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Connectivity of the precuneus-posterior cingulate cortex with the anterior cingulate cortex-medial prefrontal cortex differs consistently between control subjects and first-episode psychosis patients during a movie stimulus

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ABSTRACT

Background: Functional connectivity is altered in psychotic disorders. Multiple findings concentrate on the default mode network, anchored on the precuneus-posterior cingulate cortex (PC-PCC). However, the nature of the alterations varies between studies and connectivity alterations have not been studied during an ecologically valid natural stimulus. In the present study, we investigated the functional and structural connectivity of a PC-PCC region, where functioning differentiated first-episode psychosis patients from control subjects during free viewing of a movie in our earlier study.
Methods: 14 first-episode psychosis patients and 12 control subjects were imaged with GE 3T, and 29 patients and 19 control subjects were imaged with a Siemens Skyra 3T scanner while watching scenes from the movie Alice in Wonderland. Group differences in functional connectivity were analysed for both scanners separately and results were compared to identify any overlap. Diffusion tensor measures of 26 patients and 19 control subjects were compared for the related white matter tracts, identified by deterministic tractography.
Results: Functional connectivity was increased in patients across scanners between the midline regions of the PC-PCC and the anterior cingulate cortex-medial prefrontal cortex (ACC-mPFC). We found no group differences in any of the diffusion tensor imaging measures.
Conclusions: Already in the early stages of psychosis functional connectivity between the midline structures of the PC-PCC and the ACC-mPFC is consistently increased during naturalistic stimulus.

1. Introduction

Psychotic disorders may derive from altered connectivity patterns in the brain (Friston and Frith, 1995). However, studies comparing functional connectivity between patients and control subjects have yielded contradictory results, as both decreased and increased functional connectivity between the same regions have been observed in patients (Crossley et al., 2016b; Cui et al., 2016; Schilbach et al., 2016a, 2016b; Skudlarski et al., 2010; Whitfield-Gabrieli and Ford, 2012). Furthermore, though most intrinsic functional networks have corresponding underlying white matter connections (Van Den Heuvel et al., 2009), group differences in functional connectivity are not always accompanied by changes in structural connectivity (Camchong et al., 2011; Konrad and Winterer, 2008).

Most reviews on functional connectivity in psychotic disorders agree that results are heterogeneous, showing complex and sometimes inconsistent patterns of connectivity (Karbasforoushan and Woodward, 2012; Sheffield and Barch, 2016). However, abnormalities consistently concentrate on the default-mode network (DMN) (Miller et al., 2016; Peeters et al., 2015; Schilbach et al., 2016a, 2016b; van den Heuvel and Hulshoff Pol, 2010), and common findings also include decreased or altered connectivity (or both) between different parts of the prefrontal cortex and between cortical and subcortical regions (Sheffield and Barch, 2016). Studies have mainly concentrated on chronic patients and used resting-state data (Bluhm et al., 2007; Cole et al., 2011; Collin et al., 2011, 2013; Kraguljac et al., 2016; Mothersill et al., 2017; Peters et al., 2016; Rotarska-Jagiela et al., 2010; Schilbach et al., 2016a, 2016b; Woodward et al., 2011) or tasks related to attention, memory and self-reflection (Antonucci et al., 2016; Ćurčić-Blake et al., 2015; Holt et al., 2011; Whitfield-Gabrieli et al., 2009; Wu et al., 2014). Fewer studies have involved first-episode psychosis or at-risk patients (Alonso-Solís et al., 2012; Cui et al., 2016; Guerrero-Pedraza et al.,

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2012; Shim et al., 2010; Zhang et al., 2013). Only a few resting-state studies have specifically studied the connectivity of the precuneus-posterior cingulate cortex (PC-PCC) region (Peeters et al., 2015; Shim et al., 2010; Woodward et al., 2011; Wu et al., 2014). These studies revealed reduced connectivity with bilateral superior parietal lobule (Schilbach et al., 2016a, 2016b) and increased connectivity with the default-mode regions (Woodward et al., 2011), especially with the medial prefrontal cortex and inferior parietal lobule (Peeters et al., 2015). Overall, psychotic disorders seem to relate predominantly to integrative brain functions and hub regions of the brain (Crossley et al., 2016).

