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Hippocampus-Centered Network Is Associated With Positive Symptom Alleviation in Patients With First-Episode Psychosis

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ABSTRACT

BACKGROUND: Previous functional magnetic resonance imaging studies have reported widespread brain functional connectivity alterations in patients with psychosis. These studies have mostly used either resting-state or simple-task paradigms, thereby compromising experimental control or ecological validity, respectively. Additionally, in a conventional functional magnetic resonance imaging intrasubject functional connectivity analysis, it is difficult to identify which connections relate to extrinsic (stimulus-induced) and which connections relate to intrinsic (non–stimulus-related) neural processes.

METHODS: To mitigate these limitations, we used intersubject functional connectivity (ISFC) to analyze longitudinal functional magnetic resonance imaging data collected while 36 individuals with first-episode psychosis (FEP) and 29 age- and sex-matched population control participants watched scenes from the fantasy movie *Alice in Wonderland* at baseline and again at 1-year follow-up. Furthermore, to allow unconfounded comparison and to overcome possible circularity of ISFC, we introduced a novel approach wherein ISFC in both the FEP and population control groups was calculated with respect to an independent group of participants (not included in the analyses).

RESULTS: Using this independent-reference ISFC approach, we found an interaction effect wherein the independent-reference ISFC in individuals with FEP, but not in the control group participants, was significantly stronger at baseline than at follow-up in a network centered in the hippocampus and involving thalamic, striatal, and cortical regions, such as the orbitofrontal cortex. Alleviation of positive symptoms, particularly delusions, from baseline to follow-up was correlated with decreased network connectivity in patients with FEP.

CONCLUSIONS: These findings link deviation of naturalistic information processing in the hippocampus-centered network to positive symptoms.

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Psychosis refers to a mental state of distorted sense of reality characterized by delusions and hallucinations. Despite many known behavioral aberrations associated with psychosis, the neural mechanisms underlying psychotic disorders are poorly understood. According to the disconnection hypothesis, psychotic disorders result from aberrant connectivity at different hierarchical levels from synapses to brain regions (1). For example, analysis of resting-state functional magnetic resonance imaging (fMRI) functional connectivity (FC) in 415 patients with schizophrenia identified concurrently increased thalamosensorimotor connectivity and decreased thalamofrontal connectivity (2). Corroborating these findings, a recent meta-analysis of 17 fMRI studies on FC networks in patients with psychosis or individuals at high risk for developing psychosis reported hypoconnectivity in the middle frontal, cingulate, and thalamic regions and hyperconnectivity in the motor, somatosensory, temporal, occipital, and insular cortices (3). Together, these studies point toward thalamocortical disconnectivity in the pathophysiology of psychotic disorders. However, associations between the FC networks and symptoms or other behavioral measures have been inconsistent, thus impeding the interpretation of the FC alterations.

Most studies on brain network alterations in psychosis have been cross-sectional investigations of seed-based FC of resting-state networks, which provide only a limited view of brain network connectivity in psychotic disorders. Compared with cross-sectional studies, longitudinal studies, in which participants are followed over time with repeated observations of the same variables, provide better control for associating FC alterations with changes in symptoms or behavior. Moreover, in resting-state paradigms, functional data are collected without any specific task, thereby impeding interpretation of the results due to lack of experimental control because the ongoing thoughts and feelings are likely to differ between participants. Resting-state fMRI FC is also highly susceptible to spurious connectivity caused by head movements (4) and non-neuronal physiological signals from heart rate and respiration (5,6).

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By contrast, FC studies using simplistic task paradigms, such as auditory oddball or delayed matching to sample tasks, achieve high experimental control at the expense of ecological validity, capturing only a narrow field of information processing. Another challenge in fMRI FC studies using simple stimulus paradigms and resting state is the relationship of connections to extrinsic (stimulus-induced) versus intrinsic (non–stimulus-related) neural processes. Intersubject FC (ISFC) has been introduced to overcome these challenges (7). ISFC is a combination of conventional FC and intersubject correlation (8) because it measures FC between a brain region of one subject and other regions in other subjects. Such correlated activity is more unlikely to be related to intrinsic neural processes or non-neuronal artifacts than conventional within-subject FC measures.

ISFC can be used to quantify aberrant FC in patients by comparing functional brain signal time courses of patients with those of control participants. To allow unconfounded comparison, it is important that ISFC in both the patient and control groups is computed with respect to a common reference group as opposed to computing within-group ISFC for both groups. Using the same control group as a reference group first to quantify the deviance and then to compare the results of the patient group with would suffer from circularity. To overcome such circularity, we introduced an approach in which ISFC in both patient and control groups is calculated with respect to an independent group of participants (not included in analyses).

Using this independent-reference ISFC (irISFC) approach on longitudinal fMRI data collected during movie watching, we conducted whole-brain, data-driven analysis of brain network abnormalities in patients with first-episode psychosis (FEP). Movie stimuli effectively tap into naturalistic information processing and, as naturally engaging stimuli, can improve fMRI data quality, especially in clinical populations that have difficulties limiting head motion during scanning (9). Numerous fMRI studies have used movie stimuli in both healthy (8,10,11) and patient (12–14) populations. In addition, movie stimuli together with ISFC analysis has previously been used to study fMRI FC in neurodevelopmental disorders (15,16).

