Original Article

CHRONIC STRESS

Chronic Stress
Volume 2: 1–10

DOI: 10.1177/2470547018815232
journals.sagepub.com/home/css
SAGE

Temporoparietal Junction Functional Connectivity in Early Schizophrenia and Major Depressive Disorder

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Abstract

Background: The temporoparietal junction (TPJ) has been linked to lower-level attentional and higher-level social processing, both of which are affected in schizophrenia (SZ) and major depressive disorder (MDD). We examined resting functional connectivity of bilateral anterior and posterior TPJ in SZ and MDD to evaluate potential anomalies in each disorder and differences between disorders.

Methods: Resting-state functional magnetic resonance imaging data were acquired from 24 patients with SZ, 24 patients with MDD, and 24 age-matched healthy controls. We performed seed-based functional connectivity analyses with seed regions in bilateral anterior and posterior TPJ, covarying for gender and smoking.

Results: SZ had reduced connectivity versus controls between left anterior TPJ and dorsolateral prefrontal cortex (dlPFC) and posterior cingulate cortex (PCC); between left posterior TPJ and middle cingulate cortex, left dorsal PFC, and right lateral PFC; between right anterior TPJ and bilateral PCC; and between right posterior TPJ and middle cingulate cortex, left posterior insula, and right insula. MDD had reduced connectivity versus controls between left posterior TPJ and right dlPFC and between right posterior TPJ and PCC and dlPFC. SZ had reduced connectivity versus MDD between right posterior TPJ and left fusiform gyrus and right superior-posterior temporal cortex.

Conclusion: Functional connectivity to the TPJ was demonstrated to be disrupted in both SZ and MDD. However, TPJ connectivity may differ in these disorders with reduced connectivity in SZ versus MDD between TPJ and posterior brain regions.

Keywords

functional connectivity, major depressive disorder, schizophrenia, seed-based fMRI, temporoparietal junction

Received 20 August 2018; Accepted 3 November 2018

Introduction

Lower-level attentional and higher-level processing of social information are affected in schizophrenia (SZ) and major depressive disorder (MDD). The temporoparietal junction (TPJ) plays a role in processing socially relevant information. Carter et al.[1] found that TPJ activity during a functional magnetic resonance imaging (fMRI) task predicted future decisions in a social context. The TPJ is a cortical region located at the boundary of the temporal and parietal lobes surrounding the posterior end of the Sylvian fissure and has been referred to as the angular gyrus, Brodmann area (BA) 39, posterior superior temporal sulcus, or posterior

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inferior parietal sulcus.[2] The left TPJ is associated with processing language and semantics,[3] while the literature has shown that the right TPJ is involved in both lower-level attentional processes and higher-level processing of social information.[2,4]

Bzdok et al. used connectivity-based parcellation and found two functionally distinct regions of the right TPJ, anterior and posterior regions. They reported that the anterior region of the right TPJ correlated with a midcingulate-motor-insular network that is associated with attention and was anti-correlated with a parietal network that is associated with social cognition and memory retrieval.[2] They reported that the posterior region of the right TPJ showed the exact opposite correlation pattern and that it is involved in theory of mind.[2] Mars et al.[5] identified three separate regions of the TPJ: a dorsal region functionally connected primarily with the lateral anterior prefrontal cortex, a ventral anterior region functionally connected with the ventral prefrontal cortex and anterior insula, and a posterior region functionally connected with the posterior cingulate, temporal pole, and anterior medial prefrontal cortex. They concluded that the TPJ can be subdivided into subregions based on its structural and functional connectivity.[5]

The TPJ also plays a role in computations concerning awareness, including a ventral attention network involved in bottom-up attention driven by salience through the middle frontal gyrus and inferior frontal gyrus, and a frontoparietal control network involved in top-down executive control through the dorsolateral prefrontal cortex (dlPFC).[6] Another study reported right TPJ resting connectivity to a ventral attention network and to the dlPFC and concluded that the right TPJ may be a key region for the integration of sensory stimuli and contextual frames in action control.[7] Corbetta and Shulman[8] wrote a review article on attention and reported that the temporoparietal cortex is part of a ventral attentional system specialized for detecting behaviorally relevant stimuli that works as a ''circuit breaker'' for a dorsal system involved in preparing and applying goal-directed (top-down) selection for stimuli and responses. More recently, Posner et al.[9] wrote a review on brain networks of attention and reported that these networks arise in infancy and that methods of training attention may improve performance and ameliorate pathology in conditions such as SZ.

