Predicting Pain-Related Empathy through Resting-State Networks Analysis

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Abstract

Empathy involves understanding and sharing others' emotions. In this study, we explore the neural correlates of empathy through analysis of resting-state functional connectivity (rsFC). In

the analysis, we investigated the default mode network (DMN) and salience network (SN).

Despite evidence suggesting correlations between the activity of these networks during resting state fMRI and empathy, the so far used methods are limited to trait empathy surveys and photos.

In our study, we employed a more ecologically valid experimental paradigm to measure empathy. Participants viewed both their romantic partner and a stranger experiencing pain during fMRI scanning. We find negative correlations between overall empathy and the connectivity of the medial prefrontal cortex and precuneus (nodes of DMN). There is also a negative correlation between empathy towards a stranger and connectivity of the right amygdala and right anterior insula (nodes of SN). This suggests that the changes in both networks reflect individual differences in empathy.

Introduction

Empathy involves both emotional and cognitive processes. The emotional aspect, known as affective empathy, involves sharing emotions with others. On the other hand, cognitive empathy refers to the ability to judge others' emotions accurately. In this study, we explore empathy through analysis of resting-state functional connectivity (rsFC), which examines functional connections when an individual is at rest. Previous research suggests that the neural mechanisms underlying empathy involve resting-state networks, particularly the Default Mode Network associated with cognitive empathy (DMN) and the Salience Network (SN) linked to affective empathy (Winters et al., 2021). State empathy has been rarely studied in the context of rsFC, most studies examining resting-state fMRI and empathy focused on trait empathy– a stable intrinsic condition that is assessed through surveys (Bilevicius et al., 2018; Dun et al., 2020; Esménio et al., 2019; Takeuchi et al., 2014; Uribe et al., 2019; Winters et al., 2021; Yue et al., 2021). As far as we know, there is only one study that investigated how rsFC predicts state empathy, which was assessed in response to pain-related photo stimuli (Otti et al., 2010). More often, studies investigate neural correlates of empathy with task fMRI during stimulus presentation. The stimuli are usually photos and videos (Jauniaux et al., 2019), and few studies have assessed empathy in response to viewing someone else undergoing pain (Edwards et al., 2017; López-Solà et al., 2020). We explore rsFC to predict empathy in the context of observing a romantic partner and a stranger experiencing pain. By exposing a female participant to the observation of a person in pain, we can get a more ecologically valid assessment of empathy. The current study can help us understand individual differences in empathy and the neural networks responsible for these differences.

What is represented in the brain when someone experiences pain-related empathy? One theory suggests that empathy involves the sharing of the experience and activates brain networks that represent somatic pain in the observer (Krishnan et al., 2016). The development of such theories is grounded in prior research demonstrating heightened activation of the anterior insula (AI), and the anterior cingulate cortex (ACC) in response to empathic reactions within painrelated contexts (Lamm et al., 2011; Saarela et al., 2007; Zhao et al., 2021). The insula and ACC are central nodes of the so-called "salience network" (SN), which plays a role in bottomattentional processes (Wiech et al., 2010). Another significant subcortical region often considered part of a salience network is the amygdala, which influences attention through physiological arousal (Borders, 2020). Studies provide evidence for the role of SN in empathy (Bilevicius et al., 2018; Dun et al., 2020; Uribe et al., 2019; Yue et al., 2021). Some argue that the SN activity might be a misleading indicator of empathy as viewing someone in pain is inherently attention-drawing, and that may be why there is a strong correlation with these attention-related regions, and not because of their relation to empathy. This limitation is addressed by our study design, which compares the magnitude of empathy in two conditions: viewing a stranger and viewing a romantic partner in real-time pain. Findings show that these conditions lead to different magnitudes of empathy, suggesting that empathic response is positively associated with someone's closeness to a person (López-Solà et al., 2020).

Another theory suggests that pain-related empathy could be self-reflective and involves mentalizing the observed pain (Krishnan et al., 2016). Such theories are based on findings indicating the involvement of the DMN in empathy (Bilevicius et al., 2018; Esménio et al., 2019; Takeuchi et al., 2014; Winters et al., 2021; Yue et al., 2021). The DMN consists of the medial prefrontal cortex (mPFC), the posterior cingulate cortex (PCC), the precuneus (PCU), it is thought to be involved in mind-wandering and self-referential processing (van Buuren et al., 2010). PCU's role in empathy response can also be explained by its involvement in visuo-spatial imagery, first-person perspective taking and bodily self-associative processing (Cavanna & Trimble, 2006; Lyu et al., 2023). Similarly, to AI and ACC, mPFC takes part in attentional mechanisms, but besides that, mPFC suggests that it mediates empathy through its involvement in emotional judgments (Seitz et al., 2006), and its role in recognizing others' emotions (Balconi et al., 2011). Similarly, studies on rsFC suggest the higher connectivity of DMN is associated with higher empathy (Esménio et al., 2019; Takeuchi et al., 2014; Winters et al., 2021).