We analyzed data from 36 FEP and 29 population control group participants (PCs), who watched the same movie stimulus during fMRI at baseline and at 1-year follow-up. The irISFC in both the FEP and PC groups was calculated with respect to an independent group of 15 PC participants. We chose a movie with both realistic and fantasy scenes to better capture the aspects related to evaluating what is real and what is not. Our aim was to identify aberrant functional brain networks in the FEP group during naturalistic information processing and to investigate whether longitudinal changes in irISFC within these networks are associated with longitudinal changes in symptoms or behavior.

METHODS AND MATERIALS

Additional details on the materials and methods used in this study are provided in the Supplement.

Participants and Movie Stimulus

The main analysis sample comprised 36 patients with FEP and 29 participants in the PC group (Tables 1 and 2; Supplemental Methods and Materials). All participants were shown 5 continuous audiovisual clips from the movie *Alice in Wonderland* (17) totaling 7 minutes 20 seconds. For a detailed description of the movie stimulus, see Rikandi *et al.* (13). The 5 clips were presented without breaks and projected onto a semitransparent screen centered in the participant's visual field. Stimulus timing was controlled by Presentation Software (Neurobehavioral Systems Inc.). Sound was conveyed through plastic tubes attached to porous EAR-tip (Etymotic Research Inc.) earplugs. To insulate against MRI scanner noise, foam pads were placed inside and outside the head coil. The volume of the audio track was adapted according to the participant's subjective preference, ensuring that it was clearly audible over scanner noise.

Imaging and Preprocessing

The fMRI data were acquired with a 3T Magnetom Skyra (Siemens AG) with a 32-channel head coil at the Advanced Magnetic Imaging Centre, Aalto NeuroImaging, Aalto University

Table 1. Information on the PC and FEP Participants Included in the Main Analysis

	Time Point	PC, n = 29	FEP, n = 36	p Value
Sex, Female	–	9	13	
Age, Years	BL	26.7 (6.1)	24.9 (4.8)	.18
	FU	28.1 (6.3)	26.0 (4.8)	.12
Global Assessment of Functioning	BL	80.3 (10.5)	38.5 (9.3)	<.001
	FU	80.9 (11.6)	56.0 (15.7)	<.001
Hallucinations, BPRS 10	BL	1.00 (0)	2.53 (2.0)	<.001
	FU	1.03 (0.2)	1.11 (0.4)	.34
Delusions, BPRS 11	BL	1.03 (0.2)	3.56 (2.1)	<.001
	FU	1.03 (0.2)	1.89 (1.6)	.005
Disorganization, BPRS 12+15	BL	2.00 (0)	3.00 (1.6)	.001
	FU	2.03 (0.2)	2.33 (1.0)	.1
Positive Symptoms Sum, BPRS 10+11+12+15	BL	0.03 (0.2)	5.08 (3.7)	<.001
	FU	0.10 (0.3)	1.33 (2.2)	.003
Negative Symptoms Sum, BPRS 16, SANS 1+2+3	BL	0.34 (1.0)	4.42 (3.1)	<.001
	FU	0.48 (1.0)	3.75 (3.8)	<.001
Antipsychotic Medication Dose, Chlorpromazine, mg	BL	0 (0)	307.8 (256.1)	<.001
	FU	2.07 (11.1)	250.3 (245.5)	<.001
CPT-IP: dPrime	BL	2.90 (0.6)	2.59 (0.7)	.09
	FU	2.81 (0.6)	2.71 (0.7)	.08
Framewise Displacement, mm	BL	0.08 (0.02)	0.09 (0.04)	.06
	FU	0.09 (0.02)	0.08 (0.03)	.14
Identification	BL	23.8 (28.7)	37.7 (29.7)	.06
	FU	20.4 (24.9)	19.5 (21.9)	.88
Realism	BL	8.72 (23.7)	8.08 (17.0)	.9
	FU	5.69 (14.5)	12.2 (23.5)	.2

Values are n or group mean (SD), and p values are from two-sample t tests (two-tailed). Positive and negative symptoms sum scores were rescaled to 0–6.

BL, baseline; BPRS, Brief Psychiatric Rating Scale; CPT-IP, Continuous Performance Test Identical Pairs Version; FEP, first-episode psychosis; FU, 1-year follow-up; PC, population control; SANS, Scale for the Assessment of Negative Symptoms.

Table 2. Main Diagnoses in the PC and FEP Participants Included in the Main Analysis, According to DSM-IV

Diagnosis	PC, n = 29	FEP, n = 36
Major Depressive Disorder	10[a] (34.5%)	–
Anorexia Nervosa	1 (3.4%)	–
Obsessive-Compulsive Disorder	1 (3.4%)	–
Social Anxiety Disorder	1 (3.4%)	–
Panic Disorder With Agoraphobia	1 (3.4%)	–
Schizophrenia	–	12 (33.3%)
Schizophreniform Disorder	–	5 (13.9%)
Schizoaffective Disorder	–	1 (2.8%)
Psychotic Depression	–	2 (5.6%)
Bipolar Disorder Type I	–	6 (16.7%)
Brief Psychotic Disorder	–	2 (5.6%)
Psychosis Not Otherwise Specified	–	8 (22.2%)

Values are presented as n (%).
FEP, first-episode psychosis; PC, population control.
[a]Seven participants were in remission, and 1 was in partial remission.

