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ACCELERATED HIGH-FREQUENCY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION ENHANCES MOTOR ACTIVITY IN RATS

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Abstract—High-frequency repetitive transcranial magnetic stimulation (HF-rTMS) is currently accepted as an evidence-based treatment option for treatment-resistant depression (TRD). Additionally, HF-rTMS showed beneficial effects on psychomotor retardation in patients. The classical HF-rTMS paradigms however are unlikely to replace electroconvulsive therapy, a more potent alternative for TRD albeit with important side-effects. Therefore, recent studies have investigated 'accelerated' HF-rTMS protocols demonstrating promising clinical responses in patients with TRD. Since the neuronal effects of accelerated HF-rTMS are underinvestigated, we evaluate here the possible metabolic and neurochemical effects of this treatment alternative. More specifically, we measured the effect on brain glucose metabolism and monoamines/metabolites, as well as on the spontaneous motor activity in rats. We found that brain glucose metabolism and monoamines remained generally unaffected after accelerated HF-rTMS, with the exception of reduced total striatal 5-hydroxyindolacetic acid (a metabolite of serotonin) levels. Interestingly, when compared to sham stimulation, the velocity, the total distance traveled as well as the percentage of movement, as measured by the open-field test, were significantly enhanced after accelerated HF-rTMS showing an increased motor activity. Our current results indicate that the accelerated HF-rTMS-induced increase in motor activity in rats, may be related to the striatal neurochemical effect. **© 2017 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: accelerated HF-rTMS, motor activity, FDG-PET, monoamines, brain.

INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique where no anesthetics are required and side-effects are barely induced. This technique has wide applications in neurology and psychiatry (Lefaucheur et al., 2014). In patients, it is currently accepted as an evidence-based treatment option for major depression, as up to 15% of patients suffering from major depression do not respond to the available antidepressant drugs (Berlim and Turecki, 2007a). High-frequency (HF)-rTMS is thereby mostly applied to the left dorsolateral prefrontal cortex (DLPFC) (Berlim and Turecki, 2007b) however, response rates are rather limited (Mitchell and Loo, 2006). Electroconvulsive therapy (ECT) has been proven to be a more potent alternative for treatment-resistant depression (TRD) but the use of anesthetics and the risk for cognitive impairments increase the need for alternative treatments.

According to the meta-analysis performed by Berlim and coworkers, the classical high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) paradigms are unlikely to replace ECT (Berlim et al., 2013; Micallef-Trigona, 2014). Therefore, in order to increase the clinical response of TRD, recent studies have investigated 'intensified' or 'accelerated' HF-rTMS protocols (Holtzheimer et al., 2010; Hadley et al., 2011; Zeeuws

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Abbreviations: [^{18}F]-FDG, 2-deoxy-2-(^{18}F)fluoro-D-glucose; 5-HIAA, 5-hydroxyindolacetic acid; 5-HT, serotonin; CT, computed tomography; DA, dopamine; DLPFC, dorsolateral prefrontal cortex; DOPAC, 3,4-dihydroxyphenylacetic acid; ECT, electroconvulsive therapy; EMG, electromyography; HF-rTMS, high-frequency repetitive transcranial magnetic stimulation; MEP, motor-evoked potential; MT, motor threshold; PET, positron emission tomography; sgACC, subgenual anterior cingulate cortex; SUV_{glu}, glucose corrected standardized uptake value; TRD, treatment-resistant depression; VOI, volume of interest.

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et al., 2011; Baeken et al., 2013). A case report described successful treatment of an ECT-resistant depressed woman with accelerated HF-rTMS consisting of 20 HF-rTMS sessions administered during four consecutive days (daily five sessions of 1560 stimuli each and a total amount of 31,200 pulses after 4 days) instead of classical protocols consisting of a daily single session with a duration varying from 2 to 9 weeks (Zeeuws et al., 2011). Furthermore, the same HF-rTMS paradigm, in a placebo-controlled study consisting of 20 unipolar patients with TRD, was found to be safe and well-tolerated and proved its benefits since 35% of the patients showed immediate clinical response (Baeken et al., 2013).

