Neuropsychologia 99 (2017) 360–367

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

# Offline continuous theta burst stimulation over right inferior frontal gyrus and pre-supplementary motor area impairs inhibition during a go/no-go task

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ARTICLE INFO

*Keywords:*
Continuous theta burst stimulation
Response inhibition
Response initiation
Go/no-go task
Startling acoustic stimulus
Behavioural control

ABSTRACT

In a typical go/no-go task a single imperative stimulus is presented each trial, either a go or no-go stimulus. Participants are instructed to initiate a known response upon appearance of the go-signal and withhold the response if the no-go signal is presented. It is unclear whether the go-response is prepared in advance of the imperative stimulus in a go/no-go task. Moreover, it is unclear if inhibitory control processes suppress preparatory go-activation. The purpose of the present experiment was 1) to determine whether the go-response is prepared in advance of stimulus identification with the use of a startling acoustic stimulus (SAS), and 2) investigate the inhibitory role of the right inferior frontal gyrus (rIFG) and pre-supplementary motor area (preSMA) during the performance of a go/no-go task with the use of continuous theta burst stimulation (cTBS). The experiment consisted of three phases; a pre-cTBS phase in which participants completed a go/no-go and simple-RT task, followed by offline cTBS to temporarily deactivate either rIFG or preSMA (with a sham control), then a post-cTBS phase which was identical to the pre-cTBS phase. Results revealed that stimulation to both cortical sites impaired participants' ability to withhold movements during no-go trials. Notably, rIFG or preSMA stimulation did not affect the latency of voluntary go-responses and did not enable the SAS to involuntarily trigger responses. These findings suggest that preparation and initiation of the go-response occurs after the imperative stimulus, with the rIFG and preSMA involved in inhibiting the go-response once the stimulus is identified as a no-go signal.

## 1. Introduction

Donders' seminal paper (1969) showed that reaction time (RT) in a go/no-go task was faster than in a choice RT task but nevertheless slower than in a simple RT task. From these findings he concluded that during a go/no-go task the motor response was selected and prepared in advance, with the increase in RT from a simple RT task accounted for by the time required to identify the imperative stimulus and decide whether to go or not. Since the work of Donders, several other studies have confirmed the proposal that a response is prepared in advance of the imperative stimulus in go/no-go tasks (Danek and Mordkoff, 2011; Miller and Low, 2001).

A unique test of this hypothesis used a startling acoustic stimulus (SAS) to probe the preparatory state of the response (Carlsen et al., 2008). The presentation of a SAS has been shown to trigger the early release of the movement during simple RT tasks but not during choice RT tasks (Carlsen et al., 2004), suggesting that a SAS has the ability to trigger movements involuntarily so long as they are sufficiently prepared. As such, it was hypothesized that startle would trigger the prepared movement during the go/no-go task. Contrary to the hypothesis, presentation of the SAS concurrent with the imperative stimulus had no effect on RT (i.e., did not lead to the early release of the movement), suggesting that the movement was in fact *not* prepared in advance during a go/no-go task, and thus response programming occurred after the go-signal similar to a choice RT task (Carlsen et al., 2008). However, an alternative interpretation of these results is that the movement was indeed prepared in advance, but the response could not be triggered by startle due to interference from inhibitory control processes put in place to ensure that the movement was not initiated before the stimulus was identified during a no-go trial.

Evidence of inhibitory control on "go" response-related preparatory activation during a go/no-go task has been shown using EEG and its associated measure known as the lateralized readiness potential (LRP) (Danek and Mordkoff, 2011). In brief, as movement onset approaches, the readiness potential becomes lateralized such that the electrode placed over the motor cortex contralateral to the response side becomes

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http://dx.doi.org/10.1016/j.neuropsychologia.2017.04.007
Received 21 November 2016; Received in revised form 4 April 2017; Accepted 5 April 2017
Available online 06 April 2017

more negative than the electrode over the ipsilateral motor area. It has been suggested that the LRP can measure limb specific motor activation and can therefore be used to infer the amount of activation related to processes underlying movement preparation and initiation (Leuthold et al., 2004; Miller and Hackley, 1992). Interestingly, similar mean LRP amplitudes have been found between simple RT and go/no-go RT tasks prior to go-signal onset, indicating similar levels of limb specific advance preparation in the two tasks (Danek and Mordkoff, 2011). More importantly, for the question of interest, the mean LRP amplitude at the time of response initiation has consistently been shown to be greater for go/no-go task than the simple RT task (Mordkoff and Grosjean, 2001; Mordkoff et al., 1996). To account for these findings, it has been suggested that there is a high state of motor preparedness in both the simple RT and go/no-go tasks during the foreperiod. The elevated initiation threshold seen in the go/no-go task is due to inhibitory control processes. These same inhibitory processes may be responsible for preventing the SAS from triggering the prepared response in the work by Carlsen et al. (2008).

