



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



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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

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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.

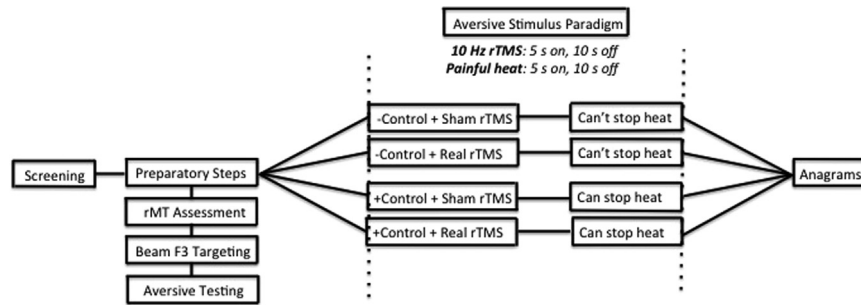
At the end of the 45th trial, all participants were asked to rate how much control they felt that they had over the thermode. The rating scale ranged from "no control" (1) to "complete control" (10).

### 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



**Fig. 1.** A schematic representation of the study methodology. After screening measures, each healthy control underwent rMT assessment, Beam F3 targeting and aversive stimulus testing (to find the stimulus consistently rated as “7 out of 10”). Next, each participant was randomized into one of four groups: –CS, –CR, +CS, +CR. During the aversive stimulus paradigm, a thermode delivered a fixed temperature. Those without control experienced a full five seconds of heat. Those with control could terminate the heat early if they executed a secret button sequence. Immediately following the aversive stimulus paradigm, each participant was tested using the anagram task.

experimenter was blind to participants' rTMS assignment but knew about the aversive stimulus group assignment. All data were locked prior to unblinding and data analysis.

This study consisted of a  $2 \times 2$  non-crossover design. Thus, there were 4 groups: +C/S ( $n=14$ ), +C/R ( $n=14$ ), –C/S ( $n=13$ ), and –C/R ( $n=14$ ). Analysis of variance (ANOVA) tests were implemented using IBM SPSS Statistics Version 21 (New York, NY). Time is presented as average in seconds plus or minus standard error ( $\pm$  SE). Outcome measures include perceived control, anagram solving speed, anagram give-up rate and anagram give-up speed.

### 2.9. Participant debriefing

All participants were debriefed after experiments were completed. These debriefing sessions focused on the manipulation of controllability during the aversive stimulus paradigm.

## 3. Results

### 3.1. Demographics and baseline measures

A one-way ANOVA revealed a significant difference in age between the four groups ( $p=0.04$ ; Table 1). A post-hoc analysis using Fisher's Least Significant Difference (LSD) test showed that the mean age of the +C/S group was significantly younger than the mean age of the –C/S group ( $p=0.025$ ). No additional post-hoc differences were detected. Moreover, there were no significant differences between the four groups in terms of baseline depression ( $p=0.85$ ), baseline anxiety ( $p=0.46$ ), sex ( $\chi^2(3)=0.68$ ; NS), race ( $\chi^2(9)=0.42$ ; NS), rMT ( $p=0.95$ ), or test temperature ( $p=0.24$ ).

### 3.2. Perceived control

Participants in the +C/S group ( $9.3 \pm 0.2$ ) and +C/R group ( $9.2 \pm 0.2$ ) believed that they had more control over the aversive stimulus than participants in the –C/S group ( $2.2 \pm 0.5$ ) and the –C/R group ( $3.0 \pm 0.7$ ). A one-way ANOVA revealed a significant difference between these groups ( $F(3,63.7)$ ,  $p < 0.001$ ). Post hoc analyses revealed that the +C/S group was significantly different from the –C/S group ( $p < 0.001$ ) and the –C/R group ( $p < 0.001$ ). Moreover, the +C/R group was significantly different from the –C/S group ( $p < 0.001$ ) and the –C/R group ( $p < 0.001$ ). The difference in perceived control between the –C/S and the –C/R group was over a third of a standard deviation ( $d=0.34$ ) but was ultimately not significant ( $p=0.27$ )(Fig. 2).

