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Empathic control through coordinated interaction of amygdala, theory of mind and extended pain matrix brain regions

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Abstract

Brain regions in the "pain matrix", can be activated by observing or reading about others in physical pain. In previous research, we found that reading stories about others' emotional suffering, by contrast, recruits a different group of brain regions mostly associated with thinking about others' minds. In the current study, we examined the neural circuits responsible for deliberately regulating empathic responses to others' pain and suffering. In Study 1, a sample of college-aged participants (n=18) read stories about physically painful and emotionally distressing events during functional magnetic resonance imaging (fMRI), while either actively empathizing with the main character or trying to remain objective. In Study 2, the same experiment was performed with professional social workers, who are chronically exposed to human suffering (n=21). Across both studies activity in the amygdala was associated with empathic regulation towards others' emotional pain, but not their physical pain. In addition, psychophysiological interaction (PPI) analysis and granger causal modeling (GCM) showed that amygdala activity while reading about others' emotional pain was preceded by and positively coupled with activity in the theory of mind brain regions, and followed by and negatively coupled with activity in regions associated with physical pain and bodily sensations. Previous work has shown that the amygdala is critically involved in the deliberate control of self-focused distress – the current results extend the central importance of amygdala activity to the control of other-focused empathy, but only when considering others' emotional pain.

Key Words: fMRI, empathy, physical pain, emotional suffering, cognitive control, social distancing, psychophysiological interaction, PPI, granger causality modeling, GCM

The ability to empathize with others is a hallmark of a healthy interpersonal life. People unable to experience empathy are either considered socially impaired (autistic) or socially deviant (sociopathic). And yet, the ability to deliberately regulate our empathic responses is equally important – for example, parents must make decisions about their children's long term health at the expense of their immediate comfort and managers must make decisions for the good of a company at the expense of an individual worker. Particularly for people whose professions place them in frequent contact with human suffering (hospice volunteers, child oncologists, social workers), the ability to distance oneself from others' suffering may be more than just personally adaptive – it may be professionally necessary to avoid burnout or 'compassion fatigue' (Figley, 1995; Krasner et al., 2009; Shanafelt et al., 2012).

While the neural mechanisms involved in regulating first-person aversive emotional responses have been extensively studied over the past decade (Ochsner et al., 2004a; Ochsner et al., 2004b; Ochsner et al., 2012), the neural mechanisms underlying control of empathic responses are less well understood. What candidate neural mechanisms might underpin deliberate control of empathic responses? One possibility is that controlling other-focused empathy may involve the same circuitry that controls self-focused emotional experiences. The brain region most consistently implicated in a range of emotion regulation strategies is the amygdala.

The Amygdala

The amygdala is best known for its role in mammalian fear conditioning, facilitating the learning, encoding and expression of negative associations (LeDoux, 2003). In humans the amygdala responds to a wide range of emotionally salient stimuli, particularly distressing stimuli associated with threat (Zald, 2003), such as fearful or angry faces (Hariri et al., 2002; LeDoux, 2003; Whalen et al., 2001), threatening images (Anticevic et al., 2012; Eippert et al., 2007), the threat of physical pain (Simons et al., 2014; Wager et al., 2004), and even threatening words (Hamann and Mao, 2002; Isenberg et al., 1999; Laeger et al., 2012; Straube et al., 2011). People with amygdala lesions

experience pronounced deficits in facial emotion recognition (Adolphs et al., 2005; Adolphs et al., 1999; Young et al., 1996), and impaired conditioning to fearful faces (Bechara et al., 2002); these impairments in emotion processing also disrupt performance in more cognitively complex tasks, like decision-making (Bechara et al., 1999).

Importantly, activity in the amygdala is subject to deliberate control. When instructed to decrease emotional responses to aversive stimuli – for example, through changing the construal of an upsetting stimulus to make it more neutral (Ochsner et al., 2002), or through psychologically distancing themselves from the emotional event (Ochsner et al., 2004b) – participants report less distress and show decreased amygdala activity. Dampening emotional responses to distressing stimuli is also associated with increased activity in regions within the ventromedial and lateral prefrontal cortex (VMPFC, LPFC), and the anterior cingulate cortex (ACC) (Ochsner et al., 2004b; Phan et al., 2005; Urry et al., 2006), leading to a dominant view that emotional responses are generated by the amygdala and other sub-cortical and cortical structures (especially the nucleus accumbens and ventromedial prefrontal cortex), and controlled by top-down input from regions within the ventral, lateral and medial prefrontal and anterior cingulate cortex (Ochsner et al., 2012). Neuroimaging support for this model comes from both resting state and task-induced functional connectivity studies. At rest, the amygdala is negatively coupled with LPFC and dorsal ACC, and positively coupled with MPFC (Henckens et al., 2012; Mishra et al., 2014; Robinson et al., 2010; Yue et al., 2013), though this pattern varies across amygdala sub-regions (Roy et al., 2009). Resting state coupling is also disrupted in psychiatric conditions associated with disregulated fear and threat, such as schizophrenia, social anxiety and post-traumatic stress disorder (Blackford et al., 2014; Brown et al., 2013; Unschuld et al., 2014). During deliberate reappraisal of negative emotional stimuli, psychophysiological interaction (PPI) analysis shows increased inverse coupling between amygdala and regions in the LPFC, anterior cingulate cortex (ACC) and dorsal ACC (Banks et al., 2007; Lee et al., 2012; Yue et al., 2013). In sum, the amygdala is implicated in processing emotionally evocative stimuli, and is strongly and inversely coupled, both at rest and during emotional evaluation tasks, with regions in the medial and lateral PFC, and the dorsal ACC.

Amygdala and Empathy

Like self-focused negative emotions, other-focused empathic responses are subject to deliberate regulation. When faced with another's misfortunes, we may feel deeply for (or with) them, or we may control our empathic responses, whether out of altruism, to focus on helping (Batson and Oleson, 1991) or out of selfishness, to minimize personal distress (Cialdini et al., 1997). Thus, a plausible initial hypothesis is that regulation of empathic responses would depend on the same mechanisms, and the same role for the amygdala, as regulation of self-focused negative emotions.

However, evidence for amygdala involvement in empathic responses is mixed. Prior experiments have manipulated empathic responses to another person's physical pain by changing either the relationship between the participant and the target, or by changing the focus of the participant's attention. When empathy is reduced by making the target less sympathetic (e.g. a cheater), there is no reduction in amygdala activity when the target receives a painful electric shock (Singer et al., 2006). Similarly, distracting the participant's attention from images of body parts in physical danger leads to decreased activation in regions of the 'pain matrix' (including anterior cingulate cortex (ACC) and insula), but not the amygdala (Gu and Han, 2007). By contrast, when empathy was reduced by asking participants to focus on the perpetrator, or cause, of a traumatic experience, rather than on the victim, amygdala activity is actually *increased* (Akitsuki and Decety, 2009; Decety et al., 2008; Ruby and Decety, 2004). One possible interpretation of these last results is that focusing on an attacker induces a perception of threat that increases amygdala response. In all, the prior evidence does not clearly suggest decreased amygdala activity when empathy for physical pain is reduced.

An open question, however, is whether the neural mechanisms of empathic control depend on the nature of the target's experience. In previous research, we found that strikingly different brain regions are recruited while reading about another person's experience of physical pain (e.g. breaking a bone) versus emotional suffering (e.g. suspecting a partner of cheating) (Bruneau et al., 2012a, 2013; Bruneau et al., 2012b). Stories about physical pain elicit activity in the same regions as experiencing or directly observing physical pain, including regions associated with dimensions of pain that are

considered ‘affective’ (AMCC, AI) and ‘sensory’ (secondary sensory (S2)) (Hofbauer et al., 2001; Rainville et al., 1997) as well as regions sensitive to bodily sensations (medial frontal gyrus (MFG), premotor (PM)) (Davis et al., 2002; Zacks et al., 1999) or bodily motion (extrastriate body area (EBA)) (Peelen et al., 2006) – for simplicity, we will refer to these regions together as the ‘extended pain matrix’ for the remainder of the manuscript. By contrast, stories about emotional suffering elicit activity in regions associated with thinking about others' thoughts, especially medial prefrontal cortex (MPFC), but also temporo-parietal junction (TPJ), anterior superior temporal sulcus (aSTS) and medial precuneus (PC). One possibility is therefore that the role of the amygdala in empathy regulation differs, depending on the group of brain regions that need to be regulated; specifically, the amygdala may be disproportionately involved in the regulation of responses in Theory of Mind (ToM) brain regions to other people’s emotional suffering, as opposed to responses in the extended pain matrix regions to other people's physical pain.

Some patterns in the existing literature are consistent with this hypothesis. First, bilateral amygdala lesions impair emotional responses to others’ suffering, despite leaving the cognitive appreciation of their state intact (Hurlemann et al., 2010). Second, exogenous oxytocin administration in neurotypical adults enhances both amygdala responses and reported empathy for others’ suffering (Hurlemann et al., 2010). However, oxytocin administration has no effect on amygdala activity or reported unpleasantness while watching another person in the same room receive physically painful shocks (Singer et al., 2008). Thus, to understand the role of the amygdala in empathy, and empathic regulation, it may be necessary to explicitly distinguish between empathic responses toward others’ pain versus their suffering.

Current Study

In the current study, we asked participants to either empathize with a target, or to deliberately control and withhold their empathic response through social distancing, while reading stories describing either the target’s physically painful or emotionally upsetting experience. Participants in the first experiment were untrained college students;

we then replicated the experiment with a sample of professional social workers. The primary results suggest that the amygdala is involved in the regulation of empathy for others' emotional suffering, but not for others' physical pain. We further investigated this pattern by testing the functional and effective connectivity between the amygdala and brain regions involved in understanding others' mental and bodily experiences.

Study 1

Methods

Participants

Nineteen naive right-handed college or graduate school participants engaged in the experiment for payment. An a priori participant exclusion threshold was set at 5 degrees or 5 millimeters of movement in any direction on any run. One participant moved excessively during the scan and was removed from the analysis, resulting in 18 participants (M_{age} = 22.2 years, SD = 3.6, 14 females). All participants had normal or corrected to normal vision, and gave written informed consent in accordance with the requirements of MIT's Committee on the Use of Humans as Experimental Subjects.

Design and Materials

Participants were shown short verbal narratives, 12 depicting physically painful (PP) events and 12 depicting emotionally painful (EP) events. The stories were randomly drawn from a larger set of 24 PP and 24 EP stories. To avoid empathy fatigue, participants were also presented with 24 stories describing neutral, non-painful events (not analyzed here; for full list of stimuli, see supplemental material, and Bruneau, Pluta and Saxe, 2012). Each story was presented for 16 s, followed by a 12 s inter-stimulus interval. In the final 4 seconds of the presentation, a single prompt appeared below the scenario asking participants, "How much empathy do you feel for the main character's pain/suffering?" Responses were made on an MRI safe button box ranging from (1) 'none' to (4) 'a lot'. Each of 3 runs contained 16 stories: 4 PP stories, 4 EP stories and 8 neutral stories. The order of conditions and scenarios were counterbalanced across runs

and across participants. Stimuli were presented in white 24-point font on a black background via Matlab 7.0 with an Apple G4 powerbook.