The function of the TPJ may be relevant to SZ and MDD, but perhaps in different ways. Few previous studies have specifically examined functional connectivity of the TPJ in psychiatric illness. Poeppl et al.[10] investigated the subregional connectivity of the right TPJ in MDD and found altered connectivity with regions involved in cognitive and behavioral control, visuospatial processing, reward, and memory retrieval and social cognition. They suggested an imbalance of connectivity of subregions of the right TPJ in MDD rather than a disruption in connectivity of the entire right TPJ.[10] Vercammen et al.[11] examined functional connectivity of bilateral TPJ and a priori defined regions comprising the networks involved in inner speech and auditory hallucinations and found that in patients with SZ auditory hallucinations were associated with reduced functional connectivity of the TPJ. Following that previous study, Vercammen et al.[12] then tested whether repetitive transcranial magnetic stimulation (rTMS) would affect functional connectivity of the TPJ in SZ. They reported symptomatic improvement following rTMS along with increased connectivity between the left TPJ and the right insula and therefore concluded that rTMS can affect functional connectivity of the TPJ.[12] Lastly, Mondino et al.[13] found reduced resting-state functional connectivity in patients with SZ between the left TPJ and left anterior insula following 10 sessions of frontotemporal transcranial direct current stimulation, which correlated with a reduction in auditory verbal hallucination severity. Similarly, Gavrilescu et al.[14] found reduced interhemispheric auditory cortex connectivity in patients with SZ who had a history of auditory hallucinations.

Other previous studies have reported on TPJ activity in SZ rather than functional connectivity. Reduced fMRI activation in the TPJ has been demonstrated during the perception of biological motion (a visual perceptual phenomenon, whereby dozens of moving point-lights attached to joints of a human body is perceived as human action) in SZ versus controls.[15] Another previous study examined the morphology of the TPJ in patients with SZ who had persistent auditory hallucinations and reported an association between auditory hallucination self-other attribution and the sulcal pattern of the inferior parietal lobule/TPJ.[16] Hwang et al.[17] measured seed-based functional connectivity of bilateral dlPFC in subthreshold depression, a mild stage of depression. They reported reduced functional connectivity to the TPJ compared to controls, and this reduction was associated with depressive symptom scores.[17]

The present study was designed to measure the functional connectivity to bilateral anterior and posterior regions of the TPJ in both SZ and MDD early in illness. This is the first study to our knowledge that specifically measured the connectivity to bilateral anterior and posterior TPJ using seed-based fMRI in both SZ and MDD. Our objective was to determine if functional connectivity between the anterior and posterior TPJ and cortical regions is deficit in SZ and MDD and if SZ and MDD differ in a way that could explain the different clinical presentation in these disorders. We hypothesized that there would be deficient connectivity between subregions of the TPJ and regions involved in higher-level functions including executive control and theory of mind in patients with SZ and regions involved in reward processing and

emotion regulation in MDD and that connectivity deficits would more prominently involve the right posterior TPJ.

Methods

Participants

Participants were recruited from the local community and through the First Episode Mood and Anxiety Program and the Prevention and Early Intervention in Psychosis Program in London, Ontario, Canada. Included in this study were 24 patients with SZ and 24 patients with MDD both early in illness along with 24 healthy controls (HC); groups were matched for age, handedness, and parental education level. Gender differed between groups; controls were split evenly with 12 males and 12 females; there were 21 males and 3 female patients with SZ; and there were 8 male and 16 female patients with MDD. An experienced rater (B. S.) and psychiatrist (P. C. W.) used the Structural Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition[18] to obtain a consensus diagnosis for all patients and to exclude psychiatric diagnoses in HC. All patients were outpatients and were symptomatic at the time of scan and clinical assessment. Symptom severity was rated immediately prior to the fMRI scan using the Scale for the Assessment of Positive Symptoms (SAPS)[19] and the Scale for the Assessment of Negative Symptoms (SANS)[20] in patients with SZ and the Montgomery–Åsberg Depressive Scale[21] in patients with MDD. A history of drug or alcohol abuse in the previous year, mental retardation, hypertension, diabetes, hepatic/renal insufficiency, or any other neurological condition were used as exclusionary criteria for patients and HC. HC with a first- or second-degree relative with a known psychiatric disorder were also excluded. The research ethics board at the University of Western Ontario approved this study protocol.

