OXFORD

Pattern similarity and connectivity of hippocampal-neocortical regions support empathy for pain

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Abstract

Empathy is thought to engage mental simulation, which in turn is known to rely on hippocampal-neocortical processing. Here, we tested how hippocampal-neocortical pattern similarity and connectivity contributed to pain empathy. Using this approach, we analyzed a data set of 102 human participants who underwent functional MRI while painful and non-painful electrical stimulation was delivered to themselves or to a confederate. As hypothesized, results revealed increased pattern similarity between first-hand pain and pain empathy (compared to non-painful control conditions) within the hippocampus, retrosplenial cortex, the temporo-parietal junction and anterior insula. While representations in these regions were unaffected by confederate similarity, pattern similarity in the dorsal medial prefrontal cortex was increased the more dissimilar the other individual was perceived. Hippocampal-neocortical connectivity during first-hand pain and pain empathy engaged largely distinct but neighboring primary motor regions, and empathy-related hippocampal coupling with the fusiform gyrus positively scaled with trait measures of perspective taking. These findings suggest that shared representations and mental simulation might contribute to pain empathy via hippocampal-neocortical pattern similarity and connectivity, partially affected by personality traits and the similarity of the observed individual.

Key words: empathy; fMRI; functional connectivity; hippocampus; representational similarity analysis (RSA)

Introduction

Empathy describes sharing the emotional state of another person and is crucial for successful social interactions. The so-called 'shared representations account' suggests that empathy for an affective state engages similar neural processes as experiencing the affective state directly (Zaki *et al.,* 2016; Lamm *et al.,* 2019). In line with this assumption, previous studies implicated the dorsal anterior cingulate cortex (or anterior mid-cingulate cortex;

dACC/aMCC) and the anterior insula in the first-hand experience of pain and empathy (Fan *et al.,* 2011; Lamm *et al.,* 2011; Rütgen *et al.,* 2015; Marsh, 2018). Furthermore, a recent study revealed neurons within the rat ACC that coded not only for first-hand pain but also fired when rats witnessed a conspecific receiving footshocks (Carrillo *et al.,* 2019). These data, however, stand in contrast to results from multivariate analyses that reported both shared and distinct representations during experienced emotions and empathy (Corradi-Dell'Acqua *et al.,* 2011, 2016;

Krishnan *et al.,* 2016), altogether fueling a long-standing debate on the neural underpinnings.

Besides affect sharing, empathy is thought to depend on self-other distinction and mentalizing, i.e. mentally simulating the stance of another person (Lamm *et al.,* 2019). Social cognition theories of mental simulation posit that individuals use their own mental states as models to understand the mental states and actions of others (Gallese and Goldman, 1998). This has been associated with neural processing focused predominantly on the medial prefrontal and posterior cingulate cortex (MPFC and PCC; Gallagher *et al.,* 2000, 2002; Amodio and Frith, 2006; Saxe and Powell, 2006; Spreng and Grady, 2010), and the temporo-parietal junction (TPJ; Saxe and Kanwisher, 2003; Saxe and Wexler, 2005). The hippocampus and adjacent medial temporal lobe (MTL) structures have well-documented roles in recalling past (Scoville and Milner, 1957; Zola-Morgan and Squire, 1990; Vargha-Khadem, 1997; Frankland and Bontempi, 2005; Rugg and Vilberg, 2012; Kim, 2016) and simulating (future) events (Buckner and Carroll, 2007; Schacter and Addis, 2007; Hassabis *et al.,* 2007a, 2007b; Hassabis and Maguire, 2009). Surprisingly, the potential contributions of these areas to empathic processing have been largely neglected (but see Beadle *et al.,* 2013; Stern *et al.,* 2019). Here, we capitalized on hippocampal processing within a sizable sample of healthy participants that engaged in an empathy for pain task.

One-hundred-and-two participants underwent functional MRI while painful and non-painful electrical stimulation was delivered to themselves or to a confederate (Figure 1A and B). Importantly, this task was designed to elicit mental simulation processes while attenuating contributions of mirror neuron activity or motor mimicry. Participants were thus presented with a cue indicating the upcoming pain intensity rather than with pictures of the confederate in painful or non-painful situations. First, we hypothesized that if mental simulation contributes to pain empathy, participants should base the evaluation of another individual's pain on representations of their previous, first-hand pain experiences. This should involve similar neural representations between first-hand pain and pain empathy within the hippocampus and regions important for mental simulation and pain empathy, including the MPFC, PCC, TPJ, dACC/aMCC, and the anterior insula. For quantification, we derived the multivoxel pattern similarity across single trials, embedded within a whole-brain representational similarity analysis (RSA) framework. Second, we expected this to be dovetailed with the recall of recent information from memory. We thus tested increases in task-based connectivity during pain empathy between the hippocampus and neocortical regions that should also be involved when experiencing pain first-hand (Frankland and Bontempi, 2005). Third, because mental simulation was shown to depend on perceived similarity with the other individual (Mitchell *et al.,* 2006; Majdandžić *et al.,* 2016), we further took into account individual ratings of confederate similarity and explored its relationship with neural pattern similarity. Lastly, we stratified our results with trait measures of empathy. By means of this integrative approach, we expected to shed new light on the engagement of hippocampal-neocortical regions, and thus the role of memory-based mental simulation processes in pain empathy.

