

Modular-Level Functional Connectome Alterations in Individuals With Hallucinations Across the Psychosis Continuum

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Functional connectome alterations, including modular network organization, have been related to the experience of hallucinations. It remains to be determined whether individuals with hallucinations across the psychosis continuum exhibit similar alterations in modular brain network organization. This study assessed functional connectivity matrices of 465 individuals with and without hallucinations, including patients with schizophrenia and bipolar disorder, nonclinical individuals with hallucinations, and healthy controls. Modular brain network organization was examined at different scales of network resolution, including (1) global modularity measured as Q_{\max} and Normalised Mutual Information (NMI) scores, and (2) within- and between-module connectivity. Global modular organization was not significantly altered across groups. However, alterations in within- and between-module connectivity were observed for higher-order cognitive (e.g., central-executive salience, memory, default mode), and sensory modules in patients with schizophrenia and nonclinical individuals with hallucinations relative to controls. Dissimilar patterns of altered within- and between-module connectivity were found bipolar disorder patients with hallucinations relative to controls, including the visual, default mode, and memory network, while connectivity patterns between visual, salience, and cognitive control modules were unaltered. Bipolar disorder patients without hallucinations did not show significant alterations relative to controls. This study provides evidence for alterations in the modular organization of the

functional connectome in individuals prone to hallucinations, with schizophrenia patients and nonclinical individuals showing similar alterations in sensory and higher-order cognitive modules. Other higher-order cognitive modules were found to relate to hallucinations in bipolar disorder patients, suggesting differential neural mechanisms may underlie hallucinations across the psychosis continuum.

Key words: transdiagnostic/bipolar disorder/schizophrenia/resting-state/top-down and bottom-up processing

Introduction

Hallucinations are experienced in a range of clinical disorders, with prevalence rates of 60–80% in patients with schizophrenia and 50–60% in bipolar disorder,¹⁻⁴ which can severely impact quality of life.⁵ A minority (5–15%) of individuals without a need for care also report hallucinations.⁶⁻⁸ Consequently, hallucinations have been suggested to exist along a psychosis continuum, ranging from nonpathological experiences in the general population to severe psychotic disorders.⁹ Patients with bipolar disorder might hold a position in between both ends of this spectrum. Thus far, most studies have investigated hallucinations within specific diagnoses. A comparison across the psychosis continuum may enhance our understanding of transdiagnostic neural mechanisms related to

hallucinations, which can contribute to better treatment options, and could enhance development of computational models of hallucinations.^{10–12}

Network connectomics can be a valuable tool to investigate complex neural phenomena such as hallucinations.^{13,14} This study investigated hallucinations across the psychosis continuum using a network approach, with a particular focus on the modular organization. As rest, large-scale functional networks form identifiable modules,¹⁵ communities of brain regions that are strongly interconnected and share relatively low connectivity with regions outside of their module.^{16,17} An altered modular organization is suggested to underlie psychotic symptoms, such as hallucinations.^{18–21}

Firstly, alterations of the global modular network organization with regard to hallucinations were investigated. Previous studies have investigated the global modular organization in the context of psychotic disorders in general, showing alterations in schizophrenia, individuals at high risk for psychosis, and bipolar disorder.^{22–24}

Secondly, alterations in within- and between-module connectivity were investigated. Prior functional MRI (fMRI) studies have reported hyperactivation in the sensory cortex during the experience of hallucinations in schizophrenia and nonclinical individuals.^{25–27} This observation generated theories that hallucinations may result from neuronal activity in sensory cortices that is not adequately controlled by higher-order cognitive modules.^{28–32} Previous functional connectivity studies have indeed shown that hallucinations in schizophrenia may be related to abnormal connectivity and organization of large-scale brain modules, including the central-executive, default-mode, salience, memory, and sensory modules.^{31–40} Dynamic fMRI studies corroborate these findings by showing altered interactions between the default-mode and central-executive networks in hallucinating patients with schizophrenia.^{41–44} To summarize, these studies have shown that hallucinations in schizophrenia stem from altered top-down and bottom-up processing,²⁸ reflected by altered interactions within- and between sensory and higher-order cognitive networks.

As of yet, it remains to be determined if similar connectivity alterations in modular organization are found in hallucinating individuals with other psychiatric diagnoses and in nonclinical individuals, which would suggest a shared neural mechanism across the psychosis continuum. To this end, resting-state fMRI scans of 465 individuals were obtained, including patients with schizophrenia, bipolar-I disorder, nonclinical individuals with a lifetime history of hallucinations, as well as healthy controls without hallucinations. We hypothesized that individuals with hallucinations would show transdiagnostic alterations in the modular network organization as compared to healthy controls, including: 1) global modular organization and; 2) within- and between-module connectivity. Specifically between sensory and higher-order

cognitive modules, including the auditory, visual, default-mode, and central-executive networks, regardless of diagnosis.

