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Psychophysiological effects of an iTBS modulated virtual reality challenge including participants with spider phobia

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ABSTRACT

Preliminary evidence suggests beneficial effects of transcranial magnetic stimulation (TMS) on anxiety. The objective of this study was to investigate the effects of intermittent theta burst stimulation (iTBS) as a form of TMS on acute anxiety provoked by a virtual reality (VR) scenario.

Participants with spider phobia ($n = 41$) and healthy controls ($n = 42$) were exposed to a spider scenario in VR after one session of iTBS over the prefrontal cortex or sham treatment.

Participants with spider phobia reacted with more anxiety compared to healthy controls. Their heart rate and skin conductance increased compared to baseline. Contrary to expectations, iTBS did not influence these reactions, but modulated heart rate variability (HRV). Sympathetic influence on HRV showed an increase in the active iTBS group only. This study does not support the idea of beneficial effects of a single session of iTBS on anxiety, although other protocols or repeated sessions might be effective.

1. Introduction

Converging evidence from many studies suggests that raised activity of the amygdala plays a key role in the development of fear and anxiety. According to this model, pathological anxiety is the result of inadequate amygdala activation to non-threatening stimuli. Since the prefrontal cortex (PFC) has an inhibitory effect on the amygdala, this hyperactivity is attributed to a dysfunction of the PFC which results in an insufficient suppression of the amygdala (Eden et al., 2015; Etkin & Wager, 2007; Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003). For example, Nishimura et al. (2007) reported hypoactivation of the left PFC in patients with panic disorder. Regarding spider phobia, Johanson, Risberg, Tucker, and Gustafson (2006) found an increase in bilateral prefrontal cerebral blood flow in initially strongly anxious patients with spider phobia after successful cognitive psychotherapy (Johanson et al., 2006). Within the PFC the dorsolateral prefrontal cortex (DLPFC) has been shown to play a role in the processing of information with emotional content (Dolcos, LaBar, & Cabeza, 2004; Meyer-

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Lindenberg et al., 2005). However, other regions within the PFC like the dorsomedial prefrontal cortex may play an equally or even more important role in the interaction with the amygdala regarding anxiety (Robinson, Charney, Overstreet, Vytal, & Grillon, 2012; Robinson, Krimsky, Lieberman, Allen, Vytal, & Grillon, 2014).

Such a model of a dysbalance regarding the interaction of PFC and amygdala constitutes the use of transcranial magnetic stimulation (TMS) to modulate cortical activity non-invasively and thus influences the function of the PFC (Diemer, Vennewald, Domschke, & Zwanzger, 2010; Pallanti & Bernardi, 2009). Despite a paucity of evidence at a neural network-level for the capability of prefrontal cortical TMS to influence the activity of the amygdala, TMS has been investigated in a repetitive form (rTMS) as a potential therapeutic intervention in depression (Herwig et al., 2007; Padberg et al., 1999; Pallanti & Bernardi, 2009; Plewnia et al., 2014) and panic disorder (Deppermann et al., 2014; Dresler et al., 2009; Zwanzger et al., 2002; Zwanzger, Fallgatter, Zavorotnyy, & Padberg, 2009), aiming at an increase of PFC function. Intermittent theta burst stimulation (iTBS) is a more intense, innovative form of TMS that comprises the repeated application of bursts of stimuli and facilitates excitation in cortical circuits (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). In addition to the above described model of prefrontal top-down control, the "valence hypothesis" is another neurobiological model which has often been used to explain the pathogenesis of anxiety disorders and depression (Vennewald, Diemer, & Zwanzger, 2013). Accordingly, approach related emotions are rather modulated in the left hemisphere, while avoidance related emotions are rather modulated in the right hemisphere. In line with this idea, the most widely studied forms of TMS in major depression and anxiety disorders are low frequency rTMS over the right DLPFC and high frequency rTMS over the left DLPFC (Lefaucheur et al., 2014). At least in the context of major depression, a review by Chen et al. (2013) came to the conclusion that both stimulation protocols are equally effective (Chen et al., 2013). Since other interventions (e.g., antidepressant medication) have been demonstrated to be effective in both psychiatric disorders, its successful use in the treatment of depression makes TMS a promising therapeutic option in anxiety disorders. As there is not enough evidence which suggests to favor one over the other stimulation technique (Lefaucheur et al., 2014), we decided to investigate iTBS over the left DLPFC which is comparable to high frequency rTMS (Huang et al., 2005), since this suits the model of prefrontal top–down control as well as the "valence hypothesis". However, it should be kept in mind that these hypotheses simplify both, the underlying neural network as well as the mode of action of TMS, which are not fully understood yet and are for sure more complex and involve more brain regions than just the PFC and amygdala. For example, Chervyakov, Chernyavsky, Sinitsyn, and Piradov (2015) reviewed the literature about putative and established mechanisms explaining the therapeutic effects of TMS (Chervyakov et al., 2015). They point out that TMS does not just induce the transmission of electrical signals to neurons, but also affects neurotransmitters, gene expression, the activity of certain enzymes, cerebral blood flow and many other processes within the brain.

