Aberrant Cortical Integration in First-Episode Psychosis During Natural Audiovisual Processing

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ABSTRACT

BACKGROUND: Functional magnetic resonance imaging studies of psychotic disorders have reported both hypoactivity and hyperactivity in numerous brain regions. In line with the dysconnection hypothesis, these regions include cortical integrative hub regions. However, most earlier studies focused on a single cognitive function at a time, assessed by delivering artificial stimuli to patients with chronic psychosis. Thus, it remains unresolved whether these findings are present already in early psychosis and whether they translate to real-life–like conditions that require multisensory processing and integration.

METHODS: Scenes from the movie Alice in Wonderland (2010) were shown to 51 patients with first-episode psychosis (16 women) and 32 community-based control subjects (17 women) during 3T functional magnetic resonance imaging. We compared intersubject correlation, a measure of similarity of brain signal time courses in each voxel, between the groups. We also quantified the hubness as the number of connections each region has.

RESULTS: Intersubject correlation was significantly lower in patients with first-episode psychosis than in control subjects in the medial and lateral prefrontal, cingulate, precuneal, and parietotemporal regions, including the default mode network. Regional magnitude of between-group difference in intersubject correlation was associated with the hubness.

CONCLUSIONS: Our findings provide novel evidence for the dysconnection hypothesis by showing that during complex real-life–like stimulus, the most prominent functional brain alterations in psychotic disorders relate to integrative functions. Presence of such abnormalities in first-episode psychosis rules out long-term effects of illness or medication. These methods can be used in further studies to map widespread hub alterations in a single functional magnetic resonance imaging session and link them to potential downstream and upstream pathways.

Keywords: Default mode network, Disintegration, First-episode psychosis, Functional magnetic resonance imaging, Intersubject correlation, Natural stimulation

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Schizophrenia and other psychotic disorders have been suggested to result from a compromised integration of neural signals from specialized subsystems in the brain, such as perception, language, memory, and emotions (1–3). In task-related functional magnetic resonance imaging (fMRI) studies, differences between patients with schizophrenia and healthy control subjects vary depending on the experimental task (4) with remarkably little regional overlap across tasks (5). A recent meta-analysis suggested, however, that functional changes in patients with chronic schizophrenia converge on several hub regions, such as the medial and lateral prefrontal cortex, anterior cingulate cortex, thalamus, and lateral temporal areas (5), that integrate signals from many parts of the brain (6,7). Whether such involvement of cortical hub regions occurs already in early psychosis or is simply a consequence of the chronic disorder remains unknown.

There is also no consensus regarding the most pronounced aberrations in brain function that alter the processing of the rich and complex everyday situations in patients with psychosis. Studying brain activity of subjects who view a movie provides an excellent assay for investigating such complex processing (8). An audiovisual movie can include sensory, motor, emotional, motivational, social, and cognitive contents in a narrative context. To construct a subjective understanding of the movie, the movie events must be integrated with the individual’s semantic and autobiographical memory and with the present context (9,10).

Compared with resting-state fMRI studies (11), where brain activity is recorded without any specific tasks or external stimuli, fMRI recordings during a movie provide the advantage that a significant proportion of the measured brain signals reflects stimulus-driven activity that can be compared between groups and time points. In intersubject correlation (ISC) analysis (12), voxelwise functional time series is correlated with the time series of the same voxel in other individuals, providing a measure of how synchronous the brain activity of an individual is with respect to other subjects of the group.
This measure has been used to study patient groups (13–17). For example, in a recent study, ISC was lower during movie viewing in patients with depression compared with a control group in regions important in the regulation of emotions and attention (17). In another study, participants with a diagnosis of Asperger’s syndrome showed lower ISC in regions contributing to social information processing (15). Despite ISC analysis showing promise to reveal diagnostically relevant brain substrates of psychiatric disorders, to our knowledge, only one study with 15 patients with first-episode psychosis (FEP) using naturalistic stimuli has been conducted (18).

Disintegration is a central tenet in theories of psychotic disorders (19). In terms of graph theory, measures of centrality estimate how connected a certain region of the brain is to other regions (20). In this approach, highly connected regions are often coined as hubs (21). Hubs are involved in higher-order, multisensory processing (21,22), presumably integrating information from areas with which they are connected (21,23,24).