School of Science. The fMRI data were preprocessed using FSL software (http://www.fmrib.ox.ac.uk) and in-house MATLAB (version 9.4 R2018a; The MathWorks, Inc.) code (BRAMILA pipeline v2.0, available at https://version.aalto.fi/gitlab/BML/bramila/). For details, see Supplemental Methods and Materials.

Independent-Reference Intersubject Functional Connectivity

The irISFC was calculated as intersubject, interregional temporal correlations (using Pearson's correlation) across all pairs of brain regions of Brainnetome (18) and cerebellar connectivity (19) atlases, with 274 brain regions (Figure 1). Two regions of the Brainnetome atlas fell outside the Montreal Neurological Institute brain mask, resulting in 272 regions being included in analyses.

The irISFC in both the FEP and PC groups was calculated with respect to 15 PC participants who did not participate in the follow-up (but who met other inclusion criteria; 9 females; ages 20–43 years, mean 25.9 ± 5.8 SD). None of the 15 PC reference group participants had positive symptoms. Four had a nonpsychotic diagnosis: 2 depressive disorder not otherwise specified (1 current and 1 in remission), 1 major depressive disorder (in remission), and 1 alcohol abuse.

The region-specific time courses were extracted by taking the first principal component across voxels within the region. The resulting correlation matrices were symmetrized (i.e., because correlation between region A of participant 1 and region B of participant 2 does not equal to correlation between region B of participant 1 and region A of participant 2) by averaging over the reciprocal interregional connections and finally averaging over the 15-PC reference group to obtain a single connectivity matrix per participant. Prior to averaging, the correlation matrices were Gaussianized using Fisher's z transformation and finally reverted to the correlation scale using inverse Fisher's z transformation.

In addition to the main irISFC analysis calculated over the whole stimulus length, we calculated time-windowed irISFC with a 10-repetition time sliding window, resulting in 235 correlation matrices per participant. These correlation matrices were processed identically to those in the main irISFC analysis.

Statistical Analyses

Differences in irISFC were statistically tested using the Network-Based Statistic toolbox (https://www.nitrc.org/projects/nbs/) (20). As the main analysis, we conducted a two-way mixed analysis of variance with time point as the within-subjects factor and group as the between-subjects factor. Time-varying framewise displacement and antipsychotic medication dose (AMD) were included as nuisance

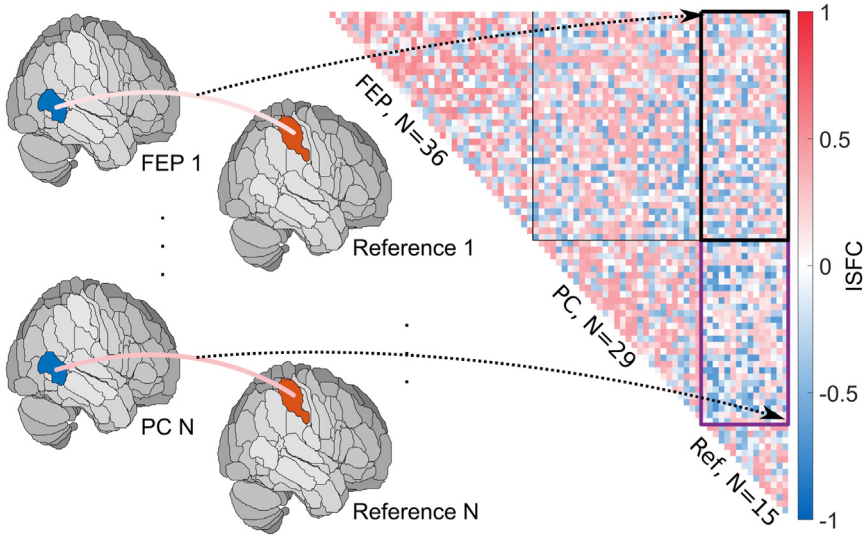

Figure 1. Schematic illustration of the independent-reference intersubject functional connectivity (ISFC) method. The figure shows the calculation of independent-reference ISFC between 2 exemplar brain regions (highlighted in blue and red on the left). In both the first-episode psychosis (FEP) and population control (PC) groups, intersubject interregional temporal correlations of the functional magnetic resonance imaging signals were calculated across all pairs of brain regions with respect to the reference group of 15 independent PC participants. The resulting correlation matrices (on the right) were averaged over the 15-PC reference group to obtain a single connectivity value per participant per brain region pair. Repeating the illustrated calculation for all pairs of brain regions results in a region-to-region (272 × 272) connectivity matrix for each FEP and PC participant.

covariates in all tests. For details on the network-based statistic procedure, see Supplemental Methods and Materials.

For post hoc tests for the significant analysis of variance group × time point interaction, we used the Wilcoxon rank-sum test (two-tailed) for comparisons between groups at a time point and Wilcoxon signed-rank test (two-tailed) for comparisons between time points within a group. The *z* values, *p* values, and Wilcoxon effect sizes (*r*) are reported from these tests.

We tested the association of irISFC with symptom/behavioral scores using Pearson's correlation. Participant-wise irISFC values were derived by averaging across the (Fisher's *z*-transformed) connections of the identified networks. Correlation tests between irISFC and symptom/offline rating scores were adjusted for framewise displacement and AMD by regressing them out of both irISFC measures and symptom/behavioral scores (before partitioning the data into groups) using linear regression.

