Posterior medial frontal cortex regulates sympathy: A TMS study

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In line with the ultrasociality characteristic of our species (Richerson & Boyd, 1998), observing suffering typically elicits sympathy, or affective states of shared valence with the welfare of others that are associated with behavioral inclinations to provide help. Sympathy is not necessarily equivalent to empathy, in which one processes the experiences of others as though they were happening to oneself, activating some of the same neural mechanisms (Decety & Chaminade, 2003; Hein & Singer, 2008; Zaki & Ochsner, 2012). For example, another’s anxiety might evoke sympathetic feelings of sadness, but not empathically evoke anxiety (De Vignemont & Singer, 2006). In this way, empathy may be regarded as a mode encompassed within the broader construct of sympathy.

Sympathy has been linked with prosocial behavior in terms of charitable donations (Ma et al., 2011), willingness to experience physical pain in another’s stead (Hein et al., 2011), and other displays (Morelli et al., 2014). However, given the limited energetic, material, social and temporal resources available to any organism, and the clear variation in adaptive incentives to share resources with others experiencing need, prosociality cannot be indiscriminate. All else being equal, for example, we are incentivized to provision aid to kin moreso than to acquaintances, and to acquaintances moreso than to strangers or adversaries. Accordingly, to the extent that sympathetic concern proximately mediates helping behavior, the degree of sympathy individuals feel in response to other’s misfortune should be regulated and contingent.

A growing body of research indicates that the degree of sympathy that individuals experience is indeed moderated by a number of contextual determinants. For example, the perceived moral character (Singer et al., 2006), group membership (Avenanti et al., 2010; Johnson et al., 2002; Xu et al., 2009), or interpersonal closeness (Cheng et al., 2010) of a suffering person have all been found to moderate sympathy. Guo et al. (2012) observed diminished activation of brain regions associated with empathic responses, such as simulating physical suffering (e.g., insula), when participants viewed models framed as receiving a large financial reward in exchange for experiencing pain relative to when viewing models framed as enduring pain without reward. In a complementary pattern of findings, Christov-Moore
and Iacoboni (2016) measured functional connectivity between regions associated with empathic responses and regions associated with top-down control. The strength of this functional connectivity was found to modulate later monetary sharing decisions in a Dictator Game. They also observed that activity in regions associated with empathic responses positively predicted prosocial sharing, whereas regions associated with top-down control predicted less sharing, particularly when the recipient was framed as in need of money. A follow-up study utilizing transcranial magnetic stimulation (TMS) confirmed that shared monetary allotments were more generous when top-down control regions (e.g., dorsal medial prefrontal cortex [DMPFC]) had been down-regulated (Christov-Moore et al., 2017). In sum, sympathy and related helping behavior appear to be strategically regulated on the basis of social context by top-down control networks. The present study is primarily intended to explore the contribution of the posterior medial frontal cortex (PMFC) to sympathy regulation.

**Posterior medial frontal cortex, sympathy, and social regulation**

The PMFC encompasses a number of functionally separable subregions thought to monitor for discrepancies, conflicts or errors of various types as part of executive control systems enabling adaptive compensatory adjustments (Botvinick et al., 2001; Bush et al., 2002; Ridderinkhof et al., 2004; Rushworth et al., 2007; Izuma & Adolphs, 2013; Ullsperger et al., 2004; for a recent review, see Ninomiya et al., 2018). For example, the dorsal anterior cingulate cortex (DACC) and the anatomically proximal DMPFC have been implicated in monitoring and control functions such as those measured in the Stroop and Go/No-Go tasks (Bush et al., 2002; Venkatraman et al., 2009). The rostral cingulate zone (RCZ; Picard & Strick, 1996), partially overlapping with DACC (Amadio & Frith, 2006) has been similarly linked with behavioral adjustments to meet task goals (Cohen & Ranganath, 2007; Gehring et al., 1993; di Pellegrino et al., 2007). The pre-supplementary motor area (pre-SMA) has direct and indirect projections to the RCZ (Picard & Strick, 1996) and is similarly related to both performance-monitoring and executive control (Ninomiya et al., 2018; Ridderinkhof et al., 2004). For example, pre-SMA activity correlates with error-detection in the Go/No-Go paradigm (Hester et al., 2004) and with successful performance in inhibition tasks (e.g., Cai & Leung, 2011; Obeso et al., 2013).

