ORIGINAL RESEARCH

Structural equation modeling approach between salience network dysfunction, depressed mood, and subjective quality of life in schizophrenia: an ICA resting-state fMRI study

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Purpose: Quality of life (QOL) is an important clinical outcome for patients with schizophrenia, and recent studies have focused on subjective QOL. We evaluated the causal relationship between psychosocial aspect of subjective QOL, symptoms, cognitive functions, and salience network (SN) dysfunction in schizophrenia using structural equation modeling (SEM).

Patients and methods: We performed a cross-sectional study of 21 patients with symptomatically stabilized schizophrenia and 21 age-, sex-, and education level-matched healthy controls who underwent resting-state functional magnetic resonance imaging. We evaluated SN dysfunction in schizophrenia using independent component analysis (ICA). We rated participant psychopathology using the Positive and Negative Syndrome Scale (PANSS), the Brief Assessment of Cognition in Schizophrenia (BACS), and the Calgary Depression Scale for Schizophrenia (CDSS). We rated psychosocial aspect of subjective QOL using the Schizophrenia Quality of Life Scale (SQLS) psychosocial subscale. We applied SEM to examine the relationships between SN dysfunction, PANSS positive and negative scores, CDSS total scores, BACS composite scores, and SQLS psychosocial subscale scores.

Results: In second-level analysis after group ICA, patient group had significant lower right pallidum functional connectivity (FC) within the SN than the controls did (Montreal Neurological Institute [MNI] $[x\ y\ z] = [22\ -2\ -6]$) ($p = 0.027$, family-wise error [FWE] corrected). In SEM, we obtained a good fit for an SEM model in which SN dysfunction causes depressed mood, which in turn determines psychosocial aspect of subjective QOL (chi-squared $p = 0.9$, root mean square error of approximation (RMSEA) < 0.001, comparative fit index [CFI] = 1.00, and standardized root mean square residual [SRMR]= 0.020).

Conclusion: We found a continuous process by which SN dysfunction causes depressed moods that determine psychosocial aspect of subjective QOL in schizophrenia. This is the first report that offers a unified explanation of functional neuroimaging, symptoms, and outcomes. Future studies combining neuroimaging techniques and clinical assessments would elucidate schizophrenia's pathogenesis.

Keywords: depressed mood, salience network, schizophrenia, structural equation modeling, subjective quality of life, resting-state fMRI

Introduction

Living in the community is thought to contribute to quality of life (QOL).[1] Most patients commonly have the deficit of functional outcome,[2,3] which is defined as a wide range of real-world functions including independent living, financial management,

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employment, and leisure/social activities,[4] persistently. QOL is therefore an important clinical outcome for patients with schizophrenia.[5]

QOL in patients with schizophrenia has been measured subjectively and objectively. Objective QOL includes indicators of health and living conditions, sociodemographic items, and a functioning role in society, whereas subjective QOL includes indicators of general and domain-specific life satisfaction.[6] Because patients exhibit cognitive dysfunction,[7] their subjective QOL has historically been considered unreliable,[8] but it is currently contended that symptomatically stable patients can assess their own QOL.[9] However, researchers should note that objective and subjective QOLs can differ due their potentially different influencing factors.[10,11]

Subjective QOL for patients with schizophrenia is associated with multiple factors including depressed mood,[12] positive symptoms,[13] negative symptoms,[14,15] neuroleptic doses,[10] and cognitive function,[16] but studies have reported conflicting results, such as QOL being positively correlated with cognitive function[17,18] or unrelated to it.[13,19,20] This inconsistency suggests spurious correlations or asymmetric relationships between factors associated with subjective QOL,[21] such that one factor affects others, or several factors reciprocally affect each other. A causal interpretation of cross-sectional data is needed prior to any randomized experiments mechanistically examining subjective QOL. Understanding the neural basis of patients' behavior is particularly important for optimizing future experiments.

In recent years, magnetic resonance imaging (MRI) has been used to elucidate the pathology of schizophrenia. Resting-state functional MRI (rsfMRI) studies have reported associations between resting-state network (RSN) abnormalities and psychiatric symptoms.[22–25] Previous studies have focused on dysfunctions in three important RSNs: the default mode network (DMN), the central executive network (CEN), and the salience network (SN).[26] Specifically, the SN, which includes the frontoinsular cortex and anterior cingulate cortex,[27] plays a central role among them. The SN identifies salient stimuli, regulates the DMN and CEN related to subsequent processing, and forms emotions.[28,29] Therefore, SN dysfunction has been proposed as a crucial mechanism for several schizophrenia symptoms[30] and is related to depressed mood, positive and negative symptoms, and cognitive function in psychiatric diseases.[31] This suggests that it affects subjective QOL, but the exact interrelationships between SN dysfunction, subjective QOL, depressed mood, positive symptoms, negative symptoms, and cognitive function remain unclear, as do the relative contributions of each of these determinants.

