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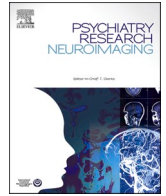
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Delineating insight-processing-related functional activations in the precuneus in first-episode psychosis patients

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ABSTRACT

Poor insight is a central characteristic of psychotic disorders, and it has been suggested to result from a general dysfunction in self-reflection. However, brain processing of clinical insight and more general self-reflection has not been directly compared. We compared tasks on (1) self-reflection on psychosis-related mental functioning (clinical insight, in patients only), (2) self-reflection on mental functioning unrelated to psychosis (general metacognition), and (3) semantic control during blood-oxygenation-level-dependent (BOLD) functional magnetic resonance imaging with 19 first-episode psychosis patients and 24 control participants. Arterial-spin-labeling (ASL) images were collected at rest. Clinical insight was evaluated with the Schedule for the Assessment of Insight. In patients, posterosuperior precuneus showed stronger activation during the insight task than during the semantic control task, while anteroinferior precuneus and posterior cingulate cortex (PCC) showed stronger activation during the insight task than during the general metacognition task. No significant group differences in brain activation emerged during the general metacognition task. Although the BOLD measures did not correlate with clinical insight measures, ASL-measured cerebral blood flow (CBF) values did correlate when extracted from the task-selective precuneus/PCC areas: higher CBF correlated with higher clinical insight scores. These results suggest that regions in the posteromedial cortex are selective for clinical insight.

1. Introduction

Poor insight into illness is common in psychotic disorders (Lincoln et al., 2007; Lysaker et al., 2018). Most patients with schizophrenia have impaired insight into their symptoms and the consequences of their illness, and this contributes to the prognosis (Lincoln et al., 2007; Lysaker et al., 2018). The etiological models of insight have not reached an overarching consensus (Osatuke et al., 2008). While some models pertain to a more biologically based anosognosia (Arango and Amador, 2011), others consider the socioemotional motivations to be primary (Klaas et al., 2017), and still others try to integrate these views (Lysaker et al., 2018).

Both structural and functional brain imaging have been used to study the neural correlates of insight into illness in psychotic disorders (Chakraborty and Basu, 2010; Lysaker et al., 2018; Vohs et al., 2016; Xavier and Vorderstrasse, 2016). Structural imaging studies have shown

somewhat mixed results: positive associations between insight scores and various brain measures—most consistently gray and white matter volume and cortical thickness—have been reported but sometimes negative associations as well (Xavier and Vorderstrasse, 2016), and some studies (including a recent larger study) have shown null results (Béland et al., 2019; Xavier and Vorderstrasse, 2016). Some converging associations between better insight and increased gray matter volume have been seen in the regions comprising the cortical midline structures (CMS) (Shad, 2018), which include the anterior (ACC) and posterior cingulate cortex (PCC), the medial prefrontal cortex (MPFC) and the precuneus (Northoff et al., 2006; Northoff and Bermpohl, 2004). But temporal, lateral frontal, occipital, and subcortical associations have also been reported (Lysaker et al., 2018).

It has been theorized that insight is associated with self-awareness and self-reflection (van der Meer et al., 2010). Functional imaging studies of insight have indeed focused on functional imaging during a

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self-reflection task (Bedford et al., 2012; Raji et al., 2012; Shad and Keshavan, 2015; van der Meer et al., 2013) or on the connectivity (Chen et al., 2016; Clark et al., 2018; Ćurčić-Blake et al., 2015; Gerretsen et al., 2014) in self-referential-processing neurocircuitry (Northoff and Berm-pohl, 2004). These activations or connectivity are then correlated with a clinical insight measure. The self-reflective task often concerns an evaluation of trait-adjective statements (e.g., "I am honest"), but some studies have used stimuli relating to mental illness (e.g., "I am unstable" or "I am crazy") (Bedford et al., 2012) or clinical insight (including statements regarding the need for treatment and the consequences of illness in addition to illness-related items) (Gerretsen et al., 2015; Raji et al., 2012).

Insight into illness involves reflecting on one's symptoms of psychosis and noticing that changes in one's mental functioning associate with a disorder. On the other hand, self-reflection directed to one's mental functioning in general, such as cognitive and emotional processes, is often called metacognition (Fernandez-Duque et al., 2000; Grant et al., 2002), and insight into illness has thus been construed as a form of metacognition (David et al., 2012; Vohs et al., 2016). However, insight into psychosis and more general metacognition have not previously been directly compared.