Materials and methods

This study was part of a larger project investigating the effects of placebo analgesia on pain and pain empathy (Rütgen *et al.,* 2015). In brief, participants had been randomly assigned to a
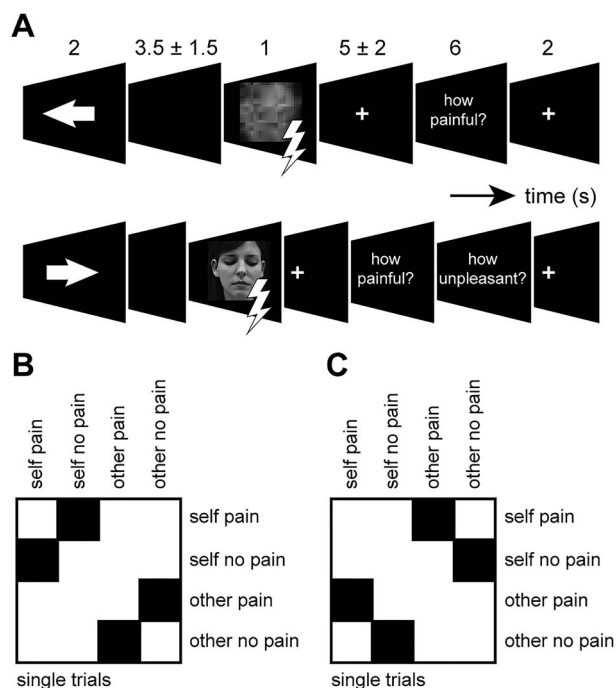
Fig. 1. Pain empathy task and representational similarity analysis (RSA). (A) Examples for self- and other-directed trials during the pain empathy task. Participants first received a cue if the electrical shock was directed at themselves (upper row) or at the confederate (lower row). Arrow color provided information about the intensity of the upcoming electrical stimulation (red, painful; green, non-painful; not shown here). Participants then saw either a scrambled photo of themselves or a photo of the confederate showing a neutral or painful facial expression during non-painful and painful trials, respectively. After this, participants were asked to rate pain and unpleasantness during one-third of the trials. RSA was performed across single trials of the pain empathy task after trials were sorted according to task conditions (i.e. self pain, self no pain, other pain and other no pain): (B) pattern similarity was computed between (self pain × self no pain) and (other pain × other no pain) trials (C) and between (self pain × other pain) and (self no pain × other no pain) trials. Pattern similarity values were extracted from the respective quadrants (marked in black).

placebo or control group and completed a pain empathy task, as well as an affective touch task (not discussed here), followed by the structural scan and a resting-state period (not discussed here), all inside the MR scanner. We previously reported results from univariate activation analysis of the pain empathy task, comparing placebo and control groups (Rütgen *et al.,* 2015). Here, we provide a novel analysis focused on pattern similarity and hippocampal connectivity during pain empathy. Separate analyses yielded highly similar results in both subgroups and no significant differences between the groups (not reported further). Since we were interested in generalized contributions of shared representations and mental simulation processes to pain empathy, we thus collapsed our analyses across the two groups.

Participants

One-hundred-and-two participants were included in this analysis (see Rütgen *et al.,* 2015 for details) (70 females, age range = 19–38 years, mean age = 25). All were right-handed, healthy, had normal or corrected-to-normal vision and gave written informed consent prior to participation. The study was reviewed and approved by the ethics committee of the Medical University of Vienna (Vienna, Austria).

Task and procedures

Electrical stimulation and pain calibration. Individual intensity values (mA) for electrical stimulation were determined during pain calibration. This involved a staircase procedure where participants were asked to rate pain intensity after every electrical shock (500 ms) using a 7-point scale (1, 'perceptible, but no painful sensation'; 7, 'extremely painful'). The same scale was used for pain intensity ratings throughout the study. Electrical stimulation was delivered using a Digitimer DS5 Isolated Bipolar Constant Current Stimulator (Digitimer Ltd, Clinical & Biomedical Research Instruments) and a bipolar concentric surface electrode attached to the dorsum of the left hand. Shock delivery was controlled manually using Cogent (version 1.32, www.vislab.ucl.ac.uk/cogent.php).

Pain empathy task. During the pain empathy task, participants received a cue (2 s) if the electrical shock was directed at themselves (arrow pointing left, self-directed trial; Figure 1A) or at another participant (arrow pointing right, other-directed trial; Figure 1B). Additionally, the color of the arrow informed the participant about the upcoming stimulation intensity (red, painful; green, non-painful). The other participant was a member of the experimental team and actually never received any shocks. After a brief delay jittered between 2 and 5 s (mean = 3.5 s), participants saw a photo of the shock recipient on the screen (1 s; self-directed trial: scrambled photo of themselves; other-directed trial: photo of the confederate with painful/neutral facial expression), and a brief electrical shock (500 ms) was delivered (during self-directed trials only). This was followed by a fixation period ranging from 3 to 7 s (mean = 5 s) and affect ratings (6 s) which were collected during one-third of the trials (self-directed pain ratings: 'How painful was this stimulus for you?', other-directed affect ratings: 'How painful was this stimulus for the other person?', and 'How unpleasant did it feel when the other person was stimulated?'). Trials were separated with a short fixation period (2 s). In total, participants completed 15 trials per condition (i.e. self-directed painful, self-directed non-painful, other-directed painful, other-directed non-painful). The task was programmed and presented with Cogent (version 1.32, www.vislab.ucl.ac.uk/cogent.php) and lasted for approx. 16 min.

Stimulation intensities during self-directed trials were set to individually calibrated stimulation intensities related to pain ratings of 1 (i.e. non-painful trial) and 7 (i.e. painful trial) throughout the task. The average stimulation intensities were 0.15 ± 0.14 mA (mean $\pm$ SEM; pain intensity rating of 1) and 0.74 ± 0.6 mA (pain intensity rating of 7) during non-painful and painful trials, respectively.

Post-experimental ratings and questionnaire data. After MR scanning, participants rated how similar they perceived the confederate, how much they liked the other person, perceived affiliation with the other person, attributed strength, neediness and agreeableness. Here, we focused on perceived confederate similarity only ('How similar was the other person to you?'; 1, 'dissimilar'; 9, 'very similar'). This rating was not available for one participant and we thus excluded this person from all analyses that involved confederate similarity (i.e. $N = 101$). To assess trait empathy, participants completed the Interpersonal Reactivity Index online prior to the start of the experiment (IRI; subscales personal distress, perspective taking, empathic concern, fantasy; Davis, 1983).

MRI data acquisition

Imaging data were acquired using a 3 Tesla MRI scanner (Tim Trio, Siemens, Erlangen, Germany) equipped with a 32-channel head coil. We obtained approx. 500 T_2*-weighted BOLD images during the pain empathy task, using a multiband-accelerated echoplanar imaging (EPI) sequence. Parameters were as follows: TR = 1800 ms, TE = 33 ms, flip angle = 60°, interleaved slice acquisition, 54 axial slices, FOV = 192 × 192 × 108 mm, matrix size = 128 × 128, voxel size = 1.5 × 1.5 × 2 mm. Structural scans were acquired using a magnetization-prepared rapid gradient echo (MP-RAGE) sequence with the following parameters: TR = 2300 ms, TE = 4.21 ms, 160 sagittal slices, FOV = 256 × 256 mm, voxel size = 1 × 1 × 1.1 mm.

