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Investigations of motor-cortex cortical plasticity following facilitatory and inhibitory transcranial theta-burst stimulation in schizophrenia: A proof-of-concept study

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ABSTRACT

Impaired neural plasticity has been proposed as an important pathophysiological feature underlying the neurobiology and symptomatology of schizophrenia. In this proof-of-concept study, we aimed to explore cortical plasticity in schizophrenia patients with two different transcranial theta-burst (TBS) paradigms. TBS induces Ca^{2+}-dependent long-term-potentiation (LTP)-like and long-term-depression (LTP)-like plasticity in the human motor cortex. A total of 10 schizophrenia patients and 10 healthy controls were included in this study. Cortical excitability was investigated using transcranial magnetic stimulation in each study participant before and after TBS applied to the left primary motor-cortex on two different days. cTBS600 was used to induce LTD-like and cTBS300 was used to induce LTP-like plasticity in the absence of any prior motor-cortex activation. Repeated measures ANOVAs showed a significant interaction between the timecourse, the study group and the stimulation paradigm (cTBS600 vs. cTBS300) for the left, but not for the right hemisphere. Healthy controls showed an MEP amplitude decrease at a trend level following cTBS600 and a numeric, but not significant, increase in MEP amplitudes following cTBS300. Schizophrenia patients did not show an MEP amplitude decrease following cTBS600, but surprisingly a significant MEP decrease following cTBS300. The proportion of subjects showing the expected changes in motor-cortex excitability following both cTBS paradigms was higher in healthy controls. These preliminary results indicate differences in cortical plasticity following two different cTBS protocols in schizophrenia patients compared to healthy controls. However, the incomplete plasticity response in the healthy controls and the proof-of-concept nature of this study need to be considered as important limitations.

1. Introduction

Schizophrenia can be considered as a disorder of disturbed neural plasticity. This theory allows for the integration of robust neurobiological findings, such as impaired GABAergic and glutamatergic transmission, and clinical symptoms ranging from positive symptoms, reduced self-monitoring and cognitive deficits (Balu and Coyle, 2011; Stephan et al., 2009). Functional and structural impairments in glutamatergic N-methyl-D-aspartate (NMDA) receptors that lead to receptor hypofunction (Javitt et al., 2012), alterations in plasticity modulating genes (Balu and Coyle, 2011), impairments in GABAergic neurotransmission (Benes, 2011; Benes and Berretta, 2001) and reduced cortical responses following non-invasive brain stimulation (NIBS) (Hasan et al., 2013a) are just some lines of evidence supporting the plasticity hypothesis of schizophrenia. In particular, NIBS provide a possible method by which to modulate and evaluate cortical plasticity in awake humans, and thus are promising tools for research and treatment proposes. Studies that have used different NIBS techniques applied

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to the human motor cortex and compared healthy controls to schizophrenia patients have consistently demonstrated reduced motor-cortical plasticity responses in schizophrenia patients (for review see (Hasan et al., 2013a)). In detail, long-term potentiation (LTP)-like plasticity of the primary motor cortex has been shown to be reduced in chronic schizophrenia patients following paired-associative stimulation (Frantseva et al., 2008), anodal transcranial direct current stimulation (Hasan et al., 2011c) and a cortical reorganization paradigm (use-dependent plasticity) (Daskalakis et al., 2008). Conversely, long-term depression (LTD)-like plasticity has been consistently reduced using low-frequency repetitive transcranial magnetic stimulation (Fitzgerald et al., 2004; Oxley et al., 2004) and cathodal tDCS (Hasan et al., 2012, 2011b). Another NIBS paradigm, closely related to animal high-frequency burst protocols, was introduced in 2005 (theta-burst stimulation, TBS) and it was shown that, dependent on the stimulation pattern, LTP or LTD-like after-effects could be induced following very short stimulation periods (Huang et al., 2005). Recent work showed that the after-effects following different TBS paradigms are subject of a high interindividual variability (Hamada et al., 2013). However, these rapidly developing after-effects are of particular interest for clinical application, and various case studies and proof-concept-trials for a therapeutic use of TBS in schizophrenia have been recently published. In one study on eight treatment-refractory schizophrenia patients, intermittent TBS (iTBS) applied to the cerebellum resulted in an improvement in cognitive symptoms (Demirtas-Tatlidede et al., 2010), while another study showed that continuous TBS (cTBS) was not inferior to classic low-frequency TBS in reducing auditory hallucinations (Kindler et al., 2013). Moreover, single case studies indicate that cTBS applied to the temporal cortex might be a promising intervention for treatment-refractory auditory hallucinations (Eberle et al., 2010; Rachid et al., 2013; Sidhoumi et al., 2010). Investigations in healthy subjects have improved our understanding of TBS physiology and it has been suggested that the efficacy of TBS is dependent on the stimulation pattern, the activity of NMDA receptors (Huang et al., 2007; Wankerl et al., 2010), calcium homeostasis (Wankerl et al., 2010), the balance between inhibitory and facilitatory interneuronal networks (Huang et al., 2005), ongoing neural activity and metaplastic processes (Gentner et al., 2008; Hasan et al., 2011a), and on the recruitment of early and late cortical indirect waves (Hamada et al., 2013). However, despite this strong physiological evidence from healthy subject studies, little is known about TBS-effects in schizophrenia. In this first proof-of-concept study, we aimed to explore the impact of both Ca^{2+}-dependent LTP- and LTD-like inducing TBS on motor cortical plasticity in schizophrenia patients compared to healthy subjects. Given the impact of an impaired balance between neural facilitation and inhibition and reduced neural plasticity in schizophrenia, we hypothesized that schizophrenia patients would show differences in TBS-induced cortical plasticity compared to healthy controls.