We conducted a cross-sectional study to evaluate the relationship between subjective QOL, symptoms, cognitive functions, and SN connectivity of rsfMRI in symptomatically stabilized patients with schizophrenia. In evaluating subjective QOL, we focused on psychosocial aspect of that because it includes various emotional problems such as solitude, depressed mood, and despair that markedly influence overall subjective QOL.[32] And we evaluated SN dysfunction in schizophrenia using resting-state fMRI with combined group independent component analysis (ICA) for inclusion of SN connectivity in the following path analyses. Our aim was to determine the causal interpretation between psychosocial aspect of subjective QOL, symptoms, cognitive functions, and SN dysfunction in schizophrenia. To understand psychosocial aspect of subjective QOL clearly, we tried to find the biological markers which affect the symptoms and the outcomes in schizophrenia. Here, we focused on brain function as a biological marker. In patients with schizophrenia, we expected a continuous process that SN, which plays a central role in RSNs, has decreased functional connectivity (FC), causes symptoms, and concludes psychosocial aspect of subjective QOL. We used structural equation modeling (SEM) to test a theory involving non-straightforward relationships between them. The SEM is a useful statistical method for the specification of directional influences among variables in cross-sectional studies,[33] and be widely used in test of causal assumption based on cross-sectional data of psychiatric disorders.[34–36] In particular, we modeled several causal assumptions based on the existing evidence, tested our data-set using SEM, and determined the best model.

Patients and methods
Participants

This study was conducted through the Department of Psychiatry at the Tokushima University Graduate School between June 2016 and December 2016. All subjects were recruited form Tokushima University Hospital, Japan, and gave written informed consent, and the study was approved by the Tokushima University ethics committee and performed in accordance with the principles of the Declaration of Helsinki.

We enrolled 21 patients and 21 age-, sex-, and education level-matched, healthy control subjects. The patients had been diagnosed with schizophrenia based on the criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. At the time enrolment, all patients were clinically stable, as judged by a therapeutic psychiatrist. The criteria for determining clinical stability were: no schedule to change treatment contents; essentially

no psychopathological changes; judgment of clinically stable by a therapeutic psychiatrist and patients themselves. We performed psychopathological assessments on each patient before and after the study, and we observed no major changes. Each patient's clinical stability was assessed from medical records, self-reports, and the observations of psychiatric staff and relatives. The exclusion criteria were a past history or presence of any serious disorders affecting the brain or cognitive functioning, such as epilepsy, serious head injury, or brain tumor; alcohol abuse; active drug use in the past year; or pregnancy or intention to become pregnant during the study period.

The healthy control subjects were evaluated with structured clinical interviews to confirm the absence of schizophrenia and had no history of neurological or psychiatric disorders or any first-degree relatives with psychotic episodes. The demographic and clinical data of two groups are shown in Table 1. Significant difference between two groups was found in IQ (Student's t-test, $p < 0.001$) rated by the Wechsler Adult Intelligence Scale-III short form.[37,38]

Clinical assessments

Psychopathology was rated using the Positive and Negative Syndrome Scale (PANSS).[39] Cognitive function was rated using the Brief Assessment of Cognition in Schizophrenia (BACS).[40,41] Depressed mood was rated using the Calgary Depression Scale for Schizophrenia (CDSS).[42,43] Psychosocial aspect of subjective QOL was rated using the Schizophrenia Quality of Life Scale (SQLS) psychosocial subscale[32,44] (Table 1). The SQLS is a self-reported, 30-item questionnaire for measuring QOL specific to patients with schizophrenia with good reliability and validity. It is composed of three scales: psychosocial, motivation/energy, and symptoms/ side effects. Lower scores indicate higher levels of subjective QOL.[32,44] As motivation/energy subscale and symptoms/ side-effects subscale did not differ significantly between the two groups, we did not consider them for following analyses.

Image acquisition and pre-processing

All subjects underwent rsfMRI scanning while lying down with their eyes closed during resting wakefulness. We placed foam pads to prevent head movement during scanning. No stimuli were presented during scanning. For each subject, the rsfMRI scan lasted for 10 minutes.

We obtained a series of MRI scans on a 3-T Discovery MR750 device (GE Medical Systems, Chicago, IL, USA) with a 24-channel phased-array head coil at the Tokushima University Hospital Department of Radiology. Structural images were obtained using a three-dimensional axial T1-weighted fast spoiled gradient-recalled-echo (GRE) sequence (echo time = 3.03 ms, retention time = 6.93 ms, flip angle = 11°, matrix = 512 × 512, voxel size = 0.46 × 0.46 mm^2, slice thickness = 1.2 mm, inter-slice gap = 0 mm, number of slices = 392). At the same locations as those of the anatomical slices, functional images were collected in runs using a T2*-weighted GRE planar imaging sequence (echo time = 30 ms, retention time = 2,500 ms, flip angle = 80°, matrix = 64 × 64, slice thickness = 3.2 mm, number of slices = 40) sensitive to blood oxygenation level-dependent contrast. We acquired one structural T1-weighted volume and 240 functional T2*-weighted volumes.

After a quality check, both structural and functional images were processed using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm/). The slice time-corrected functional data were realigned and registered to their mean by correcting for head motion using a six-parameter rigid-body transformation. All subjects did not have excessive head motion (>2.0 mm translation and/or > 2.0° rotation) during scan. Furthermore, we also compared the differences of four head motion metrics (Mean Motion, Maximum Motion, Number of Movements, and Rotation),[45] which were calculated from the translation and rotation parameters from the rigid body correction,

Table 1 Demographic and clinical parameters of the healthy control and patient groups

Characteristics	Schizophrenia (mean ± SD)	Controls (mean ± SD)	p-value
Number (male/female)	21 (11/10)	21 (11/10)	ns[a]
Age (years)	42.3 ± 10.2	42.7 ± 10.6	ns[b]
Education level (years)	14.3 ± 1.8	15 ± 2.3	ns[c]
Handedness (right/left)	21/0	21/0	
IQ (WAIS-III short form)	83.6 ± 14.8	106.0 ±15.8	<0.001[b]
SQLS			
Psychosocial	24.5 ± 13.5	17.2 ± 7.3	<0.05[b]
Motivation/energy	13.4 ± 5.0	11.0 ± 4.0	ns[b]
Symptom/side effects	9.2 ± 9.6	5.9 ± 4.8	ns[c]
Duration of illness (years)	15.9 ± 8.4		
Drug (mg/day, CPZ equivalent[d])	380.6 ± 264.3		
PANSS			
Positive	11.9 ± 3.5		
Negative	15.7 ± 4.1		
General	29.0 ± 5.9		
CDSS total score	3.1 ± 3.3		
BACS composite score	−1.26 ± 0.84		
DIEPSS total score	1.5 ± 2.1		