Specific Aims

The current study aims to answer two hypotheses:

- (1) Higher resting-state DMN connectivity, both to the whole brain and within the DMN network itself, will be positively associated with empathy towards a partner, stranger, and the average of those two.
- (2) Higher resting-state SN connectivity, both to the whole brain and within the SN network itself, will be positively associated with empathy towards a partner, stranger, and the average of those two.

Methods

Participants

We screened 608 potential participants who we recruited by flyers. Twenty-nine females between 18 and 65 years old (Mean age = 29 years, SD = 6.67) and their romantic partners of at least 3 months were enrolled in the study. The mean relationship duration was 61.4 months (*SD* = 66 months). Individuals were excluded if they had chronic pain, were taking psychoactive medication, were pregnant, were claustrophobic, or had any MRI contraindications. The participants couldn't have prior meditation experience because of later meditation training that was part of a larger study. To reduce variability in brain lateralization patterns, we decided only to include right-handed participants. Both female volunteers and their romantic partners had to provide informed written consent acknowledging the study procedure that involved pain testing. Participants received financial compensation for their time and involvement in the study.

Procedure

Self-Report and Relationship with the Romantic Partner

The study started with the participants being briefed and signing a consent form, then answering survey questions. Female participants completed Sternberg's Triangular Love Scale (STLS), which measures love by assessing passion, commitment, and intimacy between the respondent and their romantic partner. Additionally, they completed the Inclusion of Other in the Self (IOS) scale. Data from one participant was excluded due to incomplete responses on these forms.

Pain Stimulus and Training

The thermal pain device (QST.Lab, Strasbourg, France) was placed on the ventral aspect of the right forearm, specifically the C5/6 dermatome and covered a surface of 45mm. The temperature was at a minimum of 35°C and maximum of 48°C and persisted for 5 seconds twenty times for the training. Everyone reported their pain levels with VAS with a two-button box. Stimuli and responses were measured and collected using PsychoPy (Peirce, 2007) and custom Python scripts.

Before the fMRI scan, everyone was familiarized with the pain stimulus and trained on how to use the Visual Analog Scale (VAS) [PsychoPy, (Peirce, 2007)]. During that training, the female

participants, their romantic partners, and strangers were delivered pain stimuli twenty times. The stranger did not interact with female participants or their romantic partners.

Functional MRI – Baseline (Figure 1a)

The female participants were laid down in the scanner and their respiration and pulse metrics were collected with a respiratory transducer and pulse oximeter (placed on a left index finger) respectively. An anatomical scan was performed and then resting-state BOLD scans were conducted for 9 minutes and 50 seconds during which female participants viewed a fixation cross on the projector. They had the thermal probe on, but it was unnoticeable because it was delivering a neutral temperature of continuous 35°C. This paper will focus on the neural results from resting state functional connectivity and self-reported empathy.

Pain Delivered to Participants (Figure 1b, 1c and d)

During the scans, the thermal pain stimulator was placed with a Velcro strap on the left forearm. The stimulus was set to deliver 10 noxious "heat series" to the left forearm within the overall duration of 240 seconds (8s 48°C plateaus; left forearm) while viewing flame on the projector. The 35°C intertrial intervals (ITI) were 10 seconds each, and female participants viewed a fixation cross on the projector.

Female participants had pain delivered while undergoing scanning using the protocol described above. After that, a stranger was let into the scanner room to receive the same "heat series" as the female participant. There was a mirror placed in the MRI beforehand, so the female participants could see a stranger's thermal probe that was administering the pain stimulus to the same spot on the left forearm. During the fMRI scan, the female participant could see the pain stimulus placed on the forearm and the same visual cues as before – flame icon during 48°C stimulation and fixation cross during neutral 35°C stimuli. The stranger was asked to look away

from the female participant's face, to make sure that nothing else was visible to the female participant lying in the scanner. The same procedure was later repeated for their romantic male partner after the stranger left the room (these data are not presented here).

