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Phase-locked loop for precisely timed acoustic stimulation during sleep

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HIGHLIGHTS

- Brain–computer interface to enhance slow-wave sleep.
- Acoustic stimulation that is effective and non-invasive.
- EEG power and synchronization is increased in delta band.
- Accurate phase locked algorithm to track phase of EEG during slow-wave sleep.
- Intervention has potential to enhance benefits of slow-wave sleep (memory, metabolism, immune system, and cardio-vascular health).

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ABSTRACT

Background: A brain–computer interface could potentially enhance the various benefits of sleep.
New method: We describe a strategy for enhancing slow-wave sleep (SWS) by stimulating the sleeping brain with periodic acoustic stimuli that produce resonance in the form of enhanced slow-wave activity in the electroencephalogram (EEG). The system delivers each acoustic stimulus at a particular phase of an electrophysiological rhythm using a phase-locked loop (PLL).
Results: The PLL is computationally economical and well suited to follow and predict the temporal behavior of the EEG during slow-wave sleep.
Comparison with existing methods: Acoustic stimulation methods may be able to enhance SWS without the risks inherent in electrical stimulation or pharmacological methods. The PLL method differs from other acoustic stimulation methods that are based on detecting a single slow wave rather than modeling slow-wave activity over an extended period of time.
Conclusions: By providing real-time estimates of the phase of ongoing EEG oscillations, the PLL can rapidly adjust to physiological changes, thus opening up new possibilities to study brain dynamics during sleep. Future application of these methods hold promise for enhancing sleep quality and associated daytime behavior and improving physiologic function.

1. Introduction

Slow-wave sleep (SWS) is a very distinctive feature of sleep in mammals and birds (Horne, 1992). SWS has a restorative role and it has many physiological and behavioral implications. Many studies have established that SWS is associated with the stabilization of memories for long-term storage (Diekelmann and Born, 2010). SWS diminishes with age, both in duration and intensity, and this decline correlates with memory changes from before and after sleep and with impairments in cognitive performance (Mander et al., 2013). In addition, analyses of sleep in individuals with amnestic mild cognitive impairment (aMCI) showed reduced slow-wave activity (SWA), the physiologic measurement of SWS, compared to age-matched controls (Westerberg et al., 2012). Experimental suppression of SWS also impairs metabolic function, and SWS is thought to play an important role in the regulation of cardio-metabolic function (Tasali et al., 2008). Another important function of SWS is the production and regulation of hormones, with an important example being the growth hormone (VanCauter and Plat, 1996). Recently it has been demonstrated that

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SWS may play a role in flushing toxins from the brain, particularly β-amyloid (Xie et al., 2013). Thus, enhancing SWS could have many beneficial implications for cognitive and physical health.

Given the role of sleep in declarative memory consolidation (Gais and Born, 2004; Plihal and Born, 1997), there has been great interest to enhance SWS. One such method is to pass slow oscillatory electrical activity into the brain transcranially to modulate neuronal excitability during sleep so as to increase endogenous SWA and improve consolidation. In two studies (Marshall et al., 2004, 2006), healthy young people learned lists of word pairs before going to sleep. In tests given both before and after sleep, subjects attempted to recall the second word of each pair in response to the first. Remarkably, the results showed that this method of low-frequency stimulation (LFS) during sleep increased SWA and improved memory. Recall was better if the retention interval included LFS compared to sham stimulation during sleep.

Although LFS can increase SWA, it has practical and technical limitations. From a technical standpoint, it is difficult to record EEG activity during the stimulation because of the artifacts created by the applied electrical field. Given that these sorts of stimulation methods can generate complicated patterns of activated and deactivated brain areas (Lang et al., 2005), it can be difficult to specify how the electrical stimulus influences neuronal activity. LFS is also impractical for regular use because it requires the assistance of trained technicians. Finally, while the intensity of the electrical stimulation is relatively low and likely safe in the short-term, long-term studies of efficacy and safety are lacking (Poreisz et al., 2007).

An innovative method to enhance slow waves is to use acoustic stimulation. It is well established that auditory tones can influence EEG activity by producing K-complexes, which are similar in structure and are precursors to slow waves (Amzica and Steriade, 1998). Tononi et al. (2010) showed that auditory stimulation during sleep can enhance SWA in young adults. The tones were of short duration (50 ms) and were applied using a fixed intra-tone interval (ITI) of 1 Hz. In this protocol, stimulation was delivered in a sequence of 15 consecutive tones (block ON), followed by periods when tones were not played (block OFF) (Tononi et al., 2010). The block on/off sequence was adopted to track the effect of the auditory stimulation on SWA at regular intervals during deep sleep and also to tap into hypothesized infra-slow oscillations in non-rapid eye movement (NREM) sleep that seem to occur about every 15 s (Ferri et al., 2008).

