Research Paper

Functional MRI examination of empathy for pain in people with schizophrenia reveals abnormal activation related to cognitive perspective-taking but typical activation linked to affective sharing

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Background: Schizophrenia is associated with important disturbances in empathy that are related to everyday functioning. Empathy is classically defined as including affective (sharing others' emotions) and cognitive (taking others' cognitive perspectives) processes. In healthy individuals, studies on empathy for pain revealed specific brain systems associated with these sets of processes, notably the anterior middle cingulate (aMCC) and anterior insula (AI) for affective sharing and the bilateral temporoparietal junction (TPJ) for the cognitive processes, but the integrity of these systems in patients with schizophrenia remains uncertain. **Methods:** Patients with schizophrenia and healthy controls performed a pain empathy task while undergoing fMRI scanning. Participants observed pictures of hands in either painful or nonpainful situations and rated the level of pain while imagining either themselves (self) or an unknown person (other) in these situations. **Results:** We included 27 patients with schizophrenia and 21 healthy controls in our analyses. For the pain versus no pain contrast, patients showed overall typical activation patterns in the aMCC and AI, with only a small part of the aMCC showing reduced activation compared with controls. For the other versus self contrast, patients showed an abnormal modulation of activation in the TPJ bilaterally (extending to the posterior superior temporal sulcus, referred to as the TPJ/pSTS). **Limitations:** The design included an unnecessary manipulation of the visual perspective that reduced the number of trials for analysis. The sample size may not account for the heterogeneity of schizophrenia. **Conclusion:** People with schizophrenia showed relatively intact brain activation when observing others' pain, but showed abnormalities when asked to take the cognitive perspectives of others.

Introduction

Patients with schizophrenia often present with important deficits in their social functioning even when their psychotic symptoms have abated. There is thus an increased interest in understanding the obstacles to proper functioning in patients with schizophrenia, particularly their deficits in social cognition. One aspect of social cognition that is now garnering increasing attention in schizophrenia research is empathy (i.e., the capacity to share and understand the emotional states of others).[1,2] Traditionally, affective and cognitive processes are thought to contribute to the complex multifaceted experience of empathy. The former set of processes is called upon when the affective states of others are shared (affective sharing), whereas the latter reflects effortful processes of inferring the emotional states and taking the cognitive perspectives of others.[3,4] The relative importance of each set of processes in the experience of pain empathy has been recently debated. Some authors propose that empathy for pain is based mainly on processes "functionally equivalent to those engaged by first-hand experience of pain" (i.e., shared representations between self and others),[5] whereas others argue that empathy relies instead on our capacity to adopt others' perspectives and infer their emotional states.[6]

Previous questionnaire-based research in schizophrenia has suggested abnormalities both in the cognitive and the affective processes, as evidenced respectively by lower perspective taking and increased personal distress scores compared with controls on the Interpersonal Reactivity Index (IRI[7]).[1,8–11] Recent work has highlighted important associations between

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impaired cognitive processes underlying empathy and reduced social functioning in individuals with schizophrenia[10,11] as well as between impaired affective sharing and reduced insight.[12] Despite the functional impact of empathy impairments in individuals with schizophrenia, the exploration of their neural bases is relatively recent. Yet, neuroimaging could help us to better understand the processes underlying empathy deficits in patients with this disorder.

In healthy individuals, most neuroimaging studies of empathy have focused on empathy for physical pain. This is likely because pain is one of the rare affective states with a strong physiologic component in addition to the representational dimension. Furthermore, it is relatively easy to find experimental situations that trigger pain in another person and thus elicit empathy. These neuroimaging studies have identified the bilateral anterior insula (AI) and the anterior middle cingulate cortex (aMCC), often extending to the supplementary motor area, as the core neural network underlying the affective set of empathy processes.[13,14] The cognitive processes involved in pain empathy have been consistently associated with activation in the bilateral temporoparietal junction (TPJ),[15–18] sometimes together with the precuneus[16,17] or the medial prefrontal cortex (mPFC).[15,19]

The few previous neuroimaging studies of empathy in patients with schizophrenia used various tasks and stimuli, asking participants to infer the emotional states of characters presented in verbal stories,[20] comic strips,[21–23] photographs/static pictures[11,24,25] or video clips.[26] Overall, previous neuroimaging studies reported abnormal activations in patients with schizophrenia in a variety of brain regions that authors interpreted as underlying both the affective and cognitive processes contributing to empathy. These results thus suggest alterations of both sets of empathy processes in patients with this disorder. However, there is an important heterogeneity among studies in the brain regions showing abnormal activation in patients with schizophrenia, which is not surprising given the variety of tasks used. Moreover, previous studies have often focused solely on the affective or the cognitive processes underlying empathy,[11,20,24] have investigated both of them but using different sets of stimuli,[21,23,25] or have used tasks that did not enable researchers to disentangle the activation associated with each set of processes.[26] Importantly, although tasks using physical pain stimuli are the most commonly used tasks for investigating empathy in healthy people, fMRI studies in patients with schizophrenia have typically focused on empathy for emotions such as sadness, anger or happiness. Yet, the breadth of studies in healthy individuals in the past 10 years led to the development of many validated tasks and to the accumulation of findings on the processes and brain activations underlying the experience of empathy for pain. This growing body of knowledge is relevant to guide our interpretation and understanding of findings in patients with schizophrenia.