### 3.3. Anagram task performance

#### 3.3.1. Anagram solving speed

A one-way ANOVA did not reveal a significant difference between the groups ( $F(3,1)$ ,  $p=0.66$ ). The +C/S group ( $22.8 \pm 5.1$ )

solved the anagrams faster than the –C/S group solved them ( $32.2 \pm 6.7$ ). This effect was fairly large ( $d=0.43$ ) but ultimately did not reach significance via post hoc analysis ( $p=0.27$ ). Moreover, the –C/S group ( $32.2 \pm 6.7$ ) solved the anagrams slower than the –C/R group solved them ( $24.67 \pm 4.9$ ). This effect was medium-sized ( $d=0.35$ ) but ultimately did not reach significance via post hoc analysis ( $p=0.38$ ). Interestingly, the +C/S group ( $22.8 \pm 5.1$ ) solved the anagrams faster than the +C/R group solved them ( $29.9 \pm 7.0$ ). This effect was also medium-sized ( $d=0.31$ ) but ultimately did not reach significance via post hoc analysis ( $p=0.40$ )(Fig. 3).

#### 3.3.2. Anagram give-up rate

A one-way ANOVA did not reveal a significant difference between the groups ( $F(3,1)$ ,  $p=0.55$ ). The +C/S group ( $1.8 \pm 0.8$ ) gave up on fewer anagrams than did the –C/S group ( $2.1 \pm 1.0$ ). This effect was small ( $d=0.1$ ) and did not reach significance via post hoc analysis ( $p=0.78$ ). Moreover, the –C/S group ( $2.1 \pm 1.0$ ) gave up on more anagrams than did the –C/R group ( $0.6 \pm 0.3$ ). This effect was large ( $d=0.55$ ) but ultimately did not reach significance via post hoc analysis ( $p=0.18$ ). The +C/S group ( $1.8 \pm 0.8$ ) gave up on more anagrams than the +C/R group ( $1.4 \pm 0.7$ ). This effect was small ( $d=0.14$ ) and did not reach significance via post hoc analysis ( $p=0.68$ )(Fig. 4).

#### 3.3.3. Anagram give-up speed

A one-way ANOVA did not reveal a significant difference between the groups ( $F(3,1)$ ,  $p=0.42$ ). The +C/S group ( $73.6 \pm 9.7$ ) gave up less quickly than the –C/S group gave up ( $60.4 \pm 17.7$ ). This effect was fairly large ( $d=0.43$ ) but ultimately did not reach significance via post hoc analysis ( $p=0.452$ ). Moreover, the –C/S group ( $60.4 \pm 17.7$ ) gave up more quickly than the –C/R group gave up ( $91.32 \pm 10.9$ ). This effect was large ( $d=1.0$ ) but ultimately did not reach significance via post hoc analysis ( $p=0.11$ )(Fig. 5).

## 4. Discussion

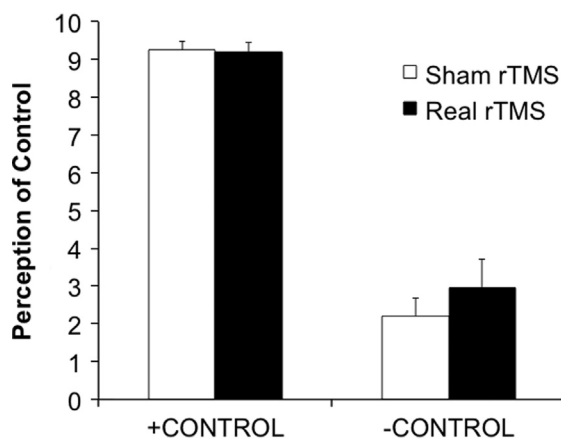
### 4.1. Assessment of hypotheses

The purpose of this pilot study was to develop a modern and salient laboratory-based LH paradigm for healthy human participants and to examine the possibility that left prefrontal rTMS offers “protection” against the cognitive effects of LH. Our first hypothesis was that the participants without control (–C) would report less control over the aversive stimulus than would participants with control (+C). Our data support this hypothesis (Fig. 2). Thus, the LH paradigm that we employed successfully induced feelings of helplessness.

**Table 1**

A table comparing the demographics and baseline characteristics of the four experimental groups.

