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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.

Keywords

fMRI, empathy, physical pain, emotional suffering, cognitive control, social distancing, psychophysiological interaction, PPI, Granger causality modeling, GCM

Disciplines

Biological Psychology | Cognition and Perception | Cognitive Psychology | Communication | Neuroscience and Neurobiology | Personality and Social Contexts | Social and Behavioral Sciences | Social Psychology

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

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1 **Abstract**

2

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

23

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

27

1

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

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

21

22 **The Amygdala**

23

24 The amygdala is best known for its role in mammalian fear conditioning,
25 facilitating the learning, encoding and expression of negative associations (LeDoux,
26 2003). In humans the amygdala responds to a wide range of emotionally salient stimuli,
27 particularly distressing stimuli associated with threat (Zald, 2003), such as fearful or
28 angry faces (Hariri et al., 2002; LeDoux, 2003; Whalen et al., 2001), threatening images
29 (Anticevic et al., 2012; Eippert et al., 2007), the threat of physical pain (Simons et al.,
30 2014; Wager et al., 2004), and even threatening words (Hamann and Mao, 2002; Isenberg
31 et al., 1999; Laeger et al., 2012; Straube et al., 2011). People with amygdala lesions

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

5 Importantly, activity in the amygdala is subject to deliberate control. When
6 instructed to decrease emotional responses to aversive stimuli – for example, through
7 changing the construal of an upsetting stimulus to make it more neutral (Ochsner et al.,
8 2002), or through psychologically distancing themselves from the emotional event
9 (Ochsner et al., 2004b) – participants report less distress and show decreased amygdala
10 activity. Dampening emotional responses to distressing stimuli is also associated with
11 increased activity in regions within the ventromedial and lateral prefrontal cortex
12 (VMPFC, LPFC), and the anterior cingulate cortex (ACC) (Ochsner et al., 2004b; Phan et
13 al., 2005; Urry et al., 2006), leading to a dominant view that emotional responses are
14 generated by the amygdala and other sub-cortical and cortical structures (especially the
15 nucleus accumbens and ventromedial prefrontal cortex), and controlled by top-down
16 input from regions within the ventral, lateral and medial prefrontal and anterior cingulate
17 cortex (Ochsner et al., 2012). Neuroimaging support for this model comes from both
18 resting state and task-induced functional connectivity studies. At rest, the amygdala is
19 negatively coupled with LPFC and dorsal ACC, and positively coupled with MPFC
20 (Henckens et al., 2012; Mishra et al., 2014; Robinson et al., 2010; Yue et al., 2013),
21 though this pattern varies across amygdala sub-regions (Roy et al., 2009). Resting state
22 coupling is also disrupted in psychiatric conditions associated with dysregulated fear and
23 threat, such as schizophrenia, social anxiety and post-traumatic stress disorder (Blackford
24 et al., 2014; Brown et al., 2013; Unschuld et al., 2014). During deliberate reappraisal of
25 negative emotional stimuli, psychophysiological interaction (PPI) analysis shows
26 increased inverse coupling between amygdala and regions in the LPFC, anterior cingulate
27 cortex (ACC) and dorsal ACC (Banks et al., 2007; Lee et al., 2012; Yue et al., 2013). In
28 sum, the amygdala is implicated in processing emotionally evocative stimuli, and is
29 strongly and inversely coupled, both at rest and during emotional evaluation tasks, with
30 regions in the medial and lateral PFC, and the dorsal ACC.

31

1 **Amygdala and Empathy**

2

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

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

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

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

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

25

26 **Current Study**

27

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

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

6 7 **Study 1**

8 9 **Methods**

10 11 **Participants**

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

19 **Design and Materials**

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

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

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

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

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

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

16 **Image Acquisition and Analysis**

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

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

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

1 signal differences between conditions (linear combinations of the beta parameters for
2 condition covariates) were submitted to second level, random-effects analysis. We
3 focused on main effects of condition (EP<>PP), and effects of task demand on each
4 condition (EP_{obj} <> EP_{emp}; PP_{obj} <> PP_{emp}). In Experiment 1, these analyses were
5 exploratory, and were conducted using SPM with an uncorrected voxelwise threshold of
6 $p < 0.001$, with a minimum of 10 contiguous supra-threshold voxels. We also report the
7 results of the same contrasts on the complete data set, correcting for multiple
8 comparisons by performing Monte Carlo permutation tests to establish empirical null
9 distributions for the peak T and cluster size in each analysis ($p < 0.05$, SnPM, Nichols and
10 Holmes, 2002; Hayasaka and Nichols, 2004; see ‘Combined Data’ following Experiment
11 2). All peak voxels are reported in MNI coordinates.

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

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

1 Finally, having identified a number of brain regions whose activity was associated
2 with amygdala activity, we examined the direction of effective connectivity between
3 these brain regions using Granger Causal Modeling. For this analysis, we used ROIs
4 derived from the whole brain analyses of the effect of task demand, and from the PPI
5 analysis. For each subject, the timecourse was extracted from all the ROIs from all
6 functional runs and multiplied by the EP (or PP) regressor to limit the connectivity
7 analysis to the intervals of one task condition. The timeseries were then normalized by
8 subtraction of mean and division by standard deviation and then concatenated across runs
9 to create a single timecourse per subject per ROI. We used the Granger Causality toolbox
10 (Barnett and Seth, 2014) to compute the bivariate Granger causality from Amygdala to all
11 other ROIs and all ROIs to Amygdala. For each Amygdala:ROI pair, and each direction
12 of influence, we computed the difference in explained variance between the full-model
13 (including the seed and target regions responses at t-1) and the reduced model (including
14 only the seed region at t-1, i.e. the autoregressive model; Ding et al., 2006). We then
15 tested whether the direction of greater influence (i.e. Amygdala→ROI or
16 ROI→Amygdala) was consistent across subjects, during EP stories. A reliable
17 asymmetry in the direction of influence provides evidence that the inferred GC is not
18 simply an artifact of a temporally synchronous correlation between two noisy, auto-
19 correlated timeseries. For regions in which the direction of influence was consistent, we
20 tested whether this effect was selective for EP stories, by comparing the strength of
21 Granger causality between the same pair of regions in the same direction, during EP
22 versus PP stories. GCM has been criticized because spurious results can be driven by
23 differences in the hemodynamic response function or vasculature across brain regions
24 (Webb et al., 2013). By determining whether Granger Causality between a pair of regions
25 is specific to one condition versus another, we control for confounds associated with
26 heterogeneity associated with vascularization and hemodynamics across brain regions.