Thus, as a measure of hubness and integration of brain areas, we calculate the regional weighted degree centrality across the brain.

In the current study, we used ISC analysis to compare brain activation during a movie presentation between patients with FEP and control subjects. As the boundaries between reality and fantasy are distorted in patients with psychotic disorders, the stimulus involved scenes from the movie Alice in Wonderland (2010) containing both realistic and fantasy material. We expected ISC to be lower in patients with FEP, especially in brain regions relevant for multimodal, higher-level processing and integration, as determined by the region’s hubness, such as the medial parietal and frontal and lateral prefrontal regions. Furthermore, we hypothesized such regions to be associated, at least in part, with the fantasy content of the movie.

METHODS AND MATERIALS

This study is a part of the Helsinki Early Psychosis Study from which we have recently published a machine-learning study (25) that focused on transient moment-to-moment changes of brain signals during movie fMRI. Although we used almost identical data here, the research question and analysis methods are different, as we focus on ISC between signal time courses during the entire 7-minute, 20-second movie stimulus.

Participants

The Ethics Committee of the Hospital District of Helsinki and Uusimaa approved the study (diary numbers 257/12/03/03/2009 and 226/13/03/03/2013), and all participants gave written informed consent before participation. Capacity of patients to give informed consent was assessed by the clinician responsible for treatment. From hospitals and outpatient clinics of the Helsinki University Hospital and the Department of Psychiatry, Helsinki City Health Department, we recruited 51 patients with FEP who were having their first contact with psychiatric care for a psychotic disorder. Psychotic symptoms were evaluated with the Brief Psychiatric Rating Scale–Extended (26). The inclusion criterion was scoring ≥4 in the items either for Unusual Thought Content or for Hallucinations. Patients with substance-induced psychotic disorder or psychotic disorder owing to a general medical condition were excluded. Diagnostic assessment was done on the basis of the Research Version of the Structured Clinical Interview for DSM-IV Axis I Disorders interview (27) and on a careful review of all medical records by a senior psychiatrist. Current medication use was asked in the interview and confirmed from medical records. The clinical assessment of the patients and control subjects has been previously described in more detail (28).

We recruited 32 control subjects of the same age group (18–40 years) through the Finnish Population Register Centre, excluding subjects who were not eligible for MRI; had a history of psychosis; or had a chronic neurological, endocrinological, or cardiovascular disease. Patients with FEP who had epilepsy or structural brain anomalies or who were not eligible for MRI were excluded from this analysis. All participants had normal or corrected-to-normal vision.

Acquisition of fMRI Data

Owing to a scanner update during the study, we acquired fMRI data with two 3T MRI scanners at Aalto AMI Centre, Aalto Neuroimaging, Aalto University School of Science: first with a Signa VH/i scanner (GE Healthcare Ltd., Chalfont St Giles, United Kingdom) with a 16-channel head coil and later with a MAGNETOM Skyra scanner (Siemens Healthcare, Erlangen, Germany) with a 32-channel coil. The imaging parameters were the same for both scanners. Whole-brain blood oxygen level-dependent (BOLD) signal data were acquired with a gradient echo-planar sequence (repetition time 1.8 seconds, echo time 30 ms, flip angle 75°, field of view 24 cm, matrix size 64 × 64, 36 slices with a thickness of 4 mm). Fourteen patients and 11 control subjects were studied with the Signa VH/i scanner, and 37 patients and 21 control subjects were studied with the MAGNETOM Skyra scanner. We included participants from both scanners in the same analysis because multisite fMRI studies have shown that a 10% increase in total sample size will increase statistical power as opposed to using only single-scanner data (29); in our case, the 10% increase would mean 6 subjects ([37 + 21] × 0.1 = ~6)]. T1-weighted structural images with 1-mm isotropic voxels and T2-weighted structural images were also acquired, and a clinical neuroradiologist evaluated these scans for brain abnormalities.