In addition, we conducted correlation analyses to study the relationship between brain functioning and dynamic characteristics of the movie-related experience. Here, we used time-windowed irISFC and online ratings of the movie stimulus. The group-specific irISFC values were averaged across the connections of the identified network before the correlation was calculated. The ratings were convolved with canonical double-gamma hemodynamic response function. Five time points were cut from the beginning and end of the rating to match the midpoints of the 235 10-repetition time time windows (i.e., first time window covers time points 1–10, with midpoint at 5.5). Correlations were calculated between time-windowed irISFC and symptom/behavioral scores, resulting in time series of correlation coefficients. These correlation coefficient time series were then correlated with the online ratings of the movie stimulus to study the relationship between symptom-related brain functioning and the dynamic movie-related experience. Autocorrelation of time series was accounted for when calculating correlation *p* value by estimating effective degrees of freedom (21). For information on the offline and online ratings of the movie stimulus, see Supplemental Methods and Materials.

RESULTS

Group and Longitudinal Differences in irISFC

We found no statistically significant main effects for either the within-subjects or between-subjects factors in analysis of variance. However, a network showing significant interaction was found (referred to hereafter as interaction network; permutation $p = .027$, cluster-level statistic = 241.0, 52 regions, 65 connections) (Figure 2A).

We then tested for differences in irISFC between baseline and follow-up separately in the FEP and PC groups and between the FEP and PC groups separately at baseline and at

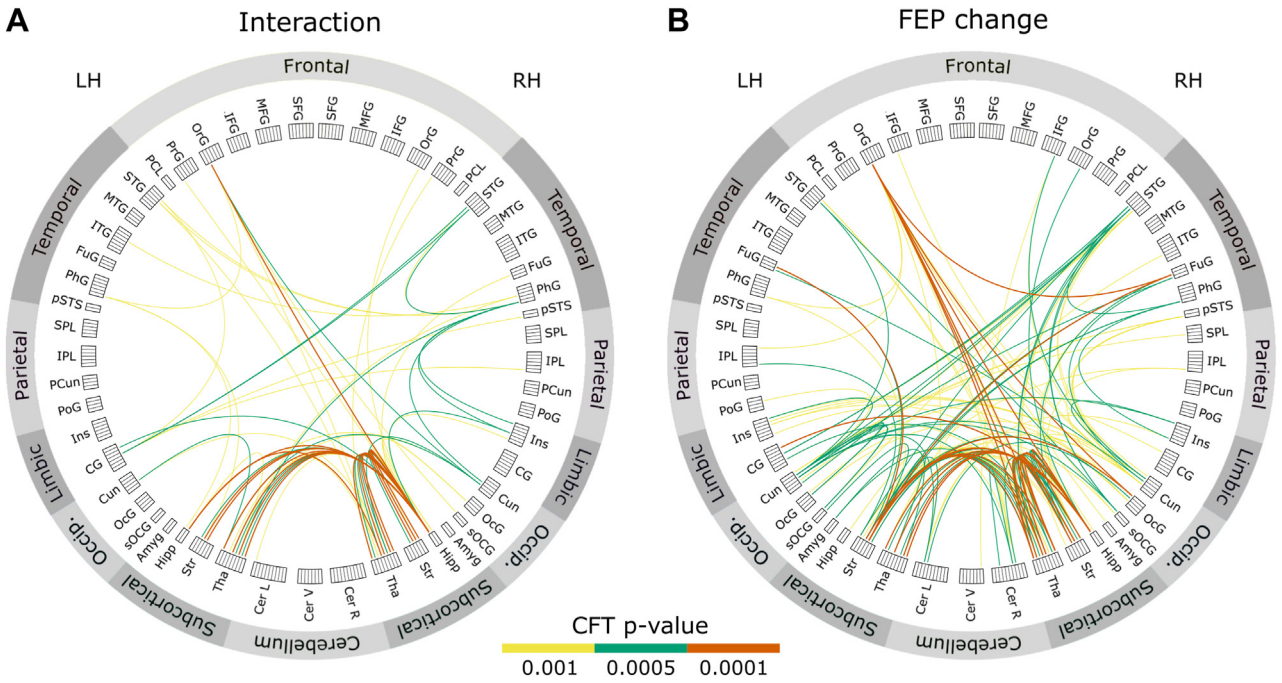

Figure 2. Differences in extrinsic brain networks between groups and time points. **(A)** Network showing statistically significant group (first-episode psychosis [FEP] vs. population control) × time of visit (baseline vs. follow-up) independent-reference intersubject functional connectivity interaction and **(B)** network showing significantly stronger independent-reference intersubject functional connectivity at baseline than at follow-up in the FEP group. The outer circle shows the lobes of the brain, and the inner circle shows the brain regions within the lobes. The color of the connection indicates the cluster-forming threshold (CFT). The connections are multiple comparisons corrected at $p < .05$ using network-based statistics (20). Regions are from the Brainnetome atlas. Amyg, amygdala; Cer, cerebellum; CG, cingulate gyrus; Cun, cuneus; FuG, fusiform gyrus; Hipp, hippocampus; IFG, inferior frontal gyrus; Ins, insula; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; L, left; LH, left hemisphere; MFG, middle frontal gyrus; MTG, middle temporal gyrus; occip, occipital; OcG, occipital gyrus; OrG, orbital gyrus; PCL, paracentral lobule; PCun, precuneus; PhG, parahippocampal gyrus; PoG, postcentral gyrus; PrG, precentral gyrus; pSTS, posterior superior temporal sulcus; R, right; RH, right hemisphere; SFG, superior frontal gyrus; sOCG, superior occipital gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus; Str, striatum; Tha, thalamus; V, vermis.

