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Changes of oscillatory brain activity induced by repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in healthy subjects

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ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) modulates brain activity in different ways according to the stimulation parameters. Although the after-effects of rTMS over motor cortex are well documented in healthy individuals, less is known about the stimulation of dorso-lateral prefrontal cortex (DLPFC). Here, we studied in 20 healthy subjects how cortical oscillations are modulated by four different active rTMS protocols (1 Hz, 10 Hz, continuous and intermittent theta bursts — cTBS and iTBS) of the left DLPFC, and by a sham protocol used as a control condition, by comparing the spectral power of pre- and post-rTMS electroencephalographic (EEG) recordings of 15 min duration. EEG spectrum was estimated with the fast Fourier transform (FFT) and partitioned using the common physiological frequency bands: delta (1–4 Hz), theta (3.5–7 Hz), alpha (7.5–13 Hz), low beta (14–22 Hz), high beta (22–30 Hz) and gamma (30–45 Hz). Statistical analyses of EEG changes induced by rTMS were computed with Statistical Parametric Mapping (SPM) for EEG, in every frequency band, at the scalp level and at the cortex level. We found for every active protocol a significant decrease of delta and theta power on left prefrontal electrodes, mainly localised in the left DLPFC. In higher frequency bands (beta and gamma), the decrease of power in the DLPFC was also observed contralaterally. Protocol-specific amplitude effects were found in the prefrontal cortex bilaterally in all frequency bands, but also in parietal and temporal regions in low EEG frequencies. In high frequencies, EEG power in the prefrontal cortex increased after rTMS for 10 Hz and iTBS protocols, but this effect did not survive the comparison to Sham responses. Because large delta and theta activity is usually associated with cortical inhibition, observed rTMS-induced EEG changes in low frequencies suggest that rTMS of DLPFC transiently decreases local cortical inhibition. Importantly, local responses take place in association with other unknown mechanisms that modulate inter-hemispheric connectivity between homologous regions, resulting in the increase or decrease of fast activity in each prefrontal lobe, depending on the stimulation protocol. Only decreases of fast activity following active rTMS could be detected as significant when compared to Sham stimulation.

Introduction

Transcranial magnetic stimulation (TMS) uses a brief electric current passing through a magnetic coil positioned on the scalp to create a transient high-intensity magnetic field that focuses on the cortex and induces neuronal responses (Di Lazzaro et al., 2011; Hallett, 2007). The application of many pulses (repetitive TMS, rTMS) can modulate brain's activity during periods that outlast the stimulation time and is thus of potential interest for therapeutic applications, such as depression (Dell'Osso et al., 2009; George, 2010; Richieri et al., 2011), schizophrenia with auditory hallucinations (Hasan et al., 2013; Homan et al., 2012), migraines (Brigo et al., 2012; Magis et al., 2012) or stroke (Hummel et al., 2008; Jung et al., 2012).

It is supposed that the inhibitory and excitatory properties of rTMS protocols depend on the stimulation parameters, particularly the frequency of stimulation and the temporal structure of the paradigm, *i.e.* whether the series of pulses are applied continuously or not (Classen and Stefan, 2008). Those properties can be efficiently estimated when stimulating the motor cortex by recording motor evoked potentials (MEPs) on peripheral muscles. From such electromyographic (EMG) recordings, it has been shown that low-frequency stimulation (≤1 Hz) usually produces lasting decrease in motor cortex excitability, whereas high-frequency stimulation (≥5 Hz) induces facilitatory effects (Di Lazzaro et al., 2011; Hayashi et al., 2004; Houdayer et al., 2008; Noh et al., 2012; Romero et al., 2002). Similarly, theta burst stimulation (TBS, burst of three 50 Hz pulses repeated every 200 ms) is supposed to produce opposite neuronal after-effects depending whether bursts

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are applied continuously (cTBS, inhibitory) or intermittently (iTBS, excitatory) (Hoogendam et al., 2010; Huang et al., 2005). When stimulating outside the motor cortex, electroencephalographic (EEG) signals during or just following single pulse TMS provide similar valuable information about the changes in cortical activity, either locally or at remote locations from the site of stimulation (Ilmoniemi et al., 1997; Rosanova et al., 2009). Concerning rTMS, a recent review and meta-analysis of EEG/rTMS studies pointed out that it exists a certain degree of inter-study variability in the observed EEG after-effects (Thut and Pascual-Leone, 2010). In addition, the classical dichotomy between low vs. high frequency rTMS and inhibition vs. excitation has been challenged by a series of studies of EEG power changes following rTMS at different frequencies (1 Hz, 5 Hz, 20 Hz) that all showed increases of cortical motor oscillations in alpha and beta bands (Brignani et al., 2008; Fuggetta et al., 2008; Veniero et al., 2011). However, EEG oscillatory activity is only an indirect measure of inhibitory and excitatory properties of underlying neuronal networks. Still, from recordings in anesthetised animals combining extracellular and EEG recordings (Contreras and Steriade, 1995), it has been shown a direct correlation between low frequencies of EEG and hyperpolarisation waves, suggesting that amplitude of low frequency EEG positively correlate with large-scale neuronal inhibition. Importantly, it has also been shown that in the range of beta–gamma bands (20–80 Hz), oscillatory power was positively correlated with inhibitory transmission of fast-spiking cells (Cardin et al., 2009), making this band an indirect marker of local inhibition (see (Buzsáki and Wang, 2012) for a recent review on the mechanisms of gamma oscillations).