Notes: [a]Chi-square test; [b]Student's t-test; [c]Mann–Whitney U-test; [d]CPZ equivalents were calculated according to Inagaki and Inada.[75]
Abbreviations: BACS, Brief Assessment of Cognition in Schizophrenia; CDSS, Calgary Depression Scale for Schizophrenia; CPZ, chlorpromazine; DIEPSS, Drug Induced Extra-Pyramidal Symptoms Scale; PANSS, Positive and Negative Syndrome Scale; SQLS, Schizophrenia Quality of Life Scale; WAIS-III, Wechsler Adult Intelligence Scale-III; ns, not significant.

between groups. There were no significant differences in these head motion metrics between patients and controls. Therefore, the imaging data of all subjects were taking into consideration in further analyses. The realigned images were indirectly normalized to Montreal Neurological Institute (MNI) space. The resulting data were smoothed with an isotropic 8 mm full-width at half-maximum Gaussian kernel.

Group ICA

Pre-processed images were analyzed with group ICA using the Group ICA fMRI Toolbox (GIFT; http://mialab.mrn.org/software/gift/index.html)[46,47] implemented in Matlab (MathWorks, Natick, MA, USA). For computational feasibility, the previously concatenated data from all subjects were reduced using principal component analysis, after which ICA was performed with the infomax algorithm.[48] This identified a spatial map of 20 consistent spatially independent components for each subject that was reconstructed using group ICA and converted to z-values. To identify the component that represented the SN, the components were sorted in GIFT using cross-voxel correlation with an SN template from Shirer et al (http://findlab.stanford.edu/functional_ROIs.htm).[49] The component with the highest spatial correlation with the SN template was selected as the SN. Subject-specific SN components were then entered into second-level analysis in SPM8.

Model specification

In order to apply SEM, we developed the hypotheses based on previous studies as follows. SN dysfunction has been reported to be related to depressed mood, positive and negative symptoms, and cognitive function in psychiatric disease.[31] Subjective QOL has been reported to be most related to depressed mood in schizophrenia.[50] It has also been reported that subjective QOL is related to positive and negative symptoms in schizophrenia.[15] It has been reported that subjective QOL is related to negative symptoms rather than positive symptoms.[14] In contrast, it has been reported that subjective QOL is related to positive symptoms rather than negative symptoms.[13] Furthermore, subjective QOL has been reported to be related to cognitive function in schizophrenia.[16]

By considering these previous studies, we proposed that symptoms (positive, negative, or depressed mood) or cognitive function mediate the relationship between SN dysfunction and psychosocial aspect of subjective QOL. Based on our hypotheses, we made the following models (Figure S1). To examine the mediation effect of symptoms and cognitive function between SN dysfunction and psychosocial aspect of subjective QOL, we tested the coefficient for direct and indirect relationship between SN dysfunction and psychosocial aspect of subjective QOL in models 5–8.

Model 1: SN dysfunction influences psychosocial aspect of subjective QOL indirectly via positive symptoms.[13,15,31]

Model 2: SN dysfunction influences psychosocial aspect of subjective QOL indirectly via negative symptoms.[14,15,31]

Model 3: SN dysfunction influences psychosocial aspect of subjective QOL indirectly via depressed mood.[31,50]

Model 4: SN dysfunction influences psychosocial aspect of subjective QOL indirectly via cognitive function.[16,31]

Model 5: SN dysfunction influences psychosocial aspect of subjective QOL, both directly and indirectly via positive symptoms.

Model 6: SN dysfunction influences psychosocial aspect of subjective QOL, both directly and indirectly via negative symptoms.

Model 7: SN dysfunction influences psychosocial aspect of subjective QOL, both directly and indirectly via depressed mood.

Model 8: SN dysfunction influences psychosocial aspect of subjective QOL, both directly and indirectly via cognitive function.

Statistical analyses

We compared subject-specific SN component maps in the patient and control groups using two-sample t-tests. Z-values of these maps were used to calculate FC strength. We used voxel- and cluster-level family-wise error (FWE) corrections to guard against type I errors. And then, mean FC z-values were extracted from the region with significant differences between two groups for purposes of following path analyses.

Depending on whether the Shapiro–Wilk test indicated normal or non-normal distributions, we used Pearson's or Spearman's correlation coefficients to analyze correlations between SN dysfunction, positive symptoms, negative symptoms, depressed mood, cognitive function, and psychosocial aspect of subjective QOL. In addition, correlation analyses between chlorpromazine-equivalent antipsychotic doses and experimental variables, Drug Induced Extra-Pyramidal Symptoms Scale (DIEPSS) and experimental variables were conducted to assess the effects of medications and side effects. These analyses were performed in SPSS version 22 (IBM, Armonk, NY, USA). All tests were two-sided, and Bonferroni corrections were applied to maintain an overall type I error rate of 0.05.

