



## A pilot study to investigate the induction and manipulation of learned helplessness in healthy adults



Joseph J. Taylor<sup>a</sup>, Daniel J. Neitzke<sup>a</sup>, George Khouri<sup>a</sup>, Jeffrey J. Borckardt<sup>a</sup>, Ron Acierno<sup>a,b</sup>, Peter W. Tuerk<sup>a,b</sup>, Matthew Schmidt<sup>a</sup>, Mark S. George<sup>a,b,\*</sup>

<sup>a</sup> Medical University of South Carolina, Charleston, SC, USA

<sup>b</sup> Ralph H. Johnson VA Medical Center, Charleston, SC, USA

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### ABSTRACT

Eliminating the controllability of a noxious stimulus may induce a learned helplessness (LH) that resembles aspects of depression and post-traumatic stress disorder (PTSD). This study examined whether repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex (DLPFC) promotes resilience in an aversive stimulus model of LH. All 55 participants were told that an undisclosed sequence of button presses would terminate an aversive stimulus on their forearm. In truth, only half had control (+C). The other half had no control (−C). All participants received real (R) or sham (S) left DLPFC rTMS during the paradigm (+C/R, −C/S, +C/S, −C/R). We evaluated the cognitive effects of LH using an anagram task. The LH paradigm successfully reduced perceived control in the −C groups. As predicted, the +C/R and +C/S groups tended to give up less quickly and take less time to solve each anagram than did the −C/S group. Superior anagram performance in the −C/R group approached statistical significance. Our preliminary results suggest that manipulating the controllability of an aversive stimulus may induce an LH effect that manifests as impaired anagram performance. Further research is needed to refine this model and determine if DLPFC rTMS mitigates any LH effects.

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### 1. Introduction

The prefrontal cortex (PFC) and the dorsal raphe nucleus (DRN) appear to mediate the perception of ‘control’ that is compromised in learned helplessness (LH) models of depression and post-traumatic stress disorder (PTSD) (Amat et al., 2005; Christianson et al., 2008; Christianson et al., 2009; Hammack et al., 2012; Robbins, 2005). The evidence for this control circuit is primarily derived from studies that employ the rat model of LH developed by Seligman and Beagley (1975). In this paradigm, yoked healthy rats are subjected to intermittent stressors such as tail shocks. One animal is provided a lever in its cage that, when pressed, terminates the shock. The other yoked animal has no control lever. Animals without a control lever develop behaviors that resemble depression (social withdrawal) or PTSD (hyper-startle) whereas animals with a control lever do not display such symptoms (Maier, 1984). In other words, stress only induces symptoms of depression or PTSD if it is perceived as uncontrollable.

The PFC may modulate the protective effects of perceived control via top-down regulation of the DRN and its serotonergic projections (Hammack et al., 2012; Robbins, 2005). Inhibiting the PFC promotes the development of withdrawal (helplessness), even when a noxious stimulus is subsequently escapable (Amat et al., 2005). By contrast, activating the PFC abolishes the ‘depression’ that results from inescapable stress (Christianson et al., 2009). These findings suggest that the ‘concept of control’ engages and depends upon prefrontal regulatory pathways.

There are preliminary data to suggest that stimulating PFC with transcranial magnetic stimulation (TMS), a minimally invasive brain stimulation technology used to focally inhibit or excite cortical regions, may ameliorate fear conditioning in rats and PTSD symptoms in humans (Baek et al., 2012; Boggio et al., 2010; Watts et al., 2012). Although left prefrontal repetitive TMS (rTMS) is FDA approved for treatment-resistant depression, little is known about its mechanism of action for depression or PTSD. A number of techniques have been used to examine the effects of TMS, including electromyography (EMG) and functional imaging of “online” (e.g. interleaved TMS/fMRI) and “offline” stimulation (Siebner et al., 2009). These investigations show that rTMS has the capacity to influence subcortical networks via cortical nodes. Moreover, the neurophysiological effects of rTMS persist after the stimulation

\* Corresponding author at: Medical University of South Carolina, Brain Stimulation Laboratory, 67 President St., Charleston, SC 29425, USA.

