



## Research report

# Functional co-activation within the prefrontal cortex supports the maintenance of behavioural performance in fear-relevant situations before an iTBS modulated virtual reality challenge in participants with spider phobia



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## HIGHLIGHTS

- In spider phobia, left IFG activation is reduced after emotionally irrelevant words.
- After phobic words, co-activation was increased between IFG and contra-lateral PFC.
- As performance was not impaired, this was interpreted as a compensatory mechanism.
- (sham)iTBS/VR leads to activation adjustment between the phobic and control group.
- Simultaneously, arousal ratings decreased significantly in the phobic group.

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## ABSTRACT

A number of studies/meta-analyses reported moderate antidepressant effects of activating repetitive transcranial magnetic stimulation (rTMS) over the prefrontal cortex (PFC). Regarding the treatment of anxiety, study outcomes are inconsistent, probably because of the heterogeneity of anxiety disorders/study designs. To specifically evaluate the impact of rTMS on emotion regulation in fear-relevant situations we applied a sham-controlled activating protocol (intermittent Theta Burst Stimulation/iTBS) over the left PFC (F3) succeeded by a virtual reality (VR) challenge in  $n = 41$  participants with spider phobia and  $n = 42$  controls. Prior to/after iTBS and following VR prefrontal activation was assessed by functional near-infrared spectroscopy during an emotional Stroop paradigm. Performance (reaction times/error rates) was evaluated. Stimuli were rated regarding valence/arousal at both measurements.

We found diminished activation in the left inferior frontal gyrus (IFG) of participants with spider phobia compared to controls, particularly elicited by emotionally-irrelevant words. Simultaneously, a functional connectivity analysis showed increased co-activation between the left IFG and the contra-lateral hemisphere. Behavioural performance was unimpaired. After iTBS/VR no significant differences in cortical activation between the phobic and control group remained. However, verum-iTBS did not cause an additional augmentation. We interpreted our results in terms of a prefrontal network which gets activated by emotionally-relevant stimuli and supports the maintenance of adequate behavioural reactions.

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The missing add-on effects of iTBS might be due to a ceiling effect of VR, thereby supporting its potential during exposure therapy. Concurrently, it implies that the efficient application of iTBS in the context of emotion regulation still needs to be studied further.

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## 1. Introduction

With a life time prevalence of up to six percent, spider phobia is the most common specific phobia of the animal type which mostly affects women [14]. As in other anxiety disorders, an inadequate top-down regulation of subcortical structures such as the modulation of the amygdala by the prefrontal cortex (PFC) is assumed to be a core feature [4,10,19,29,47]. While the amygdala is thought to be associated with vigilance and flight reactions [34,40] the PFC is involved in the regulation of emotion [18,54]. The dorsolateral prefrontal cortex (DLPFC) specifically, as a main neural correlate of executive function, plays an important role regarding goal-oriented inhibition of emotional responses [3,6]. While the inferior frontal gyrus (IFG) comprises a major part of Broca's area, known for its role in language processing [16], it could also be linked to emotion regulation [18], as well as response suppression and attentional control, especially but not exclusively in the non-dominant hemisphere [23,53].

Diverging prefrontal brain activation patterns have been observed in response to fear-inducing stimuli. While some studies found prefrontal hypoactivation [4,29,47] other findings showed enhanced activation [41,48,52]. An explanation for these controversial outcomes might be the different cognitive processes involved in the specific tasks applied.

Within this framework, the "Valence hypothesis" is a neurobiological model which postulates hypo- as well as prefrontal hyperactivation depending on the context of the task. In accordance with this hypothesis, the left hemisphere plays a major role in the modulation of approach related emotions while the right hemisphere mainly modulates avoidance related emotions [56].

Bringing together the valence hypothesis and the model of inadequate top-down regulation found in anxiety disorders, we decided to apply an activating repetitive transcranial magnetic stimulation (rTMS) protocol on the left hemisphere in order to enhance prefrontal activation and associated cognitive control during a situation which induces avoidance related emotions.