MRI Data Acquisition

All imaging data were acquired with a 3T MRI scanner (Siemens Tim Trio, Erlangen, Germany) equipped with a 32-channel head coil located at the Centre for Functional and Metabolic Mapping (Robarts Research Institute, University of Western Ontario). Anatomical whole-brain T1-weighted images (MPRAGE, 1 mm isotropic resolution) were acquired and used for spatial normalization of the functional data. Functional data were acquired during a 10-minute whole-brain resting-state scan (2D T2*-weighted gradient echo, echo-planar, $TR = 3$ s, $TE = 20$ ms, 3 discarded volumes, 200 functional volumes, parallel to the AC-PC plane, 2 mm isotropic resolution). Participants were instructed to keep their eyes closed and let their minds wander and to not fall asleep during the resting-state scan; all participants reported that they were able to stay awake.

Seed-Based Resting Functional Connectivity Analysis

The resting-state functional data underwent standard imaging preprocessing using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Each image volume within one scan was aligned to the first volume to correct for motion; six movement parameters (translation in x, y, z and rotation in yaw, pitch, roll) were measured using the INRIAlign toolbox (http://www-sop.inria.fr/epidaure/Collaborations/IRMf/INRIAlign). The functional images were normalized into the standard Montreal Neurological Institute (MNI) space using the T1-weighted anatomical images and then smoothed with a 6-mm kernel (3D Gaussian, full width at half-maximum, SPM8). ARtifact detection Tools (http://www.nitrc.org/projects/art) was used to flag excessive movement (>2 mm) and mean global image intensity outliers and to generate multiple regressors for each participant containing the six realignment parameters and the motion-flagged image volumes. Participants with greater than two flagged image volumes were excluded from further analyses, which included two patients with SZ.

Functional connectivity was measured using seed-based connectivity analyses, as previously detailed,[22] between bilateral anterior and posterior TPJ regions[2] and the rest of the brain. Briefly, the average BOLD time series were extracted from the functional scans from four 8-mm radius spherical seed regions after band-passed filtering (0.012–0.1 Hz). The center seed positions were taken from Bzdok et al. and were located in the left anterior TPJ (−58, −39, 16), right anterior TPJ (58, −39, 16), left posterior TPJ (−54, −54, 16), and right posterior TPJ (54, −54, 16) (x, y, z MNI coordinates). Functional connectivity maps for each seed region for each participant were generated using a first-level, within-participant, general linear model analysis with the extracted time series as the regressors of interest. The six realignment parameters and flagged image volumes were entered into the general linear model as regressors of no interest to mitigate residual movement and artifacts. Positive correlation t-maps were carried forward to the second-level analysis, which represent the correlation strength of the seed region to each voxel in the brain. Second-level, between-group, connectivity differences were examined using the first-level t-maps for each of the four TPJ seed regions ($N = 72$, $df = 67$, cluster-level family-wise error corrected [FWE]-corrected at $p < 0.05$) as in Chumbley and Friston.[23] Between-group comparisons included gender and tobacco smoking status as covariates of no interest to help mitigate the clear gender and smoking status differences between groups.

Results

Clinical Measures

Table 1 lists participant demographic and clinical data. Groups were matched for handedness and parental education level, and patients with SZ and patients with MDD were matched for illness duration. Gender differed between groups with more male patients with SZ and more female patients with MDD, and the HC group had an equal number of males and females. The patients with SZ had more tobacco smokers than both other groups. Age differed slightly, but significant statistically, between patients with MDD and controls ($t = 2.10$, $p = 0.041$) and did not differ between patients with SZ and controls nor between patients with SZ and patients with MDD.

Chlorpromazine equivalent levels, SANS, SAPS, and Montgomery–Åsberg scores did not correlate with any of the reported significant group differences in TPJ functional connectivity.

Seed-Based Resting Functional Connectivity

Functional connectivity maps for each seed region were generated for all participants, and clusters of significant group differences are listed in Table 2 along with BA, cluster size, peak coordinates, *T*-score, peak *p* value, and cluster *p* value ($p < 0.05$, FWE-corrected). Group differences are also shown in Figure 1 for the anterior TPJ seeds and in Figure 2 for the posterior TPJ seeds, overlaid on normalized T1-weighted anatomical images. Any non-significant group comparisons were omitted from Table 2 and the figures.

Left Anterior TPJ Seed Connectivity

Reduced connectivity was found in patients with SZ compared to controls between the left anterior TPJ seed region and the bilateral dlPFC, bilateral posterior cingulate cortex (PCC), right inferior occipital cortex, and bilateral parietal cortex (Figure 1(a)). Reduced connectivity was found in patients with MDD compared to controls between the left anterior TPJ seed region and the bilateral parietal cortex and left superior frontal cortex (Figure 1(c)).

Right Anterior TPJ Seed Connectivity

Reduced connectivity was found in patients with SZ compared to controls between the right anterior TPJ seed region and the bilateral PCC and bilateral parietal

Table 1. Participant demographic and clinical data.