In this study, we investigated brain activation related to insight processing in first-episode psychosis (FEP) patients. This is in contrast to most earlier studies which have focused on samples with longer duration of illness. Studying a FEP sample has certain advantages: insight early on into the disease process has prognostic value (Ramu et al., 2019), and studies have shown that the long-term use of antipsychotic medication could affect the brain structure in schizophrenia patients (Fusar-Poli et al., 2013). We used three different tasks during blood-oxygenation-level-dependent (BOLD) functional magnetic resonance imaging (fMRI): (1) a clinical insight task demanding self-reflection on psychosis-related mental functioning, (2) a self-reflection task on mental functioning unrelated to psychosis (general metacognition), and (3) a semantic control task. Furthermore, we quantified cerebral blood flow (CBF) with arterial spin labeling (ASL) during the resting state after these tasks. Brain responses during the general metacognition task against the semantic control task were compared between groups. Our first hypothesis was that control participants would have greater brain activity during the general metacognition task (especially in the CMS) than FEP patients, given the previously reported differences in brain activation during self-related processing in this patient group (Nelson et al., 2009; Potvin et al., 2019; van der Meer et al., 2010). We further hypothesized that responses in some of these CMS brain regions are selective to clinical insight. Finally, we hypothesized that during the insight task and during the resting state after the tasks, the functioning of the insight-related brain regions would associate with a measure of clinical insight.

2. Methods and materials

2.1. Participants and clinical evaluation

Patients (age 18–40) from the catchment area of the Helsinki and Uusimaa hospital district and the Helsinki City Psychiatry Department who were contacting a health care unit due to a first episode of psychosis were recruited for the Helsinki Early Psychosis study. The inclusion criterion was a score of at least four either on delusions (Unusual thought content) or hallucinations in the Brief Psychiatric Rating Scale–Expanded (Ventura et al., 1993). Control participants were recruited in the study through the Population Register Center, matched based on participant age, sex, and region of residence. Twenty-three FEP patients and 28 control participants were administered the current fMRI task during a Magnetic Resonance Imaging session. From these analyses, we excluded participants with a diagnosed neurological disorder (1 patient). We also excluded participants having a maximum head movement of >2 mm during scanning (2 patients, 1 control participant). One

control was excluded for not having all the stimuli presented due to technical issues. We further visually inspected the functional images for whether the task conditions (as compared to periods of rest) consistently elicited activity in the visual cortex, and due to deviant overall activity, one patient and two control participants were excluded from the analysis. Thus, the group-level analyses included 19 FEP patients and 24 control participants.

The diagnostic assessment of all patients was based on both the Research Version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 2007) and a review of all medical records by a senior psychiatrist (JS). The interview was conducted by a research nurse or psychologist, and the diagnostic decision was made by the psychiatrist. Clinical insight was assessed by the interviewer with the semistructured Scheduled Assessment of Insight–Expanded (SAI-E) (Kemp and David, 1997). Antipsychotic medication doses were transformed to chlorpromazine equivalent doses according to Leucht et al. (2016).

2.2. Brain imaging

Whole-brain BOLD fMRIs were collected at Aalto AMI Centre, Aalto NeuroImaging, Aalto University School of Science with a 3-Tesla MAGNETOM Skyra scanner (Siemens Healthcare, Erlangen, Germany) and a 32-channel coil. Echo-planar imaging sequence was used with repetition time/echo time (TR/TE) 2300/30 ms, flip angle 75°, matrix 64 × 64, field of view (FOV) 240 mm, and 40 slices; these resulted in a voxel size of 3.75 × 3.75 × 4 mm. The imaging was discontinued after the completion of the behavioral task, and thus the number of volumes varied (range 299–442 volumes) between subjects.