Several studies have also explored the neuronal impact of rTMS treatment in both healthy subjects and patients suffering from major depression (Knoch et al., 2006; Sibon et al., 2007; Baeken et al., 2009, 2011; Kito et al., 2012). For example Knoch et al. demonstrated in healthy men that changes in the regional cerebral blood flow induced by prefrontal rTMS differ upon hemisphere stimulated and vary with stimulation frequency (Knoch et al., 2006). Recently, we demonstrated for the first time a decreased metabolic activity of the subgenual anterior cingulate cortex (sgACC) after accelerated HF-rTMS of the left DLPFC which was associated with a beneficial clinical outcome in patients with TRD (Baeken et al., 2014, 2015). The latter brain area is reported to be metabolically hyperactive during depressive episodes (Drevets et al., 2008), and successful treatments in general attenuate this sgACC metabolic activity, indicating that HF-rTMS affects disturbed cortico-limbic pathways when clinically depressed. Since the investigation possibilities in human studies are ethically restricted, research on the effects of rTMS in laboratory rats has been performed demonstrating, among others, changes in neurotransmitter systems (Ben-Shachar et al., 1997; Ben-Shachar et al., 1999; Keck et al., 2000, 2002; Kanno et al., 2004). In this pilot study we investigated possible metabolic and neurochemical effects of such an accelerated HF-rTMS paradigm using a circular TMS coil on healthy rats. Since the therapeutic effects of most antidepressants are associated with alterations of brain monoamines, we investigated the effect of accelerated HF-rTMS on the total content of dopamine (DA), serotonin (5-HT) and their metabolites in different brain areas. Additionally, given that brain glucose metabolism is an indirect indication of neuronal activity, we also measured the uptake of the positron emission tomography (PET) tracer 2-deoxy-2-(^{18}F)fluoro-D-glucose ([^{18}F]-FDG) in different brain structures. Moreover, besides the typical depressive mood and lack of interests, major depression also comprises psychomotor retardation. Indeed, prior research in medication-free patients reported decreased motor activity during wakefulness (van Londen et al., 1998; Volkers et al., 2003). Interestingly, we previously reported that a classical HF-rTMS paradigm (10 HF-rTMS sessions spread over 10 days), resulted in decreased psychomotor retardation in patients with TRD (Baeken et al., 2010). Moreover, we also noticed increased motor activity in patients with TRD after accelerated HF-rTMS treatment (20 HF-rTMS sessions spread over 4 days) (C Baeken, Department of Psychiatry, Universitair Ziekenhuis Brussel, Center for Neurosciences, Vrije Universiteit Brussel, personal communication). Besides, prefrontal rTMS significantly improved the psychomotor speed after active stimulation of the right DLPFC in healthy females (Baeken et al., 2012). Therefore, besides the aforementioned metabolic and neurochemical assessments, the motor activity was also explored following this accelerated stimulation paradigm in rats.

EXPERIMENTAL PROCEDURES

Animals

Twelve male Sprague–Dawley rats (Janvier, France), weighing 250–275 g (7 weeks old) at the start of the experiment, were used. Rats were housed in our animal housing facilities and had *ad libitum* access to water and food. Experiments were carried out according to the European Ethics Committee (86/609/EEC) and were approved by the Antwerp University Ethics Committee for Animal Experiments (ECD 2011 30). All efforts were made to minimize animal suffering and the minimal number of animals necessary to produce reliable scientific data was used.

Experimental procedure

All rats were first handled and trained during five consecutive days to remain immobile in a conical cylinder to minimalize stress during the experiment and to increase reproducible positioning of the coil as well as to habituate to the acoustic effect of the coil during stimulation (coil is placed at a distance) (Fig. 1A). Immediately after the handling session on the 4th day of the handling period, rats were transported to the open field room (15 min) and were allowed to acclimatize during 1 h. This was followed by the open field test during which the spontaneous motor activity was measured (Section ‘‘Open-field test”) (delay between the training session and open-field test was 1 h and 15 min). The next day, in order to assess the brain glucose metabolism, animals were subjected to [^{18}F]-FDG-μPET imaging (Section ‘‘[^{18}F]-FDG-μPET-CT imaging”) immediately after the handling session. Thereafter, animals were randomly divided into the rTMS and sham group. During the HF-rTMS/sham stimulation period (Section ‘‘Accelerated HF-rTMS stimulation”), each animal received daily five suprathreshold HF-rTMS sessions or sham stimulation during four consecutive days. On the 4th day of the HF-rTMS/sham stimulation, after the last stimulation session, rats were allowed to acclimatize during 1 h in the open field room and were subsequently subjected to the open field test. The following day, brain glucose metabolism post HF-rTMS/sham treatment was assessed using [^{18}F]-FDG-μPET imaging. After the final scans, rats were sacrificed using a guillotine (after being shortly anesthetized by inhalation of a mixture of isoflurane and medical oxygen). The brains were removed from the skull and both left and right motor cortices, medial prefrontal cortices, striata and

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