Title
Abnormal Information Flow in Schizophrenia Is Linked to Psychosis.

Journal
Schizophrenia Bulletin, 48(6)

Authors
Subramaniam, Karuna
Kudo, Kiwamu
Hinkley, Leighton
et al.

Publication Date
2022-11-18

DOI
10.1093/schbul/sbac075

Peer reviewed

Schizophrenia Bulletin vol. 48 no. 6 pp. 1384–1393, 2022
https://doi.org/10.1093/schbul/sbac075
Advance Access publication September 8, 2022

Abnormal Information Flow in Schizophrenia Is Linked to Psychosis

Yingxin Jia[1], Kiwamu Kudo[1,2], Leighton B.N. Hinkley[1], Melissa Fisher[3], Sophia Vinogradov[3], Srikantan Nagarajan[1], and Karuna Subramaniam[*,4]

[1]Department of Radiology and Biomedical Imaging, University of California, San, Francisco, CA 94143, USA; [2]Medical Imaging Business Center, Ricoh Company, Ltd., Kanazawa, Japan; [3]Department of Psychiatry, University of Minnesota, Minneapolis, MN 55454, USA; [4]Department of Psychiatry, University of California, San Francisco, CA 94143, USA

*To whom correspondence should be addressed; Department of Psychiatry, University of California, San Francisco, 513 Parnassus Avenue, HSE604, San Francisco, CA 94143, USA; tel: 1-415-476-6888, fax: 1-415-502-4302, e-mail: karuna.subramaniam@ucsf.edu

***Background and Hypothesis*: Prior research has shown that patients with schizophrenia (SZ) show disruption in brain network connectivity that is thought to underlie their cognitive and psychotic symptoms. However, most studies examining functional network disruption in schizophrenia have focused on the temporally correlated coupling of the strength of network connections. Here, we move beyond correlative metrics to assay causal computations of connectivity changes in directed neural information flow, assayed from a neural source to a target in SZ. *Study Design*: This study describes a whole-brain magnetoencephalography-imaging approach to examine causal computations of connectivity changes in directed neural information flow between brain regions during resting states, quantified by phase-transfer entropy (PTE) metrics, assayed from a neural source to an endpoint, in 21 SZ compared with 21 healthy controls (HC), and associations with cognitive and clinical psychotic symptoms in SZ. *Study Results*: We found that SZ showed significant disruption in information flow in alpha (8–12 Hz) and beta (12–30 Hz) frequencies, compared to HC. Reduced information flow in alpha frequencies from the precuneus to the medio-ventral occipital cortex was associated with more severe clinical psychopathology (ie, positive psychotic symptoms), while reduced information flow between insula and middle temporal gyrus was associated with worsening cognitive symptoms. *Conclusions*: The present findings highlight the importance of delineating dysfunction in neural information flow in specific oscillatory frequencies between distinct regions that underlie the cognitive and psychotic symptoms in SZ, and provide potential neural biomarkers that could lead to innovations in future neuromodulation treatment development.**

Key words: psychotic symptoms/resting-state MEG/phase-transfer entropy

Introduction

Schizophrenia is a debilitating psychiatric disorder in which patients suffer from severe cognitive and psychotic symptoms, thought to result from functional dysconnectivity (ie, disrupted temporally correlated neural oscillatory frequency patterns).[1,2] However, the neural underpinnings of the causes and directionality of this functional dysconnectivity remain unknown. Current medications are inadequate with up to 40% of patients with schizophrenia (SZ) remaining symptomatic,[3] thus compelling the need to understand the neurobiology underlying cognitive and psychotic symptoms in SZ. One of the most consistent well-replicated findings in the literature suggests that psychosis arises from aberrant salience processing that results from functional dysconnectivity between cortical regions in which SZ attribute reduced salience to relevant stimuli and increased salience to irrelevant stimuli.[1,4] Such aberrant salience processing induces a pathological heightened significance of commonplace incidences, leading to cognitive distortions and positive psychotic symptoms of hallucinations and delusions in SZ.[1,4]

In the present study, we capitalize on the high spatiotemporal resolution of magnetoencephalography imaging (MEG) to record spontaneous neuronal activity during rest in SZ and healthy control participants (HC). In our prior studies, we have examined temporal correlations in resting-state neural oscillations which are quantified by the imaginary coherence between a voxel and the rest of the brain.[2,5] Here, the goal is to move beyond correlative paradigms to causal approaches in schizophrenia research to identify novel biomarkers for future treatment development. Specifically, here we implement innovative phase-transfer entropy (PTE) metrics, which enable causal computations of connectivity changes in directed neural information flow between brain regions,

assayed from a neural source to an endpoint in SZ.[6–8] This is achieved by quantifying how much information in the future of a region-of-interest (ROI) target is predictable when knowing the past state of the neural source. We hypothesized that SZ will manifest frequency-specific deficits in measures of neural information flow compared with HC, and that these underlying neural deficits would be linked to the cognitive and psychotic symptoms in SZ.

We examined changes in directed neural information flow at rest across all frequency bands (delta/theta [2–8 Hz], alpha [8–12 Hz], beta [12–30 Hz], and gamma [30–50 Hz] bands), with focus on alpha and beta band frequencies, in clinically stable SZ and HC, using functional connectivity MEG PTE metrics. Alpha and beta oscillations play a critical role in long-range integrative connectivity processes, making them an ideal candidate for examining changes in directional information flow between distant cortical regions.[1,2,9] Alpha band oscillations represent an idling rhythm that are dominant during rest across both MEG and electroencephalogram (EEG) recordings,[10] and functionally overlap with resting-state networks found in functional magnetic resonance imaging (fMRI) studies.[11,12] We have previously shown that SZ manifests disrupted spontaneous alpha oscillations during rest (8–12 Hz) that correlated with worsening psychotic symptoms.[2] Given that alpha rhythms are the dominant rhythm during rest that show disruption in SZ, in which alpha decoupling in SZ correlated with worsening psychopathology,[2] here we predicted to find disruptions in the alpha band in SZ, compared to HC. Beta oscillatory frequencies are also considered to be critical for mediating cognitive salience to relevant information, with the insula representing a key node of the salience network whose functioning is disrupted in SZ.[1,13] Disruption in beta oscillatory frequencies have previously been shown during a MEG salience detection task that was specifically designed for HC and SZ participants to distinguish relevant stimuli from irrelevant stimuli in order to delineate the neural mechanisms underlying salience detection in HC and SZ.[1] The authors found that while HC showed increased beta oscillatory synchrony in response to salient relevant stimuli compared to irrelevant stimuli, SZ showed reductions in beta synchrony to relevant stimuli which impeded their ability to perform salience detection tasks.[1] These prior findings suggest that disruptions in alpha and beta oscillations in SZ underlie aberrant salience detection and cognitive symptoms in SZ, leading to perceptual distortions and psychotic symptoms.[1,2]