Intermittent theta burst stimulation iTBS [26], is a modern form of activating rTMS which is able to modulate cortical activation non-invasively by electro-magnetic induction. Compared to traditional rTMS, a longer-lasting effect is obtained with shorter stimulation. In this context, studies point to an enhancing effect of approximately an hour after a one-time application of an iTBS protocol [20].

So far, a number of studies and meta-analyses have found moderate antidepressant effects using repeated rTMS [39]. In the context of anxiety disorders, far fewer studies exist and results are inconsistent [35]. This might be due to the complexity of some of these study designs where many active factors may have led to confounding effects. For example, in a previous study conducted by our workgroup [7], panic disorder patients received repeated iTBS application while taking part in cognitive behavioural group therapy. To simplify the interpretation of study outcomes it might, however, be easier to look at an assessable number of specific factors separately.

Recently, virtual reality (VR) exposure has become more established as an alternative to in-vivo exposition in the treatment of pathological fear. Its advantages include a better controllability of

the therapeutic setting as well as a high compliance with patients [43]. At the same time, studies have shown that VR is able to induce a significant increase in subjectively received fear as well as psychophysiological arousal (heart rate, skin conductance) [8,9,15].

Within the framework of psychiatric research, functional near-infrared spectroscopy (fNIRS) is an imaging method with particularly good acceptance among participants due to its uncomplicated and fast application compared to other imaging methods, e.g. functional magnetic resonance imaging (fMRI) [12]. As an optical imaging method, fNIRS exploits the fact that near-infrared light can penetrate scalp and skull. Because the chromophores oxyhaemoglobin (O<sub>2</sub>Hb) and deoxyhaemoglobin (HHb) have distinct absorption spectra in the near-infrared range, it is possible to deduce regional oxygenation patterns by measuring the relative amount of reflected light [13], with a spatial resolution of approximately 3 cm and a depth penetration of about 2.5 cm [21].

Altogether, this study aimed at examining the impact of one-time iTBS application over the PFC prior to a fearful situation. To do so, a VR environment was used to confront participants suffering from spider phobia with virtual spiders after receiving sham-controlled iTBS. Before and after the iTBS/VR combination, prefrontal activation was assessed by fNIRS while the participants completed an emotional Stroop paradigm.

The advantage of an emotional Stroop paradigm is that participants are not asked to willingly influence their emotions (potentially triggering more individual strategies and therefore more diverging results) but still need to ignore phobic or fearful content of the presented stimuli if they want to complete the task in an adequate manner.

In this regard, a number of authors [11,57] reported increased activation in the IFG and other prefrontal areas elicited by anxiety provoking words during an emotional-word Stroop paradigm in a sample of patients with panic disorder. On a behavioural level, the difficulty of focusing on the mere task without getting distracted by anxiety-provoking stimuli is further supported by the fact that diverging reaction times (RTs) in emotional Stroop tasks have been shown [11,30,36].

Specifically, in this paper we report the results concerning the following hypotheses:

- a Phobic participants require more cognitive control when trying to respond to phobia-related stimuli in an adequate manner and therefore display increased DLPFC/IFG activation patterns.
- b At the same time, we still expect decreased behavioural performance (RTs, error rates) to fear-related stimuli compared to healthy controls reflecting the difficulties in implicit emotion regulation during the confrontation with phobic words.
- c iTBS followed by a VR challenge further promotes prefrontal activation elicited by emotional stimuli in participants with spider phobia and is associated with an improved behavioural outcome as well as a temporary adjustment of subjectively perceived valence and arousal ratings of the presented words.
- d In addition to a standard fNIRS analysis of cortical activation patterns, we also investigated the functional connectivity within the PFC in order to get a better understanding of the interplay of the different sub-regions during emotional control processes.

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