HELDA
HELSINGIN YLIOPISTO
HELSINGFORS UNIVERSITET
UNIVERSITY OF HELSINKI

UNIVERSITY OF HELSINKI

https://helda.helsinki.fi

Functional network connectivity and topology during naturalistic stimulus is altered in first-episode psychosis

Rikandi, Eva

2022-03

Rikandi , E , Mäntylä , T , Lindgren , M , Kieseppä , T , Suvisaari , J & Raij , T T 2022 , '
Functional network connectivity and topology during naturalistic stimulus is altered in
first-episode psychosis ' , Schizophrenia Research , vol. 241 , pp. 83-91 . https://doi.org/10.1016/j.schres.2022.01.00

http://hdl.handle.net/10138/344251
https://doi.org/10.1016/j.schres.2022.01.006

cc_by
publishedVersion

Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.

This reprint may differ from the original in pagination and typographic detail.

Please cite the original version.

Schizophrenia Research 241 (2022) 83–91

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Functional network connectivity and topology during naturalistic stimulus is altered in first-episode psychosis

Eva Rikandi [a,b,c,*], Teemu Mäntylä [a,b,c], Maija Lindgren [a], Tuula Kieseppä [d], Jaana Suvisaari [a], Tuukka T. Raij [b,d]

[a] Department of Public Health and Welfare, National Institute for Health and Welfare, Helsinki, Finland
[b] Department of Neuroscience and Biomedical Engineering, and Advanced Magnetic Imaging Centre, Aalto NeuroImaging, Aalto University School of Science, Espoo, Finland
[c] Department of Psychology and Logopedics, Helsinki University, Helsinki, Finland
[d] Department of Psychiatry, Helsinki University and Helsinki University Hospital, Helsinki, Finland

ARTICLE INFO

Keywords:
Psychosis
Naturalistic stimulus
fMRI
Functional connectivity
Networks

ABSTRACT

Background: Psychotic disorders have been suggested to derive from dysfunctional integration of signaling between brain regions. Earlier studies have found several changes in functional network synchronization as well as altered network topology in patients with psychotic disorders. However, studies have used mainly resting-state that makes it more difficult to link functional alterations to any specific stimulus or experience. We set out to examine functional connectivity as well as graph (topological) measures and their association to symptoms in first-episode psychosis patients during movie viewing. Our goal was to understand whole-brain functional dynamics of complex naturalistic information processing in psychosis and changes in brain functional organization related to symptoms.

Methods: 71 first-episode psychosis patients and 57 control subjects watched scenes from the movie Alice in Wonderland during 3 T fMRI. We compared functional connectivity and graph measures indicating integration, segregation and centrality between groups, and examined the association between topology and symptom scores in the patient group.

Results: We identified a subnetwork with predominantly decreased links of functional connectivity in first-episode psychosis patients. The subnetwork was mainly comprised of nodes of and links between the cingulo-opercular, sensorimotor and default-mode networks. In topological measures, we observed between-group differences in properties of centrality.

Conclusions: Functional brain networks are affected during naturalistic information processing already in the early stages of psychosis, concentrated in salience- and cognitive control-related hubs and subnetworks. Understanding these aberrant dynamics could add to better targeted cognitive and behavioral interventions in the early stages of psychotic disorders.

1. Introduction

Psychotic disorders may result from an altered dynamics of how different parts of the brain interact (Friston, 1998). It has been proposed that psychotic symptoms are a manifestation of glutamate-driven and dopamine-related aberrant salience attribution in patients, where the recognition of salient stimuli is disrupted (Coyle et al., 2020; Kapur, 2003). This may relate to the dysregulated brain dynamics proposed by the dysconnectivity hypothesis, that has been supported by findings of alterations in functional brain network connectivity (Baker et al., 2014; Fornito et al., 2011; O'Neill et al., 2018; Palaniyappan and Liddle, 2012; Satterthwaite and Baker, 2015; van den Heuvel and Fornito, 2014; Whitfield-Gabrieli et al., 2009; Whitfield-Gabrieli and Ford, 2012) as well as network organization and structure (Lynall et al., 2010; Morgan et al., 2018) of patients with psychotic disorders.

Functional connectivity provides a useful tool in understanding interactions between brain regions by measuring the correlation of the fMRI-derived BOLD signal time series between different regions of

* Corresponding author at: Department of Public Health and Welfare, National Institute for Health and Welfare, Helsinki, Finland.
E-mail address: eva.rikandi@thl.fi (E. Rikandi).

https://doi.org/10.1016/j.schres.2022.01.006
Received 28 March 2021; Received in revised form 1 January 2022; Accepted 2 January 2022
Available online 29 January 2022
0920-9964/© 2022 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

interest. Earlier studies have found widespread alterations in functional connectivity in psychotic disorders (Gong et al., 2017), usually concentrated in frontal regions or fronto-parietal connections (Baker et al., 2014; Fornito et al., 2011; O'Neill et al., 2018; van den Heuvel and Fornito, 2014) but also in networks associated with salience processing (Baker et al., 2014; O'Neill et al., 2018; Palaniyappan and Liddle, 2012) and in the default-mode network (Whitfield-Gabrieli and Ford, 2012; Woodward et al., 2011). Salience networks consist of hubs in the anterior cingulate and anterior insular cortices and include nodes in the thalamus, hypothalamus, amygdala and ventral striatum (Seeley, 2019). The default-mode network is comprised of bilateral nodes in the medial prefrontal, medial and lateral temporal and medial and lateral parietal regions (Raichle, 2015). It has been suggested that aberrant connectivity patterns are more dominant in frontal regions in the early stages of psychotic disorders and become more widespread during the course of the illness (Li et al., 2016) and that with the advancing stages of psychotic disorders, the underlying brain mechanisms change from mainly frontal hyperconnectivity to hypoconnectivity (Anticevic et al., 2015).

Using graph theory metrics (Bullmore and Sporns, 2009), functional connectivity can be utilized to observe properties beyond the co-activation of different regions and to describe how the functional brain network topology is organized. So far, studies implementing graph theory to identify functional connectivity patterns of the brain have predominantly used resting-state data (Farahani et al., 2019). Earlier research suggests that in psychotic disorders there is less integration and hub domination (Lynall et al., 2010), less segregation (Peeters et al., 2016), and less redundancy, resulting in more vulnerable hubs (Crossley et al., 2016). Differences in network topology are shown to predate first-episode psychosis (Lord et al., 2012), and several studies have found aberrant network topology to associate with positive symptoms (Kang and Sponheim, 2017; Rotarska-Jagiela et al., 2010; Su et al., 2015) and poorer response to treatment (Palaniyappan et al., 2016).

Movies are a promising stimulus in understanding complex information processing in the brain (Baldassano et al., 2018). They can be seen as condensed representations of everyday life and are shown to effectively synchronize brain activity across subjects (Hasson et al., 2004; Simony et al., 2016). Movies are increasingly used in neuroscience to understand a variety of cognitive and emotional brain-related functions that are similar across subjects (Lahnakoski et al., 2014; Malinen et al., 2007; Sanchez-Alonso et al., 2021; Sonkusare et al., 2019) and have recently revealed novel and promising results in psychosis-related brain functioning (Yang et al., 2020), including in our own previous work (Mäntylä et al., 2018; Rikandi et al., 2017; Rikandi et al., 2018).