follow-up (for separate tests for each group and time point, see Figure S1). We found a network of stronger irISFC at baseline versus follow-up in the FEP group (referred to hereafter as the FEP change network; paired-samples t test: permutation p = .0008, cluster-level statistic = 77.2, 85 regions, 162 connections) (Figure 2B). The FEP change network shared 32 connections with the interaction network (Figure S2). Table 3 shows the most strongly interconnected regions for both the interaction network and FEP change network. No significant differences were found between baseline and follow-up in the PC group or between the FEP and PC groups at baseline or at follow-up. To identify the direction of the group and time point differences underlying the interaction effect, we conducted post hoc tests on the irISFC in the interaction network (Figure 3). Wilcoxon rank-sum tests revealed that compared with the PC group, the irISFC in the FEP group was stronger at baseline (z = 3.41, p = .0006, r = 0.42) and weaker at follow-up (z = 4.15, p = .00003, r = 0.51). Compared with baseline, irISFC at follow-up was increased in the PC group (z = 3.88, p = .0001, r = 0.51) and decreased in the FEP group (z = 4.37, p = .00001, r = 0.51). See Figure S3 for results with irISFC values adjusted for AMD and framewise displacement and Figure S4 for results with matched group sizes.

As a control, we calculated irISFC for 8 predefined networks from Yeo *et al.* (22), including visual, sensorimotor, and subcortical networks. Supporting the specificity of the observed networks, none of the predefined networks showed significant differences between conditions (Figure S5). Moreover, to control for the possibility that highly variable connections across the reference group might have resulted in inaccurate irISFC estimates, we calculated the correlation between connection-specific variance in the reference group and the statistics of the interaction network. The correlation was not significant (all connections: r = 0.01, p = .79; significant connections at corrected $p < .05$: $r = -0.13$, p = .31), implying that reference group variability was not significantly confounding the results. In addition, given the apparent influence of antipsychotic medication on brain function, we tested the correlation between longitudinal changes in AMD and irISFC in the interaction network in the FEP group and found no significant correlation ($r = -0.05$, p = .75), implying that the observed network was not medication related.

As a supplemental analysis, we tested which network connections best differentiated FEP participants from PC participants by using support vector machine classification based on irISFC connectivity matrices (see Supplemental Results and Figure S6). With significantly above chance–level accuracies, the classifier further highlighted the hippocampus as the hub region underlying the best classification.

Finally, to analyze local differences, we calculated local voxel-to-voxel irISFC and independent-reference intersubject correlation (irISC) for selected regions of interest (ROIs) of the observed networks and again found the most significant differences in the hippocampus (Supplemental Results, Figure S7).

Correlation of irISFC With Symptoms and Behavior

We conducted exploratory symptom/behavioral correlations in the two networks (Figure 2A, B). First, we tested whether longitudinal change in irISFC in the interaction network correlated with longitudinal change in symptom scores. Because the interaction network derived from data of both the FEP and

Table 3. The Most Strongly Modulated Connections in the Interaction Network and FEP Change Network

Network	Region	Nodal Degree	Sum of Statistics (F)
Interaction Network			
Cortical	R posterior parahippocampal gyrus, area TH	8	115.9
	L posterior cingulate gyrus	5	74.1
	L orbital gyrus	5	72.7
	L posterior parahippocampal gyrus, area TH	3	37.9
	R transverse temporal gyrus	2	34
	R superior temporal gyrus (TE1.0/TE1.2)	2	31.3
	R occipital polar cortex	2	30.4
	R posterior parahippocampal gyrus, area TL	2	28.8
	R ventral dysgranular and granular insula	2	28.7
	L superior temporal gyrus (TE1.0/TE1.2)	2	26.7
Subcortical	R caudal hippocampus	30	535.3
	L caudal hippocampus	4	61.5
	L medial prefrontal thalamus	3	57.3
	L occipital thalamus	3	48.8
	R posterior parietal thalamus	3	45
	L nucleus accumbens	3	43.9
	R sensory thalamus	3	40.1
	L rostral temporal thalamus	2	36.1
	R globus pallidus	2	33.2
	R rostral hippocampus	2	30.4
FEP Change Network			
Cortical	L orbital gyrus	13	53.8
	L rostral cuneus	8	32.5
	R superior temporal gyrus (TE1.0/TE1.2)	8	31.7
	R rostral cuneus	8	30.6
	L caudal cuneus	7	30.2
	R rostral lingual gyrus	8	29.8
	R medioventral fusiform gyrus	6	25.5
	R caudoposterior superior temporal sulcus	6	23.4
	R caudal superior temporal gyrus	5	18.3
	R middle occipital gyrus	4	17
Subcortical	R caudal hippocampus	26	116.3
	L ventromedial putamen	18	78.7
	L nucleus accumbens	12	48.1
	R posterior parietal thalamus	9	37
	R lateral prefrontal thalamus	8	35.2
	R medial prefrontal thalamus	8	33.3
	R ventral caudate	7	28.2
	R ventromedial putamen	7	28.1
	R nucleus accumbens	6	25.5
	R rostral temporal thalamus	6	25.4

The nodal degree (i.e., number of connections) and sum of statistics of the connections are shown. Cortical and subcortical regions are separated in subsections.
FEP, first-episode psychosis; L, left; R, right.

