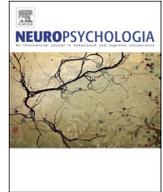




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## When pain really matters: A vicarious-pain brain marker tracks empathy for pain in the romantic partner

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## ABSTRACT

In a previous study (Krishnan, 2016) we identified a whole-brain pattern, the Vicarious Pain Signature (VPS), which predicts vicarious pain when participants observe pictures of strangers in pain. Here, we test its generalization to observation of pain in a close significant other. Participants experienced painful heat (Self-Pain) and observed their romantic partner in pain (Partner-Pain). We measured whether (i) the VPS would respond selectively to Partner-Pain and (ii) the Neurologic Pain Signature (NPS), a measure validated to track somatic pain, would selectively respond to Self-Pain, despite the high interpersonal closeness between partners. The Partner-Pain condition activated the VPS ( $t = 4.71$ ,  $p = 0.00005$ ), but not the NPS ( $t = -1.03$ ,  $p = 0.308$ ). The Self-Pain condition activated the NPS ( $t = 13.70$ ,  $p < .00005$ ), but not the VPS ( $t = -1.03$ ,  $p = 0.308$ ). Relative VPS-NPS response differences strongly discriminated Partner-Pain vs. Self-Pain (cross-validated accuracy = 97%,  $p < .00001$ ). Greater interpersonal closeness between partners predicted greater VPS responses during Partner-Pain ( $r = 0.388$ ,  $p = 0.050$ ) and greater unpleasantness when observing the romantic partner in pain ( $r = 0.559$ ,  $p = 0.003$ ). The VPS generalizes across empathy paradigms and to an interactive social setting, and strongly activates when observing a close significant other in pain. VPS responses may be modulated by relevant interpersonal relationship factors. Self-Pain and Partner-Pain evoke non-overlapping large-scale neural representations.

### 1. Introduction

The capacity to understand and share the feelings of others is crucial for interpersonal relationships and a healthy, functioning society. Empathic responses promote mutual understanding, caring and interpersonal attachment, and provide a foundation for socially appropriate behavior. Understanding the neurophysiological underpinnings of empathy can inform our understanding of brain disorders—e.g., psychopathy and autism—and individual differences in interpersonal functioning beyond clinical settings.

Over the previous decade and a half, neuroimaging research on the neural mechanisms of empathy has developed substantially (Bernhardt and Singer, 2012; Lamm et al., 2011; Zaki et al., 2016). However, there is a need to identify neural markers of empathy that are specific, reproducible, and generalizable across different paradigms. Such markers can provide a basis for comparing empathy with other psychological

constructs at a biological level, and for comparing empathy-related brain responses across groups of individuals and across treatments.

The development and validation of distributed neural markers of a given construct, such as vicarious pain, can help reduce the complexity of hundreds of thousands of brain measures into integrated brain measures (“pattern response” magnitude) that indicate how much each subject's brain activity map resembles the specific brain pattern/s. This approach provides a framework that allows more direct comparison of results across empathy-related studies conducted in different laboratories, populations, and MRI scanners. The use of neural markers may therefore help to characterize the degree of overlap/non-overlap between different empathy experiences across studies, which may facilitate interpretability and integration of knowledge across different studies.

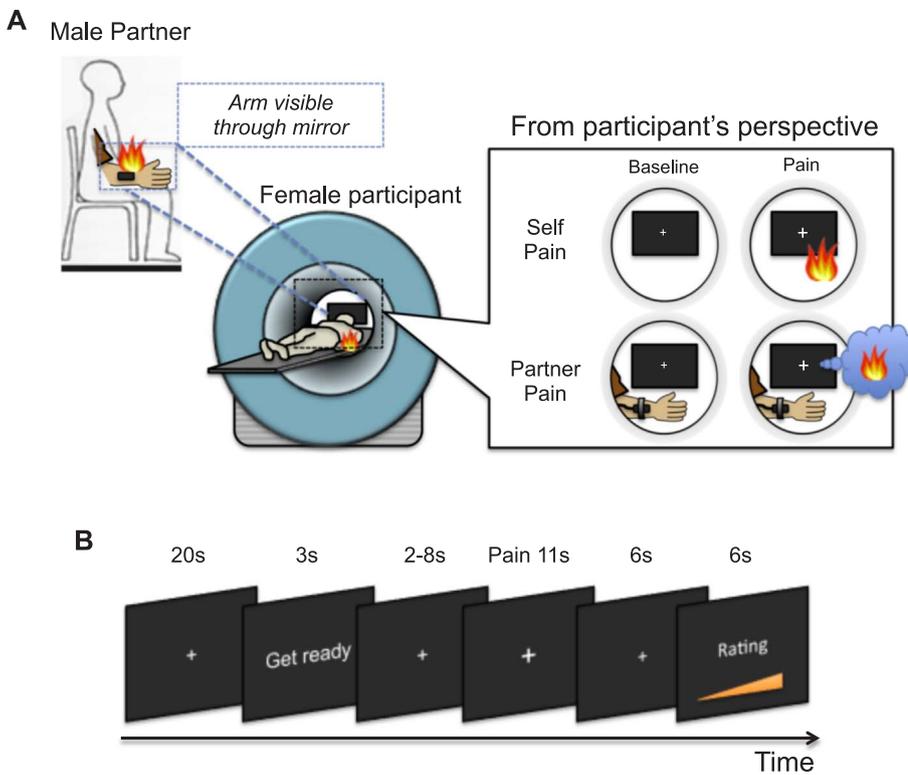
In this context, a recent functional Magnetic Resonance Imaging (fMRI) study identified a whole-brain multivariate pattern for a