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

1 **Results**

2

3 *Behavioral:*

4 Participant responses were analyzed using a 2 condition (EP vs PP) x 2 task
5 demand (Empathize vs Objective) within-subject ANOVA. Participants reported feeling
6 more empathy for targets during the Empathize ($M = 2.91, SD = 0.65$) versus Objective
7 ($M = 2.13, SD = 0.58$) tasks (main effect of condition, $F(1,17) = 37.6, p < 0.001, \eta^2 =$
8 0.69). Reported empathy was higher during emotional pain (EP) ($M = 2.69, SD = 0.50$)
9 versus physical pain (PP) conditions ($M = 2.35, SD = 0.54$) (main effect of condition,
10 $F(1,17) = 9.6, p = 0.007, \eta^2 = 0.36$); there was no significant condition x task interaction
11 ($F(1,17) = 0.5, p > 0.45$). Note that mean self-reports were lower than previously
12 published (Bruneau et al., 2012b), likely because half of the conditions here asked that
13 participants disengage their empathy.

14

15 *Neuroimaging:*

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

27

28 *Figure 1, Table 1 about here*

29

30 Also replicating previous work (Bruneau et al., 2013; Corradi-Dell'Acqua et al.,
31 2013), a similar pattern of activity was observed when we examined neural responses that

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

3 Next, we turned to the main contrast of interest: the effect of task demand
4 (remaining objective (obj) versus empathizing (emp)) on neural responses to others in
5 physical pain and emotional suffering. To determine if empathic control (obj > emp) of
6 EP and PP were associated with activity in similar or distinct brain regions, we looked at
7 objective versus empathize tasks separately in the EP and PP conditions. For the EP
8 scenarios, instructions to control empathic responses versus empathize ($EP_{obj} > EP_{emp}$)
9 resulted in increased activity across right lateral prefrontal cortex, and decreased activity
10 in the amygdala, bilaterally, and regions along the left STS, left
11 hippocampus/parahippocampus and left visual cortex (Figure 2, Table 2). By contrast,
12

13
14 *Figure 2, Table 2 about here*

15
16 empathic control in response to physically painful scenarios ($PP_{obj} > PP_{emp}$) resulted in
17 activity in the right anterior insula and a region of the right lateral prefrontal cortex
18 distinct from that observed for EP (Table 3) and decreased activity in small regions in
19 primary and secondary sensory/motor cortex. There were no significantly de-activated
20 voxels in amygdala for the $PP_{obj} > PP_{emp}$ contrast (Table 3), even at a relaxed threshold of
21 $p < 0.05$, uncorrected. These results suggest that empathic control affects amygdala
22 activity, but only when empathizing with emotional (and not physical) experiences. We
23 followed up on this suggestion in two subsequent analyses.
24

25
26 *Table 3 about here*

27
28 First, we measured activity in anatomically defined amygdala regions of interest
29 (ROIs). The left and right amygdalae were sensitive to task demand only when presented
30 with EP stories: there was a significant interaction between condition and task demand in
31 right amygdala (repeated measures ANOVA, $F(1,17) = 10.4$, $p = 0.005$, $\eta^2 = 0.38$) and a

1 trend in the same direction in the left amygdala ($F(1,17) = 3.1, p < 0.10, \eta^2 = 0.16$)
2 (Figure 2; for mean responses across conditions, see Supplemental Figure 2). Planned
3 post-hoc paired t-tests revealed that amygdala activity was greater for EP_{emp} than EP_{obj} in
4 right amygdala ($t(17) = 3.1, p = 0.007$), but not in left amygdala ($t(17) = 1.5, p = 0.16$).
5 By contrast, the effect of task demand during PP stories was slightly, but not
6 significantly, and in the opposite direction (left: $t(17) = 1.1, p = 0.28$; right: $t(17) = 1.5, p$
7 $= 0.16$).

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

20

21

22

Figure 3, Table 4 about here

23

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

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

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

20
21 *Figure 4 about here*

22
23 Finally, in order to characterize the effective connectivity between amygdala and
24 the ToM and extended pain matrix brain regions, we turned to Granger Causal Modeling.
25 GCM examines how well prior activity (t-1) in one (seed) region can predict current
26 activity (t) in another (target) region, after taking into account the autocorrelation (t-1) in
27 the target region. We tested whether any of the regions identified by the PPI analysis
28 showed a reliably asymmetric GC predictive relationship with the amygdala. Of the ToM
29 brain regions, only the right STS showed a reliably asymmetric GC relationship with the
30 amygdala: during EP, right STS activity was more predictive of amygdala activity than
31 the reverse. By contrast, all of the extended pain matrix brain regions (AMCC, right

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

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

10
11
12 *Figure 5 about here*
13
14

15 **Discussion**

16
17 Study 1 replicated previous work using the same physically and emotionally
18 painful scenarios: reading about others in physical pain (versus emotional pain) activates
19 regions associated with bodily sensations/motion (bilateral secondary sensory, EBA), as
20 well as the primary components of the ‘pain matrix’ (bilateral insula, AMCC), while
21 reading about others in emotional pain (versus physical pain) activates regions associated
22 with mentalizing: bilateral TPJ extending down the anterior STS, PC, MPFC (Bruneau et
23 al., 2013; Bruneau et al., 2012b).

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

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

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

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

22 23 **Study 2**

24
25 In Study 2, we aimed to replicate the results from Study 1 in a group of
26 participants with extraordinary experience with human suffering: trained social workers.
27 As experts in empathic control, we reasoned that social workers might be particularly
28 able to comply with the task demands, and thus would increase the power of the
29 experiment to reveal the neural mechanisms underlying empathic control. The main goal
30 of this experiment was thus to test the replicability of the results of Study 1; in addition,
31 we tested whether expertise and training in empathic control lead to differences in the

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

4 5 **Methods**

6 7 **Participants**

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

18 **Design and Materials**

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

21 First, participants performed a theory of mind localizer task (Dodell-Feder et al.,
22 2011) after the completion of the main experiment. Second, after the neuroimaging study,
23 participants rated the EP and PP stimuli they had seen inside the scanner for the amount
24 of personal distress and empathic concern they elicited (Batson et al., 1997).

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

27 28 **Results**

29
30 *Behavioral:*

1 Using a 2 condition (EP, PP) x 2 task demand (Empathize, Objective) ANOVA,
2 we found that participants reported feeling more empathy for targets during the
3 Empathize ($M = 3.40$, $SD = 0.31$) versus Objective ($M = 2.51$, $SD = 0.59$) task blocks
4 (main effect of demand, $F(1,17) = 46.5.6$, $p < 0.001$, $\eta^2 = 0.73$). Empathy ratings were
5 slightly higher for stories about emotional pain (EP) ($M = 3.14$, $SD = 0.41$) than physical
6 pain (PP) ($M = 2.77$, $SD = 0.42$) (main effect of condition, $F(1,17) = 19.0$, $p < 0.001$, $\eta^2 =$
7 0.53); there was no significant condition x task interaction ($F(1,17) = 0.1$, $p > 0.70$).