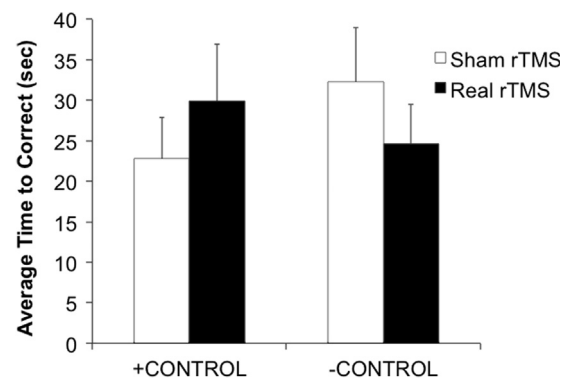
	+CS (N=14)	+CR (N=14)	–CS (N=13)	CR (N=14)	Significance
<b>Age</b>					
Mean ( $\pm$ SD)	24.36 (2.95)	26.07 (4.65)	27.85 (5.52)	23.79 (1.37)	$p=0.04$
Range	18–30	22–41	20–38	22–26	
<b>Sex</b>					
Male	8	6	5	8	$\chi^2(3)=0.68$ ; NS
Female	6	8	8	6	
<b>Race</b>					
African American	2	3	3	0	$\chi^2(9)=0.42$ ; NS
Caucasian	11	8	10	13	
Indian	1	2	0	1	
Asian	0	1	0	0	
<b>Aversive stimulus (<math>^{\circ}</math>C)</b>					
Mean ( $\pm$ SD)	44.52 (3.35)	45.29 (1.68)	46.3 (1.56)	46.04 (2.38)	$p=0.24$
Range	34.9–47.4	41.9–47.6	43.8–49.8	41.7–50.1	
<b>Motor threshold</b>					
Mean ( $\pm$ SD)	55.64 (5.65)	53.93 (7.76)	55 (7.43)	54.21 (10.8)	$p=0.95$
Range	49–68	39–70	42–72	41–74	
<b>CES-D</b>					
Mean ( $\pm$ SD)	0.29 (1.03)	0.29 (0.80)	0.08 (0.27)	0.14 (0.52)	$p=0.85$
Range	0–4	0–3	0–1	0–2	
<b>GAD</b>					
Mean ( $\pm$ SD)	1.50 (2.03)	1.07 (1.67)	1.15 (1.7)	0.5 (0.63)	$p=0.46$
Range	0–7	0–5	0–6	0–2	



**Fig. 2.** A graph depicting perception of control ratings in each of the four experimental groups. The aversive stimulus paradigm induced a statistically significant difference in perceived control between the groups with control and the groups without control ( $p < 0.001$ ). The presence of real versus sham rTMS did not affect perception of control in those with control. By contrast, the individuals without control who received real rTMS reported feeling slightly more control over the aversive stimulus than those without control who received sham rTMS. Time is presented as average in seconds plus or minus standard error ( $\pm$  SE).

Our second hypothesis was that participants who could not control an aversive stimulus ( $-C$ ) would perform worse on a subsequent anagram task than would participants with control over an aversive stimulus ( $+C$ ). To evaluate this hypothesis, we examined performance between the  $-C/S$  group and the  $+C/S$  group. Our data exhibit general trends across multiple parameters that support our hypothesis. The  $+C/S$  group solved anagrams faster (Fig. 3) and persisted longer before giving up (Fig. 5) than did the  $-C/S$  group. These findings, however, did not reach statistical significance.

Our third hypothesis was that participants who could not control an aversive stimulus ( $-C$ ) would perform better on an anagram task if they received real rTMS ( $-C/R$ ) versus sham rTMS ( $-C/S$ ). Once again, our data exhibit non-significant trends across multiple parameters that support our hypothesis. The  $-C/R$  group reported more control over the aversive stimulus than did the  $-C/S$