Movie Stimulus

During fMRI, the participants were shown five episodes in sequence from the movie Alice in Wonderland, directed by Tim Burton (Walt Disney Pictures, Burbank, CA, 2010; dubbed in Finnish) (total duration 7 minutes, 20 seconds equaling 245 echo-planar imaging volumes). This film is in part animated, but human actors are present in every scene. The scenes show Alice’s wedding followed by her trip through a rabbit hole to Wonderland and subsequent fantasy events [see (25) for detailed description]. The movie was projected onto a semi-transparent screen centered in the participant’s visual field, and stimulus timing was controlled by Presentation Software (Neurobehavioral Systems, Inc., Berkeley, CA). Sound was conveyed through plastic tubes, which were attached to porous EAR-tip (Etymotic Research Inc., Elk Grove Village, IL) earplugs. To insulate 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
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preference, ensuring it was loud enough to be clearly audible over scanner noise.

**Analysis of ISC Images**

**Computation of Voxelwise ISC.** Functional volumes were preprocessed in FSL ([http://www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)). They were then realigned for movement correction, coregistered with the structural images, normalized to Montreal Neurological Institute template, and smoothed with a Gaussian kernel with 8-mm full width at half maximum. After regressing out individual head motion, we used ISC toolbox ([30](http://www.alivelearn.net/xjview)) to compute the voxelwise temporal Pearson correlation between every pair of subjects. To allow between-group comparisons, ISCs were calculated separately for the patient and control groups. This resulted in subjectwise ISC images, where voxel intensities reflect how similar each voxel’s time course was in relation to the other subjects in the same group. A similar approach has been used in recent between-group ISC comparisons in Asperger’s syndrome ([15](http://www.alivelearn.net/xjview)) and depression ([17](http://www.alivelearn.net/xjview)). We calculated the ISCs separately for participants studied with different scanners. Before the ISC images were entered into group-level analyses, they were smoothed with an 8-mm full width at half maximum kernel to account for inaccuracies in normalization and to enhance comparability between groups and scanners.

**Group-Level Analysis.** ISC differences between the groups were analyzed using nonparametric two-sample tests with SPM ([http://www.fil.ion.ucl.ac.uk/spm/](http://www.fil.ion.ucl.ac.uk/spm/)) extension SnPM13 ([http://warwick.ac.uk/snpm/](http://warwick.ac.uk/snpm/)) and 5000 permutations. We pooled the ISC images from both scanners owing to good agreement between different scanners in previous functional imaging studies ([31](http://www.alivelearn.net/xjview), [32](http://www.alivelearn.net/xjview)). As a further characterization of the spatial distribution of ISC differences, we calculated the overlap of the group difference map with resting-state networks of a liberally thresholded seven-network parcellation map of the cerebral cortex ([35](http://www.alivelearn.net/xjview)). This parcellation was chosen because of its availability and popularity as well as big sample size (1000 subjects). The results were visualized using MRicroGL ([http://www.mccauslandcenter.sc.edu/mricrogl/home](http://www.mccauslandcenter.sc.edu/mricrogl/home)).

We also extracted signal time courses from 1) the regions that were most strongly synchronized in patients and control subjects during the movie (auditory and visual areas shown in [Supplemental Figure S1](http://www.alivelearn.net/xjview)) and 2) the regions showing the largest group difference (default mode network [DMN]). Group differences in each time point were studied to find common features of the movie that might contribute to the results. See [Supplemental Methods](http://www.alivelearn.net/xjview) for details.

**Rating of Movie Content by an Independent Control Group**

Because the separation of reality from fantasy is considered central in psychoses, an independent group of control subjects (n = 17, 10 men and 7 women, mean age 26.5 years) not participating in the fMRI recording rated the moment-to-moment realism of the movie events. Each participant was asked to evaluate, by moving a mouse on a continuous scale, how likely the currently seen events would happen in real life (see [http://emotion.utu.fi/softwaredata/](http://emotion.utu.fi/softwaredata/)). The data were recorded as a value between 0 (very unlikely) and 1 (very likely) every 200 ms and were downsampled to 1 repetition time to be used in modeling brain activity. This regressor was entered into a general linear model in first-level SPM analysis. Mean optic flow ([36](http://www.alivelearn.net/xjview)) was added as a nuisance covariate to control for visual changes based on the movement of objects in the scene. Resulting contrast images were then compared between groups as well as analyzed as one pooled sample with SnPM to show areas where BOLD signal associated significantly with the fantasy ratings across patients and control subjects. ISC differences were then corrected for multiple comparisons within these areas to show whether fantasy processing–related and ISC difference areas overlap.