To our knowledge, the only fMRI study assessing empathy for pain in schizophrenia conducted to date was the recent study by Horan and colleagues.[27] Their study relied on the task developed by Lamm and colleagues[17] in which participants were presented with aversive tones and then with video clips showing individuals listening to such tones (presented as medical patients receiving a treatment involving the painful sounds). Horan and colleagues[27] manipulated perspective taking by asking participants to imagine themselves or another person experiencing the pain in the video clips. They also manipulated cognitive appraisal by telling participants that the treatment had been effective or not for each individual. The authors performed region of interest (ROI) analyses, focusing on the aMCC and bilateral AI. Group comparisons across all task conditions revealed no significant group difference in these brain regions. However, a significant perspective × group interaction emerged, such that patients exhibited greater activation for the other condition than for the self condition in these regions, whereas the control group showed the reverse pattern of activation. Additionally, in whole brain analyses, controls exhibited greater activation than patients in the posterior cingulate and precuneus for the self versus other contrast. Conversely, for the other versus self contrast, patients showed greater activation than controls in the bilateral frontal poles. These results led the authors to conclude that although patients show relatively intact sensitivity to the pain of others, between-group differences were observed when the modulatory impact of perspective taking was considered. Although TPJ activation is often observed for other versus self contrasts,[15–18] neither controls nor patients showed differences in activation in that brain region in the study by Horan and colleagues.[27] In addition, their study included only stimuli depicting pain, which did not allow the observation of painful versus nonpainful situations to be compared.

The present fMRI study aimed to improve our understanding of empathy dysfunctions in patients with schizophrenia by investigating the neural correlates associated with both the affective and cognitive processes contributing to empathy. To benefit from the knowledge acquired studying healthy indivdiuals, we chose a well-known pain empathy task based on the presentation of hands in painful or nonpainful situations (to manipulate the affective processes) while instructing participants to imagine either themselves or an unknown person in these situations (to manipulate cognitive perspective taking).[15,16,18] This task thus provides a means to examine both the affective and cognitive processes involved in empathy separately using the same set of stimuli as well as the interaction between them. Moreover, we recently showed in a group of healthy participants (also included in this study) that a pseudodynamic version of this task elicited typical bilateral AI/aMCC and TPJ activations associated respectively with the affective and cognitive processes constituting the experience of pain empathy.[18]

Given previous knowledge on the neural bases of empathy for physical pain in healthy people and findings from questionnaire-based and fMRI studies in schizophrenia, we expected that patients would show abnormal activations compared with controls in the core regions associated with both the affective and the cognitive processes involved in pain empathy. More specifically, in line with the increased scores on the personal distress scale of the IRI,[1] we expected patients to show greater activations than controls in the bilateral AI and aMCC (typically associated with affective

sharing[13,14]). We also hypothesized that patients would show decreased activations in the bilateral TPJ (involved in the cognitive processes underlying empathy[15–18]) compared with controls given previous findings of lower perspective taking scores on the IRI.[1] Then, we expected that patients' activations in the bilateral AI and aMCC would correlate with their personal distress scores on the IRI while activations in the bilateral TPJ would correlate with their perspective taking scores. Finally, we sought to explore associations between brain activations in these regions and patients' symptomatology and level of functioning.

Methods

Participants

We recruited adults with schizophrenia or schizoaffective disorder (DSM-IV-TR) and healthy controls, matched for age, sex and parental socioeconomic status[28] to participate in this study. To be included, healthy controls had to have no personal or familial history of psychotic disorders. All participants underwent a semistructured diagnostic interview based on the Structured Clinical Interview for DSM-IV-TR (SCID)[29] that also included the Positive and Negative Syndrome Scale (PANSS)[30] as an assessment of patients' symptomatology. Questions about functioning were also integrated in order to rate the Schizophrenia Objective Functioning Instrument (SOFI).[31] All participants completed the matrix reasoning and the vocabulary subtests of the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV)[32] to estimate their IQ. All participants were informed of the study requirements and provided written consent before their participation. All patients were stabilized outpatients recruited via their treating psychiatrists, who judged that they were able to participate in the study and provide their informed consent. The local ethics committee of the Centre de recherche CERVO, formerly the Centre de Recherche de l'Institut Universitaire en Santé Mentale de Québec, approved this study.

Measures of empathic traits

We used the IRI, a 28-item self-report questionnaire previously used in a schizophrenia population,[1] to assess personal traits associated with the cognitive (perspective taking and fantasy subscales) and affective (personal distress and empathic concern subscales) processes contributing to empathy experience.[7] We also considered the recent proposal of Koller and Lamm,[33] who subdivided the perspective taking subscale into "cognitive-comparative" and "self-projection and simulation" dimensions.

Functional MRI task

Stimuli

The stimuli used during fMRI all depict a right hand performing a daily life action. As shown in Appendix 1, Figure S1, available at jpn.ca, our validated stimuli consisted of pseudodynamic scenarios, each comprising 3 coloured pictures presented in a rapid succession (150 ms, 150 ms and 5500–6100 ms) to reinforce the impression of an ecological movement.[18,34–36] The present task involved 3 manipulations.

1) Stimulus outcome (pain v. no pain): Each stimulus resulted in either a painful or nonpainful event. Pain and no pain conditions were visually similar, with only the last picture differing.
2) Instruction (self v. other): Instructions required participants to imagine that the hand was either their own (self) or that of an unknown person (other).
3) Visual perspective (first v. third person): Stimuli were acquired by capturing the same scenario using 2 different cameras — 1 positioned according to a first person visual perspective (arm at a 0° ± 45° angle) and 1 positioned according to a third person visual perspective (arm at 180° ± 45° angle).