Methods and Materials

Subjects

The study sample consisted of 465 subjects, including 73 patients with bipolar-I disorder with a lifetime history of hallucinations (BD-H), 40 patients with bipolar-I disorder without a lifetime history of hallucinations (BD), 95 patients with a schizophrenia spectrum disorder and lifetime hallucinations (SCZ-H), 35 nonclinical individuals with hallucinations (NC-H), and 222 healthy controls without hallucinations (HC). All subjects were at least 18 years of age and provided written informed consent. Participants were recruited as part of five different studies, all carried out at the Department of Psychiatry of the University Medical Center Utrecht. See [supplementary material](#) for details on recruitment and study procedures.

The presence of lifetime hallucinations was assessed by trained researchers using the Comprehensive Assessment of Symptoms and History Interview (CASH⁴⁵) or Structured Clinical Interview for DSM-IV (SCID⁴⁶), both comparable semi-structured interviews assessing symptomatology and hallucination modality. Hallucination severity was determined with the Positive and Negative Syndrome Scale (PANSS⁴⁷) in schizophrenia patients, and with the Psychotic Symptoms Rating Scales (PSYRATS⁴⁸) in nonclinical individuals.

Data Acquisition and Preprocessing

See the [supplementary methods](#) for more information on data acquisition, preprocessing, and motion correction strategies.

Functional Network Construction

We used $N = 264$ regions of Power atlas.¹⁵ The procedures of the functional network construction are described in the [supplementary methods](#).

Global Modular Organization

Using a modularity maximization method,⁴⁹ we identified brain network modules with a Louvain-like greedy algorithm⁵⁰ implemented in MATLAB.⁵¹ Details are described in the [supplementary methods](#)

First, modularity value Q^w was calculated to assess how well the network can be subdivided into modules. Q^w of the weighted network, with N nodes for a given module partition, is defined as the proportion of edges G that fall within modules, subtracted by the proportion that would be expected due to random chance.¹⁶ The Q^w value ranges from 0–1, with a value close to 1 indicating a

strongly modular network. As a rule of thumb, networks with a maximum value of $Q^{\max} \geq 0.3$ are considered to be modular networks.¹⁶

Second, to examine whether the composition of nodes into modules differed across groups, we calculated Normalized Mutual Information (NMI⁵²) scores. Significant differences in NMI scores between the participant groups (i.e., NC-H, SCZ-H, BD-H, BD) and healthy controls would suggest group-differences in the composition of modules.

MATLAB tools developed by Danielle Bassett's group (available at <http://www.danibassett.com/resources.html>) were used to compute a consensus modularity partitioning and calculate NMI scores.

Within- and Between-Module Connectivity

We used a priori determined modules of the Power atlas¹⁵ to examine alterations in within- and between modules in relation to hallucinations. See [figure 1](#) for an overview of the fourteen modules. In this study, we left out the “uncertain” module, and hence calculated all measures across the remaining thirteen modules, including: 1) *within-module* connectivity for each module; and 2) *between-module* connectivity between each pair of modules. Within-module connectivity was calculated as the mean connectivity strength of all connections between nodes within a module and is a measure of the functional cohesion of a module. Between-connectivity was calculated as the mean connectivity strength of all nodes in one module to all nodes of another module and thus reflects inter-modular integration.

To examine differences in within- and between-module connectivity in relation to hallucinations, we 1) compared each of the four participant groups (NC-H, SCZ-H,

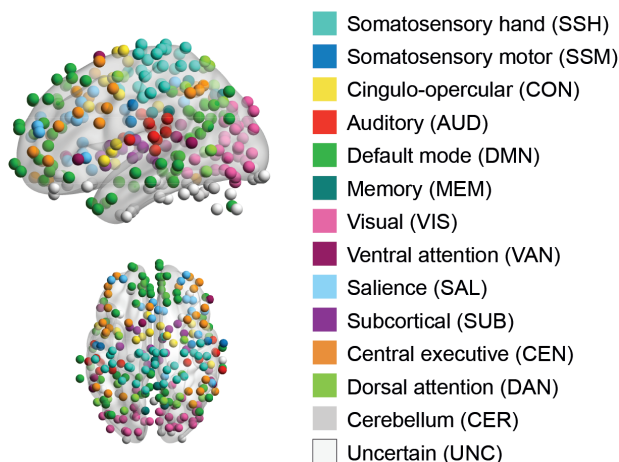


Fig. 1. A priori based modules of the Power atlas used for within- and between-module connectivity. Each node ($N = 264$) is color-coded according to their a-priori defined module label as determined by Power et al. (2011).¹⁵ This image was made in BrainNetViewer.