**Control for Potential Confounders**

Attentional differences might account for some group differences in ISC because attention modulates sensory and cognitive processing ([37](http://www.alivelearn.net/xjview)–[42](http://www.alivelearn.net/xjview)). To control for attentional differences across groups, we computed a map of ISCs in the auditory and visual cortices balanced for scanners and groups ([11](http://www.alivelearn.net/xjview) subjects included from each group for each scanner, total n = 44). This map was thresholded at pseudo t > 22 [for a definition of pseudo t, see e.g. ([43](http://www.alivelearn.net/xjview)) to include only the brain regions that showed the strongest ISC across participants, i.e., the visual and auditory cortices ([Supplemental Figure S1](http://www.alivelearn.net/xjview)). We then extracted eigenvalues for subjectwise ISCs in this mask. These eigenvalues were entered as a nuisance covariate in a whole-brain ISC group comparison. In addition, age, sex, scanner, mean framewise head movement computed according to Jenkinson et al. ([44](http://www.alivelearn.net/xjview)), and chlorpromazine daily dose equivalents calculated according to Andreasen et al. ([45](http://www.alivelearn.net/xjview)) (except for seriptinid, which was not available in Andreasen et al. and was calculated according to Hautke et al. ([46](http://www.alivelearn.net/xjview))) were entered as nuisance covariates to exclude potential confounds in the group ISC analyses. As a complementary control for attentional confounds, we report results in the [Supplemental Results](http://www.alivelearn.net/xjview) where the group differences are controlled by extracted ISCs from the dorsal attention network. To further exclude confounding factors, we studied ISC group differences separately for subgroups of patients divided by median framewise displacement and for the Siemens scanner subgroup ([Supplemental Results](http://www.alivelearn.net/xjview)). We also plotted ISC values to identify outliers that might contribute to findings and report a complementary ISC analysis less susceptible to outliers in [Supplemental Results](http://www.alivelearn.net/xjview).

**Degree Centrality and ISC Differences**

To test whether the ISC differences and the integrative functions of the brain coincide, we computed the Pearson correlation coefficient between the ISC group difference and hubness across voxels. We used the SPM contrast image...
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Table 1. Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>FEP Group</th>
<th>Control Group</th>
<th>Test Statistic</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, Female</td>
<td>16/51 (31%)</td>
<td>17/32 (53%)</td>
<td>$\chi^2 = 3.88$</td>
<td>.049*</td>
</tr>
<tr>
<td>Age, Years</td>
<td>23.2 (20.9–27.8)</td>
<td>24.7 (23.0–33.8)</td>
<td>U = 593</td>
<td>.037**</td>
</tr>
<tr>
<td>Head Motion, mm</td>
<td>0.53 (0.37–0.76)</td>
<td>0.56 (0.31–0.64)</td>
<td>U = 789</td>
<td>.801</td>
</tr>
<tr>
<td>GAF</td>
<td>35 (31–40)</td>
<td>90 (81.3–90)</td>
<td>U = 4.5</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>Positive Symptoms*</td>
<td>7 (3–10)</td>
<td>0</td>
<td>U = 112</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>Negative Symptoms*</td>
<td>5 (3–10)</td>
<td>0</td>
<td>U = 121</td>
<td>&lt; .001*</td>
</tr>
</tbody>
</table>

Values are reported as n (%) or median and 1st–3rd quartiles.
FEP, first-episode psychosis; GAF, Global Assessment of Functioning (74,75); MDD, major depressive disorder; NOS, not otherwise specified.
*Statistically significant difference.
**Positive symptoms represent the sum score from Brief Psychiatric Rating Scale (26) items Hallucination, Unusual thought content, Bizarre behaviour, and Conceptual disorganisation. Negative symptoms represent Brief Psychiatric Rating Scale item Blunted affect and items Alogia, Anhedonia/associaility, and Avolition/apathy from the Scale for the Assessment of Negative Symptoms (76). The Brief Psychiatric Rating Scale item scores were scaled to 0–6 before calculating the sum score.

