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State-like changes in the salience network correlate with delusion severity in first-episode psychosis patients

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ABSTRACT

Background and hypothesis: Delusions are characteristic of psychotic disorders; however, the brain correlates of delusions remain poorly known. Imaging studies on delusions typically compare images across individuals. Related confounding of inter-individual differences beyond delusions may be avoided by comparing delusional and non-delusional states within individuals.

Study design: We studied correlations of delusions using intra-subject correlation (intra-SC) and inter-subject correlation of functional magnetic resonance imaging (fMRI) signal time series, obtained during a movie stimulus at baseline and follow-up. We included 27 control subjects and 24 first-episode psychosis patients, who were free of delusions at follow-up, to calculate intra-SC between fMRI signals obtained during the two time points. In addition, we studied changes in functional connectivity at baseline and during the one-year follow-up using regions where delusion severity correlated with intra-SC as seeds.

Results: The intra-SC correlated negatively with the baseline delusion severity in the bilateral anterior insula. In addition, we observed a subthreshold cluster in the anterior cingulate. These three regions constitute the cortical salience network (SN). Functional connectivity between the bilateral insula and the precuneus was weaker in the patients at baseline than in patients at follow-up or in control subjects at any time point.

Conclusions: The results suggest that intra-SC is a powerful tool to study brain correlates of symptoms and highlight the role of the SN and internetwork dysconnectivity between the SN and the default mode network in delusions.

1. Introduction

Psychotic disorders are characterized by a disrupted sense of reality, manifesting as reality distortion symptoms (delusions and hallucinations). The most recent version of the Diagnostic and statistical manual of mental disorders (DSM-5) defines delusions as “fixed beliefs that are not amenable to change in light of conflicting evidence”, with content that “may include a variety of themes (e.g. persecutory, referential, somatic, religious, grandiose)”, and hallucinations as “perception-like experiences that occur without external stimulus” while being “vivid and clear, with the full force and impact of normal perceptions, and not under voluntary control” (*Diagnostic and statistical manual of mental disorders: DSM-5*, 2013). Often studied together, it remains unknown whether delusions and hallucinations share a common underlying mechanism or represent embodiments of separate brain dysfunctions. Delusions have been suggested to arise from a number of different cognitive abnormalities, such as dysfunctions in theory of mind or cognitive bias (). Considering the prevalence of studies on behavioral correlates of delusions, surprisingly few brain imaging studies on delusions have been conducted to date. Delusions have been observed to correlate with increased connectivity between the anterior cingulate and left thalamus (Csukly et al., 2020), and the anterior cingulate and the hippocampus (Schott et al., 2015). In a study on 19 patients with schizophrenia with severe delusions, Zhu et. al., using arterial spin labeling, observed lower cerebral blood flow in the anterior cingulate when compared to patients without severe delusions (Zhu et al., 2016).

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A recent review on structural changes associated with delusions across diagnoses (schizophrenia, bipolar disease, Alzheimer's disease, and Parkinson's disease) observed reduced grey matter volume in, among other areas, the bilateral insula. While the mechanisms underlying reality distortion symptoms are not fully understood, there is robust evidence for dysfunctional dopamine signaling during psychosis (Howes & Kapur, 2009). The "aberrant salience hypothesis" postulates that elevated midbrain dopamine signaling leads to an aberrant distribution of salience to stimuli that typically would be unattended. Such dysfunctions could promote non-existing associations through cognitive bias, leading to the formation of delusions (Broyd et al., 2017). Supporting this theory, hypersalience has been observed in delusion-prone individuals and patients with schizophrenia (Balzan et al., 2013). While mesostriatal pathways are involved, the wide-ranging brain imaging correlates, in conjunction with the diverse genetic and psychosocial risk factors of psychotic disorders, point to larger-scale brain dysfunction underlying reality distortion (Radua et al., 2018; Schizophrenia Working Group of the Psychiatric Genomics, 2014).

A part of such system is the cortical salience network (SN), which consists of the anterior cingulate cortex and bilateral insula (Seeley et al., 2007). Schizophrenia and positive symptoms are associated with both structural (Baiano et al., 2007; Ellison-Wright & Bullmore, 2010; Koutsouleris et al., 2008; Palaniyappan et al., 2011) and functional (Pu et al., 2012; Raij et al., 2016; White et al., 2013) changes in the SN. Additionally, it has been suggested that the SN plays a central role in balancing the activity of the intrinsic default mode network (DMN) (Raichle et al., 2001), located in the posterior cingulate cortex/precuneus, medial prefrontal cortex and angular gyrus, and the extrinsic central executive network (CEN), situated in the posterior parietal cortex and dorsolateral prefrontal cortex (Menon, 2011; Menon & Uddin, 2010; Seeley et al., 2007). Furthermore, dysfunction of such cortical networks could contribute to mesostriatal dopamine dysregulation and abnormal salience (Raij et al., 2015).

Resting-state studies have provided important insights on connectivity alteration, but they tell us little about symptom-related activation. Such activation can be addressed using tasks and modelling of the task-related activation, but modelling is challenging, and tasks are often simplistic relative to naturalistic conditions. Inter-subject correlation (ISC) analysis uses fMRI time series of other subjects to model activation during temporally locked tasks, and studies using naturalistic stimuli have shown high voxel-voxel synchronization across subjects (Hasson et al., 2004; Kauppi et al., 2010). While this has advanced the field (Mantyla et al., 2018), a remaining challenge is that the blood oxygen level-dependent (BOLD) signal varies across subjects, and correcting for these differences has proved challenging (Dubois & Adolphs, 2016). Furthermore, inter-individual differences may be associated with the symptom of interest, thus confounding the results (Hasson et al., 2009).

Intra-subject correlation (intra-SC) analysis (Hasson et al., 2004) uses the same subject's voxelwise fMRI signal time series as a model, measured in a separate scan. This method allows us to study symptom-linked state-like activation patterns when subjects are compared to their own symptom-free state. As many individual characteristics are matched between measurements, intra-SC provides enhanced control for many potential confounders. By comparing the fMRI signal in first-episode psychosis (FEP) patients at baseline (when delusions were present) and at follow-up (when no delusions were present), we evaluated the state-like changes that accompany delusions. In particular, we correlated the magnitude of these state-like changes with the symptom severity at onset. In addition, we compared the functional connectivity of the salience network regions that in the first analysis correlated with delusions between groups and assessed state-related changes in connectivity in patients and between groups. Finally, we used a sliding time-window intra-SC analysis to study whether changes in realism of the scenes related to strength of correlations between intra-SC and symptom scores.