The main goal of our study was to extend knowledge about aberrant brain functional patterns which are already present at the early stages of psychotic disorders and related to the processing of complex, everyday-like information. To our knowledge, this is the first study to use naturalistic stimulus to examine the topology of functional brain networks of first-episode psychosis patients. Furthermore, we examined how both positive and negative symptoms relate to aberrant brain topology. When comparing patients to control participants, we expected to find widespread differences in functional connectivity and hub-related topology, and that these differences associate with symptoms. In the long run, a better understanding of the underlying functional dynamics during an ecologically valid stimulus, and its association to symptoms, could lead to better targeted and more effective cognitive and behavioral interventions in early psychosis.

2. Methods and materials

2.1. Subjects

We included 71 adult first-episode psychosis patients receiving treatment in hospitals and outpatient clinics and 57 control subjects from the Helsinki Early Psychosis Study (Mäntylä et al., 2015; Raij et al., 2016; Rikandi et al., 2017). We excluded subjects with current or previous neurological disorders (based on an interview and MRI) and excessive head motion during scanning (framewise displacement >0.5 mm in >2.5% of time points). 12 patients and 4 control subjects were excluded due to movement. We also excluded unarguably substance induced psychotic disorders at baseline, with one patient receiving a substance induced psychosis diagnosis at 2-month follow-up. Psychosis was defined as a score of at least 4 in the items assessing unusual thought content (delusions) or hallucinations in the Brief Psychiatric Rating Scale, Expanded version 4.0 (BPRS) (Ventura et al., 1993). Diagnostic interviews were carried out by trained clinical professionals using the Structured Diagnostic Interview for DSM-IV (SCID) (First et al., 2002). All diagnoses were verified by a senior psychiatrist, together with the interviewer, including an extensive review of all available medical records. The medical records were also used to ensure that patients had no earlier psychiatric treatment contacts for psychosis. Imaging was done as soon as patients had commenced treatment and they were able to provide informed consent, typically within weeks of admission.

2.2. Functional imaging

The 3 T magnetic imaging was conducted at the Advanced Centre of Magnetic Imaging of Aalto University School of Science. Due to a pre-scheduled scanner change, imaging data was collected with two separate scanners. 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. We used the same imaging parameters for both scanners, acquiring whole-brain blood oxygen level–dependent (BOLD) signal data with a gradient echo-planar sequence (245 volumes, repetition time 1.8 s, echo time 30 ms, flip angle 75°, field of view 24 cm, matrix size 64 × 64, 36 slices with a thickness of 4 mm). 14 patients and 11 control subjects were imaged with the Signa VH/i scanner, and the remaining 57 patients and 46 control subjects were imaged using the MAGNETOM Skyra scanner. We included data from both scanners, as earlier multisite fMRI studies have shown it to be beneficial for increasing statistical power (Suckling et al., 2008). We also acquired T1-weighted structural images with 1-mm^3 isotropic voxels and T2-weighted structural images. More detailed imaging parameters and the description of the movie stimulus are presented in our earlier research (Mäntylä et al., 2018; Rikandi et al., 2017) as well as in Supplementary text A.1 and Supplementary Table C.1. We preprocessed the functional data using DPARSFA pipeline (Chao-Gan and Yu-Feng, 2010). Images were resliced, realigned and normalized to MNI template. We regressed out white matter and cerebral fluid signals and corrected for movement using Friston 24 (Friston et al., 1996).

2.3. Constructing functional connectivity matrices

For each subject, we created a 160 × 160 functional connectivity matrix according to a parcellation (division into nodes) of the brain included in the GraphVar software (Kruschwitz et al., 2015) that is based upon a meta-analysis of shared functionality across a range of tasks of different modality (Dosenbach et al., 2006, 2010). We applied a functionality-based (rather than anatomical) parcellation because it was more suitable given the goals and the stimulus of the present study. The parcellation consists of 160 5 mm radius nodes, divided into the default-mode network (34/160 nodes), sensorimotor network (33/160 nodes), occipital network (22/160 nodes), cerebellum (18/160 nodes) and two independent cognitive control networks, the fronto-parietal (21/160 nodes) and cingulo-opercular (32/160 nodes) networks (Fig. 1). The fronto-parietal network consists of the dorsolateral prefrontal cortex and parietal regions and may initiate and adapt control and to be related to error detection (Dosenbach et al., 2008). The cingulo-opercular network consists of the anterior insula/frontal operculum, dorsal anterior cingulate/medial superior frontal cortex and the anterior prefrontal cortex and may act as a “set maintenance” system, relating to the control

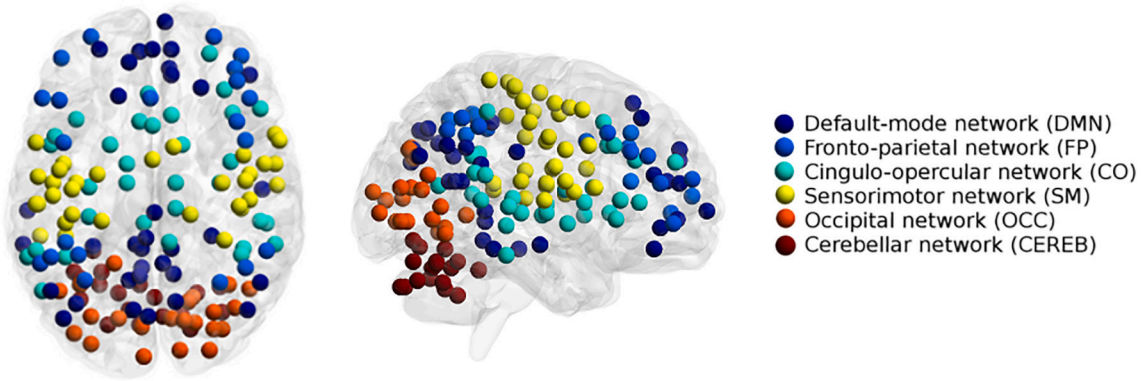


Fig. 1. Visualization of the 160 nodes of the parcellation and division into subnetworks by color codes.

of goal-oriented behavior (Dosenbach et al., 2008). The results of this study are presented and discussed according to the functionality and labeling of the parcellation. All node coordinates are available in the download package of GraphVar software (https://www.nitrc.org/projects/graphvar/).

We extracted BOLD signals from all seed regions using DPARSFA and constructed the connectivity matrices and performed all subsequent graph-metric analyses using GraphVar software (Kruschwitz et al., 2015). Links, or connections between nodes, were Fisher z-transformed Pearson correlation coefficients of the nodes' BOLD signals.

2.4. Between-group differences in functional connectivity

To identify subnetworks where functional connectivity is altered in patients, we used network-based statistics (Zalesky et al., 2010) as implemented in the GraphVar software. Network-based statistics is based upon the same underlying principles as traditional cluster-based thresholding. We identified all pairs of nodes where functional connectivity was significantly different between groups (using cluster-forming threshold of $p < 0.01$), generated randomized data with 5000 iterations and then extracted statistically significant (FDR $p < 0.05$) subnetworks, or graph components, in which all pairs of nodes of the network were interconnected by links that differed between groups.