BD-H, BD) with the healthy controls; 2) directly compared the various hallucinating groups with each other (NC-H, SCZ-H, BD-H); and 3) as an exploratory analysis, we compared participants with and without (lifetime) hallucinations *within* diagnostic groups (BD-H versus BD; SCZ-H versus SCZ). As all schizophrenia patients experienced lifetime hallucinations, we were not able to divide this group into a strict “current versus lifetime” hallucinations group. Instead, we divided the schizophrenia group based on PANSS⁴⁷ item-P3, such that current hallucinations are defined as P3-score > 3 , and not-currently hallucinating patients as those with a P3-score < 3 (“lifetime”). The latter results are reported in the [supplementary results](#) and [supplementary figure 6](#).

Symptom Correlates

Symptom correlates between functional connectivity, PANSS and PSYRATS-items are reported in the [supplementary material](#).

Statistical Analysis

Permutation testing was used to examine significant differences in Q^{\max} , NMI scores, and within- and between module connectivity. This statistical method is well-suited for analyzing unbalanced designs, including differences in sample sizes between groups, without losing power.⁵³ All permutation testing was done using 10 000 permutations at $P < .05$, False Discovery Rate (FDR) corrected. Age and sex were regressed out of the data before permutation testing, see [supplementary material](#) for more details.

NMI scores were calculated between all possible pairs of participants within the same group (e.g., SCZ-H) to calculate a true mean within-group NMI. Group labels were then randomly permuted 10 000 times, after which the permuted mean within-group NMI was calculated in the combined groups (e.g., SCZ-H and CTRL). P -values were computed as the number of iterations where the permuted mean within-group NMI was higher than the empirical within-group NMI, divided by the total number of permutations.

To assess within- and between-module connectivity, group labels were randomly permuted 10 000 times and mean within- and between-module connectivity values were calculated in each iteration, resulting in an empirical (null-)distribution of group-differences that can arise under the null-hypothesis. P -values were calculated as the proportion of iterations in which the permuted mean within- and between-module connectivity was greater than the empirical mean within-module connectivity. To correct for multiple testing, results are reported at $P < .05$ false discovery rate (FDR). To assess whether a more stringent correction would change the nature of our findings, we report results corrected for Family Wise Error (FWE) in [supplementary figure 2](#).

Results

Participants

A total of 465 participants were included in this study, see [table 1](#) for an overview of demographic and clinical characteristics. A total of 84.2% of the SCZ-H group; 52.1% in BD-H and 22.5% in BD used antipsychotics medication. In the BD-H group, 56.2% used lithium, compared to 65% in the BD group.

The hallucinating groups also differed in hallucinatory modality ($P < .001$ for both auditory and visual modalities), as SCZ-H patients and NC-H reported a higher percentage of auditory hallucinations (80% and 100% against 53% for bipolar patients), whereas the NC-H group reported the highest percentage of visual hallucinations (80%), against 69.9% and 52.6% for BD-H and SCZ-H group.

Global Modular Organization

The networks of all participants exhibited a modular community structure reflected by Q^{\max} values ≥ 0.3 , see [supplementary figure 2](#). Modularity was not significantly different across any of the participant groups compared to HC: SCZ-H patients ($P = 0.570$); NC-H ($P = .918$), BD-H ($P = .876$), and BD ($P = .816$), see [figure 2a](#) for the maximum Q^{\max} score per group.

As compared to HC, NMI scores did not show significant differences in SCZ-H patients ($P = .962$), NC-H ($P = .985$), BD-H ($P = .079$) and BD ($P = .272$), see [figure 2b](#). This finding was not influenced by differences in age, sex, and duration of illness across the groups, see [supplementary material](#) for more details.

Table 1. Participant Characteristics on Demographic and Clinical Variables ($n = 465$)^a.