Participants were given two tasks [adapted from Batson et al. (1997)]:

> "Empathize: While reading each of the following stories, try to imagine how the main character in the story feels about what has happened and how it affects his or her life. Do not worry about attending to all the details of the story, just concentrate on trying to imagine how the main character feels."

> "Remain Objective: While reading each of the following stories, try to be as objective as possible about what has happened to the main character and how it affects his or her life. Try to remain detached as you read each scene, and think about the situation clinically, as if you were a social worker or a doctor."

In each run, each task applied to 8 of the 16 stories in an ABBA design (either the first and last 4 stories, or the middle 8 stories, counterbalanced across runs). This resulted in a 2 (physical vs. emotional pain) x 2 (empathize vs. remain objective) within-subjects experimental design.

Image Acquisition and Analysis

Participants were scanned using a Siemens Magnetom Tim Trio 3T System (Siemens Solutions, Erlangen, Germany) in the Athinoula A. Martinos Imagining Center at the McGovern Institute for Brain Research at MIT using 30 3-mm-thick near axial slices with near whole brain coverage (TR= 2 s, TE=30 ms, flip angle= 90). The experiment was modeled using a boxcar regressor.

MRI data were analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) and custom software. Each participant's data were motion corrected, and then normalized onto a common brain space (Montreal Neurological Institute, EPI Template). Data were smoothed using a Gaussian filter (full width half maximum = 5 mm).

For whole brain analyses, we used a modified linear model including both covariates of interest (the experimental conditions) and nuisance covariates (run effects). We modeled the conditions as a boxcar (matching the onset and duration of each 16 second stimulus) convolved with a standard double gamma hemodynamic response function (HRF). Time-series data were subjected to a high-pass filter (1 cycle/256 s). To identify voxels in which effects of condition were reliable across participants, BOLD

signal differences between conditions (linear combinations of the beta parameters for condition covariates) were submitted to second level, random-effects analysis. We focused on main effects of condition (EP<>PP), and effects of task demand on each condition (EP_{obj} <> EP_{emp}; PP_{obj} <> PP_{emp}). In Experiment 1, these analyses were exploratory, and were conducted using SPM with an uncorrected voxelwise threshold of $p<0.001$, with a minimum of 10 contiguous supra-threshold voxels. We also report the results of the same contrasts on the complete data set, correcting for multiple comparisons by performing Monte Carlo permutation tests to establish empirical null distributions for the peak T and cluster size in each analysis ($p<0.05$, SnPM, Nichols and Holmes, 2002; Hayasaka and Nichols, 2004; see 'Combined Data' following Experiment 2). All peak voxels are reported in MNI coordinates.

Anatomical regions of interest in the bilateral amygdalae were defined by manually drawing masks on each subject's normalized anatomical image using the paint function in MRIcron. Average beta responses for each condition were determined within each amygdala ROI, and full time-courses were extracted from the anatomical ROIs to be used as seeds for connectivity analysis. All data extracted from the ROIs were subjected to the same high pass filtering as used in the GLM calculation.

To assess functional connectivity within individuals, we used a psychophysiological interaction model (PPI). Each participant's data were re-modeled with regressors for: four conditions (EP, PP, and two sets of neutral stories, each modeled as a boxcar convolved with the standard HRF; the psychological regressors), the time course in the anatomically-defined bilateral amygdala (the physiological regressor), and the interaction of the timecourse in the amygdala and the EP condition, and of the timecourse in the amygdala and the PP condition (the psychophysiological regressors). The contrast of these final two regressors was used to identify regions where activity was more correlated with the amygdala during EP than PP trials, controlling for overall correlations with the amygdala, and overall task responses. The connectivity analyses were conducted separately by stimulus condition, but collapsed across the two task demands.

Finally, having identified a number of brain regions whose activity was associated with amygdala activity, we examined the direction of effective connectivity between these brain regions using Granger Causal Modeling. For this analysis, we used ROIs derived from the whole brain analyses of the effect of task demand, and from the PPI analysis. For each subject, the timecourse was extracted from all the ROIs from all functional runs and multiplied by the EP (or PP) regressor to limit the connectivity analysis to the intervals of one task condition. The timeseries were then normalized by subtraction of mean and division by standard deviation and then concatenated across runs to create a single timecourse per subject per ROI. We used the Granger Causality toolbox (Barnett and Seth, 2014) to compute the bivariate Granger causality from Amygdala to all other ROIs and all ROIs to Amygdala. For each Amygdala:ROI pair we evaluated Granger Causality by computing the difference in explained variance between the full-model and the reduced model (Ding et al., 2006). For each ROI, we tested whether the direction of greater influence (i.e. Amygdala→ROI or ROI→Amygdala) was consistent across subjects, during EP stories. A reliable asymmetry in the direction of influence provides evidence that the GC results are not simply an artifact of a temporally synchronous correlation between two noisy, auto-correlated timeseries. For regions in which the direction of influence was consistent, we tested whether this effect was selective for EP stories, by comparing the strength of Granger causality between the same pair of regions in the same direction, during EP versus PP stories. GCM has been criticized because spurious results can be driven by differences in the hemodynamic response function or vasculature across brain regions (Webb et al., 2013). By determining whether Granger causality between a pair of regions is specific to one condition versus another, we control for confounds associated with heterogeneity associated with vascularization and hemodynamics across brain regions.

Note that the PPI and GCM analyses of Study 1 were exploratory; the results of these tests serve as the basis of hypotheses that could be independently tested in Study 2. Thus we describe the pattern of results (threshold $t > 2.1$), and show the results in the Figures, but do not report statistics (i.e. p-values) for these tests.

Results

Behavioral:

Participant responses were analyzed using a 2 condition (EP vs PP) x 2 task demand (Empathize vs Objective) within-subject ANOVA. Participants reported feeling more empathy for targets during the Empathize ($M = 2.91$, $SD = 0.65$) versus Objective ($M = 2.13$, $SD = 0.58$) tasks (main effect of condition, $F(1,17) = 37.6$, $p < 0.001$, $\eta^2 = 0.69$). Reported empathy was higher during emotional pain (EP) ($M = 2.69$, $SD = 0.50$) versus physical pain (PP) conditions ($M = 2.35$, $SD = 0.54$) (main effect of condition, $F(1,17) = 9.6$, $p = 0.007$, $\eta^2 = 0.36$); there was no significant condition x task interaction ($F(1,17) = 0.5$, $p > 0.45$). Note that mean self-reports were lower than previously published (Bruneau et al., 2012b), since half the conditions here asked that participants disengage their empathy.

Neuroimaging:

We used an initial whole brain analysis to examine neural responses to scenarios depicting others in emotional pain (EP) versus physical pain, and others in physical pain (PP) versus emotional pain, across both task demands (Objective, Empathize). Consistent with previous work (Bruneau et al., 2012a; Bruneau et al., 2012b; Corradi-Dell'Acqua et al., 2013) the EP > PP contrast revealed activity in brain regions associated with mentalizing (bilateral temporoparietal junction (TPJ) down the superior temporal sulcus (STS) to the temporal poles, precuneus, and medial prefrontal cortex (mPFC)), while the PP > EP contrast was associated with activity in the extended pain matrix (bilateral insula, AMCC and dorsal cingulate cortex (pain matrix), as well as S2, PM, MFG and EBA) (Figure 1, Table 1). Activity was bilateral for all regions, but was stronger in the left hemisphere.

Figure 1, Table 1 about here

Also replicating previous work (Bruneau et al., 2013; Corradi-Dell'Acqua et al., 2013), a similar pattern of activity was observed when we examined neural responses that

were correlated with the amounts of pain and suffering depicted in each story, using a parametric item analysis (Supplemental Figure 1A).

Next, we turned to the main contrast of interest: the effect of task demand (remaining objective (obj) versus empathizing (emp)) on neural responses to others in physical pain and emotional suffering. To determine if empathic control (obj > emp) of EP and PP were associated with activity in similar or distinct brain regions, we looked at objective versus empathize tasks separately in the EP and PP conditions. For the EP scenarios, instructions to control empathic responses versus empathize ($EP_{obj} > EP_{emp}$) resulted in increased activity across right lateral prefrontal cortex, and decreased activity in the amygdala, bilaterally, and regions along the left STS, left hippocampus/parahippocampus and left visual cortex (Figure 2, Table 2). By contrast,

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Figure 2, Table 2 about here

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empathic control in response to physically painful scenarios ($PP_{obj} > PP_{emp}$) resulted in activity in the right anterior insula and a region of the right lateral prefrontal cortex distinct from that observed for EP (Table 3) and decreased activity in small regions in primary and secondary sensory/motor cortex. There were no significantly de-activated voxels in amygdala for the $PP_{obj} > PP_{emp}$ contrast (Table 3), even at a relaxed threshold of $p < 0.05$, uncorrected. These results suggest that empathic control affects amygdala activity, but only when empathizing with emotional (and not physical) experiences. We followed up on this suggestion in two subsequent analyses.

Table 3 about here

First, we measured activity in anatomically defined amygdala regions of interest (ROIs). The left and right amygdalae were sensitive to task demand only when presented with EP stories: there was a significant interaction between condition and task demand in right amygdala (repeated measures ANOVA, $F(1,17) = 10.4$, $p = 0.005$, $\eta^2 = 0.38$) and a

trend in the same direction in the left amygdala ($F(1,17) = 3.1$, $p < 0.10$, $\eta^2 = 0.16$) (Figure 2; for mean responses across conditions, see Supplemental Figure 2). Planned post-hoc paired t-tests revealed that amygdala activity was greater for EP_{emp} than EP_{obj} in right amygdala ($t(17) = 3.1$, $p = 0.007$), but not in left amygdala ($t(17) = 1.5$, $p = 0.16$). By contrast, the effect of task demand during PP stories was slightly, but not significantly, and in the opposite direction (left: $t(17) = 1.1$, $p = 0.28$; right: $t(17) = 1.5$, $p = 0.16$).

Second, we performed a PPI analysis. PPI analysis identifies brain regions where activity covaries with that of a seed region differentially across conditions. Activity in the bilateral amygdalae while processing EP (versus PP) vignettes covaried positively with regions of the ToM network (bilateral TPJ, bilateral anterior STS and precuneus), and covaried negatively with activity in extended pain matrix brain regions (AMCC, right insula (pain matrix), and left S2, left MFG, left PM, and left EBA (bodily sensations/motion); see Figure 3 and Table 4). Each of ToM brain regions (bilateral TPJ, precuneus and bilateral anterior STS) that were positively coupled with the amygdala during EP versus PP overlapped with the brain regions identified by the EP versus PP contrast. All the extended pain matrix brain regions negatively coupled with the amygdala during EP versus PP (AMCC, right insula, left MFG, left S2, left PM, left EBA) overlapped with the brain regions identified by PP versus EP.