MRI data pre-processing

A detailed description of data preprocessing was reported previously (Rütgen *et al.*, 2015). In brief, data were processed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) and Matlab (The Mathworks, Natick, MA, USA), including slice time correction, spatial realignment, normalization to the Montreal Neurological Institute (MNI) standard space and spatial smoothing with a Gaussian kernel (6 mm full-width at half maximum, FWHM).

fMRI data modeling

First, we used representational similarity analysis (RSA; Kriegeskorte *et al.*, 2008) to quantify neural pattern similarity during the pain empathy task. To this end, we obtained single-trial estimates by modeling trials as separate regressors (Mumford *et al.*, 2012), time-locked to the onset of each trial's anticipation cue (Figure 1A and B). Events were estimated as a boxcar function with the duration set until the offset of the delivery screen (mean = 6.5 s, range = 5–8 s) and were convolved with a canonical hemodynamic response function. Rating periods (6 s) were combined within a task regressor of no interest, and the six realignment parameters were appended to capture the effects of head motion. A high-pass filter with a cutoff at 128 s was applied. This resulted in 60 single-trial beta estimates per subject that were used for subsequent RSA.

Second, we used psychophysiological interaction analysis (PPI; Friston *et al.*, 1997) to test connectivity during the pain empathy task. We thus adapted the first-level analysis such that trials of each condition were collapsed into four task regressors of interest (i.e. self pain, self no pain, other pain, other no pain; Rütgen *et al.*, 2015). The remaining regressors were modeled identically to the analysis above, and contrasts were computed to assess connectivity differences between pain and no pain conditions (i.e. self pain > self no pain, other pain > other no pain).

Representational similarity analysis (RSA)

We moved a spherical searchlight (Kriegeskorte *et al.*, 2006; see also Wagner *et al.*, 2016) with a radius of 8 mm (251 voxels) throughout the brain volume while only considering searchlights that contained at least 30 gray matter voxels. Single-trial beta estimates from voxels within a given searchlight were extracted and reshaped into a trial × voxel matrix, whereby trials were sorted according to the four experimental conditions (i.e. self pain, self no pain, other pain and other no pain). Data were z-scored across trials to remove mean activation differences,

and voxel patterns of each trial were correlated with the voxel patterns of all other trials, resulting in a trial × trial similarity matrix. This matrix was then Fisher's z-transformed and pattern similarity scores were calculated by averaging across the respective quadrants of the similarity matrix. First, we assessed pattern similarity for painful and non-painful electrical stimulation, separately for self- vs other-directed conditions ([self pain × self no pain], [other pain × other no pain]; Figure 1B). Second, and central to our hypothesis, we assessed pattern similarity between self- and other-directed trials during painful vs non-painful electrical stimulation ([self pain × other pain], [self no pain × other no pain]; Figure 1C). The pattern similarity values were then assigned to each searchlight's center voxel, yielding four 3-dimensional whole-brain pattern similarity maps per subject.

Group-level significance was tested with paired-sample t-tests, comparing pattern similarity (i) of self- vs other-directed trials during painful and non-painful electrical stimulation (i.e. [self pain × self no pain] vs [other pain × other no pain]) and (ii) between self- and other-directed trials during painful vs non-painful electrical stimulation (i.e. [self pain × other pain] vs [self no pain × other no pain]). We applied cluster-inference with a cluster-defining threshold of P < 0.001 and a cluster-probability threshold of P < 0.05 family-wise error (FWE) corrected for multiple comparisons for all analyses. The corrected cluster size threshold (i.e. the spatial extent of a cluster that is required in order to be labeled as significant) was calculated using the SPM extension 'CorrClusTh.m' and the Newton-Raphson search method (script provided by Thomas Nichols, University of Warwick, United Kingdom, and Marko Wilke, University of Tübingen, Germany; http://www2.warwick.ac.uk/fac/sci/statistics/staff/academic-research/nichols/scripts/spm/). Anatomical nomenclature was obtained from the Laboratory for Neuro Imaging (LONI) Brain Atlas (LBPA40, http://www.loni.usc.edu/atlases/; Shattuck et al., 2008).

Association of pattern similarity with confederate similarity and trait empathy. We further tested if pattern similarity between self- and other-directed trials during the pain empathy task was associated with the perceived similarity of the confederate, as well as with the different aspects of trait empathy (i.e. IRI subscales). We calculated individual difference maps, subtracting pattern similarity between self- and other-related non-painful trials from pattern similarity between self- and other-related painful trials in a voxel-wise manner (i.e. [self pain × other pain] − [self no pain × other no pain]). These pattern similarity-difference maps were then submitted to separate linear regression analyses with individual ratings of perceived confederate similarity or trait empathy added as a covariate of interest.

Connectivity analysis

We performed two PPI analyses (contrasts self pain > self no pain, other pain > other no pain) with a seed placed within the anatomical boundaries of the left hippocampus (based on the Automatic Anatomical Labeling atlas; Tzourio-Mazoyer et al., 2002). The first eigenvector of the seed's time course was extracted (i.e. the physiological factor) and adjusted for average activation during the task using an F-contrast. The eigenvector was then convolved with the respective task condition (i.e. the psychological factor), and connectivity positively related to this interaction was investigated. Contrasts were then submitted to one-sample t-test for random-effects, second-level analysis.