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

14 *Neuroimaging:*

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

23 Also replicating Study 1, instructions to remain objective versus empathize in the
24 EP scenarios ($EP_{obj} > EP_{emp}$) resulted in increased activity across lateral prefrontal cortex,
25 and decreased activity in bilateral amygdala (Figure 2A). Unlike Study 1, the ($EP_{obj} >$
26 EP_{emp}) contrast also yielded increased activity in other regions associated with cognitive
27 control: anterior insula bilaterally (Chang et al., 2012), and dorsal cingulate cortex (Table
28 2).

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

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

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

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

26 Granger causal modeling using the same independent ROIs generated in Study 1
27 revealed the same, and even stronger, causal relationships as found in Study 1 (see Figure
28 5): activity in right and left STS reliably predicted activity in the amygdala (rather than
29 the reverse) during EP (both $t(20) > 2.9, p < 0.01$), and this relationship was stronger in
30 EP than PP in right STS ($t(20) = 2.6, P < 0.02$) but not left STS ($t(20) = 0.1, n.s.$).
31 Activity in AMCC, right insula, IS2, left MFG, left PM and left EBA were predicted by

1 the amygdala during EP (all $t_s > 2.8$, $p_s < 0.02$); this relationship was stronger in EP than
2 PP in IS2 ($t(20) = 2.9$, $p < 0.01$), but not the other regions (all $t_s < 0.5$).

3 Finally, activity in right LPFC (identified based on the response to $EP_{obj} > EP_{emp}$
4 in Study 1) was also reliably predicted by activity in the amygdala ($t(20) = 11.4$, $p_s <$
5 0.001), although this predictive relationship was not reliably greater in EP than PP ($t(20)$
6 $= 0.7$, n.s.).

8 **Discussion**

10 The main results of Study 2 replicate those of Study 1 in almost every detail,
11 using independent functional ROIs generated from Study 1. First, stories about PP
12 (versus EP) evoked activity in the regions of the extended pain matrix (AMCC, insula,
13 S2, and PM, MFG, EBA), while stories about EP (versus PP) evoked activity in the ToM
14 network (TPJ, PC, anterior STS, MPFC). Second, empathic control resulted in increased
15 right LPFC activity during both PP and EP stories, but decreased amygdala activity only
16 during EP stories. Third, activity in ToM regions was positively coupled to, and
17 predicted, amygdala activity during EP, and activity in extended pain matrix regions was
18 negatively coupled to, and predicted by, the amygdala during EP. Finally, just as in Study
19 1, activity in the amygdala preceded and predicted activity in the right LPFC.

21 **Combined Data**

23 One benefit of two independent datasets is that exploratory analyses in the first
24 dataset can be used to generate specific hypotheses that are then tested with confirmatory
25 analyses in independent data; independent confirmatory tests are particularly compelling
26 for functional and effective connectivity, where replications are rare. At the same time,
27 neuroimaging studies with limited numbers of participants suffer from low-powered
28 analyses, potentially masking real effects. In order to perform higher-powered analyses
29 on the neuroimaging data, and to explore possible differences between the two groups of
30 participants, we also conducted analyses on the combined sample of participants ($N =$
31 39).

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

4 5 **Results**

6
7 In the behavioral data, social workers (Study 2) reported higher levels of empathy
8 overall compared to control participants (Study 1; $F(1,34) = 9.4$, $p = 0.004$, $\eta^2 = 0.22$),
9 but there were no significant interactions between Study and condition, task demand or
10 condition x task demand (all F s < 0.5 , all p s > 0.4).

11 Combining the fMRI results across studies, deliberate control of empathy for
12 emotional pain ($EP_{obj} > EP_{emp}$) resulted in decreased activity in the bilateral amygdala
13 and the left hippocampus/parahippocampus, and increased activity in right LPFC, dorsal
14 ACC, and left orbitofrontal cortex (OFC) (corrected for multiple comparisons using
15 Monte Carlo based permutations, $p < 0.05$; Figure 6A; Table 5). By contrast, deliberate
16 control of empathy for physical pain ($PP_{obj} > PP_{emp}$) did not result in decreased activity in
17 any brain regions, and resulted in increased activity in bilateral anterior insula, dorsal and
18 anterior ACC, right OFC, and right TPJ (Figure 6B; Table 5). The interaction between
19 empathic control of emotional pain and empathic control of physical pain ($EP_{emp} > EP_{obj}$)
20 $> (PP_{emp} > PP_{obj})$ yielded a single region of significance, in the left amygdala (MNI: -18, -
21 2, -14; peak T : 5.5; extent: 121 voxels); there were no suprathreshold voxels for any
22 other interaction.

23 In the PPI analysis (also corrected for multiple comparisons using Monte Carlo
24 based permutations, $p < 0.05$) the amygdala was more strongly associated during EP
25 (versus PP) with regions in the theory of mind network (bilateral TPJ, PC, bilateral
26 anterior STS), and more strongly associated during PP (versus EP) with regions of the
27 extended pain matrix (AMCC, right Insula, left S2, left MFG, left PM, left EBA; Figure
28 3B). This pattern held when examining left and right amygdala separately (Supplemental
29 Figure 3).

30 Finally, we compared neural responses directly between the two Experiments for
31 the main contrast of interest ($EP_{obj} > EP_{emp}$); since participants in Study 2 were older than

1 those in Study 1, we included age as a covariate in the analysis. Activity during empathic
2 control ($EP_{obj} > EP_{emp}$) was greater for social workers in the right anterior insula (38, 32,
3 0; peak T: 4.4), left anterior insula/orbitofrontal cortex (-28, 16, -14; peak T: 4.2), left
4 hippocampus (-24, -28, -10; peak T: 4.5), right STS (58, -20, -16; peak T: 3.8) and
5 midbrain/ventral tegmental area (-4, -24, -10, peak T: 4.4) (at a voxelwise threshold of p
6 < 0.001). None of the regions survived corrections for multiple comparisons, indicating
7 that these results are merely suggestive of differences that may warrant further
8 investigation.

9

10 **General Discussion**

11

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

1 These results help resolve seemingly disparate findings from three different
2 empathy-related literatures. First, lesion and pharmacological studies implicate the
3 amygdala in processing others' emotional states. For example, bilateral amygdala lesions
4 impair components of perception that may be integral to empathy for suffering: gaze
5 perception and the recognition of others' emotional expressions (Adolphs et al., 1999;
6 Young et al., 1996), and for a pair of twins, relative to matched neurotypical controls,
7 bilateral amygdala lesions impaired ability their to empathize with others' suffering
8 (Hurlemann et al., 2010). The current results suggest that the amygdala is a critical part of
9 the network involved in marshaling empathic responses to others' negative emotions.

