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Inter-individual variability in cortical excitability and motor network connectivity following multiple blocks of rTMS

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ABSTRACT

The responsiveness to non-invasive neuromodulation protocols shows high inter-individual variability, the reasons of which remain poorly understood. We here tested whether the response to intermittent theta-burst stimulation (iTBS) – an effective repetitive transcranial magnetic stimulation (rTMS) protocol for increasing cortical excitability – depends on network properties of the cortical motor system. We furthermore investigated whether the responsiveness to iTBS is dose-dependent.

To this end, we used a sham-stimulation controlled, single-blinded within-subject design testing for the relationship between iTBS aftereffects and (i) motor-evoked potentials (MEPs) as well as (ii) resting-state functional connectivity (rsFC) in 16 healthy subjects. In each session, three blocks of iTBS were applied, separated by 15 min. We found that non-responders (subjects not showing an MEP increase of ≥10% after one iTBS block) featured stronger rsFC between the stimulated primary motor cortex (M1) and premotor areas before stimulation compared to responders. However, only the group of responders showed increases in rsFC and MEPs, while most non-responders remained close to baseline levels after all three blocks of iTBS. Importantly, there was still a large amount of variability in both groups.

Our data suggest that responsiveness to iTBS at the local level (i.e., M1 excitability) depends upon the pre-interventional network connectivity of the stimulated region. Of note, increasing iTBS dose did not turn non-responders into responders. The finding that higher levels of pre-interventional connectivity precluded a response to iTBS could reflect a ceiling effect underlying non-responsiveness to iTBS at the systems level.

Introduction

Theta-burst stimulation (TBS) is an effective repetitive transcranial magnetic stimulation (rTMS) protocol, which allows modulation of cortical excitability upon a rather short period of stimulation (Huang et al., 2005). However, a growing number of studies report that the responsiveness to rTMS/TBS shows high inter-individual variability, sometimes even resulting in no overall alteration of cortical excitability (Hamada et al., 2013; Hinder et al., 2014; López-Alonso et al., 2014). Recent studies suggest that 50% - 73% of subjects are non-responders to rTMS/TBS (Hamada et al., 2013; Hinder et al., 2014).

To date, the reasons for this inter-individual variability remain poorly understood. Hamada et al. (2013) suggested that the differential recruitment of subtypes of cortical interneurons embedded in different cortico-cortical circuits may account for about 50% of the inter-individual variability. Based on a combined functional magnetic resonance imaging (fMRI)-TMS study, we recently demonstrated that the differential recruitment of these interneuron networks by TMS correlates with the functional connectivity between premotor areas and the primary motor cortex (M1) (Volz et al., 2014). This implies a relationship between responsiveness to TBS and motor network connectivity. However, in that study no aftereffects of iTBS on cortical excitability (motor-evoked potentials, MEPs) were investigated. Other studies also suggested a tight relationship between rTMS-induced aftereffects and network connectivity of the stimulated region (Cárdenas-Morales et al., 2014; Andoh and Zatorre, 2011, 2013; Downar et al., 2014; Salomons et al., 2014). For instance, the amount of pre-interventional

Abbreviations: AP, anterior–posterior; APB, abductor pollicis brevis; AMT, active motor threshold; ANOVA, analysis of variance; dPMC, dorsal premotor cortex; EPI, echo planar imaging; FD, framewise displacement; FDR, false discovery rate; fMRI, functional magnetic resonance imaging; FOV, field of view; FWE, family wise error; GLM, general linear model; iTBS, intermittent theta-burst stimulation; LM, latero-medial; MEP, motor-evoked potential; M1, primary motor cortex; RMSE, root mean squared error; RMT, resting motor threshold; rsFC, resting-state functional connectivity; rTMS, repetitive transcranial magnetic stimulation; SMA, supplementary motor area; TBS, theta-burst stimulation; TE, echo time; TR, repetition time.

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premotor-M1 connectivity in the activated motor system was strongly related to the individual susceptibility to cortical excitability enhancing intermittent TBS (iTBS) (Cárdenas-Morales et al., 2014). Furthermore, decreased levels of baseline connectivity have been associated with non-responsiveness to rTMS in clinical treatments (Salomons et al., 2014).

Moreover, we could recently show that increases in cortical excitability after iTBS are paralleled by increases in resting-state functional connectivity (rsFC) (Nettekoven et al., 2014). Both, increases at the local (MEPs) as well as at the systems level (rsFC) were found to be dose-dependent with an additional increase after three blocks of iTBS (3 x 600 pulses). However, in that study we did not address the question of individual differences in iTBS responsiveness and relationships with motor network connectivity. Therefore, it is unclear whether the group-level effect observed after the application of a higher iTBS dose in the first study stems from non-responders showing responsiveness after repeated stimulation, which would suggest that responsiveness is dose-dependent (i.e., a lacking MEP increase in the first block followed by MEP increases after additional blocks of stimulation). Alternatively, the group-level effect might be driven by an amplification of iTBS effects exclusively in a subgroup of subjects (i.e., "responders"), indicating that individual factors determine responsiveness (Hamada et al., 2013). Furthermore, it is still open whether responders and non-responders also differ in their response to iTBS at the level of motor network connectivity, i.e., in the increase of rsFC after iTBS as well as in their rsFC at baseline.