In a complementary array of findings, the PMFC has been broadly associated with monitoring and top-down control of social processes. Imaging studies link PMFC activation with the influence of social cues (e.g., Berns et al., 2010; Campbell-Meiklejohn et al., 2010; Falk et al., 2010), such as registering disagreement with the consensus of others and subsequently modifying one’s opinions in conformity paradigms (Izuma & Adolphs, 2013; Izuma et al., 2015; Klucharev et al., 2009); TMS down-regulation of PMFC (RCZ/pre-SMA) reduces social conformity (Klucharev et al., 2011). Beyond conformity, TMS down-regulation targeting the RCZ/pre-SMA region of PMFC has also been found to increase positive appraisals of an immigrant character despite the character’s caustic criticism of the sample’s national in-group, indicating a role for PMFC in registering and responding to out-group antagonists (Holbrook et al., 2016; but see, 2020, for a failure of replication using a collegiate rather than national group framing). The DACC component of PMFC has been found to respond to social exclusion (Eisenberger, 2012), particularly from in-group, self-rewrlesing individuals (Krill & Platek, 2009). These overall findings relate PMFC with registering relevant social information and modulating responses to align with contextually relevant social goals, suggesting a potential function of PMFC in the regulatory inhibition of sympathy. If so, then down-regulating PMFC via TMS should disinhibit sympathetic responses to cues of suffering, particularly when the suffering individual is framed as a social antagonist. We tested this prediction in the present study.

**PMFC and mentalizing**

In addition to modulating sympathy, down-regulating PMFC appears likely to influence the capacity for mentalizing (i.e., representing the mental states of other agents) given that sympathy entails representing the experiences of others, and that medial frontal cortex activity has been robustly associated with mentalizing ability (Frith & Frith, 2006; for a meta-analytic review, see Van Overwalle, 2011). As a partner within mentalizing networks, DMPFC activity has been correlated with cognitive perspective-taking regarding the thoughts and intentions of other people (Abu-Akel & Shamay-Tsoory, 2011), representing the subjective values held by others (Piva et al., 2019) and representing the personality traits of others (Baetens et al., 2014). DMPFC has been robustly linked with mentalizing as measured in a variety of experimental tasks, primarily with regard to inferring cognitive rather than affective states (Molenberghs et al., 2016). The pre-SMA has also been implicated as part of mentalizing networks in a meta-analysis of neuroimaging correlates of performance in studies of judgments of others’ personal traits (e.g., friendliness) or of the “Mind in the Eyes” task (Baron-Cohen et al., 2001;
In the present study, we included a task in which participants attempt to infer the cognitive versus affective states of a character framed as an antagonist, anticipating that down-regulating PMFC would reduce mentalizing ability, given that PMFC activity appears to track mentalizing ability. Although mentalizing and sympathetic prosociality may coincide in some contexts (Waytz et al., 2012), there are also contexts in which they may theoretically be predicted to diverge (e.g., when inferring the knowledge states or feelings of an unsympathetic enemy). Accordingly, the measure of mentalizing an antagonistic individual was also intended to explore the potential dissociability of sympathy and mentalizing.

**PMFC and self-other overlap**

Finally, we also assessed potential links between PMFC, sympathy, and representing others as connected with the self. The conceptual merging of representations of others with representations of the self has been widely related to empathy (Chambers & Davis, 2012; Galinsky et al., 2005), and a recent study found that participants manipulated to feel a sense of affiliative closeness with another person reported feeling a greater self-other overlap that mediated an increase in their prosocial monetary sharing with that person (Feng et al., 2020). To explore the potential relationship with sympathy, we included a commonly used measure to assess whether down-regulating PMFC would reduce self-other overlap, and whether sympathy and self-other overlap would positively correlate.

Although the constructs of sympathy, self-other overlap, and mentalizing appear interrelated, and to be potentially instantiated in some of the same underlying neural circuits, the extent of their psychological or biological overlap is unclear. The present study attempted to shed light on the associations between these constructs as well as the extent to which they are modulated by PMFC activity. On a translational level, understanding the determinants of sympathy may ultimately contribute to clinical or social interventions to bolster prosocial cooperation.