The task thus followed a 2 (pain v. no pain) × 2 (self v. other) × 2 (first person v. third person visual perspective) design resulting in 8 conditions: PS1 (pain, self, first person visual perspective), PS3 (pain, self, third person visual perspective), PO1 (pain, other, first person visual perspective), PO3 (pain, other, third visual perspective) and 4 no pain (NP) equivalents (Appendix 1, Table S1).

Procedure

During the task, participants were asked to imagine and rate the level of pain they (self) or an unknown person (other) would feel in each situation by using a button pad with their left hand to move a cursor along a visual analogue scale ranging from "no pain" to "maximum pain." The initial cursor position was randomized across the trials.

Participants completed 2 fMRI runs, each including 32 pain and 32 no pain stimuli presented either in a first person or a third person visual perspective (counterbalanced). The self and other conditions were presented in blocks, with 4 blocks of each condition for each run. Before each block, the self/other instruction appeared on the screen for 10 seconds (the words "self" or "other" were also displayed below the image during the rating period). Eight stimuli and 3 fixation crosses of jittered duration (2500–8500 ms) were presented in each block.

Behavioural analyses

For each scenario, the final cursor position on the scale was converted into scores ranging from 0 (no pain) to 100 (maximum pain). Response time was defined as the time between the onset of the scale and participants' final ratings. Despite a floor effect on no pain ratings, the effects tested by a 2 (controls v. patients) × 2 (pain v. no pain) × 2 (self v. other) analysis of variance (ANOVA) were normally distributed.

Functional MRI data acquisition and processing

We used a Philips Achieva 3 T scanner to measure changes in blood oxygen–level dependent (BOLD) signal (T_2*-weighted) using a gradient echo-planar imaging (EPI) sequence (repetition time [TR] 3000 ms, echo time [TE] 35 ms, field of view [FOV] 230 mm, flip angle 90°, 128 × 128 matrix, 45 slices of 3 mm, no gap, voxel size 1.8 mm × 1.8 mm × 3 mm). In each session 195 EPI volumes were acquired along the anterior–

posterior commissure (AC–PC) plane. Structural images were acquired using a MPRAGE sequence (TR 8.2 ms, TE 3.7 ms, FOV 250 mm, flip angle 8°, 256 × 256 matrix, 180 slices/volume, slice thickness 1 mm, no gap, voxel size 1 mm^3).

Statistical analysis

Data were analyzed using SPM8 (Wellcome Department of Imaging Neuroscience). Images were corrected for slice timing and realigned to correct for head movements. Larger volume-to-volume movements (> 0.5 mm between 2 adjacent volumes) were corrected using the ArtRepair toolbox. Structural images were then coregistered to the mean realigned EPI image using a linear rigid transformation (6 motion parameters) and segmented. Segmentation parameters were used to normalize functional data into a standard anatomic space based on the ICBM-152 template (Montreal Neurological Institute [MNI]). Functional images were resampled at a resolution of 2 mm^3 and then spatially smoothed using an 8 mm isotropic Gaussian kernel. For each participant, we then defined a design matrix including a separate regressor for each of our 8 conditions (Appendix 1, Table S1) corresponding to the time interval between the onset of the first image and the end of the response period. The design matrix also included 7 regressors of noninterest (instructions and 6 movement regressors). Low-frequency noise was removed using a 440 s high-pass filter (minimum intertrials within a single condition interval).

Whole-brain analyses were conducted to isolate brain regions related to both the affective and the cognitive sets of empathy processes at the participant and group levels. For brain activations associated with affective processes, we computed the pain > no pain contrast: (PS1 + PS3 + PO1 + PO3) > (NPS1 + NPS3 + NPO1 + NPO3). To isolate the activations associated with the cognitive perspective taking manipulation, we computed the PO1 > PS1 contrast. This choice was based on our recent observation that in healthy participants, the brain areas related to the cognitive processes are specifically recruited when hands are presented in a first person visual perspective.[18] These first-level contrasts (pain > no pain and PO1 > PS1) were then used to assess regions of common activation between patients and controls by computing conjunctions between the 1-sample *t* tests of both groups (we used the masking procedure as well as 1-way ANOVAs, as implemented in SPM, to perform this conjunction). We then examined between-group differences in both directions using 2-sample *t* tests.

We also examined the effect of the cognitive perspective taking manipulation for the no pain scenarios and compared it to the pain conditions with the (PO1 > PS1) > (NPO1 > NPS1) contrasts to investigate the specificity to the pain condition.

We performed all analyses using a voxel threshold of $p < 0.001$ with a cluster size (k) of 90 voxels, corresponding to a whole-brain corrected $p < 0.05$ based on Monte Carlo simulation. In addition, for brain regions where we had our a priori hypotheses (i.e., aMCC and bilateral AI for the pain > no pain contrast and bilateral TPJ for the PO1 > PS1 contrast), we also reported activations at a cluster threshold of $k \geq 10$. This less conservative threshold corresponds to a previous standard in neuroimaging studies that is still used in some recent work[37] and allows for a desirable balance between type I and type II errors.[38]