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**Fig. 1.** Schematic representation of experimental design. A. Female participants and their male partners in the scanner room and information accessible to the female partner during scanning. B. Example of trial design schematics for Self-Pain and Partner-Pain runs.

particular kind of empathic pain—vicarious pain elicited by observing pictures of others in pain (Krishnan et al., 2016). This pattern, named the Vicarious Pain Signature (VPS), can be used to track the intensity of vicarious pain in new individuals and studies. The VPS responded more strongly when images of others' pain elicited high compared to low vicarious pain ratings in 100% of test participants. In contrast, the VPS did not respond at all during the direct experience of first-person physical pain. Conversely, a previously validated signature for physical pain, the Neurologic Pain Signature (NPS) (Wager et al., 2013), tracked the intensity of first-person, but not vicarious pain. These studies suggest that distributed whole-brain representations of vicarious pain and first-person pain, or 'Self-Pain,' may differ. It is worth noting that the VPS is merely one distributed brain measure that captures some of the experiences and components that are related to empathy for pain. In this context, we do not imply that the VPS is the only signature for vicarious pain or empathy, particularly as empathy is a much broader construct with multiple definitions, aspects, and contributing processes (e.g., Klimecki et al., 2013, 2014). We also do not claim that it is a pure measure of vicarious pain (in the sense of (Sternberg, 2001)), nor do we claim that it is binary (on or off at any given time), or that it is a complete model of the brain systems that contribute to vicarious pain.

Establishing the generalizability of measures and findings across studies and paradigms is crucial for developing a cumulative science of empathy. Signatures like the VPS and NPS can contribute to this effort by providing measures whose predictions can be tested and validated in new studies. The VPS accurately tracked vicarious pain in one particular context, but it is unclear whether it generalizes to other, more ecologically valid, empathy paradigms. The VPS was developed using a "picture-based" paradigm, in which participants observed pictures of painful actions inflicted on strangers' upper and lower limbs. In contrast, the other commonly used empathy paradigm—which we refer to as "cue-based" empathy—involves a two-person setting in which a person in the scanner observes a partner experiencing pain in real time (e.g. (Lamm et al., 2011; Singer et al., 2004; Singer et al., 2008)). The two paradigms have several important differences. Responses in picture-based paradigms could be partly driven by visuospatial salience.

By contrast, cue-based empathy requires the cognitive interpretation of an otherwise neutral cue's meaning to generate empathic experience. Further, as the target person is usually a friend or romantic partner of the observer, cue-based paradigms may arguably generate, in agreement with related observations (Cheng et al., 2010; Cikara and Fiske, 2011; Hein and Singer, 2008; Lamm et al., 2011; Singer et al., 2006; Wang et al., 2016; Xu et al., 2009), stronger empathic responses, reduce automatic aversive reactions elicited by 'painful' images (Preston and de Waal, 2002; Singer and Lamm, 2009), and increase ecological validity (Lamm et al., 2011).

It is unclear whether the VPS should generalize to cue-based empathy. Previous studies have identified both similarities and differences in brain responses to picture-based versus cue-based paradigms (Lamm et al., 2011). For example, a meta-analysis showed overlapping activation in the anterior insula (aIns) and dorsal anterior cingulate cortex (dACC), but cue-based paradigms elicited larger activations in regions associated with mentalizing and theory of mind (Lamm et al., 2011). Another open issue is whether the VPS, or even the NPS, will respond to others' pain when the other is a close significant person. Higher degrees of interpersonal relationship predict greater distress at another's pain and greater activity in the dACC and aIns (e.g. (Cheng et al., 2010; Hein and Singer, 2008; Singer et al., 2006; Wang et al., 2016; Xu et al., 2009)). The neural dissociation between self-pain and other-pain that we observed previously may thus be limited only to the observation of pain in strangers; observing pain in a close significant other may activate the NPS, which would argue in favor of a more similar whole-brain state as first-person pain when the other's pain really matters.

Here, we examine the overlap and differences between self-pain and partner-pain using a cue-based empathy paradigm. We first assess overlaps and differences in brain activation using a standard univariate analysis approach. We then prospectively test VPS and NPS selective responses for Self-Pain and Partner-Pain. The study provides a measure of discriminative accuracy between self- and partner-pain based on VPS and NPS responses. Lastly, we assess whether perceived closeness with the romantic partner modulates both brain activation responses and specific VPS responses to partner's pain.

