



**HAL**  
open science

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

Marina López-Solà, Leonie Koban, Anjali Krishnan, Tor Wager

## ► To cite this version:

Marina López-Solà, Leonie Koban, Anjali Krishnan, Tor Wager. When pain really matters: A vicarious-pain brain marker tracks empathy for pain in the romantic partner. *Neuropsychologia*, 2020, 145, pp.106427. 10.1016/j.neuropsychologia.2017.07.012 . hal-04756905

**HAL Id: hal-04756905**

**<https://hal.science/hal-04756905v1>**

Submitted on 28 Oct 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

**Authors:**

Marina López-Solà<sup>1,2,3\*</sup>  
Leonie Koban<sup>2,3</sup>  
Anjali Krishnan<sup>4</sup>  
Tor D. Wager<sup>2,3</sup>

**Affiliations:**

<sup>1</sup> Department of Anesthesiology, Cincinnati Children's Hospital, University of Cincinnati.

<sup>2</sup> Institute of Cognitive Science, University of Colorado Boulder, U.S.A.

<sup>3</sup> Department of Psychology and Neuroscience, University of Colorado Boulder, U.S.A.

<sup>4</sup> Department of Psychology, Brooklyn College of the City University of New York, U.S.A.

**\*Please address correspondence to:**

Marina López-Solà, PhD.

Assistant Professor.

Department of Anesthesiology, Cincinnati Children's Hospital.

3333 Burnet Avenue

MLC2 7031 Pain Research Center

Location R8 Room 547.

Cincinnati, Ohio 45229

Telephone: 303-817-2410

**Competing interests statement:** All authors declare that they have no competing interests.

### 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 ( $t=4.71$ ,  $p=.00005$ ), but not the NPS ( $t=-1.03$ ,  $p=.308$ ). The Self-Pain condition activated the NPS ( $t=13.70$ ,  $p<.00005$ ), but not the VPS ( $t=-1.03$ ,  $p=.308$ ). Relative VPS-NPS response differences strongly discriminated Partner-Pain vs. Self-Pain (cross-validated accuracy=97%,  $p<.000001$ ). Greater interpersonal closeness between partners predicted greater VPS responses during Partner-Pain ( $r=.388$ ,  $p=.050$ ) and greater unpleasantness when observing the romantic partner in pain ( $r=.559$ ,  $p=.003$ ). 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.

**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.

**Key words:** Somatic pain, Vicarious Pain, Empathy for pain, Romantic Partners, fMRI, Brain, Multivariate Pattern Analysis.

**Major Research Organism:** Humans

**Funding:** This work was supported by grant R01DA035484 (T.D.W.). Dr. López-Solà's work was supported by a Beatriu de Pinós-A Postdoctoral Fellowship (2010\_BP\_A\_00136) from the Government of Catalunya, Spain.

## 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 & Singer, 2012; Lamm, Decety, & Singer, 2011; Zaki, Wager, Singer, Keysers, & Gazzola, 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. 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, Leiberg, Lamm, & Singer, 2013; Klimecki, Leiberg, Ricard, & Singer, 2014)). We also do not claim that it is a pure measure of vicarious pain (in the sense of (S. 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.

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

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, Chen, Lin, Chou, & Decety, 2010; Cikara & Fiske, 2011; Hein & Singer, 2008; Lamm, et al., 2011; Singer, et al., 2006; Wang, et al., 2016; Xu, Zuo, Wang, & Han, 2009), stronger empathic responses, reduce automatic aversive reactions elicited by ‘painful’ images (Preston & de Waal, 2002; Singer & 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 & 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.

### 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 (Figure 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 0-100). 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, 1992)) (minimum 1, maximum 7:  $5.38 \pm 1.09$ , range: 4 to 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 & 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) responses or, contrarily, greater NPS (self pain marker) responses during partner pain.

### ***VPS and NPS responses during Partner-Pain and Self-Pain***

Figure 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.

Figure 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 Figure 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, Brett, Andersson, Wager, & Poline, 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), dorsolateral 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 (Figure 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 (Figure 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 Figure 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 Figure 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 Figure 1D).

### ***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. Figure 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.