Correlations

In the patients group, we investigated associations between brain activations and empathic traits for the brain regions where we had a priori hypotheses and where we observed between-group differences. We used the MarsBaR toolbox to define ROIs using 6 mm (3 voxels) radius spheres centred on the peak coordinates and extracted mean β values for each ROI. For the ROI related to the pain > no pain contrast (see the whole-brain investigation of pain observation section in Results), we extracted mean β values specifically for the pain condition. Similarly, for ROIs associated with the PO1 > PS1 contrast (i.e., bilateral TPJ/pSTS; see the whole-brain investigation of the cognitive perspective taking manipulation section in Results), mean β values were extracted specifically for the PO1 condition. We considered the left and right TPJ separately, as we could not assume the functional homogeneity of these 2 brain regions.[39,40] We computed Pearson correlations between these mean β values and IRI subscores of interest, perspective taking that targets the cognitive processes contributing to empathy, and personal distress that targets the affective processes. These specific subscales were selected because they are representative of the construct and because previous questionnaire-based studies of schizophrenia reported abnormal scores on these specific subscales.[1] We also explored the association between the mean β values and patients' symptomatology (PANSS 5-factor model[41]) as well as patients' level of functioning (each of the 4 SOFI subscales[31]).

Results

Study sample

We included 27 adults with schizophrenia or schizoaffective disorder and 21 matched healthy controls in our analyses. All participants were right-handed and had no history of head injury or neurologic disorders. Table 1 summarizes the demographic and clinical characteristics of the 2 groups.

Empathic traits

As reported in Table 2, patients showed reduced perspective taking ($t_{46} = 2.27$, $p = 0.028$) and elevated personal distress scores ($t_{46} = –2.13$, $p = 0.039$) on the IRI compared with controls. No significant difference was found for empathic concern ($t_{46} = –0.18$, $p = 0.86$) or fantasy scores ($t_{46} = –0.53$, $p = 0.60$). Considering the subdivision of the perspective taking subscale proposed by Koller and Lamm,[33] controls presented with mean scores of 8.57 ± 1.12 for the "cognitive-comparative" dimension and 7.00 ± 1.55 for the "self-projection and simulation" dimension. Patients showed mean scores of 7.93 ± 2.09 and 7.00 ± 1.84 for the "cognitive-comparative" and the "self-projection and simulation" dimensions, respectively. The groups did not differ significantly for the "cognitive-comparative" dimension ($t_{46} = 1.37$, $p = 0.18$) and showed

the same mean scores for the "self-projection and simulation" dimension ($t_{46} = 0.00$, $p > 0.99$). As we used a different version of the IRI in the present study (the original 28-item version) than that used by Koller and Lamm[33] (16-item version), we computed the 2-sample t test this time for the mean scores on items that were specific to the 28-item version of the IRI and found a significant group difference ($t_{46} = 3.66$, $p = 0.001$).

Table 1: Demographic and clinical characteristics of participants

Characteristic	Group; no. or mean ± SD		Statistical comparison	p value
	Schizophrenia ($n = 27$)	Control ($n = 21$)		
Sex, male:female	23:4	17:4	$\chi^2 = 0.151$	$p = 0.70$
Age, yr	29.7 ± 8.6	29.2 ± 7.9	$t = –0.198$	$p = 0.84$
Parental socioeconomic status*	45.8 ± 15.5	41.6 ± 14.9	$t = –0.922$	$p = 0.36$
IQ†	99.9 ± 15.2	109.3 ± 15.4	$t = 2.121$	$p = 0.039$
Schizophrenia:schizoaffective disorder	18:9	—	—	—
Illness duration, yr	7.6 ± 7.9	—	—	—
Antipsychotic medication, atypical:typical:atypical + typical	24:0:3	—	—	—
Chlorpromazine equivalent, mg	547.7 ± 474.7	—	—	—
PANSS‡				
Positive	13.8 ± 6.5	—	—	—
Negative	16.0 ± 6.3	—	—	—
Cognitive/disorganization	9.6 ± 3.0	—	—	—
Depression/anxiety	8.5 ± 3.1	—	—	—
Excitement/hostility	6.6 ± 3.0	—	—	—
SOFI§				
Living situation	74.3 ± 16.4	—	—	—
Instrumental activities of daily living	68.1 ± 17.5	—	—	—
Productive activities and role functioning	44.1 ± 26.7	—	—	—
Social functioning	59.7 ± 16.4	—	—	—

PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; SOFI = Schizophrenia Objective Functioning Instrument.
*Assessed using the Hollingshead index.
†Assessed using the matrix reasoning and the vocabulary subtests of the Wechsler Adult Intelligence Scale – Fourth Edition.
‡Five-factor model by Lehoux and colleagues.[41]
§Data available for 26 patients.

Table 2: Empathic traits and behavioural results on the fMRI task

Trait/result	Group; mean ± SD		Statistical comparison	p value
	Schizophrenia ($n = 27$)	Control ($n = 21$)		
Empathic traits (IRI)				
Empathic concern	26.4 ± 3.9	26.2 ± 4.0	$t = –0.18$	$p = 0.86$
Personal distress	18.0 ± 5.2	14.9 ± 4.8	$t = –2.13$	$p = 0.039$
Fantasy	21.4 ± 6.1	20.6 ± 4.3	$t = –0.53$	$p = 0.60$
Perspective taking	25.4 ± 4.3	27.9 0 ± 2.9	$t = 2.27$	$p = 0.028$
Mean pain ratings (out of 100)*				$p < 0.001$
Pain other	63.4 ± 15.0	65.5 ± 10.9		
Pain self	61.5 ± 13.3	63.5 ± 15.2		
No pain other	4.9 ± 7.3	3.5 ± 5.6		
No pain self	4.7 ± 5.3	3.5 ± 5.6		
Mean response time, ms*				$p < 0.001$
Pain other	2470.5 ± 465.3	2453.5 ± 440.9		
Pain self	2501.6 ± 404.9	2412.3 ± 393.5		
No pain other	2002.0 ± 407.0	1842.7 ± 234.6		
No pain self	2168.4 ± 431.7	1886.9 ± 267.7		

IRI = Interpersonal Reactivity Index; SD = standard deviation.
*Data available for 26 patients.