Figure 3, Table 4 about here

The negative association between amygdala and extended pain matrix brain regions for EP versus PP could be due either to (1) negative associations between amygdala activity and pain matrix brain regions during EP tasks, or (2) positive associations between amygdala activity and pain matrix brain regions during PP tasks. Similarly, positive associations between amygdala and ToM brain regions during EP versus PP could be due to (1) positive associations between amygdala activity and ToM regions during EP or (2) negative associations between amygdala activity and ToM regions during PP. To distinguish between these possibilities, we extracted separate beta

estimates for the psychophysiological regressors involving EP and PP for each participant in each region that showed a significant PPI effect, and investigated whether these beta values were greater or less than zero. (Note that these measures are exploratory, and differences between the PPI regressors are non-independent of the voxel selection criterion; for confirmatory analyses in independent data, and statistical analyses, see Study 2).

All of the brain regions identified to be significantly more positively coupled with amygdala during EP (versus PP) were driven by positive correlations with the amygdala during the EP condition (Figure 4); in only one region (the PC) was there a (relatively weak) negative correlation with the amygdala during PP. By contrast, four of the extended pain matrix brain regions showed *negative* correlations with the amygdala during EP: AMCC, right insula, left S2 and left MFG; two of these brain regions (left S2 and right insula) also showed positive correlations with the amygdala during PP. Correlations in left PM and left EBA were not reliably different from zero in either condition. Therefore, these data suggested that although extended pain matrix brain regions were generally more active during PP versus EP, the differential correlation of these brain regions with the amygdala across conditions apparently reflected *negative* (or inverse) correlations during EP.

Figure 4 about here

Finally, in order to characterize the effective connectivity between amygdala and the ToM and pain matrix brain regions, we turned to Granger Causal Modeling. GCM examines how well prior activity (t-1) in one region can predict current activity (t) in another region, after taking into account the autocorrelation (t-1) in the first region. We tested whether any of the regions identified by the PPI analysis showed a reliably asymmetric GC predictive relationship with the amygdala. Of the ToM brain regions, only the right STS showed a reliably asymmetric GC relationship with the amygdala: during EP, right STS activity was more predictive of amygdala activity than the reverse. By contrast, all of the extended pain matrix brain regions (AMCC, right insula, left S2,

left MFG, left PM, left EBA) showed the reverse causal association: amygdala activity during EP was more predictive of activity in each region than the reverse (Figure 5a); in AMCC, left S2, left MFG and left PM, this predictive relationship was stronger in EP than PP.

We also conducted a GCM analysis to test the effective connectivity between the amygdala and the region of right LPFC where activity was increased by instructions to control empathy for emotional suffering (based on the contrast $EP_{obj} > EP_{emp}$). Activity in the right LPFC was reliably preceded and predicted by activity in the amygdala, specifically during EP but not PP (Figure 5b).

Figure 5 about here

Discussion

Study 1 replicated previous work using the same physically and emotionally painful scenarios: reading about others in physical pain (versus emotional pain) activates regions associated with bodily sensations/motion (bilateral secondary sensory, EBA), as well as the primary components of the 'pain matrix' (bilateral insula, AMCC), while reading about others in emotional pain (versus physical pain) activates regions associated with mentalizing: bilateral TPJ extending down the anterior STS, PC, MPFC (Bruneau et al., 2013; Bruneau et al., 2012b).

The key novel result of Study 1 is that the deliberate control of empathy resulted in increased activity in right LPFC and decreased activity in bilateral amygdala, selectively during stories about emotional suffering (EP), and not during those about physical pain (PP). These results are consistent with two lines of previous evidence: deliberate regulation of affective responses to emotionally evocative stimuli results in increased lateral prefrontal and decreased amygdala activity (Ochsner et al., 2012), and the amygdala is insensitive to manipulations of empathy for others' physical pain (Singer et al., 2008).

PPI and GCM analyses further suggested that amygdala activity during EP (versus PP) stories was positively coupled with (and predicted by) ToM brain regions and negatively coupled with (and predicted) extended pain matrix brain regions. These results suggest a possible mechanism for the amygdala's role in empathy for emotional suffering: activity in the amygdala may be caused by information about another person's negative emotion (coming from anterior STS), and then lead to reduced activity in regions involved in representing bodily states and pain (the extended pain matrix). Instructions to control or reduce empathy for suffering then lead to reduced activity in the amygdala, possibly accompanied by reduced regulation of these networks.

One surprising result of Study 1 concerned the direction of Granger Causal influence between the amygdala and the right LPFC. The current study replicated many previous experiments (Ochsner et al., 2002; Ochsner et al., 2004b; Phan et al., 2005) in finding opposite effects of the task demands on activity in right LPFC (*increased* activity when controlling empathy for EP) versus the amygdala (*decreased* activity when controlling empathy for EP). A common assumption is that this pattern reflects a modulatory signal from LPFC which causes the decreased response in the amygdala; however we found GC influence in the opposite direction: activity in the amygdala preceded and predicted activity in right LPFC, specifically during the EP condition.

However, many of the analyses conducted in Study 1 were exploratory. In order to test the robustness and replicability of all of these results, we conducted a replication experiment in an independent sample of participants.

Study 2

In Study 2, we aimed to replicate the results from Study 1 in a group of participants with extraordinary experience with human suffering: trained social workers. As experts in empathic control, we reasoned that social workers might be particularly able to comply with the task demands, and thus would increase the power of the experiment to reveal the neural mechanisms underlying empathic control. The main goal of this experiment was thus to test the replicability of the results of Study 1; in addition, we conducted exploratory analyses to test whether expertise and training in empathic

control may lead to differences in the patterns of neural activity observed during the task. In particular, we were interested in examining differences in the recruitment of cognitive control regions in social workers (Study 2) versus controls (Study 1).

Methods

Participants

Twenty-one naive right-handed social workers (M_{age} = 30.6 years, *SD* = 5.5, 17 females) were recruited through an ad in a social worker newsletter to engage in the experiment, for payment. Participants had on average 6.1 years of experience (*SD* = 4.4) and when asked to indicate in a survey their profession, reported either the broader category of 'social worker' (8/21) or their specialty (e.g. clinician, mental health counselor, intensive foster care). An a priori participant exclusion threshold was set at 5 degrees or 5 millimeters of movement in any direction on any run. No participants exceeded this threshold, so all were included in analysis. All participants had normal or corrected to normal vision, and gave written informed consent in accordance with the requirements of MIT's Committee on the Use of Humans as Experimental Subjects.

Design and Materials

Experimental design, methods, and analysis were identical to Study 1, with the following two additions:

First, participants performed a theory of mind localizer task (Dodell-Feder et al., 2011) after the completion of the main experiment. Second, after the neuroimaging study, participants rated the EP and PP stimuli they had seen inside the scanner for the amount of personal distress and empathic concern they elicited (Batson et al., 1997).

Behavioral ratings made in the scanner were lost for 2 participants due to equipment failure (broken button boxes).

Results

Behavioral:

Using a 2 condition (EP, PP) x 2 task demand (Empathize, Objective) ANOVA, we found that participants reported feeling more empathy for targets during the Empathize (M = 3.40, SD = 0.31) versus Objective (M = 2.51, SD = 0.59) task blocks (main effect of demand, $F(1,17) = 46.5.6$, $p < 0.001$, $\eta^2 = 0.73$). Empathy ratings were slightly higher for stories about emotional pain (EP) (M = 3.14, SD = 0.41) than physical pain (PP) (M = 2.77, SD = 0.42) (main effect of condition, $F(1,17) = 19.0$, $p < 0.001$, $\eta^2 = 0.53$); there was no significant condition x task interaction ($F(1,17) = 0.1$, $p > 0.70$).

After scanning, participants also reported how much empathic concern (EC) and personal distress (PD) they felt in response to each of the stimuli. While levels of empathic concern were higher for stories involving EP (M = 73.5, SD = 10.0) versus PP (M = 62.1, SD = 12.9; $t(18) = 5.9$, $p < 0.001$), personal distress was similar across stories involving EP (M = 43.2, SD = 25.6) and PP (M = 41.4, SD = 26.4; $t(18) = 0.7$, $p > 0.45$).

Neuroimaging:

Replicating the results from Study 1, the EP > PP contrast was associated with activity in the bilateral TPJ, PC, anterior STS and MPFC. These regions overlapped with the regions identified in the same group of participants by a theory of mind localizer task (Supplemental Figure 1B). By contrast, the PP > EP contrast was associated with activity in the extended pain matrix (AMCC, bilateral insula, S2, MFG and EBA) (Figure 1). Similar patterns of activity were observed for neural responses correlated with the amounts of pain and suffering depicted in the stimuli using a parametric item analysis (Supplemental Figure 1B).

Also replicating Study 1, instructions to remain objective versus empathize in the EP scenarios ($EP_{obj} > EP_{emp}$) resulted in increased activity across lateral prefrontal cortex, and decreased activity in bilateral amygdala (Figure 2A). Unlike Study 1, the ($EP_{obj} > EP_{emp}$) contrast also yielded increased activity in other regions associated with cognitive control: anterior insula bilaterally (Chang et al., 2012), and dorsal cingulate cortex (Table 2).

For the PP scenarios, empathic control ($PP_{obj} > PP_{emp}$) resulted in elevated activity in the right anterior insula and a region of the right lateral prefrontal cortex, and decreased activity in small regions in primary and secondary sensory/motor cortex. There

were no suprathreshold voxels in amygdala for this contrast, even at a relaxed threshold of $p < 0.05$, uncorrected.

For participants in Study 2, analysis in anatomically defined amygdala ROIs revealed a marginally significant interaction between condition (EP, PP) and task demand (Empathize, Objective) in the right amygdala ($F(1,20) = 3.4$, $p = 0.08$, $\eta^2 = 0.15$), and a significant interaction in the left amygdala ($F(1,20) = 7.8$, $p = 0.01$, $\eta^2 = 0.28$). Planned post-hoc paired t-tests revealed that amygdala activity was marginally greater for EP_{emp} than EP_{obj} in right amygdala ($t(20) = 1.9$, $p = 0.08$), and significantly greater for EP_{emp} than EP_{obj} in left amygdala ($t(20) = 2.9$, $p = 0.008$) (Figure 2B; for mean responses across conditions, see Supplemental Figure 2). As with Study 1, activity was slightly but non-significantly higher for PP_{obj} than PP_{emp} in both amygdalae (left: $t(20) = 0.6$, $p = 0.50$; right: $t(20) = 0.3$, $p = 0.80$).