After the task, we used a Q2TIPS pulsed ASL (PASL) sequence to quantify CBF during the resting state. This complements BOLD fMRI, which has a complex relationship with CBF and related neuronal activity. Although pseudo-continuous ASL (pCASL) has a better signal-to-noise ratio, CBF values measured with PASL and pCASL are strongly correlated with each other (Boudes et al., 2014). We collected the PASL images with TR 2.3 s, labeling time 0.7 s, post-labeling delay 1.8 s, TE 12 ms, 90° flip angle, nine 8-mm thick slices with 2-mm gaps between slices and 4 × 4 mm in-plane resolution. We acquired altogether 90 time points and an equilibrium magnetization image (MO).

We collected structural high-resolution MPRAGE-T1 images with TR/TE = 2530/3.3 ms (inversion time, TI 1100 ms), flip angle = 7°, matrix 256 × 256, FOV = 256 mm, 176 slices with 1 mm³ isotropic voxels for spatial normalization of the functional images and exclusion purposes.

2.3. Behavioral task during fMRI

We presented statements from three categories: clinical insight, general metacognition, and general knowledge (semantic control). Sixteen statements from each category were preordered into blocks of 4 statements from the same category. After each 4-statement block, a 30 s fixation cross was shown. Each cycle contained one block from each category in random order. A headline above every statement reminded the participant which type of statement was currently being evaluated: either "With respect to psychosis" for clinical insight statements (INS) (e.g., "There is something wrong with my mental health" or "I need treatment for my mental health"), "Irrespective of psychosis" for general metacognition statements (MC) (e.g., "I usually know very clearly why I behaved in a certain way" or "I analyze my thoughts a lot"), or "With respect to general knowledge" for semantic control (GK) (e.g., "All life forms on Earth require water"). The clinical insight statements (Birchwood et al., 1994; McEvoy et al., 1989) and general metacognition statements, including statements from the "insight" subscale of Grant et al. (2002) and "cognitive self-consciousness" factor from Wells and Cartwright-Hatton (2004), were modified from validated questionnaires. The insight statements concerned different aspects of insight,

including attribution of symptoms to illness and treatment need. The metacognition statements tapped into emotional, behavioral, and cognitive self-awareness. The insight and general metacognition statements have been previously used (Raij et al., 2016) and were amended and appended here with four general metacognition statements to balance the number of statements (see Supplementary Table 1 for statements). We used a semantic control task (c.f. Johnson et al., 2002; Modinos et al., 2011) to consider task demands that are not specific to clinical insight and general metacognition tasks, including semantic processing, attention, long-term memory retrieval, judgment formation, and sensorimotor processing.

The task was presented with Presentation software (Neurobehavioral Systems, Inc., Berkeley, CA) through a back-projection screen and a mirror mounted on the head coil. The participants evaluated each statement on a visual analog scale (VAS) with values ranging from 0 to 100. The VAS was presented as a line with the endpoints labeled “Completely disagree” on the left and “Completely agree” on the right. The participants responded by moving a cursor appearing in the middle of the VAS after the first button press: left- and right-hand thumb presses moved the cursor in the respective directions. After 2 s of no further button presses, the position of the cursor was recorded and the next statement was presented. If no button was pressed, the statement was shown for 15 s.

2.4. Analysis of behavioral performance and demographic data

We analyzed behavioral and demographic data with IBM SPSS Statistics 25. The response time—calculated from the presentation of the written stimulus to the recording of the answer (i.e., 2 s after moving the cursor)—was compared between categories with the Wilcoxon signed-rank test. We compared scalar behavioral and demographic variables that deviated from the normal distribution between samples with the Mann–Whitney *U* test and within a sample with the Wilcoxon signed-rank test. We used the χ^2 test for nominal variables. Spearman’s correlation coefficient (*rho*) was calculated between the mean of insight responses during scanning, i.e., 16 responses, each varying between 0 and 100, and SAI-E total scores. Some of the metacognition statements were reversed, that is, 0 represented disagreement with a negative statement and thus responses to them were calculated as 100 – (response). A repeated measures *t*-test was used to compare the patients’ responses to different types of statements.

2.5. Preprocessing and analysis of imaging data

2.5.1. fMRI

The BOLD images were preprocessed with Data Processing Assistant for Resting-State fMRI-Advanced (v4.3_170105; (Yan et al., 2016) running with Statistical Parametric Mapping (SPM12; <https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). They were slice-timing corrected and realigned. T1 images were reoriented to the anterior commissure–posterior commissure line with the origin at the anterior commissure, and the brain was extracted with FMRIB Software Library’s (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>) Brain Extraction Tool. The BOLD images were coregistered with an individual structural T1 image. The structural image was normalized to a common MNI152 space with “New segment” and Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra (DARTEL), and the resulting normalization parameters were then applied to the functional images. Finally, the images were smoothed with an 8-mm full-width-half-maximum Gaussian kernel.