2. Materials and methods

2.1. Subjects

Ninety-seven voluntary FEP patients from psychiatric wards and outpatient clinics within the Hospital District of Helsinki and Uusimaa and the City of Helsinki, and sixty-two control subjects from the civil registry, excluding individuals with a history of psychotic episodes (but not other mental disorders), participated in imaging studies in the Helsinki Early Psychosis Study. Patients with psychotic disorders induced by substance use or caused by a general medical condition were excluded from the study. The initial evaluation was performed after initiation of treatment and after receiving written consent from the participants. The study was approved by the Ethics Committee of the University Hospital District of Helsinki and Uusimaa. 55 patients and 41 control subjects participated in a one-year follow-up scan (average follow-up time 1.24 years, range 0.94 – 2.57 years). We included 24 FEP patients who presented without delusions during the follow-up study and 27 age- and sex-matched control subjects to observe state-like changes associated with delusions. As such, this subsample is likely not fully representative of FEP patients. Any further reference to the presence of delusions refers only to the baseline as no patients presented with delusions during the follow-up. Regarding head movement, we included only subjects with fMRI framewise displacement of<0.5 mm during at least 95 % of the scan, and no more than an average of 0.2 mm during either the baseline of follow-up study. For details on subject exclusion, see Fig. 1.

2.2. Measures

All measures were obtained at baseline and follow-up. Reality distortion symptoms were evaluated using the Brief Psychiatric Rating Scale Extended (BPRS-E) (Ventura et al., 1993), and psychosis (inclusion criteria for the Helsinki Early Psychosis Study) was defined as a score of four or higher for either hallucinations (BPRS-10) or unusual thought content (i.e., a global measure of the severity of delusions, BPRS-11) at the peak of the psychotic episode. Patients and control subjects were evaluated using the Research Version of SCID I (First et al., 2002), and a senior psychiatrist (JS) confirmed the final DSM-IV diagnoses based on the SCID-I interview and medical records from mental health treatment contacts. We measured level of functioning using the Global Assessment of Functioning (GAF) scale (Aas, 2011).

At baseline, all but two patients were using antipsychotic medication (risperidone n = 6, olanzapine n = 9, quetiapine n = 3, aripiprazole n = 1, ziprasidone and quetiapine n = 1, quetiapine and risperidone n = 1, quetiapine and chlorpromazine n = 1). During the follow-up study, 16 patients were using antipsychotic medication (olanzapine n = 6, risperidone n = 3, aripiprazole n = 2, clozapine n = 2, quetiapine n = 1, ziprasidone n = 1, quetiapine and perphenazine n = 1). Most of the patients who were not using antipsychotic medication were using either mood stabilizing medication or antidepressants. We calculated chlorpromazine equivalent dosages at baseline and follow-up using the DDD (defined daily doses) method (Leucht et al., 2016).

The BPRS-10 and BPRS-11 items are rated on a 7-point scale, ranging from absence of the assessed symptom to extreme severity. Here, both scores were calculated based on the symptoms in the week prior to the interview. In the BPRS interview, we rated symptom separately for the past week and for the peak symptom severity during the episode. The BPRS-E manual describes delusions as: "patently absurd, clearly false or bizarre ideas that are expressed with full conviction" and hallucinations as: "reports of perceptual experiences in the absence of relevant external stimuli" (Ventura et al., 1993). As patients were selected based on being free of delusions during the second measurement, the BPRS-11-score at onset is equal to the magnitude of change between baseline and follow-up i.e., the deviation from a delusion-free state. Due to an interest in delusions as a separate dimension of reality distortion symptoms, we

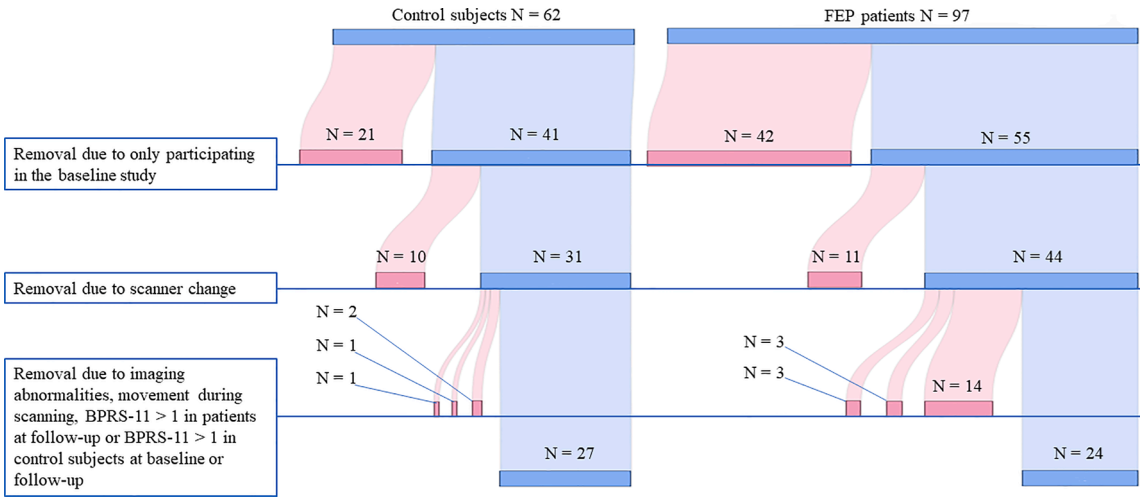


Fig. 1. Flow-chart of subject exclusion. From the Helsinki Early Psychosis Study, 97 FEP patients and 62 control subjects participated in imaging studies. 41 patients and 21 control subjects were excluded as they did not participate in the follow-up study. A further 11 patients and 10 control subjects were scanned with a different MRI scanner at baseline and were thus excluded as scanner differences could interfere with the results. In addition, 14 patients and one control subject were excluded due to presenting with measurable symptoms on the BPRS-11 item during the follow-up-study, and one control subject was excluded due to presenting with measurable symptoms on the BPRS-11 item during the baseline study. Finally, three patients were excluded due to movement during either the baseline or follow-up fMRI scanning, and three patients and one control subject were removed due to neurological disease or structural abnormalities in the structural MRI images that could potentially interfere with analyses. FEP = first-episode psychosis, BPRS-11 = unusual thought content item in the Brief Psychiatric Rating Scale.

included only patients who did not present with delusions at follow-up.