Mental state during imaging is critical for the findings on brain functioning. Different tasks evoke distinct patterns of activity, resulting in group differences highly dependent on the task used (Goghari et al., 2010) and the resting state is characterised by wandering of the mind, during which the content of thoughts is impossible to control. In order to understand the complexity of functional connectivity changes related to integrative brain functions, the stimulus must match in richness to everyday life (Hasson and Honey, 2012). Movies have gained popularity as such stimulus in neuroscience (Bartels and Zeki, 2005; Lahnakoski et al., 2014; Malinen et al., 2007) as they synchronise brain activity across subjects (Hasson et al., 2004) and demand multimodal information to be integrated with semantic and autobiographical memory as well as the present context (Binder et al., 2009; Hasson et al., 2015). Our Helsinki Early Psychosis Study has been the first to use a movie stimulus in psychosis research.

The PC-PCC has a central role in a wide range of integrative cognitive tasks (Cavanna and Trimble, 2006; Utevsky et al., 2014), and both its metabolism and functioning are altered in psychotic disorders (Leech and Sharp, 2013). In an earlier study of the same sample and stimulus, we used machine learning to classify FEP patients and control subjects on the basis of brain functioning during movie viewing. As one of the core symptoms in psychosis is the diminished ability to recognize what is real and what is not, we chose a movie with both realistic and fantasy content to evoke the kind of processing that is thought to be central to the disorder. In our previous study, we used signal change in relation to six previous time points to identify voxels and volumes that best differentiated patients and control subjects that then served as inputs to the classifiers in the machine-learning phase (Rikandi et al., 2017). We identified 194 voxels where activation was highly related to the classification, 134 of which formed a bilateral cluster in the precuneus, adjacent to the PCC (Rikandi et al., 2017). Our results suggested that in this cluster, functioning is different in FEP patients during the integration of information from a variety of modalities. However, how distinct regions in the brain relate to this altered functioning remains unclear.

In this study, we investigated functional connectivity alterations of the PC-PCC, an integrative hub region of the DMN, in early psychosis and in which functioning differentiated FEP patients and matched control subjects with nearly 80% accuracy (Rikandi et al., 2017). Based upon the results of the functional connectivity analysis, we then analysed underlying structural white matter differences. Earlier findings of resting-state and simple task studies have found psychosis-related changes to be concentrated in the hub regions of the brain, mainly the DMN. We therefore hypothesized that differences in functional connectivity between the two groups would concentrate in the nodes of the DMN. Furthermore, we expected these differences to be related to structural connectivity.

2. Materials and methods

2.1. Participants

As in our previous study, the study sample consisted of 46 patients and 32 control subjects from the Helsinki Early Psychosis Study (Rikandi et al., 2017). The FEP patients were treated for first-episode psychosis in hospitals and outpatient clinics of the Helsinki University Hospital. The criteria for psychosis were defined as a score of 4 or higher in either the Unusual thought content or Hallucinations in the Brief Psychiatric Rating Scale Extended (BPRS-E) (Ventura et al., 1993). We excluded patients with previous psychotic episodes, contraindications for magnetic resonance imaging or neurological abnormalities in the MRI scan. Birth year, sex and residence-matched control subjects were recruited via the Finnish Population Registration System. Diagnostic assessment of patients was based on the Research Version of the Structured Clinical Interview for DSM-IV Disorders – Axis I (SCID-I) (First et al., 2002 (Revision: 2007)) complemented with a comprehensive review of symptoms from medical records. A SCID-I interview was also performed on control subjects to exclude a history of psychotic disorder.