	SCZ-H ($n = 95$)	BD-H ($n = 73$)	BD ($n = 40$)	NC-H ($n = 35$)	HC ($n = 222$)	<i>P</i> value
Age, mean (SD), years	32.5 (10.9)	46.5 (11.4)	51.6 (11.8)	42.1 (15.0)	40.8 (14.5)	<.001*
Sex, m/f	64/31	36/37	21/19	9/26	119/103	.001*
Handedness, R/L	81/8	65/8	33/7	26/9	185/36	.128
Duration of illness, years	9.3 (9.7)	15.9 (12.9)	1	NA	NA	<.001*
Motion, mm						
Relative mean displacement ^b	0.1 (0.04)	0.1 (0.03)	0.1 (0.04)	0.1 (0.03)	0.1 (0.03)	<.001*
Diagnosis, No. (%)						
Schizophrenia	57 (60.0)					
Schizoaffective disorder	15 (15.8)					
Schizophreniform disorder	1 (1.1)					
Schizotypal personality	1 (1.1)					
Psychosis NOS	20 (21.1)					
Bipolar-I disorder		73 (100)	40 (100)			
Medication, No. (%)				NA	NA	
Antipsychotics	80 (84.2)	38 (52.1)	9 (22.5)			
Lithium	5 (5.3)	41 (56.2)	26 (65.0)			
Anti-depressants	21 (22.1)	16 (21.9)	10 (25.0)			
Hallucinations lifetime, No. (%)						
Auditory	95 (100)	73 (100)	0 (0.0)	35 (100)	0 (0.0)	<.001*
Visual	76 (80.0)	39 (53.4)	0 (0.0)	35 (100)	0 (0.0)	<.001*
Hallucinations current, No. (%)						
Delusions lifetime, No. (%)	50 (52.6)	51 (69.9)	0 (0.0)	28 (80.0)	0 (0.0)	<.001*
Childhood trauma scores, mean (SD)	68 (71.6)	63 (86.3)	0 (0.0)	12 (34.3)	1 (0.5)	

Note: NC-H, nonclinical individuals with hallucinations; BD-H, bipolar-I disorder with lifetime history of hallucinations; BD, bipolar-I disorder without lifetime history of hallucinations; SCZ-H, schizophrenia spectrum disorder with hallucinations.

^aDifferences between continuous variables were tested with a one-way ANOVA, and differences in dichotomous variables with Chi-square tests.

^bThe relative root mean square (RMS) displacement was calculated by FSL MCFLIRT. Significance was set at $P < .05$. Significant differences are indicated by an asterisk (*). Current hallucinations includes experiences in the last month. The current hallucinations in the SCZ-H were based on the $P3 > 2$ PANSS, and in NC-H with the frequency item of the PSYRATS. Number of cases with missing data: Duration of illness $n = 16$ SCZ-H; $n = 55$ BD-H; $n = 39$ BD; Diagnosis $n = 1$ SCZ-H; Antipsychotics $n = 10$ HC; $n = 5$ SCZ-H; $n = 3$ BD-H; $n = 1$ BD. Lithium $n = 10$ HC; $n = 6$ SCZ-H. Antidepressants; $n = 10$ HC; $n = 16$ SCZ-H; Lifetime hallucinations $n = 4$ HC; Auditory $n = 4$ HC; $n = 11$ SCZ-H; $n = 2$ BD-H. Visual $n = 5$ HC; $n = 15$ SCZ-H. Olfactory $n = 5$ HC; $n = 17$ SCZ-H. Tactile $n = 5$ HC; $n = 14$ SCZ-H. Current hallucinations: SCZ-H = 23. Lifetime delusions; $n = 5$ HC; $n = 3$ NC-H; $n = 21$ SCZ-H; childhood trauma; $n = 74$ HC; $n = 10$ NC-H; $n = 78$ SCZ-H; $n = 2$ BD-H; BD = 2.