The first-level (within-subject) contrast images were modelled with default options on SPM12. All the 4-statement blocks were modeled with a boxcar function, building one regressor for each statement category. The regressors were convolved with a canonical hemodynamic response function with no time or dispersion derivatives, and the model included a high-pass filter with a 128 s cutoff and SPM’s default autoregressive

model for serial correlations in the signal. As unanswered questions were rare—one patient left one insight statement, and two patients and one control left one general metacognition statement unanswered—all blocks were included in the fMRI models. Altogether block durations had a mean of 40.8 s, standard deviation (SD) of 6.6 s, and a range between 29.9 and 66.7 s in our sample.

The resulting first-level contrast images were entered into group-level permutation tests executed on Statistical Nonparametric Mapping (SnPM13, v13.1.08; <http://warwick.ac.uk/snpm>) with 10,000 permutations and variance smoothing of 8 mm. A gray matter template from SPM8 with a threshold of 0.4 was used as a mask to constrict the analyses to the gray matter. The use of SPM8 template was a matter of convenience as we had used such a mask in previous studies—all the preprocessing steps and first-level analyses were executed in SPM12. With three different statement categories, we focused on the following comparisons: (1) a group comparison between patients and controls in the “MC > GK” contrast, also reporting one-sample statistics from both groups; (2) “INS > GK” contrast within the patient group; and (3) “INS > MC” contrast within the patient group. The latter two contrasts engender the clinical-insight-selective brain regions. In all these analyses, familywise-error-corrected *p* < 0.05 at the voxel level was deemed significant. MRICroGL was used for visualizing results (<http://www.mccau.landcenter.sc.edu/mricrogl/home>).

2.5.2. ASL

For the analysis of ASL images, we manually reoriented the images in SPM12 and used ASLtbx2 to preprocess and analyze the data (Wang et al., 2008). We corrected the images for movement, coregistered the ASL images with the same anatomical image as the BOLD fMRIs (all collected with the same head position), and smoothed the ASL images with an 8-mm full-width-half-maximum Gaussian kernel. We then subtracted control images from the labeled images and computed CBF maps for each image pair by using the ASLtbx default formula for PASL (see Supplementary Material, Eq.1). We used global normalization (i.e., voxelwise CBF was divided by global CBF) to compensate for global signal differences and the Structural Correlation based Outlier Rejection (SCORE) algorithm, which has been shown to increase the effect size in PASL data (Dolui et al., 2017). Finally, we used parameters from the normalization of structural images to normalize the coregistered mean CBF images. We then extracted individual CBF eigenvariates from the clusters that were selective to clinical insight in the BOLD-fMRI analysis.

2.5.3. Correlation of brain measures with clinical insight scores

We correlated the patient group’s activation strengths with the SAI-E total score in the SnPM and computed the two-tailed Spearman’s correlation between the extracted regional CBF values and clinical insight in IBM SPSS Statistics 25. The correlation analyses were controlled for age, sex, antipsychotic equivalent dose, and mean framewise displacement during BOLD imaging (Jenkinson et al., 2002). The response times were included in correlations of BOLD contrast images as a response time difference between the conditions used in the particular BOLD contrast. Due to the limited sample size, we conducted the control analyses as a series of regressions with one nuisance variable at a time. To avoid circularity in the analysis (Kriegeskorte et al., 2009), the correlations with BOLD activity were corrected for multiple comparisons.

2.6. Ethics statement

The Ethics Committee of the Hospital District of Helsinki and Uusimaa approved the study protocol (diary numbers 257/12/03/03/2009 and 226/13/03/03/2013). The clinician responsible for treatment assessed the patients’ capacity to give informed consent based on clinical judgment. Before participation, all participants gave written informed consent.

3. Results

3.1. Participant characteristics

The characteristics of the final sample are presented in Table 1. All patients were medicated, with a mean CPZ equivalent dose of 341.7 mg (range 30–900 mg).