Whereas rTMS of dorsolateral prefrontal cortex (DLPFC) is commonly used for treating depression (Avery et al., 2006; Fitzgerald et al., 2003; George, 2010; George et al., 1995; Pascual-Leone et al., 1996), only a limited number of studies performed in healthy subjects described brain's responses to this type of stimulation (Graf et al., 2001; Griskova et al., 2007; Grossheinrich et al., 2009; Okamura et al., 2001). While the responses to motor cortex rTMS are relatively consistent across studies in healthy controls, it is not the case for DLPFC rTMS because of the heterogeneity of the population samples and of the experimental design. The main experimental factors that introduced variability in reported rTMS effects are the pulse parameters (Arai et al., 2005; Classen and Stefan, 2008; Taylor and Loo, 2007), the different ways of targeting the DLPFC between experimenters and the different anatomy of the underlying gyri between subjects (Thielscher et al., 2010).

In this study, we overcome these potential confounds by studying the EEG after-effects of five rTMS protocols (sham, 1 Hz, 10 Hz, iTBS, cTBS) of the left DLPFC performed on the same subjects by the same experimenter (A. W.-K.). In contrast to the previous studies where only one or two active protocols were compared to sham, the same subject underwent here all five protocols. From such repeated measures, we wanted to evaluate which rTMS protocol induces the most significant after-effects and whether patterns of cortical responses differ between rTMS protocols. To that end, statistical results on modifications of EEG oscillatory activity by rTMS are presented below at the group level.

Materials and methods

Participants

The study was approved by the regional ethical committee of Grenoble University Hospital (CPP Sud-Est I, ID RCB: 2011-A00114-37) and a written informed consent to participate in the study was obtained from all participants. Twenty healthy volunteers (10 males, 10 females), aged 21 to 60 (mean 31.2 ± 10.3 years) were enrolled for five rTMS sessions with concurrent EEG recordings. Two successive experimental sessions in the same subject were separated by at least 1 week and up to 10 days. All sessions for a given subject were performed under identical conditions, at the same time of the day. Three subjects were left-handed as assessed by the Edinburgh handedness inventory (Oldfield, 1971). The group was recruited after a preliminary interview performed by a psychiatrist (D. S.). None had neurological or psychological disorder or any contraindication for TMS. All subjects were familiarized with the TMS and the experimental protocol, but none of them had received rTMS previously.

rTMS protocols

During the first rTMS/EEG session, the resting motor threshold (RMT) of the right thumb abductor was measured with pre-gelled surface electrodes connected to an EMG amplifier (MEP Monitor, Tonika Elektronic A/S, Denmark) when stimulating the left primary motor cortex (Pascual-Leone et al., 1996). The motor threshold was defined as the lowest stimulation intensity that induced in 10 trials at least 5 motor evoked potentials of at least 50 μV peak-to-peak amplitude.

For all rTMS sessions, the stimulation was guided by a neuronavigation system (Premium Edition, Localite GmbH, Germany) to precisely define the neuroanatomical target of TMS from a T1-weighted magnetic resonance image (MRI) of subject's brain (Herwig et al., 2001). The TMS coil was then positioned in every session over the left DLPFC target point, defined as the intersection between Brodmann areas 9 and 46 along the middle frontal gyrus. Active rTMS was performed using a MagPro X100 TMS stimulator (Tonica Elektronik A/S, Denmark) with butterfly coil MCF-B65 (Tonica Elektronik A/S, Denmark). In sham rTMS condition, a MCF-P-B65 Placebo coil (Tonica Elektronik A/S, Denmark) was used to reduce the emitted magnetic field by approximately 80% with identical sound level and mechanical outline as with active MCF-B65 coil. The coil was placed tangentially to the scalp to produce the highest level of the stimulation on the cortical region parallel to the coil (Chen et al., 2003). The handle was placed backward and laterally, approximately at 45° from the midline perpendicular to the central sulcus. In case of head movement during the experiment, the coil was manually repositioned to its initial position.

Repetitive TMS protocols (1 Hz, 10 Hz, iTBS, cTBS, Sham) were constructed following the safety guidelines of the International Society of Transcranial Stimulation (ISTS) (Rossi et al., 2009). They all included between 792 and 800 pulses distributed into four periods for a total duration of 15 min. Inter-trains were included in between stimulation periods to homogenise total duration of every protocol (Fig. 1). Stimulation amplitude was 80% of RMT for cTBS and iTBS protocols, 120% of RMT for 1 Hz and 10 Hz protocols, and 24% (including coil attenuation) for Sham protocol. The pattern of the Sham protocol was identical to the one used for 1 Hz stimulation. Protocol order was randomly distributed between subjects, and subjects were not told about which protocol was used at the time of recording.

Self-evaluation of mood changes

A visual analogue scale (VAS) was used to proceed to a subjective assessment of mood changes by every participants during the few hours following each rTMS session. The VAS consisted 10 cm horizontal lines with anchors at both poles and indicating mood changes from happy/unhappy, joyful/sad, relaxed/tense, calm/excited, vivid/gloomy, smiling/serious. During the evening of the rTMS day, participants were asked to mark those 6 items between −5 and 5. A positive/negative score reflected a positive/negative valence of mood alteration. The sum over items was used to parsimoniously quantify mood changes (score range from −30 to 30).

EEG acquisition

Participants were seated in a reclining armchair with neck and back supported with a pillow, arms relaxed and eyes closed. They were asked to inhibit eye movements and blinks during recordings. In case of drowsiness detected online from EEG waves, the experimenter told