The PPI analysis confirmed the hypotheses derived from exploratory analyses of Study 1. In the whole brain PPI analysis, the correlation with the amygdala was higher during EP than PP in regions including bilateral TPJ, precuneus and bilateral anterior STS; and lower during EP than PP in regions of the extended pain matrix, including AMCC, bilateral secondary sensory, and left MFG (Figure 3A). We further interrogated these correlations by extracting the beta estimates of the psychophysiological regressors in Study 2 from ROIs defined by the PPI analysis in Study 1. We tested the hypothesis that each pattern observed in a region in Study 1 would replicate in the independent data in Study 2. During EP, the psychophysiological interaction betas were reliably greater than zero in all regions of the ToM network (all ts > 2.3, all ps < 0.05), and reliably below zero in AMCC, left MFG and left S2 (all ts > 3.3, ps < 0.005). Also replicating Study 1, during PP, the psychophysiological regressor was greater than zero in lEBA and lPM (ts > 3.0, ps < 0.01; Figure 4B).

Granger causal modeling using the same independent ROIs generated in Study 1 revealed the same, and even stronger, causal relationships as found in Study 1 (see Figure 5): activity in right and left STS reliably predicted activity in the amygdala (rather than the reverse) during EP (both $t(20) > 2.9$, $p < 0.01$), and this relationship was stronger in EP than PP in right STS ($t(20) = 2.6$, $P < 0.02$) but not left STS ($t(20) = 0.1$, n.s.). Activity in AMCC, right insula, lS2, left MFG, left PM and left EBA were predicted by

the amygdala during EP (all ts > 2.8, ps < 0.02); this relationship was stronger in EP than PP in lS2 ($t(20) = 2.9$, $p < 0.01$), but not the other regions (all ts < 0.5).

Finally, activity in right LPFC (identified based on the response to $EP_{obj} > EP_{emp}$ in Study 1) was also reliably predicted by activity in the amygdala ($t(20) = 11.4$, ps < 0.001), although this predictive relationship was not reliably greater in EP than PP ($t(20) = 0.7$, n.s.).

Discussion

The main results of Study 2 replicate those of Study 1 in almost every detail, using ROIs generated from the completely independent data from Study 1. First, stories about PP (versus EP) evoked activity in the regions of the extended pain matrix (AMCC, insula, S2, and PM, MFG, EBA), while stories about EP (versus PP) evoked activity in the ToM network (TPJ, PC, anterior STS, MPFC). Second, empathic control resulted in increased right LPFC activity during both PP and EP stories, but decreased amygdala only during EP stories. Third, activity in ToM regions was positively coupled to, and predicted, amygdala activity during EP, and activity in extended pain matrix regions was negatively coupled to, and predicted by, the amygdala during EP. Finally, just as in Study 1, activity in the amygdala preceded and predicted activity in the right LPFC.

Combined Data

One benefit of two independent datasets is that exploratory analyses in the first dataset can be used to generate specific hypotheses that are then tested with confirmatory analyses in independent data; independent confirmatory tests are particularly compelling for functional and effective connectivity, where replications are rare. At the same time, neuroimaging studies with limited numbers of participants suffer from low-powered analyses, potentially masking real effects. In order to perform higher-powered analyses on the neuroimaging data, and to explore possible differences between the two groups of participants, we also conducted analyses on the combined sample of participants (N = 39).

We have previously reported on the EP versus PP contrasts, and therefore focused the combined analyses on the task demand contrasts (EP_{emp} versus EP_{obj}, PP_{emp} versus PP_{obj}, and the interactions between these), and the PPI analysis.

Results

In the behavioral data, social workers (Study 2) reported higher levels of empathy overall compared to control participants (Study 1; $F(1,34) = 9.4$, $p = 0.004$, $\eta^2 = 0.22$), but there were no significant interactions between Study and condition, task demand or condition x task demand (all Fs < 0.5, all ps > 0.4).

Combining the fMRI results across studies, deliberate control of empathy for emotional pain ($EP_{obj} > EP_{emp}$) resulted in decreased activity in the bilateral amygdala and the left hippocampus/parahippocampus, and increased activity in right LPFC, dorsal ACC, and left orbitofrontal cortex (OFC) (corrected for multiple comparisons using Monte Carlo based permutations, p<0.05; Figure 6A; Table 5). By contrast, deliberate control of empathy for physical pain ($PP_{obj} > PP_{emp}$) did not result in decreased activity in any brain regions, and resulted in increased activity in bilateral anterior insula, dorsal and anterior ACC, right OFC, and right TPJ (Figure 6B; Table 5). The interaction between empathic control of emotional pain and empathic control of physical pain ($EP_{emp} > EP_{obj}$) > ($PP_{emp} > PP_{obj}$) yielded a single region of significance, in the left amygdala (MNI: -18, -2, -14, peak T: 5.5, extent: 121 voxels); there were no suprathreshold voxels, at this corrected threshold, for any of the other interactions.

In the PPI analysis (also corrected for multiple comparisons using Monte Carlo based permutations, p<0.05) the amygdala was more strongly associated during EP (versus PP) with regions in the theory of mind network (bilateral TPJ, PC, bilateral anterior STS), and more strongly associated during PP (versus EP) with regions of the extended pain matrix (AMCC, right Insula, left S2, left MFG, left PM, left EBA; Figure 3B). This pattern held when examining left and right amygdala separately (Supplemental Figure 3).

Finally, we compared neural responses directly between the two Experiments for the main contrast of interest ($EP_{obj} > EP_{emp}$). Activity during empathic control ($EP_{obj} >$

EP_{emp}) was greater for social workers in regions within the bilateral anterior insulae, dACC, left parahippocampus, thalamus and left STS (at a voxelwise threshold of $p < 0.001$, uncorrected; Supplemental Figure 4). None of this activity survived corrections for multiple comparisons, indicating that these results are merely suggestive of differences that may warrant further investigation.

General Discussion

The primary goal of the present studies was to examine the neural mechanisms of empathic control: our ability to deliberately dial up or dial down empathy. Previous work has shown that the neural responses to others' pain depend upon the type of pain being experienced: reading about others in physical pain activates the 'extended pain matrix', including AMCC and bilateral insula, while reading about others in emotional pain activates regions in the theory of mind network, including bilateral TPJ, PC, bilateral anterior STS and MPFC (Bruneau et al., 2012a, 2013; Bruneau et al., 2012b; Corradi-Dell'Acqua et al., 2013). Are empathic responses to others' physical and emotional pain also *regulated* by distinct networks? Across two studies, we first replicate the distinct patterns of activity that result from reading about others experiencing emotional versus physical pain, and then provide clear evidence, replicated across two independent samples, that amygdala activity decreases while regulating empathic responses to others' emotional suffering, but not their physical pain. While reading about others' emotional suffering, amygdala activity was positively coupled with theory of mind brain regions, and negatively coupled with regions within the pain matrix. Granger Causality Modeling supported the separation of these networks: while activity in the STS preceded and predicted amygdala activity, activity in regions of the extended pain matrix (AMCC, right insula, left S2, left PM, left MFG and left EBA) followed and were predicted by amygdala activity.

These results help resolve seemingly disparate findings from three different empathy-related literatures. First, lesion and pharmacological studies implicate the amygdala in processing others' emotional states. For example, bilateral amygdala lesions impair components of perception that may be integral to empathy for suffering: gaze

perception and the recognition of others' emotional expressions (Adolphs et al., 1999; Young et al., 1996), and for a pair of twins, relative to matched neurotypical controls, bilateral amygdala lesions impaired ability their to empathize with others' suffering (Hurlemann et al., 2010). The current results suggest that the amygdala is a critical part of the network involved in marshaling empathic responses to others' negative emotions.

Second, cognitive control studies demonstrate that the amygdala response to generally distressing stimuli is dampened by a variety of deliberative techniques, including suppression, reappraisal and social distancing (Eippert et al., 2007; Ochsner et al., 2002; Ochsner et al., 2004b; Phan et al., 2005; Urry et al., 2006). Interestingly, many of the cognitive control studies include pictures from the International Affective Picture System (IAPS) involving emotional pain (people crying, funeral scenes), physical pain (gruesome injuries), and fear or threat (a striking snake, a pointed gun). A possibility suggested by the current data is that deliberately controlling emotional responses may particularly reduce amygdala responses to the subset of images involving others in emotional pain; this hypothesis could be tested in future research.

Third, the amygdala is active when experiencing physical pain oneself, but not when another is experiencing that same pain (Simons et al., 2014; Singer et al., 2004; Singer et al., 2006; Wager et al., 2004). Administration of oxytocin, which has been shown to decrease amygdala-dependent processes such as fear learning or threat perception (Kirsch et al., 2005), has also been shown to dampen the amygdala response to first-hand physical pain, but has no effect on amygdala activity when another is experiencing that same pain (Singer et al., 2008). These results are consistent with the data from the present study, which show that the amygdala is insensitive to the deliberate control of empathy for others experiencing *physically* painful events. In sum, the amygdala appears to play a key role in regulating only empathy for suffering, and not for physical pain.

However, one previous study appears to challenge this synthesis. Lamm and colleagues showed participants short video clips of others (actually paid actors) responding to a 'medical treatment' that involved painful and unpleasant auditory stimuli (Lamm et al., 2007). While participants were not directly instructed to control neural responses to the stimuli, a condition manipulation led participants to believe that the

treatment was either successful or unsuccessful. If the treatment was successful, participants could presumably reappraise patient's discomfort (i.e. it hurts him now, but he'll be better for it); a subset of the participants expressed a related form of re-appraisal during debriefing. This study reported decreased amygdala activity in the successful versus unsuccessful treatment condition. Thus, this prior study may have observed decreased amygdala activity during regulation of empathy for physical pain. However, another possibility is that while watching the facial grimaces of the actors, and especially while considering the unsuccessful treatment outcomes, participants experienced empathy for the patient's inferred emotional suffering (e.g. fear, disappointment). Knowing that the treatment was successful may not have altered the perception of the patient's physical pain, but may have decreased participant's empathy for the patient's emotions, and thus implicated the amygdala. This hypothesis could be tested in future research.

The current data suggest a selective role for the amygdala in the empathic regulation of emotional pain. Which brain regions are implicated in the empathic regulation of physical pain? We found that dorsal cingulate, bilateral anterior insula/aperculum, and right TPJ showed increased activity when participants were instructed to remain objective; no region was reliably more activated (across studies) when participants were instructed to respond more empathically to another's physical pain. However, prior studies have observed reduced activity in the extended pain matrix (especially AMCC and insula) when observing or reading about physical pain experienced by distant versus close or relevant others (a lover versus acquaintance, Cheng et al., 2010; an in-group member versus a member of an unfamiliar out-group, Bruneau et al., 2012a). It seems likely that the portion of the anterior insula activated by these previous studies represents the pain matrix sub-region of the insula, whereas the insula region activated in the current study represents a well-characterized and distinct sub-region within the insula slightly dorsal and anterior to the pain matrix sub-region, known to be sensitive to deliberation and cognitive control (Chang et al., 2012). Understanding why these different sub-regions are seemingly so sensitive to task manipulations that appear to be very similar is a topic that will require further study, for example by examining, within-subject, regulatory responses to empathic control of

physical pain using automatic (close versus distant other) versus deliberate ('empathize' versus 'remain objective') processes.