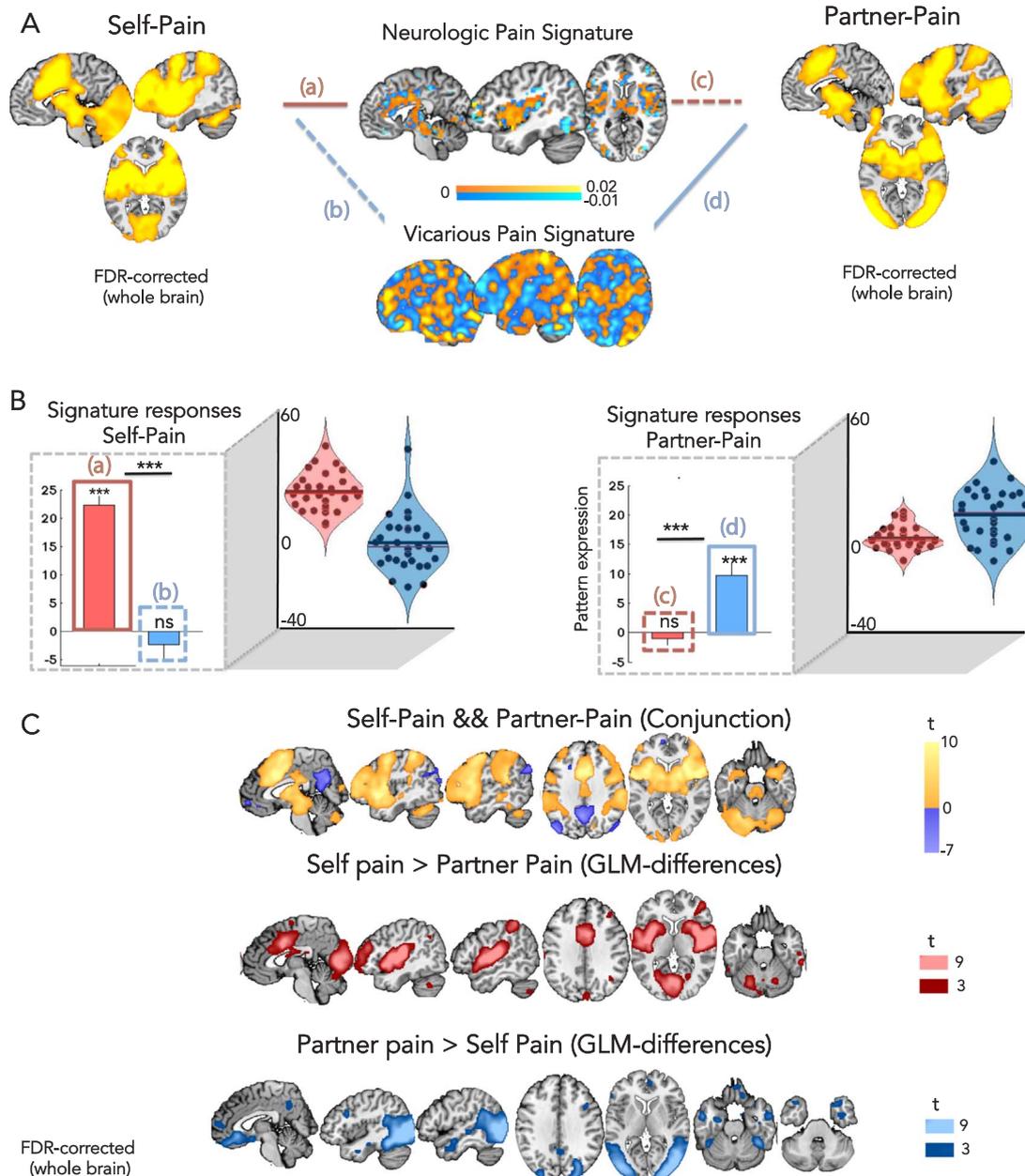
## 2. Results

Thirty female participants underwent a cue-based empathy paradigm during fMRI scanning (cf. (Singer et al., 2004)). Each participant observed her romantic partner in pain (Partner-Pain condition) through a mirror system installed in the scanner. Pain in the romantic partner was indicated by a symbolic visual cue (Fig. 1). In separate trials, the same participants received painful heat stimulation (Self-Pain condition). Both, Self-Pain and Partner-Pain were preceded by an anticipation condition of variable duration.

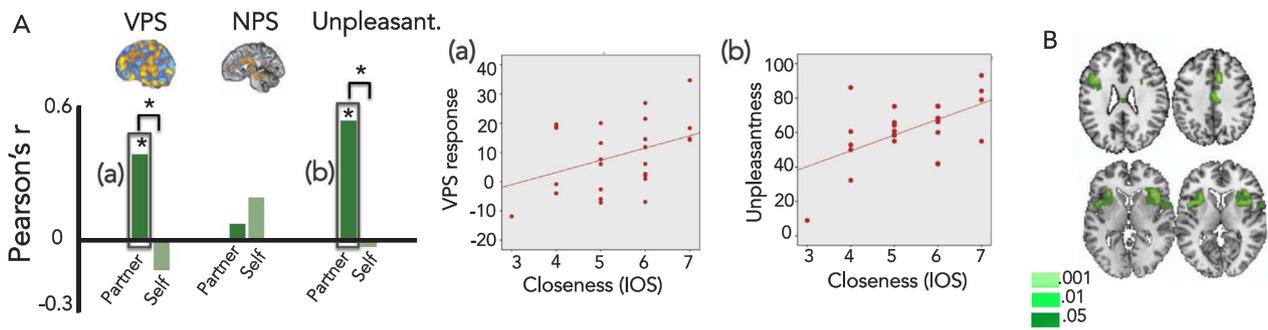
Both experiences of Self-Pain and Partner-Pain evoked significant unpleasantness ( $49.18 \pm 14.00$  and  $62.87 \pm 18.18$ , respectively, on a visual analog scale (VAS) from 0 to 100). Women rated the experience

of Partner-Pain as more unpleasant than their first-person pain experience ( $t = 3.62$ ,  $p = 0.001$ ).