**Predictions**

**PMFC and sympathy**

We predicted that an adversarial character described as suffering physical harm would elicit greater sympathy following down-regulation of PMFC compared to down-regulation of a control site (MT), given the role of PMFC in contextually regulating affiliative or prosocial response contingent on social information. We also anticipated an increase in sympathy for an affiliative character in the PMFC condition, given prior evidence that down-regulating PMFC increases prosocial inclinations toward non-antagonistic individuals (Christov-Moore et al., 2017).

**PMFC and mentalizing an adversary**

We predicted that down-regulatory TMS of PMFC would decrease the capacity to mentalize, given the established role of aspects of PMFC in mentalizing performance.

**Effects of character framing**

We predicted that participants would report greater sympathy and self-other overlap with the character presented as an affiliative ally relative to the character presented as an adversarial critic.

**Exploratory questions**

**PMFC and self-other overlap**

We tentatively anticipated that representations of self-other overlap with the adversarial character would be greater in the PMFC down-regulation condition, given the role of PMFC in regulating empathic responses.

**Association between sympathy and mentalizing**

We explored the extent to which, when regarding a person framed as adversarial, sympathy for their suffering would track the mentalizing capacity to infer their cognitive or affective states.

**Association between sympathy and self-other overlap**

We explored the extent to which sympathy would correlate with self-other overlap.

**Materials and methods**

The study was pre-registered after data collection had commenced, but prior to analysis (see https://osf.io/yct8/). The full materials and dataset are available in the Supplemental Online Materials (SOM).

**Participants**

Undergraduates at the University of California, Merced, were recruited for a study, ostensibly consisting of a series of unrelated measures, in exchange for $15 and two research credits. Participants were prescreened by e-mail for history of neurological disorders and other contraindications to TMS (see SOM), as well as for feeling at least a moderate degree of personal identification with the university community. For purposes of
research reported elsewhere, prospective participants who identified as either atheists or as devoutly religious during pre-screening were also excluded (see Holbrook et al., 2020). Six participants who indicated that they would like to stop TMS due to discomfort were compensated and excused without penalty, and one participant was dropped due to extremely brief mean response latencies during the mentalizing task (< 755 ms relative to the overall sample mean of 3,670 ms), indicating having rushed through the task without taking it seriously. The final sample for the sympathy and self-other overlap measures consisted of 95 participants (63.2% female, $M_{\text{age}} = 20.0$ years, $SD = 1.41$). 64.2% of the participants identified as Latinx, 11.6% South Asian, 9.5% East Asian, 5.3% Black, 5.2% White, 4.2% Other. A technical problem prevented ten participants from receiving the mentalizing task, leaving a subsample of 85 participants for this measure (63.5% female, $M_{\text{age}} = 19.9$ years, $SD = 1.43$, 62.4% Latinx, 12.9% South Asian, 9.4% East Asian, 4.7% Black, 5.9% White, 4.8% Other). The sample size was based on the samples used in Klucharev et al. (2011) and Holbrook et al. (2016). The study was approved by the University of California, Merced, Institutional Review Board, and written informed consent was obtained from all participants.

**Design**

In a between-subjects design participants received down-regulation of either PMFC or MT/V5, then performed several distracter or unrelated tasks before completing measures of sympathy, self-other overlap, and mentalizing, then answered demographic questions.

**Down-regulating PMFC via continuous theta burst stimulation**

TMS stimulates the brain non-invasively by producing a rapidly varying magnetic field over the stimulated subject’s scalp (Fregné & Pascual-Leone, 2007), up- or down-regulating targeted regions and thereby permitting causal inference about the contribution of that region to cognition. We targeted the RCZ/pre-SMA area in the present experiment. However, as this TMS intervention does not clearly discriminate between associated regions that may have been collaterally down-regulated, we characterize the intervention as applying to the PMFC.

