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Circadian regulation of slow waves in human sleep: Topographical aspects

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ABSTRACT

Slow waves (SWs, 0.5–4 Hz) in field potentials during sleep reflect synchronized alternations between bursts of action potentials and periods of membrane hyperpolarization of cortical neurons. SWs decline during sleep and this is thought to be related to a reduction of synaptic strength in cortical networks and to be central to sleep's role in maintaining brain function. A central assumption in current concepts of sleep function is that SWs during sleep, and associated recovery processes, are independent of circadian rhythmicity. We tested this hypothesis by quantifying all SWs from 12 EEG derivations in 34 participants in whom 231 sleep periods were scheduled across the circadian cycle in a 10-day forced-desynchrony protocol which allowed estimation of the separate circadian and sleep-dependent modulation of SWs. Circadian rhythmicity significantly modulated the incidence, amplitude, frequency and the slope of the SWs such that the peaks of the circadian rhythms in these slow-wave parameters were located during the biological day. Topographical analyses demonstrated that the sleep-dependent modulation of SW characteristics was most prominent in frontal brain areas whereas the circadian effect was similar to or greater than the sleep-dependent modulation over the central and posterior brain regions.
The data demonstrate that circadian rhythmicity directly modulates characteristics of SWs thought to be related to synaptic plasticity and that this modulation depends on topography. These findings have implications for the understanding of local sleep regulation and conditions such as ageing, depression, and neurodegeneration which are associated with changes in SWs, neural plasticity and circadian rhythmicity.

Introduction

Sleep is thought to reflect a recovery process (Achermann and Borbely, 2003; Daan et al., 1984; Tononi and Cirelli, 2006), the timing of which is gated by the circadian pacemaker located in the suprachiasmatic nucleus (Edgar et al., 1993). The most widely investigated electrophysiological markers of the sleep-dependent recovery process are EEG low-frequency (<4 Hz), high amplitude (>75 μV) slow waves (SWs) which have been implicated in sleep-dependent memory consolidation (Rasch and Born, 2013) and age-related changes in cognition (Pace-Schott and Spencer, 2011). The sleep SWs as quantified by visual scoring (Tilley et al., 1987), period amplitude analyses (Uchida et al., 1999) or as slow-wave activity (SWA, EEG power density 0.75–4.5 Hz), decline in the course of sleep and increase in response to the duration and intensity of prior wakefulness (Dijk, 2009; Hung et al., 2013). The sleep-dependent decline in SWs is also observed intra-cortically in humans (Csercsa et al., 2010; Nir et al., 2011). At the cellular level, SWs reflect alternating periods of neuronal activation and silence (Steriade et al., 1993b) and are generated in cortical and thalamo-cortical networks (Steriade et al., 1993a). The characteristics of SWs and the sleep and wake dependent variation in SWs have been investigated in animals (Vyazovskiy et al., 2007), humans (Bersagliere and Achermann, 2010; Nir et al., 2011; Riedner et al., 2007), and large-scale computer models of cortical networks (Esser et al., 2007). It has been concluded that synaptic potentiation during wakefulness and synaptic suppression during sleep are the main mechanisms underlying SW variations. In fact, one leading (Tononi and Cirelli, 2006, 2012, 2014), although challenged (Frank, 2012; Frank and Cantera, 2014) theory, has postulated that SWs are involved in maintaining synaptic homeostasis (Turrigiano, 2008) by reducing synaptic strength, i.e. the number and efficacy of synapses. Furthermore, it is hypothesized that parameters of individual SWs, such as their incidence, amplitude, duration, and the slope, reflect the progression of this process (Nir et al., 2011; Riedner et al., 2007; Vyazovskiy et al., 2007). Although many of these SW parameters change in response to time awake and time asleep, the slope has been demonstrated to be the most sensitive

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indicator of changes in synaptic strength within neuronal networks (Esser et al., 2007; Riedner et al., 2007; Vyazovskiy et al., 2007).

The change in synaptic strength and associated characteristics of the SWs are presumed to be sleep-dependent and a direct contribution of circadian rhythmicity has been largely ignored. The notion that synaptic plasticity and its marker are primarily sleep-dependent has been based to a larger extent on a comparison of early and late sleep in animals (Vyazovskiy et al., 2007) and humans (Riedner et al., 2007). However, in those comparisons sleep-dependent and circadian factors are confounded because during a 12-hour light period in the rat or an 8-hour sleep period in humans we also traverse 1/2 and 1/3 of a circadian cycle, respectively. Rigorous assessment of a circadian influence on sleep processes requires that sleep is scheduled to many different phases of the circadian cycle, while controlling for the effects of time awake and time asleep. These requirements are met in forced desynchrony protocols which have provided evidence that SWs may be indeed modulated to some extent by circadian rhythmicity (Dijk and Czeisler, 1995), but these findings have not been considered in current models of the regulation of slow waves (Tononi and Cirelli, 2014). This may in part be because in those previous analyses, topographical, i.e. local aspects of slow wave regulation were not considered and the analyses were based on a rather gross measure of slow waves, i.e. spectral power density in the slow wave range. Here, we provide a comprehensive analysis of the circadian modulation of key characteristics of slow waves, and report for the first time that when assessed in a forced desynchrony protocol the incidence, amplitude, duration and in particular slope parameters of SWs during human sleep are to a considerable extent modulated by circadian rhythmicity and that the relative contribution of this circadian effect to the regulation of slow waves, varies widely along the anterior–posterior cortical axis.