Empathy and Pain Scores (Figure 1c and d)

To collect the pain and empathy felt by the female participants, after each scan, we collected VAS for pain (0 = "no pain sensation" to 10 = "most intense pain sensation imaginable") and empathy (0 = "not at all unpleasant" to 10 = "most unpleasant sensation imaginable"). VAS was visible on a projector screen with an MRI-compatible mirror and the same two-button box used before to record all the participants' answers. While collecting those scores only one (out of three participants) was present to minimize the influence of the other individuals. To assess pain scores after each heat series, participants were asked "How would you rate the pain intensity of the heat series you just received?". To assess empathy scores after the pain was administered to a stranger and the romantic partner, the female participants were asked "How unpleasant did it feel for you when your partner (or the stranger) received the heat series?" Additionally, the female participant was also asked how much pain they felt, and how much pain they believed the stranger or romantic partner felt.

Figure 1.

Female participants during resting state fMRI(a); female participants during pain stimulation (b); viewing stranger during pain stimulation (c); viewing romantic partner during pain stimulation (d).



Data Acquisition

We used GE Discovery MR750 3T scanner with a body transmit coil and 32-channel receive-only head coil (Nova Medical, Wilmington, MA) to get anatomical and functional images. The high-resolution structural scans were taken using a T1-weighted sagittal 3D FSPGR sequence. The parameters for this scan were as follows: TI = 450 ms; FA = 8 degrees, TE = 3.18ms; FOV = 240 mm; voxel dimensions = 0.94x0.94x1.2 mm; slice thickness = 1.2 mm; locations per slab = 176; matrix size = 256x192; and scan duration = 225 seconds.

The BOLD resting-state data were acquired using a 2D GRE EPI sequence with the following imaging parameters: Multiband Acceleration Factor = 6, Slices = 60, Slice Spacing = 0 mm, TR = 800ms, TE = 30ms, FA = 52 degrees, matrix size = 90 x 90, FOV = 216mm, Voxel Size = $2.4 \times 2.4 \times 2.4 \times 2.4 \text{ mm}^3$, scan time = 590 seconds.

Analysis of Neuroimaging Data

Preprocessing

For the preprocessing and network to-whole brain analysis we used FSL version 6.0 [FMRIB Software Library (Center for FMRIB, University of Oxford, Oxford, UK)]. Regions of interest were found using Harvard-Oxford Cortical and Subcortical Structural Atlases and were called as follows: Cingulate Gyrus, Posterior Division (PCC), Frontal Medial Cortex (mPFC), Precuneus (PCU), Cingulate Gyrus, Anterior Division (ACC), Left and Right Amygdala. Anterior Insula(AI) mask was created using a sphere for left AI (r = -0.515, p = .014; radius = 9 mm, peak coordinates: x = -36, y = 18, z = 3) right AI (r = 0.540, p = .010; radius = 9 mm, peak coordinates: x = 36, y = 18, z = 0) (Y. Li et al., 2020). After binarizing with a probability of 40%, we used FLIRT, and the functional images were coregistered to their common stereotaxic space (the Montreal Neurological Institute 152-brain template (MNI152); 2 mm³ resolution) so the seed regions in standard space could be linearly transformed to each participant's image.

Within-Network Preprocessing

For each region of interest (mPFC, PCU, PCC, ACC, AI, amygdala) eigenvariate values (projection onto the first principal component) were extracted from each BOLD scan. After visual inspection, we deleted the initial 8 seconds of data, which is a standard practice to eliminate the effects of physiological adjustments from the subject and allow the scanner's magnetization process to reach its steady state. Pairwise correlations were calculated between each region for each participant. Fisher's Z transformation was then applied to normalize the correlation coefficients and stabilize their variance, and a high pass filter was applied with a threshold of 0.005 Hz. For the group-level analysis, a Pearson two-tailed correlation analysis was employed to assess the relationship between the correlation of extracted values of two regions within a network (connectivity) and individual levels of empathy. Furthermore, we utilized a Pearson two-tailed correlation analysis to investigate the associations between IOS and STLS scores with empathy and the same connectivity within a specific network. In the analysis, we controlled for the pain unpleasantness and intensity reported by female participants, as these factors could affect the variations in empathy. The overall empathy score was calculated by averaging the levels of empathy towards a stranger and a romantic partner.

Network-to-Whole-Brain Preprocessing

In the first-level FEAT fMRI analyses, we employed an interleaved slice timing correction and applied spatial smoothing using a Gaussian kernel with a full-width at half maximum (FWHM) of 6 mm. Temporal filtering was carried out with a high-pass filter (sigma = 100.0s). BOLD data were linearly registered to the main structural images acquired from BET and then nonlinearly registered to the common stereotaxic space (the Montreal Neurological Institute 152-brain template (MNI152); 2 mm³ resolution) using a wrap resolution of 10 mm. Utilizing the FAST algorithm (Smith et al., 2004), we segmented the anatomical data into white matter partial volume and extracted their values. To mitigate white matter artifacts, these values were included as a nuisance covariate of no interest in the first-level analyses (Behzadi et al., 2007; Fox et al., 2005; Leber, 2010; Restom et al., 2006). Temporal derivative and filtering were also applied. Mean time series values corresponding to DMN-whole brain and SN-whole brain rsFC were calculated (FSLmeants), respectively, and the first 1.6 seconds were removed to eliminate initial scanner instabilities and physiological noise, ensuring cleaner and more reliable data for subsequent analyses.