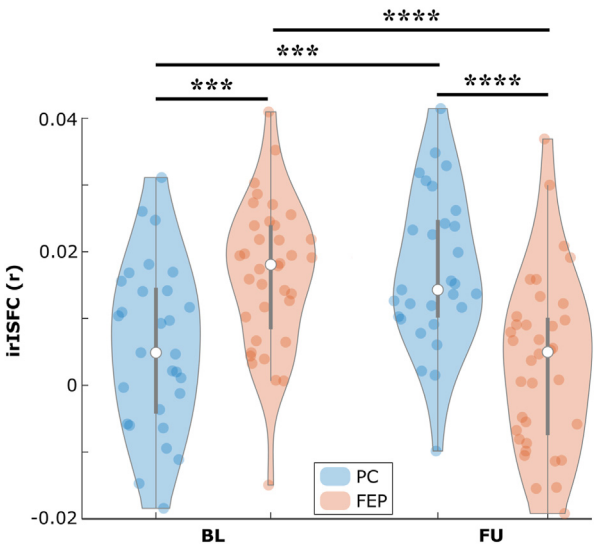

Figure 3. Mean independent-reference intersubject functional connectivity (irISFC) within the interaction network separately for the population control (PC) and first-episode psychosis (FEP) groups at baseline (BL) and follow-up (FU). The violin plots show the median (white dot), interquartile range (black vertical bar), the lower/upper adjacent values (thin black vertical lines extending from the bar) together with kernel density estimates and individual data points. Asterisks indicate statistically significant differences (***$p < .001$, ****$p < .0001$).

PC groups and because there were longitudinal changes in both positive and negative symptoms also in the PC group (Table 1), we calculated the correlation across both groups. Change in positive symptom sum scores correlated positively with change in irISFC in the interaction network (r = 0.38, p = .002) (Figure 4A). Post hoc correlation tests revealed that the strongest correlation among positive symptoms was for delusions (Brief Psychiatric Rating Scale 11; r = 0.34, p = .005) (Figure S8A), with a significant correlation also for hallucinations (Brief Psychiatric Rating Scale 10; r = 0.25, p = .047).

We also tested whether longitudinal change in irISFC in the FEP change network was related to longitudinal change in symptom scores within the FEP group. Again, change in positive symptom sum scores correlated positively with change in irISFC (r = 0.33, p = .048) (Figure 4B), with the strongest correlation for delusions (Brief Psychiatric Rating Scale 11; r = 0.35, p = .034) (Figure S8B). Positive correlation here signifies that the decrease in irISFC from baseline to follow-up was associated with alleviation of positive symptoms (particularly delusions) in the FEP group. Change in negative symptom sum scores did not correlate significantly with change in irISFC (r = 0.27, p = .11).

We then tested for correlations between irISFC and the offline ratings of the movie stimulus (realism and identification). Longitudinal change in irISFC in the interaction network correlated with longitudinal change in identification (i.e., how strongly the participants identified with the protagonist; r = 0.34, p = .005) (Figure 4C). Similarly, longitudinal change in irISFC in the FEP change network correlated positively with longitudinal change in identification within the FEP group (r = 0.43, p = .009) (Figure 4D). No significant correlations were observed for the realism rating.

In addition, we tested for correlations between the identification scores and irISFC in the interaction network separately at baseline and follow-up (Figure S9). We found a significant correlation in the FEP group at baseline (r = 0.35, p = .036) and a near-significant correlation in the PC group at follow-up (r = 0.34, p = .07). The difference in the correlation coefficients between baseline and follow-up (PC: $r_{\text{follow-up}-\text{baseline}} = 0.34 - 0.006 = 0.34$; FEP: $r_{\text{follow-up}-\text{baseline}} = 0.11 - 0.35 = -0.24$) showed a statistically significant difference between the groups (z = 2.24, p = .025). For correlations between the time-windowed irISFC (Figure S10) and online ratings of the movie stimulus, see the Supplemental Results and Figure S11.

DISCUSSION

We investigated aberrations in functional brain connectivity underlying psychosis during naturalistic information processing using a novel irISFC method. Our results revealed a significant interaction whereby irISFC in the FEP group was stronger at baseline than follow-up in a hippocampus-centered network involving thalamic, striatal, and cortical regions. The decrease in irISFC from baseline to follow-up in the FEP group correlated with alleviation of positive symptoms. The correlation between longitudinal change in irISFC and positive symptoms covaried with the rated salience of the movie stimulus so that strong positive correlation between irISFC and positive symptoms was associated with low salience of the movie stimulus (and vice versa).

Increased irISFC in Hippocampothalamocortical Network in FEP

The network showing abnormal irISFC in the FEP group included several sensorimotor regions, including the bilateral superior temporal gyrus, cuneus gyrus, and precentral gyrus. This agrees with earlier findings reporting thalamosensorimotor hyperconnectivity in psychotic disorders (2,3). However, the most prominent connections of the network were not the most task relevant (i.e., between primary auditory or visual areas) (see Figure 2 vs. Figure S1) but rather between subcortical and higher cortical regions. These included, for example, the orbitofrontal cortex, which has been linked with many functions (23) but has more recently been proposed to support, together with the hippocampus, so-called cognitive maps allowing flexible goal-directed behavior and decision making through outcome predictions based on prior knowledge (24). Aberrant integration of predictions with sensory information and the resulting prediction error signals that update the internal belief model have been proposed to explain psychotic symptoms (25–28). Prior fMRI studies using paradigms that enable assessing the impact of beliefs induced by prior experience on perception have shown that FC between orbitofrontal and visual cortices was associated with delusional ideation in healthy individuals (29) and enhanced in patients with schizophrenia compared with healthy control participants (30). Therefore, our finding of enhanced orbitofrontal connectivity at baseline in the FEP group could reflect an aberration in the brain's predictive mechanism whereby higher-level predictions modulate perception to conform with (delusional) beliefs (see also Supplemental Results and Figure S6).