We, therefore, re-analyzed the entire data set of our previous study (Nettekoven et al., 2014) with respect to individual responsiveness at the MEP level as well as fMRI network level, a question that we did not address in the original publication. To assess changes in MEP size and rsFC, 16 healthy subjects received three blocks of iTBS applied over left M1 and a control stimulation over the vertex (Nettekoven et al., 2014). We assigned subjects to two groups: responders and non-responders. Assignment was based upon subjects' increase in MEP amplitudes after one iTBS block. We hypothesized that (i) responders show decreased rsFC between premotor areas and M1 compared to non-responders at baseline (Hamada et al., 2013; Salomons et al., 2014; Volz et al., 2014) and that (ii) a higher dose of iTBS will primarily modulate cortical excitability and rsFC in responders rather than in non-responders (Hamada et al., 2013; Nettekoven et al., 2014).

Methods

Subjects

All data have previously been included in a publication on general dose-dependent effects of iTBS on MEPs and resting-state connectivity (Nettekoven et al., 2014). We here re-analyzed the entire data set with respect to individual responsiveness at the MEP level as well as fMRI network level. Accordingly, data from 16 healthy, right-handed subjects were included (7 males, mean ± SD age: 27 ± 3 years, range: 23–35 years; no history of neurological or psychiatric diseases). Right-handedness was verified using the Edinburgh Handedness Inventory (Oldfield, 1971). All subjects provided informed written consent. The study was carried out according to the declaration of Helsinki (1969, last revision 2008) and had been approved by the local ethics committee.

Experimental design

A detailed description of the procedure has been previously published (Nettekoven et al., 2014). We here summarize the important steps. Fig. 1 illustrates the experimental design. We used a single-blind, vertex-stimulation controlled, cross-over within-subject design to test for the effects of multiple serially applied iTBS blocks on (i) cortical excitability (MEP sessions) and (ii) rsFC (resting-state fMRI sessions) to further elucidate mechanisms underlying the individual responsiveness to iTBS. Each subject participated in two MEP sessions (A, B) and two resting-state fMRI sessions (C, D). In each of the four sessions iTBS was repeated three times separated by 15 min, leading to a total of 1800 pulses (i.e., iTBS600, iTBS1200, iTBS1800) per session to examine the effect of dose (please cf. Nettekoven et al., 2014; Volz et al., 2013). Respectively, MEPs were measured at baseline and after each block of iTBS in the MEP sessions (A, B), and resting-state fMRI was measured at baseline and after each block of iTBS in the resting-state fMRI sessions (C, D). In two of the four sessions stimulation was applied over the left M1 (A: M1-iTBS_MEPs, C: M1-iTBS_rs-fMRI), and in the other two sessions over the parieto-occipital vertex (B: sham-iTBS_MEPs, D: sham-iTBS_rs-fMRI) (Herwig et al., 2007, 2010). Sessions were separated by at least one week to avoid carry-over effects. The order of M1- and sham-iTBS was randomized across subjects.

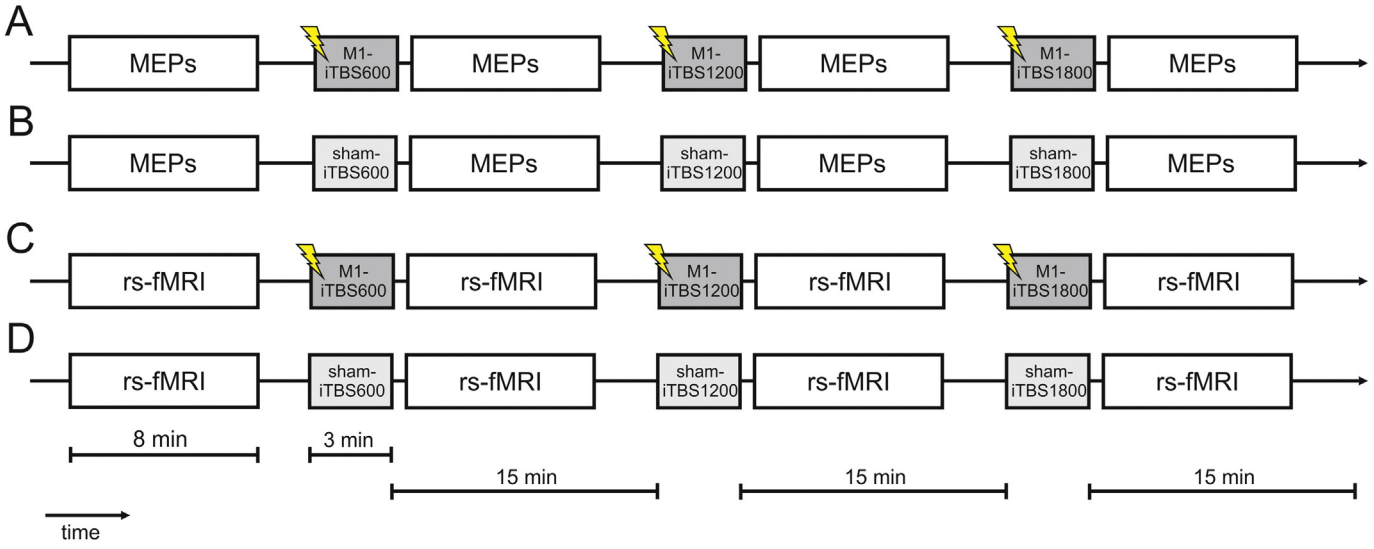

Fig. 1. Experimental design. Using a within-subjects design each subject took part in four sessions to assess (i) MEPs before and after **(A)** M1-iTBS and **(B)** sham-iTBS as well as to assess (ii) rs-fMRI before and after **(C)** M1-iTBS and **(D)** sham-iTBS. In each session three iTBS blocks were applied separated by 15 min. Each iTBS block consisted of 600 pulses, leading to a total of 1800 pulses. MEPs/rs-fMRI measurements were started approximately 3 min after the end of a given iTBS block.