To test the relationship between empathy scores and seed-to-voxel connectivity maps, we fit group-level models, regressing empathy scores on connectivity maps. A two-tailed test was used to assess both the effect of the intercept (mean connectivity of DMN or SN) and the regressor (empathy scores). Correction for multiple tests was performed using cluster-level inference with a significance threshold set at Z = 2.3.

Results

Empathy and Pain Ratings

Paired samples t-test was performed, and female participants reported higher empathy towards their romantic partner (M = 2.73, SD = 0.4) than towards a stranger (M = 1.74, SD = 0.3) when watching them undergo painful stimulation, t(28) = 2.604, p = .015. When experiencing pain themselves, the female participants reported an average pain intensity of 2.5 (SD = 2.8) and pain unpleasantness of 2.4 (SD = 2.8).

Within- Network Connectivity

None of the hypotheses were supported, as no positive correlations were found between the connectivity within the SN and DMN and empathy. However, some significant effects were observed in the opposite direction than hypothesized, indicating negative correlations between the connectivity of certain regions and empathy. The findings presented are partial correlations, controlling for the influence of pain unpleasantness and intensity as reported by female participants since differences in empathy scores could be attributed to varying perceptions of the pain stimulus.

Does DMN Connectivity Correlate with Overall Empathy? (Figure 2a)

There was a significant negative correlation between the connectivity of mPFC and PCU with overall empathy, r(25) = -.50, p = .001. This refers to the average empathy reported towards a stranger and a romantic partner. However, no significant correlations were found between the connectivity of mPFC and PCC or between PCC and PCU connectivity and overall empathy (details in Appendix A).

Does DMN Connectivity Correlate with Empathy Towards a Partner or Stranger? (Figure 2b and 2c)

Similarly, there was a significant negative correlation between the connectivity of mPFC and PCU with empathy towards a stranger (r(25) = -.48, p = .014), and towards a partner (r(25) = -.40, p = .042). No significant correlations were found between the connectivity of mPFC or PCU and PCC and empathy towards a stranger. Similarly, no significant correlations were found between the connectivity of mPFC or PCU and PCC and empathy towards a partner (details in Appendix A).

Figure 2.

The weaker the connectivity between mPFC and PCU, the higher the empathy towards a stranger(a). The negative correlation between mPFC and PCU connectivity is only marginally significant for the romantic partner (b). There was a significant correlation between overall empathy and connectivity of mPFC and PCU, both nodes of DMN(c).



Does SN Connectivity Correlate with Overall Empathy?

There were no significant correlations were found between the connectivity of SN regions and overall empathy (details in Appendix B).

Does SN Connectivity Correlate with Empathy towards a Partner or Stranger? (Figure 2d)

There was a significant negative correlation between the connectivity of right AI and right amygdala and empathy towards a stranger, r(25) = -.41, p = 0.038. No other significant

correlations were found between the connectivity of SN regions and empathy towards a stranger or romantic partner (details in Appendix B).

Relationship with the Romantic Partner (Figure 3a and 3b)

After controlling for pain felt by the female participants, there was a negative correlation between STLS passion subscale and empathy towards a stranger (r (25) = -.40, p = .044). In contrast, there was a positive correlation between the STLS passion subscale connectivity of the right amygdala and the right AI (r (25) = .42, p = .035). There was also a negative correlation between the empathy for strangers and the STLS intimacy subscale (r (25) = -.45, p = .02 and IOS scale (r(25) = -.403, p = .041). Other results are available in Appendix C.

Figure 3.

The stronger the connectivity between right AI and right amygdala, the higher the passion towards a romantic partner (a). The higher the passion towards a romantic partner, the lower the empathy towards a stranger (b).



Network-to-Whole-Brain Connectivity

None of the hypotheses were supported. A higher-level FEAT analysis was conducted to find correlations between the DMN mean time series and empathy towards a partner, a stranger,

and the average of the two. We tested positive and negative contrasts between empathy variables using a cluster-corrected threshold of Z = 2.3 and a cluster significance threshold of p < 0.05. No significant correlations were found between DMN and whole-brain connectivity with empathy variables. Similarly, no significant correlations were found between SN and whole-brain connectivity with empathy variables.

