SmartSleep: quantifying slow wave activity enhancement

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Abstract

Slow wave sleep is hypothesized to be the most restorative portion of sleep. Recent research shows that slow wave sleep can be enhanced through external intervention (electric, magnetic, or auditory), which also benefits memory consolidation.

Philips has developed a closed-loop, sleep-wearable system that uses an electroencephalogram (EEG) to detect deep sleep in real time and delivers auditory stimulation to enhance slow wave sleep without causing arousals. The effectiveness of this system has been tested in a double-blind pilot study involving 27 participants who used the system at home for 10 nights (five nights in the stimulation condition and five nights in a sham). The primary outcome of this study was the statistically significant enhancement of slow wave activity (SWA, EEG power in the 0.5-to-4-Hz band) in the stimulation condition as compared to the sham one.

1. Introduction

Sleep is considered essential to support healthy brain function and maintain physical health. Sleep regulation consists of two main processes: the sleep-dependent process and the sleep-independent process. The sleep-dependent process addresses sleep need, which builds up during wakefulness and dissipates during sleep [1]. The circadian clock governs the sleep-independent process. On a typical night, sleep usually alternates between rapid eye movement (REM) and non-rapid eye movement (NREM) sleep, whose stages are designated as N1, N2, and N3. N3 sleep is also referred to as deep sleep or slow wave sleep (SWS). Slow wave sleep plays a pivotal role in the optimization of memory consolidation and is believed to be mediated by synaptic downscaling during sleep [2, 3].

Various studies show that sleep deprivation impairs cognitive function and extended wakefulness inflicts stress on neurons that are essential for alertness and cognition [4, 5, 6]. Many of the beneficial effects of sleep on the restoration of brain function are thought to be mediated primarily by slow waves in NREM sleep.

Slow wave activity (SWA) is defined as the power of the electroencephalogram (EEG) in the delta band (between 0.5 and 4 Hz). SWA is a quantitative measure of the number and amplitude of slow waves [3]. Given the importance of slow wave sleep, various pharmacological and peripheral (electric/magnetic/sensory) stimulation methods have been proposed to enhance slow waves. Among these, auditory stimulation has proven to be an effective strategy, as it is non-pharmacological, safe, and reliable [7, 8, 9].

SmartSleep (Philips Respironics, Murrysville, PA) was developed as a closed-loop system that uses auditory stimulation to enhance slow wave activity. In this paper, the outcomes from a clinical study using this closed-loop auditory stimulation system are discussed.

2. Closed-loop enhancement to slow wave sleep

SmartSleep is a wearable system that monitors the user's sleep through real-time processing of the EEG signal acquired from a frontal (Fpz standard) location with respect to the right mastoid. The EEG signal is filtered in the 0.5-to-4-Hz band, where sleep-relevant information is found. The higher-frequency spectral content of the EEG (15–30 Hz) is used to detect sleep microarousals and to quantify the risk of disturbing sleep due to auditory stimulation. The presence of deep sleep is detected by considering the spectral properties of EEG and the number of slow waves per unit of time.

The system operation is illustrated in Figure 1. From the ongoing EEG signals, the first step consists of detecting sleep microarousals (henceforth referred to as "arousals" for convenience), which is achieved by calculating the EEG power in the alpha (8–12 Hz) and beta (15–30 Hz) frequency bands and comparing the numbers to pre-established thresholds. The presence of an arousal delays the onset of the next auditory stimulation. Ongoing stimulation stops if an arousal is detected.

If no arousal is detected, then the system attempts to detect N3 (slow wave) sleep by calculating EEG power in the delta frequency band (0.5–4 Hz) and quantifying the density of slow waves. If the duration of detected N3 sleep is at least 1.5 minutes and sleep depth (ratio between delta and beta powers) exceeds a pre-established threshold, then auditory stimulation is delivered.

Auditory stimulation consists of 50-millisecond-long tones separated from each other by a fixed one-second-long intertone interval. The volume of each tone is modulated by sleep depth such that loud (soft) tones are played during deeper (shallower) sleep.