In the present study, we move beyond correlative metrics to evaluate whether *causal* computations of impaired directed neural information flow in alpha and beta band frequencies at rest are linked to impaired cognition and psychopathology in SZ. We hypothesized that disrupted information flow in alpha and beta band frequencies would be observed in SZ compared to HC, and this impaired neural information flow would induce cognitive and psychotic symptoms in SZ.

Methods

Participants and Procedures

This study embodies the baseline MEG portion of a NIMH-funded R01 (R01MH122897) study in schizophrenia. Twenty-one volunteer chronically ill SZ outpatients and 21 HC participants, matched at a group level on age and gender, participated in this MEG study at the University of California San Francisco (UCSF) (see table 1). Inclusion criteria were Axis I diagnosis of schizophrenia (determined by the Structured Clinical Interview for DSM-IV [SCID])[14] or, for HC subjects, no Axis I or Axis II psychiatric disorder (SCID—Nonpatient edition), no substance dependence or current substance abuse, good general physical health, age between 18 and 60 years, and English as the first language. All subjects gave written informed consent for this protocol approved by the Committee on Human Research at UCSF, and then underwent a series of baseline behavioral assessments and imaging.

Clinical and Neurocognitive Assessments

SZ subjects received clinical and cognitive assessments 1 day prior to MEG imaging. Clinical symptoms were assessed with the Positive and Negative Syndrome Scale,[15] which rates each symptom on a scale of 1 (absent) to 7 (extreme). All clinical and cognitive assessments were performed by 2 trained clinical licensed psychologists with interrater reliabilities greater than 0.90 for the Positive and Negative Syndrome Scale (PANSS). Cognition was assessed with the MATRICS Consensus Cognitive Battery (MCCB)[16] which included assessments of processing speed (assayed with the Trail Making Test) and executive functioning (assayed with NAB Mazes) (see table 2). The Trail Making Test examines processing speed in which participants draw a line as fast as possible to connect consecutively numbered circles placed irregularly. The NAB Mazes consist of mazes of increasing difficulty, which examine executive functioning abilities. Participants must complete each maze as quickly as

Table 1. Demographics (Mean, SD) of Healthy Comparison (HC) and Schizophrenia Subjects (SZ)

	HC	SZ	
	(N = 21)	(N = 21)	P value
Age	42 (11.6)	45 (8.5)	0.3
Gender	15M, 6F	16M, 5F	0.7
Illness duration (y)	N/A	23 (13.6)	N/A
Chlorpromazine (CPZ) equivalents	N/A	297 (148)	N/A

Table 2. Cognitive and Clinical Symptoms (Mean, SD) in Schizophrenia Subjects (SZ)

Cognitive and Clinical Symptom Scores	SZ (N = 21)
MATRICS speed of processing	38.9 (12.5)
MATRICS executive functioning	42.0 (14.4)
PANSS positive symptoms	2.55 (1.2)
PANSS negative symptoms	2.39 (0.74)

possible, while following maze-completion rules (ie, no crossing solid boundary lines, and making a continuous line without picking up the pen from the page). Both processing speed and executive functioning tests entail salience detection—necessitating participants to filter out irrelevant information and select salient relevant information. In the present study, SZ performance on these tasks was comparable to prior reports.[17]

Data Acquisition

Each participant underwent 4 min of continuous resting-state recording inside a magnetically shielded room with a 275-channel whole-head MEG system (MEG International Services Ltd., Coquitlam, British Columbia, and Canada) consisting of 275 axial gradiometers. This study protocol required participants to be in a supine position with eyes closed (sampling rate = 1.2 KHz). Subjects were instructed immediately prior to the scan to close their eyes but to stay awake throughout the 4 minute resting-state scan. All subjects confirmed after the resting-state scan that they stayed awake throughout the resting-state scans.

To provide anatomical head models for MEG analysis, a high-resolution 3D T1-weighted whole-brain magnetic resonance imaging (MRI) was acquired for each subject using a 3T Siemens scanner. For each subject, the outline of the brain on the structural scans was extracted, and the segmented brain was treated as a volume conductor model for the source reconstruction described below. Three fiducial coils (nasion, left, and right preauricular points) were placed to localize the position of the head relative to the MEG sensor array. Coregistration of the MEG data with each individual's structural MRI was performed based on 3 fiducial coil positions (nasion and left and right preauricular).

Data Preprocessing

The first step in data preprocessing was to down-sample all the raw data to 600 Hz, and remove cardiac, muscle, and eye-twitch artifacts using independent component analysis.[18] For each subject, a consecutive 4-min signal was digitally filtered using a bandpass filter of 0.7–150 Hz. Noisy epochs which contained artifacts due to head motion were removed based on a visual inspection of the data. In addition, dual signal subspace projection (DSSP)[19] was applied to the filtered sensor signal to remove environmental noise using lead field vectors computed with an individual head model. Finally, we applied Zapline noise filtering techniques to remove power line noise between 60 Hz and 120 Hz.[20]

Source Reconstruction

For source reconstruction, isotropic voxels (6.5 mm) were generated from a template MRI, resulting in 7560 voxels. The generated voxels were then warped to an individual head model. For each voxel, individual magnetic lead field vectors were calculated as a forward model using a single-shell model approximation.[21] The voxels for each participant were then indexed to the Brainnetome atlas.[22] The Brainnetome atlas contains 48 modules (which are further subdivided into 246 smaller brain regions). In our analyses, we focused on the 48 modules for which MEG source reconstructions are considered to work well.