Availability of raw data, RSA code, and unthresholded statistical maps

All anonymized data are available upon request to the authors. The RSA code is openly available on GitHub (https://github.com/isabellawagner/searchlight-rsa) and unthresholded statistical maps are accessible on NeuroVault.org (https://identifiers.org/neurovault.collection:6545).
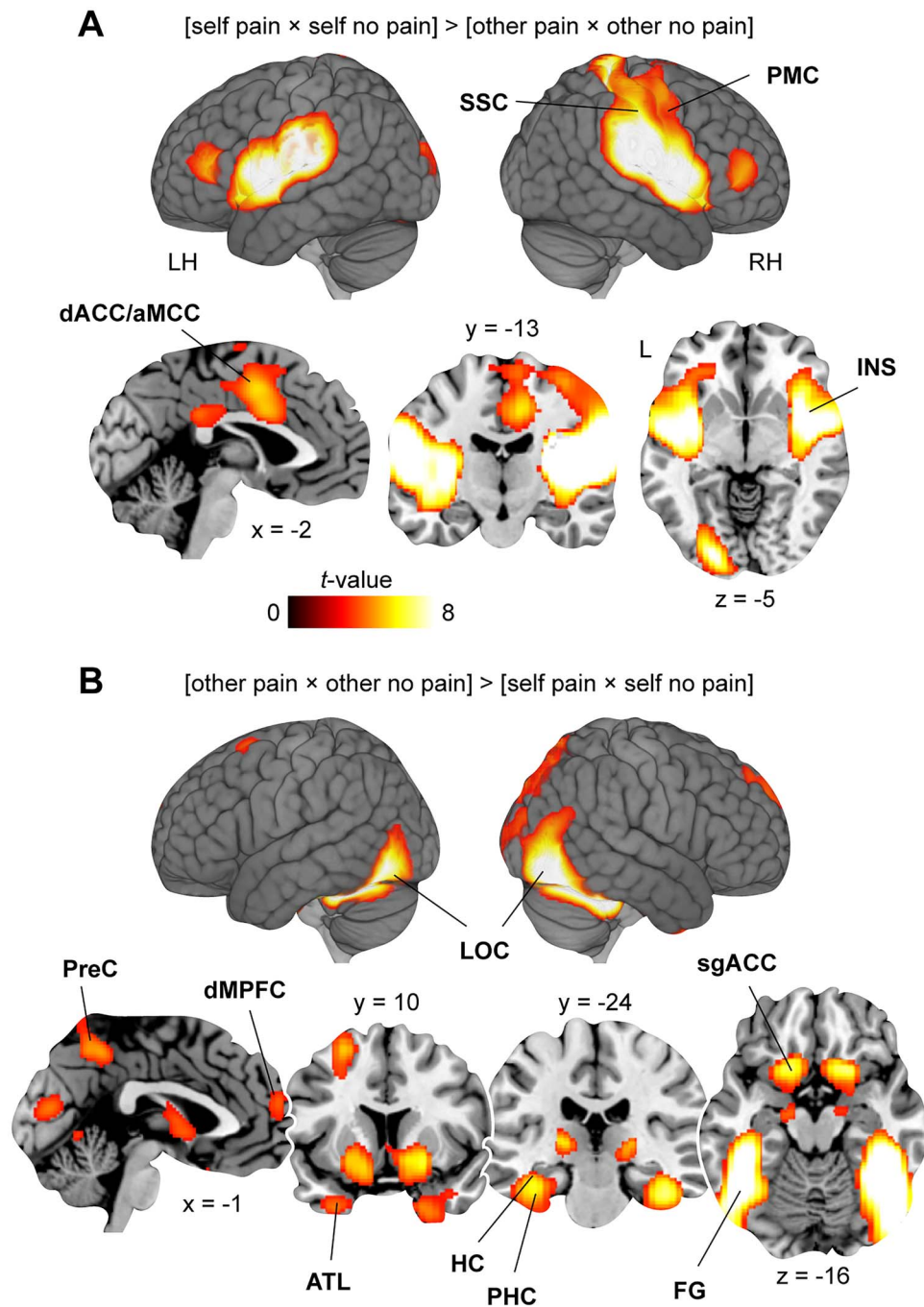
Results

Pattern similarity specific for self- and other-directed electrical stimulation

As the first analysis step, we investigated general differences between the neural representations of self- compared to other-directed painful and non-painful electrical stimulation across trials using whole-brain multivoxel pattern similarity (i.e. the main effect of stimulation target; [self pain × self no pain] vs [other pain × other no pain]). Results revealed increased pattern similarity within bilateral insula, dACC/aMCC, right primary motor and somatosensory cortices (note that electrical stimulation was delivered to the left hand) and (lateral) occipital regions during self- compared to other-directed electrical stimulation (contrast [self pain × self no pain] > [other pain × other no pain]; Figure 2A, Table 1). Conversely, during other- compared to self-directed electrical stimulation, we found increased pattern similarity in bilateral fusiform gyrus and surrounding inferior temporal cortex, hippocampus and parahippocampal gyrus, striatum and subgenual ACC, as well as anterior and posterior midline structures (contrast [other pain × other no pain] > [self pain × self no pain]; Figure 2B, Table 1). To provide a manipulation check of the results, we conducted additional analysis that captured pattern similarity specific for painful (compared to non-painful) first-hand pain and pain empathy (see Supplementary Figure S1 and Supplementary Table S1).

Pattern similarity of first-hand pain and pain empathy

The next step comprised the critical test of our main hypothesis, i.e. if mental simulation contributed to pain empathy, participants should utilize first-hand pain experiences to evaluate the pain of another individual. This should be associated with increased multivoxel pattern similarity (a proxy for similar neural representations) in the hippocampus and surrounding MTL. Furthermore, we expected increased pattern similarity in distributed regions known to play a role in mental simulation and pain empathy such as the MPFC, PCC, TPJ, dACC/aMCC, and the anterior insula. We reasoned that empathic processing should be increased during pain and thus tested our predictions by contrasting the pattern similarity of self- and other-directed electrical stimulation between painful and non-painful trials (i.e. [self pain × other pain] vs [self no pain × other no pain]).

Results showed increased pattern similarity between self- and other-directed painful compared to non-painful electrical stimulation within the left hippocampus, bilateral retrosplenial cortex, extending into the fusiform gyrus and inferior temporal cortex, (lateral) occipital regions, bilateral TPJ, bilateral anterior insula and the right primary motor cortex (contrast [self pain × other pain] > [self no pain × other no pain]; Figure 3A, Table 2). Effects for self-other similarity during non-painful relative to painful electrical stimulation were located in left visual and somatosensory cortices (contrast [self no pain × other no pain] > [self pain × other pain]; not shown in figure, see Table 2). Thus, as expected, the multivoxel patterns between first-hand

Fig. 2. Pattern similarity specific for self- and other-directed electrical stimulation. Increased pattern similarity during (A) [self pain × self no pain] > [other pain × other no pain] and (B) [other pain × other no pain] > [self pain × self no pain]. Results are shown at P < 0.001 (P < 0.05, FWE-corrected at cluster-level; see also Table 1). L, left; LH, left hemisphere; RH, right hemisphere. Structure labels: SSC, somatosensory cortex; PMC, primary motor cortex; dACC/aMCC, dorsal anterior cingulate cortex/anterior mid-cingulate cortex; INS, insula; LOC, lateral occipital cortex; PreC, precuneus; dMPFC, dorsal medial prefrontal cortex; ATL, anterior temporal lobe; HC, hippocampus; PHC, parahippocampal gyrus; sgACC, subgenual ACC; FG, fusiform gyrus.

pain and pain empathy appeared similar in the hippocampus, inferior temporal and retrosplenial cortex, TPJ, primary motor cortex and anterior insula.

