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Wakefulness delta waves increase after cortical plasticity induction

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HIGHLIGHTS

- iTBS-induced (intermittent theta burst stimulation) plasticity increases delta EEG.
- Delta waves emerge as effectors of cortical plasticity in wakefulness besides sleep.
- In patients affected by brain lesions, the meaning of slow EEG waves can be reinterpreted.

ABSTRACT

Objective: Delta waves (DW) are present both during sleep and in wakefulness. In the first case, DW are considered effectors of synaptic plasticity, while in wakefulness, when they appear in the case of brain lesions, their functional meaning is not unanimously recognized. To throw light on the latter, we aimed to investigate the impact on DW exerted by the cortical plasticity-inducing protocol of intermittent theta burst stimulation (iTBS).
Methods: Twenty healthy subjects underwent iTBS (11 real iTBS and nine sham iTBS) on the left primary motor cortex with the aim of inducing long-term potentiation (LTP)-like phenomena. Five-minute resting open-eye 32-channel EEG, right opponens pollicis motor-evoked potentials (MEPs), and alertness behavioral scales were collected before and up to 30 min after the iTBS. Power spectral density (PSD), interhemispheric coherence between homologous sensorimotor regions, and intrahemispheric coherence were calculated for the frequency bands ranging from delta to beta.
Results: Real iTBS induced a significant increase of both MEP amplitude and DW PSD lasting up to 30 min after stimulation, while sham iTBS did not. The DW increase was evident over frontal areas ipsilateral and close to the stimulated cortex (electrode F3). Neither real nor sham iTBS induced significant modifications in the PSD of theta, alpha, and beta bands and in the interhemispheric coherence. Behavioral visuo-analogic scales score did not demonstrate changes in alertness after stimulations. No correlations were found between MEP amplitude and PSD changes in the delta band.
Conclusions: Our data showed that LTP induction in the motor cortex during wakefulness, by means of iTBS, is accompanied by a large and enduring increase of DW over the ipsilateral frontal cortex.
Significance: The present results are strongly in favor of a prominent role of DW in the neural plasticity processes taking place during the awake state.

1. Introduction

Delta waves (DW, <4 Hz) are the most prominent electroencephalographic (EEG) feature of human non-rapid eye movement (NREM) sleep, which have their origin in cortical layers. Several studies proposed them as sensors for weighing synaptic efficacy and possible effectors of sleep-dependent synaptic plasticity (for a review, see Tononi and Cirelli, 2012). This evidence relies on several animal experiments demonstrating that DW recorded over the scalp are the EEG counterpart of near-synchronous transitions between up and down states involving large populations of cortical neurons (Steriade et al., 1993, 2001). Large-scale simulations (Esser et al., 2007) and human studies (Riedner et al., 2007; Vyazovskiy et al., 2009) show that the amplitude and slope of DW are proportional to the number of cortical neurons entering such up/down states near-synchronously. This synchrony is directly related to the number and strength of synaptic connections among them. The data indicating that DW can be effectors of sleep cortical

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plasticity come mainly from high-density EEG studies in humans. For instance, sleep DW increase locally over the parietal cortex following learning of a visuomotor task (Huber et al., 2004). On the contrary, the arm immobilization during the day is followed by reduced sleep DW over the contralateral sensorimotor cortex, which goes in parallel with a decrease of motor performance and of sensory responses evoked by the stimulation of the nerve of the arm, consistently with the induction of a synaptic depression (Huber, 2006). Along this line, neuromodulatory techniques (i.e., paired-associative stimulation) able to induce synaptic cortical plasticity change the DW amount during sleep (Huber et al., 2008). DW changes triggered by the induction of cortical plasticity mainly occur in the stimulated regions, but are not necessarily confined to the site of the stimulation (Huber et al., 2007; Bergmann et al., 2008; De Gennaro et al., 2008). On the other hand, spontaneous DW during NREM sleep originate at a well-defined site (more frequently in prefrontal–orbitofrontal regions) and propagate in an orderly fashion to the rest of the scalp as a traveling wave (Massimini et al., 2004). In wakefulness, DW are almost absent in physiological conditions, but they appear when a subcortical brain lesion occurs requiring an intact cortex (Gloor et al., 1977; Steriade et al., 1993, 2001). Therefore, wakefulness DW are interpreted as a lesional sign, despite conclusive data about their functional significance still being missing. From a mere physical point of view, an increase of DW may originate from a higher number of synchronously oscillating neurons or from a stronger activity of such neurons. Both of these theories converge towards the hypothesis of a focused information processing, which might aim to induce local or network plasticity (Carmichael and Chesselet, 2002; Topolnik et al., 2003; Mazevet et al., 2003; Assenza et al., 2013). Although wake (injury-related) and sleep DW do not share generating pathways and topographical distribution, they are similar due to their EEG frequency and their neocortical origin; furthermore, they share the association with cortical plasticity phenomena. This evidence led us to investigate the causality of the linkage between wake DW and neuronal plasticity in humans. Therefore, we noninvasively induced cortical plasticity to explore changes of the EEG slow activity during wakefulness. Intermittent theta burst stimulation (iTBS), a robust neuromodulatory technique able to induce a reliable and prolonged shift in cortical excitability via long-term potentiation (LTP)-like plastic phenomena (Huang and Kandel, 2005; Di Lazzaro et al., 2008), was provided to healthy individuals to test our hypothesis.