Theta burst stimulation (TBS) is a form of patterned TMS. TBS protocols have been modeled from repetitive electrical stimulation protocols that induced long term potentiation or long-term depression in animal studies (Huang et al., 2005). Continuous theta burst stimulation (cTBS) reduces activity for approximately one hour, in an effect similar to long-term depression (see Holbrook et al., 2018). Following the procedure used in the original study, we stimulated the right PMFC in the experimental condition: RCZ, Brodman areas 24, 32, 6 and 9. In the control condition, we stimulated right middle temporal visual area (MT/V5; see SOM Figures S1 and S2). Following Klucharev et al. (2011), we selected MT/V5 as the control stimulation site as the contributions of this region to visual processing (Born & Bradley, 2005) appear unrelated to the executive control functions associated with PMFC.

The cTBS protocol was administered using a Magstim Rapid2 at target locations in 50 Hz triplets of pulses delivered at 5 Hz intervals over 40 seconds, for a total of 600 pulses at 80% of the subject’s active motor threshold (AMT). If a subject’s 80% of AMT was a greater intensity than can safely be administered with our system, then we stimulated at the maximum intensity that was safe (e.g., 45% of maximum stimulator output). Due to a number of pilot participants reporting significant pain during cTBS over PMFC – resulting from sensitivity of the stimulation location and the relative subjective intensity of stimulation from the double cone coil – any participant with an AMT above 40% of our machine’s maximal stimulus output did not undergo cTBS stimulation of PMFC and was excluded from the experiment.

AMT in the PMFC condition was determined as the intensity at which we observed at least five out of ten motor-evoked potentials (MEPs) of at least 100 µV greater than the background noise, measured from the anterior tibialis (AT) using surface-electrode electromyography (EMG) with single pulse TMS to the AT motor hotspot. For single pulse TMS, the double cone coil (Magstim, 2 × 126 mm, Carmarthenshire, United Kingdom) was fit over the head and held with the handle vertical to the AT hotspot, with the coil orientation parallel to the anterior–posterior midline. The anterior

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1 In addition to the present research on sympathy, mentalizing, and self-other overlap, the study session also included measures of religiosity and group bias submitted for separate publication, as they involve distinct theoretical considerations (Holbrook et al., 2020). Those facets of the study session included a between-subjects manipulation involving writing about a threatening versus neutral topic. Follow-up analyses confirm that this task had no significant effects on any of the outcome measures reported here, and controlling for the writing manipulation does not alter the pattern or significance of any of the present findings. Accordingly, the writing task is not discussed further. (The full materials are available at https://osf.io/yqc8/)

2 A computer error was discovered during data collection; 16 participants had inadvertently skipped one or more blocks. We corrected the issue and ran 16 further participants, producing a final sample just short of our pre-registered target of 100. However, the window for recruitment had closed and the total of 96 (before dropping one participant for overly fast response latencies) was deemed sufficient.
tibialis region of primary motor cortex was chosen for motor thresholding because the tibia representation and the PMFC are located at similar depth within the medial cortex. The location of PMFC was calculated for each participant according to the size of their head, using the international 10–20 system (Klem et al., 1999), as in the original study and in other TMS studies (e.g., Kucharek et al., 2011; Knoch et al., 2009). Using this system, we measured the head and located electrode placement area F2 as the PMFC stimulation site. For cTBS, the double cone coil was fit over the head with the handle vertical over the PMFC stimulation site, and the coil orientation parallel to the anterior–posterior midline.

AMT in the control condition (MT/V5) was determined as the intensity at which we observed at least five out of ten motor-evoked potentials (MEPs) of at least 100 μV greater than the background noise, measured from the first dorsal interosseus (FDI) using surface-electrode electromyography (EMG) with single pulse TMS to the FDI hotspot. For single pulse TMS, the figure of eight coil (Magstim, D702 double 70 mm coil, Carmarthenshire, United Kingdom) was placed tangential to the head at an angle of ~45° from the anterior–posterior midline. The FDI region of primary motor cortex was chosen for motor thresholding because the hand representation and MT/V5 are located at similar depth within the cortex. MT/V5 was also located using the 10–20 system, and electrode area PO8 was the site for coil placement. For cTBS, the figure of eight coil was placed tangential to the head, with coil orientation parallel to the anterior–posterior midline. (The full details of the protocol are provided in the SOM.)

Next, participants performed the experimental tasks alone at a computer station in a nearby room.