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

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

1 However, one previous study appears to challenge this synthesis. Lamm and
2 colleagues showed participants short video clips of others (actually paid actors)
3 responding to a ‘medical treatment’ that involved painful and unpleasant auditory stimuli
4 (Lamm et al., 2007). While participants were not directly instructed to control neural
5 responses to the stimuli, a condition manipulation led participants to believe that the
6 treatment was either successful or unsuccessful. If the treatment was successful,
7 participants could presumably reappraise patient’s discomfort (i.e. it hurts him now, but
8 he’ll be better for it); a subset of the participants expressed a related form of re-appraisal
9 during debriefing. This study reported decreased amygdala activity in the successful
10 versus unsuccessful treatment condition. Thus, this prior study may have observed
11 decreased amygdala activity during regulation of empathy for physical pain. However,
12 another possibility is that while watching the facial grimaces of the actors, and especially
13 while considering the unsuccessful treatment outcomes, participants experienced
14 empathy for the patient’s inferred emotional suffering (e.g. fear, disappointment).
15 Knowing that the treatment was successful may not have altered the perception of the
16 patient’s physical pain, but may have decreased participant’s empathy for the patient’s
17 emotions, and thus implicated the amygdala. This hypothesis could be tested in future
18 research.

19 The current data suggest a selective role for the amygdala in the empathic
20 regulation of emotional pain. Which brain regions are implicated in the empathic
21 regulation of physical pain? We found that dorsal cingulate, bilateral anterior
22 insula/aperculum, and right TPJ showed increased activity when participants were
23 instructed to remain objective; no region was reliably more activated (across studies)
24 when participants were instructed to respond more empathically to another’s physical
25 pain. However, prior studies have observed reduced activity in the extended pain matrix
26 (especially AMCC and insula) when observing or reading about physical pain
27 experienced by distant versus close or relevant others (a lover versus acquaintance,
28 Cheng et al., 2010; an in-group member versus a member of an unfamiliar out-group,
29 Bruneau et al., 2012a). It seems likely that the portion of the anterior insula activated by
30 these previous studies represents the pain matrix sub-region of the insula, whereas the
31 insula region activated in the current study represents a well-characterized and distinct

1 sub-region within the insula slightly dorsal and anterior to the pain matrix sub-region,
2 known to be sensitive to deliberation and cognitive control (Chang et al., 2012).
3 Understanding why these different sub-regions are seemingly so sensitive to task
4 manipulations that appear to be very similar is a topic that will require further study, for
5 example by examining, within-subject, regulatory responses to empathic control of
6 physical pain using automatic (close versus distant other) versus deliberate ('empathize'
7 versus 'remain objective') processes.

8

9 *Psychophysiological interactions*

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

28 PPI analysis showed that the amygdala was negatively associated with right
29 lateral PFC regions while participants read stories about emotional suffering (EP). That
30 is, in both studies, greater activation in LPFC was associated with reduced activation in
31 the amygdala, but only when the stories described emotional suffering. There was no

1 coupling between LPFC and amygdala when the stories described physical pain. The
2 region of LPFC identified by this analysis overlapped well with a recent meta-analysis of
3 regions involved in emotion regulation (Buhle et al., 2013). The right lateralization of
4 LPFC is also consistent with patterns of activity attributed to specific regulation
5 techniques: while emotion reappraisal tends to elicit activity in left LPFC, social
6 distancing (i.e. imagining that the empathy target is a stranger versus a close friend) tends
7 to generate activity in right LPFC (Erk et al., 2010). Thus, deliberate control of empathic
8 responses to suffering may depend on the interaction of the amygdala with a specific
9 region of right LPFC involved in cognitive control through social distancing.

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

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

26 In Experiment 2 the amygdala was also positively coupled during EP with
27 VMPFC and Ventral Striatum (VS). This is consistent with a number of studies that have
28 identified the amygdala, VMPFC and VS as a functional network associated with
29 emotional processing (Ochsner et al., 2012). While many studies highlight the role of
30 VMPFC in cognitive control of emotion, recent meta-analytical data support the
31 involvement of dACC and LPFC, but not VMPFC, during cognitive control tasks (Buhle

1 et al., 2013). One possibility is that the VMPFC may not have a direct effect, but may
2 instead mediate the effects of other regions on the amygdala during emotion regulation
3 (Urry et al., 2006).

4 More broadly, it will be important in future studies to compare the current neural
5 distinctions between empathy for pain and suffering with work illustrating distinctions
6 across other dimensions, such as cognitive versus affective empathy. For example, lesion
7 studies have shown a double dissociation between medial and lateral prefrontal cortex
8 damage, and impaired cognitive empathy (trait perspective taking) versus emotional
9 empathy (trait personal distress) assessed with self-report measures (the interpersonal
10 reactivity index (IRI)) (Shamay-Tsoory et al., 2008). Understanding how this
11 cognitive/emotional empathy distinction relates to empathy for pain/suffering and
12 personal distress/empathic concern could potentially be addressed in a study that
13 incorporates stimuli orthogonally varying each of these dimensions.

14 15 *Granger Causal Modeling*

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

1 these conditions are met, as in the current studies, GCM results can provide evidence of a
2 functionally specific asymmetric predictive link between activity in two brain regions.

3 In both experiments, we found that the regions identified in the PPI analysis are
4 not only distinguished by their opposing correlative association with the amygdala, but
5 also by predictive relationships with the amygdala: regions associated with theory of
6 mind (particularly right anterior STS) ‘granger caused’ amygdala activity, while
7 amygdala activity ‘granger-caused’ activity in the extended pain matrix (AMCC, right
8 insula, and left S2, left PM, left MFG, left EBA).

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

23 Perhaps the most surprising result of the GCM analyses is that LPFC activity,
24 which is anti-correlated with amygdala activity during EP stories, was preceded and
25 predicted by amygdala activity. Many previous studies have observed that increased
26 activity in LPFC regions is often accompanied by decreased activity in amygdala; we
27 found a similar pattern in the contrast between remaining objective and actively
28 empathizing. An intuitive interpretation of this anti-correlation is that increased activity
29 of LPFC is causing (through deliberate regulation) the decreased activation in the
30 amygdala (Ochsner et al., 2012). However, the current results suggest that the
31 predominant direction of granger causal influence is the reverse: amygdala activity

1 predicts LPFC activity. While contrary to the assumed direction of causality, it is at least
2 possible that amygdala activity could precede LPFC during empathic regulation:
3 anatomical connections are bidirectional between amygdala and prefrontal cortex, the
4 amygdala is capable of responding to some stimuli (e.g. threat) prior to even visual
5 cortex, and the amygdala is composed of a number of both afferent and efferent nuclei. A
6 more definitive test of the causal association between LPFC and amygdala could
7 potentially be done through direct manipulation of the circuit, for example, with
8 transcranial magnetic stimulation (TMS). In addition, higher resolution imaging of the
9 amygdala may reveal the specific amygdala nuclei involved in empathic control, which
10 would connect to literatures on nucleus specific connectivity.