	Healthy controls ($n = 24$) Mean (SD)	Patients with schizophrenia ($n = 24$) Mean (SD)	Patients with MDD ($n = 24$) Mean (SD)
Gender, male/female	12/12	21/3	8/16
Age, years	23.8 (4.3)	23.2 (4.2)	21.2 (4.3)
Handedness, right/left	21/3	23/1	21/3
Parent education level[a]	3 (1)	3 (1)	3 (1)
Smoking status,[b] yes/no	0/24	13/11	2/22
Illness duration, range	–	13.7 (10.9)	13.5 (10.4)
SAPS, mean	–	10.3 (11.9)	–
SANS, mean	–	22.5 (14.5)	–
Montgomery–Åsberg, mean	–	–	22.7 (8.5)
On neuroleptics, atypical/typical/none	–	21/2/1	1/0/23
On antidepressants, yes/no	–	–	16/8
CPZ eq, mg/day	–	258.0 (222.5)	–

CPZ eq: chlorpromazine equivalent dose; MDD: major depressive disorder; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms; SD: standard deviation.

Independent samples *t*-tests found group differences: in gender between the SZ group and both other groups (HC/SZ: $p < 0.005$; HC/MDD: $p = 0.251$; SZ/MDD: $p < 0.001$), in age between the MDD group and HC group (HC/SZ: $p = 0.603$; HC/MDD: $p < 0.05$; SZ/MDD: $p = 0.120$), and in tobacco smoking status between the SZ group and both other groups (HC/SZ: $p < 0.001$; HC/MDD: $p = 0.155$; SZ/MDD: $p < 0.001$). No group differences were found in handedness or parental education.

[a]1: grade 10 or below; 2: grade 11–13; 3: college/university 1–3 years; 4: college/university 4 years or more.

[b]Smoking status obtained by self-report.

[c]Illness duration: in months from first psychotic symptom in patients with schizophrenia and from diagnostic threshold level met in patients with MDD.

Table 2. Clusters of between-group seed connectivity differences.

Region	BA	k[a]	Peak MNI coordinates (x, y, z)	Peak T score[b]	Peak p value (FWE)[c]	Cluster p value (FWE)[c]
Left anterior TPJ seed						
Schizophrenia < Controls						
L inferior parietal cortex	40	220	(−36, −36, 38)	5.66	0.014	0.001
R superior frontal cortex (dlPFC)	8	128	(24, 30, 48)	5.10	0.088	0.021
R parietal, postcentral gyrus	3	425	(42, −30, 60)	4.89	0.166	0.000
L superior parietal cortex	40/7	143	(−26, −42, 56)	4.69	0.284	0.013
R parietal cortex, precuneus	19	325	(30, −72, 46)	4.60	0.355	0.000
R/L PCC	31/7	949	(2, −62, 38)	4.60	0.361	0.000
R inferior medial occipital cortex	18/19	115	(14, −68, −10)	4.53	0.426	0.034
L parietal cortex, angular gyrus	39	154	(−40, −64, 38)	4.48	0.474	0.009
R superior frontal cortex	6	157	(24, 12, 64)	4.47	0.485	0.008
L superior frontal cortex	6	110	(−18, 26, 62)	4.44	0.509	0.040
Major depressive disorder < Controls						
R superior parietal, postcentral gyrus	3	1282	(42, −30, 60)	5.32	0.044	0.000
L superior frontal cortex	6	138	(−16, −2, 56)	4.46	0.492	0.015
L parietal, postcentral gyrus	1	127	(−32, −38, 70)	4.31	0.644	0.022
L superior parietal cortex	40/7	225	(−20, −42, 66)	4.22	0.745	0.001
Right anterior TPJ seed						
Schizophrenia < Controls						
L inferior parietal cortex	40	138	(−36, −36, 34)	5.82	0.008	0.016
R/L inferior PCC	30	425	(2, −64, 10)	5.05	0.102	0.000
R parietal, postcentral gyrus	3	381	(44, −28, 62)	4.54	0.403	0.000
L parietal, precuneus	19	189	(−36, −70, 44)	4.40	0.550	0.003
Major depressive disorder < Controls						
R/L parietal, postcentral gyrus	3	2073	(44, −28, 62)	5.41	0.032	0.000
L inferior occipital, lingual gyrus	19	300	(−24, −64, −8)	4.76	0.235	0.000
Left posterior TPJ seed						
Schizophrenia < Controls						
R parietal, postcentral gyrus	3	1411	(42, −28, 60)	5.51	0.024	0.000
L inferior parietal cortex	40	1314	(−34, −38, 36)	5.39	0.035	0.000
L dorsal anterior/middle cingulate	24/32	162	(−2, 6, 44)	4.89	0.164	0.007
L superior middle frontal gyrus	6	148	(−20, 10, 66)	4.56	0.391	0.011
R anterior middle frontal gyrus	10	119	(32, 52, 10)	4.02	0.908	0.029
Major depressive disorder < Controls						
L temporal, fusiform gyrus	37	120	(−48, −46, −20)	6.04	0.004	0.028
R parietal, postcentral gyrus	3	1541	(42, −28, 56)	5.40	0.033	0.000
L parietal, postcentral gyrus	3	125	(−44, −20, 54)	4.68	0.291	0.024
R superior frontal, precentral gyrus	4	181	(32, −22, 60)	4.42	0.532	0.004
R superior frontal cortex	6	126	(16, 4, 66)	4.13	0.824	0.023
Right posterior TPJ seed						
Schizophrenia < Controls						
R parietal, postcentral gyrus	3	1547	(42, −28, 56)	5.68	0.013	0.000
L superior frontal cortex	6	1174	(−26, −18, 64)	5.42	0.032	0.000
L/R medial frontal cortex	6	173	(−6, −8, 56)	5.35	0.041	0.004
L superior temporal cortex	22	442	(−50, −16, 4)	5.34	0.042	0.000
R/L inferior medial occipital cortex	18/17	960	(10, −78, 2)	5.21	0.064	0.000
L/R medial frontal cortex	6	248	(−12, −28, 52)	4.48	0.474	0.000