including all the brain voxels (not only voxels of significant differences) from a two-sample t test on ISC differences of control subjects versus patients as a group difference map.
The same nuisance covariates were included as in the main analysis. Hubness was measured in control subjects as weighted degree centrality [see e.g. (47)], a measure of the amount of functional connectivity of a voxel across the brain by using the same BOLD data as in the ISC analysis. Pre-processing for the degree centrality computation included MaxCorr (25,48) to reduce movement-related artifacts, and the fMRI signals from the cerebrospinal fluid and white matter were extracted and regressed out to restrict potential confounding effects of movement. Weighted degree centrality was then computed in DPARSF (49) with a default threshold connectivity value of 0.2. SPM second-level one-sample contrast image was computed to represent mean voxelwise weighted degree among the control subjects. Voxelwise spatial correlation between the ISC difference map and the hubness map was calculated within a mask: only voxels in SPM gray matter template (threshold voxel value = 0.4) and in the map of ISC in control subjects thresholded with familywise error-corrected voxel-level

Figure 1. Differences in intersubject correlation strength, adjusted for nuisance variables (see text), between control and first-episode psychosis groups. Significantly ($p < .05$, voxel-level familywise error-corrected) stronger intersubject correlation in the control group is displayed; color bar indicates pseudo t value [for pseudo t, see (43)]. In the transverse slices, the left hemisphere is up, and in the coronal slice, left is left. ACC/MPFC, anterior cingulate cortex/medial prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; LTPJ, left temporoparietal junction; MTG, middle temporal gyrus; PC/PCC, precuneus/posterior cingulate cortex; RTPJ, right temporoparietal junction; VLPFC, ventrolateral prefrontal cortex.
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p < .001 were included. The ISC map was used to exclude gray matter areas with signal loss owing to susceptibility artifacts.

RESULTS

Participant Characteristics

Table 1 presents the characteristics of the participants. Patients were on average 1.5 years (median) younger than control subjects, and the patient group included more men (69% vs. 47%). Chlorpromazine equivalent daily dose was on average 365 mg (range, 0–1214 mg) in the patients.

ISC Findings

ISC was strongest in both groups in visual and auditory cortices but significantly weaker in patients than in control subjects in the precuneus/posterior cingulate cortex (precuneus/PCC), anterior cingulate cortex/medial prefrontal cortex (ACC/MPFC), bilateral posterior middle temporal gyrus (MTG), angular gyrus, supramarginal gyrus, inferior parietal