3.2. Behavioral results

The patients agreed with the INS statements with a mean of 70.75 on the 0–100 scale, SD ±16.26. On average, this result did not differ from their responses to MC (mean 65.45, SD = 10.90, $t(18) = 1.14, p = 0.27$) or GK (mean 75.53, SD = 12.90, $t(18) = 1.20, p = 0.25$) statements. The patients took less time on the INS statements (7933.1±1410.2 ms) than on the MC statements (8575.2±1671.9 ms; $Z = -2.78$, two-tailed $p = 0.005$) and GK statements (8911.0±1632.9 ms; $Z = -3.06$, two-tailed $p = 0.002$). Because of this, these two response time differences were included as covariates in their respective BOLD analyses. The response times between the two latter did not differ in the patients ($Z = -1.33$, two-tailed $p = 0.184$) or the controls (MC: 8050.7±1417.0 ms; GK: 8044.9±1112.2 ms; $Z = -0.06$, two-tailed $p = 0.954$). Patients' endorsement of insight-related statements during scanning correlated with their interviewer-rated SAI-E total scores ($rho = 0.65, p = 0.003$, two-tailed).

3.3. fMRI results and correlation with insight

In the contrast MC > GK, both groups showed significant activation in the bilateral posterosuperior precuneus (Fig. 1; Table 2). There were no significant group differences in this contrast.

Table 1
Sample characteristics.

	FEP patients (n, % or median, IQR) ^a	Controls	Test statistic	P level
Sex (males)	17/19 (89%)	19/24 (79%)	$\chi^2 = 0.827$	$p = 0.363$
Age (years)	24.8 (21.0–27.8)	23.8 (21.7–28.3)	$U = 219.0$	$p = 0.826$
Mean framewise displacement (mm)	0.061 (0.048–0.09)	0.065 (0.053–0.09)	$U = 211.0$	$p = 0.678$
No vocational or higher education ^b	10/19 (52.6%)	9/24 (37.5%)	$\chi^2 = 0.985$	$p = 0.321$
SAI-E total score	16.0 (14.0–19.0)	—	—	—
BPRS total score ^c	41.0 (32.0–48.0)	24.5 (24.0–26.0)	$U = 13.0$	$p < 0.001$
GAF	40.0 (32.0–40.0)	85.0 (75.0–90.0)	$U = 0.0$	$p < 0.001$
Schizophrenia, paranoid type	2 (10.5%)	—	—	—
Schizophreniform disorder	8 (42.1%)	—	—	—
Schizophrenia, undifferentiated type	4 (21.1%)	—	—	—
Brief psychotic disorder	1 (5.3%)	—	—	—
Psychotic disorder, NOS	4 (21.1%)	—	—	—

^a IQR = interquartile range, 25th percentile–75th percentile.

^b These numbers include participants who have a high school diploma. Four patients and 2 controls did not have either a high school diploma, vocational education, or other higher education.

^c The BPRS total score is the total score of 24 BPRS-E items, giving a range of 24–168, evaluated based on the last 7 days. Abbreviations: FEP = first-episode psychosis; SAI-E = Schedule for Assessment of Insight–Expanded; BPRS = Brief Psychiatric Rating Scale; GAF = General Assessment of Functioning; NOS = Not otherwise specified.

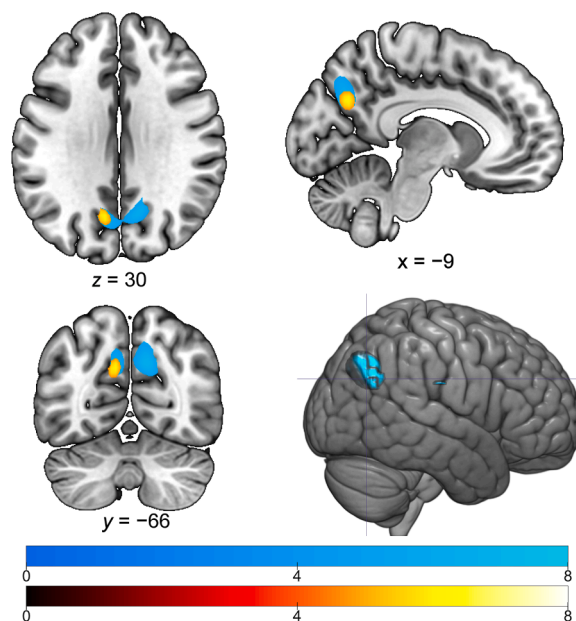


Fig. 1. One-sample contrast general metacognition > general knowledge (semantic control) in patients ($n = 19$, warm colors) and controls ($n = 24$, cool colors) (FWE-corrected $p < 0.05$), showing the activation difference in the posterosuperior precuneus in both groups. The crosshair in the lower right image shows the position of axial and coronal slices. The color bars show the Pseudo-T values. Left hemisphere is on the left.