Discussion

We hypothesized that the higher resting-state DMN connectivity, both to the whole brain and within the DMN network itself, would be positively associated with empathy towards a partner, stranger, and the average of those two. However, our hypothesis was not supported. Instead, we found the opposite effect: weaker connectivity between the medial prefrontal cortex (mPFC) and the precuneus (PCU) was associated with higher empathy towards strangers, partners, and the average of the two when we controlled for the pain experienced by female participants. No other significant relationships were observed between DMN connectivity and empathy.

The results suggest that connectivity within the DMN may play a significant role in individuals' differences in empathy, regardless of their level of closeness. One explanation for this result could be drawn from clinical research on patients with depression. Evidence suggests that depressed patients have higher within DMN connectivity than healthy participants during rsFC (Leibenluft & Pine, 2013). This could be attributed to increased self-concern (F. Li et al., 2014), rumination (Berman et al., 2011), excessive self-centered thinking, and difficulty thinking about others. Even though in our study we research only healthy individuals, studies like this suggest that *higher connectivity within the DMN is associated with lower empathy due to this increased self-referential thinking*. Previous studies investigating rsFC do not support our results

(Bilevicius et al., 2018; Esménio et al., 2019; Takeuchi et al., 2014; Winters et al., 2021; Yue et al., 2021); however, the differences could be attributed to the different assessments of empathy. All these studies researched trait empathy rather than state empathy and they often chose different nodes of DMN or researched different kinds of connectivity.

Weaker connectivity within the DMN might suggest a more distinct specialization of certain regions that are relevant to empathy. This weaker connectivity might facilitate participants in smoothly transitioning between different subfunctions of the DMN, which could be crucial for processing empathy and social cognition effectively. While the specific nodes of the DMN studied by van Buuren et al. differ from our investigation, their work on higher DMN activity during self and other referential processing provides important insights. Their findings highlight that during self-referential tasks, connectivity between regions like the PCC and mPFC decreases compared to tasks focusing on others (van Buuren et al., 2010). This shift in connectivity underscores a distinct cognitive processing mode between self and other considerations. Our observation of weaker connectivity within the DMN may enable participants to process information about others more easily, as the shift between self- and other-referential processing could be smoother.

We also hypothesized that the higher resting-state SN connectivity, both to the whole brain and within the SN network itself, will be positively associated with empathy towards a partner, stranger, and the average of those two. The hypothesis was not supported, and some significant effects were observed in the opposite direction than hypothesized, showing that the weaker connectivity between the right anterior insula and right amygdala, the higher the empathy towards the stranger but not the partner when controlling for pain felt by female participants. Female participants also reported lower empathy towards a stranger than their partner. No other significant correlations were found for SN connectivity.

The findings indicate a broader range of vicarious pain experiences among female participants when empathizing with strangers compared to romantic partners. This variability is likely influenced by the SN, known for its role in affective empathy (Winters et al., 2021). In contrast, empathy levels toward romantic partners and SN connectivity in the resting-state appear to be more consistent across individuals. Because female participants feel less empathy toward strangers compared to their partners, the weaker connectivity within their SN is likely contributing to this lower empathy. Resting state activity of the anterior insula is shown to be important for interoception (Simmons et al., 2013), while the amygdala is associated with physiological arousal (Borders, 2020). *The increased connectivity between these areas and decreased empathy for strangers suggests that the differences in empathy and connectivity patterns may be associated with specific activation of brain circuits related to interoception and physiological arousal, but only in response to specific social contexts, such as interactions with a stranger but not with a romantic partner.*

Interestingly, the more passionate feelings female participants reported towards their romantic partner (STLS passion subscale), the less empathy they felt towards a stranger. In addition, the higher the reported passion, the higher the connectivity of the right anterior insula and right amygdala. One possible explanation for this result is the positive correlation between passion and oxytocin (Grebe et al., 2017). Oxytocin is known to be associated with heightened empathy towards in-group than out-group members (De Dreu & Kret, 2016). This suggests that the passion towards the romantic partner may lead to increased empathy for in-group members

(partners) and decreased empathy towards outgroup members (strangers). It's important to note that there are negative correlations between empathy for strangers and reported intimacy with a partner, as well as negative correlations between empathy for strangers and reported self-other distinction. However, these measures are not correlated with the connectivity of the right AI and right amygdala. This suggests that other brain regions also play a role in the differences between empathy for strangers and partners.

Limitations

The conclusions drawn from this study should be interpreted with caution as it is the first to investigate rsFC and state pain-related empathy. Our experiment involved only female participants reporting empathy towards two male individuals (a partner and a stranger). Future research should include participants of different sexes to provide a more comprehensive understanding. Additionally, developing an experimental paradigm to demonstrate the directionality of the results could further elucidate the observed effects. Future studies should increase the sample size to improve statistical power, especially for network-to-whole brain analysis.