Materials and methods

The study received a favourable opinion from the University of Surrey Ethics Committee and conformed to the Declaration of Helsinki. All participants provided written informed consent before participation in the study. Participants were recruited using advertisements in local newspapers, on local radio and specialized websites. The 271 respondents to the advertisements were screened using multiple sleep, chronotype and health related questionnaires (Lazar et al., 2012). From this pool we selected 36 participants who were able to participate in the experiment during the available time slots and met the stringent inclusion/exclusion criteria. The criteria included consumption of less than 14 units of alcohol per week, no travel across more than 2 time zones during the preceding three months, no shift work, no smoking, and no current medication. Participants were in good mental and physical health as assessed by a standard physical exam, including biochemical profile, full blood count and coagulation screen, and urine analyses for drug of abuse. All participants were free of sleep complaints and underwent a full clinical polysomnography screening to exclude sleep disorders such as sleep apnoea. For more details on recruitment and selection see Hasan et al. (2012).

Pre-laboratory phase

The study started with a 2-week-long period of monitoring of the habitual sleep–wake cycle by sleep diary and actigraphy (Actiwatch L; Philips Respironics, Best, The Netherlands). The data from the first week of actigraphy were used to calculate the average habitual sleep–wake timing of each participant, whereas during the second week, which occurred immediately preceding the laboratory phase of the study, participants were required to maintain a stable sleep–wake rhythm in accordance with their average habitual schedule. Compliance was monitored by actigraphy.

Laboratory phase: forced desynchrony protocol

The forced desynchrony protocol lasted for 10 consecutive days and was modified from a protocol described previously (Dijk and Czeisler, 1995) (Fig. 1). During this time period, all participants were resident in the sleep and circadian research unit of the Surrey Clinical Research Centre of the University of Surrey. After a baseline assessment, the sleep–wake cycle was scheduled to 28 h, of which 9 h 20 min were spent in bed in darkness followed by 18 h 40 min of scheduled wake periods in a dim light environment (<5 lx), with no access to information about clock time. During the forced desynchrony, consecutive

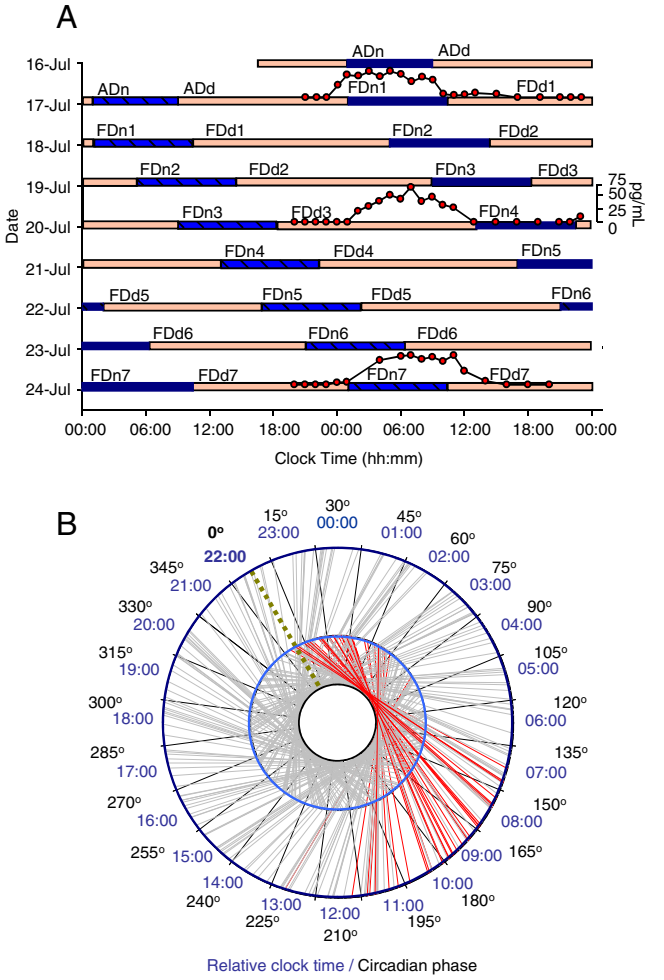

Fig. 1. The forced desynchrony protocol. A. Double raster plot of the 28-h forced desynchrony protocol with a representative example of sleep timing and melatonin profile (BB0102, male, 23 years, in vivo circadian period: 24.24 h). Consecutive 24-h periods are plotted next to and below each other. After an 8-hour adaptation night (ADn) followed by an adaption day (ADd) participants were scheduled to a 28-h sleep–wake cycle, in which 9 h and 20 min were scheduled for sleep (blue bars) and 18 h and 40 min for wakefulness (yellow bars). Thus, sleep and wake timing were shifted by 4 h every 'day' while at the same time the ratio of sleep and wakefulness remained 1:2, just as during a normal 24-hour day. Melatonin was assessed at baseline (FD1), FD4 and FD7 in order to assess phase and period of the central circadian pacemaker. Blood samples for melatonin concentration assessment were scheduled to be taken hourly but occasionally samples could not be collected due to technical or logistical problems. B. The forced desynchrony protocol represented on a 24-h angular plot indicating each individual baseline (FDn1) sleep period (red lines) against the circadian phase and relative clock time, which corresponds to the habitual sleep timing, duration and circadian phases covered by usual sleep studies. Grey lines indicate all sleep periods scheduled across the circadian cycle (N = 231) during the 10-day protocol for the 34 participants. Each sleep period indicates the time course between the scheduled bedtime (internal light blue circle) and wake-up time (external dark blue circle). The dotted green line indicates the average clock time at circadian phase zero, corresponding to the timing of the dim light melatonin onset.