Measures

Motor and visual distracter tasks
Participants initially completed approximately ten minutes of a distracter motor task (Bush & Shin, 2006), visual estimation tasks involving guessing the number of colors that were originally present in grayscale images of jellybeans and seashells, and two unrelated measures. The filler and visual estimation tasks were intended to ensure that down-regulation had taken effect (Huang et al., 2005) and to defray suspicion about the study’s intent. The sympathy, self-other overlap and mentalizing measures required approximately twelve-to-fifteen minutes, and were encountered approximately fifteen-to-twenty minutes post-stimulation, depending on the pace of the participant in completing the distracter tasks and measures intended for separate publication.

However, as the cTBS method utilized here reduces activity for approximately one hour, the study session was timed to conclude well within the period of down-regulation.

Sympathy
Participants were asked to read two essays ostensibly written by transfer students, an adversarial student sharply critical of the UC Merced community, and an affiliative student who praises the UC Merced community (see the SOM for the full text). After reading each essay, participants were asked to vividly imagine that the transfer student was later hit by a car and injured, then rate the extent to which they felt “Sympathetic,” “Sorry,” “Sad,” and “Hope they are OK” when thinking about the person being hurt using a Likert-type scale (1 = No feeling at all; 8 = Intense feeling; [adversarial student: α = .91; affiliative student: α = .94]). The precise location and severity of injuries was left unspecified.

Self-other overlap
Participants next rated their feelings of self-other overlap with each student character according to a modified version of the Inclusion of Other in the Self Scale (IOS; Aron et al., 1992), composed of seven pairs of circles, ranging from non-overlapping to almost entirely overlapping. Participants were asked to imagine that the pairs of circles represented themselves and the other student, then select the option that best described how closely connected they felt with that person according to this visual metaphor.

Mentalizing an adversary
Following the measures of sympathy and feelings of connection, participants completed a modified version of the Yoni test (Shamay-Tsoory & Aharon-Peretz, 2007), which assesses the ability to infer mental states based on verbal cues, eye gaze and facial expression (Inquisit 5 [Computer software]; see SOM Figure S2).

In each trial, the face of a character named “Yoni” is shown in the middle of the screen surrounded by four images appearing in each corner of the computer screen, belonging to either faces or to another category (e.g., vehicles, fruits, animals). In the present version of the task, the Yoni character is introduced with an angry facial expression accompanied by the caption “This is Yoni – Yoni HATES UC Merced students”. Participants were then trained to use a mouse to click on the image which the participant believes that Yoni is referring to, based on an incomplete sentence appearing at the top of the screen as well as visible cues, such as Yoni’s eye gaze or facial
expression, or the eye gaze or facial expressions of other faces to which Yoni refers. The Yoni task includes cognitive, affective, or physical control items which are comparable with regard to visual and linguistic complexity. Responses to the cognitive or affective items require mental inferences based on eye gaze, facial expression or verbal cues; responses to control items solely require assessment of physical attributes. Each domain contains trials of both first-order and second-order levels of complexity. In the first-order mentalizing trials, Yoni’s mental state must be inferred (e.g., “Yoni is thinking of ...” [cognitive first order] or “Yoni loves ...” [affective first order]). In the second-order mentalizing trials, the four images are of faces of other, unnamed characters (e.g., “Yoni is thinking of the fruit that ... wants” [cognitive second order], or “Yoni loves the fruit that ... loves” [affective second order]). In the cognitive trials, the verbal and facial cues were emotionally neutral, whereas the affective trials included positively valenced (i.e., “Yoni loves ...”) or negatively valenced (i.e., “Yoni does not love ...”) verbal and facial cues (i.e., happy or sad expressions). Following Shamay-Tsoory and Aharon-Peretz (2007), the items were presented in three phases: i) first-order cognitive, affective, and physical control trials (8 per domain), ii) first-order cognitive and affective trials (4 per domain) and second-order affective trials (24), and iii) second-order cognitive trials (24), affective trials (12), and physical control trials (6) (see SOM Figure S3). The primary outcome variable consisted of the error rates within each domain; response latencies were also collected for exploratory purposes and to make certain that participants attended to the task (i.e., did not merely click through the trials).