11

12 *Differences between groups*

13 Our a priori hypothesis was that social workers, who have extraordinary
14 experience with others' emotional suffering, may show behavioral and neural differences
15 in their abilities to regulate empathy, particularly towards others' emotional suffering.
16 However, we found that self-reported empathy in social workers during empathic control
17 (versus actively empathizing) was not distinct from controls, and neural responses during
18 the key contrast (EP_{emp} versus EP_{obj}) were no different from controls, after correcting for
19 multiple comparisons. At a more lenient threshold, social workers did show more activity
20 during empathic control ($EP_{\text{obj}} > EP_{\text{emp}}$) in bilateral anterior insula regions that have been
21 associated with cognitive control (Buhle et al., 2013; Urry et al., 2006). Social workers
22 also showed more activity in hippocampus, which we would predict to arise selectively
23 more in social workers who likely have direct personal experiences controlling empathy
24 for people facing similar situations to those depicted in the emotional pain scenarios, and
25 ventral tegmental area, which may be associated with finding more reward while
26 regulating (rather than engaging) empathy. While these differences were present even
27 after accounting for age, they did not survive corrections for multiple corrections, and
28 should therefore be interpreted with caution. It is possible that the nature of the stimuli
29 failed to reveal real differences between the groups in empathic regulation. For example,
30 more severe examples of emotional pain may be more likely to draw out differences in
31 empathic regulation between groups. In support of this, a number of social workers

1 mentioned during debriefing that the stimuli in the experiment were less severe than their
2 everyday experiences on the job. Further work will need to be done to determine if
3 differences in activity or coupling with amygdala during empathic control are associated
4 with age, training or some other factor, and whether these differences have behavioral
5 consequences. Studies aimed specifically at dissociating these possibilities are currently
6 underway.

7 The relative lack of expertise effects in the current study is seemingly in contrast
8 to previous studies that have examined expertise effects on baseline responses to others'
9 physical pain in Eastern Medicine physicians in China viewing images of body parts
10 being pricked by pins (versus Q-tips). In both ERP (Decety et al., 2010) and fMRI
11 (Cheng et al., 2007) measurements, these physicians showed weaker neural response to
12 the pinpricks than controls in early N110 and late P3 ERP signals, and insula and anterior
13 cingulate hemodynamic responses. However, in these studies the participants observed
14 targets receiving pin pricks reminiscent of acupuncture, in which the physicians (but not
15 the controls) were trained. The subjective measures of the pain intensity and
16 unpleasantness from the stimuli assessed after the study reflected this training: controls
17 interpreted the pinpricks as more than twice as painful as did the acupuncture specialists.
18 It is therefore difficult to determine how much of the difference in activity was due to
19 insensitivity to others' pain, or to privileged information (i.e. that acupuncture pinpricks
20 are, in fact, not very painful).

21

22 *Conclusions*

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

1 empathy paradigms ask participants to empathize with others' emotional pain, while
2 other paradigms require empathy for others' physical pain.

3 Across two studies, one with control participant and one with professional social
4 workers, we examined the effect of deliberate regulation of empathy on neural activity.
5 We found that regulating empathy for equally distressing stories about others' pain and
6 suffering resulted in very different patterns of neural activity: consistent across both
7 independent samples, the regulation of empathy for suffering activated regions in the
8 right LPFC, and deactivated bilateral amygdala, while regulation of empathy for physical
9 pain activated largely distinct regions including a region in anterior insula, and had no
10 effect on amygdala. Amygdala activity while reading about others' emotional suffering
11 was positively associated with activity in a number of theory of mind brain regions,
12 particularly the anterior STS, and was negatively associated with regions in the extended
13 pain matrix. Together, these data provide insight into the mechanisms of empathic
14 control, and offer further evidence for the neural dissociation of empathy for others' pain
15 versus their suffering.

16

17 **Acknowledgments**

18

19 The authors wish to thank Adele Luta for her help recruiting and running
20 participants, and William Johnston for his technical support. This work was supported by
21 a grant from Defense Advanced Research Projects Agency (DARPA) #D12AP00077.

22

1 **Tables and captions**

2

3 **Table 1.** Brain regions active while reading about others' emotional pain (EP) versus
 4 physical pain (PP). Brain regions, MNI coordinates, cluster extent and peak t-value
 5 presented for each contrast in each study. Bold type indicates regions identified in both
 6 Studies 1 and 2. Data from Studies 1 and 2 are reported at an uncorrected voxelwise
 7 threshold of $p < 0.001$, $k > 10$). MT = middle temporal lobe, TPJ = temporoparietal
 8 junction, MPFC = medial prefrontal cortex, PM = premotor, FFA = fusiform face area,
 9 Hipp = hippocampus, MFG = middle frontal gyrus, S2 = secondary sensory, PCC =
 10 posterior cingulate cortex, PC = precuneus, AMCC = anterior middle cingulate cortex,
 11 EBA = extrastriate body area, OFC = orbitofrontal cortex, PM = premotor, VC = visual
 12 cortex.
 13

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

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

R S2	38	-48	42	106	4.1	L S1	-14	-52	66	91	5.5
						R PM	50	12	18	78	5.1

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1 **Table 2. Effect of Task Demand: Emotional Pain.** Brain regions active while reading
2 about others' emotional pain (EP) during the 'empathize' task demand (EP_{emp}) versus the
3 'objective' task demand (EP_{obj}). Brain regions, MNI coordinates, cluster extent and peak
4 t-value presented for each contrast in each study. Bold type indicates regions identified in
5 both Studies 1 and 2. Data from Studies 1 and 2 are reported at an uncorrected voxelwise
6 threshold of $p < 0.001$, $k > 10$). Parahipp = parahippocampus, Hipp = hippocampus, STS
7 = superior temporal sulcus, LPFC = lateral prefrontal cortex, ACC = anterior cingulate
8 cortex, OFC = orbitofrontal cortex, AI = anterior insula, VS = ventral striatum.
9