To obtain source-localized activity for all the brain modules, an array-gain scalar beamforming approach[23] was applied to the 240-sec resting-state sensor time series. Beamformer weights were computed in the time domain, and the data covariance matrix for beamforming were calculated using the whole 240-sec sensor time series. The applied beamforming provided voxel-level source time courses on the 6.5-mm volumetric grids in the brain. For each of the 48 brain modules from the Brainnetome atlas, the representative source time course was extracted by applying principal component analysis (PCA) to the voxel time courses within each module and taking its first principal component. Before the connectivity metrics were calculated, the 48 representative source time courses were filtered into different frequency bands: delta/theta (2–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), and gamma (30–50 Hz) bands. Computations of source reconstruction and connectivity metrics described in this section were performed using MATLAB.

Phase-Transfer Entropy

Transfer entropy (TE) is a specific version of entropy or conditional mutual information, and represents information flow from source signal X to a target signal Y. PTE is used to evaluate pairwise directional interactions between ROI time courses and represents information flow between the ROIs based on the phase time series.[24,25] PTE is thus an extension of TE[26] based on phase information. For PTE computations, the phase time series are used as source signals to estimate pairwise directional interactions. PTE was first introduced by Paluš and Stefanovska,[24] and then systematically evaluated by Lobier et al.[6,25] For PTE computations between all ROIs, the source signal X denotes the phase time series of one ROI sending phase information, and the target signal Y

denotes the phase time series of another ROI receiving phase information (see Supplementary Methods for complete details).

PTE for all pairwise cortical ROIs can be expressed in the form of a matrix. Since there are 48 regional Brainnetome ROIs, the dimension of the obtained PTE matrix is 48 × 47. The regional PTEs (vectors of regional measures) can be obtained by averaging across the components of the PTE matrix along the target (y) array dimension and the source (x) array dimension. PTE_{out} results from averaging along the target array and indicates the regional information outflow at a source brain region; while PTE_{in} results from averaging along the source array and indicates the regional information inflow at a target brain region. In other words, regional PTE corresponds to node strength, as depicted in graph theory.[27]

To evaluate deviations in directional information flow in SZ patients, we computed Z-scores for every patient relative to the mean and standard deviation of the HC group. A negative z-score indicates a decrease in PTE, while a positive z-score indicates an increase in PTE. To evaluate PTE metrics in each group, we used 1-sample t-tests to compute regional $z_{k,}$ and the obtained P values were corrected for multiple comparisons (FDR $P < .05$). To compare PTE metrics between SZ and HC groups, 2-sample t-tests were performed. Statistical significance was determined after multiple comparison FDR corrections (FDR $P < .05$). Regression coefficients were obtained to show the strength of associations between directed neural information flow (regional z_k) with cognition and clinical symptom scores, with significant associations at $P < .05$. The BrainNet Viewer toolbox[28] was used to depict directional information flow in the brain.[28]

Results

We found that SZ showed significant differences in the magnitude of directed information flow in both alpha (8–12 Hz) and beta bands (12–30 Hz) compared to the HC group, which were significant at strict FDR-corrected thresholds ($P < .05$) (see figures 1 and 2). Information flow showed regional diversity in the strength of outflow and inflow. For example, HC showed both high information outflow and inflow in the beta band (ie, about 0.03) between the right middle temporal gyrus (R.MTG) and the right insula (R. Ins). Both high information inflow and outflow between R.MTG and R.Insula were quantitatively greater in HC compared to SZ (figure 2B). By contrast, SZ showed regional diversity in the alpha band, with significantly greater information outflow from the precuneus (Pcun) to the medial ventral occipital cortex (MVOcc) (figure 2A). We did not find significant group differences in either delta/theta or gamma bands that survived FDR-corrected thresholds. Together, these findings indicate that regional information outflow and inflow are significantly altered in SZ, and that these changes are localized in