2.5. Between-group differences in graph metrics

To identify differences between groups in graph metrics, we used the connectivity matrices to construct unweighted networks using relative thresholding (threshold value equals the percentage of the strongest connections, i.e., the highest correlation coefficients) in the range of 0.1–0.3 and steps of 0.01 (i.e., networks consisting of 10%, 11%, 12% … 30% of the strongest connections were created). Excluding weaker connections is recommended, as it reduces noise by including connections that are more likely to be relevant (Rubinov and Sporns, 2010). For each subject, we then calculated graph metrics to infer segregation, integration and centrality. Segregation was measured with global and local clustering, transitivity and modularity, and integration was measured with global and local characteristic path length, and centrality was measured with degree and betweenness (Bullmore and Sporns, 2009). Descriptions of the measures and variables are presented in Table 1. Group differences of each metric were analyzed on the whole-brain level. We constructed the networks and calculated graph measures using the Brain Connectivity Toolbox (Rubinov and Sporns, 2010) as implemented in the GraphVar software.

2.6. Symptom associations to graph metrics

To analyze the association between psychotic symptoms and network topology in patients, we constructed three symptom score variables. We used BPRS items to construct positive symptom scores and BPRS items combined with items for alogia, anhedonia and avolition-apathy from the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989) to construct negative symptom scores. The following symptom variables were constructed: Delusions and hallucinations (BPRS items 10 and 11), disorganization (BPRS items 12, bizarre behavior and 15, conceptual disorganization) and negative symptoms (BPRS item 16, blunted affect and the three SANS items). Symptom associations were analyzed on the whole-brain level.

Table 1
Descriptions of the measures and variables of the topological analysis.

Measure	Measure description	Variables	Variable description
Segregation	How specialized a node or a subnetwork is in its functioning	Global clustering	Mean value of the fraction of node's neighbors that are neighbors of each other
		Local clustering	Fraction of node's neighbors that are neighbors of each other
		Transitivity (global)	Ratio of triangles to triplets in the network
		Modularity	The degree to which the network can be subdivided into specialized delineated groups
Integration	How efficiently a node or a subnetwork combines information from different parts of the brain	Global characteristic path length	The average shortest path length in the network
		Local characteristic path length	Average shortest path length of the node to the rest of the network
Centrality	How centrally a node is positioned and how well it is connected to other nodes	Degree	Number of links connected to the node
		Betweenness	Number of inclusion in shortest paths

2.7. Statistical analyses

For all statistical analyses, we used general linear model (GLM) as implemented in the GraphVar software. We controlled all models for age, sex and scanner and conducted permutation analysis with 5000 iterations. We used FDR-corrected $p < 0.05$. Of the calculated graph (topological) metrics, we only report results that, after the multiple

comparison correction for all variables, thresholds and nodes, reached statistical significance in all network thresholds (i.e. we excluded results that were not consistently significant across thresholds), as interpreting results of single thresholds is not recommended by the developers of the software (Kruschwitz et al., 2015). The brain networks were visualized with the BrainNet Viewer (http://www.nitrc.org/projects/bnv/) (Xia et al., 2013).

3. Results

3.1. Descriptive statistics

Descriptive statistics of all subjects, CPZ equivalents (Leucht et al., 2016) and mean symptom scores are presented in Table 2. There were no statistical differences in the distribution of sex, mean age or mean head motion during scanning between patients and control subjects. Patients had slightly less years of education and clearly lower social and occupational functioning (Goldman et al., 1992). Subjects were predominantly Caucasian, with one patient being of non-European descent. Frequencies of different diagnoses, comorbidities and antipsychotic medication of patients are presented in Supplementary Table A.1. The most prevalent diagnoses were schizophrenia, schizophreniform disorder and psychotic disorder not otherwise specified. The most prevalent comorbidities were depressive disorders and anxiety or somatoform disorders.

3.2. Between-group differences in functional connectivity

We identified a statistically significant graph component of 64 nodes and 97 links (i.e. a statistically significant subnetwork of interconnected nodes connected with links, where functional connectivity differed between groups). The component predominantly consisted of links where patients had decreased functional connectivity (Fig. 2a). The nodes that had a high number of links were mostly situated in the cingulo-opercular network, sensorimotor network and default-mode network (Fig. 2b). Although the component contained nodes from all the subnetworks, the fronto-parietal, occipital and cerebellar networks were underrepresented. Most of the links were within the cingulo-opercular network and between the cingulo-opercular and sensorimotor network (Fig. 2 b). The links where patients had increased functional connectivity were mostly within the default-mode network and between the default-mode and fronto-parietal networks. The nodes with most links were situated bilaterally in the insula (node 73: 32, −12, 2; node 74: −30, −14, 1), bilaterally in the basal ganglia (node 66: −20, 6, 7; node 67: 14, 6, 7) and in the right prefrontal cortex (node 4: 9, 51, 16). Nodes with links to several other (three or more) networks (suggesting a hub region of the component) were situated in the right prefrontal cortex (node 4: 9, 51, 16; node 39: 39, 42, 16), the right inferior temporal lobe (node 12: 52, −5, −13) the left temporal lobe (node 86: −59, −47, 11), the right parietal lobe (node 81: 58, −41, 20), the right fusiform gyrus (node 79: 54, −31, −18) and bilaterally in the insula (node 73: 32, −12, 2; node 74: −30, −14, 1). Detailed information of the component, including all node coordinates, is presented in Supplementary Table B.1.

Table 2
Descriptive information of the subjects.

	FEP group *n* (%), mean ± SD	Control group *n* (%), mean ± SD	Test statistic	*P* value (two-tailed)
Sex (female)	24/71 (33.8%)	22/57 (38.6%)	$\chi 2 =$ 0.316	0.574
Age (yrs)	26.0 ± 5.7	26.8 ± 6.0	$t =$ 0.777	0.651
Head motion (FD)	0.090 ± 0.037	0.079 ± 0.023	$U =$ 0.925	0.355
Years of education	13.73 ± 3.16	14.97 ± 2.38	$t =$ 2.455	0.0154
Social and occupational functioning (SOFAS)	37.55 ± 8.65	86.54 ± 6.48	$t =$ 35.495	<0.0001
Ethnicity (Caucasian)	70/71 (98.6%)	57/57 (100%)		
Chlorpromazine equivalent (CPZE)	65/71 (91.5%), 374.771 ± 272.274			
Symptom scores	mean ± SD, 95% confidence interval			
Delusions and hallucinations	11.0 ± 2.7, 10.4–11.7			
Disorganization	5.1 ± 2.6, 4.5–5.7			
Negative symptoms	5.5 ± 3.7, 4.6–6.4			

SD = standard deviation, FEP = first-episode psychosis, FD = frame displacement.

3.3. Between-group differences in graph metrics

Patients had decreased centrality (degree) in the left mid-insula (node 74: −30, −14, 1) (Fig. 3a). Additionally, we observed significant between-group differences across all thresholds in several nodes that did not pass multiple comparisons correction. These results are presented in Fig. 3b, Supplementary text A.2.1 and in Supplementary Fig. 1.

3.4. Symptom associations with graph metrics

We found no statistically significant associations with symptom scores. However, we observed significant symptom associations across all thresholds in several nodes that did not survive multiple comparisons correction. These results are presented in Supplementary text A.2.2 and in Supplementary Figs. 2, 3 and 4.