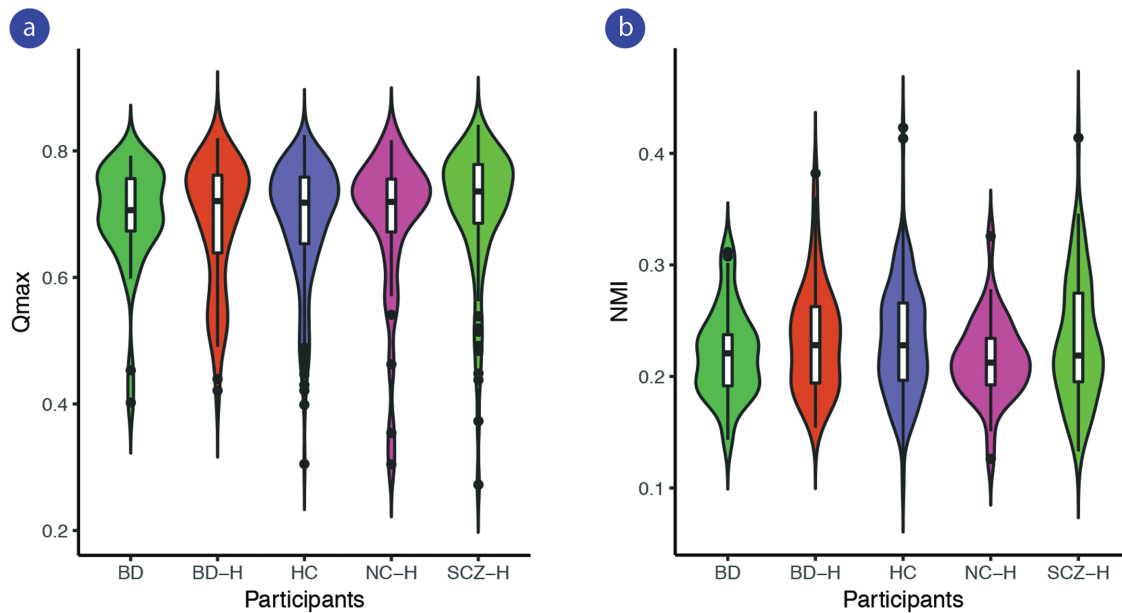


Fig. 2. Global modular organization scores per participant group. Violin plots depict the distribution of a) Qmax and b) NMI scores per participant group. De white boxes within the violin plots indicate the mean and standard deviations. All plots were generated before controlling for age and gender. None of the groups differed significantly at $P < .05$ (after regressing out age and sex, corrected for multiple comparison). These plots were generated using R package ggplot. Abbreviations: BD bipolar disorder without hallucinations; BD-H bipolar disorder with hallucinations; NC-H nonclinical individuals with hallucinations; NMI normalised mutual information; SCZ-H schizophrenia spectrum disorder with hallucinations.

Within- and Between-Module Connectivity

We found significantly altered within- and between-module connectivity in participants with hallucinations compared to HC. SCZ-H and NC-H groups showed increased within-module connectivity of the somatosensory and auditory modules. Increased between-module connectivity was found between the auditory module and several higher-order cognitive (i.e., central-executive, salience, memory, cingulo-opercular), default-mode, somatosensory, and subcortical modules, suggesting decreased segregation between these modules. Furthermore, decreased between-module connectivity was found between the visual module and higher-order cognitive (i.e., central-executive, salience), default-mode and subcortical modules in NC-H and SCZ-H, suggesting increased segregation between these modules. See [figure 3a](#) for an overview of the significant alterations in NC-H and SCZ-H. The corresponding FDR-corrected P -values of these alterations can be found in [supplementary figure 2a](#).

In BD-H patients compared to HC, we observed increased between-module connectivity of the visual, memory, cerebellar and default-mode modules and increased within-module connectivity of both the memory and visual network, suggesting decreased segregation between these modules. Decreased connectivity between the auditory and somatosensory module was observed in BD-H compared to HC, suggesting increased segregation. We did not observe any alterations in within- or between-module connectivity in the BD relative to HC. See [table 2](#) and [figure 3a](#) for the alterations in both groups

of BD patients, and [supplementary figure 5a](#) for the corresponding P -values.

When comparing the hallucination groups with each other, NC-H and SCZ-H participants did not significantly differ in within- and between-module connectivity, see [figure 3b](#). Both NC-H and SCZ-H showed similar alterations to BD-H participants. SCZ-H participants showed increased connectivity between sensory (i.e., auditory) and higher-order cognitive modules (i.e., cingulo-opercular, dorsal attention, salience), suggesting decreased segregation between auditory and higher-order cognitive modules compared to BD-H. Specifically, cingulo-opercular and ventral attention modules showed significantly altered connectivity to other modules. NC-H showed similar alterations when compared to BD-H participants. In these individuals, the somatosensory and dorsal attention modules showed most altered connections to other modules, see [figure 3b](#).