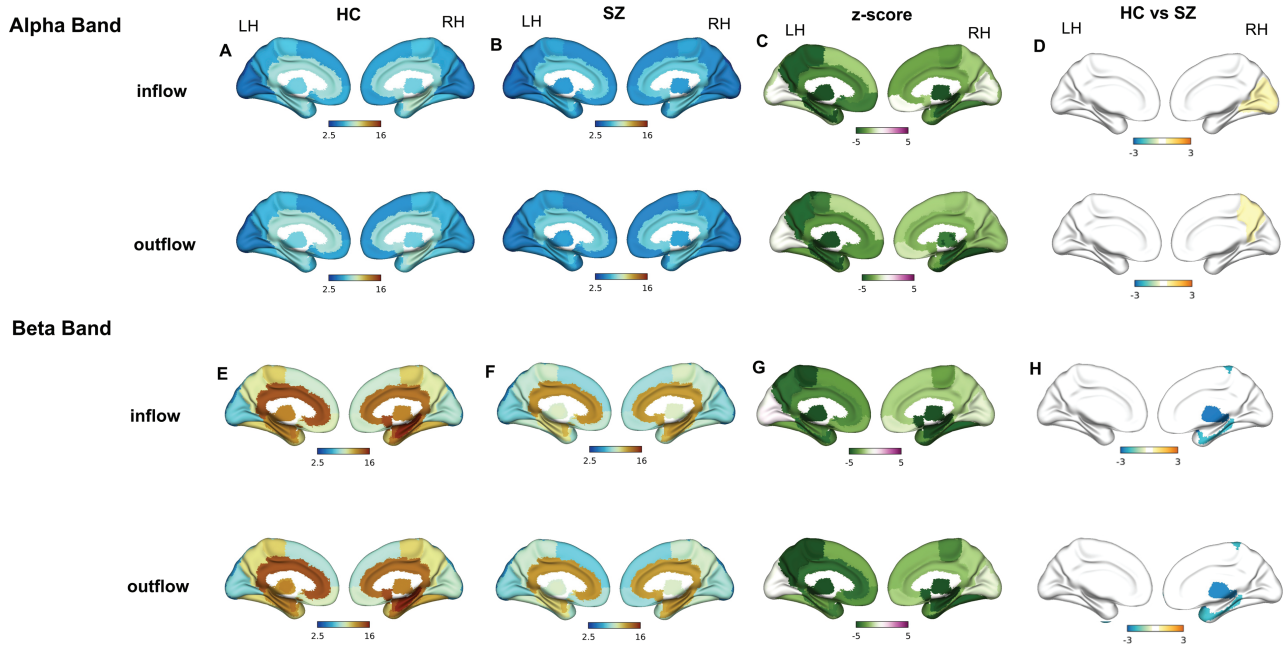

Fig. 1. Information flow in alpha and beta bands based on phase-transfer entropy (PTE). Regional information inflow and outflow patterns for HC (A, E) and SZ (B, F) are shown for alpha and beta frequency bands. For visualization, 1000×regional PTE values are displayed. Regional information inflow and outflow patterns in Schizophrenia (SZ) compared with HC are shown in (C and G) based on z-scores for every patient relative to the mean and standard deviation of the healthy control (HC) group. (D and H) show results from the two sample (t-test) with information flow that survived FDR correction ($P < .05$).

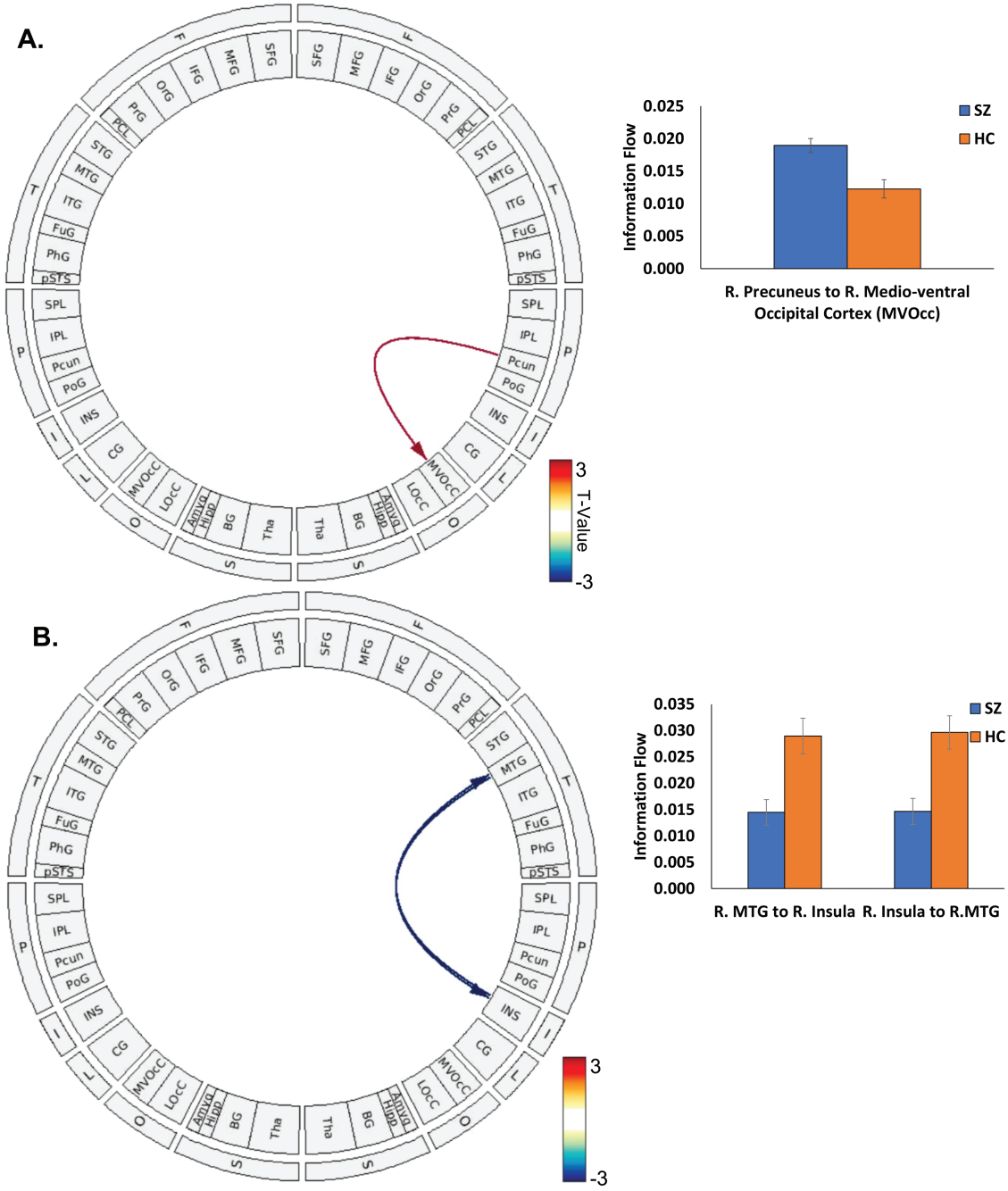

Fig. 2. Information flow connectogram in Schizophrenia (SZ) compared to healthy comparison (HC) depicting only information flow that survived FDR correction ($P < .05$) for alpha (A) and beta (B) bands.

specific regions across distinct frequency bands observed most prominently in alpha and beta bands.

Next, we examined the association between information flow metrics with cognition and clinical symptoms in SZ. We found that in the alpha band, reduced information flow from the precuneus to the medial ventral occipital cortex was associated with higher positive psychotic symptoms (ie, more severe hallucinations and delusions) in SZ (figure 3). In the beta band, both reduced information inflow and outflow between R.MTG and R.Insula were associated with greater impairments in processing speed and executive functioning in SZ (figure 4). We did not find any associations between information flow metrics with age, gender, illness duration, or antipsychotic medication (all P's > .05).