Psychophysiological interactions

Another way to characterize the role of the amygdala in empathic regulation is by examining the network of brain regions that the amydala is associated with during the task. We examined task-dependent amygdala connectivity first through psychophysiological interactions (PPI). The promise of PPI is that it can help identify functional brain networks by determining how activity in a seed brain region correlates with other target brain regions differentially, depending on the experimental condition. However, the interpretation of PPI results can be difficult, especially because (i) many PPI models do not include a regressor corresponding to an overall main effect response to all experimental conditions; (ii) PPI results can be driven either by a positive correlation during the experimental condition or negative correlation during the control condition; and (iii) many studies do not test the generalization of PPI results to independent data. In the current experiments, to address these issues, we therefore (i) included separate regressors for all experimental conditions, instead of just the contrast of interest, as psychological regressors; (ii) tested whether the PPI effects were driven by positive correlations with the experimental condition or negative correlations with the control condition; and (iii) replicated the key results in an independent sample, using independently localized regions. These methodological steps allow us to be confident of the interpretation and generalizability of the PPI results we report.

PPI analysis showed that the amygdala was negatively associated with right lateral PFC regions while participants read stories about emotional suffering (EP). That is, in both studies, greater activation in LPFC was associated with reduced activation in the amygdala, but only when the stories described emotional suffering. There was no coupling between LPFC and amygdala when the stories described physical pain. The region of LPFC identified by this analysis overlapped well with a recent meta-analysis of regions involved in emotion regulation (Buhle et al., 2013). The right lateralization of LPFC is also consistent with patterns of activity attributed to specific regulation techniques: while emotion reappraisal tends to elicit activity in left LPFC, social

distancing (i.e. imagining that the empathy target is a stranger versus a close friend) tends to generate activity in right LPFC (Erk et al., 2010). Thus, deliberate control of empathic responses to suffering may depend on the interaction of the amygdala with a specific region of right LPFC involved in cognitive control through social distancing.

The PPI analysis also showed that the amygdala was positively associated during EP with bilateral TPJ, bilateral aSTS and PC; in Experiment 2, a theory of mind localizer confirmed that the regions identified by the PPI analysis overlapped with the theory of mind network. That is, increased activity in the amygdala during EP stories was associated with increased activity in ToM regions.

One unexpected discovery was that during the same stories, the amygdala was also *negatively* associated with regions in the extended pain matrix (AMCC, S2, MFG). That is, increased activity in the amygdala during EP stories was associated with decreased activity in regions implicated in responses to others physical pain. Previously, we showed that brain regions that were sensitive to emotional pain were also de-activated by stories depicting increasing levels of physical pain (Bruneau et al., 2013). An interesting possibility is that brain regions responding to others' pain and suffering are not only distinct, but also potentially antagonistic. In other words, increasing concern for what is going on in another person's mind (empathy for emotional suffering) might be aided by removing the distraction of attention towards what is going on in his or her body (physical sensations, even pain).

In Experiment 2 the amygdala was also positively coupled during EP with VMPFC and Ventral Striatum (VS). This is consistent with a number of studies that have identified the amygdala, VMPFC and VS as a functional network associated with emotional processing (Ochsner et al., 2012). While many studies highlight the role of VMPFC in cognitive control of emotion, recent meta-analytical data support the involvement of dACC and LPFC, but not VMPFC, during cognitive control tasks (Buhle et al., 2013). One possibility is that the VMPFC may not have a direct effect, but may instead mediate the effects of other regions on the amygdala during emotion regulation (Urry et al., 2006).

More broadly, it will be important in future studies to compare the current neural distinctions between empathy for pain and suffering with work illustrating distinctions

across other dimensions, such as cognitive versus affective empathy. For example, lesion studies have shown a double dissociation between medial and lateral prefrontal cortex damage, and impaired cognitive empathy (trait perspective taking) versus emotional empathy (trait personal distress) assessed with self-report measures (the interpersonal reactivity index (IRI)) (Shamay-Tsoory et al., 2008). Understanding how this cognitive/emotional empathy distinction relates to empathy for pain/suffering and personal distress/empathic concern could potentially be addressed in a study that incorporates stimuli orthogonally varying each of these dimensions.

Granger Causal Modeling

Granger Causality Modeling allowed us to take the connectivity analysis a step further. GCM identifies asymmetric predictive relations between time series. Although it remains unclear whether Granger Causality indicates actual causality (Granger, 1969), differences in Granger Causality across participants predict individual differences in behavior (reaction time) (Wen et al., 2012), illustrating that GCM can provide behaviorally relevant information. In the initial analysis, GCM identifies whether the response in one brain region predicts the subsequent response in another brain region. However, a key challenge for GCM is that in noisy autocorrelated time series like fMRI data, two correlated brain regions may spuriously appear to predict one another (because each one is a noisy estimate of the correlated signal). Thus, in order to interpret GCM results as providing evidence for a functional predictive relationship between regions, it helps to provide evidence that (i) there is a systematic asymmetry in the direction of the prediction between the two regions, and ideally (ii) that the predictive link between regions depends on the experimental condition. It is also desirable (but unusual) to test whether the GCM effects observed generalize to an independent dataset. When all of these conditions are met, as in the current studies, GCM results can provide evidence of a functionally specific asymmetric predictive link between activity in two brain regions.

In both experiments, we found that the regions identified in the PPI analysis are not only distinguished by their opposing correlative association with the amygdala, but also by predictive relationships with the amygdala: regions associated with theory of mind (particularly right anterior STS) ‘granger caused’ amygdala activity, while

amygdala activity 'granger-caused' activity in the extended pain matrix (AMCC, right insula, and left S2, left PM, left MFG, left EBA).

Taken together, one interesting result of these analyses is the involvement of the anterior STS in the deliberate control of empathy for emotional pain. This region was positively correlated with amygdala during EP stories, and was the only region where activity reliably preceded and predicted subsequent amygdala responses to EP stories. In study 1, this same region also showed evidence of task modulation, being more active when subjects were instructed to empathize with EP stories versus remain objective. These results suggest an association of anterior STS with empathy that is consistent with human lesion data: patients with frontotemporal lobar dementia (FTLD) characterized by temporal (rather than frontal) degradation show a disproportionate loss of warmth in their response to for others' emotions and suffering (Perry et al., 2001). Caregiver ratings of patients' Empathic Concern (EC) are specifically associated with anterior temporal lobe grey matter volume (Rankin et al., 2006). Anterior STS may thus be involved in facilitating the connection between understanding what another person is feeling, and generating an empathic emotional response.

Perhaps the most surprising result of the GCM analyses is that LPFC activity, which is anti-correlated with amygdala activity during EP stories, was preceded and predicted by amygdala activity. Many previous studies have observed that increased activity in LPFC regions is often accompanied by decreased activity in amygdala; we found a similar pattern in the contrast between remaining objective and actively empathizing. An intuitive interpretation of this anti-correlation is that increased activity of LPFC is causing (through deliberate regulation) the decreased activation in the amygdala (Ochsner et al., 2012). However, the current results suggest that the predominant direction of granger causal influence is the reverse: amygdala activity predicts LPFC activity. While contrary to the assumed direction of causality, it is at least possible that amygdala activity could precede LPFC during empathic regulation: anatomical connections are bidirectional between amygdala and prefrontal cortex, the amygdala is capable of responding to some stimuli (e.g. threat) prior to even visual cortex, and the amygdala is composed of a number of both afferent and efferent nuclei. A more definitive test of the causal association between LPFC and amygdala could

potentially be done through direct manipulation of the circuit, for example, with transcranial magnetic stimulation (TMS). In addition, higher resolution imaging of the amygdala may reveal the specific amygdala nuclei involved in empathic control, which would connect to literatures on nucleus specific connectivity.

Differences between groups

Our a prior hypothesis was that social workers, who have extraordinary experience with others' emotional suffering, may show behavioral and neural differences in their abilities to regulate empathy, particularly towards others' emotional suffering. However, we found that self-reported empathy in social workers during empathic control (versus actively empathizing) was not distinct from controls, and neural responses during the key contrast (EP_{emp} versus EP_{obj}) were no different from controls, after correcting for multiple comparisons. At a more lenient threshold, social workers did show more activity during empathic control ($EP_{obj} > EP_{emp}$) in regions associated with dACC and bilateral anterior insula, which have been associated with cognitive control (Buhle et al., 2013; Urry et al., 2006), as well as hippocampus/parahippocampus, which we would predict to arise selectively more in social workers who likely have direct personal experiences empathizing with people facing similar situations to those depicted in the emotional pain scenarios. The two samples also differed across other dimensions (e.g. age), so these suggestive results could be due to factors other than profession. It is possible that the nature of the stimuli failed to reveal real differences between the groups in empathic regulation. For example, more severe examples of emotional pain may be more likely to draw out differences in empathic regulation between groups. In support of this, a number of social workers during debriefing that the stimuli in the experiment were less severe than their everyday experiences on the job. Further work will need to be done to determine if differences in activity or coupling with amygdala during empathic control are associated with age, training or some other factor, and whether these differences have behavioral consequences. Studies aimed specifically at dissociating these possibilities are currently underway.

The relative lack of expertise effects in the current study is seemingly in contrast to previous studies that have examined expertise effects on baseline responses to others'

physical pain in Eastern Medicine physicians in China viewing images of body parts being pricked by pins (versus Q-tips). In both ERP (Decety et al., 2010) and fMRI (Cheng et al., 2007) measurements, these physicians showed weaker neural response to the pinpricks than controls in early N110 and late P3 ERP signals, and insula and anterior cingulate hemodynamic responses. However, in these studies the participants were specifically exposed to pin pricks reminiscent of acupuncture, in which the physicians (but not the controls) were trained. The subjective measures of the pain intensity and unpleasantness from the stimuli assessed after the study reflected this training: mean responses were over two-fold higher for controls versus acupuncture specialists. It is therefore difficult to determine how much of the difference in activity was due to insensitivity to others' pain, or privileged information (i.e. that acupuncture pinpricks are, in fact, less painful).

Conclusions

Empathic control may be a necessary skill across a range of human experiences (e.g. making parenting and managerial decisions), and may be particularly for professionals from fields that surround themselves with human suffering (e.g. social workers, hospice professionals, child oncologists). However, very little research has examined empathic control directly. While much past research has highlighted the amygdala as the brain region most consistently implicated in the experience and control of emotional responses to personally distressing stimuli, the role of the amygdala in other-focused empathy is mixed, with some studies showing clear amygdala involvement, and others none at all. One possible explanation for these past results is that some empathy paradigms ask participants to empathize with others' emotional pain, while other paradigms require empathy for others' physical pain.

Across two studies, one with control participant and one with professional social workers, we examined the effect of deliberate regulation of empathy on neural activity. We found that regulating empathy for equally distressing stories about others' pain and suffering resulted in very different patterns of neural activity: consistent across both independent samples, the regulation of empathy for suffering activated regions in the right LPFC, and deactivated bilateral amygdala, while regulation of empathy for physical

pain activated largely distinct regions including a region in anterior insula, and had no effect on amygdala. Amygdala activity while reading about others' emotional suffering was positively associated with activity in a number of theory of mind brain regions, particularly the anterior STS, and was negatively associated with regions in the extended pain matrix. Together, these data provide insight into the mechanisms of empathic control, and offer further evidence for the neural dissociation of empathy for others' pain versus their suffering.