The method of fixed ITI acoustic stimulation was also shown to enhance slow waves by another research group (Ngo et al., 2013a). Stimulation at 0.8 Hz beginning prior to sleep delayed sleep onset and enhanced SWA. Further stimulation studies showed that the response can change as a function of the timing of the stimulus relative to the phase of the slow EEG rhythms (Dang-Vu, 2012; Ng et al., 2013; Schabus et al., 2012). These results may reflect the up and down phases of slow-wave oscillations, which correspond to periods of neuronal activity and quiescence (Volgushev et al., 2006). Therefore, the ability to synchronize auditory stimulation to a particular phase of the slow wave could lead to more consistent enhancement of slow waves.

To take into consideration these phase-dependent responses to stimulation, we adopted a more complex stimulation approach. Ngo et al. (2013b) introduced a method that allows the auditory stimulation to be approximately tuned to the phase of the slow wave. Their results showed that this phase-dependent auditory stimulation can increase slow oscillations as well as phase-coupled spindle activity. In addition, they showed that stimulation to enhance slow waves leads to improved declarative memory performance. Presumably, the enhancement of SWA is beneficial because it is conducive to neuronal synchronization, and because spindle activity reflects an essential aspect of memory consolidation (Oudiette et al., 2013). Furthermore, phase-dependent stimulation could also be tuned to the down state, in which case it did not enhance SWA and did not have an effect on memory (Ngo et al., 2013b).

In this paper, we describe the reasoning behind using a methodology with a phase-locked loop (PLL) to improve sleep. This work demonstrates that the PLL is a superior algorithm to track a signal, such as in modeling EEG slow waves, and identify a target phase for real-time application, such as with delivery of stimuli a particular slow-wave phase. Phase targeting is important because different slow-wave phases correspond to different physiological states that directly influence neural activity, and stimulation at different phases can produce different effects. We include some physiological results but do not include a complete investigation of the effectiveness of the method in enhancing slow-wave sleep in a group of participants. Rather, we provide here a comprehensive methodological analysis that focuses on the phase-tracking ability of the PLL. It remains to show how the method compares with other methods and how effective and reliable it is for individuals with normal sleep patterns or with abnormal sleep patterns, as in older individuals. Ong et al. (Submitted) have described an initial application of this method to study sleep in a group of young participants.

2. Material and methods

2.1. Phase-locked loop

2.1.1. PLL theory

We have independently developed a new method for phase-tracking auditory stimulation that consists of an adaptive feedback algorithm based on a PLL that tracks the phase of the underlying EEG and delivers tones at a particular preferential phase (Riedner et al., 2013). This stimulation method is more general (it can be applied easily to any particular target phase), flexible (it adapts automatically to the slow wave individual characteristics), accurate and precise (it targets the right phase much better and more consistently) than the slow-wave detection procedure described by Ngo et al. or the more recent one described by Cox et al. (2014).

A PLL is a control system that generates an output signal whose phase is related to the phase of an input reference signal. When it is implemented as an electronic circuit, it typically consists of a variable frequency oscillator and a phase detector. This circuit compares the phase of the input signal with the phase of the signal derived from its output oscillator and adjusts the frequency of its oscillator to keep the phases matched. The signal from the phase detector is used to control the oscillator in a feedback loop.

Because frequency is the time derivative of phase, keeping the input and output phase in lock step implies keeping the input and output frequencies in lock step. Consequently, a phase-locked loop can track an input frequency, or it can generate a frequency that is a multiple of the input frequency. The former property is used for demodulation (Viterbi and Cahn, 1964), and the latter property is used for indirect frequency synthesis (Farazian et al., 2013).

Phase-locked loops are widely employed in radio, telecommunications, computers, and other electronic applications (Talbot, 2012). They can be used to recover a signal from a noisy communication channel, generate stable frequencies at a multiple of an input frequency, or distribute clock timing pulses in digital logic designs such as microprocessors. The PLL can also be implemented in a purely software realization.

There are many proposals in the literature for using the PLL in biomedical applications, as for example to model interactions of biochemical reactions (Hinze et al., 2011), to analyze circadian rhythms (Kimura and N, 2005; Schilling, 1982), to describe