E-mail address: [georgem@musc.edu](mailto:georgem@musc.edu) (M.S. George).

paradigm ends. (George and Aston-Jones, 2010; George et al., 2010, 2013). Thus, prefrontal rTMS may have the capacity to modulate the circuit linked to the 'concept of control'.

The purpose of this study was to develop a laboratory-based LH paradigm that would enable us to study in humans that which has been studied in animals. Using a derivation of an LH model employed in the 1970s (Gatchel and Proctor, 1976; Hiroto and Seligman, 1975), we sought to induce LH and investigate whether prefrontal rTMS offers any "protection" from its cognitive effects. Our measurements consisted of perceived control ratings and anagram task performance. There were four study hypotheses. First, we hypothesized that participants who could not control the aversive stimulus (–C) would report less perceived control than would participants who could control the aversive stimulus (+C). Second, we hypothesized that –C participants would perform worse than +C participants on the anagram task. Third, we hypothesized that –C participants who received left prefrontal rTMS (R) would perform as well as +C participants on the anagram task. Fourth, we hypothesized that +C/R participants would perform better on the anagram task than +C/S participants. The last hypothesis was intended to help us evaluate the possibility that rTMS could be a neuroenhancement that improves cognitive performance and/or increases stress resilience.

## 2. Materials and methods

The Institutional Review Board of the Medical University of South Carolina approved this sham-controlled study. Fifty-five healthy adults participated.

### 2.1. Screening procedures

Prospective participants were interviewed over the phone. In order to qualify for the study, each healthy control had to be 18–45 years of age without a history of seizures, depression or pain conditions. Stimulants and other medications that lower seizure threshold were also part of the exclusion criteria. Qualified individuals were invited to a screening visit during which they provided their informed consent to participate. At this screening visit, all participants completed the Center for Epidemiological Studies 10-item depression scale (CESD) and the Generalized Anxiety Disorder Scale (GAD). We sought to study a non-depressed, non-anxious group and thus the cutoff for inclusion on both of these measures was a score of 10 (Kroenke et al., 2007; Zich et al., 1990). Women provided a urine sample that was tested for human chorionic gonadotropin to ensure that they were not pregnant.

### 2.2. Study overview

First, participants underwent resting motor threshold (rMT) assessment, left dorsolateral prefrontal cortex (DLPFC) localization and preliminary aversive stimulus testing (Fig. 1). Next, participants received real (R) or sham (S) left DLPFC rTMS during an aversive stimulus paradigm. Prior to the start of this paradigm, participants were told that they could terminate the aversive stimulus if they executed an undisclosed sequence of button presses (Supplemental Material). In truth, only half of the participants were able to turn off the aversive stimulus (+C). The other half experienced the aversive stimuli regardless of whether or not they figured out the correct button sequence (–C). Immediately following the aversive stimulus paradigm, all participants rated their perceived control and completed an anagram task. The anagram task served as a measure of cognitive resilience and performance following LH (Gatchel and Proctor, 1976; McLaughlin et al., 2010).

### 2.3. Motor threshold assessment and prefrontal localization

A Neuronetics Model 2100 Therapy System with an iron-core, solid-state figure-of-8 coil (Neuronetics, Inc.; Malvern, PA) was used to assess rMT and to administer rTMS. The TMS machine was initially set to 55% of its maximal output. Single pulses were administered near the primary motor cortex until the area on the scalp that produced contraction of abductor pollicis brevis (APB) was identified. Custom-developed software that employs adaptive parameter estimation by sequential testing (PEST) data was used to determine rMT, or the minimum machine output necessary for visible APB contraction 50% of the time that pulses were delivered (Borckardt et al., 2006). Once rMT was determined, the location on the scalp that approximately corresponds to BA 9 of the left DLPFC was found using a Beam F3 method (Beam et al., 2009). The coil was positioned approximately 45 degrees counterclockwise with respect to the midsagittal line.