Finally, participants completed demographic questions, including an item probing their degree of identification with the university (1 = Not important to me at all; 2 = Moderately important to me; 3 = Extremely important to me). Once the survey was complete, participants were thanked, compensated and debriefed.

**Results**

Preliminary analyses confirmed that the samples in each TMS condition (PMFC N = 48; MT/VS N = 47) were comparable with regard to ethnicity, age, sex and education level at the university, ps .153 – .988.

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6.3% of the sample reported no feeling of personal identification, 75.8% reported moderate identification, and 17.9% reported extreme identification with the university. Exploratory follow-up analyses confirm that the observed pattern of effects of the TMS manipulation on sympathy for both authors holds, and in fact grows more significant (ps ≤ .01, η²’s > .07), when excluding those participants who reported no personal identification with the university.

**Sympathy**

A mixed-design ANOVA including target identity (adversarial versus affiliative) as a within-subjects factor and TMS condition as a between-subjects factor confirmed that, in line with the intended character framings, the adversarial student elicited significantly less sympathy than the affiliative student, F(1, 93) = 20.17, p < .001, η² = .18. There was no significant interaction between character and TMS condition, p = .799, η² < .01. As anticipated, down-regulating PMFC increased reported sympathy for the adversarial student relative to MT/VS stimulation (PMFC: M = 4.89, SD = 1.84; MT/VS: M = 3.94, SD = 2.01), F(1, 93) = 5.79, p = .018, η² = .06, 95% CI [−1.73, −.17] (see Figure 1). Down-regulating PMFC also increased reported sympathy for the affiliative student relative to MT/VS stimulation (PMFC: M = 5.43, SD = 1.97; MT/VS: M = 4.54, SD = 2.15), F(1, 93) = 4.39, p = .039, η² = .05, 95% CI [−1.72, −.05] (see Figure 1).

**Self-other overlap**

Paralleling the effect of character framing on sympathy, a mixed-design ANOVA including target identity (adversarial versus affiliative) as a within-subjects factor and TMS condition as a between-subjects factor revealed that, as predicted, the adversarial student elicited significantly lower mean IOS ratings of self-other overlap than the affiliative student, F(1, 94) = 37.80, p < .001, η² = .29. Character framing did not interact with TMS condition, p = .106, η² = .03. Departing from the effects of TMS on sympathy, down-regulatory cTBS of PMFC did not significantly alter reported self-other overlap with either the adversarial student (PMFC: M = 1.98, SD = 1.04; MT/VS: M = 1.79, SD = .95), p = .352, or the affiliative student (PMFC: M = 2.65, SD = 1.47; MT/VS: M = 2.94, SD = 1.57), p = .353.

**Self-other overlap and sympathy**

IOS ratings were positively correlated with sympathy ratings for both the adversarial student, r(94) = .26, p = .013, and the affiliative student, r(94) = .30, p = .004.

**Mentalizing an adversary**

Preliminary analyses revealed no effects of the TMS manipulation on response latencies for any of the first- or second-order mentalizing outcomes, ps .197 – .989.
Presumably because the first-order tasks are relatively easy, preliminary analyses revealed skewed and kurtotic distributions for the first-order performance scores, with the majority of participants scoring at or near perfect accuracy (mean cognitive accuracy = 92.35%; mean affective accuracy = 93.73%; mean physical control accuracy = 86.91%). Nonparametric Mann-Whitney U tests indicated no significant effects of the TMS manipulation on either first-order cognitive (p = .336) or first-order affective mentalizing (p = .515), nor any effect on the control domain of physical association (p = .165).