Behavioural results

Behavioural data were missing for 1 patient owing to technical problems. Mean pain ratings and response times are reported in Table 2. There was a main pain/no pain effect on ratings ($F_{1,45}$ = 990.99, $p < 0.001$) and response times ($F_{1,45} = 69.76$, $p < 0.001$). For response times, trends emerged toward a main effect of self/other instruction ($F_{1,45} = 3.2$, $p = 0.08$), a group × instruction interaction ($F_{1,45} = 3.01$, $p = 0.09$) and a stimulus outcome × instruction interaction ($F_{1,45} = 3.42$, $p = 0.07$). All other effects or interactions were nonsignificant (all $F < 2.24$, all $p > 0.14$).

Functional MRI results

Whole-brain investigation of pain observation (pain v. no pain)

As reported in Fig. 1A and Table 3, the controls ∩ patients conjunction for the pain > no pain contrast revealed common activations in large clusters encompassing the aMCC extending to the supplementary motor area, the bilateral AI extending to the inferior and middle frontal gyrus, and in other frontal and parietal regions. The controls > patients comparison for this contrast (Fig. 1B and Table 3) revealed a difference in activation in a small portion of the aMCC, such that patients showed significant activation in that region that was of lesser magnitude than that in healthy controls. We found no significant group difference in the AI. No regions showed more activation in patients than controls.

Whole-brain investigation of the cognitive perspective taking manipulation (other v. self)

No significant common activation was observed for the controls ∩ patients conjunction for the PO1 > PS1 contrast. In controls, the PO1 > PS1 contrast revealed significant activation in the bilateral TPJ at the border of the posterior part of the superior temporal sulcus (TPJ/pSTS), as reported in the