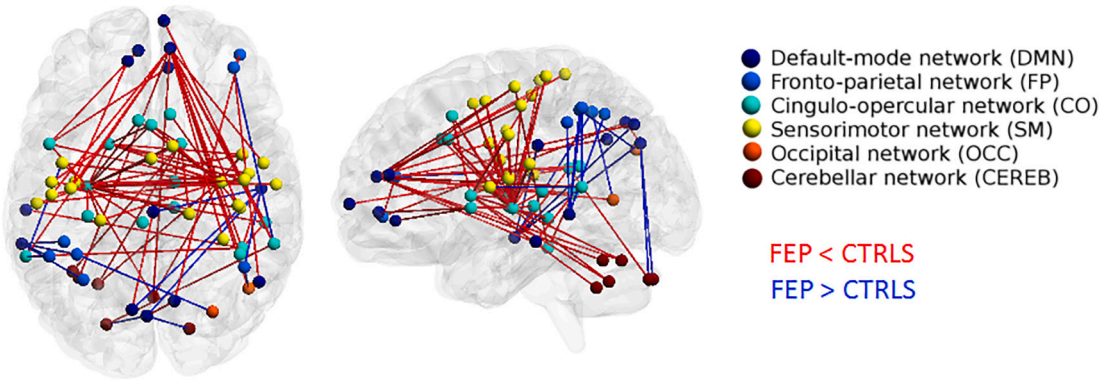
4. Discussion

We examined differences in brain functional connectivity and network topology between first-episode psychosis patients and control subjects during movie viewing and whether these measures associate with symptoms in the patients. Patients exhibited a pattern of predominantly decreased functional connectivity, concentrating in the nodes of the cingulo-opercular, sensorimotor and default-mode networks. The analysis of topology indicated decreased centrality of the left mid-insula. Our uncorrected results suggested additional group differences in centrality and integration and an association between symptom severity and centrality measures.

Disruptions in functional connectivity related to both nodes and links primarily concentrated in the cingulo-opercular network in the patient group. In the parcellation used here, the cingulo-opercular network is suggested to serve as a so-called “set maintenance” system that is involved in stable and sustained cognitive control across tasks of different modalities (Dosenbach et al., 2007, 2008). The network also includes regions typically involved in salience attribution (Seeley et al., 2007). One interpretation of our results therefore might suggest impaired ability in patients to sustain cognitive control over the processing of the complex stimulus, i.e., movie. Most of the links of decreased functional connectivity in patients were observed either within the nodes of the cingulo-opercular network or between the nodes of the cingulo-opercular and sensorimotor networks, suggesting perhaps a decreased or aberrant contribution of top-down systems involved in the processing of sensory information.

The cortical networks involved in sensorimotor gating appear to somewhat overlap with the nodes of the cingulo-opercular and

a)



b)

	Nodes in component (n)		Between-network links in component				
Network		Default mode	Fronto-parietal	Cingulo-opercular	Sensorimotor	Occipital	Cerebellum
Default mode	13	10	7	11	6	1	4
Fronto-parietal	7	7	2	2	0	2	0
Cingulo-opercular	17	11	2	34	34	0	6
Sensorimotor	19	6	0	34	2	0	0
Occipital	2	1	2	0	0	0	0
Cerebellum	6	4	0	6	0	0	0
	64	38	13	87	42	3	10

Fig. 2. a) Visualization of the observed graph component. Nodes are color-coded by subnetworks. Links are color-coded by decreased (red) or increased (blue) functional connectivity in patients. b) Frequencies of nodes and between-network links in the component.

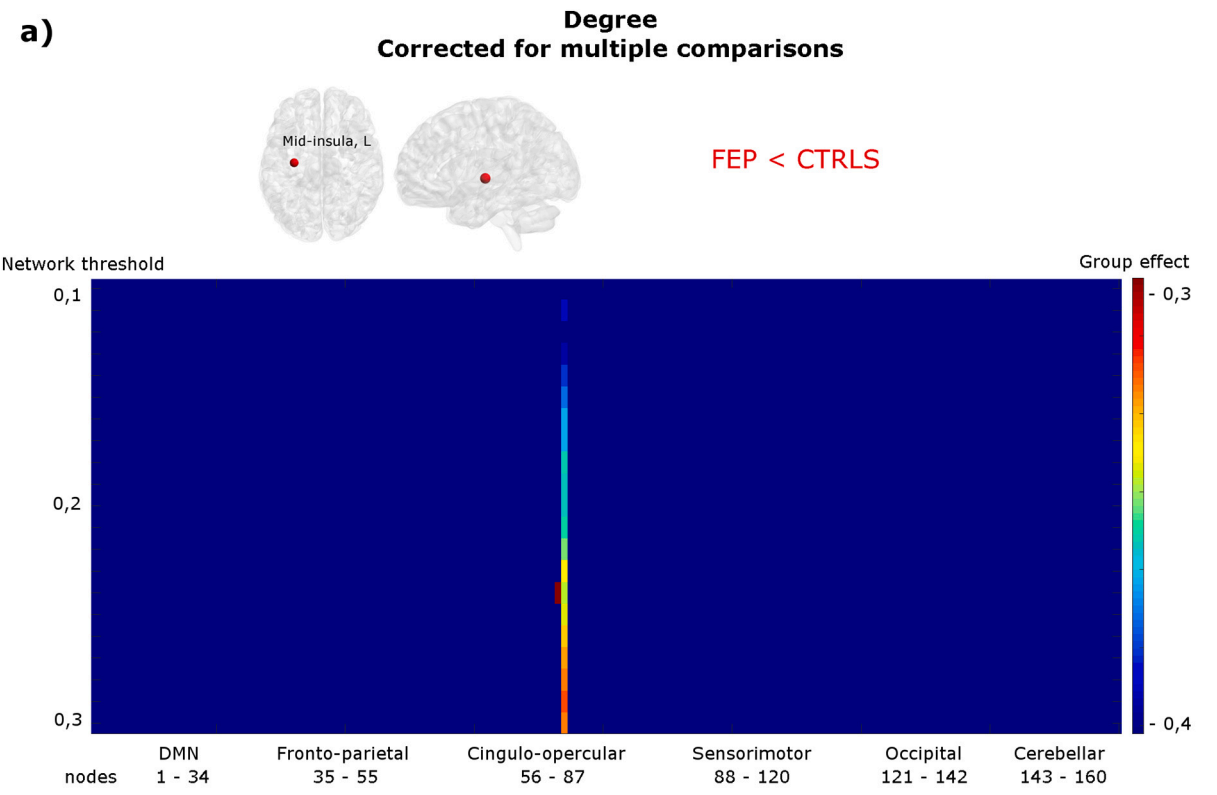
sensorimotor networks of our results (Campbell et al., 2007). Sensorimotor gating refers to the habituation of constant, unimportant stimuli, it has long been known to be impaired in patients with psychotic disorders (Braff et al., 1992) and is believed to be mediated by top-down higher order processes (Li et al., 2009). The impairment appears to be present already in the unmedicated first-episode psychosis patients (Hedberg et al., 2021) and is applicable across modalities (Haß et al., 2017). Our results might therefore reflect the impaired ability of patients to habitually ignore irrelevant aspects of the movie (i.e., impaired sensorimotor gating), a description of a cognitive skill similar to salience attribution (Kapur, 2003).