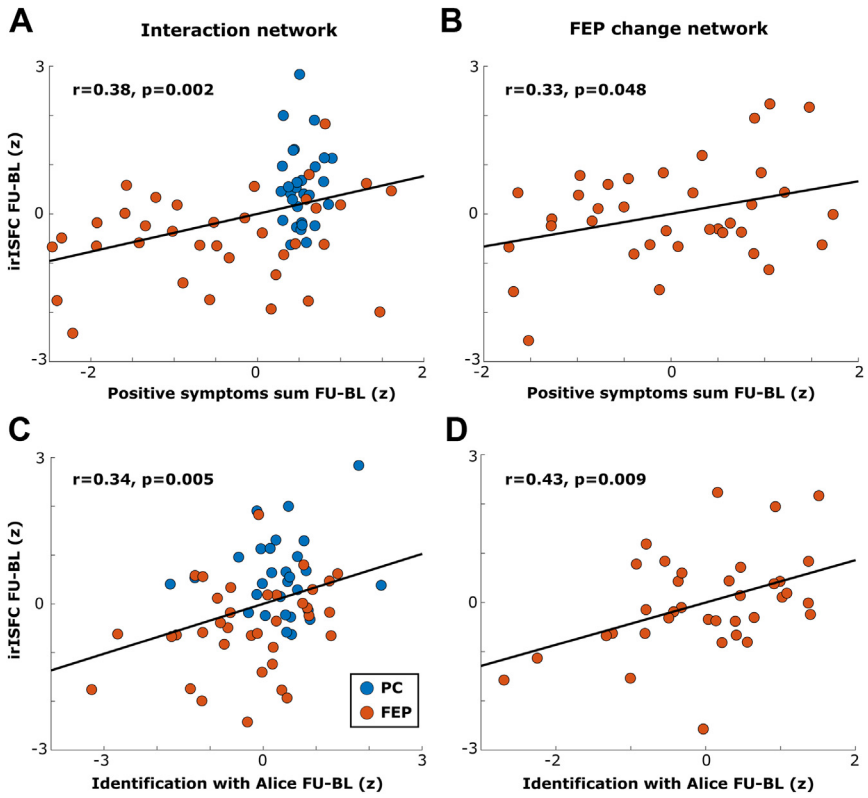

Figure 4. Correlation of network connectivity with positive symptoms and identification. **(A)** The longitudinal change in positive symptom sum scores plotted against the longitudinal change in the independent-reference intersubject functional connectivity (irISFC) in the interaction network. **(B)** The longitudinal change in positive symptom sum scores plotted against the longitudinal change in the irISFC in the first-episode psychosis (FEP) change network. **(C)** The longitudinal change in the subjective rating of how strongly the participants identified with the movie stimulus protagonist Alice and the longitudinal change in the irISFC in the interaction network. **(D)** The longitudinal change in the subjective rating of how strongly the participants identified with Alice and the longitudinal change in the irISFC in the FEP change network. The irISFC values were averaged across the connections within the network. The plotted values are the standardized *z* scores (with 0 mean and unit variance) of the residuals after regressing out antipsychotic medication dose and framewise displacement from both the irISFC values and the symptom/behavioral scores. BL, baseline; FU, follow-up; PC, population control.

The most interconnected region in the observed networks was the hippocampus. Abnormal hippocampus function in psychotic disorders is well documented (31–36). For example, projections from the hippocampus and parahippocampal gyrus to the nucleus accumbens and mesolimbic dopaminergic pathway have been highlighted in the pathophysiology of schizophrenia (37), and hippocampal hyperactivity has been proposed as a biomarker for schizophrenia (38). Moreover, delusions and hallucinations have been proposed to originate from aberrant interaction between imagery- or memory-induced hippocampal and sensory-induced cortical (and thalamic) contributions to the generation of representations that provide the basis for conscious awareness of the external world and the self (39).

Interestingly, in the observed interaction network, the irISFC increased from baseline to follow-up in the PC group (Figure 2). Supplementary analyses showed similar interaction for local irISFC and irISC in the hippocampus (Figure S7), with stronger local irISFC and irISC in PC at follow-up versus baseline. Considering that the hippocampus has a well-established role in memory function and that impairments in episodic memory are common in psychosis disorders (40–42) and present already in FEP (43), this finding could reflect group differences in episodic memory function. Such differences in hippocampus-driven episodic memory could also (at least partly) explain the stronger irISFC at follow-up (while rewatching the same movie stimulus as at baseline) in the hippocampus-centered network in the PC group.