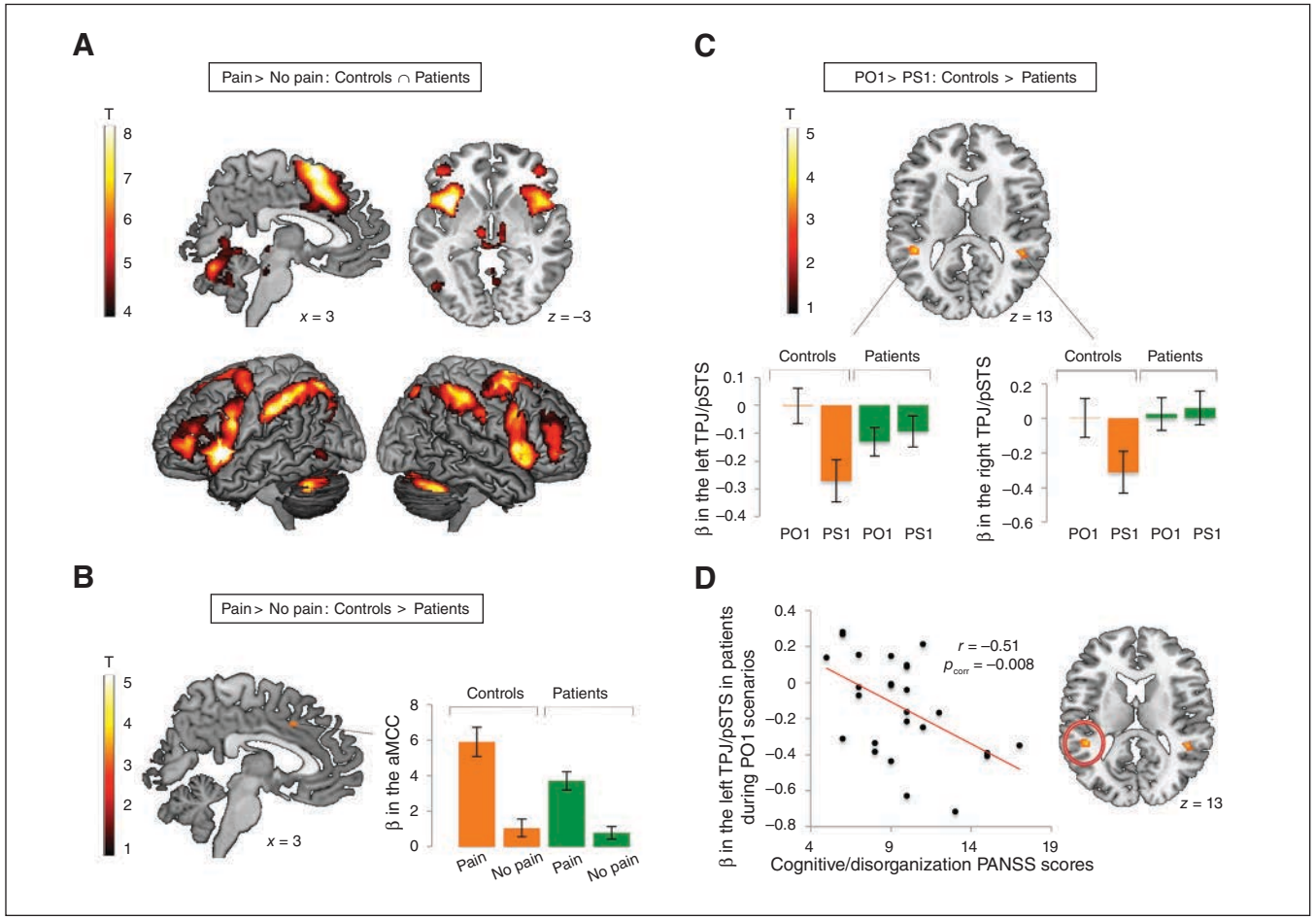

Fig. 1: Functional MRI results for the observation of pain (v. no pain) and the manipulation of cognitive perspective taking (other v. self). **A)** Conjunction of the 2 groups for the pain > no pain contrast. **B**) Between-groups comparison for the pain > no pain contrast and β values extracted for each condition and group in the region showing a significant between-groups difference. **C**) Between-groups comparison for the PO1 > PS1 contrast and β values for each condition and group in brain regions showing a significant between-groups difference. **D**) Correlation between patients' left temporoparietal junction/posterior superior temporal sulcus (TPJ/pSTS) activation during the PO1 condition and cognitive/disorganization symptoms. The threshold used for significance was $p < 0.001$, uncorrected, with k = 90. A less conservative threshold (k = 10) was used for regions with a priori hypotheses (anterior middle cingulate cortex [aMCC], bilateral anterior insula [AI] and TPJ).

study by Vistoli and colleagues[18] (the present study included the same healthy participants). Patients showed significant activation in the precuneus, but not in the TPJ/pSTS. As shown in Table 3 and Fig. 1C, the controls > patients comparison for the PO1 > PS1 contrast accordingly revealed a significant difference in activation in the bilateral TPJ/pSTS. This interaction remained significant when we included the between-groups difference in IQ as a covariate. The patients > controls comparison was not significant.

Effect of self/other instruction on no pain scenarios

As reported in more detail in Appendix 1, the NPO1 > NPS1 contrast revealed no activation in the TPJ/pSTS for either group. The (PO1 > PS1) > (NPO1 > NPS1) contrast notably revealed significant activations in the bilateral TPJ in controls, but not in patients.

Correlations

Correlations with empathic traits

Activation in the aMCC during the pain condition in patients did not significantly correlate with the IRI (personal distress: $r = –0.33$, $p = 0.09$; perspective taking: $r = 0.04$, $p = 0.83$). For the right TPJ/pSTS, activation shown by patients during the PO1 condition was positively correlated with their perspective taking score on the IRI ($r = 0.46$, $p = 0.015$). However, when considering the 2 dimensions of the perspective taking subscale of the IRI proposed by Koller and Lamm,[33] no significant associations were found for either of the 2 dimensions (cognitive–comparative dimension: $r = 0.206$, $p = 0.30$; self-projection and simulation dimension: $r = 0.312$, $p = 0.11$). Patients' activation in the right TPJ/pSTS during the PO1 condition did not correlate with their personal distress scores ($r = –0.28$, $p = 0.15$). Finally, no significant correlation was found for the left TPJ/pSTS (personal distress: $r = 0.01$, $p = 0.98$; perspective taking: $r = 0.12$, $p = 0.56$).

Exploratory correlations with symptomatology and level of functioning

No correlation was found between the aMCC or right TPJ/pSTS and the symptomatology or the level of functioning (all $r < –0.32$, all $p > 0.12$). Similarly, we found no correlation between the left TPJ/pSTS and the level of functioning (all $r < –0.27$, all $p > 0.19$). For the left TPJ/pSTS, patients' activation during the PO1 condition showed negative correlations with both the positive ($r = –0.39$, $p = 0.046$) and the cognitive/disorganization factors ($r = –0.51$, $p = 0.008$) from the PANSS. Although these correlations would not survive a strict correction for multiple comparisons (9 scores × 3 ROIs [aMCC, right and left TPJ/pSTS], corrected $\alpha = 0.05/27 = 0.002$), the correlation with the cognitive/disorganization symptoms nonetheless showed a large effect according to the guidelines

Table 3: Brain regions reaching statistical significance for each analysis of interest*

Brain region	Lat.	Cluster size (k)	MNI coordinates			*t* value
			x	*y*	*z*	
Pain > no pain: controls ∩ patients						
Superior parietal sulcus	R	750	16	–72	52	6.4
Superior occipital gyrus	R		26	–64	34	4.71
Superior parietal sulcus/precuneus	R		14	–70	42	4.49
Inferior occipital/occipito-temporal cortex	L	233	–50	–68	–4	4.65
Cerebellum (crus1)	R	3707	36	–54	–32	7.41
Cerebellum (crus1)	L		–40	–56	–32	7.2
Cerebellum (declive 6)	R		28	–66	–30	7.18
Inferior parietal/intraparietal sulcus	L	3862	–46	–36	44	8.33
Inferior parietal/supramarginal gyrus	L		–54	–26	34	8.12
Superior parietal sulcus	L		–22	–66	58	8.01
Inferior parietal/ supramarginal gyrus	R	2386	54	–32	46	7.91
Inferior parietal/intraparietal sulcus	R		44	–36	40	7.27
Inferior parietal/posterior parietal gyrus	R		48	–40	50	7.19
Anterior insula/inferior frontal cortex	L	22 920	–36	14	–4	10.45
Supplementary motor area	R		2	10	60	9.46
Anterior middle cingulate cortex	R		4	16	44	8.98
Pain > no pain: controls > patients						
Anterior middle cingulate cortex/anterior cingulate cortex	R	24	6	16	38	3.56
PO1 > PS1: controls > patients						
TPJ/pSTS	R	35	46	–44	14	4.33
TPJ/pSTS	L	92	–44	–42	12	4.47
TPJ/pSTS	L		–44	–38	4	3.84