Discussion

The aim of this study was to investigate whether individuals with hallucinations across the psychosis continuum show similar alterations in global modular network organization, and within- and between-module connectivity. We did not find differences in global modular network organization across any of the hallucination groups compared to controls, meaning that the level of modularity was similar across groups and the nodes of the brain network were similarly partitioned into modules. We found that sensory modules (i.e., auditory and visual) showed

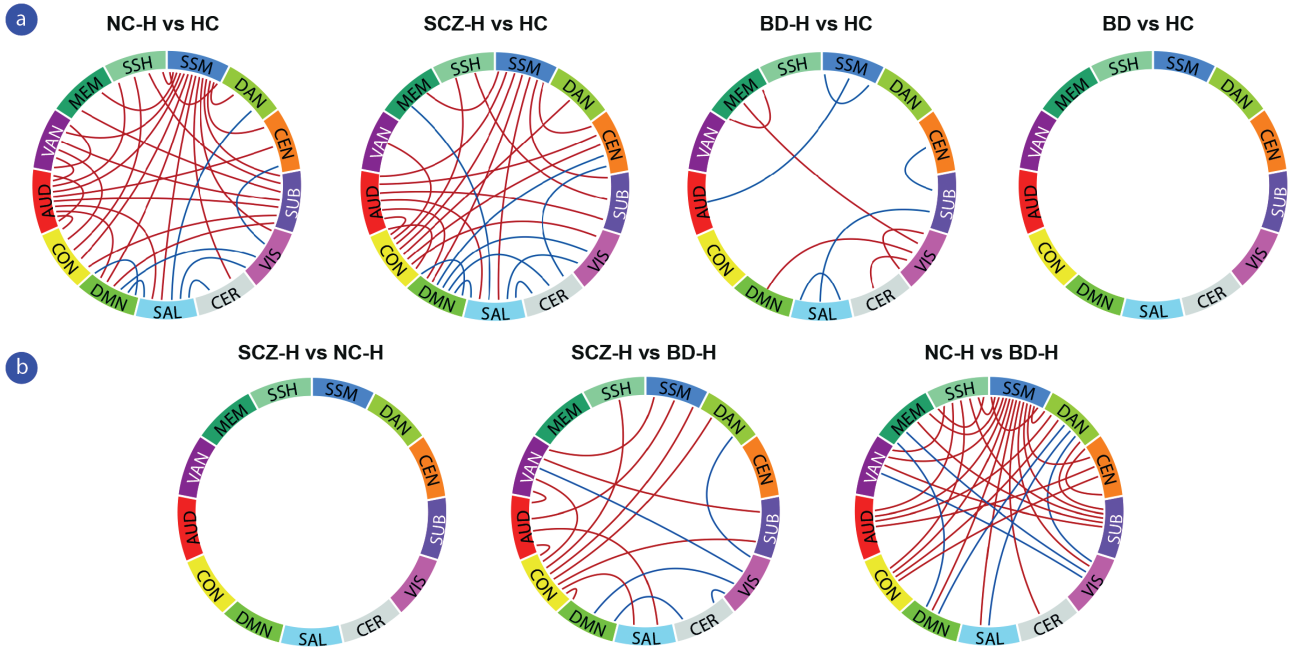


Fig. 3. Within- and between-module connectivity disturbances. Alterations in within-and between-modules connectivity of the 13 modules of the Power atlas. In panel A, the clinical and nonclinical groups are contrasted with healthy controls; 1) nonclinical individuals with hallucinations ($n = 35$) vs healthy controls ($n = 222$); 2) schizophrenia patients with hallucinations ($n = 95$) vs healthy controls ($n = 222$); 3) bipolar-I disorder patients with hallucinations ($n = 73$) vs healthy controls ($n = 222$). 4) bipolar-I disorder patients without hallucinations ($n = 40$) did not differ from controls ($n = 222$). In panel B, the groups with hallucinations are contrasted with each other; 5) schizophrenia patients with hallucinations ($n = 95$) vs nonclinical individuals with hallucinations ($n = 35$); 6) schizophrenia patients with hallucinations ($n = 95$) vs bipolar-I disorder patients with hallucinations ($n = 73$); 7) nonclinical individuals with hallucinations ($n = 35$) vs bipolar-I disorder patients with hallucinations ($n = 73$). The connections in the circle plot are color-coded based on either an increase (red) or decrease (blue) in modular connectivity when comparing the first group (e.g., NC-H) to the latter group (e.g., HC). Group differences were tested at a significance level of $P < .05$, FDR corrected. Age and sex were regressed out of the data before permutation testing. Connections within modules are indicated by lines that connect one side of the rim segment to the other. These images were created in Keynote. Abbreviations: AUD auditory; BD bipolar-I disorder without lifetime history of hallucinations; BD-H bipolar-I disorder with lifetime history of hallucinations; CEN central-executive network; CER cerebellum; CON cingulo-opercular network; DAN dorsal attention network; DMN default-mode network; HC healthy controls; MEM memory; NC-H nonclinical individuals with hallucinations; SAL salience; SCZ-H schizophrenia spectrum disorder with hallucinations; SSH somatosensory hand; SSM somatosensory mouth; SUB subcortical; VAN ventral attention network; VIS visual. For a color version of this figure, see the online version of this paper.