Other contrasts were addressed in patients only. Posterosuperior precuneus was active in the INS > GK contrast, including a small cluster in the right PCC (Fig. 2; Table 3). The precuneal activation encompassed the cluster that showed significant differences in the contrast MC > GK. The INS > MC contrast showed a more anteroinferior activation including the precuneus, PCC, and retrosplenial cortex (Fig. 2; Table 3). These results did not markedly change when response time differences were added as a covariate.

None of the BOLD contrast strengths correlated with either the on-task insight ratings or interviewer-rated insight. However, CBF in the precuneus and PCC, measured at rest after the present tasks, correlated with SAI-E scores when extracted from the clusters activated in the insight-related BOLD contrasts. These correlations were not explained by global CBF or potential confounders (Table 4 and Supplementary Table 2).

4. Discussion

Insight into illness in psychotic disorders most likely involves several processes including self-perception and social perception, as well as autobiographical and semantic memory encoding and retrieval (Lysaker et al., 2018). It has been theorized that general metacognition and insight might involve similar neuronal mechanisms (David et al., 2012; Lysaker et al., 2018; van der Meer et al., 2010). Our findings in a FEP sample suggest that reflecting upon clinical insight activates the anteroinferior precuneus and posterior cingulate cortex more strongly than general metacognition. A posterosuperior precuneal region was more active during both insight and general metacognition statements than during the evaluation of semantic control statements. Furthermore, the resting-state activation of the clinical-insight-related regions was associated with clinical insight scores. Contrary to what we expected, no group differences were found between FEP patients' and controls' BOLD responses during the general metacognition task.

Given a strong theoretical link between self-processing alterations and psychotic disorders (Nelson et al., 2009) and the importance of the CMS in self-reflection (Northoff et al., 2006; van der Meer et al., 2010),

Table 2

Statistically significant voxels (voxel-level FWE-corrected $p < 0.05$) from separate one-sample tests in the controls ($n = 24$) and first-episode psychosis patients ($n = 19$) in the general metacognition > general knowledge contrast.

	Cluster size	Peak P ^a	Peak pseudo T ^b	Peak MNI coordinates			Anatomical location
				x	y	z	
Controls	227	0.0002	6.67	12	-66	33	Bilateral posterosuperior precuneus, bilateral cuneus
	— ^c	0.0020	5.97	-9	-69	33	
	7	0.0147	5.08	0	-18	27	Midcingulate
Patients	28	0.0011	6.22	-9	-66	30	Left posterosuperior precuneus, left cuneus

^a FWE-corrected.

^b For information on pseudo T, see Nichols and Holmes (2002).

^c A local maximum within the same cluster characterized above.

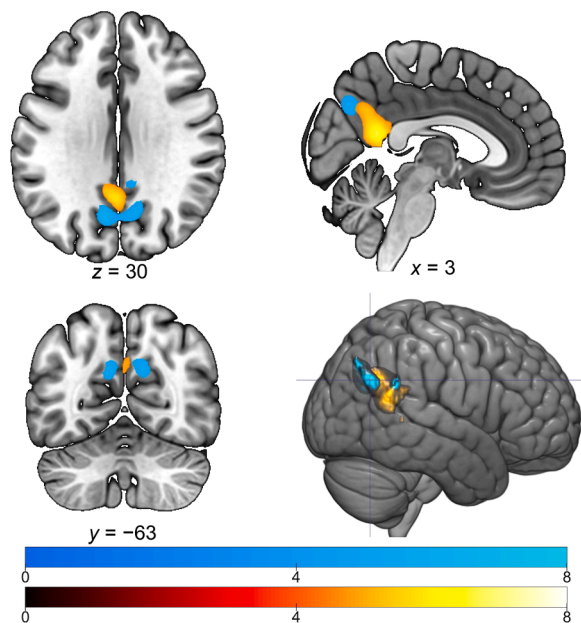


Fig. 2. One-sample contrasts for clinical insight > general metacognition (warm colors) and clinical insight > general knowledge (semantic control, cool colors) in the patients ($n = 19$) (FWE-corrected $p < 0.05$) show separable activation differences in the posteromedial cortex. The crosshair in the lower right image shows the position of axial and coronal slices. The color bars show the Pseudo-T values. Left hemisphere is on the left.