Compared to normative data, participants reported average to high perceived interpersonal closeness to their partners, as assessed using the Inclusion of Other in the Self scale (IOS (Aron and Smollan, 1992)) (minimum 1, maximum 7:  $5.38 \pm 1.09$ , range: 4–7). They also reported average to above-average scores on Sternberg's Triangular Love scale (Sternberg, 1988), used as a measure of love and bonding in the relationship (total score:  $382.36 \pm 25.41$ ) and medium to high emotional empathy scores using the Emotional Empathic Tendency Scale (Mehrabian and Epstein, 1972) ( $163.63 \pm 18.03$ ). We focus on perceived closeness due to our interest in disentangling whether greater self-partner closeness may predict greater VPS (others pain marker)



**Fig. 2.** Signature responses and brain activation during Self-Pain and Partner-Pain. **A.** Brain activation during Self-Pain and Partner-Pain conditions. In the center, brain pattern of voxel weights for the Neurologic Pain Signature and Vicarious Pain Signature. The blue and red lines represent the dot-product computations to obtain the pattern expression scores represented in Fig. 2B and C. **B.** The pink and blue bars represent the average and standard error of the pattern expression for the NPS (pink) and VPS (blue) during Self-Pain (left) and Partner-Pain (right). The violin plots represent NPS or VPS pattern expression for each subject; the horizontal lines represent the mean and median of each distribution. **C.** The top panel represents the conjunction of brain activations for Self-Pain and Partner-Pain. The middle and bottom panels represent activation differences between Self-Pain and Partner-Pain. All results are whole-brain corrected for multiple comparisons using FDR correction ( $q < 0.05$ ). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



**Fig. 3.** Correlations of brain responses with perceived closeness to the romantic partner (IOS). A. Significant positive correlation between closeness with the romantic partner and VPS responses during Partner-Pain specifically. Also, greater closeness with the romantic partner predicted greater unpleasantness during Partner-Pain specifically. \* represents significant result ( $p < 0.05$ ). (a)  $r_{\text{Partner-Pain}} = 0.39$ ,  $p = 0.05$ ; Steiger z-test of comparison of two correlation coefficients (Partner-Pain vs. Self-Pain),  $z = 2.47$ ,  $p = 0.01$ ; (b)  $r_{\text{Partner-Pain}} = 0.559$ ;  $p = 0.003$ ; Steiger z-test of comparison of two correlation coefficients (Partner-Pain vs. Self-Pain),  $z = 4.17$ ,  $p = 0.00003$ . B. Significant exploratory (uncorrected  $p < 0.001$ ,  $k > 3$  voxels) correlations between closeness and brain activation during partner pain, indicating that greater closeness with the romantic partner predicted greater activation in aIns, dACC and left DLPFC during Partner-Pain. No significant correlations of closeness were observed with during Self-Pain.

responses or, contrarily, greater NPS (self pain marker) responses during partner pain.

### 2.1. VPS and NPS responses during Partner-Pain and Self-Pain

Fig. 2A shows the one sample t-test general linear model (GLM) activation maps corresponding to *Self-Pain* and *Partner-Pain*, respectively. As observed previously (e.g., (Lamm et al., 2011; Singer et al., 2004)), both *Partner-Pain* and *Self-Pain* conditions engage largely overlapping neural circuitry.

Fig. 2B shows responses from the VPS and NPS signatures for both *Self-* and *Partner-Pain*. These responses show a clear double dissociation of brain signature responses during *Self-Pain* and *Partner-Pain* conditions. During *Self-Pain*, we observed significant NPS responses ( $t = 13.70$ ,  $p < 0.00005$ ), but not VPS responses ( $t = -1.03$ ,  $p = 0.308$ ). The NPS also showed no response during *Self-Pain* anticipation ( $t = 1.59$ ,  $p = 0.13$ ). In sharp contrast, during the *Partner-Pain* condition, we observed significant VPS responses ( $t = 4.71$ ,  $p = 0.00005$ ), but not NPS responses ( $t = -1.03$ ,  $p = 0.308$ ). The VPS did not respond to *Partner-Pain* anticipation ( $t = 1.19$ ,  $p = 0.24$ ). Importantly, relative differences (VPS – NPS) were predictive of *Partner-Pain* vs. *Self-Pain* in 97% of participants, providing strong discriminative accuracy (sensitivity: 97%, confidence interval (C.I., 91–100%), specificity: 97% (C.I., 91–100%); accuracy: 97%  $\pm$  3.3% (SE),  $p < 0.000001$ ). The results replicate using a VPS brain pattern that was developed excluding the occipital lobe (see Supplementary Fig. 2 and (Krishnan et al., 2016)), suggesting that the double dissociation between *Self-* and *Partner-Pain*, which activate the NPS and VPS, respectively, is not solely explained by different activation patterns in the visual cortex for *Self-Pain* and *Partner-Pain*.

In order to determine whether the expression of the two brain signatures was correlated across subjects, we computed the group correlation between NPS and VPS expression during *Self-Pain* ( $r = -0.25$ ,  $p = 0.19$ ), *Partner-Pain* ( $r = -0.22$ ,  $p = 0.24$ ), and *NPS-Self-Pain* with *VPS-Partner-Pain* responses ( $r = 0.09$ ,  $p = 0.63$ ). Such measures are not significantly correlated; some values show a trend towards a negative association. The results further reinforce a lack of association between the brain processes captured by the two brain markers.

For completion and comparison, we also illustrate commonalities and differences in terms of brain activation using a standard GLM approach. We observed overlapping activation (in a conjunction analysis (Nichols et al., 2005)) spanning along the caudal-rostral and dorsal-ventral neural axis for both aversive experiences including somatosensory regions, anterior/mid insula/opercula, dACC, supplementary motor area (SMA), dorsomedial prefrontal cortex (DMPFC), dorso-lateral prefrontal cortex (DLPFC), amygdala, basal ganglia, thalamus and midbrain including PAG, cerebellum and visual regions.