### **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 & 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 & 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 & Downing, 2007; Zaki, Ochsner, Hanelin, Wager, & Mackey, 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, Abdelgabar, Keysers, & Gazzola, 2015; de Vignemont & Singer, 2006; Gu, et al., 2012; Jackson, Brunet, Meltzoff, & Decety, 2006; Jackson, Meltzoff, & Decety, 2005; Krishnan, et al., 2016; Lamm, Batson, & Decety, 2007; Lamm, et al., 2011; Lamm & Singer, 2010; Singer, 2007; Singer & Lamm, 2009; Singer, et al., 2004; Singer, et al., 2006), potentially reflecting some common mechanisms between the different, yet related, psychological experiences (Cheng, et al., 2010; Corradi-Dell'Acqua, Hofstetter, & Vuilleumier, 2011; Corradi-Dell'Acqua, Tusche, Vuilleumier, & Singer, 2016; Hein & Singer, 2008; Jackson, et al., 2006; Jackson, et al., 2005; Lamm, Bukowski, & Silani, 2016b; Lamm, et al., 2011; Singer, et al., 2004; Singer, et al., 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; Corradi-Dell'Acqua, et al., 2016), although see also (Morrison & 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 Figure 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 & 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 & Singer, 2012; Corradi-Dell'Acqua, et al., 2011; Corradi-Dell'Acqua, et al., 2016; Lamm, et al., 2016b; Olsson, et al., 2016; Rutgen, et al., 2015; Singer & Lamm, 2009), “appraisal checks” (Sander, Grandjean, & Scherer, 2005; Scherer, 2009) or common “situational contexts” (Barrett, Mesquita, & Gendron, 2011). Of note, at the single subject, relevant previous work (Morrison & 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 alns 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 alns/dACC activation, in line with studies showing stronger empathy, distress and activity in alns/dACC when observing the pain of a close other compared to a stranger (Cheng, et al., 2010; Hein & 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 alns 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, Laird, & Egan, 2005; Lopez-Sola, et al., 2010; Lopez-Sola, et al., 2016; López-Solà, 2014; Peyron, Laurent, & Garcia-Larrea, 2000). At the pattern level, the NPS shows positive voxel weights in the posterior granular parts of the insula (I<sub>g</sub> area (Eickhoff, Schleicher, Zilles, & Amunts, 2006)) and the anterior part of SII (OP4 area ((Eickhoff, et al., 2006)). These regions show a pain-specific bias in sensory processing (Mazzola, Failenot, Barral, Manguiere, & Peyron, 2012). Interestingly, VPS weights are negative in overlapping voxels within these regions (Supplementary Figure 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 & Frith, 2006; Gallagher & Frith, 2003; Spreng, Mar, & Kim, 2009) including MPFC, and precuneus, TPJ and other temporal cortex regions, may be more important for encoding vicarious pain (Bird, et al., 2010; Hein, Silani, Preuschhoff, Batson, & Singer, 2010; Lamm, et al., 2011; Singer, et al., 2004; Singer, et al., 2006; Singer, et al., 2008; Zaki, Weber, Bolger, & Ochsner, 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 & Decety, 2003; Saxe & Wexler, 2005), other-self discrimination (Uddin, Molnar-Szakacs, Zaidel, & Iacoboni, 2006), external- vs. self-agency attributions (Sperduti, Delaveau, Fossati, & Nadel, 2011) and first person perspective taking of vicarious pain (Vistoli, Achim, Lavoie, & Jackson, 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; Klimecki, et al., 2014; Lutz, Brefczynski-Lewis, Johnstone, & Davidson, 2008; Simon-Thomas, et al., 2012; Weng, et al., 2013)? Would certain conditions that are associated with blunted vicarious pain responses in alns/dACC, such as psychopathy or alexythimia (Bernhardt & Singer, 2012; Bird, et al., 2010; Decety, Chen, Harenski, & Kiehl, 2013; Decety, Skelly, Yoder, & Kiehl, 2014; Decety, Skelly, & Kiehl, 2013; Lamm, Bukowski, & Silani, 2016a; Lockwood, et al., 2013; Pujol, et al., 2012; Seara-Cardoso, Viding, Lickley, & Sebastian, 2015), also reduce VPS responses? Would the VPS generalize to contexts in which one is responsible for pain in others (Koban, Corradi-Dell'Acqua, & Vuilleumier, 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, Cheon, Harada, Scimeca, & Chiao, 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.

## Materials and Methods

### *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.

### *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; Figure 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 Figure 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 Figure 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, 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 (R. J. a. B. Sternberg, M L. , 1988). We also administered the Emotional Empathic Tendency Scale (Mehrabian & Epstein, 1972) as a measure of emotional empathy tendency.

### **Statistical analyses**

**MRI acquisition and preprocessing.** Functional brain activity was acquired using a Siemens TrioTim 3T scanner, covering the brain in 26 interleaved transversal slices (3.4mm isomorphic voxels), with a T2\* weighted EPI GRAPPA sequence (TR = 1.3s, TE = 25ms, flip angle = 50°, FOV = 220mm). 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 8mm FWHM Gaussian kernel. For spatial normalization, T1 structural MPRAGE images (1mm 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 2x2x2mm. Regarding motion correction, translation and rotation estimates (x, y, z) were less than 2 mm or 2°, respectively, for all the participants.

**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.

**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 Figure 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 (Figure 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.

**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).

### **Acknowledgements**

The authors declare no conflict of interests. This work was supported by grant R01DA035484 (T.D.W.). Dr. López-Solà's work was supported by a Beatriu de Pinos-A Postdoctoral Fellowship (2010\_BP\_A\_00136) from the Government of Catalunya. Matlab code implementing the analyses presented here is available at [wagerlab.colorado.edu](http://wagerlab.colorado.edu).