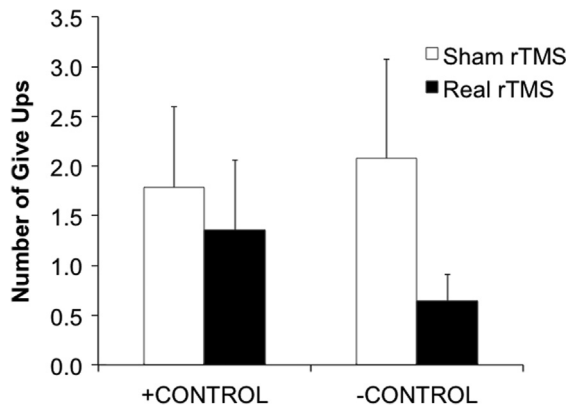


**Fig. 3.** A graph depicting the average time to a correct solution in each of the four experimental groups. In those with control, real rTMS (compared to sham) prolonged the average time that it took participants to solve the anagrams. In those without control, real rTMS (compared to sham) reduced the average time that it took participants to solve the anagrams. Time is presented as average in seconds plus or minus standard error ( $\pm$  SE).

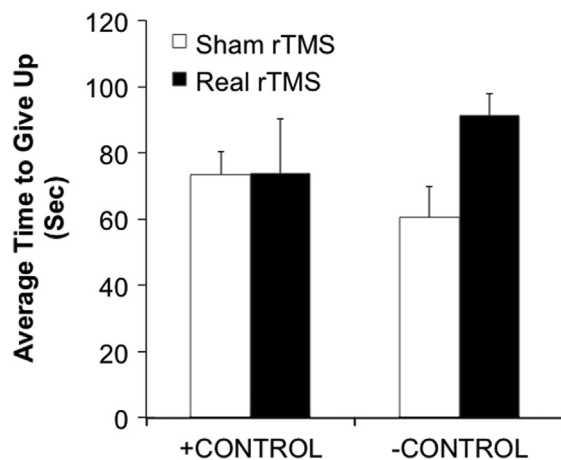
$S$  group (Fig. 2). Moreover, the  $+C/R$  group outperformed the  $-C/R$  group in every measured category, including average time to solve (Fig. 3), number of give ups (Fig. 4), and average time to give up (Fig. 5). The consistent yet statistically non-significant findings suggest that the study lacked power and/or relied on anagram manipulations that were not sufficiently refined. With respect to the latter possibility, it may be the case that contextually relevant (e.g., pain adjectives) anagrams produce greater effects. Nonetheless, the consistent trends across study parameters may indicate a detectable rTMS effect.

Our fourth and final hypothesis was that participants with control who received real rTMS ( $+C/R$ ) would perform better on the anagram task than participants with control who received sham rTMS ( $+C/S$ ). This hypothesis was aimed at evaluating left prefrontal rTMS as a cognitive enhancer in individuals not experiencing experimental manipulations of control. Our data do not support our hypothesis and, in some cases, show an opposite effect than the one that we expected to see. The addition of real rTMS to individuals with control did not affect perception of control (Fig. 2)





**Fig. 4.** A graph depicting the average number of give-ups in each of the four experimental groups. In those without control, real rTMS (compared to sham rTMS) reduced the number of give-ups. Time is presented as average in seconds plus or minus standard error ( $\pm$  SE).



**Fig. 5.** A graph depicting the average time to give up (in seconds) in each of the four experimental groups. In those with control, real rTMS (compared to sham) did not affect average time to give up. In those without control, real rTMS (compared to sham) significantly increased the average time to give up. Time is presented as average in seconds plus or minus standard error ( $\pm$  SE).

but did seem to disrupt average time to solve (Fig. 3). Yet again, however, these findings were not statistically significant.

Overall, our data support prior findings that paradigms involving aversive stimuli over which healthy young adults have no control induce transient feelings of LH (Gatchel and Proctor, 1976; Hiroto and Seligman, 1975). Immediately following such paradigms, LH participants have measurably decreased cognitive performance on an anagram task (Hiroto and Seligman, 1975; Tresselt and Mayzner, 1966). Although statistically insignificant, our results show a clear and consistent trend that left prefrontal rTMS may offer protective effects against the cognitive effects of laboratory-induced LH.

