2 EEG electrodes only (Iber et al., 2007). Furthermore, recent SWS disruption protocols using visual scoring have also used single electrodes (Landsness et al., 2009; Aeschbach et al., 2008).

Two methods were used to identify artifact. First, if alpha power or delta power was above a very high fixed threshold, which is usually due to movement or sweat artifact, then the mini-epoch was categorized as artifact. Second, if the delta power was relatively higher than the immediately preceding epochs, it was also categorized as artifact. Specifically, if the delta power was greater than the running average of the delta power for the last five non-artifactual mini-epochs, multiplied by a specified "running average factor," then the current mini-epoch was considered to be artifact. The running average factor therefore identifies as artifact those mini-epochs that demonstrate sudden bursts of spectral power, which usually correspond to arousal artifact. Since delta power progressively increases over a NREM cycle, outliers can be identified and excluded using this method that cannot be identified with the fixed thresholds in the first method. A third candidate artifact-detection method using the [delta power: alpha power] ratio, to identify EEG data with disproportionately high delta power due to eye movements, was tested but ultimately found to be ineffective and not used. The cut-off values used for artifact detection are all variables that can be adjusted through the user interface; determination of appropriate cut-off values is discussed in the next section.

If the mini-epoch was not categorized as artifact, and delta band power was above a specified threshold, then the protocol considered the EEG data to be SWS, and delivered an auditory tone through earphones. The tones were pure tones of random pitch and duration, to prevent habituation; prior studies using auditory disruption of sleep have found that there is rapid adaptation if the same tone is used throughout the night (Roehrs et al., 1994). The pitch range was determined by a hearing test at the beginning of the night, and was usually in the 25 Hz–2000 Hz range (approximately the pitch of the lowest note on a standard piano to 2 octaves above middle C). The duration of each tone varied randomly between 1 and 5 s. The first tone in a series of tones would start at the lowest detectable amplitude (volume) for the participant, determined by a hearing test prior to the polysomnogram, and with each consecutive mini-epoch that met criteria for SWS, the amplitude of the tone