Our findings involving functional connectivity are in many aspects in concurrence with earlier research using resting-state fMRI, suggesting widespread patterns of mainly decreased functional connectivity in psychotic disorders (Dong et al., 2018; van den Heuvel and Fornito, 2014) and disruptions in neurocircuitry related to cognitive control and integrative hubs in psychiatric disorders (McTeague et al., 2017). Interestingly, the results are more descriptive of the widespread hypoconnectivity patterns associated with advanced stages of psychotic disorders (Anticevic et al., 2015; T. Li et al., 2016). We observed the default-mode network having decreased links to all other subnetworks, supporting earlier views of the network acting as a collection of hubs (Crossley et al., 2016) whose functioning is altered in psychotic disorders (Bouttier et al., 2021; Whitfield-Gabrieli and Ford, 2012). We found some links of increased functional connectivity in patients, most of which were between nodes within the default-mode network. The results add to earlier findings of less deactivation of the default-mode network in psychosis (Anticevic et al., 2012; Whitfield-Gabrieli et al., 2009). Recent findings suggest that similar neural responses in the default-mode network between subjects are associated with shared interpretation of ambiguous narratives (Nguyen et al., 2019). Our results might be therefore indicative of aberrant narrative building in early psychosis.

The most robust of our topological measure findings was the between-group difference in the involvement of the left mid-insula. We observed decreased local degree of the node in patients, indicating reduced centrality. The insula is involved in salience attribution (Perini et al., 2018; Seeley et al., 2007), sustained cognitive control (Dosenbach et al., 2008) and known to be affected in psychotic disorders (Palaniyappan and Liddle, 2012). Furthermore, functional connectivity patterns of the insula have been shown to contribute to the differentiation of patients with psychotic disorders (Mikolas et al., 2016; Stoyanov et al., 2021). The left mid-insula specifically has been associated with task inhibition (Niendam et al., 2012), perception and response to positive emotional stimuli as well as several interoceptive, body-related functions and feelings (Avery et al., 2015; Craig, 2011; Duerden et al., 2013). Our results might therefore indicate a less central and less specialized role of the region in patients when processing the movie stimulus, perhaps reflecting diminished ability of sustained emotional salience attribution.

Our uncorrected results imply that the decreased centrality of the insula in patients could be bilateral and extend to several other nodes. Interestingly, also in the uncorrected results, one node with increased centrality and integration in patients exhibited an association between positive symptom severity and centrality. The node is situated in the left posterior region of the fronto-parietal network and overlaps with the precuneus. In a recent meta-analysis, both the left insula and the precuneus were implicated as displaying aberrant activity in first-episode psychosis patients during cognitive tasks (Soldevila-Matías et al., 2020). This result is also in line with our earlier findings, where in a subset of the same data, precuneus transient BOLD signal changes during movie viewing effectively differentiated patients and control subjects (Rikandi et al., 2017).

Arguably, using movie stimulus provokes more complex information processing than the resting state or simple tasks and thus provides novel insight into underlying functional brain dynamics related to several



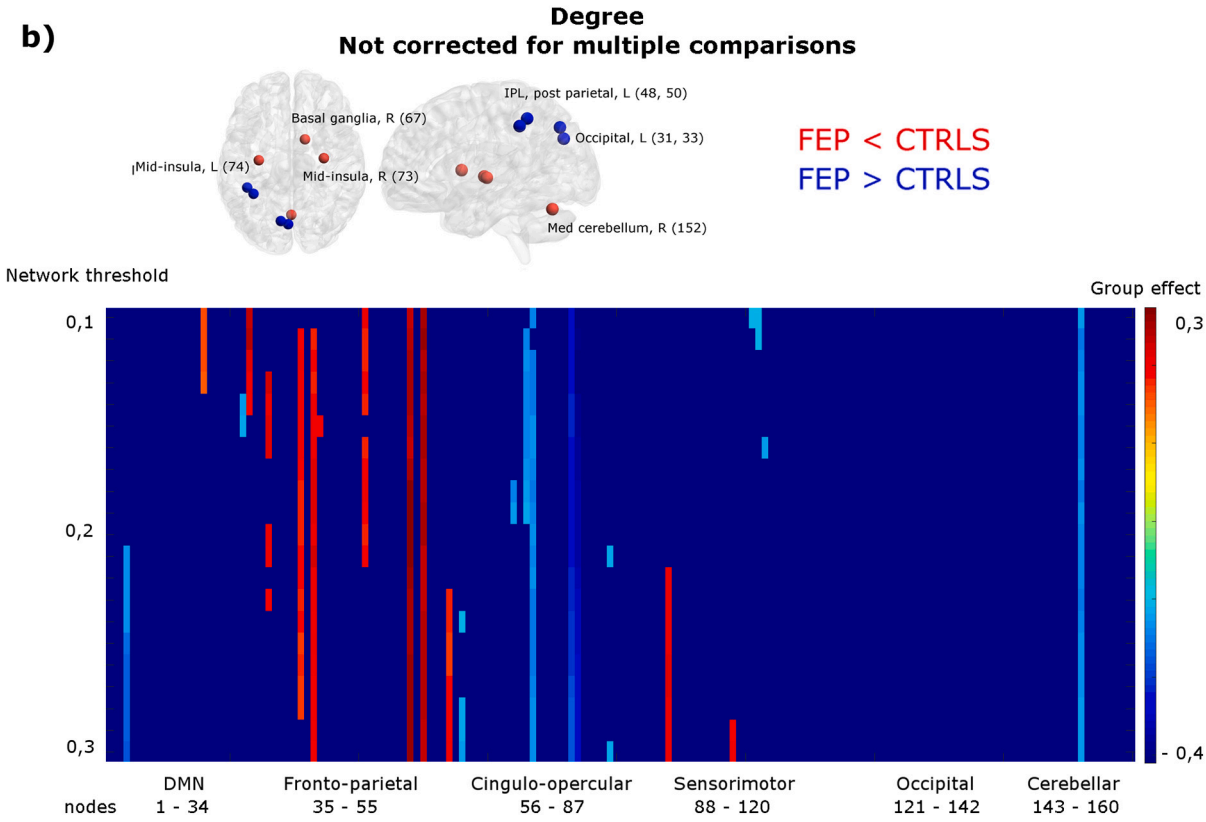


Fig. 3. a) Between-group differences in degree across all thresholds, corrected for multiple comparisons, b) not corrected for multiple comparisons.

cognitive processes. Cognitive and behavioral interventions have been shown to be effective in the treatment of psychotic disorders (Kurtz et al., 2016; Wykes et al., 2011) and understanding neuronal correlates of aberrant cognitive control and sensory processes already present during first-episode psychosis, could add to better targeted and earlier interventions. Our results suggest that during movie viewing, patients might have less co-activation of brain subnetworks related to sustained cognitive control, possibly related to emotional cues or salience attribution and habituation to non-relevant external stimuli. Therefore, early cognitive and behavioral interventions including training of ignoring irrelevant stimuli or recognizing emotionally relevant cues may prove useful in the future.

5. Limitations

The complexity of the naturalistic stimulus poses a challenge in attributing our results to any specific features of the movie. In this context, and overall, inferring cognitive processes from neuroimaging data should be approached with caution (Poldrack, 2006). It also remains unsolved, to which extent our results would overlap with resting state data. It should also be noted that network topology is fairly dependent both on the parcellation as well as how the networks are constructed. Fragmentation, or disconnected components at some densities, could have biased our results.

6. Conclusions

During naturalistic movie viewing, first-episode psychosis patients have widespread decreased functional connectivity, possibly related to impaired ability to sustain cognitive control or ignore irrelevant stimuli. Patients also have changes in functional network topology, suggesting less specialized functioning in one, possibly several regions, in some cases associated with increased symptoms. In the long run, understanding underlying functional brain dynamics of naturalistic information processing in early psychosis might contribute to better targeted cognitive and behavioral interventions.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2022.01.006.