2.3. Experiment

Patients and control subjects were presented with audio-visual scenes from the movie "Alice in Wonderland" (Tim Burton, Walt Disney Pictures, 2010; Finnish soundtrack) for a duration of 7 min and 21 *sec* during fMRI scanning at both baseline and follow-up. The stimulus was intended to include both realistic and unrealistic content for potential validity for delusions (for a detailed description of the scenes please see (Rikandi et al., 2017)). Seventeen independent control subjects rated the realism of the scenes shown, i.e., how likely it would be for these to occur in real life. We averaged the estimated realism of these evaluations to obtain a continuous regressor representing the realism of the stimulus. To account for fMRI signal lag, we convoluted this regressor using the canonical double-gamma hemodynamic response function (HRF).

2.4. Statistical analyses of behavioral variables

All statistical analyses of behavioral variables were performed using the SPSS software (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp). Due to most variables not following a normal distribution, we used non-parametric tests unless otherwise noted: Spearman's Rho test for correlation analyses, Mann-Whitney-*U* test for group comparison of continuous variables, and Chi-Square test for group comparison of dichotomous variables.

2.5. MRI acquisition

MRI images were obtained with a Siemens Skyra 3-T scanner at Aalto University, Espoo, Finland. T1 structural images were obtained with MPRAGE-sequence (TR/TE 2530 ms/3.3 ms, FOV 256 mm, slice thickness 1 mm, voxel size $1 \times 1 \times 1$ mm^3, number of slices 176). The blood oxygen level-dependent (BOLD) signal was acquired with a gradient echo-planar imaging (*EPI*) sequence (TR 1.8 s, echo time 30 ms, flip angle 75°, FOV 240 mm).

2.6. Image preprocessing

We pre-processed fMRI data using the FSL software (https://www.fmrib.ox.ac.uk) and a custom-made MATLAB (MathWorks Inc., Natick, MA, USA) code (BRAMILA pipeline v2.0, available at https://version.aalto.fi/gitlab/BML/bramila). The *EPI* images were corrected for slice timing differences, corrected for head motion, segmented, co-registered to the participant's structural image and then normalized to the Montreal Neurological Institute (MNI) template. We smoothed the functional images with a gaussian kernel of 6 mm full width at half maximum (FWHM). A Savitzky-Golay filter (Cukur et al., 2013), and a high-pass temporal filter (cut-off frequency 0.01 Hz) were applied to remove scanner drift. 24 motion-related regressors, signal from deep white matter and cerebrospinal fluid were applied to the BOLD time series to account for motion and physiological artefacts (Power et al., 2012).

2.7. Intra-SC and ISC preprocessing

We calculated intra-SC (Hasson et al., 2004) as pairwise Pearson's correlation coefficients of the voxelwise time courses between the baseline measurement and the subject-specific delusion-free follow-up measurement to assess the magnitude of deviation from an individual non-psychotic state during psychotic symptoms. Thus, voxel intensity in the intra-SC image reflects the stability of the signal over time, with low values representing greater deviation from the delusion-free state. We calculated ISC using a similar method, using an independent reference group of 15 control subjects who participated in the baseline study, but not in the follow-up study, and thus not otherwise included in this study. ISC was calculated from each subject included in this study to each of the reference subjects, and then averaged to provide a single mean correlation value for each voxel in each participant. We calculated ISC for FEP patients and control subjects from baseline and follow-up to the same independent reference group imaged during the baseline study. To calculate and visualize the intra-SC and ISC values, we used a custom-made MATLAB (MathWorks Inc., Natick, MA, USA) code.

2.8. Intra-SC and ISC whole-brain corrected analyses

For cross-sectional group level analyses, which include both regression analyses within groups and comparisons between groups, we used

the SnPM 13 toolbox for SPM (https://warwick.ac.uk/snpm) with non-parametric permutation-based testing and 4 mm FWHM variance smoothing. We masked images using a whole-brain mask in cross-sectional analyses. We calculated 10,000 permutations, and corrected voxel- and cluster-based analyses for family-wise error (FWE) for multiple comparison at $p < 0.05$. For cluster-based analyses the cluster-forming threshold was set at $p < 0.001$.

2.9. Intra-SC and ISC ROI analyses

To further study and visualize possible correlations between intra-SC and ISC measures with the severity of delusions, we extracted the raw intra-SC and ISC values from ROI obtained from whole-brain corrected SnPM analyses. To account for the effect of antipsychotic medication and hallucination severity, we calculated unstandardized residuals of intra-SC and ISC values using the logistic regression function of SPSS with BPRS-10 score and chlorpromazine equivalent doses at baseline as covariates. We used a Spearman's Rho test for correlation analyses within the FEP patient group and a Mann-Whitney-*U* test for group comparison between FEP patients and control subjects. In addition, we compared patients who presented with delusions during the baseline study vs those who did not, as well as each of these two patient subgroups vs control subjects.

2.10. Functional connectivity analyses

To calculate the functional connectivity maps we used the RESTplus toolbox (Jia et al., 2019), using the ROIs obtained in the SnPM intra-SC analyses as seeds. We calculated within-group changes over time, and differences between the groups at both time-points to further assess the delusion-related networks. For whole-brain corrected cross-sectional group level functional connectivity analyses, we used the same parameters in SnPM as for the whole-brain corrected intra-SC and ISC analyses. For longitudinal analyses, which include images from both baseline and follow-up, statistical analyses were conducted with the MRM toolbox (McFarquhar et al., 2016). We assess longitudinal changes using both whole-brain and ROI corrected analyses, with ROIs obtained from the whole-brain corrected cross-sectional functional connectivity analyses.

2.11. Realism regressor correlation analyses

The movie shown during scanning contained scenes of varying degrees of realism, as assessed by an independent reference group who did not otherwise participate in the study. We correlated realism time course with the time course of 1) magnitude of the correlation between intra-SC and baseline delusion severity and 2) difference in intra-SC strength for i) patients vs control subjects, ii) patients with delusions vs patients without delusions, iii) patients with delusions vs control subjects. Instead of correlating the whole time series of 245 TRs for the intra-SC analysis, we correlated the time course within 236 sliding time windows, each consisting of 10 subsequent TRs. We used Pearson's correlation and a two samples T-test to form the time courses 1 and 2, respectively. The Pearson correlation values and *T*-values were Fisher z-transformed and correlated with the realism time series using Pearson's correlation. We accounted here for autocorrelation using the method developed by Pyper and Peterman (Pyper & Peterman, 1998) using the following equation:

$$\frac{1}{df} \approx \frac{1}{N} + \frac{2}{N}\sum_{j}\frac{N-j}{N}\rho_{XX}(j)\rho_{YY}(j)$$

The equation is an approximation of a Monte Carlo simulation used to estimate the effective degrees of freedom (df). Rho_xx(j) and rho_yy(j) are the normalized autocorrelations of signals X and Y with N observations at lag j, respectively. We chose the maximal lag j to be N/5 as it has been shown to yield accurate results in terms of error rates (Pyper & Peterman, 1998). The MATLAB code of the equation is available at https://version.aalto.fi/gitlab/BML/bramila/blob/master/bramila_autocorr.m.