#### 4.2. The rationale for stimulating DLPFC to promote resilience

The finding that real rTMS mathematically improves anagram performance exclusively in participants without control suggests that its effects are context dependent. This result parallels findings from animal experiments in which pharmacological activation of the PFC abolishes the symptoms of depression and PTSD induced by stressful stimuli that are inescapable (Christianson et al., 2009). The animal literature has provided strong evidence that a projection between the PFC and the DRN mediates the perception of

“control” that is deficient in LH models of depression and PTSD (Amat et al., 2005; Christianson et al., 2008; Christianson et al., 2009; Hammack et al., 2012; Robbins, 2005). Most of these animal studies involve painful tactile stimulation. Unlike previous human LH paradigms that feature aversive auditory stimuli (Gatchel and Proctor, 1976) or unsolvable computer tasks (McLaughlin et al., 2010), our LH paradigm also involves painful tactile stimulation.

The present line of research may have particular relevance to PTSD, a disorder for which physical or emotional pain and perceived loss of control are diagnostically central. The circuitry underlying the LH aspect of PTSD is significantly more difficult to study in humans, in part because of the diminutive size of the dorsal raphe and related midbrain structures. A number of studies, however, have implicated the prefrontal cortex in PTSD-related phenomena. The medial PFC (MPFC) has been regularly identified as a region that contributes to the emotional dysregulation of PTSD (Celada et al., 2002; Liberzon and Sripada, 2008; Shin et al., 2006). More recently, the DLPFC has emerged as a critical structure for maintaining appropriate balance between cognitive and emotional processing. A recent fMRI study of PTSD patients found that higher DLPFC activation during anticipation of negative images was correlated with lower PTSD symptom severity as well as improved visomotor processing speed and executive functioning (Aupperle et al., 2012). Resting state fMRI analyses have also shown that combat veterans who exhibit larger magnitudes of spontaneous activity in DLPFC, thalamus and precuneus also report fewer re-experiencing symptoms (Yan et al., 2013).

Whereas the DLPFC is a node in the mesocortical system implicated in executive processing, the MPFC is a node in the mesolimbic system implicated in affective processing (Fuster, 2001; Hains et al., 2009; Kober et al., 2008). An imbalance between these two networks might be part of the pathophysiology of PTSD. A cognitive control deficit caused by a hypoactive DLPFC, for example, may disinhibit the MPFC and cause unopposed emotional reactivity. Functional imaging studies have begun to evaluate this theory. When processing emotional faces, adolescents with a history of trauma who exhibit post-traumatic stress symptoms (PTSS) exhibit decreased activity in mesocortical structures like DLPFC and increased activity in mesolimbic structures like MPFC, insula and amygdala than a group of age-matched controls (Garrett et al., 2012).

Some authors have called for novel treatments that can be used to restore the balance between mesocortical control (DLPFC) and mesolimbic affect (MPFC) (Aupperle et al., 2012). TMS is one such tool that could be used in conjunction with functional imaging to map and modulate PTSD circuitry. Preliminary studies have already shown that rTMS can reduce fear conditioning in rats and PTSD symptoms in humans (Baek et al., 2012; Boggio et al., 2010; Watts et al., 2012). Left DLPFC rTMS has also been shown to suppress the analgesic effects of perceived controllability of a painful stimulus, a finding that corroborates the trends found in this study (Borckardt et al., 2011b). Introducing such a control-enhancing intervention to existing evidence-based PTSD treatments might be particularly useful given that this disorder is marked by perceived loss of control during trauma exposure. Currently, the most effective treatment involves patients repeatedly and graphically imagining the traumatic event they experienced until the fear and anxiety responses are extinguished. Introducing rTMS into exposure trials might accelerate this process but well designed experiments are needed to evaluate this possibility.

#### 4.3. Limitations and future directions

There are a number of limitations in the current study design that might explain why the trends in our data merely approached

significance. First, the study did not feature a crossover design because practice might affect behavior during the aversive stimulus paradigm or performance on the anagram task. A crossover design might have provided the statistical power necessary to fully evaluate our study hypotheses. Alternatively, we could have kept the current study design but simply increased our sample size. Although we ran a preliminary power analysis, we had difficulty finding relevant data on which to base our estimates. This fact speaks to the novelty of our paradigm and our experimental question.