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Tables and captions

Table 1. Brain regions active while reading about others' emotional pain (EP) versus physical pain (PP). Brain regions, MNI coordinates, cluster extent and peak t-value presented for each contrast in each study. Bold type indicates regions identified in both Studies 1 and 2. MT = middle temporal lobe, TPJ = temporoparietal junction, MPFC = medial prefrontal cortex, PM = premotor, FFA = fusiform face area, Hipp = hippocampus, MFG = middle frontal gyrus, S2 = secondary sensory, PCC = posterior cingulate cortex, PC = precuneus, AMCC = anterior middle cingulate cortex, EBA = extrastriate body area, OFC = orbitofrontal cortex, PM = premotor, VC = visual cortex.

Study 1: EP>PP

Region	x	y	z	voxels	*t*
Precuneus	**0**	**-56**	**32**	**2143**	**6.6**
L MT	**-58**	**0**	**-28**	**1963**	**6.3**
L TPJ	**-40**	**-64**	**30**	**991**	**5.6**
R MT	**62**	**-6**	**-26**	**1590**	**5.6**
R TPJ	**48**	**-50**	**22**	**609**	**5.0**
VMPFC	**-2**	**36**	**-18**	2706	**5.3**
DMPFC	-12	54	36		5.4

Study 2: EP>PP

Region	x	y	z	voxels	*t*
Precuneus	**-4**	**-52**	**30**	**2213**	**14.3**
L MT	**-54**	**-8**	**-22**	**2045**	**11.7**
L TPJ	**-50**	**-58**	**22**	**1126**	**7.8**
R MT	**54**	**-2**	**-20**	**837**	**6.9**
R TPJ	**56**	**-60**	**22**	**633**	**7.2**
VMPFC	**4**	**26**	**-10**	**2174**	**8.3**
L Premotor	-46	20	42	129	6.5
R Temp Pole	40	22	-24	837	8.4
R FFA	26	-66	-14	52	6.3
Hipp/Parahipp	-24	-16	-24	80	5.2

Study 1: PP>EP

Region	x	y	z	voxels	*t*
L Insula	**-36**	**4**	**-14**	**1009**	**6.1**
R MFG	**40**	**38**	**12**	**262**	**5.8**
R S2	**60**	**-36**	**44**	**424**	**5.5**
L PCC	**-10**	**-26**	**38**	**195**	**5.5**
L S2	**-64**	**-26**	**32**	**1778**	**5.4**
AMCC	**4**	**-2**	**32**	**325**	**5.3**
R Insula	**38**	**4**	**-10**	**482**	**5.2**
L EBA	**-52**	**-68**	**-6**	**834**	**4.9**
L OFC	**-28**	**36**	**-14**	**182**	**4.8**
L PM	**-44**	**6**	**26**	**478**	**4.7**
L MFG	**-40**	**36**	**12**	**575**	**4.7**
L PM	**-24**	**8**	**58**	**191**	**4.6**
R OFC	**22**	**30**	**-18**	**58**	**4.2**
R PCC	**10**	**-36**	**44**	**58**	**4.1**
L VC	-34	-86	26	78	4.2
R S2	38	-48	42	106	4.1

Study 2: PP>EP

Region	x	y	z	voxels	*t*
L Insula	**-38**	**-2**	**-8**	**412**	**8.5**
R MFG	**46**	**44**	**6**	**651**	**7.1**
R S2	**64**	**-24**	**36**	**449**	**7.7**
L PCC	**-8**	**-30**	**42**	**275**	**5.3**
L S2	**-60**	**-30**	**38**	**1720**	**12.3**
AMCC	**2**	**0**	**36**	**261**	**7.9**
R Insula	**38**	**2**	**-12**	**391**	**7.6**
L EBA	**-44**	**-56**	**-6**	**865**	**7.5**
L OFC	**-34**	**38**	**-14**	**184**	**6.1**
L PM	**-44**	**10**	**20**	**421**	**7.6**
L MFG	**-42**	**40**	**16**	**1016**	**10.9**
L PM	**-20**	**4**	**58**	**166**	**4.0**
R OFC	**24**	**28**	**-12**	**71**	**5.2**
R PCC	**16**	**-26**	**40**	**96**	**5.7**
L PC	-20	-66	42	92	5.8
L S1	-14	-52	66	91	5.5
R PM	50	12	18	78	5.1

Table 2. Effect of Task Demand: Emotional Pain. Brain regions active while reading about others' emotional pain (EP) during the 'empathize' task demand (EP_{emp}) versus the 'objective' task demand (EP_{obj}). Brain regions, MNI coordinates, cluster extent and peak t-value presented for each contrast in each study. Bold type indicates regions identified in both Studies 1 and 2. Data from Studies 1 and 2 are reported at an uncorrected voxelwise threshold of $p < 0.001$, k > 10); Combined Data are reported correcting for multiple comparisons for the peak and cluster size, $p < 0.05$. Parahipp = parahippocampus, Hipp = hippocampus, STS = superior temporal sulcus, LPFC = lateral prefrontal cortex, ACC = anterior cingulate cortex, OFC = orbitofrontal cortex, AI = anterior insula, VS = ventral striatum.

Study 1: EPemp>EPobj

Region	x	y	z	voxels	*t*
L Amygdala	**-14**	**-6**	**-14**	**55**	**6.4**
R Amygdala	**20**	**0**	**-18**	**26**	**4.0**
L Parahipp	-16	-28	-12	16	4.2
L Parahipp	-12	-38	-4	37	4.1
L STS	-58	-30	2	149	4.1
L Inf Parietal	-36	-60	22	58	3.9
L Hipp	-32	-16	-10	15	3.5
L Striatum	-20	0	-4	10	3.4

Study 2: EPemp>EPobj

Region	x	y	z	voxels	*t*
L Amygdala	**-18**	**-2**	**-14**	**14**	**3.5**
R Amygdala	**26**	**2**	**-14**	**16**	**5.0**

Study 1: EPobj>EPemp

Region	x	y	z	voxels	*t*
R LPFC	**38**	**46**	**16**	**92**	**4.5**
R LPFC	**32**	**14**	**38**	**19**	**3.8**
R LPFC	**36**	**56**	**4**	**15**	**3.4**

Study 2: EPobj> EPem

Region	x	y	z	voxels	*t*
R LPFC	**32**	**36**	**36**	**45**	**5.8**
R LPFC	**42**	**12**	**46**	**31**	**4.1**
R LPFC	**46**	**32**	**2**	**24**	**5.0**
dACC	4	26	46	182	5.3
ACC	8	38	28		4.2
pCC	2	-24	42	10	4.6
R OFC	18	52	-16	13	4.5
R Hipp	16	-20	-24	11	4.5
L AI	-16	32	-20	22	4.4
R MFG	58	16	10	46	4.3
L VS	-8	20	-16	10	4.2
R Sup Parietal	52	-50	36	10	4.1
L OFC	-20	52	-12	16	4.1

Table 3. Effect of Task Demand: Physical Pain. Brain regions generated while reading about others' physical pain (PP) during the 'empathize' task demand (PP_{emp}) versus the 'objective' task demand (PP_{obj}). Brain regions, MNI coordinates, cluster extent and peak t-value presented for each contrast in each study. Bold type indicates regions identified in both Studies 1 and 2. Data from Studies 1 and 2 are reported at an uncorrected voxelwise threshold of $p < 0.001$, k > 10); Combined Data are reported correcting for multiple comparisons for the peak and cluster size, $p < 0.05$. PM = premotor, EBA = extrastriate body area, S2 = secondary sensory, AI = anterior insula, ACC = anterior cingulate cortex, LPFC = lateral prefrontal cortex, MFG = middle frontal gyrus, TPJ = temporoparietal junction, OFC = orbitofrontal cortex, PC = precuneus.

Study 1: PPemp>PPobj

Region	x	y	z	voxels	*t*
L PM	-58	10	22	24	3.8
L EBA	-58	-66	0	14	3.6
L S2	-62	-16	22	21	3.5

Study 2: PPemp>PPobj

Region	x	y	z	voxels	*t*
no suprathreshold voxels					

Study 1: PPobj>PPemp

Region	x	y	z	voxels	*t*
R AI	**36**	**22**	**-6**	**69**	**4.8**
R aperculum	**48**	**22**	**4**	**23**	**4.4**

Study 2: PPobj>PPemp

Region	x	y	z	voxels	*t*
R AI	**38**	**26**	**-4**	**527**	**7.1**
R aperculum	**50**	**20**	**-2**		**5.7**
ACC	0	20	32	258	6.0
R DLPFC	44	20	50	121	5.7
R MFG	32	56	18	49	5.4
Pons	6	-6	-22	16	5.3
R LPFC	56	18	28	26	5.2
R TPJ	52	-30	34	101	5.1
R OFC	30	52	-16	14	5.1
PC	6	-70	36	20	4.9
L AI	-36	16	4	95	4.9

Table 4. Psychophysiological Interaction Analysis. Brain regions positively and negatively coupled with amygdala activity while reading stories involving others in emotional pain (EP) versus physical pain (PP). Brain regions, MNI coordinates, cluster extent and peak t-value presented for each contrast in each study. Bold type indicates regions identified in both Studies 1 and 2. Data from Studies 1 and 2 are reported at an uncorrected voxelwise threshold of $p < 0.001$, k > 10); Combined Data are reported correcting for multiple comparisons for the peak and cluster size, $p < 0.05$. PC = precuneus, TPJ = temporoparietal junction, aSTS = anterior superior temporal sulcus, S1 = primary sensory cortex, LPFC = lateral prefrontal cortex, OFC = orbitofrontal cortex, VS = ventral striatum, Hipp = hippocampus, S2 = secondary sensory, AMCC = anterior middle cingulate cortex, MFG = middle frontal gyrus, AI = anterior insula, EBA = extrastriate body area, VC = visual cortex.