3. Results

3.1. Descriptives

Table 1 presents demographic and clinical data for FEP patients and control subjects. The groups did not differ regarding sex, age, or years of education. We observed a significant group difference in both delusion severity and hallucinations at baseline during the week before the imaging. In addition, the table displays the episode's peak symptom score for BPRS-10 and BPRS-11 items. In the FEP patient group, we did not observe significant correlations between delusion severity at baseline

Table 1
Demographic and clinical information.

	Control subjects [a] N = 27	FEP patients [a] N = 24	Group Difference [b]
Male	18 (66.67)	18 (75.00)	p = 0.514
Age	23.86 (20.76–40.24, 6.77)	24.66(18.40–35.87, 5.98)	p = 0.850
Years of education	15.50 (12.00–22.00, 4.00)	14.00 (10.00–22.00, 4.00)	p = 0.175
BPRS-11 baseline	1 (1–1, 0.00)	4 (1–7, 4.00)	**p < 0.001**
BPRS-11 peak symptoms baseline	1 (1–1, 0.00)	7 (1–7, 1.00)	**p < 0.001**
BPRS-11 follow-up	1 (1–1, 0.00)	1 (1–1, 0.00)	p = 1.000
BPRS-10 baseline	1 (1–1, 0.00)	1 (1–6, 3.75)	**p < 0.001**
BPRS-10 peak symptoms baseline	1 (1–1, 0.00)	6 (1–7, 5.75)	**p < 0.001**
BPRS-10 follow-up	1 (1–1, 0.00)	1 (1–3, 0.00)	p = 0.130
GAF baseline	85 (55–90, 15)	37 (25–65, 8)	**p < 0.001**
GAF follow-up	85 (40–90, 10)	64 (31–90, 23)	**p < 0.001**
CPZ baseline	0.00 (0.00–0.00, 0.00)	298.81 (0.00–900.00, 376.88)	**p < 0.001**
CPZ follow-up	0.00 (0.00–60.00, 0.00)	152.50 (0.00–642.86, 300.00)	**p < 0.001**
DSM-IV diagnosis	296.25/296.26/ 296.32/296.36 Major depressive disorder (n = 7)300.21 Panic disorder with agoraphobia (n = 1)300.23 Social phobia (n = 1)300.3 Obsessive-compulsive disorder (n = 1)307.1 Anorexia Nervosa (n = 1)311 Depressive disorder NOS (n = 1)	295.3 Paranoid schizophrenia (n = 3) 295.4 Schizophreniform disorder (n = 5)295.9 Schizophrenia undefined (n = 3)296.04/296.44 Bipolar type 1 disorder (n = 5)296.24/296.34 Major depressive affective disorder with psychotic features (n = 2)298.8 Brief psychotic disorder with psychotic features (n = 1)298.9 Unspecified psychosis (n = 5)	

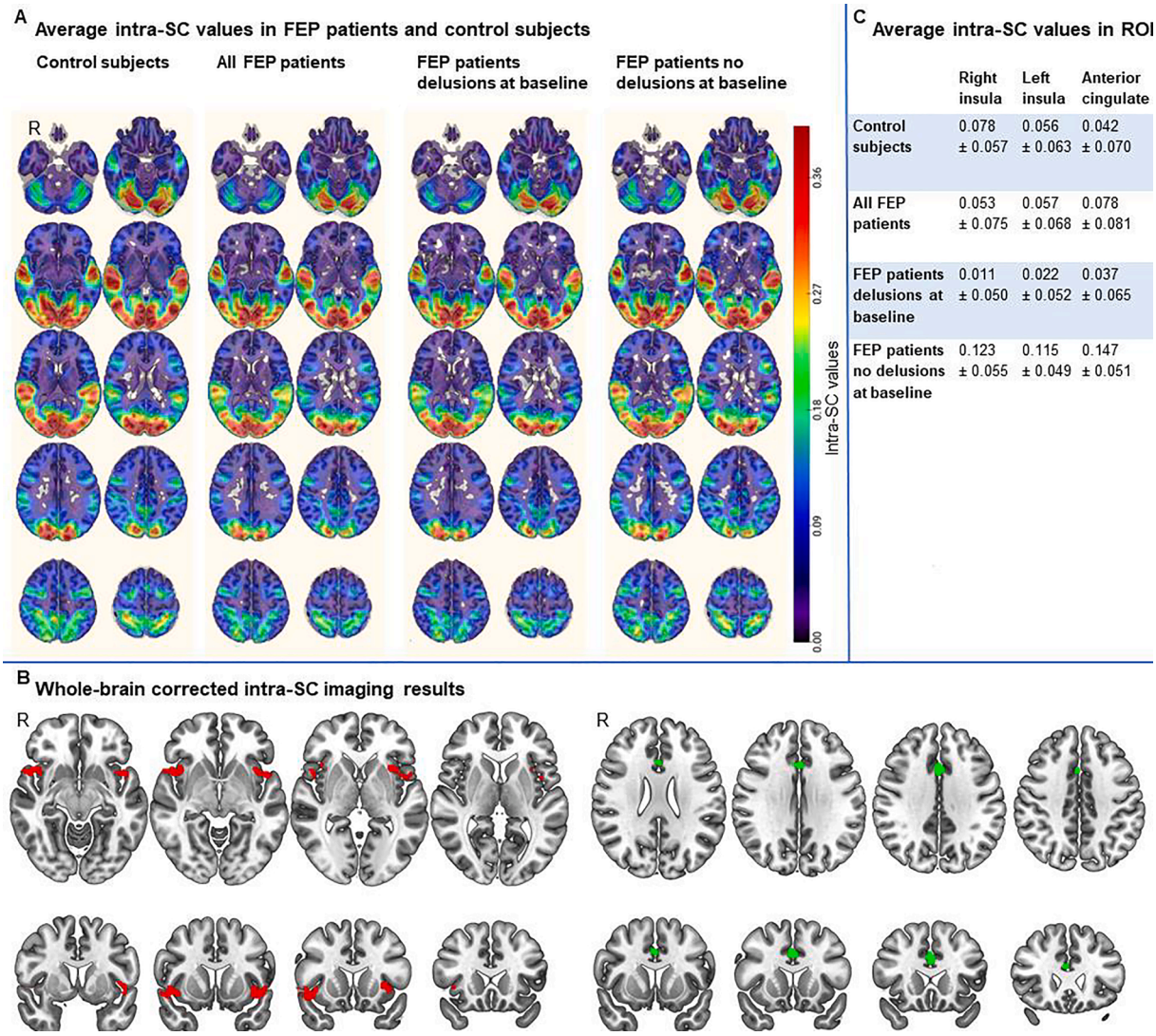
a) Frequency (%) or median (range, IQR).
b) Mann-Whitney *U* test or Pearson Chi-square test. Significant p-values shown in bold.
FEP = first-episode psychosis, BPRS-11 = "unusual thought content" item in the Brief Psychiatric Rating Scale, BPRS 10 = hallucinations item in the Brief Psychiatric Rating Scale, GAF = Global assessment of functioning, CPZ = Chlorpromazine equivalent dose.