2. Material and methods

2.1. Subjects

20 subjects (10 schizophrenia patients and 10 healthy controls) from the same geographical area participated in both experimental sessions of this study. The sample recruitment was conducted from 2011 to 2012 at the Department of Psychiatry of the University Goettingen. Subjects with dementia, neurological illnesses, severe brain injuries, or brain tumors were excluded from the study. Based on ICD-10 criteria, a consensus diagnosis was made by the clinical psychiatrist treating the patient and a member of our study group. All subjects underwent a standardized test of hand preference (Oldfield, 1971) and patients also had their psychopathology (Positive and Negative Syndrome Scale, PANSS) (Kay et al., 1987), disease severity (Clinical Global Impression, CGI) (Guy W, 1976), and psychosocial functioning (Global Assessment of Functioning, GAF) (Endicott et al., 1976) assessed. All patients were treated with antipsychotics in mono or combination therapy, and one patient received one additional antidepressant and a mood stabilizer (Table 1). For all antipsychotics, chlorpromazine (CPZ) equivalents were calculated. Written informed consent was obtained from all participants and the local ethics committee approved the protocol, which was conducted in accordance with the Declaration of Helsinki.

2.2. Transcranial theta-burst stimulation of the left motor cortex

Transcranial Theta-burst stimulation (TBS) was performed using a figure-of-eight shaped magnetic coil for repetitive application (MCF-B65) MagPro-X100 stimulator (Medtronic Co., Denmark). For both experimental setups, continuous TBS (cTBS), with each burst consisting of three stimuli with a repetition rate of 50 Hz for a duration of either 20 s (cTBS300, LTP-like plasticity) (Gentner et al., 2008) or 40 s (cTBS600, LTD-like plasticity) (Huang et al., 2005), was used. The condition intensity was set at 70% of the resting motor threshold (RMT) to avoid any influence of prior voluntary motor activation on cTBS-induced after-effects (Gentner et al., 2008; Goldsworthy et al., 2014; Huang et al., 2011a). Experimental sessions were performed either side of an interval of at least five days.

2.3. Transcranial magnetic stimulation of both motor cortices to monitor excitability changes

According to a standard procedure in our laboratory (Hasan et al., 2013b; Hasan et al., 2011c), participants were seated in a reclining chair with both arms supported passively. Electromyographic (EMG) recordings from the right and left first-dorsal interosseus muscle (FDI) were taken using standard surface electrodes. Raw signals were amplified, bandpass-filtered (2 Hz–10 kHz), and digitized using a commercially available amplifier. All recordings were manually analyzed offline. To monitor excitability changes, TMS was applied to both motor cortices (left and right M1) using a posterior-anterior current direction through a standard figure-of-eight coil (CB60) connected to a MagPro-X100 stimulator. As described previously, the coil was manually and tangentially placed with the handle pointing backwards at an angle of 45° to the midline. The stimulation sites leading to large and stable motor-evoked potentials (MEPs) were defined as optimal coil positions over the left and right

Table 1
Antipsychotic medications received by schizophrenia patients.

Patient no.	Antipsychotic medication	Dosage (mg/d)
1	Aripiprazole; Quetiapine	30;400
2	Olanzapine	10
3	Aripiprazole; Quetiapine	25; 200
4	Risperidone	4
5[a]	Ziprasidone	120
6	Aripiprazole	15
7[b]	Aripiprazole; Quetiapine	30; 150
8	Aripiprazole	10
9	Flupentixol	15
10	Aripiprazole; Quetiapine	20; 200

[a] Due to a depressive symptomatology, this patient received additional 20 mg Citalopram, 50 mg Valdoxane and 150 mg Lamotrigine per day.
[b] This patient received additional 4 mg Biperiden.