L = left; MNI = Montreal Neurological Institute; pSTS = posterior superior temporal sulcus; R = right; TPJ = temporoparietal junction.
*The threshold used for significance was $p < 0.001$, uncorrected, with k = 90. A less conservative threshold (k = 10) was used for regions with a priori hypotheses (middle cingulate cortex, bilateral anterior insula and TPJ).

by Cohen[42] and approached the corrected α threshold. In addition, this correlation was still significant when the between-groups difference in IQ was taken into account (Fig. 1D). The same correlation using activation in the PS1 condition was not significant ($r = -0.18$, $p = 0.37$), and the 2 correlations (using β values from the PO1 and PS1 conditions) were significantly different, as tested using a Fisher r to z transformation for dependent groups ($z = -1.84$, $p = 0.033$, 1-tailed).

Discussion

This study used a classic pain empathy paradigm based on the observation of hands in either painful or nonpainful everyday life situations and required participants to imagine either themselves or an unknown person in these situations.[15,16,18] Patients with schizophrenia presented with the typical pattern of activation for pain observation in brain regions including in the AI and aMCC; only a small portion of the aMCC showed significantly reduced activation compared with healthy controls. Furthermore, there was no difference between the groups in pain intensity ratings. In contrast, for the other > self contrast patients showed significantly less activation in the bilateral TPJ/pSTS than controls, with significant TPJ/pSTS activation observed only in controls. Additionally, in patients left TPJ/pSTS activation was negatively correlated with their cognitive/disorganization symptoms. Overall, these results suggest that sharing others' pain, which is related to the affective processes contributing to empathy, seems relatively preserved in patients with schizophrenia, which is consistent with the findings of Horan and colleagues.[27] In contrast, these patients seem to present with difficulties in perspective taking — a major cognitive process involved in the experience of empathy.

Brain activations linked to the affective processes involved in pain empathy are partially preserved in patients with schizophrenia

During the observation of painful (compared with nonpainful) actions, both groups activated the bilateral AI/aMCC network, which is often associated with the affective processes contributing to empathy.[13,14] Though a small portion of the aMCC was significantly less activated in patients than in controls, this effect reflected a difference in the extent of the observed activation, such that patients significantly activated the aMCC, but a small part of this region showed less important activation than that observed in controls (Fig. 1B).

Based on previous studies that used actual nociceptive stimulation,[43–45] it was proposed that when empathizing with others' pain, the AI is involved in representing and integrating others' sensory and emotional feelings, predicting affective consequences and comparing them with the observed cues (e.g., facial expressions), whereas the aMCC would support the motivation and coordination of appropriate responses (prosocial behaviour or withdrawal from pain).[19,46–49] Our results thus suggest that patients with schizophrenia normally represent and integrate others' pain, corroborating recent fMRI[27] and EEG[50] evidence showing that this affective aspect of empathy is preserved in schizophrenia.

The reduced aMCC activation that we observed in patients with schizophrenia could reflect a less efficient coordination of motivated responses to others' pain in individuals with this disorder, but other roles have also been suggested for the aMCC, including in attention and salience processing.[51] Our result could thus reflect the previously suggested abnormal salience processing in patients with schizophrenia.[52] However, Eisenberger[53] recently reviewed arguments that clearly challenge the salience processing hypothesis for the aMCC (e.g., salient stimuli, such as negative [nonpainful] emotional faces, do not activate the ACC or AI when compared with neutral faces[54]). It thus seems unlikely that salience processing impairments in patients with schizophrenia entirely account for the present between-groups difference in the aMCC.

Finally, the conjunction analysis for the pain > no pain contrast showed that both groups also exhibited activation in large clusters encompassing the inferior frontal and the inferior and superior parietal cortices. These brain regions, classically described as the human "mirror neuron system,"[55] are consistently activated during empathy paradigms based on the presentation of pictures of body parts[14] and are thought to reflect action understanding and motor resonance.[56] Our results thus suggest that these aspects could also be preserved in patients with schizophrenia, reinforcing recent evidence showing that mirroring others' experiences seems relatively intact in individuals with this disorder.[57]

Brain bases of cognitive perspective taking involved in empathy for pain are altered in patients with schizophrenia

In line with previous studies in healthy participants,[15–17] our control group exhibited bilateral TPJ/pSTS activation when imagining pain in others (compared with pain in oneself; PO1 > PS1 contrast), which is similar to the findings reported by Vistoli and colleagues.[18] In contrast, patients showed no suprathreshold activation for this contrast, leading to significant between-group differences in the TPJ/pSTS bilaterally. Regarding the role of the TPJ in taking the perspective of others during pain empathy,[15–18] this result suggests a specific difficulty with cognitive perspective taking in patients with schizophrenia. This is in line with the results of previous fMRI investigations targeting the cognitive processes involved in empathy,[11,21–23,25,26] although between-group differences in some of these previous studies were observed in different brain regions.