## References

- Aron, A. A., E N.; Smollan, D. (1992). Inclusion of Other in the Self Scale and the structure of interpersonal closeness. *Journal of Personality and Social Psychology*, 63, 16.
- Barrett, L. F., Mesquita, B., & Gendron, M. (2011). Context in Emotion Perception. *Current Directions in Psychological Science*, 20, 286-290.
- Bernhardt, B. C., & Singer, T. (2012). The neural basis of empathy. *Annual review of neuroscience*, 35, 1-23.
- Bird, G., Silani, G., Brindley, R., White, S., Frith, U., & Singer, T. (2010). Empathic brain responses in insula are modulated by levels of alexithymia but not autism. *Brain : a journal of neurology*, 133, 1515-1525.
- Cheng, Y., Chen, C., Lin, C. P., Chou, K. H., & Decety, J. (2010). Love hurts: an fMRI study. *Neuroimage*, 51, 923-929.
- Cikara, M., & Fiske, S. T. (2011). Bounded empathy: neural responses to outgroup targets' (mis)fortunes. *Journal of cognitive neuroscience*, 23, 3791-3803.
- Corradi-Dell'Acqua, C., Hofstetter, C., & Vuilleumier, P. (2011). Felt and seen pain evoke the same local patterns of cortical activity in insular and cingulate cortex. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 31, 17996-18006.
- Corradi-Dell'Acqua, C., Tusche, A., Vuilleumier, P., & Singer, T. (2016). Cross-modal representations of first-hand and vicarious pain, disgust and fairness in insular and cingulate cortex. *Nature communications*, 7, 10904.
- Cui, F., Abdelgabar, A. R., Keysers, C., & Gazzola, V. (2015). Responsibility modulates pain-matrix activation elicited by the expressions of others in pain. *Neuroimage*, 114, 371-378.
- de Vignemont, F., & Singer, T. (2006). The empathic brain: how, when and why? *Trends in cognitive sciences*, 10, 435-441.
- Decety, J., Chen, C., Harenski, C., & Kiehl, K. A. (2013). An fMRI study of affective perspective taking in individuals with psychopathy: imagining another in pain does not evoke empathy. *Frontiers in human neuroscience*, 7, 489.
- Decety, J., Skelly, L., Yoder, K. J., & Kiehl, K. A. (2014). Neural processing of dynamic emotional facial expressions in psychopaths. *Social neuroscience*, 9, 36-49.
- Decety, J., Skelly, L. R., & Kiehl, K. A. (2013). Brain response to empathy-eliciting scenarios involving pain in incarcerated individuals with psychopathy. *JAMA psychiatry*, 70, 638-645.
- Eickhoff, S. B., Schleicher, A., Zilles, K., & Amunts, K. (2006). The human parietal operculum. I. Cytoarchitectonic mapping of subdivisions. *Cerebral cortex*, 16, 254-267.
- Farrell, M. J., Laird, A. R., & Egan, G. F. (2005). Brain activity associated with painfully hot stimuli applied to the upper limb: a meta-analysis. *Human brain mapping*, 25, 129-139.
- Frith, C. D., & Frith, U. (2006). The neural basis of mentalizing. *Neuron*, 50, 531-534.
- Gallagher, H. L., & Frith, C. D. (2003). Functional imaging of 'theory of mind'. *Trends in cognitive sciences*, 7, 77-83.
- Gu, X., Gao, Z., Wang, X., Liu, X., Knight, R. T., Hof, P. R., & Fan, J. (2012). Anterior insular cortex is necessary for empathetic pain perception. *Brain : a journal of neurology*, 135, 2726-2735.