and antipsychotic dosages at baseline (r = -0.201, p = 0.347) or at follow-up (r = -0.023, p = 0.915).

3.2. Imaging results

In the FEP patient group the baseline BPRS-11 score correlated negatively with the intra-SC in the bilateral insula (right insula, MNI coordinates (48, 14, −10), cluster size = 256 voxels, p = 0.046; left insula, MNI coordinates (–32, 14, 2), cluster size = 251 voxels, p = 0.046; all results FWE corrected in whole-brain volume) (Fig. 2). In addition, we observed a subthreshold cluster in the anterior cingulate region (MNI coordinates (0, 16, 36), cluster size = 194 voxels, p = 0.080) (Fig. 2). No significant clusters survived whole-brain correction when comparing the intra-SC images of FEP patients to those of control subjects, nor when comparing patients with delusions to either control subjects or patients without delusions. For ISC analyses, no significant clusters survived whole-brain correction.

We extracted intra-SC values as well as ISC values at baseline and follow-up from the ROIs (bilateral insula and anterior cingulate), and calculated unstandardized residuals, controlling for antipsychotic medication and BPRS-10 score at baseline (referred to as adjusted ISC and intra-SC; see Fig. 3 for statistics). For FEP patients, we observed a negative correlation between the adjusted intra-SC and baseline BPRS-11 score in all three ROIs. In addition, adjusted ISC at baseline negatively correlated with baseline BPRS-11 score in the bilateral insula. In analyses between groups, the adjusted intra-SC of FEP patients with delusions at baseline was significantly lower when compared to both control subjects and patients without delusions at baseline in both insulas, and significantly lower when compared to patients without delusions at baseline in the anterior cingulate. In patients with delusions



C Average intra-SC values in ROI

	Right insula	Left insula	Anterior cingulate
Control subjects	0.078 ± 0.057	0.056 ± 0.063	0.042 ± 0.070
All FEP patients	0.053 ± 0.075	0.057 ± 0.068	0.078 ± 0.081
FEP patients delusions at baseline	0.011 ± 0.050	0.022 ± 0.052	0.037 ± 0.065
FEP patients no delusions at baseline	0.123 ± 0.055	0.115 ± 0.049	0.147 ± 0.051

Fig. 2. Results from correlation analysis between intra-SC and baseline BPRS-11 score in FEP patients. A) Visualization of the average intra-SC values in control subjects and FEP patients. The FEP patient group was further split into two subgroups based on the presence of measurable delusion symptoms at baseline using the BPRS-11 item for unusual thought content. Of the 24 patients, 15 presented with measurable symptoms. The two rightmost images display the average intra-SC for these subgroups. B) Regions of significant correlation between baseline BPRS-11 score and intra-SC in FEP patients. FEP patients showed a significant negative correlation between the BPRS-11 score and intra-SC in the bilateral insula (visualized in red on the left). In addition, we observed a subthreshold cluster in the anterior cingulate (visualized in green on the right). Due to this region constituting the third central region in the SN in addition to the bilateral insula, we elected to include it in the analysis. Results are at uncorrected threshold $p < 0.001$. C) Intra-SC values (mean and standard deviation) in ROI obtained from the correlation analysis between intra-SC and BPRS-11 score in FEP patients. Intra-SC = intrasubject correlation obtained by correlating the baseline and follow-up fMRI signals within each subject while viewing the same stimulus, FEP = first-episode psychosis, SN = cortical salience network, BPRS-11 = Brief Psychiatric Rating Scale score for unusual thought content, ROI = region of interest, R = right side. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