(continued)

Table 2. Continued.

Region	BA	k[a]	Peak MNI coordinates (x, y, z)	Peak T score[b]	Peak p value (FWE)[c]	Cluster p value (FWE)[c]
L parahippocampal gyrus	19	135	(−26, −52, −10)	4.39	0.570	0.016
L parietal cortex	7	133	(−24, −56, 34)	4.32	0.648	0.017
Major depressive disorder < Controls						
R/L parietal, precuneus	7	455	(4, −46, 48)	5.09	0.094	0.000
L/R parietal, precuneus	7	279	(−4, −52, 60)	4.72	0.270	0.000
R superior frontal cortex (dlPFC)	8	126	(28, 34, 50)	4.68	0.297	0.021
L inferior temporal, fusiform gyrus	37	119	(−46, −46, −20)	4.59	0.371	0.027
L superior frontal gyrus (dlPFC)	8/9	115	(−24, 32, 42)	4.28	0.685	0.031
Schizophrenia < Major depressive disorder						
L superior-posterior temporal cortex	21/39	138	(−42, −48, 4)	4.78	0.230	0.014
R inferior medial occipital cortex	18/17	214	(10, −78, 4)	4.40	0.558	0.001
R superior-posterior temporal cortex	41	149	(50, −34, 14)	4.18	0.783	0.010

BA: Brodmann area; dlPFC: dorsolateral prefrontal cortex; FWE: family-wise error corrected; k: cluster size; L: left; MNI: Montreal Neurological Institute; PCC: posterior cingulate cortex; R: right; TPJ: temporoparietal junction.
[a]Cluster threshold $k > 100$.
[b]T scores with degrees of freedom (1,67).
[c]All clusters with $p < 0.05$ (FWE) peak-level or cluster-level were included.