Conclusions

The study found that connectivity within the DMN and the SN is negatively correlated with empathy, indicating the involvement of both networks in individual differences in empathy, albeit in different contexts. Specifically, the DMN appears to be broadly associated with individual differences in empathy, as the results are significant regardless of the empathized person's closeness. We observed that weaker connectivity between the mPFC and the PCU correlates with higher empathy levels. In contrast, the SN seems more relevant in differentiating individual variations in empathy only towards strangers. Weaker connectivity between the right AI and the right amygdala is correlated with higher empathy specifically towards strangers. This finding suggests that the SN may play a more critical role in modulating empathy towards unfamiliar individuals. These insights highlight the complex and context-dependent nature of neural networks involved in individual differences in empathy.

References

Balconi, M., Bortolotti, A., & Gonzaga, L. (2011). Emotional face recognition, EMG response, and medial prefrontal activity in empathic behaviour. *Neuroscience Research*, *71*(3), 251–259. https://doi.org/10.1016/j.neures.2011.07.1833

Behzadi, Y., Restom, K., Liau, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage*, *37*(1), 90–101. https://doi.org/10.1016/j.neuroimage.2007.04.042

Berman, M. G., Peltier, S., Nee, D. E., Kross, E., Deldin, P. J., & Jonides, J. (2011). Depression, rumination and the default network. *Social Cognitive and Affective Neuroscience*, *6*(5), 548–555. https://doi.org/10.1093/scan/nsq080

Bilevicius, E., Kolesar, T. A., Smith, S. D., Trapnell, P. D., & Kornelsen, J. (2018). Trait Emotional Empathy and Resting State Functional Connectivity in Default Mode, Salience, and Central Executive Networks. *Brain Sciences*, 8(7), Article 7.

https://doi.org/10.3390/brainsci8070128

Borders, A. (2020). Chapter 9—Rumination, cognition, and the brain. In A. Borders (Ed.), *Rumination and Related Constructs* (pp. 279–311). Academic Press. https://doi.org/10.1016/B978-0-12-812545-8.00009-7

Cavanna, A. E., & Trimble, M. R. (2006). The precuneus: A review of its functional anatomy and behavioural correlates. *Brain: A Journal of Neurology*, *129*(Pt 3), 564–583. https://doi.org/10.1093/brain/awl004 De Dreu, C. K. W., & Kret, M. E. (2016). Oxytocin Conditions Intergroup Relations Through Upregulated In-Group Empathy, Cooperation, Conformity, and Defense. *Biological Psychiatry*, 79(3), 165–173. https://doi.org/10.1016/j.biopsych.2015.03.020

Dun, W., Fan, T., Wang, Q., Wang, K., Yang, J., Li, H., Liu, J., & Liu, H. (2020). Association Between Trait Empathy and Resting Brain Activity in Women With Primary Dysmenorrhea During the Pain and Pain-Free Phases. *Frontiers in Psychiatry*, *11*. https://www.frontiersin.org/articles/10.3389/fpsyt.2020.608928

Edwards, R., Eccleston, C., & Keogh, E. (2017). Observer influences on pain: An experimental series examining same-sex and opposite-sex friends, strangers, and romantic partners. *PAIN*, *158*(5), 846. https://doi.org/10.1097/j.pain.00000000000840

Esménio, S., Soares, J. M., Oliveira-Silva, P., Zeidman, P., Razi, A., Gonçalves, Ó. F., Friston, K., & Coutinho, J. (2019). Using resting-state DMN effective connectivity to characterize the neurofunctional architecture of empathy. *Scientific Reports*, *9*(1), Article 1. https://doi.org/10.1038/s41598-019-38801-6

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(27), 9673–9678. https://doi.org/10.1073/pnas.0504136102

Grebe, N. M., Kristoffersen, A. A., Grøntvedt, T. V., Emery Thompson, M., Kennair, L. E. O., & Gangestad, S. W. (2017). Oxytocin and vulnerable romantic relationships. *Hormones and Behavior*, *90*, 64–74. https://doi.org/10.1016/j.yhbeh.2017.02.009

Jauniaux, J., Khatibi, A., Rainville, P., & Jackson, P. L. (2019). A meta-analysis of neuroimaging studies on pain empathy: Investigating the role of visual information and observers' perspective. *Social Cognitive and Affective Neuroscience*, *14*(8), 789–813. https://doi.org/10.1093/scan/nsz055