SEM was then conducted using lavaan[51] and semTools[52] packages for R (R Project for Statistical Computing, Vienna, Austria). The model parameters were determined through re-sampling method by bootstrapping (n = 1,000). We evaluated the model fit using the chi-squared statistic ($p \geq 0.05$), the root mean square error of approximation (RMSEA < 0.05), the comparative fit index (CFI $\geq$ 0.95), and the standardized root mean square residuals (SRMR $\leq$ 0.08).[53] The path coefficient's strength was defined as weak ($r < 0.2$), moderate ($r = 0.2$–0.5), or strong ($r > 0.5$), and significance was defined as $p < 0.05$.[54] Correlation analyses and SEM were performed with ICA results, PANSS positive and negative scores, CDSS total scores, BACS composite scores, and SQLS psychosocial subscale scores. A composite score was calculated by averaging all of the six standardized primary measures from the BACS.[41]

Results
Group ICA
Using a group ICA approach, we identified a consistent SN component in all subjects. Figure 1 shows the two groups' SN spatial patterns (FWE-corrected one-sample t-test: $p < 0.05$). The groups had similar SN expressions, but the patients had significant lower right pallidum FCs within the SN than the controls did (MNI [$x\,y\,z$] = [22 −2 −6]) ($p = 0.027$, FWE-corrected) (Table 2, Figure 2A and B). For purposes of SEM, mean FC z-values were extracted from the right pallidum cluster.

Correlations between variables
The correlation analysis results are shown in Table 3. We found significant correlations between SQLS psychosocial subscale scores and CDSS total scores (Spearman's

$r = 0.785$, $p < 0.001$), and between PANSS positive and negative scores (Pearson's $r = 0.746$, $p < 0.005$). There were no significant correlations between antipsychotic doses and any experimental variables nor DIEPSS and any experimental variables.

SEM
We conducted the SEM on eight models (Figure S1). Table 4 presents their fit measures. Model 3 provided a good fit (chi-squared $p = 0.9$, RMSEA < 0.001, CFI = 1.00, and SRMR = 0.020) that was better than that of the other models, as indicated by its smaller Akaike's and Bayesian information criteria (Table 4). We did not find direct effect from right pallidum FC to SQLS psychosocial subscale scores because direct path between them had no significant association in Models 5–8. Only Models 3 and 7 had significant and moderate-to-strong associations between right pallidum FC and CDSS total scores (path coefficient = −0.43, $p = 0.02$; path coefficient = −0.43, $p = 0.02$) and between CDSS total scores and SQLS psychosocial subscale scores (path coefficient = 0.76, $p < 0.001$; path coefficient = 0.79, $p < 0.001$), which are common in both models. Direct path between right pallidum FC and SQLS psychosocial subscale scores may be removable. Model 1 was the second best model (chi-squared $p = 0.49$, RMSEA = 0.017, CFI = 1.00, and SRMR = 0.082); however, all of their paths were not statistically significant. From abovementioned findings, we concluded that Model 3 is the best model (Figure 3).

Discussion
Our goal was to explore the relationship between SN dysfunction, symptoms, and QOL in patients with schizophrenia. We hypothesized that symptoms mediate the relationship
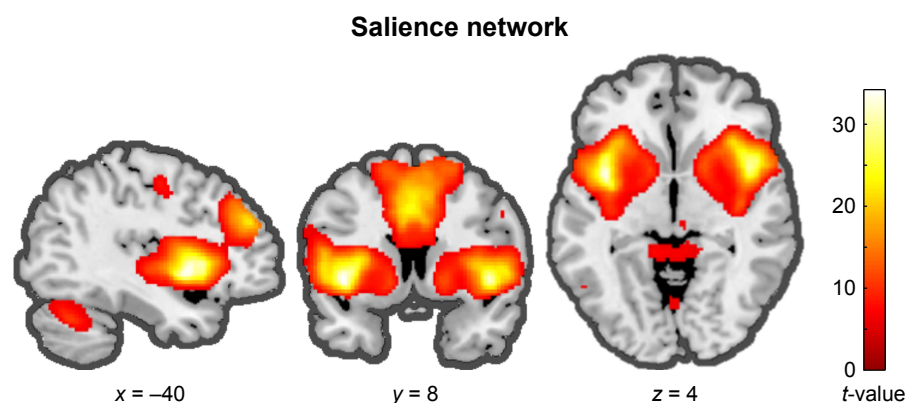
Salience network

Figure 1 The ICA analysis results.
Notes: Spatial maps are shown based on t-statistics with significance defined as FWE-corrected $p < 0.05$. This RSN map was highly correlated with the salience network,[49] which includes the insular cortex and anterior cingulate cortex. The color bar represents t-values.
Abbreviations: FWE, family-wise error; ICA, independent component analysis; RSN, resting-state network.

Table 2 Regions showing significant decreased salience network functional connectivity in patients with schizophrenia (n = 21) compared to controls (n = 21)

Region	MNI [x y z] (mm)	Voxel number	t-value	Cluster-level ($p_{FWE-corr}$)	Voxel-level ($p_{FWE-corr}$)
Right pallidum	[22 −2 −6]	245	5.8	0.010	0.027