Study 1: PPI EP>PP - positive

Region	x	y	z	voxels	*t*
PC	**6**	**-46**	**30**	**853**	**8.6**
RTPJ	**58**	**-58**	**24**	**254**	**7.6**
R aSTS	**60**	**-8**	**-22**	**224**	**6.3**
L STS	**-50**	**-42**	**0**	**73**	**5.4**
L aSTS	**-64**	**-6**	**-12**	**10**	**4.6**
LTPJ	**-38**	**-54**	**26**	**124**	**4.6**
L DLPFC	-12	38	48	23	4.2
R S1	12	-38	68	175	5.2
R DLPFC	26	24	40	94	3.7

Study 2: PPI EP>PP - positive

Region	x	y	z	voxels	*t*
PC	**4**	**-60**	**40**	**132**	**4.8**
RTPJ	**60**	**-60**	**26**	**221**	**4.5**
R aSTS	**58**	**0**	**-18**	**11**	**3.8**
L STS	**-42**	**-32**	**12**	**60**	**4.6**
L aSTS	**-48**	**-14**	**-12**	**10**	**5.3**
LTPJ	**-48**	**-58**	**24**	**86**	**3.9**
L OFC	-14	48	-22	48	5.8
R OFC	6	52	-20	24	4.9
VS	6	12	-10	17	5.2
Hipp	30	-10	-24	10	4.4

Study 1: PPI EP>PP - negative

Region	x	y	z	voxels	*t*
L S2	**-52**	**-30**	**38**	**102**	**6.0**
AMCC	**4**	**0**	**38**	**48**	**5.7**
L MFG	**-38**	**40**	**14**	**40**	**5.1**
L EBA	**-56**	**-54**	**-15**	**12**	**4.4**
L PM	-48	6	16	187	6.0
R PM	62	12	16	14	5.2
R Amygdala	22	2	-18	18	5.0
R AI	38	18	0	30	4.7
AMCC	-2	8	30	19	4.6
R PM	58	16	28	30	4.5
R MFG	38	42	22	11	4.2

Study 2: PPI EP>PP - negative

Region	x	y	z	voxels	*t*
L S2	**-62**	**-30**	**38**	**265**	**5.1**
AMCC	**-8**	**-4**	**30**	**13**	**5.3**
L MFG	**-38**	**32**	**8**	**49**	**5.6**
L EBA	**-50**	**-60**	**-6**	**94**	**5.6**
R EBA	48	-38	-18	93	6.2
R Striatum	18	2	10		
VC	8	-90	-18	12	5.6
dACC	2	26	46	41	5.1
L SMA	-22	8	60	25	4.9
L AMCC	-18	-12	20	18	4.8

Figures and legends

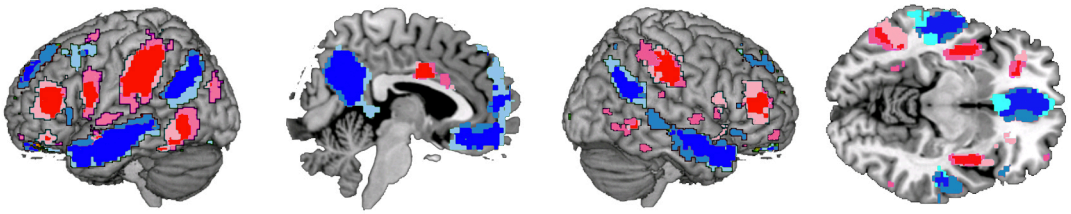

Figure 1. Neural activity associated with reading about others' physical pain and emotional pain. Neural activity identified using group-level analyses and contrasts of emotional pain versus physical pain for Study 1 (lightest blue), Study 2 (medium blue) and their conjunction (darkest blue), and for physical pain versus emotional pain for Study 1 (light pink), Study 2 (dark pink) and their conjunction (red). Across studies, reading about others in emotional pain (versus physical pain) was associated with activity in brain regions associated with mentalizing (bilateral temporoparietal junction (TPJ), precuneus (PC), medial prefrontal cortex (MPFC)), while reading about others in physical pain (versus emotional pain) was associated with activity in the extended pain matrix, including anterior middle cingulate cortex (AMCC), bilateral insulae, secondary sensory (S2) and extrastriate body area (EBA). All results presented at a threshold of $p < 0.001$, uncorrected.

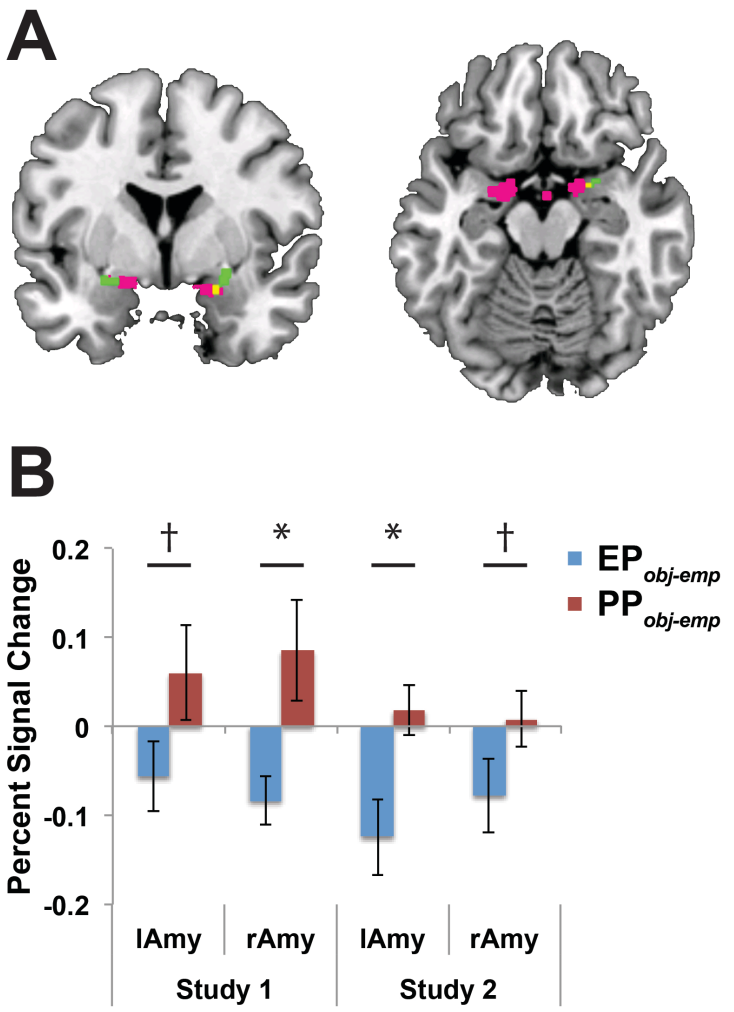

Figure 2. Neural activity associated with empathic control while reading stories about others in emotional pain. (A) Neural activity identified using group responses to stories involving emotional pain under the 'empathize' versus 'objective' task demands in Study 1 (purple) and Study 2 (green) and their conjunction (yellow). Across both studies, actively controlling empathy while reading stories about others' emotional pain ($EP_{obj} > EP_{emp}$) resulted in de-activation in bilateral amygdala. Results presented at a threshold of $p < 0.001$, $k > 10$. **(B)** The effect of empathic control on activity in anatomically defined amygdala regions of interest for stories involving emotional pain ($EP_{obj} > EP_{emp}$) and stories involving physical pain ($PP_{obj} > PP_{emp}$). * $p < 0.05$, † $p < 0.10$, EP versus PP interaction.

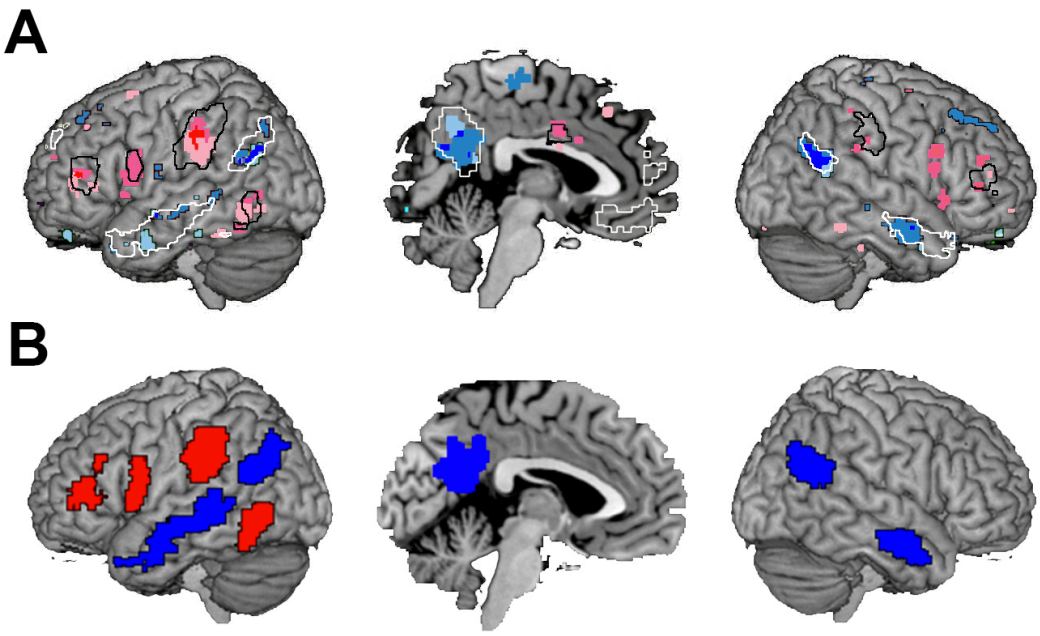

Figure 3. Psychophysical interaction (PPI) analysis. (A) Neural activity across the whole brain shows regions where activity covaried positively with bilateral amygdala during EP versus PP for Study 1 (lightest blue), Study 2 (darker blue) and their conjunction (darkest blue), or where activity covaried negatively with bilateral amygdala in Study 1 (light pink), Study 2 (dark pink) and their conjunction (red). Outlines show regions of conjunction from Figure 1 for EP > PP (white outlines) and PP > EP (black outlines). Positive correlations were observed in regions associated with EP > PP: bilateral temporoparietal junction (TPJ), anterior superior temporal sulcus (aSTS) and precuneus (PC), and negative correlations were observed in regions associated with PP > EP: (anterior middle cingulate cortex (AMCC), left secondary sensory (S2), left premotor, left middle frontal gyrus (MFG), left extrastriate body area (EBA)) and regions in the lateral prefrontal cortex (LPFC) associated with cognitive control. Results presented at a threshold of $p < 0.001$, k > 10. **(B)** Neural activity across the whole brain shows regions where activity covaried positively with bilateral amygdala during EP versus PP for the full dataset. Results voxel-cluster corrected using Monte Carlo based permutations (SnPM, $p < 0.05$).