Importantly, pain-evoked activations were stronger for the *Self-Pain* condition particularly for somatosensory regions in the posterior insula/SII (mostly absent for the *Partner Pain* condition), and also for mid/aIns/opercula, dACC/SMA, and inferior frontal gyrus (Fig. 2C). Contrarily, regions that have more traditionally been associated with mentalizing and theory of mind processes, such as the MPFC and precuneus, TPJ, superior temporal sulcus (STS) and temporal pole together with lateral visual and superior parietal regions, play a significantly greater role in *Partner-Pain* (Fig. 2C). It is noteworthy that this pattern of activation differences is congruent with the distribution of strongest and most reliable weights in the NPS and VPS patterns (Supplementary Fig. 1). Note that NPS and VPS have opposite sign weights in posterior insula and SII (positive and negative, respectively). The same opposing role is observed for the TPJ and mentalizing systems showing mostly negative weights for the NPS and positive weights for the VPS (Supplementary Fig. 1, panels B and C). On the other hand, besides the strong predominance of reliably positive weights in the NPS for insula/opercula regions, the VPS shows significant positive weights in basal ganglia/dorsal mid insula clusters, in regions overlapping with NPS positive weights (Supplementary Fig. 1D).

### 2.2. Correlations between interpersonal closeness with the partner and brain signature responses

Finally, we assessed whether individual differences in perceived closeness with the romantic partner were related to VPS responses and unpleasantness ratings during the *Partner-Pain* condition. Fig. 3 shows that greater closeness with the romantic partner predicted larger VPS responses ( $r = 0.388$ ,  $p = 0.05$ ). This relationship was selective for *Partner-Pain*, as closeness and VPS responses during *Self-Pain* were uncorrelated ( $r = -0.14$ ,  $p = 0.48$ ) and the Steiger z-test (Steiger, 1980) (which is used to statistically compare two correlation coefficients in dependent data) indicated a significant difference between *Partner-Pain* and *Self-Pain* correlation coefficients ( $z = 2.47$ ,  $p = 0.01$ ). Perceived closeness also predicted the level of unpleasantness evoked during *Partner-Pain* ( $r = 0.559$ ,  $p = 0.003$ ). This was not the case for *Self-Pain* ( $r = -0.03$ ,  $p = 0.88$ ); the Steiger z-test of comparison of two correlation coefficients (*Partner-Pain* vs. *Self-Pain*) was also statistically significant,  $z = 4.17$ ,  $p = 0.00003$ .

For comparison, we also assessed exploratory whole-brain, voxel-wise GLM correlations between closeness and brain responses during *Partner-Pain* (uncorrected  $p < 0.001$ ,  $k > 3$  voxels within the activation mask). The correlations, although preliminary, are illustrative for comparison with previous literature and with brain signature correlation results. We found a significant correlation between perceived closeness with the romantic partner and brain activation during *Partner-Pain* in the aIns/frontal opercula, dACC/SMA and left dorsolateral

prefrontal cortex.

### 3. Discussion

Establishing the generalizability of measures and findings across studies and paradigms is crucial for a cumulative science of empathy. Here we show that the VPS, a brain signature validated to track vicarious pain using a “picture-based” paradigm, generalizes to a more ecologically valid “cue-based” pain empathy paradigm (Lamm et al., 2011; Singer et al., 2004). Both paradigms are designed to evoke a vicarious pain response, and both reliably activate the dACC and aIns (Singer, 2007; Singer and Lamm, 2009; Singer et al., 2004; Singer et al., 2006), but they also differ in important ways. Vicarious pain may be more strongly driven by visual salience and attention in picture-based paradigms, and by mentalizing in cue-based, interpersonal paradigms (Bernhardt and Singer, 2012; Lamm et al., 2011). A brain measure that tracks vicarious pain in only one paradigm might be argued to primarily be tracking one of these component ‘ingredients’. Thus, the generalization of VPS responses across both paradigms suggests that it is likely tracking something more central to the experience of vicarious pain and related empathetic behaviors across multiple ‘routes of administration.’ Furthermore, we found a double dissociation in VPS and NPS responses to Partner-Pain and Self-Pain (Krishnan et al., 2016; Zaki et al., 2016), such that Self-Pain significantly activated the NPS and not the VPS, whereas Partner-Pain significantly activated the VPS but not the NPS. In line with previous work (Morrison and Downing, 2007; Zaki, Ochsner et al., 2007), this study provides novel evidence highlighting non-overlapping large-scale neural representations between self pain and vicarious pain observed in the close romantic partner. Lastly, greater interpersonal closeness between partners predicted greater VPS (but not NPS) responses, demonstrating a link with real-life interpersonal context. In sum, the VPS generalizes to an ecologically valid model of interpersonal empathy, and Self-Pain and Partner-Pain evoke non-overlapping large-scale neural representations.