- Hein, G., Silani, G., Preuschoff, K., Batson, C. D., & Singer, T. (2010). Neural responses to ingroup and outgroup members' suffering predict individual differences in costly helping. *Neuron*, *68*, 149-160.
- Hein, G., & Singer, T. (2008). I feel how you feel but not always: the empathic brain and its modulation. *Current opinion in neurobiology*, *18*, 153-158.
- Jackson, P. L., Brunet, E., Meltzoff, A. N., & Decety, J. (2006). Empathy examined through the neural mechanisms involved in imagining how I feel versus how you feel pain. *Neuropsychologia*, *44*, 752-761.
- Jackson, P. L., Meltzoff, A. N., & Decety, J. (2005). How do we perceive the pain of others? A window into the neural processes involved in empathy. *Neuroimage*, *24*, 771-779.
- Klimecki, O. M., Leiberg, S., Lamm, C., & Singer, T. (2013). Functional neural plasticity and associated changes in positive affect after compassion training. *Cerebral cortex*, *23*, 1552-1561.
- Klimecki, O. M., Leiberg, S., Ricard, M., & Singer, T. (2014). Differential pattern of functional brain plasticity after compassion and empathy training. *Social cognitive and affective neuroscience*, *9*, 873-879.
- Koban, L., Corradi-Dell'Acqua, C., & Vuilleumier, P. (2013). Integration of error agency and representation of others' pain in the anterior insula. *Journal of cognitive neuroscience*, *25*, 258-272.
- Krishnan, A., Woo, C. W., Chang, L. J., Ruzic, L., Gu, X., Lopez-Sola, 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*.
- Lamm, C., Batson, C. D., & Decety, J. (2007). The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. *Journal of cognitive neuroscience*, *19*, 42-58.
- Lamm, C., Bukowski, H., & Silani, G. (2016a). From shared to distinct self-other representations in empathy: evidence from neurotypical function and socio-cognitive disorders. *Philosophical Transactions of the Royal Society B-Biological Sciences*, *371*.
- Lamm, C., Bukowski, H., & Silani, G. (2016b). From shared to distinct self-other representations in empathy: evidence from neurotypical function and socio-cognitive disorders. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, *371*, 20150083.
- 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*, 2492-2502.
- Lamm, C., & Singer, T. (2010). The role of anterior insular cortex in social emotions. *Brain structure & function*, *214*, 579-591.
- Lockwood, P. L., Sebastian, C. L., McCrory, E. J., Hyde, Z. H., Gu, X., De Brito, S. A., & Viding, E. (2013). Association of callous traits with reduced neural response to others' pain in children with conduct problems. *Current biology : CB*, *23*, 901-905.
- Lopez-Sola, M., Pujol, J., Hernandez-Ribas, R., Harrison, B. J., Ortiz, H., Soriano-Mas, C., Deus, J., Menchon, J. M., Vallejo, J., & Cardoner, N. (2010). Dynamic assessment of the right lateral frontal cortex response to painful stimulation. *Neuroimage*, *50*, 1177-1187.
- Lopez-Sola, M., Woo, C. W., Pujol, J., Deus, J., Harrison, B. J., Monfort, J., & Wager, T. D. (2016). Towards a neurophysiological signature for fibromyalgia. *Pain*.
- López-Solà, M. P., J; Wager, TD; Garcia-Fontanals, A; Blanco-Hinojo, L; Garcia-Blanco, S; Poca-Dias, V; Harrison, BJ; Contreras-Rodríguez, O; Monfort, J;

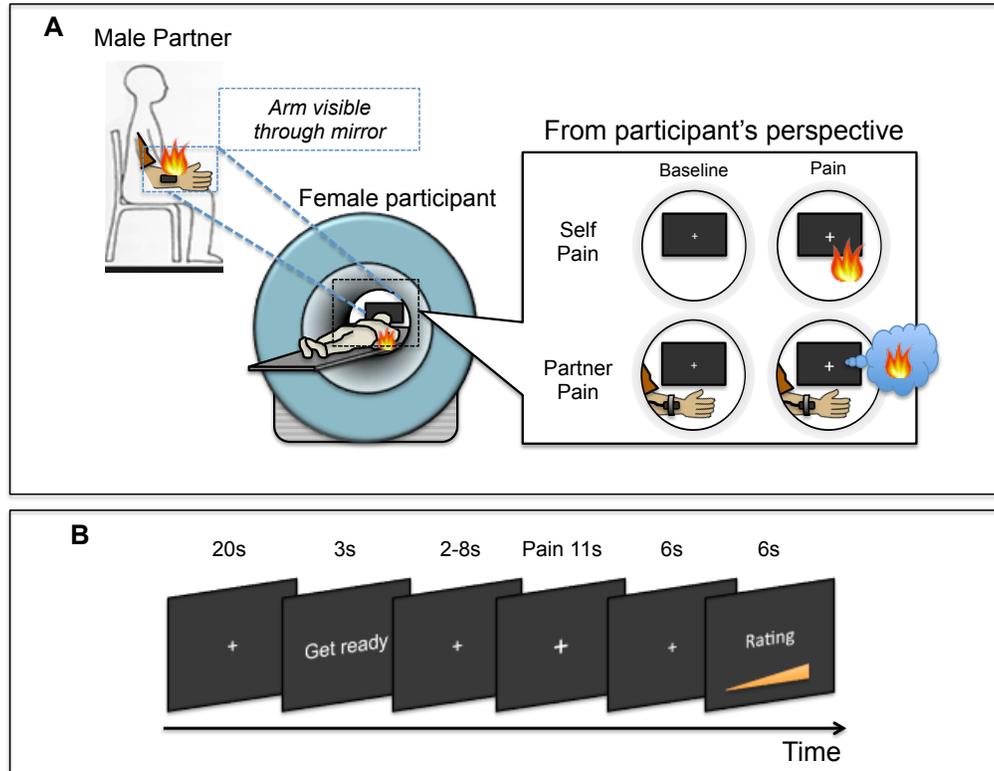
- Garcia-Fructuoso, F.; Deus, J. (2014). Altered fMRI responses to non-painful sensory stimulation in fibromyalgia patients. *Arthritis & Rheumatology*.
- Lutz, A., Brefczynski-Lewis, J., Johnstone, T., & Davidson, R. J. (2008). Regulation of the neural circuitry of emotion by compassion meditation: effects of meditative expertise. *PLoS One*, *3*, e1897.
- Mathur, V. A., Cheon, B. K., Harada, T., Scimeca, J. M., & Chiao, J. Y. (2016). Overlapping neural response to the pain or harm of people, animals, and nature. *Neuropsychologia*, *81*, 265-273.
- Mazzola, L., Faillenot, I., Barral, F. G., Mauguier, F., & Peyron, R. (2012). Spatial segregation of somato-sensory and pain activations in the human operculo-insular cortex. *Neuroimage*, *60*, 409-418.
- Mehrabian, A., & Epstein, N. (1972). A measure of emotional empathy. *Journal of personality*, *40*, 525-543.
- Morrison, I., & Downing, P. E. (2007). Organization of felt and seen pain responses in anterior cingulate cortex. *Neuroimage*, *37*, 642-651.
- Nichols, T., Brett, M., Andersson, J., Wager, T., & Poline, J. B. (2005). Valid conjunction inference with the minimum statistic. *Neuroimage*, *25*, 653-660.
- Olsson, A., McMahon, K., Papenberg, G., Zaki, J., Bolger, N., & Ochsner, K. N. (2016). Vicarious Fear Learning Depends on Empathic Appraisals and Trait Empathy. *Psychological science*, *27*, 25-33.
- Peyron, R., Laurent, B., & Garcia-Larrea, L. (2000). Functional imaging of brain responses to pain. A review and meta-analysis (2000). *Neurophysiologie clinique = Clinical neurophysiology*, *30*, 263-288.
- Preston, S. D., & de Waal, F. B. (2002). Empathy: Its ultimate and proximate bases. *The Behavioral and brain sciences*, *25*, 1-20; discussion 20-71.
- Pujol, J., Batalla, I., Contreras-Rodriguez, O., Harrison, B. J., Pera, V., Hernandez-Ribas, R., Real, E., Bosa, L., Soriano-Mas, C., Deus, J., Lopez-Sola, M., Pifarre, J., Menchon, J. M., & Cardoner, N. (2012). Breakdown in the brain network subserving moral judgment in criminal psychopathy. *Social cognitive and affective neuroscience*, *7*, 917-923.
- Ruby, P., & Decety, J. (2003). What you believe versus what you think they believe: a neuroimaging study of conceptual perspective-taking. *The European journal of neuroscience*, *17*, 2475-2480.
- Rutgen, M., Seidel, E. M., Silani, G., Riecanaky, I., Hummer, A., Windischberger, C., Petrovic, P., & Lamm, C. (2015). Placebo analgesia and its opioidergic regulation suggest that empathy for pain is grounded in self pain. *Proceedings of the National Academy of Sciences of the United States of America*, *112*, E5638-5646.
- Sander, D., Grandjean, D., & Scherer, K. R. (2005). A systems approach to appraisal mechanisms in emotion. *Neural networks : the official journal of the International Neural Network Society*, *18*, 317-352.
- Saxe, R., & Wexler, A. (2005). Making sense of another mind: the role of the right temporo-parietal junction. *Neuropsychologia*, *43*, 1391-1399.
- Scherer, K. R. (2009). Emotions are emergent processes: they require a dynamic computational architecture. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, *364*, 3459-3474.
- Seara-Cardoso, A., Viding, E., Lickley, R. A., & Sebastian, C. L. (2015). Neural responses to others' pain vary with psychopathic traits in healthy adult males. *Cognitive, affective & behavioral neuroscience*, *15*, 578-588.

