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Opposite Modulations of Thalamo-Cingulate and Fronto-IFOF Gray-White Matter Circuits Underlie Symptomatic and Cognitive Gains with Magnetic Seizure Therapy in Schizophrenia

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ABSTRACT

Magnetic seizure therapy (MST) has shown promise for treating schizophrenia, but the functional brain

changes associated with its clinical and cognitive outcomes remain unclear. We investigated gray matter – white matter (GM – WM) functional connectivity and its associations with symptom and cognitive changes following MST. Fifty-three patients with schizophrenia and 40 demographically matched healthy controls underwent baseline resting-state functional magnetic resonance imaging; 33 patients with usable pretreatment and post-treatment imaging data were included in longitudinal analyses. Functional connectivity was compared between groups and across treatment time points, and connectivity changes were examined in relation to clinical and cognitive changes. Following MST, patients showed reductions in psychotic symptoms and improvements in the MATRICS Consensus Cognitive Battery composite score and processing speed. Treatment-related connectivity changes predominantly involved GM – WM connections. Decreased connectivity within a thalamus – corona radiata – cingulate circuit was associated with symptom improvement, whereas increased connectivity involving the left inferior fronto-occipital fasciculus and frontal regions was associated with cognitive improvement. Exploratory atlas-based analyses identified spatial associations between functional connectivity patterns and normative histaminergic and serotonergic receptor distributions, including 5-HT4 receptor maps. These findings suggest that symptom and cognitive improvements following MST are associated with changes in GM – WM functional connectivity. The receptor mapping results provide an exploratory neurochemical context for these associations, rather than evidence of treatment-induced changes in neurotransmitter levels or receptor availability.

INTRODUCTION

Schizophrenia is a severe, chronic, and disabling psychiatric disorder characterized by disturbances in perception, affect, and behavior[1]. Despite continuing advances in pharmacological treatment, a substantial proportion of patients fail to achieve satisfactory clinical improvement. There is therefore an urgent demand for interventions that balance therapeutic efficacy with a favorable safety profile, especially for individuals with persistent or treatment-resistant disease[2, 3]. Magnetic seizure therapy (MST) is a novel neuromodulation technique that employs high-frequency, high-intensity magnetic stimulation to induce therapeutic seizures. Given the low skull impedance to magnetic fields, MST produces a more spatially restricted intracerebral electric field distribution than electroconvulsive therapy, which may confer advantages for cognitive function preservation[4–6]. Accumulating evidence attests to the clinical potential of MST for multiple major psychiatric disorders[6–9]. Notably, in available studies of schizophrenia, MST has shown broadly comparable antipsychotic efficacy, while appearing to be associated with fewer cognitive adverse effects and better overall tolerability[10–12].

Early head-modeling and electric-field simulation studies provided important clues, showing that the electric field generated by MST is more spatially restricted than that of electroconvulsive therapy[4, 13]. Building on these findings, several neuroimaging studies have extended the investigation to structural changes. A series of neuroplastic changes related to MST were reported in patients with schizophrenia, and the structural effects of MST and electroconvulsive therapy were compared, including changes in limbic system structures such as the hippocampus, as well as cortical thickness[14–16]. However, these studies have primarily focused on structural neuroplasticity and its relationship with cognitive safety. The neural basis for the benefits of MST treatment has not been fully elucidated. This longitudinal study is designed to uncover the neural infrastructure through which MST

exerts its therapeutic effects on psychotic symptoms in schizophrenia.

In this context, functional magnetic resonance imaging (fMRI) is particularly sensitive to functional alterations resulting from short-term treatment responses[17]. Despite its potential for characterizing functional brain reorganization following neuromodulatory interventions, direct evidence regarding functional circuit changes following MST remains limited. Cumulative evidence suggests that white matter (WM) serves more than merely a structural scaffold. Numerous studies have demonstrated detectable blood-oxygen-level-dependent (BOLD) signals within WM[18, 19], indicating that WM may act as a substrate for long distance propagation of gray matter (GM) signals. Several studies have reported that patients with schizophrenia exhibit alterations in WM functional organization, impaired interactions among WM networks, and decreased functional connectivity in major regions. Among these, altered functional connectivity involving the cingulum, uncinate fasciculus, and corpus callosum has been associated with impairments in working memory and processing speed[20], whereas functional abnormalities involving the corona radiata and thalamic radiation have been associated with clinical symptom severity and treatment-related symptom changes[21, 22]. Accordingly, the present study employs functional MRI to investigate the GM-WM network substrates that mediate MST-induced symptomatic amelioration in schizophrenia.