We replicate previous findings showing that both pain conditions robustly engaged overlapping aIns and dACC regions (Cheng et al., 2010; Cui et al., 2015; de Vignemont and Singer, 2006; Gu et al., 2012; Jackson et al., 2006; Jackson et al., 2005; Krishnan et al., 2016; Lamm et al., 2007, 2011; Lamm and Singer, 2010; Singer, 2007; Singer and Lamm, 2009; Singer et al., 2004, 2006), potentially reflecting some common mechanisms between the different, yet related, psychological experiences (Cheng et al., 2010; Corradi-Dell’Acqua et al., 2011, 2016; Hein and Singer, 2008; Jackson et al., 2006; Jackson et al., 2005; Lamm et al., 2016b, 2011; Singer et al., 2004, 2006). Two studies have shown partially shared local brain representations in aIns across different domains of aversive experiences in both self and others (Corradi-Dell’Acqua et al., 2011, 2016), although see also (Morrison and Downing, 2007). When instead of using a local approach we consider whole-brain functional activity, the NPS shows a much larger extent of reliable, positively contributing voxels in the aIns and dACC as compared to the VPS (Supplementary Fig. 1). Together, the findings may argue in favor of both, some common (local) and specific (distributed, large-scale) neural representations for self and vicarious pain (Lamm et al., 2016b). Our findings of dissociable distributed large-scale representations for vicarious and physical pain are in line with previous work (Morrison and Downing, 2007; Zaki et al., 2007) and do not imply that nothing is shared. Overlapping activations in parts of the dACC and aIns may encode “ingredients” (Zaki et al., 2016) common to physical and vicarious pain, such as negative affect, salience, arousal, “feeling states” or specific affective representations (Bernhardt and Singer, 2012; Corradi-Dell’Acqua et al., 2011, 2016; Lamm et al., 2016b; Olsson et al., 2016; Rutgen et al., 2015; Singer and Lamm, 2009), “appraisal checks” (Sander et al., 2005; Scherer, 2009) or common “situational contexts” (Barrett et al., 2011). Of note, at the single subject, relevant previous work (Morrison and Downing, 2007) has shown that specific, mostly non-overlapping locations in the dACC activate in response to

self pain and vicarious pain. Accordingly, Zaki and colleagues (Zaki et al., 2007) had originally showed that although aIns and dACC regions showed similar activity during self and vicarious pain at the group level, such regions had significantly different patterns of large scale functional connectivity for the two conditions. Our observations in the context of previous literature suggest common contributions in dACC and aIns to the experiences of self and vicarious pain, yet differentiable brain patterns that may encode the phenomenological qualities of each pain experience.

Perceived interpersonal closeness between partners significantly modulated brain responses to partner pain in two different, yet compatible ways. First, greater closeness with the romantic partner predicted greater aIns/dACC activation, in line with studies showing stronger empathy, distress and activity in aIns/dACC when observing the pain of a close other compared to a stranger (Cheng et al., 2010; Hein and Singer, 2008; Singer et al., 2006; Wang et al., 2016; Xu et al., 2009). At the same time, greater closeness between self and partner predicted stronger VPS, but not NPS, responses, indicating stronger engagement of whole-brain representations of vicarious pain. Thus, vicarious and self-pain may be characterized by both shared component processes and, at the same time, distinct configurations of these component processes across systems. As distributed signatures, the VPS and NPS include specific patterns in the dACC and aIns but also in other regions; therefore, the measurement properties of the VPS and NPS are different from those of their individual constituent regions.

A more detailed examination on the brain dissimilarities between self- and others’ pain shows clearly stronger activations for Self-Pain in the posterior insula/SII, in agreement with greater sensory processing (Farrell et al., 2005; Lopez-Sola et al., 2010, 2016; López-Solà et al., 2014; Peyron et al., 2000). At the pattern level, the NPS shows positive voxel weights in the posterior granular parts of the insula (Ig area (Eickhoff et al., 2006)) and the anterior part of SII OP4 area (Eickhoff et al., 2006). These regions show a pain-specific bias in sensory processing (Mazzola et al., 2012). Interestingly, VPS weights are negative in overlapping voxels within these regions (Supplementary Fig. 1). Therefore, processing a strong sensory input in particular regions of the posterior insula/SII may importantly contribute to somatic pain experiences involving one’s own flesh. On the other hand, brain regions traditionally associated with mentalizing and theory of mind (Frith and Frith, 2006; Gallagher and Frith, 2003; Spreng et al., 2009) including MPFC, and precuneus, TPJ and other temporal cortex regions, may be more important for encoding vicarious pain (Bird et al., 2010; Hein et al., 2010; Lamm et al., 2011; Singer et al., 2004, 2006, 2008; Zaki et al., 2009). Our observations show greater activation for Partner-Pain and mostly positive voxel weights for the VPS in mentalizing/theory of mind regions. Accordingly, the TPJ has been involved in empathy, perspective taking (Jackson et al., 2006; Ruby and Decety, 2003; Saxe and Wexler, 2005), other-self discrimination (Uddin et al., 2006), external- vs. self-agency attributions (Sperduti et al., 2011) and first person perspective taking of vicarious pain (Vistoli et al., 2016). The other regions, such as the MPFC, precuneus and STS may contribute to enhance empathic judgment accuracy (Zaki et al., 2009) and meaning to the visual cue by activating appraisals regarding the partner’s state (Lamm et al., 2011).

Extending the reproducibility and generalizability of the VPS and NPS can help establish the conditions under which they are useful as markers, and when that utility breaks down. Of note, VPS generalization to the cue-based empathy paradigm used here does not imply VPS generalization to other pain empathy contexts. For example, would the VPS also encode experiences of compassion? Would empathic training modulate it (Klimecki et al., 2013, 2014; Lutz et al., 2008; Simon-Thomas et al., 2012; Weng et al., 2013)? Would certain conditions that are associated with blunted vicarious pain responses in aIns/dACC, such as psychopathy or alexithymia (Bernhardt and Singer, 2012; Bird et al., 2010; Decety et al., 2013a, 2014, 2013b; Lamm et al., 2016a; Lockwood et al., 2013; Pujol et al., 2012; Seara-Cardoso et al.,

2015), also reduce VPS responses? Would the VPS generalize to contexts in which one is responsible for pain in others (Koban et al., 2013)? Would the VPS generalize to pain empathy experiences elicited using other methods, such as imagination or stories about pain in others? Last, would the VPS be specific for vicarious pain in humans or may it generalize to observing suffering in animals and even nature (Mathur et al., 2016)?