**Second-order performance accuracy**
As intended, the second-order tasks were more challenging (mean cognitive accuracy = 72.99%; mean affective accuracy = 75.92%; mean physical control accuracy = 78.24%), and the performance distributions satisfied parametric assumptions. Against predictions, we observed no significant decreases in mentalizing performance when down-regulating PMFC. To the contrary, relative to the control TMS condition, participants in the PMFC condition evinced greater accuracy with regard to second-order cognitive mentalizing (PMFC condition: M = 76.98% correct, SD = 16.05; MT/V5 condition: M = 69.09% correct, SD = 19.31), F(1, 83) = 4.19, p = .044, \(\eta^2_p = .05\), 95% CI [−.156, −.002]. A similar, albeit nonsignificant, pattern was observed for second-order affective accuracy (PMFC condition: M = 78.17% correct, SD = 13.38; MT/V5 condition: M = 73.71% correct, SD = 13.38), F(1, 83) = 2.71, p = .103, \(\eta^2_p = .03\), 95% CI [−.099, .009]. Finally, consistent with the hypothesis that the effects of TMS concern mentalizing performance in particular, there was no evident relationship between the TMS manipulation and accuracy in the control domain of second-order physical associations, p = .407.

**Figure 1.** TMS down-regulation of PMFC increases sympathy for the suffering of both the adversarial critic and affiliative ally relative to down-regulation of MT/V5. The violin plot outlines illustrate kernel probability density; the width of the shaded area represents the proportion of data located there, and the horizontal lines indicate the means (see text for details).
Consistent with the assumption that deliberation time should enhance performance, second-order response latencies were significantly positively correlated with accuracy for both second-order cognitive mentalizing ($r = .38$, $p < .001$; $M = 4.68$ s) and second-order affective mentalizing ($r = .27$, $p = .011$; $M = 5.35$ s).

**Mentalizing, sympathy, and self-other overlap**

No significant correlations were observed between first- or second-order cognitive or affective mentalizing and sympathy or IOS ratings of either student character, $r_i \sim -.18 - .14$, $ps \sim .09 - .99$.

**Discussion**

Down-regulating PMFC, relative to control stimulation of MT/V5, increased feelings of sympathy in response to the prospect of physical suffering, indicating a causal role of PMFC in the suppression of sympathy. Notably, down-regulation of PMFC comparably heightened sympathy toward an affiliative and an adversarial individual. Bearing in mind that both transfer student characters in this study would have been strangers from the point of view of the participants, PMFC appears to facilitate budgeting of emotional and material resources, allocating decreased sympathy to strangers, whether affiliative or adversarial. It is possible that PMFC reserves increased sympathy and the associated provision of aid for relatively close allies or kin in need. This interpretation accords with prior findings that witnessing strangers in pain evokes less empathy-related brain responses than witnessing pain in loved ones (Cheng et al., 2010), and preserves that down-regulation of PMFC would disinhibit not only sympathetic feelings but related helping behavior, as observed by Christov-Moore et al. (2017) with respect to increased financial sharing with strangers. Future work should assess the contributions of PMFC to regulating feelings of sympathy and willingness to render aid to strangers, including in non-financial modalities (e.g., emotional support, investment of time in helping, etc.). Further, whereas we have focused here on the role of PMFC in inhibiting sympathy when encountering strangers, PMFC activity may facilitate increased sympathy when misfortune befalls a valued attachment partner rather than a stranger or adversary. Future research should explore the role of PMFC in modulating sympathy in social contexts wherein the suffering party is framed as someone with whom the participant feels a close bond (e.g., a romantic partner or family member).

Whereas much prior research on empathy has used video stimuli vividly depicting physical suffering (e.g., body envelope violations), the present study relied on brief text descriptions informing participants that the student author characters had been hit by a car and injured. This approach provides a reasonable model of real-world circumstances in which information about the misfortune of others is conveyed secondhand via news feeds, social media, text messages, and so on, but raises doubt about whether the heightened feelings of sympathetic sorrow and concern reported here involved heightened empathy. Activity in participants’ pain networks correspondent to that of the imagined accident victims may not have been aroused, if only because the text stimuli left the location and severity of the victims’ injuries unspecified. As such, the present findings with regard to sympathy should not be taken as evidence that down-regulating PMFC increases empathy in particular. Future work utilizing more graphic and specific depictions of the character’s suffering, combining PMFC down-regulation with brain imaging, would help to confirm the generalizability of these effects to empathy.