- Simon-Thomas, E. R., Godzik, J., Castle, E., Antonenko, O., Ponz, A., Kogan, A., & Keltner, D. J. (2012). An fMRI study of caring vs self-focus during induced compassion and pride. *Social cognitive and affective neuroscience*, 7, 635-648.
- Singer, T. (2007). The neuronal basis of empathy and fairness. *Novartis Foundation symposium*, 278, 20-30; discussion 30-40, 89-96, 216-221.
- Singer, T., & Lamm, C. (2009). The social neuroscience of empathy. *Annals of the New York Academy of Sciences*, 1156, 81-96.
- Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R. J., & Frith, C. D. (2004). Empathy for pain involves the affective but not sensory components of pain. *Science*, 303, 1157-1162.
- Singer, T., Seymour, B., O'Doherty, J. P., Stephan, K. E., Dolan, R. J., & Frith, C. D. (2006). Empathic neural responses are modulated by the perceived fairness of others. *Nature*, 439, 466-469.
- Singer, T., Snozzi, R., Bird, G., Petrovic, P., Silani, G., Heinrichs, M., & Dolan, R. J. (2008). Effects of oxytocin and prosocial behavior on brain responses to direct and vicariously experienced pain. *Emotion*, 8, 781-791.
- Sperduti, M., Delaveau, P., Fossati, P., & Nadel, J. (2011). Different brain structures related to self- and external-agency attribution: a brief review and meta-analysis. *Brain structure & function*, 216, 151-157.
- Spreng, R. N., Mar, R. A., & Kim, A. S. (2009). The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis. *Journal of cognitive neuroscience*, 21, 489-510.
- Steiger, J. (1980). Tests for comparing elements of a correlation matrix. *Psychological Bulletin*, 87, 7.
- Sternberg, R. J. a. B., M L. . (1988). *The Psychology of Love*. New Heaven, CT: Yale University Press.
- Sternberg, S. (2001). Separate modifiability, mental modules, and the use of pure and composite measures to reveal them. *Acta psychologica*, 106, 147-246.
- Uddin, L. Q., Molnar-Szakacs, I., Zaidel, E., & Iacoboni, M. (2006). rTMS to the right inferior parietal lobule disrupts self-other discrimination. *Social cognitive and affective neuroscience*, 1, 65-71.
- Vistoli, D., Achim, A. M., Lavoie, M. A., & Jackson, P. L. (2016). Changes in visual perspective influence brain activity patterns during cognitive perspective-taking of other people's pain. *Neuropsychologia*, 85, 327-336.
- Wager, T. D., Atlas, L. Y., Lindquist, M. A., Roy, M., Woo, C. W., & Kross, E. (2013). An fMRI-based neurologic signature of physical pain. *The New England journal of medicine*, 368, 1388-1397.
- Wang, Y., Song, J., Guo, F., Zhang, Z., Yuan, S., & Cacioppo, S. (2016). Spatiotemporal Brain Dynamics of Empathy for Pain and Happiness in Friendship. *Frontiers in behavioral neuroscience*, 10, 45.
- Weng, H. Y., Fox, A. S., Shackman, A. J., Stodola, D. E., Caldwell, J. Z., Olson, M. C., Rogers, G. M., & Davidson, R. J. (2013). Compassion training alters altruism and neural responses to suffering. *Psychological science*, 24, 1171-1180.
- Xu, X., Zuo, X., Wang, X., & Han, S. (2009). Do you feel my pain? Racial group membership modulates empathic neural responses. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 29, 8525-8529.
- Zaki, J., Ochsner, K. N., Hanelin, J., Wager, T. D., & Mackey, S. C. (2007). Different circuits for different pain: patterns of functional connectivity reveal distinct networks for processing pain in self and others. *Social neuroscience*, 2, 276-291.

