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Low-frequency brain stimulation to the left dorsolateral prefrontal cortex increases the negative impact of social exclusion among those high in personal distress

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ABSTRACT

The dorsolateral prefrontal cortex (DLPFC) is thought to play a key role in the cognitive control of emotion and has therefore, unsurprisingly, been implicated in the regulation of physical pain perception. This brain region may also influence the experience of social pain, which has been shown to activate similar neural networks as seen in response to physical pain. Here, we applied sham or active low-frequency (1 Hz) repetitive transcranial magnetic stimulation (rTMS) to the left DLPFC, previously shown to exert bilateral effects in pain perception, in healthy participants. Following stimulation, participants played the "Cyberball Task"; an online ball-tossing game in which the subject participant is included or excluded. Compared to sham, rTMS did not modulate behavioural response to social exclusion. However, within the active rTMS group only, greater trait personal distress was related to enhanced negative outcomes to social exclusion. These results add further support to the notion that the effect of brain stimulation is not homogenous across individuals, and indicates the need to consider baseline individual differences when assessing response to brain stimulation. This seems particularly relevant in social neuroscience investigations, where trait factors may have a meaningful effect.

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Social pain; social exclusion; personal distress; repetitive transcranial magnetic stimulation; dorsolateral prefrontal cortex

Introduction

The dorsolateral prefrontal cortex (DLPFC) is a brain region believed to be involved in the regulation of physical pain: the experience that comes with actual or potential tissue damage. Specifically, the DLPFC is thought to play a fundamental role in pain regulation through the modulation of corticosubcortical and corticocortical pathways (Lorenz, Minoshima, & Casey, 2003). Given the importance of the DLPFC in the regulation of physical pain perception, this brain region has been targeted for its pain relief potential in investigations using repetitive transcranial magnetic stimulation (rTMS), a non-invasive method of brain stimulation. To date, studies have shown that rTMS to the DLPFC can modulate physical pain perception in healthy (e.g., Borckardt et al., 2007) and pain (e.g., Mhalla et al., 2011) populations.

Research has also shown that social pain, the experience of actual or potential damage to one's feeling of social connection or value (Eisenberger, 2012), activates similar brain regions as physical pain. As such, the DLPFC may also be involved in the regulation of social pain. Here, we utilized rTMS to explore whether we could modulate the perception of social pain by targeting the left DLPFC (L-DLPFC). We chose the L-DLPFC due to evidence of L-DLPFC stimulation exerting bilateral effects on pain perception (Brighina et al., 2011). We applied low-frequency rTMS (1 Hz), to induce a temporary decrease in excitability to this region. We expected that this manipulation would reduce the capacity of participants to regulate negative feelings, and increase the negative outcomes to social pain as measured using the "Cyberball Task," an online ball-tossing game where the participant is included or excluded (Williams, Cheung, & Choi, 2000).

We also explored whether the trait *personal distress* plays a role in the response to social exclusion following rTMS. Personal distress is a construct that describes that extent to which a person becomes distressed in difficult interpersonal situations (Davis, 1980). Given that experiences of negative social treatment have been shown to increase personal distress (Poteat & Espelage, 2007), it may be more difficult for those with already high levels

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of trait personal distress to regulate their strong emotional responses to social exclusion. Hence, we hypothesized that rTMS to the L-DLPFC, a regulatory region, would lead to more negative responses to social exclusion among those high in the trait of personal distress.

Methods

Participants

Twenty-nine right-handed healthy control participants were recruited (mean age 24.17 years, SD 6.12; male 11, female 18). Participants were randomized to receive active (n = 16; mean age 24.75 years, SD 5.45; male 6, female 10) or sham rTMS (n = 13; mean age 23.46 years, SD 7.03; male 5, female 8). Allocation to either group occurred through a computer-generated random sequence. A subset analysis of participants revealed less than 50% accuracy in guessing group allocation, with those who were accurate reporting low confidence in their guess. The study was approved by the Alfred Hospital Ethics Committee and the Monash University Ethics Committee.

Procedure

Participants completed the Interpersonal Reactivity Index (IRI) (Davis, 1980), to assess trait personal distress. The IRI has four subscales: "*Perspective Taking*," the propensity to spontaneously take on the psychological point of view of others; "*Fantasy*," the predisposition to transpose oneself imaginatively into the feelings and actions of characters in books, movies, and plays; "*Empathic Concern*," evaluating other-oriented feelings of sympathy and concern for others; and "*Personal Distress*," assessing self-oriented feelings of personal anxiety and discomfort in negative interpersonal situations. There is no overall score for the IRI as the subscales do not all correlate (or all positively). In relation to personal distress, this subscale is largely unrelated to the empathic concern and fantasy subscales and has a consistent negative correlation with the perspective-taking subscale (Davis, 1980, 1983).