2.2. Data acquisition

Magnetic imaging was conducted at the Aalto Magnetic Imaging Centre at Aalto University. Due to the prescheduled change of the MRI scanner during the study, 26 subjects (14 patients, 12 controls) were scanned using the GE Signa VH/i 3T scanner (Scanner 1) with a 16-channel head coil and 52 subjects (32 patients, 20 controls) were scanned using the Siemens Skyra 3-T scanner (Scanner 2) with a 32-channel head coil. Imaging parameters for the acquired functional, T1 and DTI images are presented in Supplementary Table 1. Diffusion data was available for 26 patients and 19 control subjects. During functional magnetic resonance imaging (fMRI), subjects were presented audiovisual scenes from the movie Alice in Wonderland (Tim Burton, Walt Disney Pictures, 2010; Finnish soundtrack) for duration of 7 min 20 s. Content of the scenes varied from realistic scenarios to increasingly unrealistic ones with animated scenes and characters. Scene contents and durations have been described in detail in Rikandi et al. (2017).

2.3. Preprocessing

2.3.1. Preprocessing of functional images

Based on an evaluation by a neuroradiologist, subjects with neurological abnormalities were excluded from the sample. Functional imaging data were preprocessed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Images were realigned, normalised to the Montreal Neurological Institute (MNI) template and smoothed with an 8-mm full-width-at-half-maximum Gaussian kernel. Linear drift, constant offset and individual motion parameters were removed using linear regression as implemented in DPARSFA (Chao-Gan and Yu-Feng, 2010). MaxCorr, a method suitable specifically for naturalistic fMRI stimulus such as movies (Pamilo et al., 2015), was further used to remove typically movement-related subject-specific artifacts as the DPARSFA regression may not remove all movement effects (Parkes et al., 2018). MaxCorr uses the data of other subjects as reference to identify and remove components related to movement and physiological noise. Finally, signal time courses extracted from the white matter and cerebrospinal fluid were regressed out from the data to further restrict movement artifacts (Yan et al., 2013).

2.3.2. Preprocessing of DTI

We only analysed the Siemens sample due to small sample size for DTI analysis in the GE sample. Preprocessing was done using the PANDA (https://www.nitrc.org/projects/panda) pipeline tool for diffusion MRI (Cui et al., 2013). The steps included resampling, removing the skull and cropping the brain, correction for the eddy-current effect, normalisation with a 2-mm resolution to a FMRIB58_FA template in the MNI space and smoothing with a full-width-half-maximum kernel size of 6 mm.

2.4. Data analysis

We used a seed region of the 134 voxels that best differentiated patients and control subjects in a previous study of the same sample

(Rikandi et al., 2017) and that clustered together in the bilateral PC-PCC (Fig. 1b). We created voxel-wise functional connectivity maps from the PC-PCC seed region using Data Processing Assistant for Resting-State fMRI Advanced Edition (DPARSFA) version 2.3 (Chao-Gan and Yu-Feng, 2010). To investigate overall functional connectivity of the seed throughout the movie, patient and control subject functional connectivity matrices from both scanners were entered into a one-sample permutation test. To test for group differences, we performed a non-parametric permutation two-sample test, as implemented in the SnPM13 (http://warwick.ac.uk/snpm) (Nichols and Holmes, 2001) toolbox for SPM12. To replicate our findings, we conducted the two-sample test separately for each scanner. Furthermore, in Scanner 2, the analysis was conducted for the sample of subjects that had both fMRI and DTI data (26 patients and 20 control subjects) and, to be reported as supplementary results, for all subjects (32 patients and 30 control subjects). For each test, we performed 10,000 permutations with a cluster-defining threshold (CDT) of $p < 0.001$ and a cluster-level threshold of $p < 0.05$ familywise-error corrected for multiple comparisons. Age, sex and mean framewise displacement parameters (Jenkinson et al., 2002) were entered into the analyses as covariates.

To test for consistency between the results of Scanner 1 and Scanner 2, we performed the two-sample *t*-tests for each sample again by using the result from the other sample as an explicit mask. We used primary threshold of $p < 0.001$ and a $p < 0.05$ familywise-error corrected threshold for multiple comparisons. All anatomical regions were identified according to the Automated Anatomical Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002).