2. Materials and methods

The study was approved by the Ethics Committee of Campus Bio-Medico University. Informed written consent was obtained from all subjects. We enrolled 20 right-handed healthy subjects (11 males). All subjects were right handed as self-reported. None of the subjects was taking drugs acting on the central nervous system.

2.1. Experimental design

The main aim of the study was to evaluate the effects of iTBS on brain activity and connectivity by means of EEG. To this end, we collected resting-state EEG and motor-evoked potentials (MEPs) produced by transcranial magnetic stimulation (TMS) before and after a real iTBS ($N = 11$, age 25 ± 5 years, six males) and a sham iTBS ($N = 9$, age 25 ± 4, five males). The change of MEP amplitude is widely accepted as an indirect measure of the effects of neuromodulatory techniques on brain excitability and, thus, of the induced motor cortical plasticity (Di Lazzaro et al., 2008). We identified four time points (Fig. 1): T_0, before iTBS (corresponding to the baseline); T_1, immediately after iTBS; T_2, 15 min after iTBS; and T_3, 30 min after iTBS. These time points were chosen to evaluate the long-lasting iTBS-dependent modulation of EEG activity and MEP. In order to estimate possible fluctuations of vigilance/attention, the following behavioral scales were administered at each time point (T_0, T_1, T_2, and T_3): sleepiness and anxiety visual analog scale (VAS) scales (ranging from 0 to 10) and Stanford Sleepiness Scale (Hoddes et al., 1971). All the experimental procedures were performed in a quiet room with the subject lying supine on a bed, with eyes opened, wearing earplugs that masked the TMS stimulus noise. Subjects were instructed to abstain from caffeine/alcohol and to maintain their regular sleep/wake schedule for at least 3 days before the experimental session. iTBS was applied over the left dominant hemisphere, whereas the activity/connectivity EEG modulations were evaluated bilaterally. Experimental sessions started at 10:00 a.m. with the placement of the EEG cap. The achievement of impedances of all electrodes below 5 kΩ required on average 20–30 min. After this technical adjustment, the first EEG recording started.

2.2. Transcranial magnetic stimulation

TMS was carried out in accordance with the safety guidelines suggested by Rossi and Hallett (2009). Considering the influence of ovarian hormones on human cortical excitability (Smith et al., 2002), the experiments with female subjects were always performed during the early follicular phase (Days 5–10, Day 1 being the first menstrual day). We employed a Rapid Magstim stimulator (Magstim Company, Dyfed, UK) connected to an eight-shaped coil with an inner diameter of 70 mm for each wing. The TMS pulse was always delivered with the coil tangentially placed to the scalp with the handle pointing anteromedially from the midline at 45°. Employing a biphasic waveform, we induced an anteroposterior followed by posteroanterior (AP–PA) current in the brain (Kammer et al., 2001). Muscle twitches triggered by TMS were recorded from the opponens pollicis (OP) of the right hand. The EMG signal was collected using Ag–Cl surface electrodes arranged in a standard tendon–belly montage, amplified, and recorded by a BrainAmp System (BrainProducts GmbH, Munich, Germany) via 1–2000-Hz filter setting with a 5-kHz sampling rate. The time window in which the poststimulus analysis was performed was set to 50 ms.

2.3. Excitability modulation assessment

After positioning the EEG cap, the hot spot for the right OP primary motor cortex (M1) and the resting motor threshold (rMT) were identified according to international guidelines (Rossini et al., 1994). We also collected the active motor threshold (aMT) corresponding to the lowest stimulator intensity able to produce an MEP amplitude of 200 μV during a 10% maximum voluntary contraction of the OP muscle (Di Lazzaro et al., 2005). At T_0, T_1, T_2, and T_3, the left M1 excitability was assessed by applying 15 single TMS pulses (inter stimulus interval of 5 s on average, 10% jittered), using a stimulator intensity output set to 120% of rMT. The maximal peak-to-peak MEP amplitude was analyzed off-line using Matlab 2011 (The Mathworks, Inc., Natick, MA, USA).

2.4. Intermittent theta burst stimulation

iTBS was delivered using the same stimulation equipment (stimulation intensity set to 80% of aMT). Real iTBS consisted of bursts of three pulses delivered at 50 Hz (20 ms between each pulse) repeated at 5 Hz (200 ms between each burst). The bursts have been combined in trains where each train consists of 10 bursts and lasts 2 s. Twenty trains have been repeated every 10 s