Pattern similarity and relation to perceived confederate similarity

It has been repeatedly posited and partly confirmed that perceived similarity between self and other should be conducive to higher empathy and affective simulation (see e.g. Majdandžić et al., 2016). Thus, we explored whether pattern similarity of first-hand pain and pain empathy might scale with how similar participants perceived the confederate. We tested this by assessing the linear cross-participant relationship between whole-brain pattern similarity of self- and other-directed painful (compared to non-painful) stimulation with confederate similarity which was rated post-experimentally. We found that increased pattern similarity was indeed negatively associated with

Table 1. Pattern similarity specific for self- and other-directed electrical stimulation

Contrast & brain region	MNI			Z value	Cluster size
	x	y	z		
[self pain × self no pain] > [other pain × other no pain]					
R supramarginal gyrus	56	−18	26	Inf	25 443
L supramarginal gyrus	−58	−20	26	Inf	14 644
L middle occipital gyrus	−18	−90	−2	7.52	2447
[other pain × other no pain] > [self pain × self no pain]					
R fusiform gyrus	40	−48	−24	Inf	21 699
L fusiform gyrus	−42	−52	−24	Inf	1058
L middle frontal gyrus	−24	8	56	5.2	607
R superior frontal gyrus	14	54	32	4.54	915

MNI coordinates represent the location of peak voxels. We report the first local maximum within each cluster. Effects were tested for significance using cluster inference with a cluster-defining threshold of $P < 0.001$ and a cluster probability of $P < 0.05$, FWE-corrected for multiple comparisons (critical cluster size: 605 voxels). L, left; R, right; Inf, infinite values.

Table 2. Pattern similarity of first-hand pain and pain empathy and relation with perceived confederate similarity

Contrast & brain region	MNI			Z value	Cluster size
	x	y	z		
[self pain × other pain] > [self no pain × other no pain]					
L lingual gyrus	−14	−66	8	Inf	34 625
R inferior frontal gyrus	38	30	2	6.1	4508
R superior frontal gyrus	12	6	66	6.03	2068
L middle frontal gyrus	−26	32	6	5.48	2719
L middle temporal gyrus	−48	−46	6	4.49	963
L middle frontal gyrus	−40	54	24	4.37	1036
[self no pain × other no pain] > [self pain × other pain]					
L middle occipital gyrus	−22	−102	−6	6.22	891
L postcentral gyrus	−36	−26	56	5.64	2181
[self pain × other pain] > [self no pain × other no pain], covariate confederate similarity, negative effect					
R superior frontal gyrus	2	46	36	4.52	553

MNI coordinates represent the location of peak voxels. We report the first local maximum within each cluster. Effects were tested for significance using cluster inference with a cluster-defining threshold of $P < 0.001$ and a cluster probability of $P < 0.05$, FWE-corrected for multiple comparisons (critical cluster sizes: paired-samples t-test, 591 voxels; linear regression, 196 voxels). L, left; R, right; Inf, infinite values.

confederate similarity in the dorsal MPFC (Figure 3B; Table 2). In other words, more similar multivoxel patterns in the dorsal MPFC during first-hand pain and pain empathy were correlated with lower perceived confederate similarity across participants. No other brain region showed a significant negative or positive relationship between pattern and confederate similarities. Furthermore, there was no significant association between pattern similarity and aspects of trait empathy (i.e. subscales of the IRI). To conclude, pattern similarity between first-hand pain and pain empathy was modulated by perceived confederate similarity within the dorsal MPFC.

Hippocampal-neocortical connectivity during first-hand pain and pain empathy

We next reasoned that if participants used representations of their previous first-hand pain experiences to evaluate the pain of others, then this should be paralleled by the recall of recent information from memory. On a neural level, this should be indexed by increased hippocampal coupling with neocortical regions that were also involved when experiencing pain first-hand. Above, we reported increased pattern similarity between first-hand pain and pain empathy within the hippocampus, whereby results appeared left lateralized (Figure 3A; Table 2). We thus placed a seed within the anatomical boundaries of the left hippocampus in order to test connectivity during self- and other-directed painful compared to non-painful electrical stimulation.