2.4.1. Analysis of underlying structural connectivity

We used Trackvis (Wang et al., 2007) to analyse integrity of the white matter tracts connecting the PC-PCC seed and the regions of altered functional connectivity. To best identify the white matter tracts connecting the regions, we obtained mask images from the pooled one-sample functional analysis of overall connectivity with a primary threshold of $p = 0.1^{-10}$. The threshold was visually defined to produce mask images that overlap with regional white matter tracts. We constructed white-matter pathways between the extracted regions by using the interpolated streamline propagation algorithm with FA thresholds 0.2–1, angle threshold 35 and step length of 0.5, applying spline filter. The values of commonly used measures to identify white matter structural alterations, fractional anisotropy (FA), medial diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) were then extracted from each individual subject from the tracts between the ROIs. A two-sample t-test between the groups was performed for individual tract-mean values using IBM SPSS statistics for Windows 24.

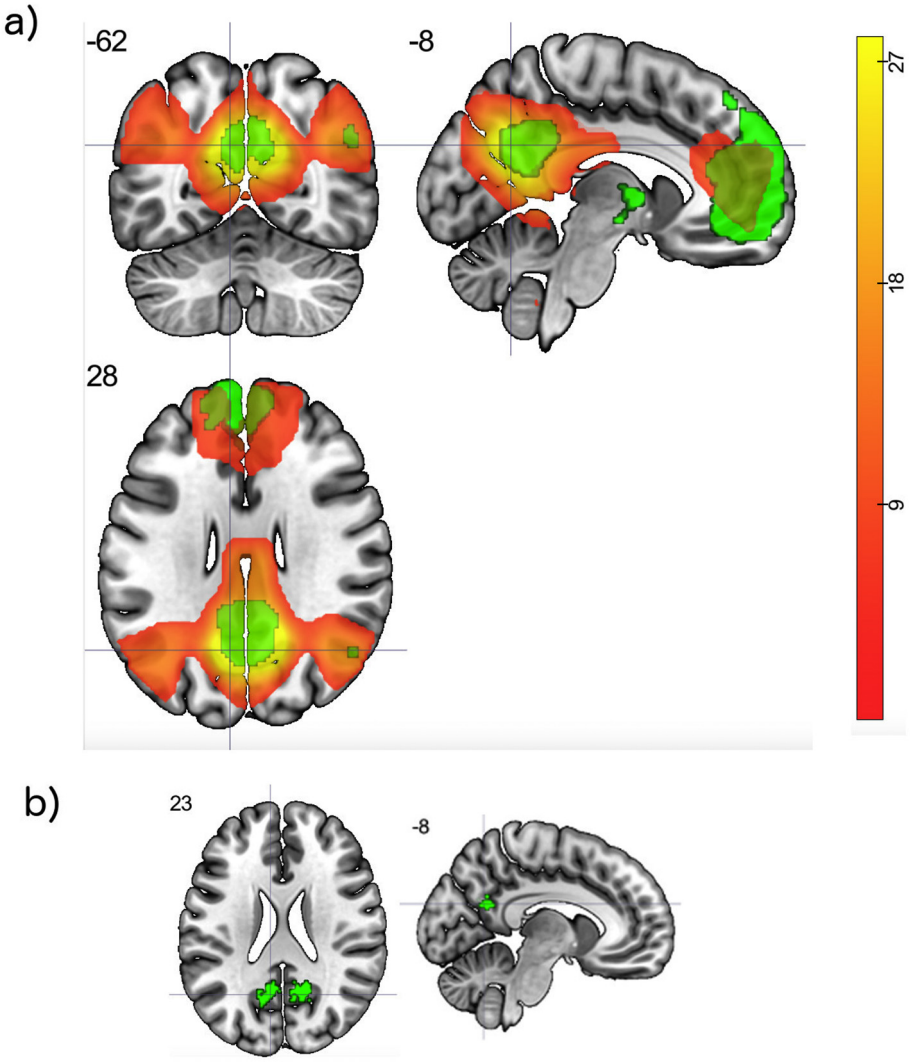

Fig. 1. a) Functional connectivity of the PC-PCC during movie viewing in patient and control subject combined data is shown in yellow. Colour bar indicates pseudo-t values. Nodes of the default-mode network (Shirer et al., 2012) are shown in green b) PC-PCC seed region.