Study 1: EPemp>EPobj						Study 2: EPemp>EPobj					
Region	x	y	z	voxel s	t	Region	x	y	z	voxel s	t
L Amygdala	-14	-6	-14	55	6.4	L Amygdala	-18	-2	-14	14	3.5
R Amygdala	20	0	-18	26	4.0	R Amygdala	26	2	-14	16	5.0
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 1: EPobj>EPemp						Study 2: EPobj>EPemp					
Region	x	y	z	voxel s	t	Region	x	y	z	voxels	t
R LPFC	38	46	16	92	4.5	R LPFC	32	36	36	45	5.8
R LPFC	32	14	38	19	3.8	R LPFC	42	12	46	31	4.1
R LPFC	36	56	4	15	3.4	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

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

10

Study 1: PPemp>PPobj						Study 2: PPemp>PPobj					
Region	x	y	z	voxels	t	Region	x	y	z	voxels	t
L PM	-58	10	22	24	3.8	<i>no suprathreshold voxels</i>					
L EBA	-58	-66	0	14	3.6						
L S2	-62	-16	22	21	3.5						
Study 1: PPobj>PPemp						Study 2: PPobj>PPemp					
Region	x	y	z	voxels	t	Region	x	y	z	voxels	t
R AI	36	22	-6	69	4.8	R AI	38	26	-4	527	7.1
R operculum	48	22	4	23	4.4	R operculum	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

11

12

1 **Table 4. Psychophysiological Interaction Analysis.** Brain regions positively and
2 negatively coupled with amygdala activity while reading stories involving others in
3 emotional pain (EP) versus physical pain (PP). Brain regions, MNI coordinates, cluster
4 extent and peak t-value presented for each contrast in each study. Bold type indicates
5 regions identified in both Studies 1 and 2. Data from Studies 1 and 2 are reported at an
6 uncorrected voxelwise threshold of $p < 0.001$, $k > 10$; combined data corrected for
7 multiple comparisons for the peak and cluster size, $p < 0.05$. PC = precuneus, TPJ =
8 temporoparietal junction, aSTS = anterior superior temporal sulcus, S1 = primary sensory
9 cortex, LPFC = lateral prefrontal cortex, OFC = orbitofrontal cortex, VS = ventral
10 striatum, Hipp = hippocampus, S2 = secondary sensory, AMCC = anterior middle
11 cingulate cortex, MFG = middle frontal gyrus, AI = anterior insula, EBA = extrastriate
12 body area, VC = visual cortex.
13

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

14
15

Combined: PPI EP>PP - positive

Region	x	y	z	voxels	t
PC	8	-54	26	1625	6.6
RTPJ	56	-56	22	742	7.5
R aSTS	58	0	-20	512	6.2
L STS	-50	-40	0	1239	4.7
L aSTS	-48	-20	-8	10	4.9
LTPJ	-44	-66	28	760	4.7

Combined: PPI EP>PP - negative

Region	x	y	z	voxels	t
L S2	-56	-32	38	825	5.9
L MFG	-38	34	8	374	4.4
L EBA	-50	-60	-4	441	5.0
L PM	-44	6	22	410	4.9

1

1 **Table 5. Effect of task demand across condition in combined dataset.** Brain regions
 2 showing superthreshold activity in the ‘empathize’ task demand versus the ‘objective’
 3 task demand separately for stories involving physical pain (PP) and for stories involving
 4 emotional pain (EP), in the combined data from Studies 1 and 2 ($N = 39$). Brain regions,
 5 MNI coordinates, cluster extent and peak t-value presented for each contrast in each
 6 condition, correcting for multiple comparisons for the peak and cluster size, $p < 0.05$.
 7 LPFC = lateral prefrontal cortex, Parahipp = parahippocampus, ACC = anterior cingulate
 8 cortex, AI = anterior insula, Oper = operculum.
 9

Combined: EPemp>EPobj

Region	x	y	z	voxel s	t
L Amygdala	-18	-2	-14	142	5.8
R Amygdala	22	0	-18	124	5.5
L Parahipp	-16	-28	-10	87	5.3

Combined: PPemp >PPobj

Region	x	y	z	voxel s	t
<i>no suprathreshold voxels</i>					

Combined: EPobj>EPemp

Region	x	y	z	voxel s	t
R LPFC	30	36	38	1785	4.6
R LPFC	42	14	44		4.8
R LPFC	44	42	-2		4.7
dACC	10	16	54	469	4.2
L AI	-18	32	-18	226	5.2

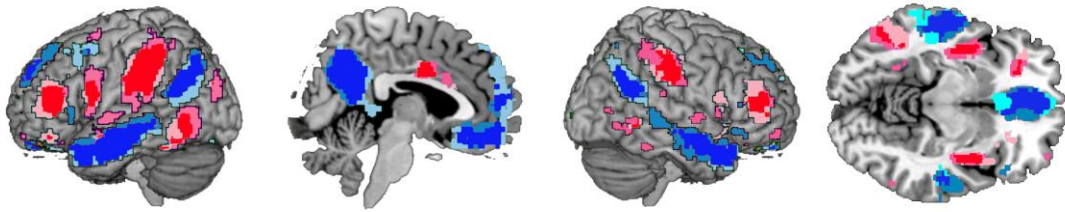
Combined: PPobj>PPemp

Region	x	y	z	voxels	t
R AI	36	24	-6	1192	6.7
R Operc	48	22	4		5.8
ACC	8	28	32	357	5.1
L AI	-40	18	0	361	4.5