Role of the funding source

This work was supported by the Sigrid Jusélius Foundation (J.S., E. R.), the Finnish Cultural Foundation (J.S. and T.M.), European Union Seventh Framework Programme (FP7/2007–2013), grant agreement no 602478 (J.S.), the Jalmari and Rauha Ahokas Foundation (T.M.), the Doctoral Program Brain and Mind of the University of Helsinki (T.M.), the Yrjö Jahnsson Foundation (#6781 to M.L.), the Päivikki and Sakari Sohlberg Foundation (M.L.), the Academy of Finland (#278171 to J.S. and T.T.R.) and the Finnish Medical Foundation (T.T.R.)

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

CRediT authorship contribution statement

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

Declaration of competing interest

All authors declare that they have no conflicts of interest.

Acknowledgement

We thank all the participants. We thank Tuula Mononen and Sanna Järvinen for coordinating the data collection and interviews, Marjut Grainger for data management and Marita Kattelus for technical assistance.

References

Andreasen, N.C., 1989. The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations. Br. J. Psychiatry 155 (S7), 49–52.
Anticevic, A., Cole, M.W., Murray, J.D., Corlett, P.R., Wang, X.-J., Krystal, J.H., 2012. The role of default network deactivation in cognition and disease. Trends Cogn. Sci. 16 (12), 584–592. https://doi.org/10.1016/j.tics.2012.10.008.
Anticevic, A., Hu, X., Xiao, Y., Hu, J., Li, F., Bi, F., Cole, M.W., Savic, A., Yang, G.J., Repovs, G., 2015. Early-course unmedicated schizophrenia patients exhibit elevated prefrontal connectivity associated with longitudinal change. J. Neurosci. 35 (1), 267–286.
Avery, J.A., Kerr, K.L., Ingeholm, J.E., Burrows, K., Bodurka, J., Simmons, W.K., 2015. A common gustatory and interoceptive representation in the human mid-insula. Hum. Brain Mapp. 36 (8), 2996–3006.
Baker, J.T., Holmes, A.J., Masters, G.A., Yeo, B.T., Krienen, F., Buckner, R.L., Öngür, D., 2014. Disruption of cortical association networks in schizophrenia and psychotic bipolar disorder. JAMA Psychiatry 71 (2), 109–118.
Baldassano, C., Hasson, U., Norman, K.A., 2018. Representation of real-world event schemas during narrative perception. J. Neurosci. 38 (45), 9689–9699. https://doi.org/10.1523/JNEUROSCI.0251-18.2018.
Bouttier, V., Duttagupta, S., Denève, S., Jardri, R., 2021. Circular inference predicts nonuniform overactivation and dysconnectivity in brain-wide connectomes. Schizophr. Res. https://doi.org/10.1016/j.schres.2020.12.045.
Braff, D.L., Grillon, C., Geyer, M.A., 1992. Gating and habituation of the startle reflex in schizophrenic patients. Arch. Gen. Psychiatry 49 (3), 206–215. https://doi.org/10.1001/archpsyc.1992.01820030038005.
Bullmore, E., Sporns, O., 2009. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat. Rev. Neurosci. 10 (3), 186–198. https://doi.org/10.1038/nrn2575.
Campbell, L.E., Hughes, M., Budd, T.W., Cooper, G., Fulham, W.R., Karayanidis, F., Hanlon, M.-C., Stojanov, W., Johnston, P., Case, V., Schall, U., 2007. Primary and secondary neural networks of auditory prepulse inhibition: a functional magnetic resonance imaging study of sensorimotor gating of the human acoustic startle response. Eur. J. Neurosci. 26 (8), 2327–2333. https://doi.org/10.1111/j.1460-9568.2007.05858.x.
Chao-Gan, Y., Yu-Feng, Z., 2010. DPARSF: a MATLAB toolbox for "Pipeline" data analysis of resting-state fMRI. Front. Syst. Neurosci. 4, 13. https://doi.org/10.3389/fnsys.2010.00013.
Coyle, J.T., Ruzicka, W.B., Balu, D.T., 2020. Fifty years of research on schizophrenia: the ascendance of the glutamatergic synapse. Am. J. Psychiatr. 177 (12), 1119–1128. https://doi.org/10.1176/appi.ajp.2020.20101481.
Craig, A.D., 2011. Significance of the insula for the evolution of human awareness of feelings from the body. Ann. N. Y. Acad. Sci. 1225 (1), 72–82.
Crossley, N.A., Mechelli, A., Ginestet, C., Rubinov, M., Bullmore, E.T., McGuire, P., 2016. Altered hub functioning and compensatory activations in the connectome: a meta-analysis of functional neuroimaging studies in schizophrenia. Schizophr. Bull. 42 (2), 434–442.
Dong, D., Wang, Y., Chang, X., Luo, C., Yao, D., 2018. Dysfunction of large-scale brain networks in schizophrenia: a meta-analysis of resting-state functional connectivity. Schizophr. Bull. 44 (1), 168–181. https://doi.org/10.1093/schbul/sbx034.
Dosenbach, N.U., Visscher, K.M., Palmer, E.D., Miezin, F.M., Wenger, K.K., Kang, H.C., Burgund, E.D., Grimes, A.L., Schlaggar, B.L., Petersen, S.E., 2006. A core system for the implementation of task sets. Neuron 50 (5), 799–812.
Dosenbach, N.U.F., Fair, D.A., Miezin, F.M., Cohen, A.L., Wenger, K.K., Dosenbach, R.A. T., Fox, M.D., Snyder, A.Z., Vincent, J.L., Raichle, M.E., Schlaggar, B.L., Petersen, S. E., 2007. Distinct brain networks for adaptive and stable task control in humans. Proc. Natl. Acad. Sci. 104 (26), 11073–11078. https://doi.org/10.1073/pnas.0704320104.
Dosenbach, N.U.F., Fair, D.A., Cohen, A.L., Schlaggar, B.L., Petersen, S.E., 2008. A dual-networks architecture of top-down control. Trends Cogn. Sci. 12 (3), 99–105. https://doi.org/10.1016/j.tics.2008.01.001.
Dosenbach, N.U., Nardos, B., Cohen, A.L., Fair, D.A., Power, J.D., Church, J.A., Nelson, S. M., Wig, G.S., Vogel, A.C., Lessov-Schlaggar, C.N., 2010. Prediction of individual brain maturity using fMRI. Science 329 (5997), 1358–1361.
Duerden, E.G., Arsalidou, M., Lee, M., Taylor, M.J., 2013. Lateralization of affective processing in the insula. NeuroImage 78, 159–175.
Farahani, F.V., Karwowski, W., Lighthall, N.R., 2019. Application of graph theory for identifying connectivity patterns in human brain networks: a systematic review. Front. Neurosci. 13 https://doi.org/10.3389/fnins.2019.00585.
First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B., 2002. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. SCID-I/P New York, NY, USA.
Fornito, A., Yoon, J., Zalesky, A., Bullmore, E.T., Carter, C.S., 2011. General and specific functional connectivity disturbances in first-episode schizophrenia during cognitive control performance. Biol. Psychiatry 70 (1), 64–72.
Friston, K.J., 1998. The disconnection hypothesis. Schizophr. Res. 30 (2), 115–125.