Note: The table lists the region's MNI coordinate, number of voxels (cluster size), peak voxel t-value, cluster-level p-value, and the voxel-level p-value.
Abbreviations: FWE-corr, family-wise error corrected; MNI, Montreal Neurological Institute.
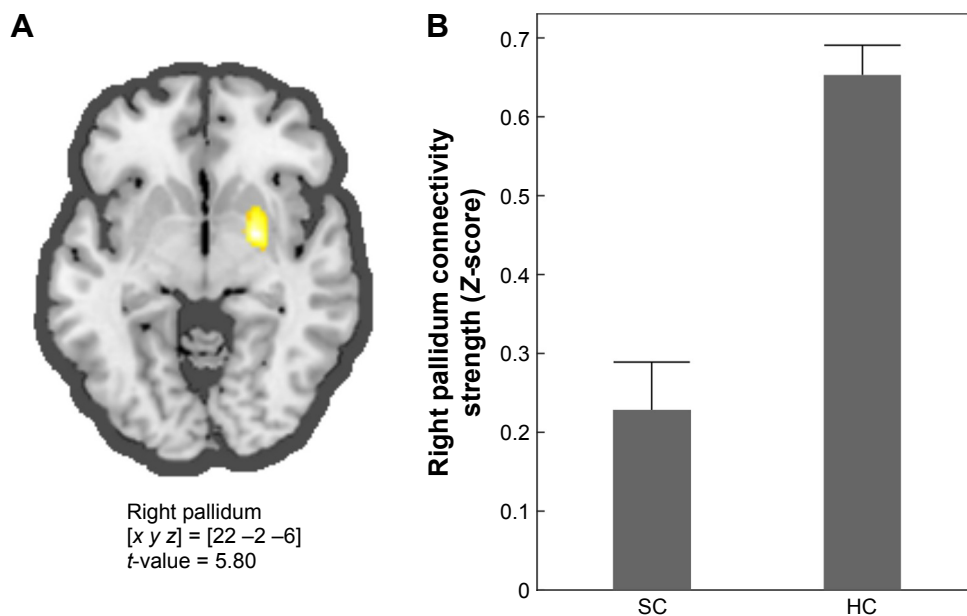
between SN dysfunction and QOL. Through SEM, we identified a causal relationship confirming this hypothesis.

The SN is thought to be a central RSN system that enables transitions between various brain states. It is therefore described as the core region in emotional regulation and cognitive processing for various stimuli.[28,29] SN dysfunction is related to depressed mood, positive and negative symptoms, and cognitive function in psychiatric diseases.[31] Furthermore, it has been proposed as a mechanism underlying several core symptoms of schizophrenia.[30] Our study is the first rsfMRI study to find an association between SN dysfunction and depressed mood in schizophrenia. This finding is important for understanding the SN's role in schizophrenia-associated psychosocial dysfunction and suggests that treating SN dysfunction could improve psychosocial functioning.

The patients exhibited reduced SN connectivity in the pallidum, an SN-associated basal ganglion located deep beneath the cerebral cortex.[55–57] Previous studies have reported that pallidum activity is related to depressive symptoms in schizophrenia[58,59] and that pallidum structural abnormalities occur in schizophrenia.[60,61] The pallidum is thought to be related to motor sensation, motivation, and desire.[62] Our patients exhibited a cluster with significantly decreased FC that was mainly located in the ventral pallidum, which plays a particularly important role in processing and executing motivated behavior.[63,64] This motivational system is related to depressive symptoms.[65] In schizophrenia, motivational deficits are associated with depressed mood that is difficult to distinguish from negative symptoms[66] or medication-induced extrapyramidal symptoms (EPS).[67] However, the CDSS evaluates depressed mood in schizophrenia independently of EPS or negative symptoms.[68,69] Consistently, we found no significant correlations between CDSS and DIEPSS and PANSS negative scores. Our finding provides further evidence that SN dysfunction in schizophrenia causes depressive symptoms independent of EPS or negative symptoms.

We also found a strong association between psychosocial aspect of subjective QOL and depressed mood. Previous

Right pallidum
[x y z] = [22 −2 −6]
t-value = 5.80

Figure 2 Group comparisons of SN FC (patients versus controls).
Notes: (**A**) Compared to the controls, the patients exhibited significantly lower SN FC in the right pallidum ([x y z] = [22 −2 −6]). (**B**) Mean right pallidum FC values (Z-score) for patients and controls. The error bars indicate standard errors.
Abbreviations: FC, functional connectivity; SN, salience network; SC, schizophrenia; HC, healthy control.

Table 3 Correlation coefficients between right pallidum FC, PANSS positive and negative scores, CDSS total scores, BACS composite scores, and SQLS psychosocial subscale scores in patients with schizophrenia (n = 21)

Variables	FC of right pallidum	PANSS positive	PANSS negative	CDSS	BACS	PS of SQLS	Drug	DIEPSS
FC of right pallidum	I							
PANSS positive	−0.257[a]	I						
PANSS negative	−0.134[a]	0.746[a,**]	I					
CDSS	−0.509[b]	0.348[b]	0.171[b]	I				
BACS	−0.024[a]	−0.082[a]	−0.190[a]	−0.187[b]	I			
PS of SQLS	−0.275[a]	0.293[a]	0.230[a]	0.785[b,***]	−0.244[a]	I		
Drug	−0.291[b]	0.351[b]	0.143[b]	0.548[b]	0.005[b]	0.597[b]	I	
DIEPSS	−0.107[b]	0.529[b]	0.384[b]	−0.047[b]	0.351[b]	−0.011[b]	−0.187[b]	I

Notes: [a]Pearson correlation; [b]Spearman correlation; **$p < 0.005$; ***$p < 0.001$.
Abbreviations: BACS, Brief Assessment of Cognition in Schizophrenia; CDSS, Calgary Depression Scale for Schizophrenia; DIEPSS, Drug Induced Extra-Pyramidal Symptoms Scale; FC, functional connectivity; PANSS, Positive and Negative Syndrome Scale; PS, psychosocial; SQLS, Schizophrenia Quality of Life Scale.