Studies investigating the inhibitory control network in the human brain have repeatedly shown that both the right inferior frontal gyrus (rIFG) and pre-supplementary motor area (preSMA) are critical nodes for inhibitory control during stop-signal and go/no-go tasks (reviewed by Aron, 2011; Chambers et al., 2009; Chikazoe, 2010; Levy and Wagner, 2011; Nachev et al., 2008). For example, neuroimaging studies consistently report activation within the rIFG, preSMA, and subcortical circuitries involving thalamic regions and the striatum during successful response inhibition (for reviews see Chambers et al., 2009; Swick et al., 2011). Complementary to the imaging data, functional contributions from rIFG and preSMA to inhibitory control has been demonstrated with the use of non-invasive brain stimulation techniques, specifically transcranial magnetic stimulation (TMS). For instance, single pulse TMS over preSMA has been shown to impair inhibitory processing during the performance of a stop-signal task (Chen et al., 2009; Obeso et al., 2013) and inhibitory repetitive TMS and inhibitory continuous theta burst stimulation (cTBS) over the rIFG have been shown to reduce inhibitory control during the performance of a stop-signal task (Chambers et al., 2007, 2006; Obeso et al., 2013; Verbruggen et al., 2010) and go/no-go task (Dambacher et al., 2014b). In addition, excitatory and inhibitory repetitive TMS of preSMA was able to improve and impair inhibitory performance respectively during the performance of a stop-signal task (Watanabe et al., 2015). Furthermore, transcranial direct current stimulation (tDCS) studies have shown that increasing rIFG or SMA/preSMA excitability (anodal stimulation) improved stopping performance, whereas decreasing preSMA excitability (cathodal stimulation) impaired stopping performance (Hsu et al., 2011; Jacobson et al., 2011).

While there is converging evidence that both rIFG and preSMA contribute to inhibitory control, the causal evidence for the involvement of both rIFG and preSMA in inhibition appears to be inconsistent between experiments and tasks. Therefore, the purpose of the current study was twofold: 1) to determine whether the go-response is prepared in advance in a go/no-go task and inhibited prior to stimulus identification with the use of a SAS, and 2) to investigate the inhibitory role of the rIFG and preSMA during the performance of a go/no-go task with the use of cTBS. The combination of cTBS and SAS allows us to determine which cortical area(s) are responsible for inhibiting go-activation and preventing overt movement during the performance of a go/no-go task. If the response is prepared in advance, but unable to be involuntarily triggered by SAS due to inhibition influencing the initiation processes, then impairing this inhibition through cTBS may allow for the involuntary release of the response by SAS.

The experiment consisted of three phases; a pre-cTBS phase where participants completed a go/no-go and simple RT task, followed by offline continuous theta burst stimulation (cTBS) to temporarily deactivate either rIFG or preSMA (Huang et al., 2005) (with a sham control), then a post-cTBS phase which was identical to the pre-cTBS. It was hypothesized that in the pre-cTBS phase, the presentation of a SAS concurrent with the stimulus would not result in the early triggering of the prepared movement. However, if rIFG and/or preSMA is involved in inhibiting the motor system and consequently preventing the SAS from triggering the prepared response, then their deactivation should increase the proportion of failed-stop responses (go during a no-go trial) and enable the SAS to involuntarily trigger the response in the post-cTBS phase.

## 2. Materials and methods

### 2.1. Participants

Data were collected from 13 healthy participants (6M, 7F; *M age* $=26$, *SD* $=3$) with normal or corrected to normal vision, and no history of neurological, sensory, or motor disorders. All participants completed three separate sessions separated by a minimum of 24 h to allow for complete washout of the effects of active stimulation (Huang et al., 2005). All participants provided written informed consent, passed a transcranial magnetic stimulation (TMS) safety-screening questionnaire, and verbally reported no drug contraindications for repetitive TMS prior to testing. The study was conducted in accordance with the ethical guidelines set by the University of Ottawa Research Ethics Board and conformed to the most recent version of the Declaration of Helsinki.

### 2.2. Experimental set-up

Participants sat facing a 24-in. LCD computer monitor with their right arm placed in a custom made force measurement device. The arm was supported and secured in a neutral position (semi-pronated with the palm perpendicular to the floor) such that the dorsal surface of the hand was in contact with a solid plate, restricting movement to concentric wrist flexion and isometric wrist extension. The plate was attached to a force transducer (Nano25 FT, ATI Industrial Automation, NC, USA), allowing measurement of force produced during an isometric wrist extension.

### 2.3. Tasks

In the pre-cTBS and post-cTBS phases, participants completed a go/no-go task followed by a simple RT task. To start a go/no-go trial, a red cue was presented (a red plus-sign in the middle of a black screen) indicating to participants to get ready, while not exerting any force against the force transducer. Following a variable foreperiod (1.5–3 s), the imperative stimulus, white O (go) or white X (no-go), replaced the warning cue. Participants were instructed to respond by performing an isometric right wrist extension movement (target force $=40\%$ of maximum voluntary force [MVF]) as fast as possible if a go-signal (O) appeared, or to refrain from making the movement if a no-go signal (X) appeared (see Fig. 1A). Participants received 25 points for responding correctly (i.e., responding to the “O” and not responding to the “X”) and responding quickly (1 point for every 7 ms below 350 ms, up to a maximum of 25 points). Participants were penalized 25 points for an incorrect response or a go-RT exceeding 500 ms.

Unlike the go/no-go task, the simple RT task started with the presentation of a white cue (instead of red) and consisted only of go trials. Participants were instructed that the cue would always be followed by a white O (go) and that they were to respond as fast as possible when the go-signal appeared. Similar to the go/no-go task, participants received 25 points for responding correctly (i.e., responding to the “O”) and responding quickly (1 point for every 1 ms below 200 ms, up to a maximum of 25 points). All other task procedures were identical to the go/no-go task.

Similar to Carlsen et al. (2008), an acoustic stimulus was presented on all trials concurrently with the imperative stimulus via a loudspeaker