The design of our study precludes the possibility that VPS responses during Partner-Pain were mostly driven by a basic change in visual input, since the change in visual input for the contrast [Activation – Baseline] was the same for Self-Pain and Partner-Pain. We also may discard the possibility that positive voxel weights in the visual cortex were driving specific VPS responses during Partner-Pain. However, the fundamental difference in primary/secondary cortical sensory processing between the two experiences, Self-Pain (mostly relying on primary/second somatosensory cortices) and Partner-Pain (mostly relying on primary/secondary visual cortices), is a fundamental one, probably deeply associated with the ultimate qualia of the two experiences, and cannot be controlled for in a strict fashion. Also, future studies are warranted to address to which degree may the VPS respond to experimental conditions involving active mental representations of valuable interpersonal information more broadly.

Future studies should quantify, in the same subjects, the amount of variance in multiple cognitive-affective outcomes (e.g., unpleasantness and intensity of the emotional experience, salience ratings, arousal ratings, autonomic responses) that is explained by shared and unshared brain patterns across self and vicarious pain (Krishnan et al., 2016; Zaki et al., 2016). Such relationships at the local regional level should also be compared with the variance explained by large-scale brain representations. By so doing we may gain knowledge regarding the degree and type of shared and specific neuro-computational mechanisms involved in the generation of these different, yet related, psychological experiences.

## 4. Materials and methods

### 4.1. Participants

We recruited 30 healthy women (mean age of  $24.5 \pm 6.65$  years) with no history of psychiatric, neurological, or pain disorders and no current pain symptoms, who were in a committed and monogamous romantic relationship for at least 3 months. All participants and their male partners gave written informed consent that was approved by the institutional review board of the University of Colorado Boulder and were paid for their participation. One additional participant was not able to complete the fMRI session due to a technical (thermode) failure.

### 4.2. Procedures

All participants and their partners first underwent a short pain calibration session to assure normal pain sensitivity and familiarize them with the heat pain stimulation. Although subjects did not receive tailored stimulation during the fMRI session, we wanted to ensure that the stimulus we were to use (47 °C, 11-second stimuli, 7.5-second plateau temperature) was within the tolerable, yet painful, range for all subjects. During the main fMRI session, we then assessed brain and behavioral responses during two experimental conditions of interest. Participants first performed one run (eight trials) of the *Self-Pain* condition, experiencing painful heat stimulation (47 °C, 11-second stimuli, 7.5-second plateau temperature; Fig. 1 for details) administered to the volar surface of the participants' left inner forearm using an MRI-compatible PATHWAY ATS (Advance Thermal Stimulation) system (16-mm diameter thermode; Medoc Ltd., Ramat Yishai, Israel). They then performed one run of the *Partner-Pain* condition, a real two-person, cued-empathy paradigm (cf., (Singer et al., 2004)). We measured brain responses in the female partner to eight identical trials of painful heat

stimulation (also 47 °C, 11-second stimuli, 7.5-second plateau temperature) that were administered to the left forearm of the male partner, who was sitting behind the magnet in the scanner room. The male partner's left forearm with the thermode attached were visible to the female partner via a mirror system; right below the visual cues presented on a screen via e-prime software (see Fig. 1). The Partner-Pain condition involved the continuous display of the partner's arm and hand that were visible through the mirror system for the entire Partner-Pain run. Contrarily, this information was not present during the Self-Pain run. Importantly, the contrast images used to compute VPS and NPS responses for both Partner-Pain and Self-Pain conditions reflected activation increases from baseline, i.e., [Partner-Pain – Baseline] and [Self-Pain minus Baseline]. The only visual change that occurred in this contrast involved, for both conditions (Self- and Partner-Pain), a lower-case fixation cross turning into a slightly larger fixation cross when pain started, and was exactly the same for Self-Pain and Partner-Pain (see Fig. 1A). Thus, there is no difference in visual input indicating the onset of self-pain and partner-pain; the only difference is in what the change in fixation cross signified (onset of self-pain or partner-pain). At the end of each trial, the female participants rated intensity and unpleasantness in the Self-Pain condition, and unpleasantness in the Partner-Pain condition ('How unpleasant was seeing your partner in pain?'). All of the women believed that the manipulation administered to the male partner was real (as it was), as assessed in an interview right at the end of the scanning session.

We collected a measure of perceived closeness with the romantic partner using the Inclusion of Other in the Self scale (IOS, Aron and Smollan, 1992) the measure was collected on 26 out of 30 subjects) and a validated measure of quality of the romantic relationship in terms of perceived love and bonding Sternberg's Triangular Love scale (Sternberg, 1988). We also administered the Emotional Empathic Tendency Scale (Mehrabian and Epstein, 1972) as a measure of emotional empathy tendency.