Moreover, at the molecular level, neurotransmitter systems provide a fundamental neurochemical basis for neuronal communication and large-scale brain network organization. Recent multimodal imaging studies have shown spatial associations between schizophrenia-related functional connectivity abnormalities and the distribution of multiple neurotransmitter receptors and transporters, including dopaminergic, serotonergic, and GABAergic systems[23, 24]. These findings suggest that macroscale functional dysconnectivity in schizophrenia is closely related to the underlying neurochemical

architecture. Therefore, investigating the spatial correspondence between MST-related connectivity changes and neurotransmitter receptor distributions may help identify candidate neurochemical systems involved in treatment-related circuit remodeling and provide directions for future molecular investigations.

In this study, we examined GM–WM functional connectivity in patients with schizophrenia before and after MST and evaluated associations between connectivity changes and changes in symptoms and cognition. We also performed exploratory analyses of the spatial correspondence between functional connectivity patterns and normative neurotransmitter receptor distributions. These analyses aimed to characterize treatment-associated functional changes and their potential neurochemical context.

METHODS

Participants

This imaging study was conducted within a previously established clinical cohort[10]. The parent clinical study was approved by the Ethics Committee of the First Hospital of Shanxi Medical University (Ethics No. 2021KX002). The study was also recorded in China’s National Medical Research Registration and Filing Information System (filing No. MR-14-26-017453). Written informed consent was obtained from all participants after a complete description of the study procedures.

Patients were eligible for inclusion if they were 18-65 years of age, right-handed, met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for schizophrenia, as independently confirmed by at least two attending psychiatrists, fulfilled the clinical indications for convulsive therapy, and had a Positive and Negative Syndrome Scale (PANSS) total score of $\geqslant$60. Exclusion criteria comprised a history of neurological disorders or head injury with loss

of consciousness; an unstable clinical condition or severe medical illness; any psychiatric disorder other than schizophrenia according to the DSM-5; alcohol or substance dependence within the preceding 6 months; MST or electroconvulsive therapy (ECT) within the preceding 6 months; contraindications to MRI, anesthesia, or convulsive therapy; a known allergy to propofol or succinylcholine; pregnancy or lactation; or an inability to complete the study assessments in Chinese.

A total of 53 eligible patients with schizophrenia had complete baseline clinical, cognitive, and MRI data and were included in the baseline case-control imaging analysis. Of these participants, 33 had valid MRI datasets at both baseline and post-treatment time points and were therefore included in the longitudinal imaging analysis. Participants were excluded from the longitudinal analysis for the following reasons: failure to complete the post-treatment MRI assessment (n = 9), failure to complete the planned MST treatment course (n = 4), excessive head motion or poor image quality (n = 3), incomplete imaging data (n = 2), and other reasons (n = 2).

In addition, 40 right-handed healthy controls group-matched to the patient group for age, sex, and years of education were recruited from the community. Healthy controls were excluded if they had a current or past psychiatric, neurological, or major medical disorder; a first-degree family history of major psychiatric or neurological illness; a history of head injury with loss of consciousness, alcohol or substance abuse; or any contraindication to MRI.

Clinical and Cognitive Assessments

Demographic and clinical data were collected at enrollment, including age, sex, years of education, family history, age at illness onset, illness duration, and antipsychotic medication dosage. Psychotic symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS), including the total

score and the positive, negative, and general psychopathology subscale scores. Cognitive function was assessed using the MATRICS Consensus Cognitive Battery (MCCB), including speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. All assessments were conducted by trained psychiatrists at baseline before MST (T0) and within 24 h after completion of the MST treatment course (T1).