studies suggested that subjective QOL is more relevant to depressed mood than are positive symptoms, negative symptoms, or cognitive function.[11,50,70] Given that we detected no significant causal roles for positive symptoms, negative symptoms, or cognitive function, our findings are consistent with these previous studies. However, the association of positive symptoms, negative symptoms, and cognitive function with SN dysfunction and subjective QOL have been reported in previous studies.[13–16,31] Our patients were symptomatically stabilized, so they did not exhibit conspicuous positive

symptoms, negative symptoms, or cognitive dysfunction, which may account for the discrepancy with the previous study. An association of depressed mood with psychosocial aspect of subjective QOL may only be seen in symptomatically stabilized patients. Furthermore, such an inconsistency might be due to the measurement of several different aspects of subjective QOL in these previous studies. SQLS is composed of three subscales: psychosocial, motivation/energy, and symptoms/side effects. The motivation/energy subscale measures various problems of motivation and activity.[32]

Table 4 Fit measures for the structural equation models

Models	Fit index							Estimates of coefficients					
	p-value (chi-square)	RMSEA	CFI	TLI	SRMR	AIC	BIC	Regression			Estimates	SE	p-value
Model 1	0.49	0.017	1.00	0.99	0.082	180.40	184.58	Positive	~	Z-score	−0.26	0.22	0.24
								PS of SQLS	~	Positive	0.29	0.24	0.23
Model 2	0.36	0.14	<0.001	14.88	0.10	182.19	186.37	Negative	~	Z-score	−0.13	0.20	0.49
								PS of SQLS	~	Negative	0.23	0.22	0.29
Model 3	0.9	<0.001	1.00	1.13	0.020	161.29	165.47	CDSS	~	Z-score	−0.43	0.19	0.02*
								PS of SQLS	~	CDSS	0.76	0.16	<0.001***
Model 4	0.3	0.20	<0.001	−17.36	0.12	182.42	186.60	BACS	~	Z-score	−0.02	0.21	0.91
								PS of SQLS	~	BACS	−0.24	0.22	0.27
Model 5	–	–	–	–	–	181.39	186.62	PS of SQLS	~	Z-score	−0.21	0.20	0.27
								Positive	~	Z-score	−0.26	0.23	0.25
								PS of SQLS	~	Positive	0.24	0.24	0.32
Model 6	–	–	–	–	–	182.80	188.02	PS of SQLS	~	Z-score	−0.25	0.20	0.21
								Negative	~	Z-score	−0.13	0.20	0.50
								PS of SQLS	~	Negative	0.20	0.20	0.33
Model 7	–	–	–	–	–	163.15	168.37	PS of SQLS	~	Z-score	0.06	0.14	0.66
								CDSS	~	Z-score	−0.43	0.18	0.02*
								PS of SQLS	~	CDSS	0.79	0.20	<0.001***
Model 8	–	–	–	–	–	182.58	187.80	PS of SQLS	~	Z-score	−0.28	0.22	0.20
								BACS	~	Z-score	−0.02	0.21	0.91
								PS of SQLS	~	BACS	−0.25	0.22	0.26

Notes: *$p < 0.05$; ***$p < 0.001$. "–" indicated as not available.
Abbreviations: AIC, Akaike's Information Criterion; BACS, Brief Assessment of Cognition in Schizophrenia; BIC, Bayesian Information Criterion; CDSS, Calgary Depression Scale for Schizophrenia; CFI, comparative fit index; PS, psychosocial; RMSEA, root mean square error of approximation; SE, standard error; SQLS, Schizophrenia Quality of Life Scale; SRMR, standardized root mean square residuals; TLI, Tucker-Levis index.
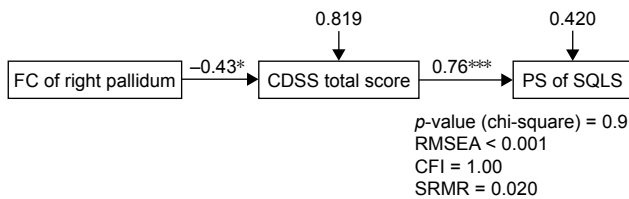
Figure 3 SEM results of the best model.

Notes: Model 3 exhibited the best fit (chi-squared p-value = 0.9, RMSEA < 0.001, CFI = 1.00, and SRMR = 0.020). The SEM revealed significant and moderate-to-strong associations between (1) right pallidum FC and CDSS total scores (path coefficient = −0.43, p-value < 0.05) and between (2) CDSS total scores and SQLS psychosocial subscale scores (path coefficient = 0.76, p-value < 0.001); *p < 0.05, ***p < 0.001.

Abbreviations: CFI, comparative fit index; FC, functional connectivity; CDSS, Calgary Depression Scale for Schizophrenia; RMSEA, root mean square error of approximation; PS, psychosocial; SEM, structural equation modeling; SN, salience network; SQLS, schizophrenia Quality of Life Scale; SRMR, standardized root mean square residuals.

The relationship between neurocognition and motivation has been reported in previous study.[71] Therefore, cognitive function may affect the motivation/energy subscale. The symptoms/side-effects subscale measures such issues as sleep disturbance, blurred vision, dizziness, muscle twitches, and dry mouth.[32] Patients with severe positive and/or negative symptoms may suffer from sleep disturbance and may use large amount of medication, which can cause more side-effects. Further studies involving various aspects of subjective QOL are needed in symptomatically diverse patients.