Following the IRI it was explained to participants that they would receive rTMS, immediately followed by the "Cyberball Task"; a simple online ball tossing game, with two other players where they would take turns to throw the ball to each other (however, this is controlled by a computer program). This task involves two conditions: "inclusion" where the participant is involved in the game of catch and "exclusion" where the participant is initially involved, but shortly becomes left out.

Participants then underwent sham or active rTMS. For the active group, rTMS was administered using a standard figure of eight coil. Participants received 1200 pulses consecutively at 1 Hz, resulting in stimulation duration of 20 minutes. Stimulation intensity was set at 120% of resting motor threshold, which was the lowest intensity inducing a visually observed motor response in three out of five trials. The rTMS protocol was identical for sham rTMS, except that the coil was angled 90° away from the head. The location of the L-DLPFC was determined using the freeware "Beam F3" (Beam, Borckardt, Reeves, & George, 2009).

Following rTMS, participants completed the Cyberball Task. The order of conditions was counterbalanced, each lasting for ~3 minutes, and followed by participants answering questions about their experience. In order to determine the success of the manipulation (i.e., inclusion or exclusion), participants were asked to guess the percentage of throws they received and to rate "The cyberball game was a painful experience" on a scale from 1 ("not at all") to 9 ("very much so") (as done in Riva, Lauro, DeWall, & Bushman, 2012).

To explore the effects of rTMS on the Cyberball task, participants were asked 12 items on a scale from 1 to 9 with greater scores reflecting greater negative experience (some items were reverse scored). The 12 items were based upon the work of Williams et al. (2000) and made up two overall domain scores: " *social distress,"* describing the extent to which several needs were threatened, and "*aversive impact,"* describing the negative experiences of social exclusion. For the social distress domain, the following needs were totaled: belongingness ("I felt rejected"), meaningful existence ("I felt invisible"), control ("I felt powerful"), and self-esteem ("I felt liked"). For the aversive impact domain, the following measures were totaled to provide an overall domain score: (1) "Intensity of ostracism," measured by "to what extent did you feel that you were being ignored or excluded by the other participants?" and "to what extent did you feel that you were being noticed or included by the other participants?"; (2) Perception of "group cohesion"; assessed by the items "how much did you like the other players?" and "how much did the other players like you?"; and (3) "mood," where participants were asked to rank how they felt at the moment for the following scales: bad–good, sad–happy, tense–relaxed, and rejected–accepted.

Data analysis

To explore the success of task manipulation, separate two-way mixed model ANOVAs were run with "rTMS allocation" (active, sham) as the between-group variable, "social inclusionary status" (included, excluded) as the repeated-measures variable, and "% of ball tosses" and "perceived unpleasantness" as the primary dependent variables. Partial eta squared (η_p^2) was used to determine the effect size.

Independent samples *t*-tests were run to explore whether rTMS had any effect on the behavioral outcomes in response to the exclusion condition with "rTMS allocation" (active, sham) as the between-group variable and "social distress" and "aversive impact" scores as the test variables.

To explore whether there was a relationship between personal distress and behavioral responses following the Cyberball Task, Pearson's correlations were used independently for the sham and active rTMS group with a *p*-value of <.01 to control for multiple comparisons. For any significant correlation, a Fisher *r*-to-*z* transformation was then run to calculate the significance between the two correlation coefficients of each group. Exploratory correlations were also run for the remaining IRI subscales and independent samples *t*-tests were used to explore whether there was any differences in subscale scores and group allocation.

Results

A main effect of condition was identified for % of ball tosses received, F (1, 27) = 67.61, $p = <.001$, $\eta_p^2 = .72$, with participants correctly identifying receiving more ball tosses in response to the inclusion (52.66% [18.86]) compared to exclusion (18.21% [13.96]) condition. No interaction effect was observed between % ball tosses received and rTMS allocation. A main effect of condition was identified for general unpleasantness of the Cyberball Task, F (1, 27) = 23.59, $p = <.001$, $\eta_p^2 = .47$, with participants reporting the exclusion (4.24 [2.37]) condition to be more unpleasant than the inclusion condition (1.83 [1.26]). No interaction effect was observed between social inclusionary status and rTMS allocation. These results indicate that participants were correctly able to distinguish between the two tasks, regardless of rTMS allocation.

Independent samples *t*-tests revealed no between-group difference for the social distress domain, *t* (27) = .043, *p* = .97, or for the aversive impact domain, *t* (27) = −–.744, *p* = .46 in response to the exclusion condition of the Cyberball Task (see Table 1).

Within the active rTMS group in response to the exclusion condition, we found a large positive correlation between personal distress and greater aversive impact scores, *r* = .66, *p* < .01, see Figure 1. This correlation was not observed within the sham rTMS group, *r* = .03, *p* = .91, nor were any other correlations between

Table 1. Behavioral mean and standard deviation scores for the "Social Distress" and "Aversive Impact" domains following Exclusion condition and Interpersonal Reactivity Index mean and standard deviation scores for each subscale.