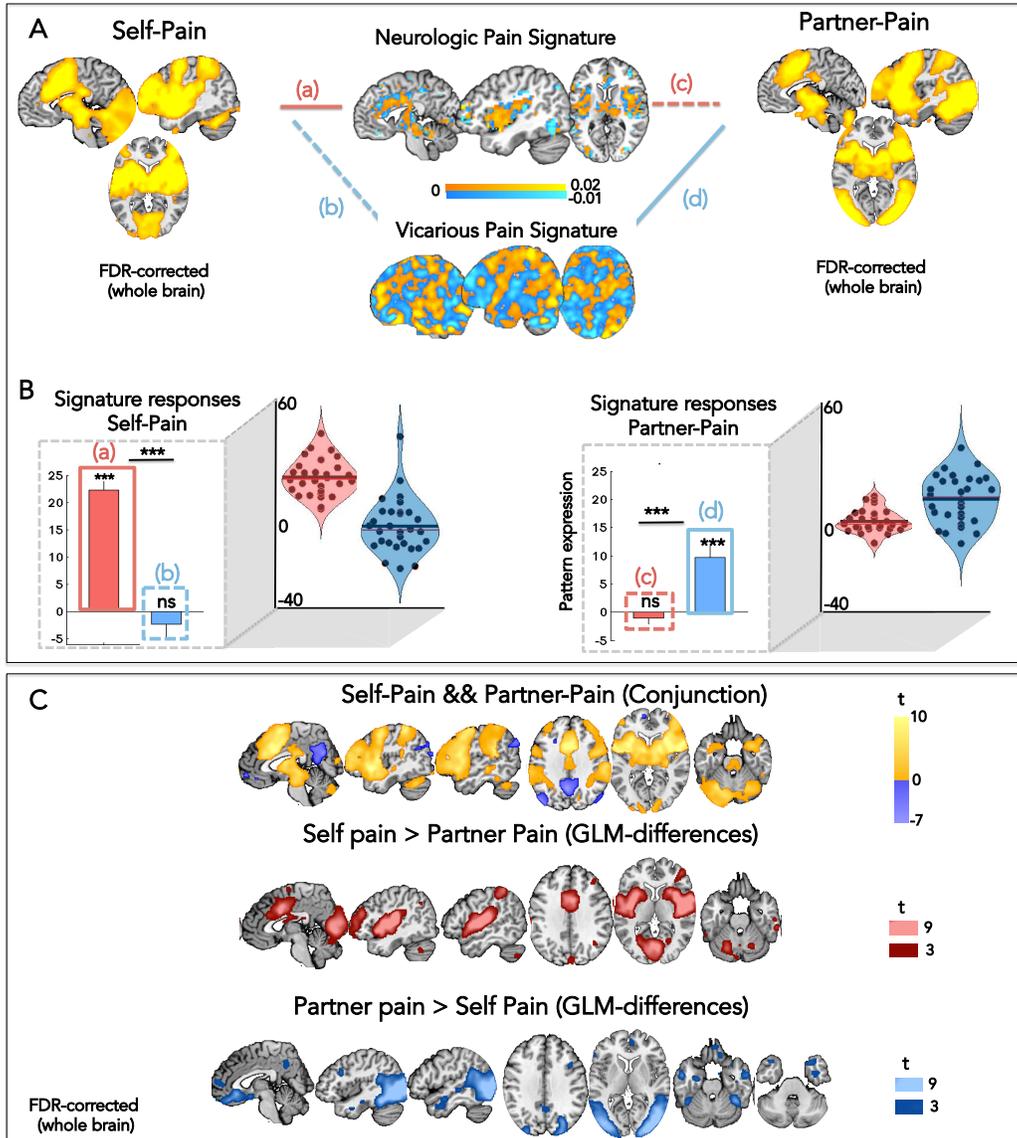
## Generalizability of a brain marker for vicarious pain