First, we found increased hippocampal coupling with bilateral insula, dACC/aMCC, thalamus, right primary motor and somatosensory cortices, lateral prefrontal and occipital regions when participants received painful electrical stimulation themselves (contrast self pain > self no pain; Figure 4A; Table 3). Second, results showed increased hippocampal connectivity with the left fusiform gyrus and right primary motor cortex when painful electrical shocks were delivered to the confederate (contrast other pain > other no pain; Figure 4B; Table 3). To test for potential overlap of hippocampal-neocortical connectivity during first-hand pain and pain empathy, we performed a conjunction analysis (i.e. [self pain > self no pain] ∩ [other pain > other no pain]). Results yielded a cluster within the right primary motor cortex (peak MNI coordinate of local maximum: $x = 52$, $y = −2$, $z = 52$, z-value = 4.14, 11 voxels, $P < 0.001$ uncorrected for multiple comparisons), which did not survive cluster-correction.
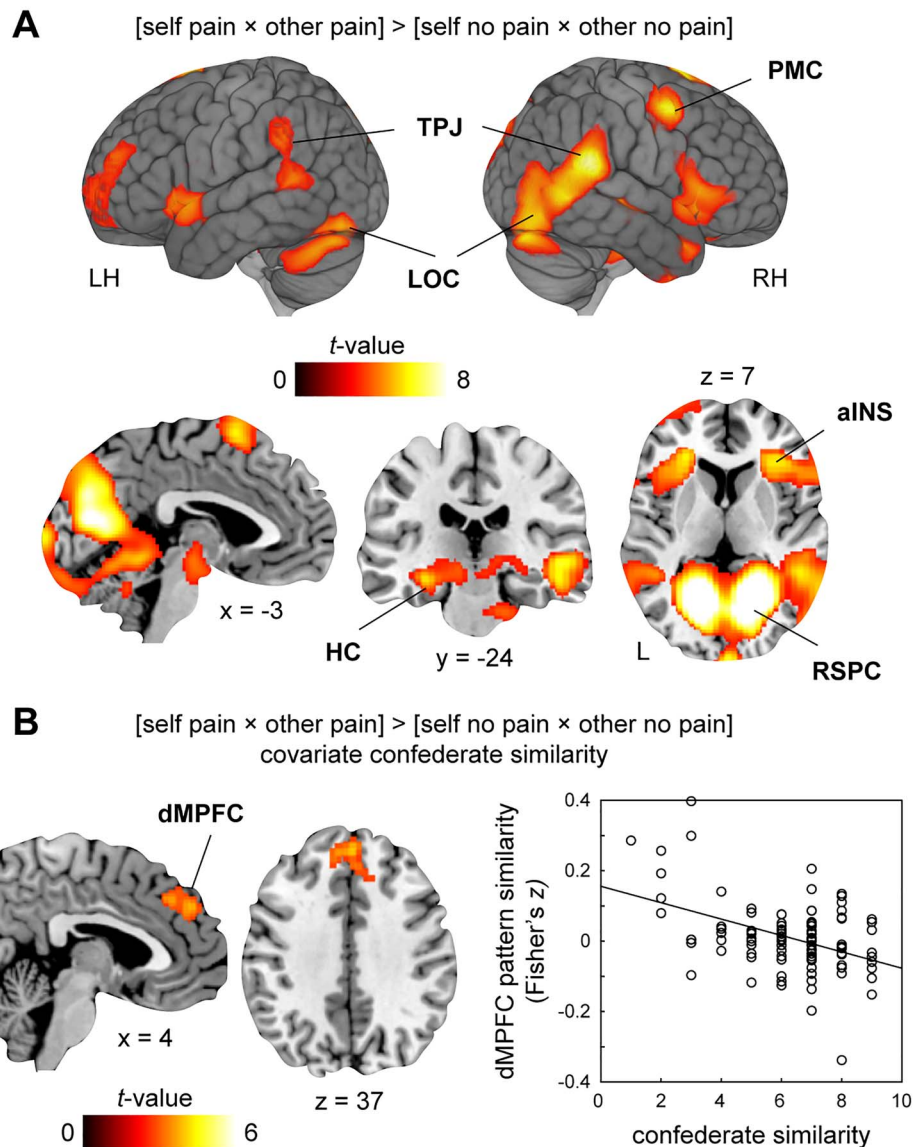
Fig. 3. Pattern similarity of first-hand pain and pain empathy and relation with perceived confederate similarity. (A) Increased pattern similarity during [self pain × other pain] > [self no pain × other no pain]. (B) Increased pattern similarity between first-hand pain and pain empathy was coupled to lower perceived confederate similarity across participants. For visualization purposes, the scatter plot shows the relationship between individual ratings of perceived confederate similarity and pattern similarity (Fisher's z values), extracted from the significant cluster within the dorsal MPFC. Results for both (A) and (B) are shown at $P < 0.001$ ($P < 0.05$, FWE-corrected at cluster-level; see also Table 2). L, left; LH, left hemisphere; RH, right hemisphere. Structure labels: TPJ, temporo-parietal junction; PMC, primary motor cortex; LOC, lateral occipital cortex; HC, hippocampus; aINS, anterior insula; RSPC, retrosplenial cortex; dMPFC, dorsal medial prefrontal cortex.

Thus, the left hippocampus appears coupled to largely distinct neocortical areas and similar regions within the primary motor cortex during both first-hand pain and pain empathy.

Hippocampal-neocortical connectivity and association with trait empathy

Last, we examined if hippocampal-neocortical coupling scaled with confederate similarity or aspects of trait empathy. Connectivity between the hippocampus and the left fusiform gyrus positively correlated with individual differences in perspective taking (i.e. the IRI subscale). Put differently, participants who scored higher on perspective taking showed stronger hippocampal-fusiform connectivity during pain empathy ($r_{\text{Pearson}} = 0.26$, $P = 0.009$, bootstrapped 95% CI based on 5000

samples [0.08 0.44], Bonferroni-corrected for multiple comparisons using a threshold of $\alpha_{\text{Bonferroni}} = 0.01$ (0.05/5); Figure 4C). There was no significant association of empathy-related hippocampus-fusiform gyrus connectivity with confederate similarity ($P = 0.557$), and no significant association with the remaining IRI subscales (IRI personal distress: $P = 0.701$, IRI empathic concern: $P = 0.053$, IRI fantasy: $P = 0.098$). In addition, there was no significant relationship between hippocampus-primary motor cortex connectivity during pain empathy and any of the behavioral measures (confederate similarity: $P = 0.976$, IRI personal distress: $P = 0.697$, IRI perspective taking: $P = 0.313$, IRI empathic concern: $P = 0.950$, IRI fantasy: 0.946). In summary, increases of hippocampal connectivity with the fusiform gyrus during pain empathy were larger in participants with higher self-reported perspective taking skills.

Table 3. Hippocampal connectivity

Contrast & brain region	MNI			Z value	Cluster size
	x	y	z		
self pain > self no pain					
R precentral gyrus	56	8	4	6.94	13 816
R middle occipital gyrus	12	−98	10	6.46	3803
L cingulate gyrus	−2	10	36	5.31	2186
R superior parietal gyrus	24	−40	76	5.18	854
R lingual gyrus	24	−68	−4	5.12	213
L middle temporal gyrus	−58	−64	12	4.86	442
L middle frontal gyrus	−36	42	10	4.6	194
R precentral gyrus	52	0	54	4.53	272
Cerebellum	−26	−62	−22	4.47	288
R inferior frontal gyrus	40	42	8	4.17	196
R lingual gyrus	22	−54	0	4.16	154
L angular gyrus	−36	−52	38	3.94	102
other pain > other no pain					
L inferior temporal gyrus	−48	−50	−16	4.25	83
R precentral gyrus	44	−6	62	3.78	137

MNI coordinates represent the location of peak voxels. We report the first local maximum within each cluster. Effects were tested for significance using cluster inference with a cluster-defining threshold of $P < 0.001$ and a cluster probability of $P < 0.05$, FWE-corrected for multiple comparisons (critical cluster sizes: self pain > self no pain, 96 voxels; other pain > other no pain, 82 voxels). L, left; R, right.

Discussion

We investigated contributions of hippocampal-neocortical representations and connectivity to pain empathy. Our analyses revealed four main findings: first, we found increased pattern similarity between first-hand pain and pain empathy within the hippocampus and a neocortical network, including inferior temporal and retrosplenial cortex, TPJ, primary motor cortex and anterior insula. Second, we showed that increased pattern similarity between first-hand pain and pain empathy within the dorsal MPFC was coupled to lower perceived confederate similarity across participants. Third, results demonstrated that hippocampal-neocortical coupling during first-hand pain and pain empathy was largely distinct but engaged neighboring regions within the primary motor cortex. Fourth, hippocampal connectivity with the fusiform gyrus during pain empathy was larger at higher self-reported skills in perspective taking. These findings suggest that shared representations and mental simulation might contribute to pain empathy via hippocampal-neocortical pattern similarity and connectivity, partially affected by personality traits and the similarity of the observed individual.