Krishnan, A., Woo, C.-W., Chang, L. J., Ruzic, L., Gu, X., López-Solà, M., Jackson, P. L., Pujol,
J., Fan, J., & Wager, T. D. (2016). Somatic and vicarious pain are represented by dissociable
multivariate brain patterns. *eLife*, *5*, e15166. https://doi.org/10.7554/eLife.15166

Lamm, C., Decety, J., & Singer, T. (2011). Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. *NeuroImage*, *54*(3), 2492–2502. https://doi.org/10.1016/j.neuroimage.2010.10.014

Leber, A. B. (2010). Neural predictors of within-subject fluctuations in attentional control. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *30*(34), 11458–11465. https://doi.org/10.1523/JNEUROSCI.0809-10.2010

Leibenluft, E., & Pine, D. S. (2013). Resting State Functional Connectivity and Depression: In Search of a Bottom Line. *Biological Psychiatry*, 74(12), 868–869. https://doi.org/10.1016/j.biopsych.2013.10.001

Li, F., He, N., Li, Y., Chen, L., Huang, X., Lui, S., Guo, L., Kemp, G. J., & Gong, Q. (2014). Intrinsic brain abnormalities in attention deficit hyperactivity disorder: A resting-state functional MR imaging study. *Radiology*, 272(2), 514–523. https://doi.org/10.1148/radiol.14131622

Li, Y., Zhang, T., Li, W., Zhang, J., Jin, Z., & Li, L. (2020). Linking brain structure and activation in anterior insula cortex to explain the trait empathy for pain. *Human Brain Mapping*, *41*(4), 1030–1042. https://doi.org/10.1002/hbm.24858

López-Solà, M., Koban, L., Krishnan, A., & Wager, T. D. (2020). When pain really matters: A vicarious-pain brain marker tracks empathy for pain in the romantic partner. *Neuropsychologia*, *145*, 106427. https://doi.org/10.1016/j.neuropsychologia.2017.07.012

Lyu, D., Stieger, J. R., Xin, C., Ma, E., Lusk, Z., Aparicio, M. K., Werbaneth, K., Perry, C. M., Deisseroth, K., Buch, V., & Parvizi, J. (2023). Causal evidence for the processing of bodily self in the anterior precuneus. *Neuron*, *111*(16), 2502-2512.e4.

https://doi.org/10.1016/j.neuron.2023.05.013

Otti, A., Guendel, H., Läer, L., Wohlschlaeger, A. M., Lane, R. D., Decety, J., Zimmer, C., Henningsen, P., & Noll-Hussong, M. (2010). I know the pain you feel—How the human brain's default mode predicts our resonance to another's suffering. *Neuroscience*, *169*(1), 143–148. https://doi.org/10.1016/j.neuroscience.2010.04.072

Restom, K., Behzadi, Y., & Liu, T. T. (2006). Physiological noise reduction for arterial spin labeling functional MRI. *NeuroImage*, *31*(3), 1104–1115.

https://doi.org/10.1016/j.neuroimage.2006.01.026

Saarela, M. V., Hlushchuk, Y., Williams, A. C. de C., Schürmann, M., Kalso, E., & Hari, R. (2007). The Compassionate Brain: Humans Detect Intensity of Pain from Another's Face. *Cerebral Cortex*, *17*(1), 230–237. https://doi.org/10.1093/cercor/bhj141

Seitz, R. J., Nickel, J., & Azari, N. P. (2006). Functional modularity of the medial prefrontal cortex: Involvement in human empathy. *Neuropsychology*, *20*(6), 743–751. https://doi.org/10.1037/0894-4105.20.6.743

Simmons, W. K., Avery, J. A., Barcalow, J. C., Bodurka, J., Drevets, W. C., & Bellgowan, P. (2013). Keeping the body in mind: Insula functional organization and functional connectivity

integrate interoceptive, exteroceptive, and emotional awareness. *Human Brain Mapping*, *34*(11), 2944–2958. https://doi.org/10.1002/hbm.22113

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23 Suppl 1*, S208-219. https://doi.org/10.1016/j.neuroimage.2004.07.051

Takeuchi, H., Taki, Y., Nouchi, R., Sekiguchi, A., Hashizume, H., Sassa, Y., Kotozaki, Y., Miyauchi, C. M., Yokoyama, R., Iizuka, K., Nakagawa, S., Nagase, T., Kunitoki, K., & Kawashima, R. (2014). Association between resting-state functional connectivity and empathizing/systemizing. *NeuroImage*, *99*, 312–322. https://doi.org/10.1016/j.neuroimage.2014.05.031