Friston, K.J., Williams, S., Howard, R., Frackowiak, R.S., Turner, R., 1996. Movement-related effects in fMRI time-series. Magn. Reson. Med. 35 (3), 346–355.
Goldman, H.H., Skodol, A.E., Lave, T.R., 1992. Revising axis V for DSM-IV: a review of measures of social functioning. Am. J. Psychiatry 149, 9.
Gong, Q., Hu, X., Pettersson-Yeo, W., Xu, X., Lui, S., Crossley, N., Wu, M., Zhu, H., Mechelli, A., 2017. Network-level dysconnectivity in drug-naive first-episode psychosis: dissociating transdiagnostic and diagnosis-specific alterations. Neuropsychopharmacology 42 (4), 933.
Haß, K., Bak, N., Szycik, G.R., Glenthøj, B.Y., Oranje, B., 2017. Deficient prepulse inhibition of the startle reflex in schizophrenia using a cross-modal paradigm. Biol. Psychol. 128, 112–116. https://doi.org/10.1016/j.biopsycho.2017.07.016.
Hasson, U., Nir, Y., Levy, I., Fuhrmann, G., Malach, R., 2004. Intersubject synchronization of cortical activity during natural vision. Science (New York, N.Y.) 303 (5664), 1634–1640. https://doi.org/10.1126/science.1089506.
Hedberg, M., Imbeault, S., Erhardt, S., Schwieler, L., 2021. Disrupted sensorimotor gating in first-episode psychosis patients is not affected by short-term antipsychotic treatment. Schizophr. Res. 228, 118–123. https://doi.org/10.1016/j.schres.2020.12.009.
Kang, S.S., Sponheim, S., 2017. 55. Abnormal claustral–cortical functional brain networks in people with schizophrenia during perception and resting: brain network dynamics underlying psychotic symptoms. Schizophr. Bull. 43 (suppl_1) https://doi.org/10.1093/schbul/sbx021.074. S28–S29.
Kapur, S., 2003. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am. J. Psychiatr. 160 (1), 13–23. https://doi.org/10.1176/appi.ajp.160.1.13.
Kruschwitz, J.D., List, D., Waller, L., Rubinov, M., Walter, H., 2015. GraphVar: a user-friendly toolbox for comprehensive graph analyses of functional brain connectivity. J. Neurosci. Methods 245, 107–115.
Kurtz, M.M., Gagen, E., Rocha, N.B.F., Machado, S., Penn, D.L., 2016. Comprehensive treatments for social cognitive deficits in schizophrenia: a critical review and effect-size analysis of controlled studies. Clin. Psychol. Rev. 43, 80–89. https://doi.org/10.1016/j.cpr.2015.09.003.
Lahnakoski, J.M., Glerean, E., Jääskeläinen, I.P., Hyönä, J., Hari, R., Sams, M., Nummenmaa, L., 2014. Synchronous brain activity across individuals underlies shared psychological perspectives. NeuroImage 100, 316–324. https://doi.org/10.1016/j.neuroimage.2014.06.022.
Leucht, S., Samara, M., Heres, S., Davis, J.M., 2016. Dose equivalents for antipsychotic drugs: the DDD method. Schizophr. Bull. 42 (suppl_1), S90–S94.
Li, L., Du, Y., Li, N., Wu, X., Wu, Y., 2009. Top–down modulation of prepulse inhibition of the startle reflex in humans and rats. Neurosci. Biobehav. Rev. 33 (8), 1157–1167. https://doi.org/10.1016/j.neubiorev.2009.02.001.
Li, T., Wang, Q., Zhang, J., Rolls, E.T., Yang, W., Palaniyappan, L., Zhang, L., Cheng, W., Yao, Y., Liu, Z., 2016. Brain-wide analysis of functional connectivity in first-episode and chronic stages of schizophrenia. Schizophr. Bull. 43 (2), 436–448.
Lord, L.-D., Allen, P., Expert, P., Howes, O., Broome, M., Lambiotte, R., Fusar-Poli, P., Valli, I., McGuire, P., Turkheimer, F.E., 2012. Functional brain networks before the onset of psychosis: a prospective fMRI study with graph theoretical analysis. Neuroimage Clin. 1 (1), 91–98.
Lynall, M.-E., Bassett, D.S., Kerwin, R., McKenna, P.J., Kitzbichler, M., Muller, U., Bullmore, E., 2010. Functional connectivity and brain networks in schizophrenia. J. Neurosci. 30 (28), 9477–9487. https://doi.org/10.1523/JNEUROSCI.0333-10.2010.
Malinen, S., Hlushchuk, Y., Hari, R., 2007. Towards natural stimulation in fMRI—issues of data analysis. NeuroImage 35 (1), 131–139. https://doi.org/10.1016/j.neuroimage.2006.11.015.
Mäntylä, T., Mantere, O., Raij, T.T., Kieseppä, T., Laitinen, H., Leiviskä, J., Torniainen, M., Tuominen, L., Vaarala, O., Suvisaari, J., 2015. Altered activation of innate immunity associates with white matter volume and diffusion in first-episode psychosis. PLoS One 10 (5), e0125112.
Mäntylä, T., Nummenmaa, L., Rikandi, E., Lindgren, M., Kieseppä, T., Hari, R., Suvisaari, J., Raij, T.T., 2018. Aberrant cortical integration in first-episode psychosis during natural audiovisual processing. Biol. Psychiatry 84 (9), 655–664.
McTeague, L.M., Huemer, J., Carreon, D.M., Jiang, Y., Eickhoff, S.B., Etkin, A., 2017. Identification of common neural circuit disruptions in cognitive control across psychiatric disorders. Am. J. Psychiatry 174 (7), 676–685. https://doi.org/10.1176/appi.ajp.2017.16040400.
Mikolas, P., Melicher, T., Skoch, A., Matejka, M., Slovakova, A., Bakstein, E., Hajek, T., Spaniel, F., 2016. Connectivity of the anterior insula differentiates participants with first-episode schizophrenia spectrum disorders from controls: a machine-learning study. Psychol. Med. 46 (13), 2695.
Morgan, S.E., White, S.R., Bullmore, E.T., Vértes, P.E., 2018. A network neuroscience approach to typical and atypical brain development. Biol. Psychiatry 3 (9), 754–766. https://doi.org/10.1016/j.bpsc.2018.03.003.
Nguyen, M., Vanderwal, T., Hasson, U., 2019. Shared understanding of narratives is correlated with shared neural responses. NeuroImage 184, 161–170.
Niendam, T.A., Laird, A.R., Ray, K.L., Dean, Y.M., Glahn, D.C., Carter, C.S., 2012. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. Cogn. Affect. Behav. Neurosci. 12 (2), 241–268. https://doi.org/10.3758/s13415-011-0083-5.
O'Neill, A., Mechelli, A., Bhattacharyya, S., 2018. Dysconnectivity of large-scale functional networks in early psychosis: a meta-analysis. Schizophr. Bull. https://doi.org/10.1093/schbul/sby094 sby094–sby094.
Palaniyappan, L., Liddle, P.F., 2012. Does the salience network play a cardinal role in psychosis? An emerging hypothesis of insular dysfunction. J. Psychiatry Neurosci. 37 (1), 17–27. https://doi.org/10.1503/jpn.100176.
Palaniyappan, L., Marques, T.R., Taylor, H., Mondelli, V., Reinders, A.S., Bonaccorso, S., Giordano, A., DiForti, M., Simmons, A., David, A.S., 2016. Globally efficient brain organization and treatment response in psychosis: a connectomic study of gyrification. Schizophr. Bull. 42 (6), 1446–1456.