The present study investigated the effect of iTBS on acute anxiety. As a model, specific spider phobia was chosen because the disorder is very common (Fredrikson, Annas, Fischer, & Wik, 1996) and anxiety can be triggered easily by presentation of spiders. For a standardized presentation we chose virtual reality (VR), a technology that permits a very realistic presentation of virtual spiders in three-dimensional scenarios by means of a head-mounted display. VR scenarios are appropriate not only to provoke subjective anxiety, but also psychophysiological changes. A review by Diemer, Muehlberger, Pauli, and Zwanzger (2014) compared thirty-eight studies on psychophysiological effects of VR in patients with anxiety disorders as well as healthy participants with and without increased trait anxiety (Diemer et al., 2014). They found that challenging situations in VR are capable of altering skin conductance levels (SCL) in patients with anxiety disorders as well as in healthy controls. Results for heart rate (HR) are inconclusive.

Since patients experience an increase of SCL and often also HR in a VR exposure scenario, it is important to further investigate whether these parameters decrease with habituation to the scenario, and how long this takes. Only few studies have so far addressed these questions. Patients with fear of flying, for example, have shown reductions in HR and SCL response to virtual flight environments after repeated exposures (Muehlberger, Herrmann, Wiedemann, Ellgring, & Pauli, 2001). Heart rate variability (HRV) is another parameter of psychophysiological arousal that provides information about influences of the autonomous nervous system on the heart. Two important sub-measures of HRV are LF, the low frequency component, mediated by the sympathetic as well as parasympathetic nervous system, and HF, mediated mainly by the parasympathetic nervous system. High LF as well as low HF point to more sympathetic and less parasympathetic influence, while low LF and high HF are associated with less sympathetic and more parasympathetic influence (Berntson et al., 1997). HRV has rarely been studied in the context of TMS. To the best of our knowledge, there is only one study on the long term effect of rTMS over the prefrontal cortex that measured HRV. Udupa et al. observed a decrease in LF/HF ratio in 30 patients with major depression after 12 sessions of high-frequency (15 Hz) rTMS over the left prefrontal cortex (Udupa et al., 2007, 2011). As for immediate effects, there have only been studies on regions other than the DLPFC, e.g., Yoshida et al. (2001) found significantly elevated LF as well as HF after low frequency (0.2 Hz) rTMS over the vertex. In contrast to them, Vernieri et al. (2014) found a decrease of LF/HF ratio after low frequency (1 Hz) rTMS over the primary motor cortex.

Closely related to emotions like anxiety and parameters of psychophysiological arousal like HR, SCL and HRV is the feeling of presence in virtual reality. Presence is defined as the impression of really being there in a certain environment, even if it is virtual (Slater, 1999). Strong emotions and arousal have repeatedly been shown to be associated with an increased feeling of presence (Diemer, Alpers, Peperkorn, Shiban, & Muehlberger, 2015).

In the present bicentric study, iTBS was combined with a VR challenge to provoke anxiety in participants with spider phobia in a single-blind, sham-controlled parallel group design. The aim of the study was to investigate the effect of iTBS on acute anxiety in spider phobia and the psychophysiological changes that go along with it. The following hypotheses were tested. (1) Watching a virtual spider scene provokes anxiety and disgust as well as the activation of the sympathetic nervous system as indicated by an increase of HR and SCL and, regarding HRV, an increase of the LF component accompanied by a decrease of the HF component in participants with spider phobia. (2) These emotional as well as psychophysiological reactions are less pronounced in healthy control participants. (3) ITBS attenuates the increase of anxiety, disgust, HR, SCL as well as the increase of the LF component and the respective decrease of the HF component in participants with spider phobia stimulated actively, but not in the sham group. (4) Participants with spider phobia display a stronger feeling of presence during virtual reality compared to healthy control participants.

2. Material and methods

2.1. Participants

Participants with spider phobia and healthy controls were recruited via local advertisements. They had to be between 18 and 65 years of age. Participants with spider phobia had to