Table 2. Group Comparison of Intersubject Correlations

<table>
<thead>
<tr>
<th>Region</th>
<th>Peak (MNI) x, y, z</th>
<th>Minimum p Value</th>
<th>Extent (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parietal, Temporal, Occipital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral precuneus, cuneus, PCC, post MCC, and calcarine cortex</td>
<td>12, –64, 24</td>
<td>.0002</td>
<td>42.9</td>
</tr>
<tr>
<td>Right MTG, including STG and ITG</td>
<td>52, –30, –4</td>
<td>.0002</td>
<td>4.2</td>
</tr>
<tr>
<td>Left TPJ, including MOG</td>
<td>–48, –76, 14</td>
<td>.0002</td>
<td>13.2</td>
</tr>
<tr>
<td>Right TPJ</td>
<td>50, –48, 20</td>
<td>.0002</td>
<td>8.7</td>
</tr>
<tr>
<td>Left calcarine and lingual gyri</td>
<td>–24, –66, 4</td>
<td>.0004</td>
<td>0.7</td>
</tr>
<tr>
<td>Right post insula and Heschl’s gyrus</td>
<td>38, –20, 12</td>
<td>.0046</td>
<td>0.7</td>
</tr>
<tr>
<td>Right fusiform gyrus</td>
<td>34, –38, –20</td>
<td>.0074</td>
<td>0.2</td>
</tr>
<tr>
<td>Right MOG</td>
<td>36, –78, 20</td>
<td>.0078</td>
<td>0.6</td>
</tr>
<tr>
<td>Left MOG</td>
<td>–34, –82, 28</td>
<td>.0012</td>
<td>1.9</td>
</tr>
<tr>
<td>Frontal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left DLPFC</td>
<td>–28, 46, 18</td>
<td>.0002</td>
<td>6.0</td>
</tr>
<tr>
<td>Left VLPFC, including STP</td>
<td>–48, 32, –12</td>
<td>.0002</td>
<td>4.5</td>
</tr>
<tr>
<td>Right ant VLPFC, including STP</td>
<td>48, 22, –16</td>
<td>.0002</td>
<td>2.7</td>
</tr>
<tr>
<td>Right post VLPFC</td>
<td>46, 22, 14</td>
<td>.0002</td>
<td>1.5</td>
</tr>
<tr>
<td>Bilateral ACC, ant MCC, and MPFC</td>
<td>0, 16, 32</td>
<td>.0004</td>
<td>5.4</td>
</tr>
<tr>
<td>Left pre- and postcentral gyrus</td>
<td>–52, –6, 48</td>
<td>.0010</td>
<td>1.0</td>
</tr>
<tr>
<td>Right DLPFC</td>
<td>26, 54, 20</td>
<td>.0010</td>
<td>6.9</td>
</tr>
<tr>
<td>Right orbitofrontal cortex</td>
<td>44, 48, –12</td>
<td>.0010</td>
<td>1.2</td>
</tr>
<tr>
<td>Left ant SFG and medial SFG</td>
<td>–14, 60, 24</td>
<td>.0010</td>
<td>0.4</td>
</tr>
<tr>
<td>Right SMA and medial SFG</td>
<td>8, 24, 60</td>
<td>.0034</td>
<td>0.6</td>
</tr>
<tr>
<td>Left post SFG and medial SFG</td>
<td>–10, 34, 52</td>
<td>.0038</td>
<td>0.6</td>
</tr>
<tr>
<td>Left SMA</td>
<td>–8, 10, 66</td>
<td>.0044</td>
<td>0.8</td>
</tr>
<tr>
<td>Right post MFG and precentral gyrus</td>
<td>34, –2, 52</td>
<td>.0078</td>
<td>0.6</td>
</tr>
<tr>
<td>Subcortical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left cerebellum (8)</td>
<td>–28, –62, –60</td>
<td>.0002</td>
<td>0.6</td>
</tr>
<tr>
<td>Bilateral cerebellum (9 and vermis 9)</td>
<td>6, –56, –46</td>
<td>.0002</td>
<td>1.4</td>
</tr>
<tr>
<td>Right cerebellum (7b, 8, and vermis 8)</td>
<td>4, –74, –44</td>
<td>.0002</td>
<td>0.9</td>
</tr>
<tr>
<td>Right cerebellum (8 and 10)</td>
<td>32, –40, –46</td>
<td>.0002</td>
<td>0.4</td>
</tr>
<tr>
<td>Left putamen</td>
<td>–20, 4, –10</td>
<td>.0010</td>
<td>0.6</td>
</tr>
<tr>
<td>Left cerebellum (crus 2 and 7b)</td>
<td>–22, –82, –44</td>
<td>.0012</td>
<td>1.1</td>
</tr>
<tr>
<td>Right cerebellum (8)</td>
<td>26, –62, –60</td>
<td>.0014</td>
<td>0.3</td>
</tr>
<tr>
<td>Left cerebellum (8 and crus 1)</td>
<td>–40, –52, –28</td>
<td>.0044</td>
<td>0.2</td>
</tr>
<tr>
<td>Right putamen</td>
<td>28, 8, –12</td>
<td>.0046</td>
<td>0.8</td>
</tr>
<tr>
<td>Left caudate nucleus</td>
<td>–12, 2, 8</td>
<td>.0096</td>
<td>0.5</td>
</tr>
<tr>
<td>Right thalamus</td>
<td>8, –12, 2</td>
<td>.0140</td>
<td>0.2</td>
</tr>
</tbody>
</table>