10

1 **Figures and legends**

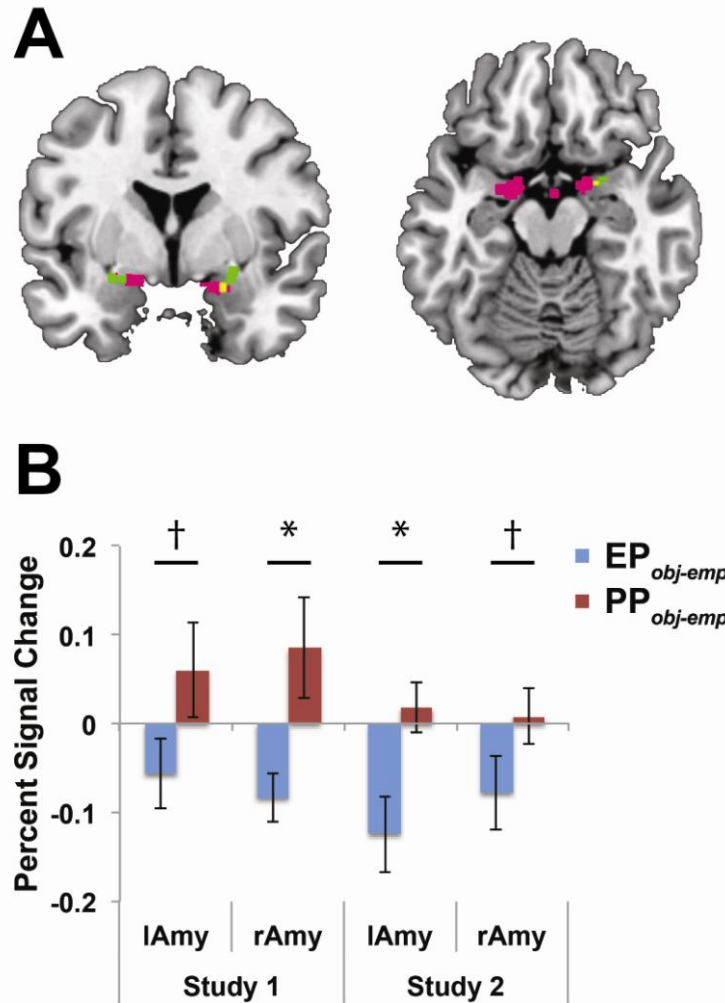
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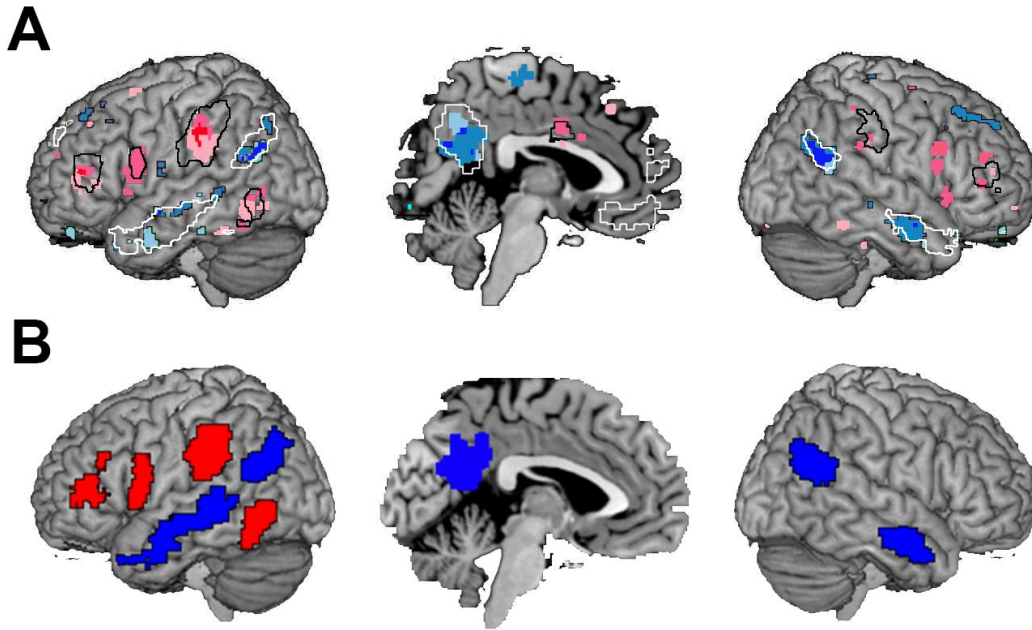
7 **Figure 1. Neural activity associated with reading about others' physical pain and**
8 **emotional pain.** Neural activity identified using group-level analyses and contrasts of
9 emotional pain versus physical pain for Study 1 (lightest blue), Study 2 (medium blue)
10 and their conjunction (darkest blue), and for physical pain versus emotional pain for
11 Study 1 (light pink), Study 2 (dark pink) and their conjunction (red). Across studies,
12 reading about others in emotional pain (versus physical pain) was associated with activity
13 in brain regions associated with mentalizing (bilateral temporoparietal junction (TPJ),
14 precuneus (PC), medial prefrontal cortex (MPFC)), while reading about others in
15 physical pain (versus emotional pain) was associated with activity in the extended pain
16 matrix, including anterior middle cingulate cortex (AMCC), bilateral insulae, secondary
17 sensory (S2) and extrastriate body area (EBA). All results presented at a threshold of $p <$
18 0.001, uncorrected.

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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.



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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, $p < 0.05$).