	Condition	Active (*n* = 16)	Sham (*n* = 13)
Social Distress d omain	Exclusion	27.31 (4.74)	27.23 (5.37)
Aversive Impact d omain	Exclusion	47.50 (10.20)	50.08 (7.96)
	Subscale	Active (*n* = 16)	Sham (*n* = 13)
Interpersonal Reactivity Index scores	Perspective Taking	17.94 (3.96)	17.77 (3.77)
	Fantasy	17.19 (6.21)	15.31 (6.47)
	Empathic Concern	20.38 (4.29)	20.62 (5.12)
	Personal Distress	11.88 (4.96)	11.69 (5.15)

the other IRI subscales and the behavioral domain scores within each rTMS group (*p* > .5; see Table1). Using the Fisher *r*-to-*z* transformation test, we found the personal distress and aversive impact score correlation coefficients of the active and sham groups to be trending toward being significantly different, *Z* = 1.81, *p* = .07 (two-tailed). Independent samples *t*-tests revealed no between-group differences in any of the four subscale scores (*p* > .05).

Discussion

Our hypothesis that 1 Hz rTMS to the L-DLPFC would increase social pain was not supported. However, our data suggest that greater negative outcomes to social exclusion following rTMS is linked to greater trait personal distress. That trait personal distress is thought to correlate negatively with overall social functioning and to correlate positively with increased emotionality (Davis, 1983) suggests that the 1 Hz rTMS to the L-DLPFC amplifies negative outcomes to social exclusion in individuals who express greater difficulty in interpersonal situations. Thus, rTMS effects, and perhaps brain stimulation more generally, may be state-dependent on individual traits.

There are several potential explanations for our overall absence of a main effect of stimulation. First, the targeted site may not play a role in the modulation of social pain. The L-DLPFC was chosen for its role in the regulation of physical pain perception; however, the dorsal anterior cingulate and anterior insula are generally accepted to be key social pain regions (Eisenberger, 2012) with the ventrolateral prefrontal cortex involved in the regulation of exclusion-induced social distress (Eisenberger, Lieberman, & Williams, 2003). It is also possible that the proposed

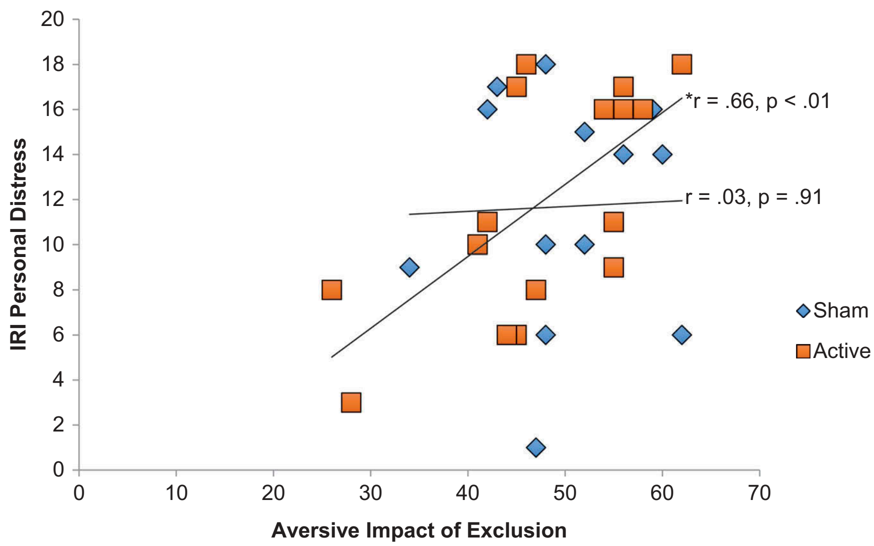

Figure 1. Positive correlation between IRI Personal Distress subscale score and Aversive Impact score following the exclusion condition in the active rTMS group.

rTMS protocol may not have been sufficient (i.e., in strength or duration) to modulate relevant function. Alternatively, inter-individual differences may have affected response to stimulation.

Indeed, we report a relationship between greater negative outcomes to social exclusion following rTMS and greater reported trait personal distress. This finding contributes toward to the idea that effects of brain stimulation may be dependent on an individual's initial brain activation state (Silvanto, Muggleton, & Walsh, 2008). This is known as "state-dependency" and describes the role of an individual's baseline brain state in their response to an external stimulus. In this context, our findings provide an important caveat to brain stimulation studies, where there is an underlying assumption that each participant's brain state is roughly equivalent. This is not necessarily the case, however. For instance, using MRI, Banissy, Kanai, Walsh, and Rees (2012) identified morphological differences in gray matter volume in 118 participants, corresponding to each of the empathy domains measured by the IRI.

Although the sample size of the study is small, we argue that the finding that trait personal distress may impact the effects of 1 Hz rTMS to the L-DLPFC on social pain is of considerable importance. Interpersonal baseline traits should be considered in brain stimulation studies exploring cognition and perception in healthy controls, where uniformity in participant brain states is typically (and perhaps incorrectly) assumed.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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