3. Results

3.1. Descriptive information

Subject descriptive information is shown in Table 1. Age and sex were controlled for in all group comparisons.

3.2. Functional connectivity

Overall functional connectivity of the PC-PCC seed region in all subjects is presented in Fig. 1. When averaged across the movie stimulus, the PC-PCC seed was functionally connected to regions overlapping with nodes of the DMN (Shirer et al., 2012). Group differences in functional connectivity are shown in Fig. 2a and b and Table 2. In Scanner 1 data, we observed increased functional connectivity in patients compared to the healthy control subjects between the seed region and a cluster overlapping the bilateral medial and superior frontal gyrus and the anterior cingulate cortex. In patients, the PC-PCC seed had decreased connectivity with bilateral lingual gyrus and the dorsal regions of the precuneus. In Scanner 2 data, patients had increased connectivity between the seed and a cluster overlapping the bilateral medial frontal gyrus, the right superior frontal gyrus and the anterior cingulum. Functional connectivity was decreased in patients between the seed region and left superior temporal gyrus. The consistency analysis revealed that, in both samples, the significant overlapping results are mainly located in the left anterior cingulate cortex and medial superior frontal gyrus (Fig. 2c, d). No overlapping regions of decreased functional connectivity were observed.

3.3. Structural connectivity

Fig. 3 illustrates the main midline clusters used in the structural connectivity analysis and the structural connectivity between these clusters. All the white matter tracts connecting the two clusters were part of the cingulum bundle. We did not observe any statistically significant differences in the tracts between the groups in any of the measures of FA ($t = -0.478$, $p = 0.635$), MD ($t = 0.706$, $p = 0.484$), AD ($t = -0.234$, $p = 0.816$) and RD ($t = 0.779$, $p = 0.440$).

4. Discussion

Our findings suggest that functional connectivity between the midline structures of the PC-PCC and the ACC-mPFC is increased during naturalistic stimulus in FEP, as demonstrated by consistent results across two separate samples. Overall, the PC-PCC seed region (Rikandi et al., 2017) was functionally connected to regions overlapping with the nodes of the default-mode network. Common diffusion measures of FA, MD, AD and RD of the white matter tracts connecting the PC-PCC and ACC were compared in the larger sample. No differences were observed, suggesting that this is not caused by white matter pathology.

The PC-PCC is a hub region, i.e. a region highly interconnected to other regions in the brain. It is a part of the posterior area of the DMN (Shirer et al., 2012) and involved in high-level integrative cognitive processes, such as episodic memory retrieval (Tulving et al., 1994), self-referential processing (Kircher et al., 2000) and mental imagery (Cavanna and Trimble, 2006). Similar to the PC-PCC, the ACC-mPFC is also a hub and a core node of the default-mode network (Andrews-Hanna et al., 2014) and associated with a wide range of integrative functions. Activation of the ACC-mPFC is related to cognitive control (Shenhav et al., 2013) and emotional processing (Etkin et al., 2015). The ACC is particularly involved in updating internal models (Kolling et al., 2016) and estimating uncertainty related to one's surroundings (O'Reilly et al., 2013). The ACC may also be involved in making action-outcome associations (Heilbronner and Hayden, 2016). The co-activation of the midline hubs is highly associated with many different aspects of self-referential processing (van der Meer et al., 2010). In fact, it has been suggested that the DMN core regions of the PC-PCC and ACC-mPFC are incremental in constructing personal meaning of perceived stimulus (Andrews-Hanna et al., 2014).