Behaviourally, there was no effect of the self/other instruction on pain ratings in healthy controls.[18] Accordingly, no significant group × self/other instruction interaction was observed. However, patients reported reduced perspective taking scores on the IRI (related to the cognitive aspect of empathy) compared with controls, consistent with previous studies.[1,8,11] This group difference on perspective taking scores was no longer significant when considering the 2 dimensions of the perspective taking subscale on the IRI proposed by Koller and Lamm.[33] This absence of significant difference can be explained by the use of different versions of the IRI between the present study (the original 28-item

version) and that of Koller and Lamm,[33] who used a 16-item version. When focusing on the items included only in the original 28-item version, we found a significant group difference. Overall, patients with schizophrenia seem to have difficulty taking the cognitive perspective of others.

Taking the perspective of others is at the very heart of our capacity to infer others' mental states, also referred to as "theory of mind" (ToM) or "mentalizing." Using a different fMRI task, we recently showed that the inferior TPJ supports social inferences, whereas the superior TPJ supports context-sensitive ToM judgments.[58] In the present study, the abnormal activation in patients with schizophrenia was in this inferior part of the TPJ, consistent with a difficulty in making social inferences about others' pain. This result extends previous findings of aberrant TPJ activation in patients with schizophrenia during the inference of others' nonemotional mental states, such as beliefs or intentions.[59]

An alternative role of the TPJ in reorienting attention to relevant stimuli has been proposed.[60] However, it seems unlikely that this hypothesis accounts for the present TPJ/pSTS activation and its alteration in patients with schizophrenia, as there is no reason to believe that reorienting attention was more involved when participants were asked to imagine others' pain (PO1 condition) than their own pain (PS1 condition). Also, because we presented the self and other conditions in pseudorandom blocks, one might suspect that the repeated task switching could have activated attention networks in controls more so than in patients. However, this hypothesis does not seem plausible, as task switching paradigms appear to involve more dorsal parietal and frontal regions.[60] Overall, the bilateral TPJ/pSTS activation was observed when participants were asked to change their cognitive perspective from the self to that of others to imagine how much pain they would feel in the situations depicted. The TPJ/pSTS activation thus seems to reflect cognitive perspective taking.

Recent fMRI findings by Horan and colleagues[27] suggested impairments in taking others' cognitive perspective and self/other distinction in patients with schizophrenia during a pain empathy task in which participants observed videos of faces expressing pain. The authors observed abnormal modulation of activity in the aMCC and bilateral AI linked to the self/other manipulation in patients with schizophrenia. We did not replicate this finding in the aMCC and AI, which could be explained by the use of different tasks and stimuli (faces v. limbs). For instance, it is possible that the self/other manipulation may have a different impact depending on the kind of stimuli (e.g., faces naturally encourage the observer to think about another person, whereas hands might require more cognitive effort to take the perspective of others).

Interestingly, we observed that the between-group differences in TPJ/pSTS activation were specific to the painful stimuli, with neither group showing activation related to the self/other manipulation for the no pain condition (Appendix 1). This specificity may reflect that participants were engaged in pain inference and hence cognitive perspective taking only when the situations required understanding others' pain.

Finally, the negative association we observed between activation in the left TPJ/pSTS and patients' cognitive/disorganization symptoms is in line with recent findings showing the negative impact of cognitive deficits (processing speed and mentalizing) on empathic abilities in patients with schizophrenia.[61] This result is also coherent with the negative association reported between social cognition performance and disorganization symptoms in patients with schizophrenia.[62] However, we did not replicate the correlation reported by Smith and colleagues[11] between activation in the aMCC and patients' social functioning. This discrepancy may reflect the use of different empathy tasks (social empathy task v. pain empathy task) and different measures of functioning.

Limitations

A first limitation of this study is that our material included hands viewed from a first-person or a third-person visual perspective, leaving fewer trials to include in the PO1 > PS1 contrast of interest. Although including the third-person perspective trials initially seemed interesting, we recently showed that the TPJ activation related to the self/other manipulation was strictly observed in the first-person condition in healthy participants,[18] and we accordingly restricted our self/other analyses to the first-person visual perspective. Another limitation is that even if our sample size compares favourably with those of other fMRI studies, the 27 patients in our sample are unlikely to be representative of the schizophrenia population as a whole, given the highly heterogeneous nature of this disorder.

Conclusion

The observation of painful scenarios led to relatively preserved brain activation and pain intensity ratings in patients with schizophrenia, but these patients did not show TPJ/pSTS activation when asked to take the cognitive perspective of others. It thus seems that taking the cognitive perspective of others, contributing to the experience of empathy, could be more specifically altered in patients with schizophrenia, with pain observation linked to the affective set of empathy processes being relatively preserved.

By refining our knowledge on empathy alteration in patients with schizophrenia, the present findings identified potential treatment targets for future therapeutic approaches, such as cognitive remediation. The efficiency of this kind of cognitive therapy is highly associated with the specificity of the cognitive target. The present findings suggest that empathy alteration in people with schizophrenia is particularly linked to difficulties in taking the cognitive perspective of others and inferring others' experiences. We thus propose that efficient cognitive remediation techniques for empathy in patients with schizophrenia should focus on these cognitive processes. The association observed between TPJ/pSTS activation and cognitive/disorganization symptoms suggests that patients with these symptoms may further benefit from such interventions, though this result certainly deserves replication. By contrast, we provided evidence suggesting that

emotion sharing and mirroring others' behaviours are relatively intact in people with schizophrenia and thus may not require as much attention to improve empathy, at least at the group level.

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