This table shows where intersubject correlations are higher in control subjects. ACC, anterior cingulate cortex; ant, anterior; DLPFC, dorsolateral prefrontal cortex; ITG, inferior temporal gyrus; MCC, middle cingulate cortex; MFG, middle frontal gyrus; MOG, middle occipital gyrus; MNI, Montreal Neurological Institute; MPFC, medial prefrontal cortex; MTG, middle temporal gyrus; PCC, posterior cingulate cortex; post, posterior; SFG, superior frontal gyrus; SMA, supplementary motor area; STG, superior temporal gyrus; STP, superior temporal pole; TPJ, temporoparietal junction; VLPFC, ventrolateral prefrontal cortex.

lobule (the latter four regions called temporoparietal junction [TPJ] for convenience), middle and inferior frontal gyrus (called dorsolateral prefrontal cortex and ventrolateral prefrontal cortex, respectively, for convenience), superior frontal gyrus, putamen, and cerebellum, as well as in right Heschl’s gyrus/posterior insula, thalamus and MTG, left precentral and postcentral gyrus, caudate nucleus, and occipital regions (Figure 1 and Table 2; see Supplemental Table S1 for mean ISC from all clusters for patients and control subjects). These differences remained statistically significant when adjusted for potential confounding effects of the ISCs from visual and auditory cortices (a proxy of attention to the stimulus) (see also Supplemental Results, Supplemental Table S2, and Supplemental Figure S4 for dorsal attention network-controlled results), age, sex, head movement, scanner, and antipsychotic dose equivalents. Compared with the resting-state atlas (35), 40% of the cortical (i.e., excluding subcortical differences) ISC difference map overlapped with the DMN, and the overlap with the other six networks was <16% for each (Figure 2). Note that in this parcellation, the somatomotor, auditory, and posterior insular cortices are included in the same network (35). Two clusters in posterior occipital lobe (cluster size \( |k| = 1.1 \text{ cm}^3, p = .0002, \text{peak at } x = -22, y = -94, z = 6; \text{and } k = 0.7 \text{ cm}^3, p = .006, \text{peak at } x = 10, y = -90, z = -12 \)) showed significantly higher ISC in the patient group than in the control group. However, these differences reached statistical significance only after the inclusion of the ISCs from visual and auditory cortices to the model as a nuisance covariate.

We show in the Supplemental Results that findings were similar in the high-motion (\( n = 26 \)) and low-motion (\( n = 25 \)) subgroups (Supplemental Figures S2 and S3). Also, the use of two scanners did not have a major effect, as most of the same clusters, as in the main analysis, showed a significant difference when using only data acquired with the Siemens scanner (Supplemental Results and Supplemental Figure S5). ISC distributions suggest that the group differences were not driven by only a few deviation patients (Supplemental Results and Supplemental Figures S6–S8). Neither the \( z \)-scored signals nor the squared differences from the group mean differed statistically significantly between the groups at any time point.

### Association With Degree Centrality

Figure 3 presents the overlap between ISC group difference and the weighted degree centrality of the control subjects. The highest degree was found in the precuneus/PCC, ACC/dorsal MPFC, lateral occipital, parietal, and temporal regions as well as the dorsolateral prefrontal cortex, all of which overlap extensively with areas where between-group ISC differences were found. The Pearson correlation coefficient \( r \) between the ISC group difference (control > patient) and the weighted degree centrality of the control subjects was 0.46, showing that the more functionally connected a region was, the greater the difference in its ISC between the patient and control groups.

### Association of BOLD Signal With Fantasy Content of the Stimulus

No group differences were found in a whole-brain analysis of the association between BOLD signal and fantasy content. In a pooled sample of both patients and control subjects, the fantasy content of the movie correlated with BOLD signals of the occipital, temporal, and parietal lobes as well as of the dorsolateral prefrontal cortices (Figure 4). These regions overlapped with the ISC group difference in bilateral precuneus/PCC, TPJ, precentral, and ventrolateral prefrontal...
DISCUSSION

We found significantly weaker ISC during movie viewing in patients with FEP than in control subjects in widespread brain regions, including precuneus/PCC, ACC/MPFC, TPJs, lateral prefrontal cortices, higher-level occipital areas, and right MTG as well as in subcortical structures. The differences between patients and control subjects remained statistically significant even after adjusting for ISCs in the visual and auditory sensory areas, which suggests that the group differences are not due to different input to primary sensory areas or due to compromised attention in the patients. Although the significant clusters in the right MTG and posterior insula/Heschl’s gyrus coincided with early auditory cortical areas, the MTG cluster extended to association cortical areas and largely overlapped with lateral temporal regions of the DMN.