The first audio tone in a sequence is time-locked to the upstate of the slow waves, and the remaining tones are delivered at a fixed intertone interval of one second. If the sleep depth is not greater than a threshold, or if the risk of disturbing sleep (as detected by change in high-frequency content) while delivering stimulation exceeds a threshold, then the tones are no longer played. The frequency of the tones is randomized in the interval between 500 and 2000 Hz to prevent habituation.

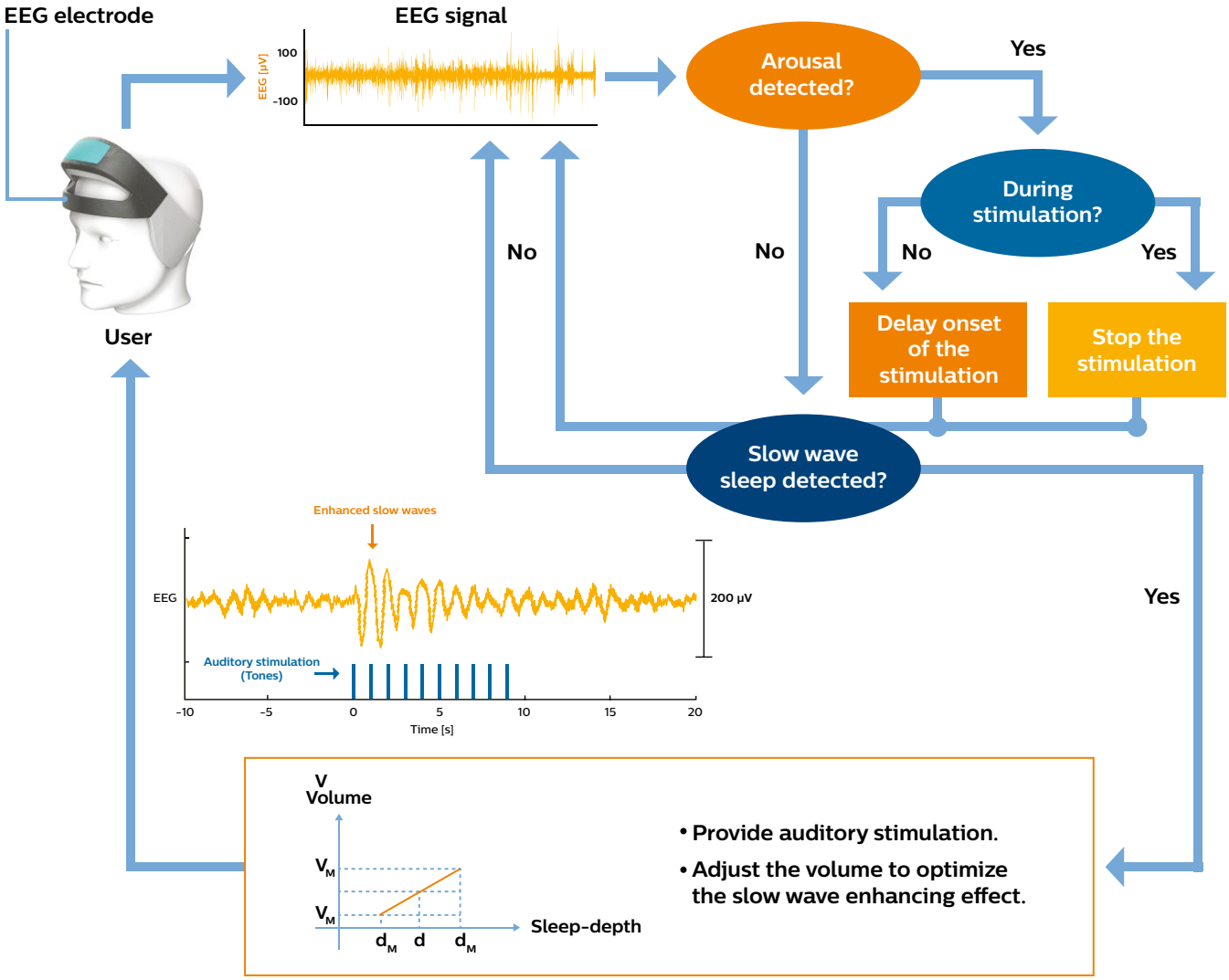

Figure 1: Closed-loop slow wave sleep enhancement

3. Clinical trial

A randomized double-blind study involving the SmartSleep device was conducted at four different clinical sites in the United States. The study was approved by a central Institutional Review Board, and all participants gave written informed consent to participate. The main focus of the study was to quantify the enhancement of slow wave activity, i.e., the EEG power in the 0.5-to-4-Hz band.

3.1 Experimental design

The study recruited chronically and mildly sleep-restricted individuals (6–7.5 hours of sleep). These subjects used the device primarily at home for a period of two weeks, with a week of washout in between. Prior to use of the device, the subjects were monitored using actigraphy to ensure that they followed a regular sleep-wake schedule. Regularity is defined as adhering to a bedtime within +/- 1 hour across the nights of the study. The study consisted of two parts, with the subjects using the device at home on weeknights (Monday through Thursday), followed by a night (Friday) of data collection in a sleep lab. The rationale for the lab night was to have a controlled environment to measure the daytime outcomes. The daytime measures included paired-associate learning (PAL), multiple sleep latency test (MSLT), psychomotor vigilance task (PVT), Karolinska Sleepiness Scale, and visual analog scales (VASs) for subjective sleep quality. The subjects were randomly assigned to either a sham or stimulation condition for Week 1, followed by the other condition during Week 2. The subjects recorded their perception of sleep quality in a diary after each night of use.

A total of 34 subjects ranging in age from 30 to 50 were enrolled in the study, with 27 of them (17 female and 10 male) completing the entire study.