- Zaki, J., Wager, T. D., Singer, T., Keysers, C., & Gazzola, V. (2016). The Anatomy of Suffering: Understanding the Relationship between Nociceptive and Empathic Pain. *Trends in cognitive sciences*, 20, 249-259.
- Zaki, J., Weber, J., Bolger, N., & Ochsner, K. (2009). The neural bases of empathic accuracy. *Proceedings of the National Academy of Sciences of the United States of America*, 106, 11382-11387.

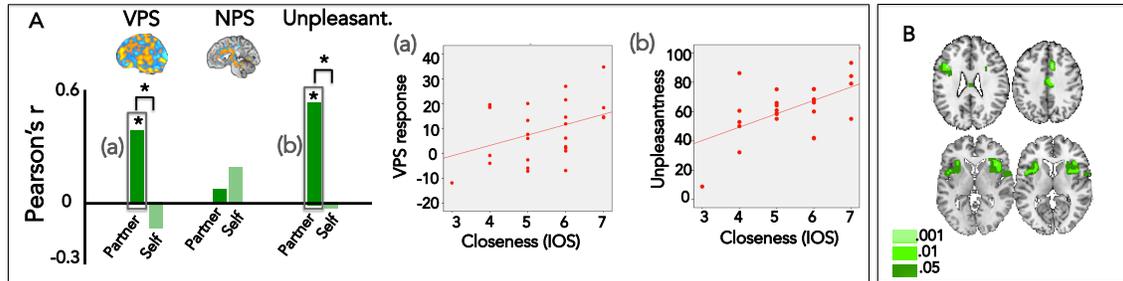
Figures



**Figure 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.

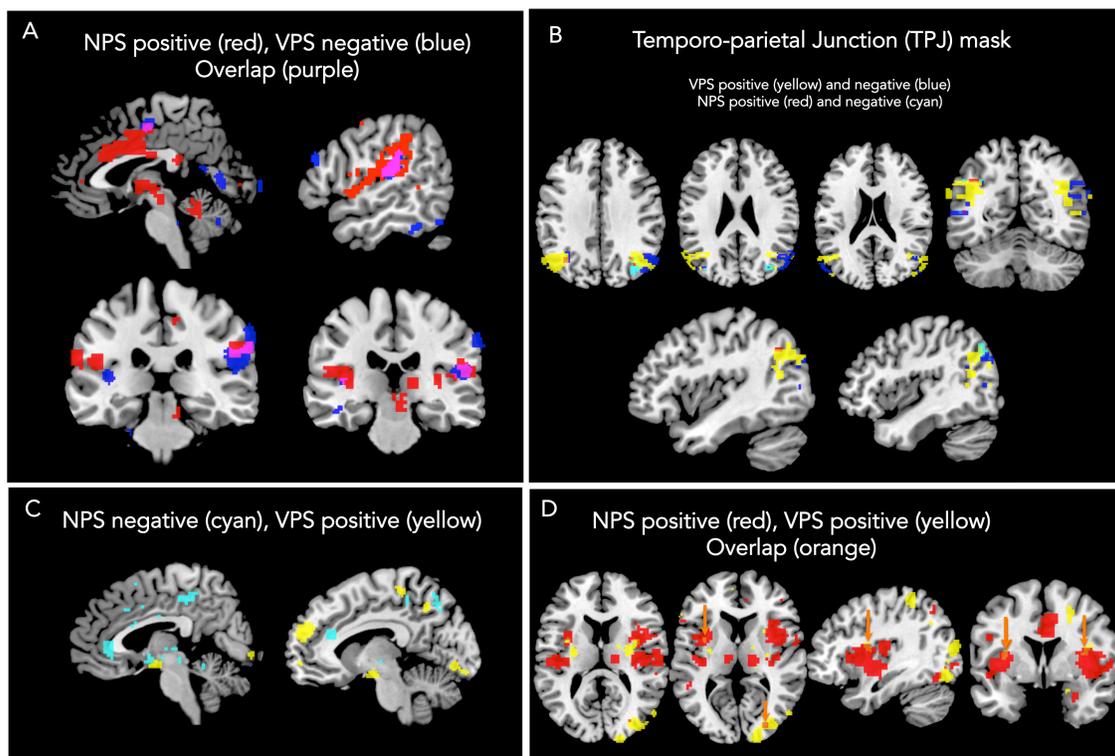


**Figure 2. Signature responses and brain activation during Self-Pain and Partner-Pain.** **A.** Brain activation during Self-Pain and Partner-Pain conditions. In the center, brain pattern of voxel weights for the Neurologic Pain Signature and Vicarious Pain Signature. The blue and red lines represent the dot-product computations to obtain the pattern expression scores represented in figure 2B and 2C. **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 ( $q < 0.05$ ).