Discussion

We present here, for the first time, direct evidence for functional disconnection in directional neural information

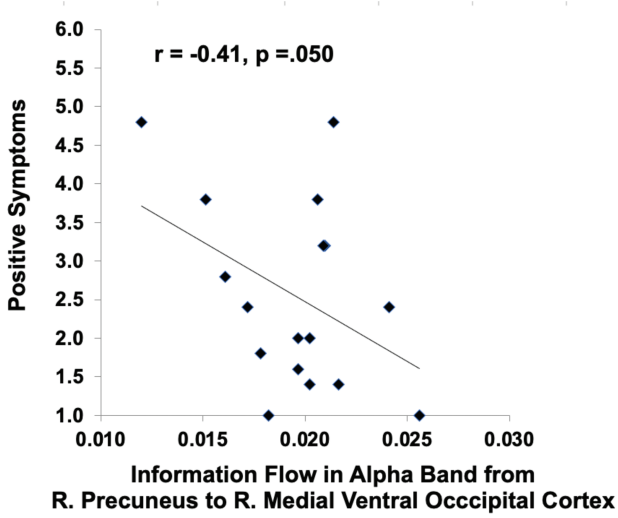

Fig. 3. Significant regression associations between information flow phase-transfer entropy (PTE) in alpha band and positive symptom severity are illustrated in Schizophrenia (SZ). Reduced information flow from the right precuneus to the right medial ventral occipital cortex was associated with more severe (ie, higher) positive psychotic symptoms.

flow between specific regions in SZ, as demonstrated through disrupted alpha and beta oscillations that were associated with worsening psychotic and cognitive symptoms, respectively. Reduced neural information flow observed in the alpha band from the precuneus to the medial ventral occipital cortex (MVOcc) was associated with more severe positive psychotic symptoms in SZ. Prior studies have shown that the precuneus represents a critical node in the default mode network and mediates spontaneous internal self-related representations and imagery during rest in HC,[29,30] while SZ show disrupted functional connectivity in the precuneus during rest.[31] We also found that both reduced information inflow and outflow between R.MTG and R.Insula were associated with greater impairments in processing speed and executive functioning. We did not find any associations between information flow metrics with age, gender, illness duration, or antipsychotic medication. These findings suggest that disrupted information flow in alpha and beta bands between these key regions reflects potential neural biomarkers that underlie the cognitive and psychotic symptoms in SZ, and may provide useful treatment targets through behavioral and neuromodulation interventions, such as transcranial magnetic stimulation therapies.

In the group comparison, of all the regions throughout the brain, SZ compared to HC, showed significant differences in spontaneous information flow to the MVOcc from the precuneus in alpha band frequencies, which survived multiple comparison FDR-corrected statistical thresholds. Furthermore, this reduced information flow to the MVOcc from the precuneus was associated with more severe positive psychotic symptoms. These findings are consistent with our prior research, in which we have previously found that SZ showed aberrant MVOcc signaling during auditory tasks (also referred to as the ventral visual fusiform area), which was shown to covary with the severity of hallucinations, which was not observed in the HC group.[32] These convergent findings between the present findings and our prior work suggest that the MVOcc may play a compensatory role during internal resting states and during auditory processing in SZ, and suggests that information flow to the MVOcc may be fundamental for discerning and filtering out irrelevant from relevant stimuli in SZ. In this capacity, reduced information flow in alpha oscillations to MVOcc may reflect underlying neural impairments in filtering out irrelevant from relevant auditory stimuli, and lead to hallucinations in which SZ appear to hear auditory stimuli (eg, voices) when there are no auditory-relevant stimuli. These findings also provide an underlying neural framework that supports Kapur's (2003) theory that psychosis arises from aberrant salience processing, in which SZ attribute reduced salience for relevant stimuli and increased salience for irrelevant stimuli, leading to positive psychotic symptoms of hallucinations and delusions.[4] The present application of PTE metrics to resting-state data enables causal computations of connectivity changes in directed neural information flow, allowing the extension of functional imaging research beyond correlative data that allow us to draw causal inferences that reduced information flow from the precuneus to the MVOcc represents one underlying neural mechanism that gives rise to psychotic symptoms.

Beta oscillatory frequencies are also considered to be fundamental for mediating cognitive salience to relevant information.[1] Palaniyappan and Liddle[33] extended Kapur's theory of abnormal salience in SZ to explain not just patients' positive psychotic symptoms but also to delineate the underlying cognitive symptoms in SZ, with their hypothesis involving the insula as a key node of the salience network whose functioning is disrupted in SZ. In particular, Liddle et al[1] implemented a salience detection MEG task specifically designed for HC and SZ participants to distinguish relevant stimuli from irrelevant stimuli in order to delineate the neural mechanisms underlying salience detection in HC and SZ. They found that HC showed increased beta oscillatory activity in the insula for relevant compared to irrelevant stimuli, while SZ showed the opposite pattern, with patients manifesting significantly greater beta oscillatory activity for irrelevant stimuli in the insula.[1] Furthermore, convergent evidence across fMRI, EEG, and MEG have all demonstrated that the insula is a critical node in the salience network,[13,34–36] with beta band oscillatory activity in the insula and surrounding temporal regions being fundamental for salience detection.[1,13] Consistent with these prior findings, in the present study, we found that