altered connectivity with higher-order cognitive modules (i.e., central-executive, cingulo-opercular, salience, memory) in all hallucinating individuals across conditions, suggesting altered top-down/bottom-up processing. These higher-order cognitive modules were altered in non-clinical individuals and schizophrenia patients but not in bipolar disorder patients. In bipolar disorder patients, connectivity alterations were found between the memory, default-mode, and visual module. As such, hallucinations appeared to be related to connectivity alterations within and between sensory and higher-order cognitive modules. However, different higher-order cognitive modules were involved in bipolar disorder as compared to schizophrenia and nonclinical individuals. Taken together, our results suggest that hallucinations do not share the same neural mechanism across the psychosis continuum.

Contrary to previous studies on global modular organization,^{22,23,54} we did not find alterations of the global modular organization. Both more^{18,19,21} and less²⁰ modular brain

networks have been suggested to underlie psychotic symptoms. A *more* modular brain could lead to a fragmented brain network that gives rise to autonomous modules which reverberate the same output into the brain's information flow, thus leading to hallucinations.^{18,19,21} In contrast, a *less* modular brain could result in an overflow of information transfer between modules, e.g. the auditory and language system, thereby contributing to hallucinations.²⁰ Our data do not support either of these hypotheses.

Our findings on within- and between-module connectivity corroborate and extend findings from prior resting-state studies on hallucinations. Consistent with previous studies in schizophrenia, we report significant alterations in the central-executive, salience, memory, and default-mode network related to the experience of hallucinations.^{33,34,36-40,55,56} In line with previous dynamic fMRI studies,⁴¹⁻⁴⁴ we report altered connectivity of the central-executive and default-mode modules in both the non-clinical and schizophrenia group. An imbalance between

Table 2. Degree of Each Module per Hallucinating Group as Compared to Healthy Controls^a

Module	NC-H (<i>n</i> = 35)	SCZ-H (<i>n</i> = 95)	BD-H (<i>n</i> = 73)
SSM	4	2	0
AUD	13	7	2
SUB	5	8	0
DMN	9	6	1
SAL	6	7	1
CON	2	2	2
VAN	4	3	4
SSH	5	1	0
VIS	6	6	2
CEN	7	3	2
MEM	3	5	0
DAN	2	1	0
CER	2	3	1

Note: AUD, auditory; BD-H, bipolar-I disorder with lifetime history of hallucinations; CEN, central-executive network; CER, cerebellum; CON, cingulo-opercular network; DAN, dorsal attention network; DMN, default mode network; mem, memory; NC-H, nonclinical individuals with hallucinations; SAL, salience; SCZ-H, schizophrenia spectrum disorder with hallucinations; SSH, somatosensory hand; SSM, somatosensory mouth; SUB, subcortical; VAN, ventral attention network; VIS, visual.

^aDegree refers to the number of connections that were found to be altered for this particular module compared to healthy controls. For example, a degree of 5 means that this module had 5 within- or between- connections that were significantly altered compared to healthy controls.

these modules could enhance the focus on internal processes, e.g., auditory processing, thereby leading to hallucinations.⁴⁴ Evidence for the involvement of the salience module in hallucinations is inconsistent, with some studies reporting decreased connectivity between the salience and the default-mode network,⁵⁷ whereas others do not find altered connectivity.⁵⁸ Increased recruitment of the somatosensory network may contribute to a more general misattribution of inner signals to external sources, possibly leading to hallucinations.⁵⁹

In line with Diederer et al.,²⁷ we do not report differences in functional connectivity alterations between nonclinical individuals and schizophrenia patients, thereby not confirming the existence of a psychosis continuum in terms of functional brain alterations. This is in contrast to previous structural MRI findings on nonclinical individuals, which show these individuals to hold an intermediate phenotype.^{60,61}

A different neural mechanism was found for bipolar disorder patients with hallucinations, including involvement of memory and visual modules. This can be explained by the high percentage of bipolar patients who reported visual hallucinations. Memory regions have also been implicated in auditory hallucinations in schizophrenia.^{36,62,63} Unintentional activation of memories may be conveyed to the visual cortex leading to hallucinations in bipolar disorder patients.^{64,65} In line with our

findings, Palaniyappan et al. report involvement of salience and executive control networks in schizophrenia, but not in psychotic bipolar disorder.⁶⁶ Both unique and similar neural correlates were reported for schizophrenia and psychotic bipolar disorder in general, regardless of hallucinations.^{67–69} Ma et al. found similar patterns of connectivity between schizophrenia, bipolar and major depressive disorder, showing the value of connectomics research across diagnoses.²⁴

Contrary to earlier findings, we do not report significant differences between nonhallucinating bipolar patients and healthy controls.⁷⁰ Both hallucinating and nonhallucinating bipolar patients were scanned in euthymic phase, which could have influenced connectivity.⁷¹ Together with the fact that the sample size of the nonhallucinating bipolar patients (*n* = 40) was much smaller than the hallucinating bipolar patients (*n* = 73), this could have contributed to the null-finding in the nonhallucinating bipolar patients.