We hypothesized that if mental simulation processes support pain empathy, participants should utilize first-hand pain experiences as a model to evaluate the pain of another individual as indicated by similar neural representations, approximated by multivoxel pattern similarity. As expected, results showed increased pattern similarity within the hippocampus, extending into inferior temporal and retrosplenial cortices, TPJ, primary motor cortex and anterior insula (Figure 3A). The hippocampus is regarded as key player for successfully remembering past (Scoville and Milner, 1957; Rugg and Vilberg, 2012; Kim, 2016) and simulating future (Addis et al., 2007; Szpunar et al., 2014; McCormick et al., 2018) or fictitious events (Hassabis et al., 2007a), and it therefore seems vital for mental construction (Schacter and Addis, 2007; Hassabis and Maguire, 2009; Bird et al., 2010; Summerfield et al., 2010) and self-projection (Buckner and Carroll, 2007; Kurczek et al., 2015). Hippocampal lesions in human patients, for instance, were shown to impair the ability to

imagine new experiences (Klein et al., 2002; Hassabis et al., 2007b). Importantly, Beadle et al. (2013) reported lower trait empathy in patients with focal hippocampal damage, along with no effect of empathy induction on empathy ratings or prosocial behavior (Beadle et al., 2013; and see also Rushby et al., 2016). These findings collectively suggest a role of the hippocampus in empathy and mental simulation. Moreover, the MPFC (Benoit et al., 2010, 2014; Kurczek et al., 2015; Schurz et al., 2015; Bertossi et al., 2016a, 2016b; Barry et al., 2019) and PCC (including precuneus and retrosplenial cortex; Vann et al., 2009; Summerfield et al., 2010; Irish et al., 2015; Schurz et al., 2015; Ramanan et al., 2018) are considered pivotal for mental construction and self-projection as well, and are also engaged during theory of mind (Frith and Frith, 1999, 2006; Uddin et al., 2007; Mar, 2011). The latter additionally involves the TPJ, possibly signaling perspective taking to simulate the mental stance of another person (Saxe and Kanwisher, 2003; Saxe and Wexler, 2005; Saxe and Powell, 2006). To summarize, the hippocampus, MPFC, PCC and TPJ constitute a distributed set of brain regions associated with memory, mental construction and simulation, self-projection and theory of mind. Here, we observed that these regions support pain empathy as well, holding similar representations when experiencing pain first-hand and when observing pain in another individual.

Empathy, however, also incorporates affect sharing and self-other distinction (Lamm et al., 2019). While the latter was associated with neural processing within the TPJ (Saxe and Kanwisher, 2003), affect sharing may depend on shared representations during the first-hand (pain) experience and empathy for it (Singer and Lamm, 2009; Decety, 2010). This was linked to neural processing within the dACC/aMCC and anterior insula (Corradi-Dell'Acqua et al., 2011, 2016; Lamm et al., 2011; Rütgen et al., 2018; Carrillo et al., 2019), including an initial, univariate analysis of the current study (Rütgen et al., 2015). Here, we partly confirmed and extended previous findings: First, we found increased pattern similarity within the dACC/aMCC and insula during first-hand pain (compared to pain empathy), while pain empathy (compared to first-hand pain) was associated with the hippocampus, fusiform gyrus, MPFC and PCC (Figure 2A and B).
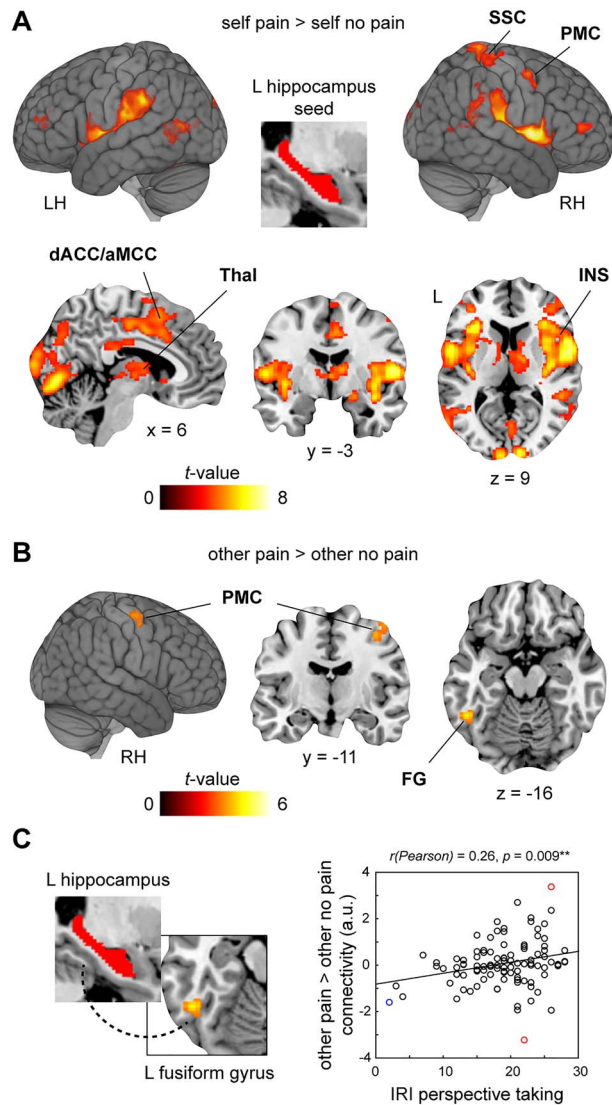
Fig. 4. Hippocampal connectivity and association with perspective taking. Hippocampal connectivity increases during (A) self pain > self no pain and (B) other pain > other no pain. The anatomical seed region within the left hippocampus is marked in red. Results are shown at $P < 0.001$ ($P < 0.05$, FWE-corrected at cluster-level; see also Table 3). (C) Connectivity of the left hippocampus with the left fusiform gyrus (a.u., arbitrary units) showed a positive relationship with perspective taking (IRI subscale). Thus, stronger coupling was associated with higher scores in perspective taking across subjects. **The correlation remained robust when removing three outliers (mean ± 3 standard deviations; one outlier in IRI perspective taking, two outliers in connectivity; $r_{Pearson} = 0.22$, $P = 0.026$, bootstrapped 95% confidence interval based on 5000 samples [0.053 0.4]), and when applying Spearman's rank correlation ($r_{Spearman} = 0.25$, $P = 0.011$, bootstrapped 95% CI [0.07 0.43]; removing three outliers: $r_{Spearman} = 0.23$, $P = 0.025$, bootstrapped 95% CI [0.05 0.41]), but none of these results survived correction for multiple comparisons ($\alpha_{Bonferroni} = 0.01$). L, left; LH, left hemisphere; RH, right hemisphere. Structure labels: SSC, somatosensory cortex; PMC, primary motor cortex; dACC/aMCC, dorsal anterior cingulate cortex/anterior mid-cingulate cortex; Thal, thalamus; INS, insula; FG, fusiform gyrus.