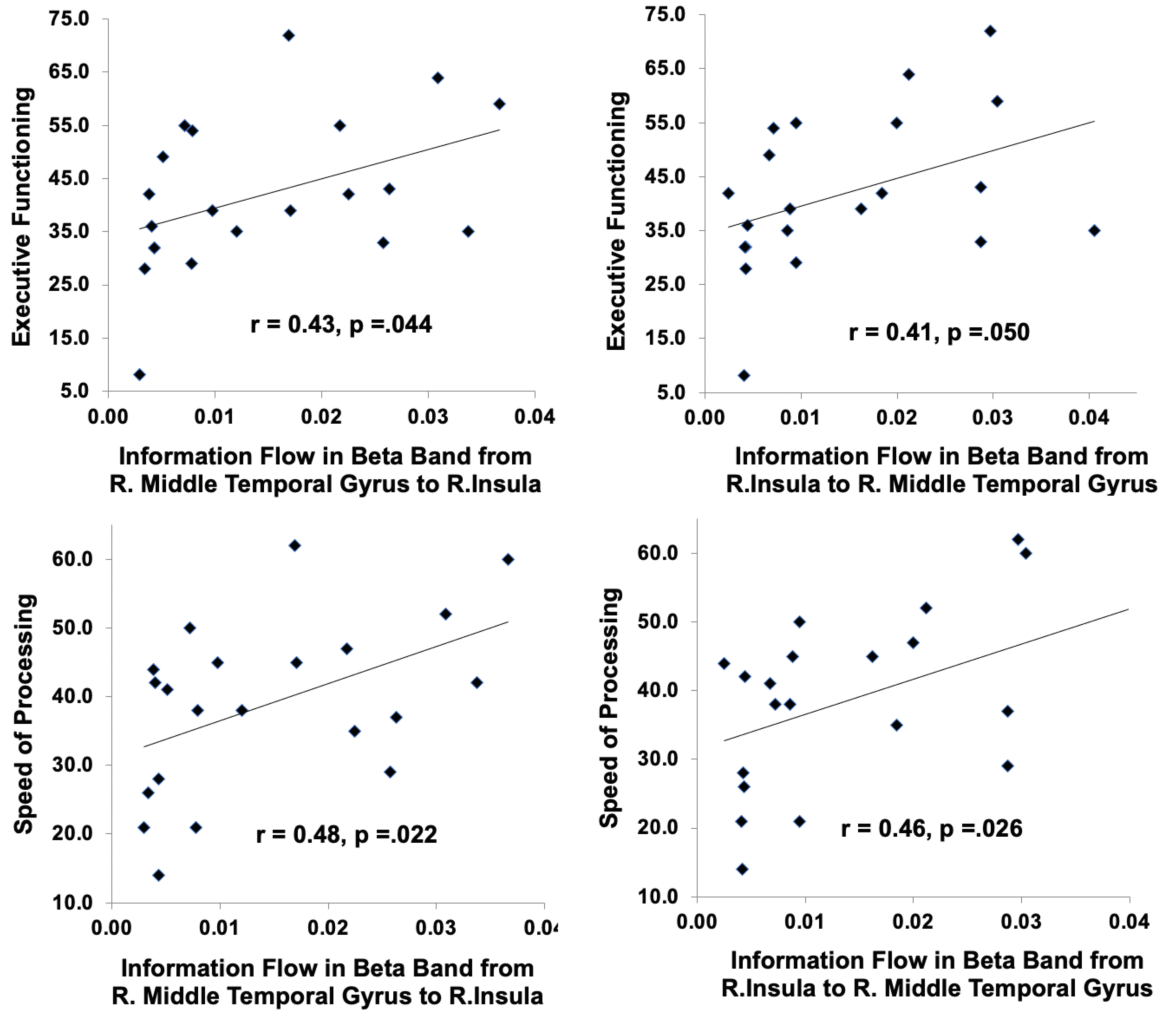

Fig. 4. Significant regression associations between information flow phase-transfer entropy (PTE) in beta band and cognition are illustrated in Schizophrenia (SZ). Reduced information inflow and outflow between the right middle temporal gyrus and right insula were associated with greater impairments in speed of processing and executive functioning.

of all the regions throughout the brain, SZ compared to HC, showed significant reductions in information inflow and outflow in beta oscillatory frequencies between the insula and MTG, thought to impair their ability to reliably differentiate relevant from irrelevant information. Additionally, our data indicate that reduced information inflow and outflow between the insula and MTG were associated with worse processing speed and executive functioning abilities. Executive functioning is a multifaceted concept, and tests the ability for participants to detect competing responses, and switch attention to select salient relevant information and filter our irrelevant information. The NAB Mazes Test is not intended to disentangle these components of executive functioning, as it is used to assay participants' overall executive functioning abilities. The Trail Making Test is a timed test that examines processing speed. The fundamental requirement of both processing speed and executive functioning tasks entails salience detection—necessitating participants to filter out irrelevant information and select salient relevant information.[37,38] Taken together, the present findings indicate that information flow in both alpha and beta frequencies between distinct neural regions are disrupted in SZ, and may provide neural biomarkers for predicting distinct phenotypic cognitive and psychotic symptoms.

Limitations and Future Research

We note that the HC group did not complete cognitive testing. As such, we were only able to examine associations between PTE metrics with cognition in the SZ group. We also note that the brain-behavior regressions were only explored within brain regions that showed group differences between the cohorts and survived stringent FDR multiple comparison corrections across 48 × 47 ROI pairs (2256 pairs) for each frequency band. We only found group differences in alpha band (from precuneus to MVOcc) and in beta band (between insula and MTG).

Associations in these two regions that were tested with PANSS subscales (positive and negative symptoms) and cognition (processing speed and executive function) were not corrected for multiple comparisons. Larger sample sizes would be needed to replicate the present findings in future studies with regression associations corrected for multiple comparisons. Finally, we note that the present findings are only applicable to medicated chronically ill SZ, and thus, we do not know whether the present findings would extend to ultrahigh risk or recent onset SZ or unmedicated patients.

Our PTE analyses are also only applicable to resting-state data (rather than task-evoked data), enabling sufficient time-points for capitalizing on the millisecond precise temporal resolution and superior spatial resolution of MEG compared with EEG, that is required for investigating the abnormalities in spontaneous information flow in SZ compared to HC.[39,40] Additionally, PTE estimates of information computation can reveal hidden dynamic interactions in resting states, which cannot be observed in task-based analyses.[41] We found significant disruptions in information flow in alpha and beta bands in SZ that were associated with worse psychotic and cognitive symptoms, respectively. The present findings are consistent with prior findings that identify the MVOcc as a region that is disrupted in SZ, whose aberrant signaling covaried with hallucination severity,[32] and the insula as a critical node in salience detection, which is disrupted both anatomically and functionally in SZ,[1,42] impacting the ability for SZ to filter out irrelevant information and select salient relevant information, leading to cognitive distortions and psychotic symptoms.[1,4] Future research using MEG task-evoked signals (eg, salience detection tasks) is required to replicate and extend the present findings to delineate precisely how disrupted information flow during rest relates to task-evoked salience detection and psychotic symptoms in SZ.