Sleep EEG and electrooculogram (EOG) data sampled at a rate of 250 samples/second was collected for 10 nights using a wearable investigational device. The EEG data was obtained from a frontal (Fpz standard) location with respect to the right mastoid, while that of the EOG likewise used the right mastoid as the reference. The data recorded during each night was stored on the investigational device (SmartSleep) and used as the primary set for analysis of slow wave activity.

3.2 Analysis methods

The raw EEG data obtained from the frontal channel was manually scored by an expert sleep technologist according to AASM rules based on 30-second-long nonoverlapping EEG epochs.

EEG signals were processed as follows. A single-pole high-pass filter was applied to remove the DC drift, and the power spectrum density (PSD) values for each six-second-long epoch were calculated. SWA was then estimated from PSD values. Signals that had very poor signal-to-noise ratio or were corrupted due to interference from other equipment, as determined by the sleep technologist, were discarded from the analysis. Less than 3% (7 of 267) of the nights were discarded due to poor signal quality.

4. Results

Analysis of the data showed that subjects had an average SWA increase of 6.8% with the stimulation condition, as reflected in Figure 2. This change in SWA was significant for the stimulation condition in relation to the sham condition, with a p value of <0.05. Analysis from Table 1 (number of arousals) shows that stimulation was provided without disturbing sleep.

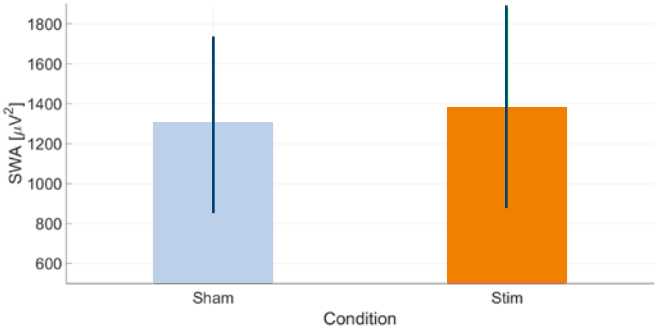

Figure 2: Comparison of average SWA value in sham and stimulation conditions

In order to confirm that stimulation does not affect sleep, a comparison of the sleep stages within the subjects was completed. Table 1 shows the comparison of sleep architecture metrics between the two conditions. Durations of total sleep time (TST), rapid eye movement (REM), and non-rapid eye movement (NREM) sleep stages (N1, N2, and N3) are not significantly different between conditions. Furthermore, the N3 detected by the algorithm versus that obtained from manual scoring showed a sensitivity and specificity of approximately 80% and 90%, respectively.