Our functional connectivity results are consistent with earlier findings in that alterations in functional connectivity in psychosis tend to concentrate in the nodes of the default-mode network (Sheffield and Barch, 2016). Furthermore, earlier resting-state studies with schizophrenia patients have found that connectivity from the DMN core node PC-PCC to other nodes of the network tends to be increased in patients (Peeters et al., 2015; Woodward et al., 2011). Our results add to these findings and suggest that at least related to the midline structures, this increased connectivity is not only present during the resting state but also when the integration of external multimodal sensory

Table 1
Descriptive information. FEP, first-episode psychosis; SD, standard deviation; FD, framewise displacement; DTI, diffusion tensor imaging; MDD, major depressive disorder; NOS, not otherwise specified.

	FEP group *n* (%), mean ± SD	Control group *n* (%), mean ± SD	Test statistic	p value
Scanner 1				
Sex (female)	4/14 (28.6%)	6/12 (50.0%)	$\chi^2 = 0.248$	0.619
Age (years)	28.2 ± 6.2	27.4 ± 6.9	$t = 0.323$	0.750
Head motion, FD (mm)	0.0495 ± 0.017	0.0534 ± 0.034	$U = 92$	0.705
Scanner 2				
Sex (female)	9/29 (31%)	11/19 (58%)	$\chi^2 = 3.407$	0.065
Age (years)	24.1 ± 4.6	26.4 ± 5.5	$t = 1.584$	0.120
Head motion (mm)	0.0657 ± 0.037	0.0635 ± 0.029	$U = 262$	0.776
DTI sample				
Sex (female)	8/26 (31%)	11/19 (58%)	3.311	0.069
Age (years)	24.1 ± 4.8	26.4 ± 5.5	$t = 1.526$	0.134

Diagnosis	FEP Scanner 1	FEP Scanner 2
Schizophrenia	10/14	12/29
Schizophreniform disorder	2/14	6/29
Schizoaffective disorder		1/29
MDD with psychotic features		1/29
Bipolar I disorder, with psychotic features		4/29
Psychotic disorder NOS	2/14	5/29