Peeters, S.C., Gronenschild, E.H., Amelsvoort, T., Os, J., Marcelis, M., 2016. Reduced specialized processing in psychotic disorder: a graph theoretical analysis of cerebral functional connectivity. Brain Behav. 6 (9).
Perini, I., Gustafsson, P.A., Hamilton, J.P., Kämpe, R., Zetterqvist, M., Heilig, M., 2018. The salience of self, not social pain, is encoded by dorsal anterior cingulate and insula. Sci. Rep. 8 (1), 6165. https://doi.org/10.1038/s41598-018-24658-8.
Poldrack, R.A., 2006. Can cognitive processes be inferred from neuroimaging data? Trends Cogn. Sci. 10 (2), 59–63.
Raichle, M.E., 2015. The brain's default mode network. Annu. Rev. Neurosci. 38, 433–447.
Raij, T.T., Mäntylä, T., Mantere, O., Kieseppä, T., Suvisaari, J., 2016. Cortical salience network activation precedes the development of delusion severity. Psychol. Med. 46 (13), 2741–2748.
Rikandi, E., Pamilo, S., Mäntylä, T., Suvisaari, J., Kieseppä, T., Hari, R., Seppä, M., Raij, T.T., 2017. Precuneus functioning differentiates first-episode psychosis patients during the fantasy movie Alice in wonderland. Psychol. Med. 47 (3), 495–506.
Rikandi, E., Mäntylä, T., Lindgren, M., Kieseppä, T., Suvisaari, J., Raij, T.T., 2018. Connectivity of the precuneus-posterior cingulate cortex with the anterior cingulate cortex-medial prefrontal cortex differs consistently between control subjects and first-episode psychosis patients during a movie stimulus. Schizophr. Res. 199, 235–242.
Rotarska-Jagiela, A., van de Ven, V., Oertel-Knöchel, V., Uhlhaas, P.J., Vogeley, K., Linden, D.E.J., 2010. Resting-state functional network correlates of psychotic symptoms in schizophrenia. Schizophr. Res. 117 (1), 21–30. https://doi.org/10.1016/j.schres.2010.01.001.
Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: uses and interpretations. NeuroImage 52 (3), 1059–1069.
Sanchez-Alonso, S., Rosenberg, M.D., Aslin, R.N., 2021. Functional connectivity patterns predict naturalistic viewing versus rest across development. NeuroImage 117630. https://doi.org/10.1016/j.neuroimage.2020.117630.
Satterthwaite, T.D., Baker, J.T., 2015. How can studies of resting-state functional connectivity help us understand psychosis as a disorder of brain development? Curr. Opin. Neurobiol. 30, 85–91.
Seeley, W.W., 2019. The salience network: a neural system for perceiving and responding to homeostatic demands. J. Neurosci. 39 (50), 9878–9882.
Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., Greicius, M.D., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J. Neurosci. 27 (9), 2349–2356. https://doi.org/10.1523/JNEUROSCI.5587-06.2007.
Simony, E., Honey, C.J., Chen, J., Lositsky, O., Yeshurun, Y., Wiesel, A., Hasson, U., 2016. Dynamic reconfiguration of the default mode network during narrative comprehension. Nat. Commun. 7, 12141.
Soldevila-Matías, P., Albajes-Eizagirre, A., Radua, J., García-Martí, G., Rubio, J.M., Tordesillas-Gutierrez, D., Fuentes-Durá, I., Solanes, A., Fortea, L., Oliver, D., Sanjuán, J., 2020. Precuneus and insular hypoactivation during cognitive processing in first-episode psychosis: systematic review and meta-analysis of fMRI studies. Rev. Psiquiatr. Salud Ment. https://doi.org/10.1016/j.rpsm.2020.08.001.
Sonkusare, S., Breakspear, M., Guo, C., 2019. Naturalistic stimuli in neuroscience: critically acclaimed. Trends Cogn. Sci. 23 (8), 699–714. https://doi.org/10.1016/j.tics.2019.05.004.
Stoyanov, D., Aryutova, K., Kandilarova, S., Paunova, R., Arabadzhiev, Z., Todeva-Radneva, A., Kostianev, S., Borgwardt, S., 2021. Diagnostic task specific activations in functional MRI and aberrant connectivity of insula with middle frontal gyrus can inform the differential diagnosis of psychosis. Diagnostics 11 (1), 95.
Su, T.-W., Hsu, T.-W., Lin, Y.-C., Lin, C.-P., 2015. Schizophrenia symptoms and brain network efficiency: a resting-state fMRI study. Psychiatry Res. Neuroimaging 234 (2), 208–218. https://doi.org/10.1016/j.pscychresns.2015.09.013.
Suckling, J., Ohlssen, D., Andrew, C., Johnson, G., Williams, S.C., Graves, M., Chen, C.-H., Spiegelhalter, D., Bullmore, E., 2008. Components of variance in a multicentre functional MRI study and implications for calculation of statistical power. Hum. Brain Mapp. 29 (10), 1111–1122.
van den Heuvel, M.P., Fornito, A., 2014. Brain networks in schizophrenia. Neuropsychol. Rev. 24 (1), 32–48. https://doi.org/10.1007/s11065-014-9248-7.
Ventura, J., Green, M.F., Shaner, A., Liberman, R.P., 1993. Training and quality assurance with the brief psychiatric rating scale: "the drift busters". Int. J. Methods Psychiatr. Res. 3 (4), 221–244.
Whitfield-Gabrieli, S., Ford, J.M., 2012. Default mode network activity and connectivity in psychopathology. Annu. Rev. Clin. Psychol. 8 (1), 49–76. https://doi.org/10.1146/annurev-clinpsy-032511-143049.
Whitfield-Gabrieli, S., Thermenos, H.W., Milanovic, S., Tsuang, M.T., Faraone, S.V., McCarley, R.W., Shenton, M.E., Green, A.I., Nieto-Castanon, A., LaViolette, P., 2009. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. Proc. Natl. Acad. Sci. 106 (4), 1279–1284.
Woodward, N.D., Rogers, B., Heckers, S., 2011. Functional resting-state networks are differentially affected in schizophrenia. Schizophr. Res. 130 (1), 86–93.
Wykes, T., Huddy, V., Cellard, C., McGurk, S.R., Czobor, P., 2011. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. Am. J. Psychiatry 168 (5), 472–485. https://doi.org/10.1176/appi.ajp.2010.10060855.

Xia, M., Wang, J., He, Y., 2013. BrainNet viewer: a network visualization tool for human brain connectomics. PLoS One 8 (7), e68910.
Yang, Z., Wu, J., Xu, L., Deng, Z., Tang, Y., Gao, J., Hu, Y., Zhang, Y., Qin, S., Li, C., Wang, J., 2020. Individualized psychiatric imaging based on inter-subject neural synchronization in movie watching. NeuroImage 216, 116227. https://doi.org/10.1016/j.neuroimage.2019.116227.
Zalesky, A., Fornito, A., Bullmore, E.T., 2010. Network-based statistic: identifying differences in brain networks. NeuroImage 53 (4), 1197–1207. https://doi.org/10.1016/j.neuroimage.2010.06.041.