many early neuroimaging studies used region-of-interest analysis focusing on the CMS. Partially consistent with our findings, these studies showed the functioning of either ACC/MPFC or precuneus/PCC—or both—being associated with self-reflection difficulties (akin to general metacognition) or clinical insight in schizophrenia patients (Holt et al., 2011; Raji et al., 2012; van der Meer et al., 2013). In agreement, resting-state connectivity studies have shown differences between patients with good and poor clinical insight in the connectivity of CMS

Table 3

Statistically significant voxels (voxel-level FWE-corrected $p < 0.05$) from separate one-sample tests in first-episode psychosis patients ($n = 19$) in the insight > general knowledge (semantic control) and insight > general metacognition contrasts.

	Cluster size	Peak P ^a	Peak pseudo T	Peak MNI coordinates			Anatomical location
				x	y	z	
INS > GK	125	0.0002	6.42	-9	-66	30	Bilateral posterosuperior precuneus, left cuneus
	— ^b	0.0034	5.48	12	-63	30	
	14	0.0207	4.79	9	-45	27	Right PCC
INS > MC	1	0.0285	4.66	0	-39	21	PCC
	197	0.0004	6.71	3	-51	18	Bilateral anteroinferior precuneus, bilateral PCC, retrosplenial cortex
	2	0.0174	5.16	6	-42	3	Right PCC

^a FWE-corrected.

^b A local maximum within the same cluster characterized above. Abbreviations: GK = semantic control task, INS = insight task, MC = general metacognition task, PCC = posterior cingulate cortex.

nodes (Gerretsen et al., 2014; Liemburg et al., 2012). Furthermore, Faget-Agius et al. (2012) reported higher resting perfusion in the precuneus associating with better insight in patients with paranoid schizophrenia, albeit in a more superior region than in our study. Adding to this literature, our findings indicate that the association between clinical insight and precuneus/PCC functioning may not be fully explained by general metacognition and that it is present already in early psychosis. The latter finding suggests that the decreased precuneus/PCC activity related to worse insight may not only be a consequence of a chronic psychotic disorder but might contribute to the construction of clinical insight.

There is evidence for modularity of brain processing in terms of the target of self-evaluation or self-awareness (David et al., 2012; Gilleen et al., 2011; McGlynn and Schacter, 1989). The present study supports this notion as different parts of the posteromedial cortex were activated during the processing of clinical insight and general metacognition statements. Considering Cavanna and Trimble's (2006) review and the Sajonz et al. (2010) study, there might be a self-referential component in the insight statements (reflected in the more anterior responses) that is not captured by the general metacognition statements, while compared to the semantic control statements, both self-reflective tasks involved

Table 4

Correlation between cerebral blood flow, measured at rest after the tasks, and clinical insight score. Bolded values are statistically significant in a two-tailed test.

Contrast ^a	SAI-E		Anatomical location
	Rho	P value	
INS > MC	0.53	0.020	Anteroinferior precuneus, PCC
MC > GK	0.38	0.105	Posterosuperior precuneus
INS > GK(1) ^b	0.56	0.013	Posterosuperior precuneus
INS > GK(2)	0.56	0.012	PCC

^a The BOLD contrast from which the cluster to extract CBF values was derived.

^b INS > GK(1) refers to the more posterior, precuneal cluster and INS > GK(2) refers to the posterior cingulate cortex (PCC) cluster. Abbreviations: INS = clinical insight task, GK = semantic control task, MC = general metacognition task, SAI-E = Schedule for the Assessment of Insight-Expanded.

posterior precuneus responses. Interestingly, a recent meta-analysis found differences in the precuneus between metacognition and mentalizing, i.e., representing the mental states of another person (Vaccaro and Fleming, 2018)—metacognition was associated with a more posterosuperior region of the precuneus while mentalizing was associated with the anterior region. This might suggest that during insight processing, both self-reflective and other-reflective components are relevant, the latter perhaps providing a self-referencing framework or the integration of these two frames of reference (Ebisch and Aleman, 2016).