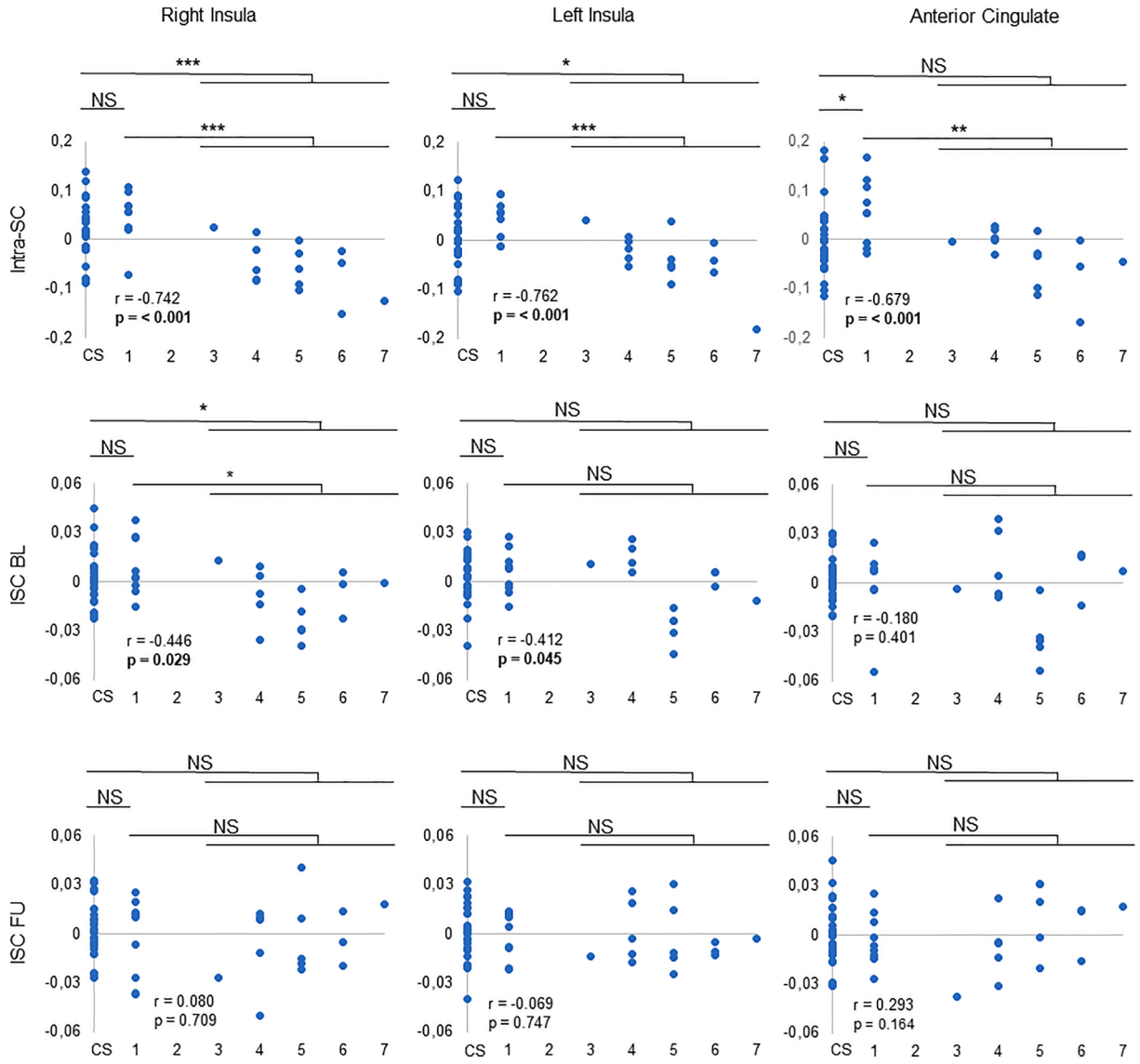


Fig. 3. Intra-SC and ISC values of the core regions of the cortical salience network, adjusted for hallucinations and antipsychotic medication. Values are plotted against the BPRS-11 score at baseline. Correlations in plots were calculated using the Spearman's rho test at $p < 0.05$ and group differences using the Mann-Whitney *U* test at $p < 0.05$. Correlation analyses were calculated across the FEP patient group and did not include the control subjects. We calculated differences between control subjects and subgroups of patients with and without delusions at the baseline. Intra-SC = intrasubject correlation, ISC = intersubject correlation, BL = baseline, FU = follow-up, FEP = first-episode psychosis, CS = control subject, BPRS-11 = Brief Psychiatric Rating Scale score for unusual thought content, ROI = region of interest. * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$, NS = not significant at $p < 0.05$. Baseline BPRS-11 score on X-axis.

present at baseline, the adjusted ISC values were significantly lower when compared to both patients without delusions at baseline and control subjects in the right insula. At follow-up, when no patients presented with delusions, adjusted ISC did not significantly differ between any of the groups. Only regarding adjusted intra-SC in the anterior cingulate did the FEP patients without delusions differ significantly from control subjects.

Using the bilateral insula as a seed, we further calculated functional connectivity maps for both the FEP patient group and the control group at baseline and follow-up. Compared to control subjects at baseline, FEP patients had weaker positive connectivity between the bilateral insula and a cluster centered around the right precuneus (MNI coordinates (20, −54, 30), cluster size = 772 voxels, $p = 0.009$, whole-brain FWE-corrected) (Fig. 4A). In longitudinal analysis, the change from baseline to follow-up was greater in the FEP group than in the control group ($p < 0.001$, corrected in the precuneus cluster above, Fig. 4A). To further disentangle the results, we extracted the functional connectivity values in the precuneus at baseline and at follow-up in both groups (Fig. 4B). Functional connectivity between the bilateral insula and precuneus was significantly weaker in the FEP patients than in control subjects at baseline (Mann-Whitney-*U* test $Z = 4.33$, $p < 0.001$). The connectivity was also weaker at baseline than at follow-up in the FEP patients (Wilcoxon signed-rank test $Z = 3.06$, $p = 0.002$). We did not observe statistically significant differences between FEP patients and control subjects at follow-up. We did not observe correlations between the BPRS-11 score at baseline and functional connectivity at baseline, at follow-up, or the magnitude of change in functional connectivity between baseline and follow-up.

To assess whether variation of realism during the movie contributed to our findings, we studied intra-SC in smaller sliding segments containing 10 TRs in the three regions (bilateral insula and anterior cingulate) highlighted in the whole-brain corrected correlation analysis between baseline BPRS-11 score and intra-SC in FEP patients. In the anterior cingulate, the time series of realism correlated with the time series of correlation strengths between intra-SC and baseline BPRS-11 score, as well as with time series of group difference of the patients

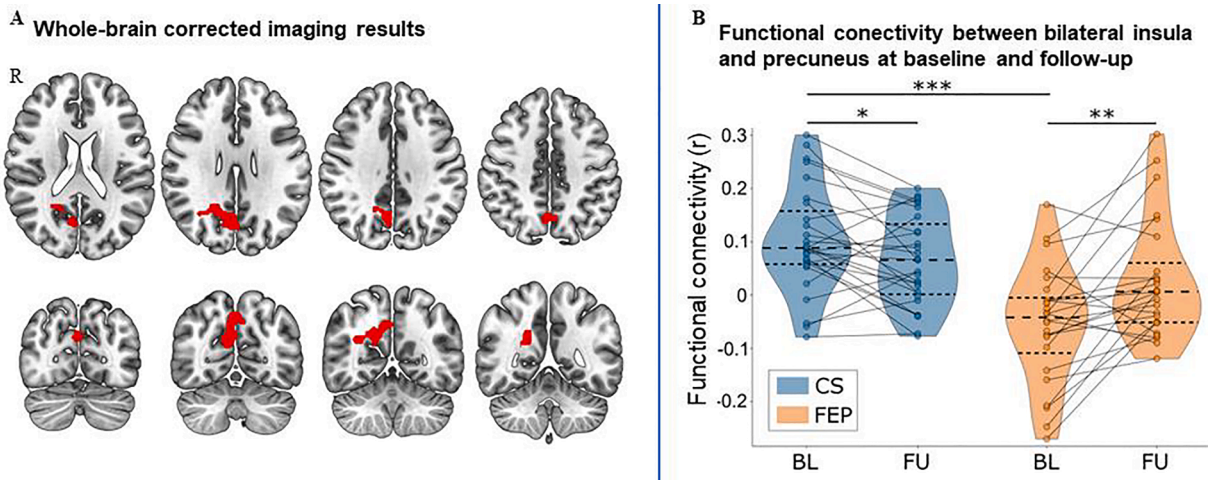


Fig. 4. Results from functional connectivity analyses. A) Functional connectivity between the bilateral insula and a cluster in the right precuneus (visualized in red) was significantly lower in FEP patients when compared to control subjects at baseline. Results are visualized at uncorrected threshold $p < 0.001$. B) In the cluster visualized in panel A, positive functional connectivity was significantly lower in FEP patients when compared to control subjects at baseline as well as when compared to FEP patients at follow-up. FEP = first-episode psychosis, CS = control subjects, BL = baseline, FU = follow-up, BPRS-11 = Brief Psychiatric Rating Scale score for unusual thought content. R = right side. * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