Our findings can be interpreted in light of the bottom-up/top-down processing theoretical model. According to the bottom-up/top-down theory, hallucinations can arise from an imbalance between bottom-up (sensory) and top-down (higher-order cognitive) information processing. Our findings are in line with such an imbalance and provide additional evidence for altered bottom-up/top-down processing with regard to hallucinations in schizophrenia and nonclinical individuals.¹³ Altered higher-order cognitive control over sensory modules could lead to reverberation of sensory information, meaning that prior beliefs are misinterpreted as sensory observations.¹¹ In support of this theory, previous studies have shown difficulties in inhibitory control as measured by cognitive tasks in schizophrenia^{72–75} and nonclinical individuals.^{76,77} Reduced inhibitory control is also reported in bipolar disorder during manic phases,⁷⁸ but to a lesser extent in euthymic phases.⁷⁹

Some methodological considerations should be taken into account. Limitations regarding clinical symptoms, duration of illness, demographic variables are discussed in Schutte et al.⁴⁰ and in the [supplementary discussion](#).

As we combined scans of several studies retrospectively, this led to differences in hallucinatory state. None of the bipolar disorder patients experienced hallucinations at the time of scanning. Some nonclinical individuals and schizophrenia patients experienced hallucinations in the week prior to scanning, which could bias results in these groups toward state-differences. Nonetheless, we did not find a correlation between connectivity and clinical hallucination-scores, suggesting that our results more likely reflect trait-related alterations.^{80,81}

Another limitation concerns differences in hallucinatory modality. Bipolar disorder patients and nonclinical individuals reported more visual hallucinations, whereas schizophrenia patients reported more auditory hallucinations. Previous studies show that altered resting-state

connectivity in the auditory, language, cognitive control, memory, and salience regions are linked to auditory hallucinations.^{31,32} However, similar networks have been implicated in visual hallucinations, suggesting a domain-general mechanism for hallucinations in addition to modality-specific alterations in sensory regions or networks.^{31,55,82–84} Future research should focus on the heterogeneity in modality and phenomenology,⁸⁵ as both can vary widely across diagnoses.^{86,87} Nonclinical individuals often report less negative content compared to schizophrenia patients,⁸⁸ which could be reflected by connectivity alterations in the salience³¹ or subcortical networks. Hallucinations in bipolar disorder may have different phenomenological characteristics and neural mechanisms when occurring either during a manic or depressive episode, as hallucinations are typically mood-congruent.⁸⁹ Future studies can assess differences in phenomenology across disorders using the Questionnaire for Psychotic Experiences (QPE).⁸⁷ Variations in phenomenology could affect functional connectivity alterations in (disorder-specific) networks, such as the cingulo-opercular or somatosensory network.⁹⁰

Motion during scanning can affect clinical studies as patients and healthy controls show different degrees of movement.^{91,92} Our analyses indicated that the residual effects of motion were minimal. We also re-run our analyses by adding motion as an additional regressor as supplementary analyses. These analyses yielded similar results, except that bipolar patients with hallucinations demonstrated less altered connectivity. Therefore, our results of a different neural mechanism for bipolar disorder should be interpreted with caution. Future studies are needed to elucidate the neural mechanism for hallucinations in bipolar disorder. Secondly, whereas a 10 mm diameter sphere is comparable to previous studies,¹⁵ the extracted functional signal can be noisy due to white matter voxels. Future studies may thus consider a range of different smaller sphere diameters to assess the potential impact of sphere magnitude on the results.

In conclusion, schizophrenia patients and non-clinical individuals with hallucinations demonstrate a largely overlapping dysconnectivity pattern, characterized by increased connectivity between higher-order cognitive and sensory processing modules. Bipolar-I disorder patients show a markedly different pattern, with increased connectivity between default-mode, memory, and visual modules, suggesting that a different mechanism may underlie hallucinations in bipolar disorder. More insight into the underlying transdiagnostic neural mechanisms could eventually guide treatment options.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin* online.

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