Second, the anagrams used in this study were comprised of five letters that were scrambled in a consistent pattern. It might be the case that more sophisticated anagrams (without patterns or size limitations) might be better for teasing out the subtle cognitive effects that were explored in this study. Emotionally relevant anagrams (e.g. related to pain or analgesia) might also yield more robust responses. Finally, giving participants more than 120 s to solve each anagram may also yield interesting between-group results.

Third, participants were only evaluated using an anagram task. PTSD and stress-related neuropsychiatric disorders can affect many different aspects of cognition and emotional processing. It might be the case that rTMS during the aversive stimulus paradigm affects learning, memory, mood or neuropsychological testing performance. Alternatively, rTMS during the aversive stimulus paradigm might have stronger effects on anagrams with emotional relevance (in this case, pain or relief-relevant anagrams). Future studies could assess these measures before and after any experimental interventions.

Fourth, each participant without control was yoked to a participant with control. The purpose of this pairing scheme was to control the duration of noxious stimulation while still fostering feelings of helplessness. We also controlled for pain severity by selecting individualized temperatures that were rated as “7 out of 10” at baseline. These measures were intended to increase our confidence that any measurable changes in anagram performance were more attributable to feelings of helplessness than they were to pain exposure. Although it is important to address these nociceptive issues, our decision to artificially manipulate noxious stimulus exposure might have limited the magnitude of the cognitive effects measured by the anagram task. Giving participants more than 5 s of pain might help to alleviate some of the possible problems associated with yoking pairs for pain exposure.

Fifth, the location of the left DLPFC was estimated using the Beam F3 method. Although this approach has been shown to be an efficient and accurate way to estimate the F3 position from the 10–20 system (Beam et al., 2009), it lacks the specificity and refinement of image-guided stimulation. Besides enhancing the accuracy of anatomical targeting, image-guided stimulation also provides the opportunity of physiological targeting. With fMRI scans revealing individualized control circuits, image-guided stimulation could be used to ensure that each individual receives their rTMS treatment in the proper PFC target.

Finally, this study used a relatively modest dose of high frequency rTMS to potentiate activity in the left DLPFC during an aversive stimulus paradigm. Future studies could explore different stimulation doses, paradigms or targets in order to enhance behavioral effects and test circuit hypotheses. Stimulating left DLPFC with 1 Hz rTMS, for example, should theoretically exacerbate the cognitive deficits induced by LH if existing theories about DLPFC function are correct. There is also some evidence that stimulating medial versus lateral PFC can selectively modulate mesolimbic versus mesocortical circuitry (Hanlon et al., 2013). These data raise the possibility that medial prefrontal stimulation may have more robust ‘protective’ effects against LH. In addition to exploring new targets, future studies should also closely evaluate the possibility of dose-dependent TMS effects. It could be the case

that a greater number of pulses are needed to induce durable behavioral changes that persist after an LH paradigm. All of these suggestions illustrate how TMS can be used to map and modulate circuits.

## 5. Conclusions

The purpose of this pilot study was to develop a laboratory-based LH paradigm for healthy human participants and to evaluate the possibility that left prefrontal rTMS “protects” against the cognitive effects of LH. Our aversive stimulus paradigm successfully induced self-reported feelings of LH. Individuals without control who received high frequency rTMS of the left DLPFC during the aversive stimulus paradigm tended to outperform individuals without control who received sham stimulation. Individuals with control who received real rTMS tended to perform similar to or worse than individuals with control who received sham rTMS. More studies are needed to refine the use of this LH paradigm and to evaluate the extent to which rTMS may ‘protect’ against the cognitive effects of uncontrollable stress.

## Conflict of interest statement

This research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Author Contributions

JT assisted in the conceptualization, approval and launch of this study. JT also collected data, analyzed data and wrote the majority of the manuscript.

DN assisted in the conceptualization of this study. DN also collected data, analyzed data and contributed to the writing of the manuscript.

GK collected data and analyzed data.

JB assisted in the conceptualization of this study.

RA and PT assisted in the conceptualization of this study. They also contributed to the writing of the manuscript.

MS assisted with data collection and contributed to the writing of the manuscript.

MG assisted in the conceptualization, approval and launch of this study. MG also contributed to the writing of the manuscript. MG oversaw all facets of this study.

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## Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.psychres.2014.05.045>.

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