### 4.3. Statistical analyses

#### 4.3.1. MRI acquisition and preprocessing

Functional brain activity was acquired using a Siemens TrioTim 3T scanner, covering the brain in 26 interleaved transversal slices (3.4 mm isomorphic voxels), with a T2\* weighted EPI GRAPPA sequence (TR = 1.3 s, TE = 25 ms, flip angle = 50°, FOV = 220 mm). SPM8 was used for preprocessing for functional images, using a standard pipeline of motion correction, slice-time correction, spatial normalization to MNI space, and spatial smoothing of images using an 8 mm FWHM Gaussian kernel. For spatial normalization, T1 structural MPRAGE images (1 mm isomorphic voxels) were first coregistered to the mean functional image and then normalized to the SPM template using unified segmentation. Preprocessed functional images were resampled at a voxel size of  $2 \times 2 \times 2$  mm. Regarding motion correction, translation and rotation estimates (x, y, z) were less than 2 mm or 2°, respectively, for all the participants.

#### 4.3.2. First level single-subject fMRI analyses

We used a GLM analysis approach as implemented in SPM8 software to estimate brain responses during (a) Self-Pain and (b) Partner-Pain conditions, for each subject.

For both *Self-Pain* and *Partner-Pain* conditions, a primary task regressor was created by convolving the painful stimulation periods (either Self-Pain or Partner-Pain) with a canonical hemodynamic response function. We also included in the model a regressor that modeled the anticipatory period and another one to model the rating period. The remaining "rest" period served as an implicit baseline. Lastly, we included in the model 24 motion regressors (3 translation and 3 rotation regressors plus their first and second derivatives). Parameter estimates were calculated at each voxel using the general linear model. A high-

pass filter was used to remove low-frequency signal fluctuations (1/180 Hz). We calculated Self-Pain and Partner-Pain (vs. implicit baseline) contrast images for each participant. The individual contrast images (for either the Self-Pain or Partner-Pain condition) were carried forward to a second level random-effects one-sample t-test analysis model (one for each condition, Self-Pain and Partner-Pain) in SPM8.

#### 4.3.3. Signature responses

We computed for each female participant a single scalar value representing their expression of the NPS pattern and the VPS pattern for the Self-Pain and Partner-Pain contrast images described above. It is worth noting that the NPS includes voxel weights in an *a priori* defined mask of brain regions that were significantly related to the term “pain” in the Neurosynth meta-analytic database (<http://neurosynth.org/>), see (Wager et al., 2013) for a detailed description and Fig. 2A for illustration. This mask was used to narrow the feature space to the voxels with high probability of being relevant for pain processing. However, the VPS includes voxel weights for the whole-brain mask (Fig. 2A), since previous literature on the topic was not extensive enough to determine a narrower feature selection for a well-established vicarious pain-processing network. For each contrast image of each female participant (Self-Pain and Partner-Pain), we computed the cross product of the vectorized activation contrast image ( $\beta_{\text{map}}$ ) with the NPS or VPS pattern of voxel weights, respectively ( $\text{NPS}-\omega_{\text{map}}$  and  $\text{VPS}-\omega_{\text{map}}$ ), i.e.,  $\beta_{\text{map}}^T \omega_{\text{map}}$ , yielding a continuous scalar value for each person [for each pattern (NPS and VPS) and condition (Self-Pain and Partner-Pain)]. We also computed the relative difference (VPS – NPS) response for classification purposes. In order to classify Partner-Pain vs. Self-Pain, we took the following steps. We first computed the response for the VPS and the NPS for each participant's beta image for each experimental condition (Partner-Pain and Self-Pain, respectively), as explained above. We then calculated the difference between VPS minus NPS response during (i) Self-Pain and (ii) Partner-Pain conditions, therefore obtaining two numbers per participant. We used publicly available Wager Lab code ([https://github.com/canlab/CanlabCore/tree/master/CanlabCore/Statistics\\_tools/roc\\_plot.m](https://github.com/canlab/CanlabCore/tree/master/CanlabCore/Statistics_tools/roc_plot.m)) to compute the forced-choice classification accuracy for how well the [NPS – VPS] difference correctly classified Self-Pain vs. Partner-Pain for each individual participant. In a single-interval test, a positive [NPS – VPS] difference would be classified as “Self-Pain”, and a negative [NPS – VPS] difference would be classified as “Partner-Pain”. In a forced-choice test, we are using the relative values for each image to classify which of two images (one for each condition) is self-pain and which is partner-pain for a given participant. The image with the more positive [NPS – VPS] value is classified as self-pain, and the other image (with a lower [NPS – VPS] value) as partner-pain. Thus, in this case, zero is a natural criterion value for classification; if the [NPS – VPS] difference for test image 1 minus the [NPS – VPS] difference for test image 2 is greater than zero, the classification is “Self-Pain”. If it is less than zero, the classification is “Partner-Pain”. We report accuracy statistics and classification P-values based on the binomial test, for the standard forced-choice criterion threshold of zero. These accuracy values are reported in the results section.

#### 4.3.4. Second level random-effects group analyses and conjunction analysis

First level contrast images for the pain regressor were carried forward to second-level one sample t-test analyses models in SPM8 to obtain significant group activation results for each condition (Self-Pain and Partner-Pain). Paired sample t-test were also computed in SPM. Lastly, we computed a conjunction mask representing the intersection between significant activations for the Self-Pain and Partner-Pain conditions following the procedure described in (Nichols et al., 2005).

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Matlab code implementing the analyses presented here is available at [wagerlab.colorado.edu](http://wagerlab.colorado.edu).

#### Major research organism

Humans

#### Funding

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#### Impact statement

A whole-brain signature of empathy transfers across two very different experimental paradigms and social contexts—yet, this pattern is separable from a brain signature of acute physical pain.

#### Competing interests statement

All authors declare that they have no competing interests.

#### Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.neuropsychologia.2017.07.012>.

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