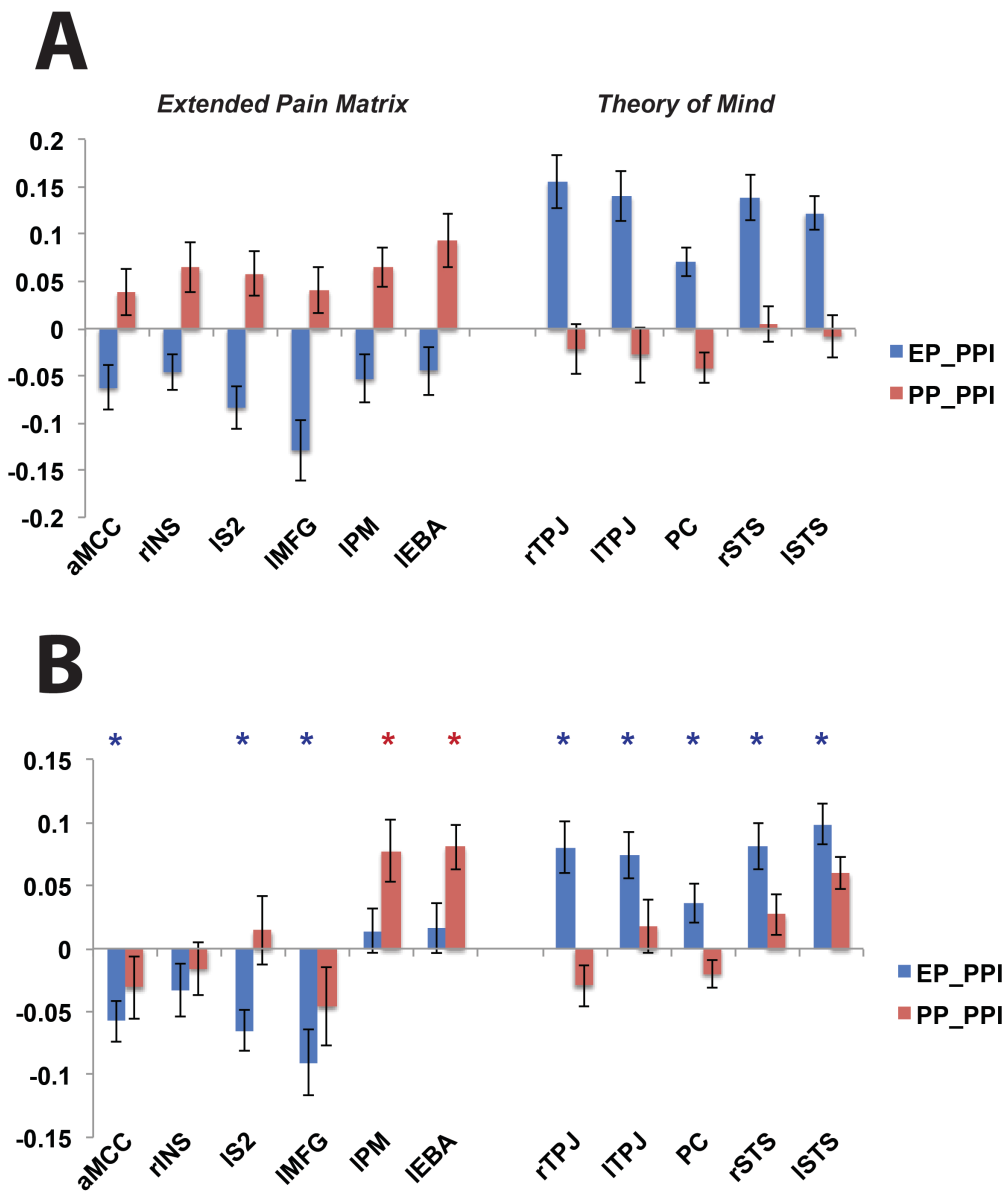

Figure 4. Response in regions identified through PPI to both EP and PP stimuli. Brain regions identified in Study 1 to be positive or negatively coupled with amygdala activity during EP versus PP were used as group ROIs for exploratory non-independent analysis in Study 1 **(A)**, and confirmatory analysis with the separate dataset from Study 2 **(B)**. Beta responses in these brain regions were calculated for both EP and PP conditions in order to determine which was driving the PPI effect. * $p < 0.05$; color of * indicates significance for EP (blue) or PP (red). Significance only reported for confirmatory analysis in Study 2. LPFC = lateral prefrontal cortex, STS = superior temporal sulcus, TPJ = temporoparietal junction, PC = precuneus, AMCC = anterior middle cingulate cortex, EBA = extrastriate body area, MFG = middle frontal gyrus, PM = premotor, S2 = secondary sensory, INS = insula.

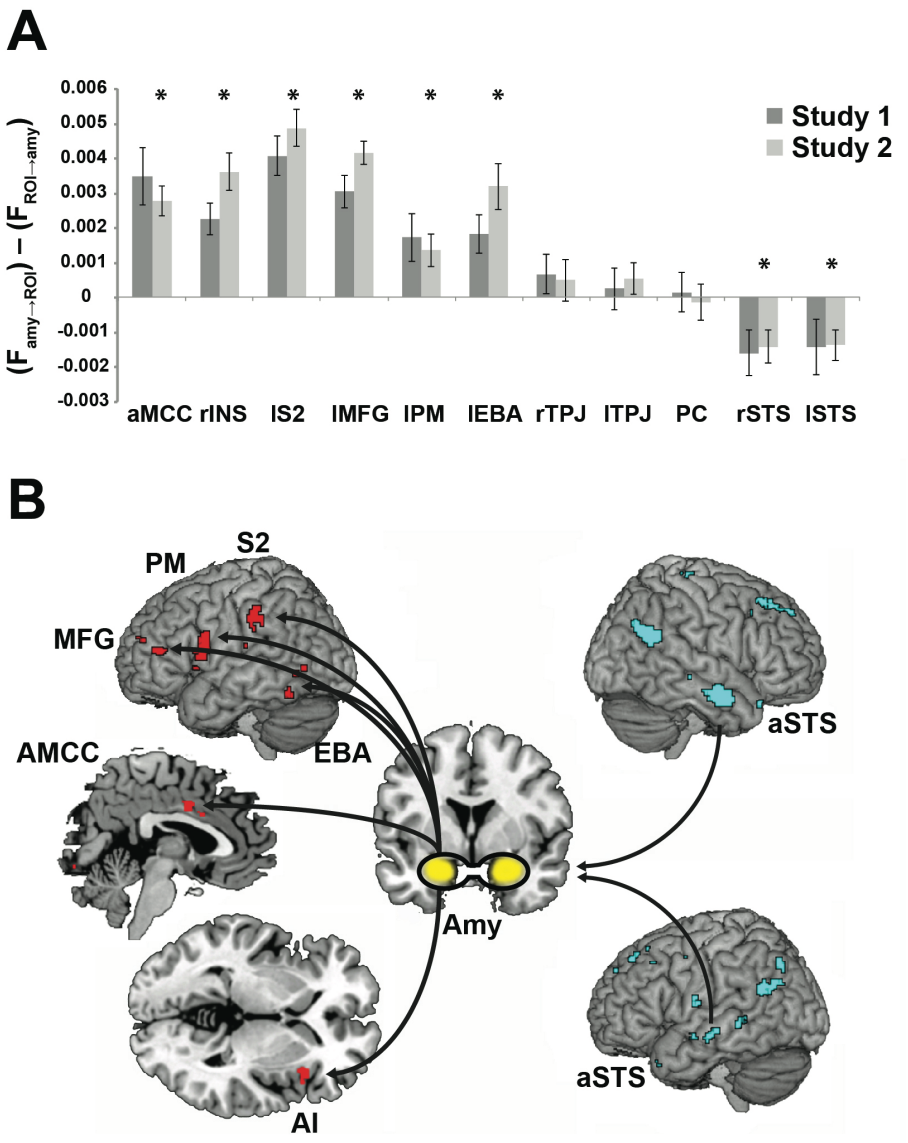

Figure 5. Granger Causality Modeling (GCM). (A) Difference between G-causality of Amygdala→ROI and ROI→Amygdala across participants in all ROIs from Study 1 (dark gray) and Study 2 (light gray). All ROIs were picked from the group analysis of the PPI data from Study 1 at $p < 0.001$, uncorrected, and used for exploratory non-independent analysis in Study 1, and confirmatory analysis with the separate dataset from Study 2. * $p < 0.05$, one-sample t-test (significance only reported for confirmatory analysis in Study 2). **(B)** Illustrative view of regions and direction of influence. Brain regions showing differential functional connectivity with the amygdala during the two conditions, in Study 1 (PP>EP in red and EP>PP in cyan). Direction of arrows denotes GCM direction of influence, measured in Study 2 ($p < 0.05$). Note that left and right amygdalae were treated together as a single ROI. aSTS = anterior superior temporal sulcus, TPJ = temporoparietal junction, PC = precuneus, AMCC = anterior middle cingulate cortex, EBA = extrastriate body area, MFG = middle frontal gyrus, PM = premotor, S2 = secondary sensory, INS = insula.

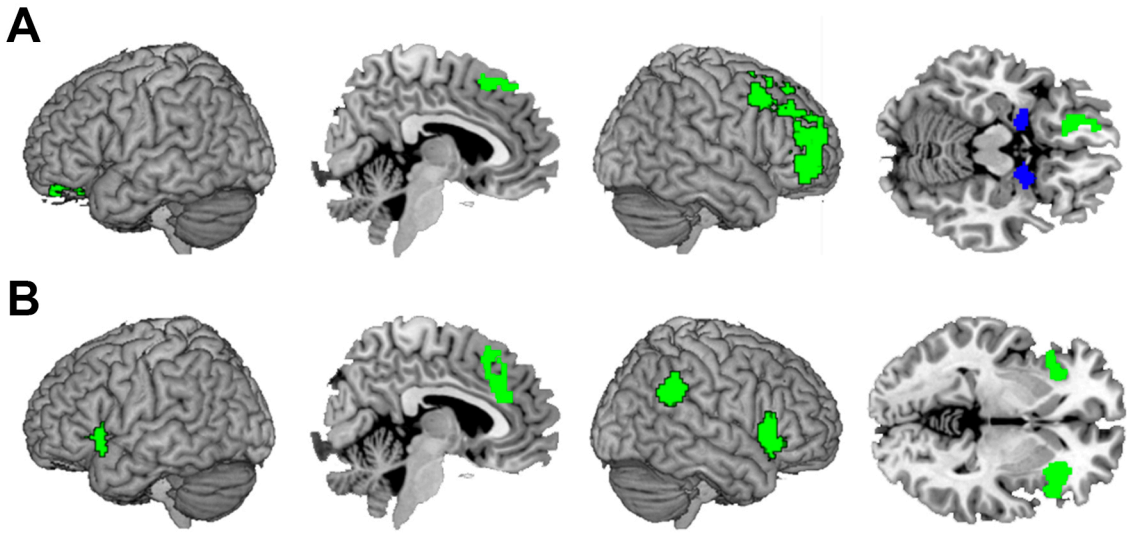

Figure 6. Brain regions associated with empathic control while reading about EP or PP. (A) Neural activity identified using the combined data from Studies 1 and 2 to stories involving emotional pain (EP) under the 'empathize' versus 'objective' task demands. Regions dampened during empathic control ($EP_{emp} > EP_{obj}$) shown in blue; regions enhanced during empathic control ($EP_{obj} > EP_{emp}$) shown in green. **(B)** Neural activity identified using the combined data from Studies 1 and 2 to stories involving physical pain (PP) under the 'empathize' versus 'objective' task demands. No regions were dampened during empathic control ($PP_{emp} > PP_{obj}$); regions enhanced during empathic control ($PP_{obj} > PP_{emp}$) shown in green. All results voxel-cluster corrected using Monte Carlo simulation using SnPM ($p < 0.05$).

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