with delusions at baseline to both control subjects and patients without delusions at baseline ($r = 0.24$, $p = 0.018$, $r = 0.30$, $p = 0.015$, and $r = 0.39$, $p < 0.001$, respectively, uncorrected) (Fig. 5). We did not observe significant correlations in the anterior cingulate when comparing all patients to control subjects, nor for any analyses in either insula.

4. Discussion

This study investigated state-like brain correlates of delusions by assessing the deviation from a symptom-free state within individuals. FEP patients with more severe delusions at baseline showed more decreased intra-SC in the SN, suggesting a change in movie processing among them. In addition, patients with delusions showed lower intra-SC and ISC values at baseline in central regions of the SN when compared to patients without delusions and control subjects. Furthermore, using a functional connectivity analysis, we observed abnormal connectivity at baseline between the bilateral insula and the precuneus, central hubs of the SN and the DMN, respectively.

Studying differences between symptomatic and symptom-free states within individuals could provide a more sensitive method and account for idiosyncratic patterns when compared to the more traditionally used ISC analyses. To our knowledge, intra-SC analyses have not previously been used to study state-like changes in brain activity in association with positive symptoms, and in accordance with earlier research, our results support the notion that SN dysfunction could contribute to the formation of delusions. Dysregulation of the CEN and DMN caused by aberrant functioning of the SN has previously been observed in patients with schizophrenia (Palaniyappan et al., 2013), and suggested to be one of the possible causes for reality distortion (Bolton et al., 2020). Decreased connectivity between the SN and DMN has been documented in FEP patients (O'Neill et al., 2019) and patients with schizophrenia (Dong et al., 2018). In an evidence integration task, Lavigne et al. found

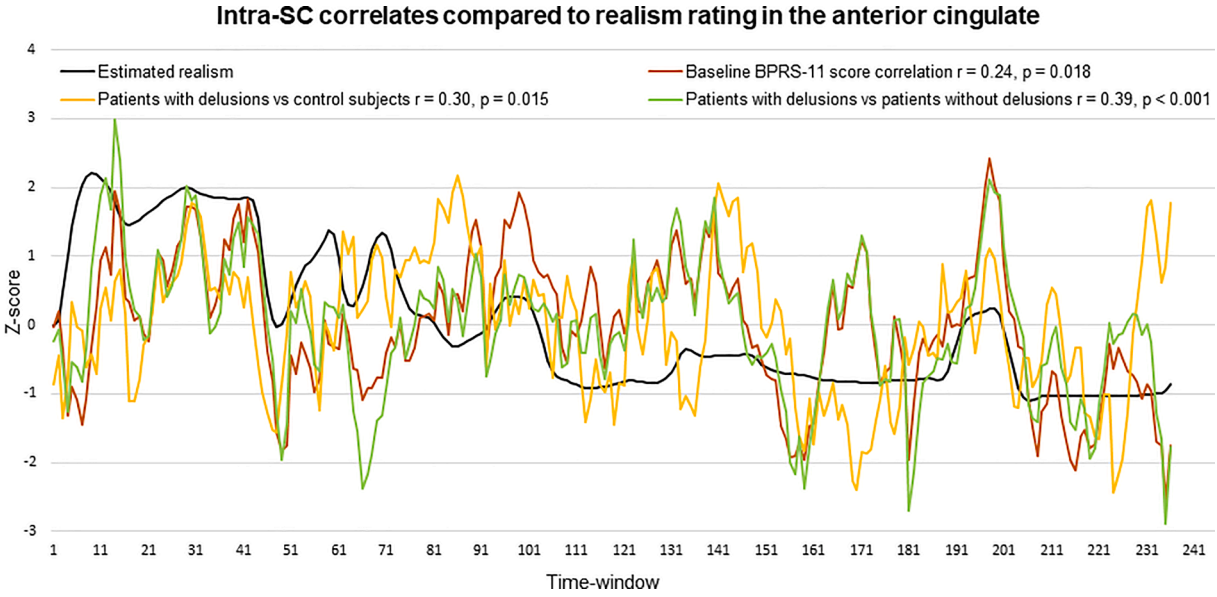


Fig. 5. Time series of symptom correlation and group difference of intra-SC plotted against the time series of realism estimates of the movie. The plot for the realism is convoluted using a hemodynamic response function. Plots are standardized to Z-scores, and r and p refer to correlation between the two time-series.

increased activity in the SN and decreased deactivation of the DMN in schizophrenia patients with present delusions when compared to non-delusional subjects (Lavigne et al., 2020). Our result shed further light on the state-like and delusion-related behavior of said decoupling as insula-DMN connectivity was lower in FEP patients when compared to control subjects only when delusions were present in the patient group.

In our study, as measured by both intra-SC and ISC analyses, FEP patients with delusions at baseline showed aberrant behavior of the SN and DMN BOLD signal in response to naturalistic movie processing. The results were mostly driven by patients with delusions displaying lower values in all three regions of the SN, while patients without delusions showed non-significantly different intra-SC and ISC values when compared to control subjects. At follow-up, when no patients presented with delusions, no differences between any of the groups were observed. Taken together, these results suggest that the processing of the stimulus was abnormal in the SN and DMN when delusions were present, but not when they had subsided.

Functional connectivity between the bilateral insula and precuneus was decreased in the patient group at baseline but normalized at follow-up. Dissimilarly from the intra-SC and ISC results, this change in functional connectivity was not driven by delusion severity. This SN-DMN decoupling represented a state-like change, but not necessarily linked to delusions. In an overlapping sample, using the same movie stimulus, voxels in the precuneus were most significant when classifying FEP patients and control subjects at baseline using a machine learning classification algorithm (Rikandi et al., 2017). In addition, in this study, classification success was related to positive symptom severity.