Uribe, C., Puig-Davi, A., Abos, A., Baggio, H. C., Junque, C., & Segura, B. (2019). Neuroanatomical and Functional Correlates of Cognitive and Affective Empathy in Young Healthy Adults. *Frontiers in Behavioral Neuroscience*, *13*.

https://www.frontiersin.org/articles/10.3389/fnbeh.2019.00085

van Buuren, M., Gladwin, T. E., Zandbelt, B. B., Kahn, R. S., & Vink, M. (2010). Reduced functional coupling in the default-mode network during self-referential processing. *Human Brain Mapping*, *31*(8), 1117–1127. https://doi.org/10.1002/hbm.20920

Wiech, K., Lin, C., Brodersen, K. H., Bingel, U., Ploner, M., & Tracey, I. (2010). Anterior insula integrates information about salience into perceptual decisions about pain. *The Journal of*

Neuroscience: The Official Journal of the Society for Neuroscience, *30*(48), 16324–16331. https://doi.org/10.1523/JNEUROSCI.2087-10.2010

Winters, D. E., Pruitt, P. J., Fukui, S., Cyders, M. A., Pierce, B. J., Lay, K., & Damoiseaux, J. S. (2021). Network functional connectivity underlying dissociable cognitive and affective components of empathy in adolescence. *Neuropsychologia*, *156*, 107832. https://doi.org/10.1016/j.neuropsychologia.2021.107832

Yamagishi, A., Lee, J., & Sato, N. (2020). Oxytocin in the anterior cingulate cortex is involved in helping behaviour. *Behavioural Brain Research*, *393*, 112790. https://doi.org/10.1016/j.bbr.2020.112790

Yue, T., Zhao, J., & Fu, A. (2021). Amplitude of Low-Frequency Fluctuations and Resting-State Functional Connectivity in Trait Positive Empathy: A Resting-State fMRI Study. *Frontiers in Psychiatry*, *12*. https://www.frontiersin.org/articles/10.3389/fpsyt.2021.604106

Zhao, Y., Zhang, L., Rütgen, M., Sladky, R., & Lamm, C. (2021). Neural dynamics between anterior insular cortex and right supramarginal gyrus dissociate genuine affect sharing from perceptual saliency of pretended pain. *eLife*, *10*, e69994. https://doi.org/10.7554/eLife.69994

Appendix A: Detailed Statistics for DMN Connectivity Correlations

		DMN correlati	ons		
Control Variables		mPFC & PCC	mPFC & PCU	PCC & PCU	
Pain intesity and unpleasantnes s felt by female participants	Empathy towards a romantic partner	.121	402	.269	
		.554	.042	.184	
		24	24	24	
	Empathy towards a stranger	.103	478	.114	
		.616	.014	.579	
		24	24	24	
	Overall empathy	.129	495	.227	
		.531	.010	.265	
		24	24	24	

Appendix B: Detailed Statistics for SN Connectivity Correlations

SN Correlations											
Control Variables		ACC & left AI	ACC & right AI	left & right AI	ACC & left amygdala	right AI & left amygdala	left AI & left amygdala	ACC & right amygdala	right AI & right amygdala	left AI & right amygdala	left & right amygdala
Pain intesity and unpleasantness felt by female participants	Empathy towards a romantic partner	056	192	168	.194	178	081	271	044	.039	271
		.785	.349	.412	.342	.383	.693	.180	.831	.850	.180
		24	24	24	24	24	24	24	24	24	24
	Empathy towards a stranger	.047	087	240	.067	001	141	320	409	181	341
		.818	.674	.238	.744	.995	.491	.111	.038	.375	.089
		24	24	24	24	24	24	24	24	24	24
	Overall empathy	011	164	227	.156	113	123	333	235	067	343
		.956	.422	.265	.447	.583	.551	.097	.249	.744	.086
		24	24	24	24	24	24	24	24	24	24

Appendix C: Detailed Statistics for STLS and IOS and empathy

		Corr	elations			
Control Variables	1	IOS	STLS total	STLS: passion	STLS: commitment	STLS: intimicay
Pain intensity and unpleasantness felt by female participants	mPFC & PCU	.047	.231	.312	.127	.134
		.820	.257	.120	.537	.514
		24	24	24	24	24
	right AI & right	.265	.351	.415	.188	.287
	amygdala	.190	.079	.035	.357	.156
		24	24	24	24	24
	Overall empathy	320	343	376	074	439
		.111	.086	.058	.719	.025
		24	24	24	24	24
	Empathy towards a romantic partner	185	235	278	.004	332
		.365	.248	.170	.985	.097
		24	24	24	24	24
	Empathy towards a stranger	403	386	398	151	453
		.041	.052	.044	.462	.020
		24	24	24	24	24

Correlations