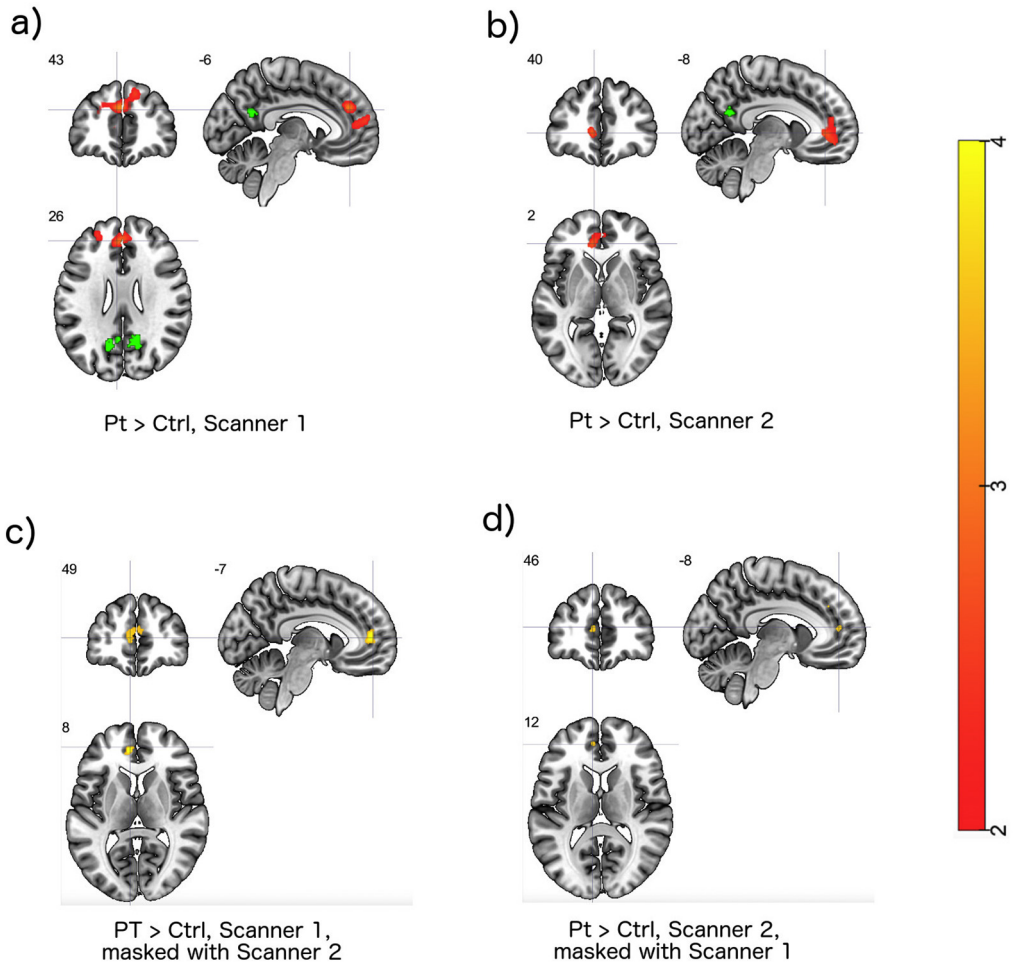

Fig. 2. a) Increased functional connectivity in patients from the PC-PCC seed (green) in Scanner 1 and b) Scanner 2. c) Region of increased FC in patients in Scanner 1, within the Scanner 2 significant result and d) in Scanner 2, within the Scanner 1 significant result. Colour bar indicates pseudo-t values.

information is needed. Furthermore, the difference is present and consistent in the early stages of psychotic disorders. In light of the discussed roles of the co-activation of the PC-PCC and ACC-mPFC and considering the core symptom of reality distortion in psychosis, this could be somehow indicative of altered self-referential, emotional processing in patients.

One of the considerable strengths of this study was the possibility to use a specific seed region known to function differently during the stimulus between these subject groups (Rikandi et al., 2017). This allowed for a more precise examination of the connectivity differences than an atlas-based seed. Furthermore, our results were highly similar across scanners, providing consistent evidence in a field of inconsistent results (Karbasforoushan and Woodward, 2012; Sheffield and Barch, 2016). The fact that we observed no differences in underlying structural connectivity between the two hubs could be due to the relatively small sample size. However, as increasing evidence suggests that changes in functional connectivity between groups are complex and task-dependent (van den Heuvel and Fornito, 2014; Whitfield-Gabrieli and Ford, 2012), it is likely that the observed functional changes cannot simply be reduced to corresponding differences in direct structural connections. Currently our results are applicable to this stimulus only. Further research with different types of movies is needed to test the generalisability of the results.

In conclusion, the functional connectivity between a cluster in the PC-PCC region and the ACC-mPFC is consistently increased in FEP patients during free viewing of a movie. No changes in direct structural connectivity between these regions were detected. These results expand earlier findings of increased functional connectivity in schizophrenia patients within the DMN during rest and pinpoint the midline structures already affected in the early stages of psychotic disorders, suggesting altered dynamics of self-referential processing in FEP patients during natural stimulation.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.03.018.

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The funding organizations had no role in study design, in the collection, analysis and interpretation of data, or in writing of the paper.

Contributors

JS, TTR and TK contributed to designing the study. ER, TM, ML and TTR undertook the gathering of data and statistical analysis. TTR was in charge of the statistical methods. ER and TTR managed the literature searches and ER wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Table 2
Cluster-level differences in functional connectivity. Cluster-level FWE-corrected statistical significance, cluster size, voxels with the most statistically significant differences (cluster centre) and their corresponding regions are presented first. A detailed description of the entire cluster is then presented (amount of voxels in each corresponding region) using AAL labels.