As delusions are characterized by a breach of objective reality, we were interested in whether processing of unrealistic external stimuli would be impaired in patients with delusions, and the scenes shown to subjects in this experiment were specifically chosen to include both realistic and unrealistic content. In the anterior cingulate, the association between delusion severity and intra-SC seemed to be greatest during the most unrealistic scenes, and similarly the intra-SC group difference between patients with delusions vs comparison groups seemed to be driven by these scenes, implying that processing of unrealistic parts of the stimulus may play a role in the results observed. A detailed description of the movie scenes has been published in the supplementary material of (Rikandi et al., 2017). The first 40 TRs of the movie take place at a garden party, where mostly live-action content is shown. The major dip in realism rating at 40TR is most likely caused by the appearance of an animated pocket-watch carrying rabbit whom Alice starts to run after. At around TR 70, Alice falls through the rabbit-hole, after which all content is to some degree unrealistic in nature. Between TRs 85 and 128 Alice grows and shrinks in size, and around TR 130 she enters Wonderland, where she sees several odd plants and animals and meets multiple characters, many of whom show unrealistic physical features. The increase in realism rating at TR 188 occurs during the only scene in Wonderland where unrealistic content somewhat subdued. During this scene Alice walks through a dark forest, and a wound on her arm is shown. During the last scenes of the movie, the Chesire cat appears, first on a tree branch, then as a head floating next to Alice, and finally drifts away and turns to smoke. The time-windows with the strongest group differences and correlation with delusion severity occur during the scenes where Alice talks to the strange characters in Wonderland, and later meets the Chesire cat. The scenes were also deemed two of the three most unrealistic parts of the movie. The scene at TR 100–130, showing the size of Alice changing, was rated as low as the previous two on the realism but did not cause as significant changes in the time-window intra-SC time series. For some reason, Alice's relatively realistic walk through the forest at TR 185–205 was accompanied by a positive correlation between intra-SC and BPRS-11 score.

In general, results from the time series correlation analysis could reflect the liberal acceptance bias, observed in subjects with delusions, increasing the probability assigned to improbable outcomes (Moritz et al., 2017; Moritz et al., 2009). Besides testing this hypothesis, further studies could assess whether and how the SN functioning relates in subjects with delusions to aberrant attribution of salience and related dysfunction in dopamine regulation, which has been suggested to cause irrelevant stimuli to receive excessive salience, leading to the formation of aberrant associations through cognitive bias, and delusions (Broyd et al., 2017; Howes & Kapur, 2009).

5. Strengths and limitations of this study

A strength of the present study is the thoroughly examined cohort, including the baseline and follow-up measurements. The methods of fMRI analyses were novel and provided well-controlled results that add to the previous literature about brain correlates of delusions.

Limitations include the final sample size in the present analyses being relatively small due to the strict criteria for inclusion in the study. While the main finding of correlation between delusion severity and intra-SC in the bilateral insula was strictly corrected for multiple comparisons, further analyses were less strictly corrected and include some circularity. These should be interpreted as preliminary and exploratory.

We used an analysis pipeline constructed before the latest recommendations on fMRI pre-processing. Thus movement, white matter, and CSF signal time series, as well as filtering were introduced stepwise, which may reintroduce some of the noise in the data (Lindquist et al., 2019). We did not observe significant correlations between the average fMRI BOLD signal and movement regressors in any of the four ROIs analyzed (Baseline: right insula R^2 0.00045 ± 0.00053; left insula R^2 0.00053 ± 0,00071; anterior cingulate R^2 0.00067 ± 0.0014; precuneus R^2 0.00035 ± 0.00049. Follow-up: right insula R^2 0.0030 ± 0.0030; left insula R^2 0.0028 ± 0,0038; anterior cingulate R^2 0.0025 ± 0.0023; precuneus R^2 0.0021 ± 0.0014 (mean R^2 across all subjects and standard deviation)). While small correlation between movement and pre-processed fMRI time series suggests such noise to have limited contribution here, it is necessary to orthogonalize regressors in further pipelines and studies.

Our primary interest in this study was correlates of delusions. We were specifically interested in this dimension of reality distortion and have attempted to control for confounders. We did not restrict inclusion based on hallucinations, and two FEP patients presented with mild hallucinations during the follow-up study. We corrected for the possible interference by hallucinations at baseline by controlling for this symptom dimension by including it as a covariate. Despite this, it should be considered that the correlates observed could represent effects of more general reality distortion instead of correlates of delusions specifically.

It should be noted that subjects in this study were selected from a larger cohort, based on not presenting with delusions during the follow-up study, and the subsample studied here could possibly represent patients who inherently present with more treatment-susceptible delusions. In the full Helsinki Early Psychosis Study cohort, remission rates were not this high, and thus more in line with previous research (Lally et al., 2017). Of 61 FEP patients who participated in BPRS-E during the follow-up study, 39 % presented with measurable delusions and 11 % with measurable hallucinations at follow-up. These remission results are higher than expected based on older studies, but more in line with more recent studies (Lally et al., 2017).

Due to ethical reasons, most FEP patients used antipsychotic medications during both the baseline and follow-up. However, we did not observe significant correlations between delusion severity and antipsychotic medication doses at either baseline or follow-up, and we included antipsychotic medication as a covariate.

While the two unrealistic scenes of the movie stimulus were primarily responsible for the changes observed, we cannot certainly attribute the reason for this to the unrealistic nature of these scenes. For example, these scenes include a high amount of computer-generated imagery content, which could affect neural responses. Further analyses of the stimulus itself could provide better insight into why these

scenes evoked the strongest alterations.

6. Conclusions

Our results support the role of the SN as a central component of delusion and build further on this hypothesis by suggesting state-like dysfunction in psychotic disorders, linked to delusion severity. Moreover, our results suggest that the dysconnectivity between large-scale cortical networks follows a similar state-like behavior. Whether and how this may contribute to delusion-related dysfunction of the *meso*-striatal pathways will be a central question in further studies.

CRediT authorship contribution statement

Jonatan M. Panula: Methodology, Software, Formal analysis, Visualization, Writing – original draft. **Jussi Alho:** Methodology, Software, Formal analysis, Writing – original draft. **Maija Lindgren:** Conceptualization, Investigation, Writing – review & editing. **Tuula Kieseppä:** Conceptualization, Investigation, Writing – review & editing. **Jaana Suvisaari:** Conceptualization, Investigation, Writing – review & editing. **Tuukka T. Raij:** Conceptualization, Investigation, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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