Correlation Between Network Connectivity and Positive Symptoms

Our exploratory correlation results showed that longitudinal change in irISFC in the hippocampothalamocortical network was associated with longitudinal change in positive symptoms (Figure 4A, B), demonstrating the relevance of this network not only to psychotic disorders but specifically to psychotic symptoms. Decrease in irISFC from baseline to follow-up in the network was related to alleviation of positive symptoms (particularly delusions) in the FEP group. This supports the hypothesis that aberrant hippocampocortical interaction underlies the formation of delusions and hallucinations (39). More generally, our findings could be interpreted in terms of source-monitoring deficits whereby self-generated actions or thoughts are misattributed to external sources (44–46). In addition to the well-known role in relaying incoming sensory information to the cortex, the thalamus has been linked to corollary discharge (47), a neural mechanism that enables the recognition of self (48). The disturbance in the sense of self, evident in psychotic disorders (49), has been proposed to result from impairment in corollary discharge mechanism (50). Thus, our findings could reflect neural aberration whereby self-generated, hippocampus-driven memory or imagery representations are confused

with incoming sensory information due to an impaired corollary discharge mechanism.

Our results also showed that the lower the salience in the movie stimulus, the stronger the positive correlation between longitudinal changes in the network connectivity and positive symptoms in the FEP group (and vice versa). Even though the salience of the movie stimulus was not rated by the FEP group but rather by an independent group of healthy individuals, this finding is compatible with the aberrant salience hypothesis (51) according to which stimuli that are not typically perceived as salient are perceived as salient by individuals with psychosis. The salience network involves the anterior cingulate and anterior insular cortices as well as subcortical structures, such as the ventral striatum and thalamus (52,53), all of which were involved in the network showing stronger connectivity at baseline compared with follow-up in the FEP group.

Correlation Between Network Connectivity and Identification With Movie Stimulus Protagonist

We also found that longitudinal change in irISFC in the hippocampothalamocortical network correlated positively with longitudinal change in how strongly the participants identified with the protagonist Alice (Figure 4C, D). In the FEP group, longitudinal decrease in irISFC correlated with decrease in identification with Alice. In addition, change in correlations between baseline and follow-up differed between the groups, with positive correlation in the FEP group at baseline but not at follow-up and a near-significant positive correlation in the PC group at follow-up but not at baseline (Figure S9). This opposite trend between the groups directly reflects the irISFC interaction effect. Given that psychosis is characterized by reality distortion and confused thinking, the fantasy content and Alice's confused thinking featured in the movie stimulus makes it plausible that the strength of identification with Alice in the FEP group is related to their own psychosis experience. Therefore, the observed positive correlation between irISFC and identification with Alice further supports the relevance of the identified network to psychosis.

Liberal identification with Alice also conforms to the concept of disrupted sense of self in psychosis. Interestingly, the right hippocampal complex (including the hippocampus proper and parahippocampal gyrus), which was the most strongly interconnected region in the observed networks, has been associated with generation of sense of self or ipseity. For example, activation of the right hippocampal complex correlated with scores measuring different aspects of self-discrepancy, such as verbal self-awareness or awareness of one's own mental health condition (54–57). Such findings have been interpreted in terms of a hippocampal comparator function whereby current information is compared against subjective knowledge about one's own cognitive abilities (54).

Limitations

Results of our study should be interpreted in the context of its limitations. First, the FEP group (n = 36) was relatively small. A recent study argued that studies aiming to capture reproducible associations between interindividual differences in fMRI-measured brain function and complex cognitive or mental health phenotypes require considerably larger sample sizes (58). That said, this requirement was directed in particular at cross-sectional resting-state fMRI studies and, as pointed out in Marek *et al.* (58), is mitigated by the use of task and longitudinal designs.

The heterogeneity (of diagnoses) in both the FEP and PC groups could also be seen as a limitation. However, limiting the FEP group only to patients with, for example, a schizophrenia diagnosis would lead to inclusion of only patients with FEP with long duration of untreated psychosis (as minimum 6 months of continuous psychotic symptoms are required for a schizophrenia diagnosis), making the sample less representative of the FEP population. In addition, diagnoses are not stable during the FEP phase, and there are genetic and brain-level overlaps in different psychotic disorders (59–62). Similarly, only healthy individuals as control participants would bias the group comparison more than control participants representative of the general population, involving both healthy individuals and individuals with nonpsychotic psychiatric disorders. Finally, while using control participants as a reference in ISFC allows capturing deviations from "normality," it would require patients with FEP as reference subjects to address the possibility of FEP-typical connectivity patterns, i.e., such time-locked connectivity that is more similar among patients than among control participants.

Conclusions

We analyzed longitudinal changes in functional brain networks in patients with FEP during a movie stimulus using a novel irISFC method that allows the isolation of stimulus-dependent FC without the confounding effects of ongoing non–stimulus-related neural processes or non-neuronal physiological noise. Using this approach, we demonstrated that a hippocampus-centered network was associated with positive symptoms in the FEP group. The more the positive symptoms, particularly delusions, were alleviated from baseline to 1-year follow-up, the more the irISFC decreased. Similarly, the level of how strongly the patients with FEP identified with the confused protagonist of the fantasy movie stimulus decreased with decreasing irISFC from baseline to follow-up. These findings suggest a neural aberration in FEP whereby self-generated, hippocampus-driven memory or imagery representations are confused with incoming sensory information, possibly due to an impaired corollary discharge mechanism, causing delusions and other positive symptoms. Such an aberration could also be understood in terms of an impaired predictive mechanism whereby higher-level predictions modulate perception to conform with delusional beliefs.

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