Mapping disorder-related brain activity alterations that are relevant to processing of natural, dynamic, and multimodal stimuli helps in understanding how the pathogenesis of psychotic disorders contributes to everyday sensory, cognitive, and affective processing. While numerous task-selective functional brain alterations have been reported in patients with FEP, they may not directly translate to brain function during everyday life (50). Natural and dynamic stimuli consistently trigger more reproducible brain activity than highly specific stimuli (51), especially in higher-level regions, and brain regions showing no net activity changes to repeated stimuli might still respond reliably to complex stimuli (52).

Several of these regions, such as the precuneus/PCC, ACC/MPFC, TPJs, and lateral prefrontal cortices (22,47), are considered as high-level areas integrating signals from multiple brain systems. Although altered low-level sensory processing...
might contribute to psychotic symptoms (53,54), the main
deficits in patients with psychosis seem to result from dis-
tegrated higher-level functions, preventing coherent, dy-
namic perceptions and the adaptive interaction of cognition
and emotions and their appropriate contextualization through
memory (2,55). The hubness, measured in control subjects, was
correlated with the magnitude of ISC group differences, sug-
gest that the largest ISC differences predominate in hub re-
gions. Accordingly, the current ISC differences overlapped with
cortical areas as defined in previous studies (21,22). Structural
and resting-state functional imaging has shown psychosis-
related alterations both in the hubs and in whole-brain network
topology supporting global integration. Such alterations have
been reported in patients with FEP (56), patients with chronic
schizophrenia (57–59), unaffected siblings of patients with
schizophrenia (60), and population-based samples of people with
subclinical psychotic experiences (61). A pooled analysis on task
fMRI studies in patients with chronic schizophrenia showed
overrepresentation of functional alterations in hubs compared
with nonhub regions (5). Our findings imply that the prominence
of hubs alterations can be quantified during a single fMRI session,
instead of using a set of multiple simple tasks (5), by employing a
naturalistic movie stimulus.

Many regions where we observed ISC differences, including
the precuneus/PCC, ACC/MPFC, and TPJ’s, overlap with the
DMN (35,62–64). In our earlier machine-learning analysis using
the same cohort, moment-to-moment changes in the BOLD
signal differentiated patients and control subjects with an
average 77.5% accuracy, based largely on the functioning of
the precuneus/PCC (25). Accordingly, the statistically most
significant ISC differences between the groups occurred in the
central hub region of the DMN—the precuneus/PCC. DMN has
been proposed to serve as a global integrator for conscious
experience (65) and to be at the top end of cortical connectivity
hierarchy (66). The precuneus/PCC, ACC/MPFC, and TPJ’s
have longer temporal receptive windows than lower-level
sensory areas, as evidenced by ISC analysis (67,68), and
may integrate information over minutes (69). In agreement, ISC
of these regions may differentiate patients with FEP and control
subjects better than processing at the word or sentence
levels (18). In the present study, the activity in the precuneus/
PCC and TPJ increased as a function of fantasy content of the
levels
sensory information with an internal model of the world based
on semantic and autobiographical memory, which are related
to hub alterations. It could also be

Conclusions

The most prominent functional brain alterations in patients
with FEP, observed while the patients were viewing a com-
plex audiovisual movie stimulus, were located in hub regions that
subserve integrative brain functions. The diffuse brain
alterations shown in previous single-task fMRI studies on
psychotic disorders might converge on the dysfunction of the
integrative hubs during processing of complex real-life–
like information. Present methods should be used in further
studies to access both upstream and downstream pathways of
hub dysfunction.

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Aberrant Integration in Psychosis During Movie Viewing


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