Wake after sleep onset (WASO) in the stim condition is lower than in the sham, showing that closed-loop auditory stimulation does not disturb sleep and may even help in maintaining sleep continuity by favoring neural synchronization during NREM sleep.

Sleep Architecture Metrics	Sham	Stim	P Value
TST	312.54 min +/- 37.68	312.45 min +/- 28.84	0.98
WASO	18.11 min +/- 13.37	12.08 min +/- 8.45	0.01*
N1	10.06 min +/- 5.48	11.06 min +/- 4.01	0.45
N2	161.85 min +/- 26.87	163.03 min +/- 18.68	0.82
N3	74.22 min +/- 19.59	70.89 min +/- 24.02	0.35
REM	66.40 min +/- 18.33	67.45 min +/- 19.07	0.66
Number of Arousals	16.73 +/- 5.44	15.98 +/- 6.4	0.50

Table 1: Comparison of sleep architecture metrics for sham and stimulation conditions

The two-process model of sleep indicates that sleep need dissipates at a rate proportional to SWA [1]. Using the SWA values for NREM epochs, the sleep-need dissipation curve can be estimated according to the method described by Garcia-Molina et al. [10].

4. Results *(continued)*

Figure 3 shows the average dissipation in sleep need from the beginning of the night to the end of the night for the two conditions. It can be observed that stimulation during deep sleep dissipates the sleep need faster relative to the sham condition.

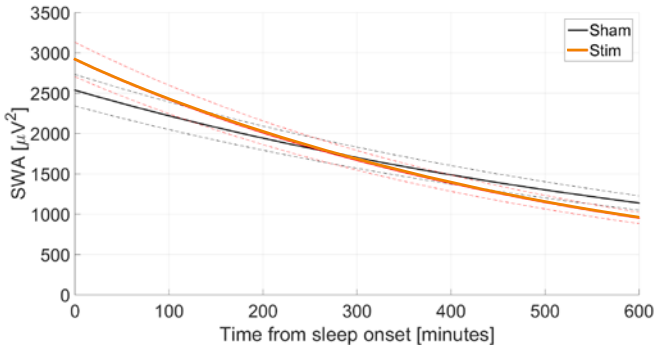

Figure 3: Comparison of average sleep-need dissipation curves in sham and stimulation conditions

As stated previously, SWA increased an average of 6.8% among all subjects, with a p value of <0.05. Furthermore, among responders (14 of 27 subjects who demonstrated a more than 5% increase in SWA), the average increase was 18%. A 5% threshold is used to identify responders because this corresponds to the SWA variability across sham nights.

The following daytime outcomes resulted in trends (p value of <0.1) that suggest differences between conditions:

- In the motor-control task, as recorded by PVT, there was a 3% improvement in speed when performing the task after the stimulation condition versus after the sham, with a p value of 0.08.
- In the MSLT task, which is a gold-standard sleepiness quantification, responders showed an average improvement of +1.3 minutes.
- At the group level, the number of words recollected in the morning was 23% higher in the stimulation condition than in the sham, with a p value of 0.09.
- VAS sleep quality was trending in the positive direction for stim versus sham, with a p value of 0.08.

5. Conclusion

It was demonstrated that the SmartSleep system reliably provides at-home auditory stimulation and enhances slow wave activity in chronically and mildly sleep-restricted individuals. Results obtained from this pilot study have shown that auditory stimulation significantly enhances SWA. This study confirms prior research that indicates that auditory stimulation enhances slow wave sleep, which mediates the restorative functions of sleep.

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