### 2.4. Preliminary aversive stimulus testing

Thermal pain was induced using the Medoc Pathway System (Israel). A contact heat evoked potential stimulator (CHEPS) thermode was attached to the left volar forearm approximately 5 cm proximal to the wrist. The thermode was programmed to heat up at a rate of 0.5 °C per second. Participants were instructed to press a button when they experienced pain that they considered to be "7 out of 10" (deCharms et al., 2005; Taylor et al., 2013, 2012). After the button press, the thermode rapidly returned to room temperature. This testing procedure was repeated 10 times during preliminary testing in order to identify the average temperature that each participant would receive during the subsequent aversive stimulus paradigm.

### 2.5. Real or sham rTMS treatments

Participants were randomly assigned to receive real (R) or sham (S) rTMS. The eSham system was implemented in conjunction with a specialized Neuronetics sham TMS coil. Two Thymapad Stimulus Electrodes (Somatics, LLC; Lake Bluff, IL) were placed on the scalp location that corresponded to left DLPFC. Studies have shown that the eSham system effectively blinds participants to TMS treatment (active versus sham) (Borckardt et al., 2011a; Taylor et al., 2012). The eSham system was only active during sham rTMS although electrodes were placed in the appropriate position during subsequent real rTMS (10 Hz, 5 s on, 10 s off, 100% rMT).

### 2.6. Aversive stimulus paradigm

Participants were seated with their heads fixed in a TMS positioning frame. The thermode was reattached to each participant's left volar forearm and the Pathway System trigger was placed in each participant's right hand. Instructions about the paradigm were given to all participants prior to the administration of rTMS or aversive stimuli (Supplemental Material).

First, participants received 5 min of 5-s on, 10-s off real or sham rTMS in order to get acclimated to the stimulation. Next, participants received 45 5-s trains of rTMS. During those trains, the thermode rapidly heated to the average temperature previously determined to be rated as "7 out of 10" during preliminary testing. The thermode remained at that temperature for a maximum of 5 s. Participants who were randomly assigned to the +C group could disable the thermode if they pressed the trigger 3 times in rapid succession. Without this button sequence, this group experienced 5 s of heat and subsequently heard a tone from the computer. This tone indicated that thermode was automatically shutting off because the participant had failed the trial. By contrast, participants in the –C group could not disable the thermode regardless of button pressing sequences. These individuals always heard a tone from the computer because they always failed the trials. Each –C participant was yoked to a +C participant in order to control the heat exposure time. At the group level, the thermode remained active for helpless individuals as long as it had remained active for controls during each respective trial in the paradigm. This group level effect was achieved via individual pairings. For example, the duration of noxious stimulation that a –C participant experienced on any given trial was predetermined by a corresponding trial on a preceding +C participant. This design enabled us to balance nociceptive exposure while selectively fostering feelings of helplessness.

At the end of the 45th trial, all participants were asked to rate how much control they felt that they had over the thermode. The rating scale ranged from "no control" (1) to "complete control" (10).

### 2.7. Solvable anagram task

Immediately following the end of the aversive stimulus paradigm, participants were asked to begin an electronic anagram task. Most of the parameters of the current anagram task, including the anagrams themselves, were derived from historical LH experiments (Gatchel and Proctor, 1976; Hiroto and Seligman, 1975; Tresselt and Mayzner, 1966). This task was administered on a desktop computer in the same room that was used for the aversive stimulus paradigm. Twenty solvable anagrams consisting of five scrambled letters were presented in a slideshow that was controlled by the experimenter. Each anagram had its letters scrambled in the same order. The experimenter noted the time that it took each participant to either provide the correct answer or affirmatively indicate that they wished to give up and proceed to the next anagram. Latency to solve anagrams has previously been used as a measure of the cognitive effects of LH (Gatchel and Proctor, 1976; McLaughlin et al., 2010). If participants did not respond within 120 s then the next anagram was presented (see Supplemental material for more information).

### 2.8. Blinding and data analysis

Participants were blind to real (R) versus sham (S) rTMS assignment as well as to aversive stimulus controllability group assignment (+C or –C). The

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