This is the first report to present a unified explanation of functional neuroimaging, symptoms, and outcomes in schizophrenia. Combining neuroimaging findings and clinical assessments provided better explanations for the mechanisms underlying psychosocial aspect of subjective QOL than were possible with clinical assessments alone. Through SEM, we found that decreased pallidum FC causes depressed moods that worsen psychosocial aspect of subjective QOL in schizophrenia. Our findings suggest that QOL may be improved by targeting depressed moods[72,73] and the SN reward system[30] through approaches such as cognitive behavioral therapy or pharmacotherapy.

This study has several limitations. First, all the patients were taking medications, so we could not exclude medication effects. However, we found no significant correlations between antipsychotic doses and any experimental variable, so we doubt that medications had an effect.

Second, we could not exclude the possibility that other networks, such as DMN and CEN, affected depressed mood and psychosocial aspect of subjective QOL. However, on additional group comparison between controls and patients, we could not find any significant group differences in DMN nor CEN (Figure S2). This suggests that SN may affect depressed mood more than DMN or CEN in symptomatically stabilized patients with schizophrenia.

Third, this was a cross-sectional study, not a prospective one. These findings derived from cross-sectional data should be confirmed by further large-scale and longitudinal research.

Fourth, psychosocial aspect of subjective QOL can be affected by socioeconomic factors such as support services, living environment, and frequency of contact with friends and family.[74] These aspects could not be controlled in our study. Further studies are necessary to explore the influence of such factors.

Finally, the relatively small sample size may limit the interpretation of our findings. Studies with larger sample sizes are needed to replicate our findings.

Conclusion

We indicated a continuous process by which SN dysfunction causes depressed moods that determine psychosocial aspect of subjective QOL in schizophrenia. Depressed mood is a common symptom of schizophrenia, and we suggested that focusing on depressed mood is important for improving patients' QOL. We think that our findings will be one of the scientific evidences leading to future studies. Combining neuroimaging techniques with clinical assessments would improve future studies into the pathogenesis of schizophrenia.

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Author contributions

M Ohta and M Nakataki designed the study. M Nakataki and T Ohmori managed the research project. M Ohta, M Nakataki, S Numata, T Tominaga, N Kameoka, H Kubo, and M Kinoshita recruited patients and discussed the results. T Takeda and K Matsuura conducted psychological examinations. M Otomo, N Takeichi, and M Harada performed fMRI. M Ohta and T Takeda organized the data. M Ohta, M Nakataki, and T Takeda searched the literature. M Ohta

analyzed the data and wrote the first draft of this manuscript. M Nakataki and T Ohmori supervised data analysis and revised the manuscript. All authors read and approved the final manuscript. All authors contributed toward data analysis, drafting, and revising the paper and agreed to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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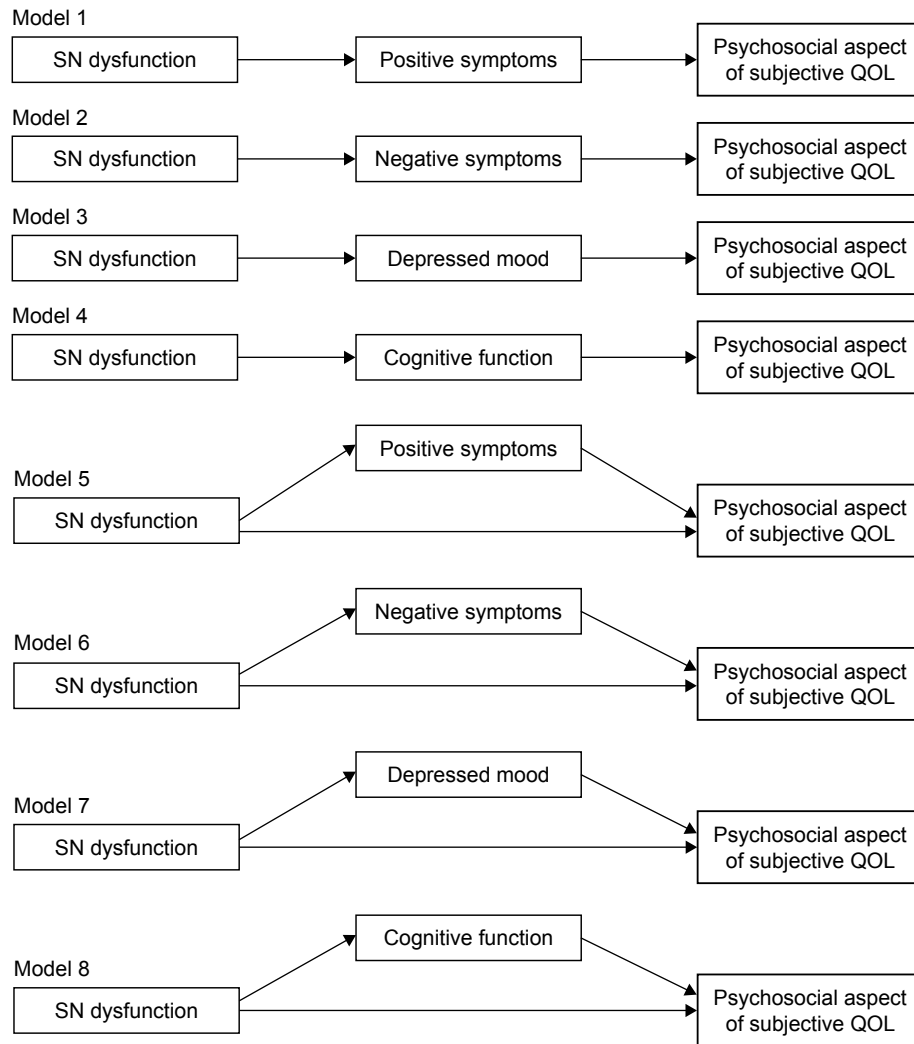
Supplementary materials