Summary

Although previous MEG studies have shown disruptions in alpha and beta bands in SZ, this is the first study to show a causal dissociation in functional disconnection in directional information flow in distinct alpha and beta frequencies bands between distinct regions that were associated with either cognitive or psychotic symptoms. In particular, reduced information flow in alpha oscillatory frequencies to MVOcc from the precuneus was associated with more severe psychotic symptoms while reduced information inflow and outflow in beta oscillatory frequencies between the insula and MTG was associated with worse cognitive symptoms. Alpha oscillations constitute a stable idling rhythm during rest,[9] and represent long-range functional cortico-cortical integration[43] which we show here, when disrupted contributes to manifestations of clinical psychotic symptoms in SZ. Disruptions in neural information flow in beta band oscillatory frequencies, on the other hand, appears to signal a faulty cognitive salience network[1] in SZ that impaired participants' processing speed and executive abilities to recognize and select environmental stimuli that are relevant. The present findings delineate disruptions in neural information flow in specific alpha and beta oscillatory frequencies between distinct regions that underlie the psychotic and cognitive symptoms in SZ, and provide potential novel neural biomarkers that could lead to innovations in future neuromodulation target treatment development. The present findings, if replicated using a larger sample size in future studies, also provide a promising neurobiological basis for precision medicine interventions, which reveal for the first time that we can use MEG PTE techniques to predict which individuals will likely manifest cognitive or psychotic symptoms in schizophrenia. In conclusion, given that the MEG resting-state scans are quick (4 min duration) and noninvasive and given that our pipelines for MEG source localization and TE analyses are automated, if the present results are replicated using a larger sample size in future studies, it is our hope that these results would provide a potential first step to individualizing new neuromodulation treatments for SZ for implementation and transition to the clinic based on spontaneous neural information flow during MEG resting states that are applicable to medicated chronically ill SZ.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

Acknowledgments

We thank all the participants for completing our studies. We thank Hirofumi Morise for writing and providing the PTE connectogram scripts. None of the authors have any conflict of interest.

Funding

This research is supported by the Brain and Behavior Research Foundation Young Investigator Award grants (formerly called NARSAD: 17680 and 28188), and a National Institute of Mental Health (NIMH) R01 grant (R01MH122897) to Karuna Subramaniam.

References

1. Liddle EB, Price D, Palaniyappan L, *et al*. Abnormal salience signaling in schizophrenia: the role of integrative beta oscillations. *Hum Brain Mapp.* 2016;37:1361–1374. doi: 10.1002/hbm.23107.