Consistent with social psychological work linking sympathy with representations of others as included in the self (Aron et al., 1992), we found that sympathy and self-other overlap were significantly positively correlated. Nonetheless, we observed no effects of the TMS manipulation on ratings of self-other overlap. Variation in self-other overlap typically pertains to individual differences in extant attachment relationships, or coordination during interpersonal interaction, rather than differences in the relative connection felt between oneself and physically separate, non-interacting strangers. This raises the possibility that participants in the present study may not have processed self-other overlap as relevant to heretofore unknown individuals encountered only via their brief essays. However, past research has demonstrated the manipulability of self-other overlap with strangers (e.g., self-other overlap ratings are increased by synchronized walking, Fessler & Holbrook, 2014, or synchronized tapping, Feng et al., 2020), and the affiliative individual in this study similarly elicited higher ratings than the adversarial critic, indicating that participants experienced meaningful variation in perceived self-other overlap despite not directly interacting with the characters. As such, the present null effects of TMS may be regarded as face-valid evidence that the regulation of sympathy by PMFC occurs somewhat orthogonally to representations of self-other overlap.

In a finding seemingly at odds with prior work linking medial frontal cortex with the Theory of Mind network, down-regulating PMFC significantly enhanced rather than decreased the capacity for second-order cognitive mentalizing. This unexpected result may be related to our choice – departing from typical practices in
mentalizing research – to portray the character as overtly antagonistic. Speculatively, when encountering individuals with whom profitable future cooperation appears unlikely, executive functions related to PMFC may reduce the information-processing resources invested in mentalizing their thoughts. Follow-up work utilizing an affiliative character would help to clarify the present result. Likewise, PMFC may indeed up-regulate mentalizing efforts against antagonists under circumstances that incentivize mind-reading (e.g., when facing another person in a zero-sum conflict involving anticipating choices related to their knowledge states or desires). For now, the prospect that PMFC inhibits mentalizing antagonistic individuals, at least in contexts where, as here, the individuals’ mental states hold little relevance for participants, warrants further inquiry, but neither this unexpected result nor our post hoc interpretation should be afforded undue weight prior to replication.

Building on a convergent prior literature, we have framed the effects of the TMS manipulation observed here in terms of down-regulation of PMFC. However, TMS can generate spreading activation to regions that are functionally downstream from or proximal to the targeted region (e.g., lateral frontal cortex). In addition, as our target site was F2, the TMS manipulation likely also affected the superior frontal gyrus (SFG), situated above PMFC. Although the convergent literature motivating this study points to the functional role of PMFC in the regulation of social responses, the possibility exists that down-regulation of SFG contributed to the observed effects, or that PMFC and SFG cooperate in regulating sympathy or mentalizing. Accordingly, neuroimaging in future work is required to determine the extent to which it is PMFC down-regulation that mediates increases in sympathy, as opposed to collateral effects on other regions. Within PMFC, imaging would also help illuminate which subcomponents regulate sympathy, and connectomic analyses might illuminate how these PMFC mechanisms articulate with other regions throughout the brain (Human Connectome Project, 2020). Relatedly, with respect to TMS administration, image-guided neuro-navigation would also help to confirm that TMS interventions accurately target PMFC as intended.

Finally, future research would ideally include a sham condition to empirically rule out the possibility that the observed effects of our TMS intervention reflect down-regulation of the control region, MT/VS, rather than PMFC. However, attributing the decrease in sympathy or increase in second-order mentalizing ability to down-regulation of MT/VS appears implausible given the previous literature associating MT/VS with perceptual processing of visual motion rather than social decision-making. Relatedly, in their research on the role of PMFC in social conformity, Klucharev et al. (2011) utilized a nearly identical cTBS procedure to that used in the present experiment and found no difference between MT/VS and sham stimulation.

**Conclusion**

The related constructs of sympathy, empathy, self-other overlap, and mentalizing are often conflated. Although the present design cannot distinguish sympathy from empathy, it does permit an overview of inter-relationships between sympathy, self-other overlap, and mentalizing. We observed patterns of positive association (i.e., sympathy and self-other overlap were positively correlated) as well as dissociation (i.e., mentalizing was not correlated with either sympathy or self-other overlap, and down-regulating PMFC increased sympathy and mentalizing performance while having no effect on self-other overlap). The overall findings speak to the need for further investigation of how cognate facets of empathy relate to distinct as well as overlapping brain networks and social functions.

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**Disclosure statement**

No potential conflict of interest was reported by the author(s).

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