Model 1

| SN dysfunction | → | Positive symptoms | → | Psychosocial aspect of subjective QOL |

Model 2

| SN dysfunction | → | Negative symptoms | → | Psychosocial aspect of subjective QOL |

Model 3

| SN dysfunction | → | Depressed mood | → | Psychosocial aspect of subjective QOL |

Model 4

| SN dysfunction | → | Cognitive function | → | Psychosocial aspect of subjective QOL |

Model 5

Positive symptoms

SN dysfunction → Psychosocial aspect of subjective QOL

Model 6

Negative symptoms

SN dysfunction → Psychosocial aspect of subjective QOL

Model 7

Depressed mood

SN dysfunction → Psychosocial aspect of subjective QOL

Model 8

Cognitive function

SN dysfunction → Psychosocial aspect of subjective QOL

Figure S1 Model specification.
Note: Based on previous studies,[1–6] we developed the hypotheses and made eight models for the purpose of SEM.
Abbreviations: QOL, quality of life; SN, salience network; SEM, structural equation modeling.
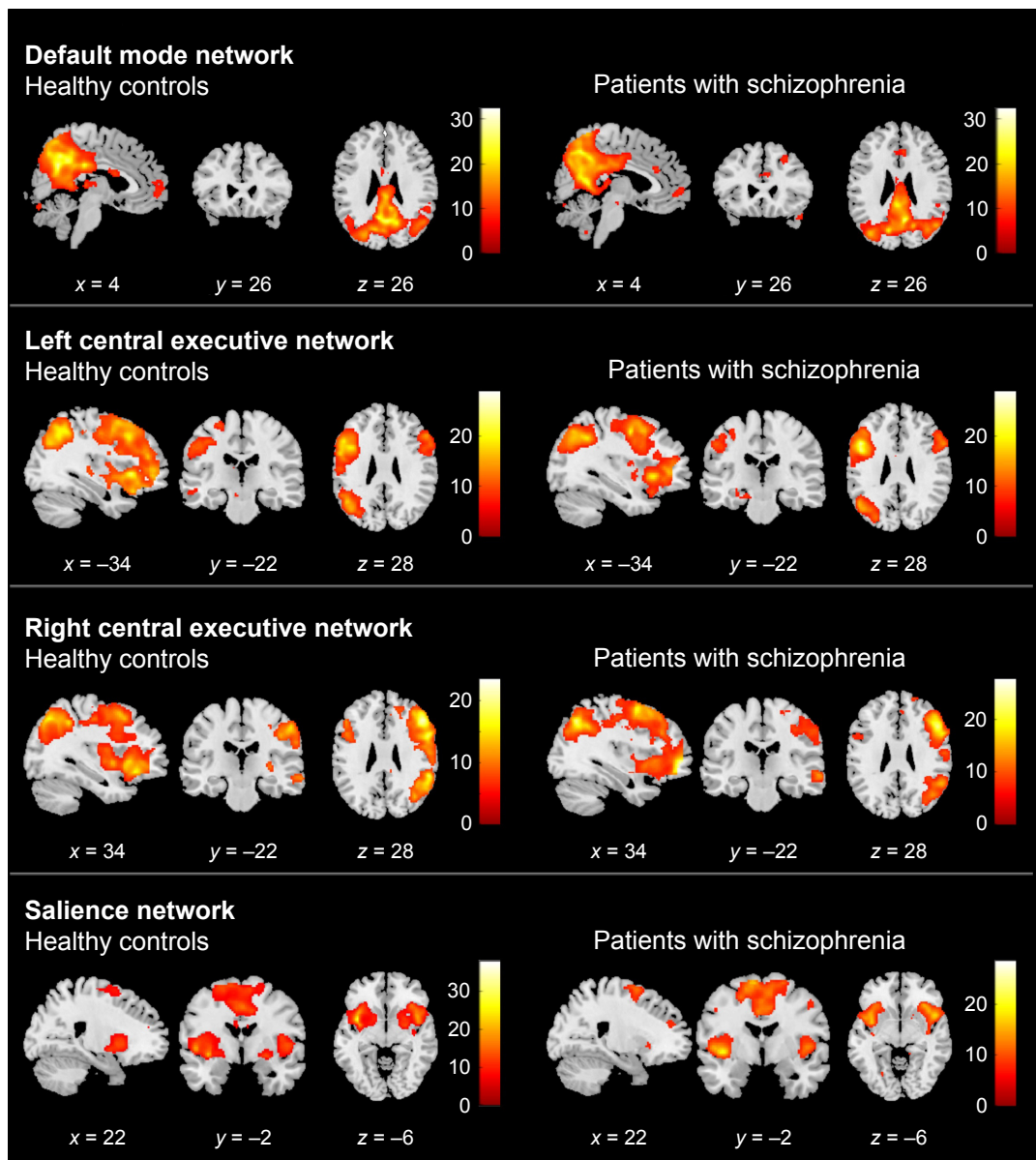
Figure S2 Comparison of connectivity maps for patients and controls across three RSNs (DMN, CEN, and SN).
Notes: Spatial maps are shown based on *t*-statistics with significance defined as FWE-corrected $p < 0.05$. Each RSN map was highly correlated with the RSN template (DMN, CEN, and SN),[7] respectively. The groups had similar DMN and CEN expressions. We could not find any significant group differences in DMN nor CEN.
Abbreviations: CEN, central executive network; DMN, default mode network; RSN, resting-state network; SN, salience network; FWE, family-wise error.

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