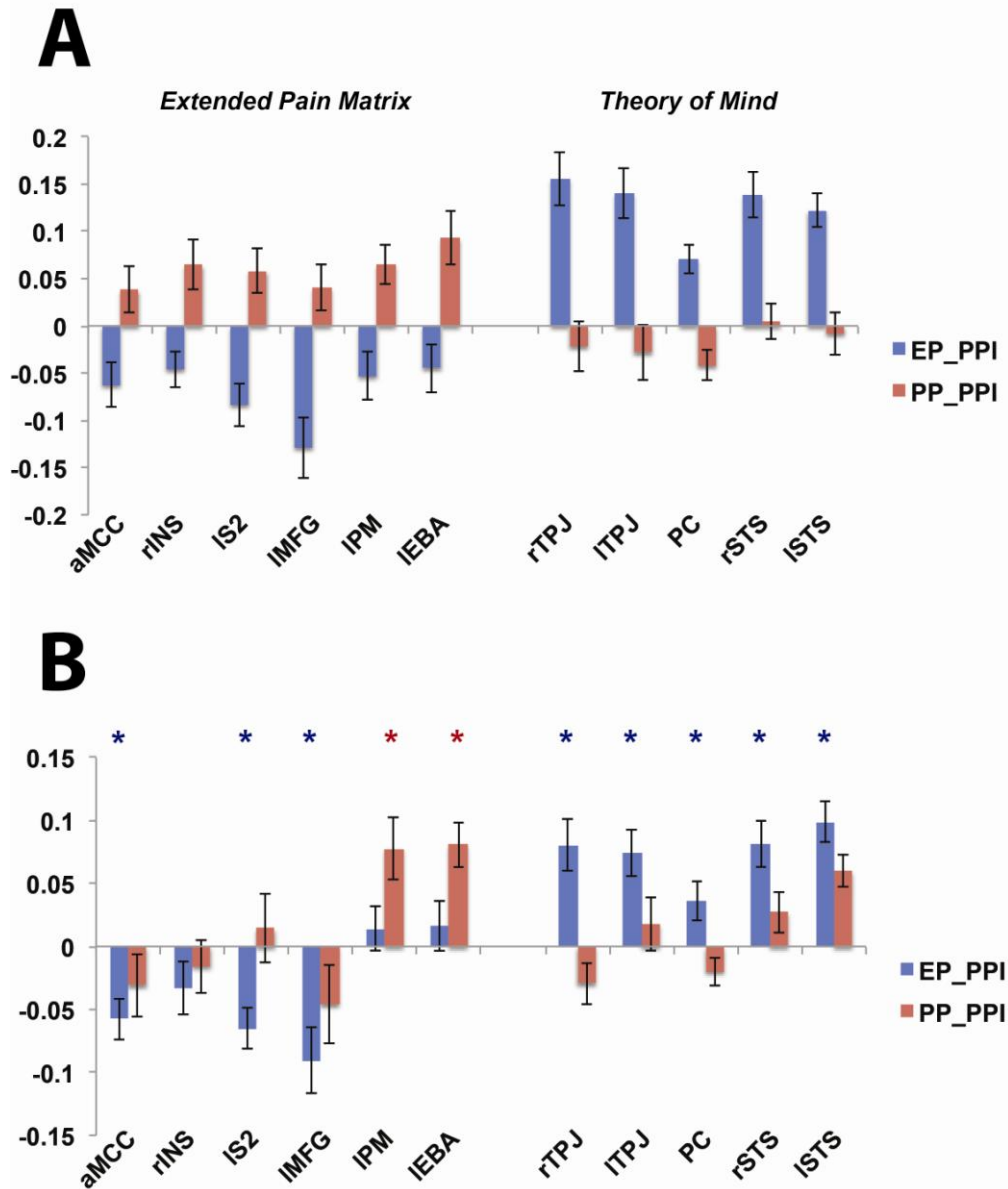
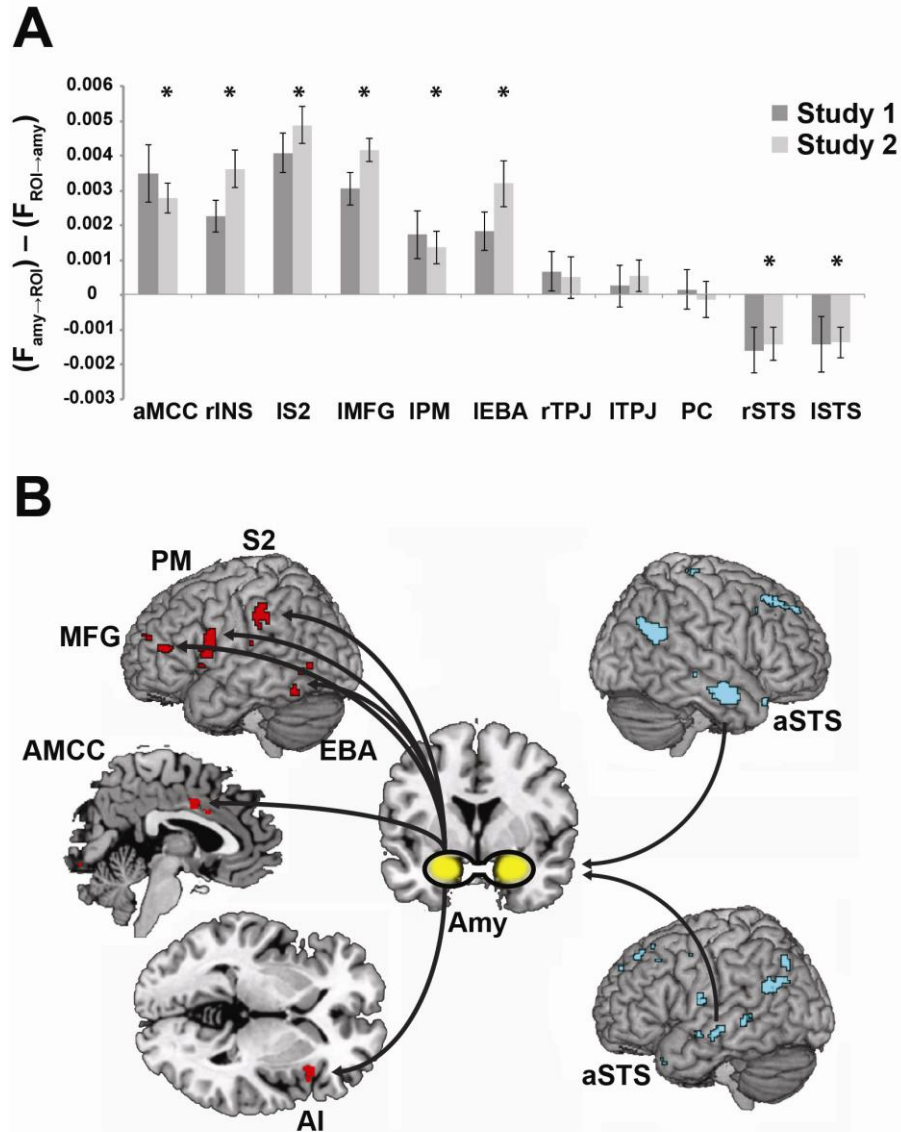


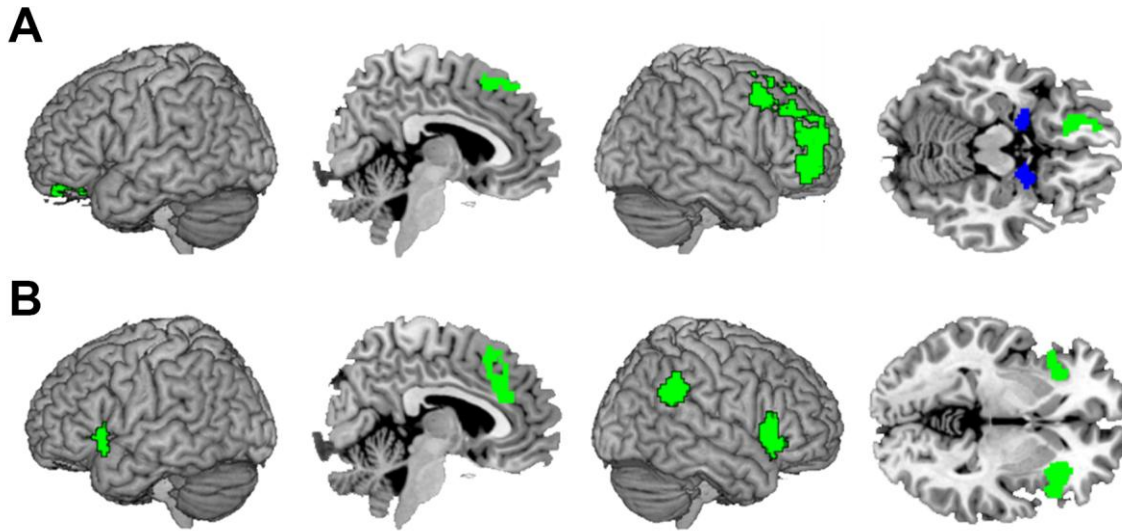
Figure 4. Response in regions identified through PPI to both EP and PP stimuli.

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.

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



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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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