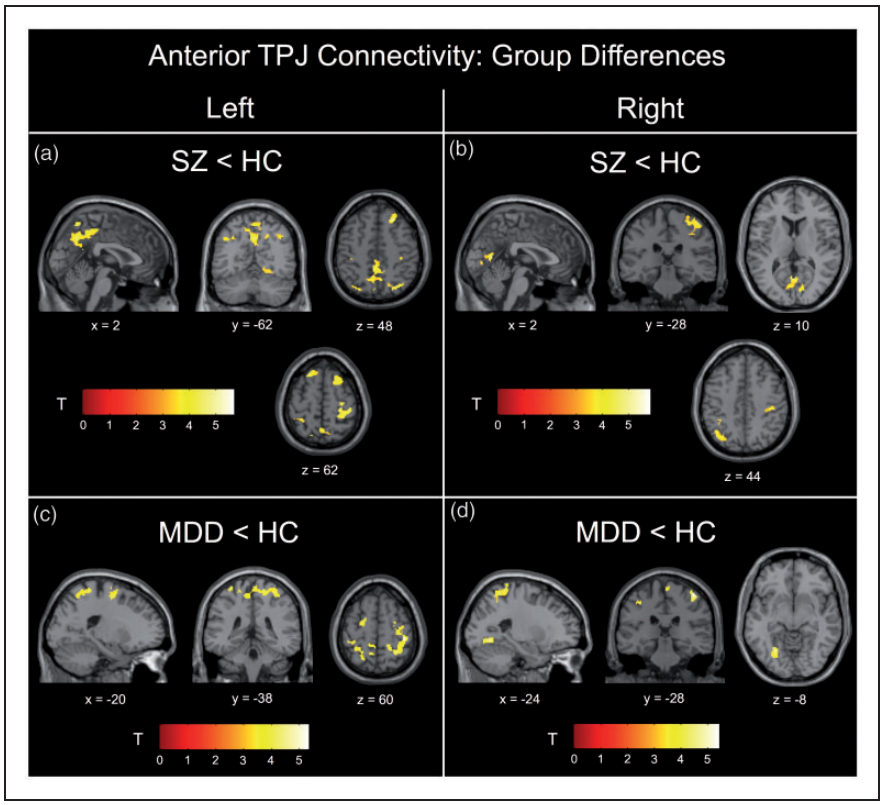

Figure 1. Between-group connectivity differences to bilateral anterior TPJ. Group differences are shown for the left anterior TPJ seed for patients with SZ < HC in (a) and patients with MDD < HC in (c). Group differences are shown for the right anterior TPJ seed for SZ < HC in (b) and MDD < HC in (d). Image slice labels are in MNI space. Statistical threshold set at cluster size $k = 100$ and $p < 0.001$ (uncorrected).
TPJ: temporoparietal junction; SZ: schizophrenia; HC: healthy controls; MDD: major depressive disorder.

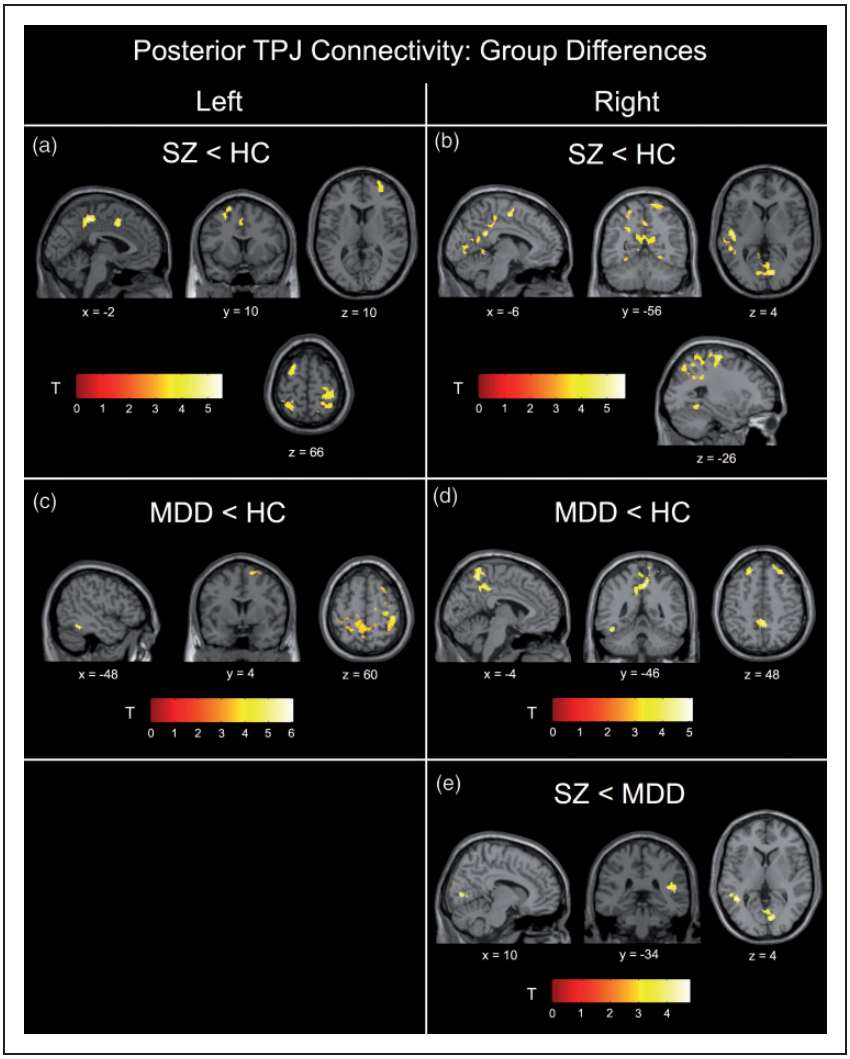

Figure 2. Between-group connectivity differences to bilateral posterior TPJ. Group differences are shown for the left posterior TPJ seed for patients with SZ < HC in (a) and patients with MDD < HC in (c). Group differences are shown for the right posterior TPJ seed for SZ < HC in (b), MDD < HC in (d), and SZ < MDD in (e). Image slice labels are in MNI space. Statistical threshold set at cluster size $k = 100$ and $p < 0.001$ (uncorrected).
TPJ: temporoparietal junction; SZ: schizophrenia; HC: healthy controls; MDD: major depressive disorder.