2. Hinkley LBN, Vinogradov S, Guggisberg AG, Fisher M, Findlay AM, Nagarajan SS. Clinical symptoms and alpha band resting-state functional connectivity imaging in patients with schizophrenia: implications for novel approaches to treatment. *Biol Psychiatry.* 2011;70:1134–1142. doi: 10.1016/j.biopsych.2011.06.029.
3. Lowe P, Krivoy A, Porffy L, Henriksdottir E, Eromona W, Shergill SS. When the drugs don't work: treatment-resistant schizophrenia, serotonin and serendipity. *Ther Adv Psychopharmacol.* 2018;8:63–70. doi: 10.1177/2045125317737003.
4. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry.* 2003;160:13–23. doi: 10.1176/appi.ajp.160.1.13.
5. Hinkley LBN, Owen JP, Fisher M, Findlay AM, Vinogradov S, Nagarajan SS. Cognitive impairments in schizophrenia as assessed through activation and connectivity measures of Magnetoencephalography (MEG) data. *Front Hum Neurosci.* 2010;3:73. doi: 10.3389/neuro.09.073.2009.
6. Engels MMA, Yu M, Stam CJ, *et al*. Directional information flow in patients with Alzheimer's disease. A source-space resting-state MEG study. *Neuroimage Clin.* 2017;15:673–681. doi: 10.1016/j.nicl.2017.06.025.
7. Hillebrand A, Tewarie P, van Dellen E, *et al*. Direction of information flow in large-scale resting-state networks is frequency-dependent. *Proc Natl Acad Sci USA.* 2016;113:3867–3872. doi: 10.1073/pnas.1515657113.
8. Rivolta D, Heidegger T, Scheller B, *et al*. Ketamine dysregulates the amplitude and connectivity of high-frequency oscillations in cortical-subcortical networks in humans: evidence from resting-state magnetoencephalography-recordings. *Schizophr Bull.* 2015;41:1105–1114. doi: 10.1093/schbul/sbv051.
9. Nunez PL, Wingeier BM, Silberstein RB. Spatial-temporal structures of human alpha rhythms: theory, microcurrent sources, multiscale measurements, and global binding of local networks. *Hum Brain Mapp.* 2001;13:125–164. doi: 10.1002/hbm.1030.
10. Nunez PL. A study of origins of the time dependencies of scalp EEG: i--theoretical basis. *IEEE Trans Biomed Eng.* 1981;28:271–280. doi: 10.1109/tbme.1981.324700.
11. Jann K, Dierks T, Boesch C, Kottlow M, Strik W, Koenig T. BOLD correlates of EEG alpha phase-locking and the fMRI default mode network. *Neuroimage.* 2009;45:903–916. doi: 10.1016/j.neuroimage.2009.01.001.
12. Mantini D, Perrucci MG, Del Gratta C, Romani GL, Corbetta M. Electrophysiological signatures of resting state networks in the human brain. *Proc Natl Acad Sci USA.* 2007;104:13170–13175. doi: 10.1073/pnas.0700668104.
13. Chand GB, Dhamala M. The salience network dynamics in perceptual decision-making. *Neuroimage.* 2016;134:85–93. doi: 10.1016/j.neuroimage.2016.04.018.
14. Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for DSM-III-R (SCID). I: history, rationale, and description. *Arch Gen Psychiatry.* 1992;49:624–629. doi: 10.1001/archpsyc.1992.01820080032005.
15. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987;13:261–276.
16. Nuechterlein KH, Green MF, Kern RS, *et al*. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *Am J Psychiatry.* 2008;165:203–213. doi: 10.1176/appi.ajp.2007.07010042.
17. Fisher M, Nahum M, Howard E, *et al*. Supplementing cognitive exercises for people with schizophrenia: an interim report. *Psychiatr Rehabil J.* 2017;40:21–32. doi: 10.1037/prj0000244.
18. Ablin P, Cardoso JF, Gramfort A. Spectral independent component analysis with noise modeling for M/EEG source separation. *J Neurosci Methods.* 2021;356:109144. doi: 10.1016/j.jneumeth.2021.109144.
19. Sekihara K, Kawabata Y, Ushio S, *et al*. Dual signal subspace projection (DSSP): a novel algorithm for removing large interference in biomagnetic measurements. *J Neural Eng.* 2016;13:036007. doi: 10.1088/1741-2560/13/3/036007.
20. de Cheveigne A. ZapLine: a simple and effective method to remove power line artifacts. *Neuroimage.* 2020;207:116356. doi: 10.1016/j.neuroimage.2019.116356.
21. Nolte G. The magnetic lead field theorem in the quasi-static approximation and its use for magnetoencephalography forward calculation in realistic volume conductors. *Phys Med Biol.* 2003;48:3637–3652. doi: 10.1088/0031-9155/48/22/002.
22. Fan L, Li H, Zhuo J, *et al*. The human brainnetome atlas: a new brain atlas based on connectional architecture. *Cereb Cortex.* 2016;26:3508–3526. doi: 10.1093/cercor/bhw157.
23. Sekihara K, Nagarajan SS, Poeppel D, Marantz A. Asymptotic SNR of scalar and vector minimum-variance beamformers for neuromagnetic source reconstruction. *IEEE Trans Biomed Eng.* 2004;51:1726–1734. doi: 10.1109/TBME.2004.827926.
24. Palus M, Stefanovska A. Direction of coupling from phases of interacting oscillators: an information-theoretic approach. *Phys Rev E Stat Nonlin Soft Matter Phys.* 2003;67:055201. doi: 10.1103/PhysRevE.67.055201.
25. Lobier M, Siebenhuhner F, Palva S, Palva JM. Phase transfer entropy: a novel phase-based measure for directed connectivity in networks coupled by oscillatory interactions. *Neuroimage.* 2014;85(Pt 2):853–872. doi: 10.1016/j.neuroimage.2013.08.056.
26. Barnett L, Bossomaier T. Transfer entropy as a log-likelihood ratio. *Phys Rev Lett.* 2012;109:138105. doi: 10.1103/PhysRevLett.109.138105.
27. Sporns O. Graph theory methods: applications in brain networks. *Dialogues Clin Neurosci.* 2018;20:111–121.
28. Xia M, Wang J, He Y. BrainNet Viewer: a network visualization tool for human brain connectomics. *PLoS One.* 2013;8:e68910. doi: 10.1371/journal.pone.0068910.
29. Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain.* 2006;129:564–583. doi: 10.1093/brain/awl004.
30. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci.* 2008;1124:1–38. doi: 10.1196/annals.1440.011.
31. Whitfield-Gabrieli S, Thermenos HW, Milanovic S, *et al*. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proc Natl Acad Sci USA.* 2009;106:1279–1284. doi: 10.1073/pnas.0809141106.
32. Herman AB, Brown EG, Dale CL, *et al*. The Visual Word Form Area compensates for auditory working memory dysfunction in schizophrenia. *Sci Rep.* 2020;10:8881. doi: 10.1038/s41598-020-63962-0.
33. Palaniyappan L, Liddle PF. Does the salience network play a cardinal role in psychosis? An emerging hypothesis of insular dysfunction. *J Psychiatry Neurosci.* 2012;37:17–27. doi: 10.1503/jpn.100176.
34. Seeley WW, Menon V, Schatzberg AF, *et al*. Dissociable intrinsic connectivity networks for salience processing and

executive control. *J Neurosci.* 2007;27:2349–2356. doi: 10.1523/JNEUROSCI.5587-06.2007.

35. Uddin LQ. Salience processing and insular cortical function and dysfunction. *Nat Rev Neurosci.* 2015;16:55–61. doi: 10.1038/nrn3857.
36. Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. *Brain Struct Funct.* 2010;214:655–667. doi: 10.1007/s00429-010-0262-0.
37. Dale CL, Brown EG, Fisher M, *et al.* Auditory cortical plasticity drives training-induced cognitive changes in schizophrenia. *Schizophr Bull.* 2016;42:220–228. doi: 10.1093/schbul/sbv087.
38. Silva MT, Laks J, Engelhardt E. Neuropsychological tests and driving in dementia: a review of the recent literature. *Rev Assoc Med Bras (1992)* 2009;55:484–488. doi: 10.1590/s0104-42302009000400027.
39. Dalal SS, Guggisberg AG, Edwards E, *et al*. Five-dimensional neuroimaging: localization of the time-frequency dynamics of cortical activity. *Neuroimage.* 2008;40:1686–1700. doi: 10.1016/j.neuroimage.2008.01.023.
40. Kudo K, Morise H, Ranasinghe KG, *et al*. Magnetoencephalography imaging reveals abnormal information flow in temporal lobe epilepsy. *Brain Connect.* 2021. doi: 10.1089/brain.2020.0989.
41. Robinson SE, Mandell AJ, Coppola R. Spatiotemporal imaging of complexity. *Front Comput Neurosci.* 2012;6:101. doi: 10.3389/fncom.2012.00101.
42. Glahn DC, Laird AR, Ellison-Wright I, *et al*. Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. *Biol Psychiatry.* 2008;64:774–781. doi: 10.1016/j.biopsych.2008.03.031.
43. von Stein A, Sarnthein J. Different frequencies for different scales of cortical integration: from local gamma to long range alpha/theta synchronization. *Int J Psychophysiol.* 2000;38:301–313. doi: 10.1016/s0167-8760(00)00172-0.