Additionally, it is important to realize that even though brain imaging was used in this study, it does not necessarily speak only to anosognosia-based etiological models of poor insight. Indeed, precuneus/PCC, especially as part of the rest of the default-mode network (Raichle, 2015), has been linked with integrative and narrative processing, with autobiographical memory, and with forming internal models of the world and oneself (Bar, 2007; Spreng and Grady, 2010; Vatansever et al., 2015)—processes which form the basis of some recent formulations of insight into illness (Lysaker et al., 2018; Vohs et al., 2016).

In the present study, we did not find an association between BOLD activation strength during the clinical insight task and clinical insight measured with SAI-E. However, an ASL analysis showed that precuneus/PCC activity during the resting state after the tasks correlated with the clinical insight score. The brain is rarely at rest, and spontaneous brain activity in an insight-processing-related hub during the resting state may reflect processes that contribute to insight.

4.1. Strengths and limitations

Here we focused on FEP patients to study insight into illness early on, as insight might have a different evolution in different chronic schizophrenia patients, while previous imaging studies have been on chronic patients. Having insight into psychosis probably involves more than evaluating which trait adjectives fit one's personality, and thus research on brain functional correlates of insight should also study the brain while the participant is evaluating clinical insight statements, as was done in the current study. We further chose statements from metacognition scales that probe into self-reflection on the everyday functioning of one's mind and thus present a suitable control for general metacognition.

It should be noted that self-reflection has been studied with various paradigms (Northoff et al., 2006), and there are multiple definitions and operationalizations of metacognition (Moritz and Lysaker, 2018; Rouault et al., 2018), and this makes comparing different studies challenging. Also, insight into illness has been measured in several ways (Amador and Kronengold, 2004). The current study captured only some aspects of these complex phenomena.

With a small sample size and underrepresentation of women, it is impossible to rule out the relevance of other brain regions in the evaluation of insight, but this study does indicate the importance of the precuneus and PCC. The vividness of mental imagery related to different statement categories might also affect the functioning of these areas (Richter et al., 2016) and could be studied in the future. The higher proportion of males in our study is probably explained by the fact that our sample focuses on rather young patients and most recruiting was done from hospitals—and men typically show earlier onset and more frequent and longer hospitalizations than females (Ochoa et al., 2012). Also, while the focus in this study has been on insight and a naturalistic FEP sample—a psychotic episode being the common factor in the patients—and while using a FEP sample is one way of controlling for the effects of long-term antipsychotic medication (Fusar-Poli et al., 2013), it is important to note that we could not control for the effects of medication and different diagnoses on BOLD signal in the current study and that the effects of these factors should be studied in the future.

The patients in our study responded more quickly to insight statements than to the other statements. This could suggest that patients with

less insight want to suppress such processing and reply faster. However, adding response time differences to the model did not markedly change the results.

5. Conclusions

In this early-psychosis study, we explicitly tested whether there is a difference in BOLD responses when evaluating clinical insight statements and general metacognition statements and found differences in the precuneus and PCC. A posterosuperior region was common to both statements, while an anteroinferior region and PCC were more active during the insight statements than during the general metacognition statements. Furthermore, we found that spontaneous activity of these regions during the resting state after the tasks correlated with interviewer-rated clinical insight. These results add to the mapping of brain correlates of clinical insight and suggest that spontaneous precuneus/PCC activity contributes to the construction of clinical insight, given its role early on in the disease process.

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The funding organizations had no role in the design of the study or in the collection, analysis, and interpretation of the data or in the writing of the manuscript and deciding to submit it for publication.

CRedit authorship contribution statement

Teemu Mäntylä: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Tuula Kieseppä:** Conceptualization, Data curation. **Jaana Suvisaari:** Conceptualization, Data curation. **Tuukka T. Raji:** Conceptualization.

Declaration of Competing Interest

None to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2021.111347](https://doi.org/10.1016/j.psychres.2021.111347).

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