cortex (Figure 1(b)). Reduced connectivity was found in patients with MDD compared to controls between the right anterior TPJ seed region and the left inferior occipital cortex and bilateral parietal cortex (Figure 1(d)).

Left Posterior TPJ Seed Connectivity

Reduced connectivity was found in patients with SZ compared to controls between the left posterior TPJ seed region and bilateral middle cingulate cortex, left dorsal prefrontal cortex (PFC), right lateral PFC, and bilateral parietal cortex (Figure 2(a)). Reduced connectivity was found in patients with MDD compared to controls between the left posterior TPJ seed region and right dlPFC, left inferior-posterior temporal cortex, and bilateral parietal cortex (Figure 2(c)).

Right Posterior TPJ Seed Connectivity

Reduced connectivity was found in patients with SZ compared to controls between the right posterior TPJ seed region and bilateral middle cingulate cortex, left posterior insula/superior-posterior temporal cortex, bilateral inferior occipital cortex, right insula, left precuneus, and bilateral parietal cortex (Figure 2(b)). Reduced connectivity was found in patients with MDD compared to controls between the right posterior TPJ seed region and the bilateral PCC, bilateral precuneus, bilateral dlPFC, left

inferior occipital cortex, and bilateral parietal cortex (Figure 2(d)). Lastly, reduced connectivity was found in patients with SZ compared to patients with MDD between the right posterior TPJ seed region and the left fusiform gyrus, right inferior occipital cortex, and right superior-posterior temporal cortex/angular gyrus (Figure 2(e)).

Discussion

We found reduced connectivity in patients with SZ compared to controls between left anterior TPJ and dlPFC and PCC; between left posterior TPJ and middle cingulate cortex, left dorsal PFC, and right lateral PFC; between right anterior TPJ and bilateral PCC; and between right posterior TPJ and middle cingulate cortex, left posterior insula, and right insula. We found reduced connectivity in patients with MDD compared to controls between left posterior TPJ and right dlPFC and between right posterior TPJ and PCC and dlPFC. Lastly, we found reduced connectivity in patients with SZ compared to patients with MDD between right posterior TPJ and left fusiform gyrus and right superior-posterior temporal cortex.

As hypothesized, we found reduced connectivity between regions involved in executive control regions and all four subregions of the TPJ in patients with SZ compared to controls; between left anterior TPJ and PCC; between left posterior TPJ and middle cingulate; between right anterior TPJ and PCC; and between right posterior TPJ and middle cingulate. Patients with MDD showed reduced connectivity compared to controls between the right posterior TPJ and the PCC, which we did not predict to be affected in MDD. The PCC is involved in executive control and is a central node of the default mode network.[24] Further, the PCC has been shown to be activated during autobiographical memory retrieval[25] and upon hearing emotional words,[26] which may explain the changes we observed in patients with MDD. Patients with SZ have been suggested to have salience anomalies which might reflect the connectivity deficits we found between the TPJ and execute control regions. We found deficit connectivity between the dlPFC and the left anterior TPJ and left posterior TPJ in patients with SZ compared to controls, and the left posterior TPJ and right posterior TPJ in patients with MDD compared to controls, which would be expected as the dlPFC is involved in emotion regulation and is a central forebrain hub connecting the directed effort, emotional encoding, and representational brain networks.[27] As predicted, we found that the most striking reduction in connectivity was to the right posterior TPJ.