Second, we tackled the question of shared neural representations between first-hand pain and pain empathy and found increased pattern similarity in a set of regions, including bilateral anterior insula (Figure 3A). The insula was associated with pain processing (Downar *et al., 2003*; Legrain *et al., 2011*) and interoceptive awareness (Craig, *2002*, *2009*), and similar

neural representations might thus signal affective sharing with the observed individual (Singer *et al., 2004*; Lamm *et al., 2011*). Somewhat surprising and unexpectedly, we could not identify increased pattern similarity within the dACC/aMCC. While previous work showed overlapping neural assemblies representing first-hand pain and pain empathy within the rodent dACC/aMCC (Sakaguchi *et al., 2018*; Carrillo *et al., 2019*), others reported a domain-general role of this region in empathic processing (Gu *et al., 2010*). Also, the dACC/aMCC seems to be recruited by regulatory processes and appears less involved in representing self- or other-related feelings (Craig, *2009*; Lamm *et al., 2011*). To conclude, we found shared neural representations between first-hand pain and pain empathy in the anterior insula that, together with the hippocampus, MPFC, PCC and TPJ, appear to support empathy, potentially via affect sharing and mental simulation.

Empathic processing and associated mental simulation might depend on how similar the individual is perceived to oneself. We found that lower perceived confederate similarity was associated with increased pattern similarity between first-hand pain and pain empathy in the dorsal MPFC (Figure 3B). The dorsal MPFC was previously implicated in self-projection and perspective taking (Kurczek *et al., 2015*; Schurz *et al., 2015*), self-inhibition/other-enhancement during mental simulation (Majdandžić *et al., 2016*) and prosocial behavior (Waytz *et al., 2012*). Mitchell *et al. (2006)* showed that judgements of similar and dissimilar others were associated with activation changes in ventral and dorsal MPFC, respectively. Furthermore, MPFC activation was shown to be greater with increasing discrepancy between self- and other-related judgements (Tamir and Mitchell, 2010). In line with this, our findings also suggest a specific role of the dorsal MPFC in mental simulation, particularly if the other individual is perceived as less similar to oneself.

Next, we hypothesized empathy-related mental simulation to be dovetailed with memory recall of the recently experienced painful stimulation. We found increased hippocampal connectivity with left fusiform gyrus and right primary motor cortex during pain empathy (Figure 4B). A neighboring region within the primary motor cortex was also engaged when participants experienced electrical stimulation to the left hand (Figure 2A). Memories are assumed to be stored in distributed neocortical networks (Marr, 1970; Frankland and Bontempi, 2005). The hippocampus is thought to coordinate memory retrieval through coupling with neocortical regions that were engaged during the actual experience (Takashima *et al., 2009*). Increased hippocampal connectivity with the right primary motor cortex during pain empathy might thus be related to the recall of recently experienced pain. Overall, however, hippocampal-neocortical coupling during first-hand pain and pain empathy was largely distinct. For instance, the former connectivity profile appeared much more distributed, which might be related to a stronger emotional response due to the direct electrical stimulation during first-hand pain (Ploghaus *et al., 2001*). Conclusions about memory recall require further research that, e.g. directly assesses memory re-activation during empathic processing. Furthermore, participants with higher trait measures in perspective taking showed stronger hippocampal coupling with the fusiform gyrus during pain empathy. This lends itself to speculate that the fusiform gyrus contributed to simulation processes, presumably coding for the content of visual imagination (O'Craven and Kanwisher, 2000; Pearson, 2019). Yet, results should be evaluated cautiously since correlations were modest and did not survive correction for multiple comparisons.

Empathy, including affect sharing (Hein *et al.,* 2010) or mental simulation (Waytz *et al.,* 2012; Gaesser and Schacter, 2014; Gaesser *et al.,* 2015, 2017, 2018, 2019), might ultimately motivate prosocial behavior. Gaesser and Schacter (2014) showed that episodic simulation and memory of helping another individual in need positively affected the willingness to help others (Gaesser and Schacter, 2014; Gaesser *et al.,* 2015). Prosocial behavior appears increased the more vividly participants engage in mental simulation or memory recall of helping behavior (Gaesser *et al.,* 2017, 2018, 2019), and this involved the MTL and TPJ (Gaesser *et al.,* 2019). While the link between empathy, mental simulation and prosocial behavior warrants further investigation, results suggest that mental simulation might contribute to empathy through neural processes in hippocampal-neocortical ensembles.

Lastly, our approach draws on an indirect investigation of mental simulation and shared representations related to pain empathy. Our results confirm our *a priori* expectations of increased hippocampal-neocortical pattern similarity and connectivity. Although an interpretation of the results in terms of mental simulation processes and memory recall during pain empathy appears likely (Frith and Frith, 1999; Buckner and Carroll, 2007; Hassabis and Maguire, 2009; Gaesser *et al.,* 2019; Lamm *et al.,* 2019), conclusions should be drawn with caution. Future studies should investigate mental simulation and empathy within the same study and could then directly link both. Nevertheless, our results provide novel insights into hippocampal processing during empathy, corroborating previous findings on empathy deficits in amnesia (Beadle *et al.,* 2013) and traumatic brain injury (Rushby *et al.,* 2016).

To conclude, our findings highlight the contributions of hippocampal-neocortical representations and connectivity to pain empathy, partially affected by personality traits and the similarity of the other individual in pain. This might potentially indicate shared representations and mental simulation during empathy, bearing important practical implications for empathy in patients suffering from hippocampal damage or fronto-temporal dementia.

Supplementary data

Supplementary data are available at *SCAN* online.

Acknowledgements

Funding

Conflict of interest

The authors declare no competing financial interests.

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