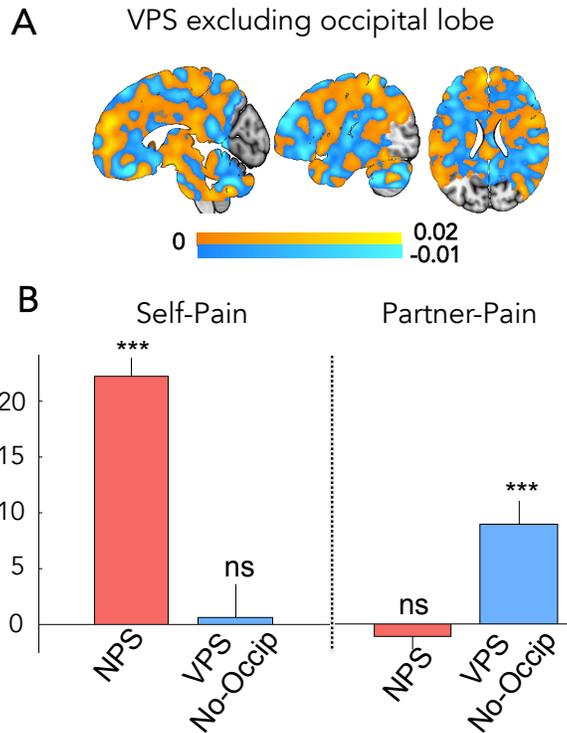


**Figure 3. Correlations of brain responses with perceived closeness to the romantic partner (IOS).** **A.** Significant positive correlations between closeness with the romantic partner and VPS responses during Partner-Pain specifically. Also, greater closeness with the romantic partner predicted greater unpleasantness during Partner-Pain specifically. \* represents significant result ( $p \leq 0.05$ ). (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  $p \leq 0.001$ ,  $k > 3$  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.

## Supplementary Material



**Supplementary Figure 1.** Overlap of positive and negative weights in VPS and NPS patterns in specific regions. **A.** Overlap of positive weights for the NPS (red) and negative weights for the VPS (blue) along the parietal operculum (SII) and the posterior insula. Activation in both sets of regions shifts the predicted response towards physical pain and away from vicarious pain, particularly where they overlap (purple). There is a predominance of positive weights for the NPS in the dorsal anterior cingulate (dACC). **B.** NPS and VPS voxel weights in the extended temporoparietal junction. The figure shows mostly positive weights for the VPS (yellow), with some surrounding negative weights for both VPS (blue) and NPS (cyan). **C.** NPS shows mostly negative weights in medial prefrontal cortex and precuneus regions (cyan), whereas the VPS shows reliably positive weights in proximal regions (yellow) within the so-called “mentalizing/default-mode” network. **D.** Positive NPS (red) and VPS (yellow) weights in the insula and dACC, and their overlap (orange). There is limited overlap in the dorsal anterior and mid-insula, but a preponderance of positive weights for the NPS only in insula and dACC.



**Supplementary Figure 2.** VPS No-Occipital and NPS pattern responses during Partner-Pain and Self-Pain. A. VPS pattern developed excluding the occipital lobe (see (Krishnan, et al., 2016)). B. Left panel: significant response of the NPS ( $t=13.70$ ,  $p < 0.00005$ ) and non-significant response of the VPS\_No-Occipital ( $t=0.218$ ,  $p=0.828$ ) during the Self-Pain condition. Right panel: non-significant response of the NPS ( $t=-1.03$ ,  $p = 0.308$ ) and significant response of the VPS\_No-Occipital ( $t=4.354$ ,  $p=0.00015$ ) during the Partner-Pain condition. Importantly, relative differences (VPS – NPS) were predictive of Partner-Pain vs. Self-Pain in 93% of participants (Sensitivity: 93% Confidence Interval (C.I., 85%-100%), Specificity: 93%, C.I., 84%-100%), providing strong discriminative accuracy (accuracy: 93%  $\pm$  4.6% (SE),  $P = 0.000001$ ) and replicating the results obtained with whole-brain VPS pattern (see main text).

**Supplementary Text 1:**

For completeness, we also report exploratory correlations between VPS responses and stable relationship (Sternberg Triangular Love Scale) and empathy (EETS) measures. VPS responses significantly correlated with Emotional Empathic Tendency Scale scores during the Partner-Pain condition ( $r=0.458$ ,  $p=0.01$ ), and not during the Self-Pain condition ( $r=0.138$ ,  $r=0.467$ ). The two correlation coefficients appeared to be statistically significantly different ( $z=2.21$ ,  $p=0.026$ ) using the Steinberg-z test for dependent data (Steiger et al., 1980). The VPS was not correlated with quality of the relationship, neither for the Partner-Pain condition, nor for the Self-Pain condition ( $p$ -values  $> 0.75$ ).