Patients with SZ had less connectivity than controls to the left and right insula, an area connected to ventral frontal attentional regions associated with salience and internal representations; the ventral attentional network has been shown to be linked to the TPJ.[6,7] The only statistically significant difference between patients with SZ and MDD was reduced connectivity in patients with SZ between the right posterior TPJ and the left fusiform gyrus, right inferior occipital gyrus, and right superior-posterior temporal cortex/angular gyrus. The right posterior TPJ might be expected to demonstrate reduced connectivity as this region is associated with theory of mind and processing of social information,[2,4] which is often disrupted in patients with SZ.[28,29]

To our knowledge, no previous study has examined TPJ connectivity in both MDD and SZ. However, Poeppl et al.[10] examined right TPJ functional connectivity in 72 patients with MDD and 76 matched HC and suggested an imbalance of connectivity of subregions of the right TPJ in MDD rather than a disruption in connectivity of the entire right TPJ. Specifically, they found that the posterior right TPJ had reduced connectivity in MDD compared to controls to behavioral control (posterior medial frontal cortex) and visuospatial processing (dorsal visual cortex) regions and increased connectivity in MDD compared to controls to cognitive control (left dlPFC, parahippocampus), reward (subgenual anterior cingulate cortex, medial orbitofrontal cortex, PCC), and memory retrieval and social cognition (precuneus) regions.[10] Further, they found the opposite/antagonistic pattern in the right anterior TPJ as in the right *posterior* TPJ.[10] The current study is consistent with this study in that we found differences in connectivity to the subregions of the TPJ in MDD, and in SZ, but we did not detect an antagonistic relationship between the anterior and posterior regions of the TPJ. As in that previous paper,[10] we found decreased connectivity between the right anterior TPJ and a visuospatial processing region (left inferior occipital cortex) in MDD compared to controls. In contrast to that previous paper,[10] we found decreased rather than increased connectivity between the right posterior TPJ and memory retrieval and social cognition (precuneus) and cognitive control (dlPFC) regions. Further, the current study did not find the differences reported in that previous paper in connectivity between the right TPJ and reward and behavioral control regions between MDD and controls.

Several demographic and methodological differences between the current study and the Poeppl et al. study may account for the discrepant findings. The Poeppl et al. study had a larger sample size (72 MDD/76 controls) compared to the 24 subjects in each group in the current study; the subjects in that previous study were older (38 years) and the patients were more chronic in their illness than the current study (23 years); and the current study had more females than males in patients with MDD. Further, the Poeppl et al. study measured

positive and negative connectivity (or correlation polarity) to the TPJ seeds in each group separately and then compared groups,[10] while the current study measured connectivity differences between groups directly.

Limitations

Several limitations of our study must be mentioned. The majority of the patients in this study were stable on medication. Antipsychotic medication has been shown to affect thalamocortical connections,[30] but this is unlikely to account for the differences we observed in patients with SZ compared to controls as we did not find similar differences in patients with SZ compared to patients with MDD, which would be expected if antipsychotic medication was solely responsible for the observed differences in patients with SZ. Further, there was no significant correlation between chlorpromazine equivalent dose and the observed significant differences. It is unclear how antidepressant medication might affect resting networks,[31] and therefore, we did not address this in our study.

As in all resting-state fMRI studies, it is difficult to ensure subjects were at rest during the scan even though they confirmed after the scan that they were in fact awake, with their eyes closed, and let their minds wander. However, the literature consistently identifies resting networks in controls and in SZ and MDD. Although results are related to resting-state abnormalities, they are not without implications for conditions of cognitive challenge, including elongation of task-facilitated stimulus encoding in memory-search and related paradigms.[27,32,33] Formal theory[34] has integrated the latter with context-processing deficit,[35,36] which arguably incorporates impairment in the processing of social stimuli, including those involved in theory of mind.[37]

Other limitations include the relatively small sample size of this study compared to some other studies and the differences in gender and tobacco smoking status between our groups. We did however covary for gender and smoking status in our analyses to help mitigate any potential differences attributed to gender or smoking. Lastly, although there was a slight difference in age between patients with MDD and controls, we did not covary for age.

Conclusion

This is the first study that directly measured the functional connectivity using a seed-based approach to bilateral anterior and posterior TPJ in SZ, MDD, and HC. Patients with SZ showed deficit connectivity compared to controls between executive control regions and all four subregions of the TPJ and deficit connectivity compared to patients with MDD to the right posterior TPJ. Patients with MDD showed deficit connectivity compared to controls between the right posterior TPJ and an emotion regulation region, but we did not detect the expected deficit in reward processing regions. As expected, we detected more widespread deficits in connectivity to the posterior versus anterior TPJ and more deficits in the right versus left hemisphere. Functional connectivity to the TPJ was demonstrated to be disrupted in both SZ and MDD. However, TPJ connectivity may differ in these disorders with reduced connectivity in SZ versus MDD between TPJ and posterior brain regions.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Financial support is acknowledged from the Canadian Institutes of Health Research (grant number 12078) and the Tanna Schulich Chair in Neuroscience and Mental Health.

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