Cluster-level p-value (FWE)	Cluster size (voxels)	Peak voxels (x, y, z)	Pseudo-t	p (FWE)	Corresponding region (AAL)	Cluster information	
						Voxels (n)	Region (AAL)
Increased FC in patients							
Scanner 1							
0.0115	878	−4, 42, 28			Medial superior frontal gyrus L	401	Medial superior frontal gyrus L
		−2, 54, 14			Medial superior frontal gyrus L	186	Medial superior frontal gyrus R
		12, 42, 42				88	Middle frontal gyrus L
						62	Anterior cingulum R
						59	Superior frontal gyrus R
						37	Superior frontal gyrus L
						4	Middle cingulum R
Scanner 2							
0.0300	454	−8, 38, 0			Anterior cingulum L	235	Anterior cingulum L
		−6, 44, −6			Medial orbitofrontal gyrus L	77	Medial orbitofrontal gyrus L
		−12, 52, −4			Medial orbitofrontal gyrus L	29	Medial superior frontal gyrus L
						27	Medial orbitofrontal gyrus R
						17	Anterior cingulum R
						13	Medial superior frontal gyrus R
Scanner 1 masked with Scanner 2	108	−4, 48, 12	4.40	0.0025	Anterior cingulum L	76	Anterior cingulum L
		6, 52, 16	3.83	0.0087	Medial superior frontal gyrus R	15	Medial superior frontal gyrus R
						2	Anterior cingulum R
Scanner 2 masked with Scanner 1	2	−8, 36, 32	3.42	0.0246	Medial superior frontal gyrus L	2	Medial superior frontal gyrus L
	16	−8, 48, 12	3.36	0.0276	Anterior cingulum L	16	Anterior cingulum L
	4	4, 50, 16	3.29	0.0323	Anterior cingulum R	4	Superior frontal gyrus L
Decreased FC in patients							
Scanner 1							
0.0016	1751	22, −52, −2	6.08	0.0018	Lingual gyrus R	668	Lingual gyrus R
		20, −66, 14	4.03	0.4069	Calcarine R	505	Calcarine R
		14, −44, 6	3.47	0.8512	Precuneus R	175	Precuneus R
						129	Cuneus R
						100	Fusiform R
						65	Parahippocampal R
0.0107	959	−22, −48, −4	5.5	0.0109	Lingual gyrus L	451	Lingual gyrus L
		−22, −68, 4	5.14	0.0293		132	Calcarine R
		−10, −48, 6	3.78	0.6050		112	Fusiform gyrus L
						66	Parahippocampal gyrus L
						44	Precuneus L
Scanner 2							
0.0139	569	−44, −22, 0	4.18	0.2870	Superior temporal gyrus, L	386	Superior temporal gyrus, L
		−60, −36, 12	4.06	0.3863	Superior temporal gyrus, L	81	Middle temporal gyrus L
		−52, −12, 0	3.81	0.6281	Superior temporal gyrus, L	6	Insula L

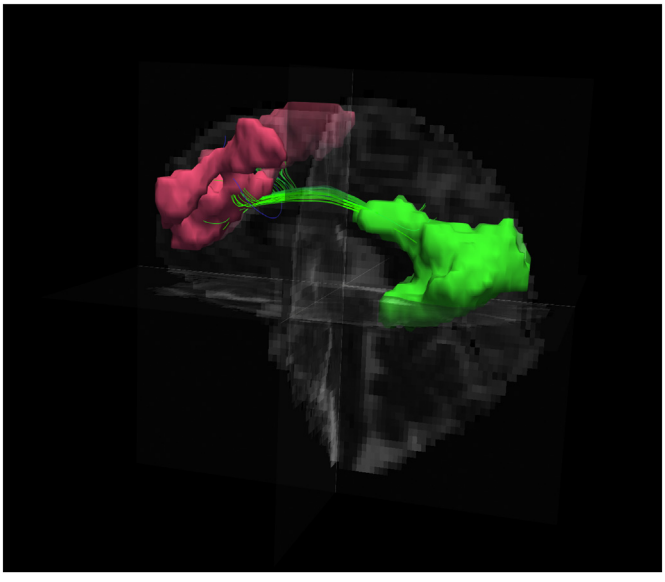

Fig. 3. Visualization of one subject's white matter tracts between the PC-PCC and the ACC-mPFC clusters.

Conflict of interest

All authors declare that they have no conflicts of interest.

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