MST Procedure

MST was performed under general anesthesia according to our previously reported study[10]. Stimulation was delivered using an NS7000 magnetic stimulator (Yiruide, Wuhan, China) with a circular coil. The coil was positioned over the vertex. MST was administered at a frequency of 100 Hz and 100% machine output, with a pulse width of 350 ± 20 μs. The stimulation duration was initially set at 4 s and gradually increased to a maximum of 10 s according to the individual seizure threshold and seizure adequacy. MST was administered once daily on consecutive weekdays, with a total of 5-8 sessions completed over approximately 2 weeks.

MRI Acquisition

MRI data were acquired using a 3 T Siemens Skyra scanner (Erlangen, Germany) with a 32-channel head coil. Post-treatment MRI was performed within 48 h after the final MST session. Resting-state functional images were obtained using an echo-planar imaging sequence with the following parameters: repetition time (TR) = 2.62 s, echo time (TE) = 30 ms, flip angle = 90°, field of view (FOV) = 192 × 192 mm², slice thickness = 3 mm, matrix size = 64 × 64, and 210 whole-brain volumes comprising 47 contiguous axial slices. During scanning, participants were instructed to keep their eyes closed, remain

still, and relax without focusing on any specific thought. A high-resolution 3D T1-weighted anatomical image was also obtained for each participant (TR = 1900 ms, TE = 3.98 ms, flip angle = 8°, matrix size = 174 × 192, 192 contiguous sagittal slices, slice thickness = 1 mm). All T1-weighted images were reviewed by a radiologist to exclude visible brain abnormalities or structural damage.

Image Preprocessing and FC Construction

MRI data were processed using SPM12 (www.fil.ion.ucl.ac.uk/spm) and MATLAB (www.mathworks.com). The 3D T1-weighted images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) employing the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) algorithm in SPM12. The preprocessing of resting-state fMRI data included the following steps: after removing the first 10 time points for signal stabilization, slice timing and head motion correction were applied (motion criteria: <3 mm and <3°). Nuisance regression was performed using 24 motion parameters and CSF signals. A scrubbing procedure (FD > 0.5) identified and regressed out high-motion time points. Functional images were then co-registered to individual T1-weighted images, normalized to MNI space, and resampled to 2-mm isotropic voxels. Spatial smoothing (FWHM = 6 mm), linear detrending, and band-pass filtering (0.01-0.10 Hz) were applied to reduce noise. Furthermore, to avoid confounding between GM and WM functional signals, during the smoothing step, individual GM and WM masks-generated from segmented structural images were used to smooth the functional signals within GM and WM regions separately. The separately smoothed images were then combined into a complete preprocessed functional image for subsequent statistical analysis. Using the Johns Hopkins University (JHU) white matter atlas and the Automated Anatomical Labeling 3 (AAL3) atlas as templates, we extracted the average BOLD signal time series

from each region of interest (ROI). Correlation matrices for WM-WM, GM-WM, and GM-GM connections were then constructed by calculating pairwise Pearson's correlation coefficients between ROI time series at the ROI level. Finally, Fisher's r-to-z transformation was applied to the correlation coefficients to improve their normality for subsequent statistical analysis.

Group-level Comparison of Functional Connectivity

At baseline, independent-samples t tests were used to compare GM-GM, GM-WM, and WM-WM functional connectivity between patients with schizophrenia and healthy controls. Paired-samples t tests were employed to compare functional connectivity before and after treatment, with the results corrected for multiple comparisons using the false discovery rate (FDR) method. For functional connections showing significant changes, changes in connectivity strength were extracted and subsequently subjected to correlation analyses with changes in clinical symptom scores to investigate the neural mechanisms underlying symptom improvement following MST.

Neurotransmitter Receptor Density Association Analysis

To construct a comprehensive cortical atlas of neurotransmitter receptor density, PET imaging data from 1,238 healthy participants were compiled. This atlas encompassed 19 receptors, transporters, and binding sites across nine major neurotransmitter systems. Subsequently, using a PLS model, these neurotransmitter maps were projected onto the AAL3 brain atlas. For each neurotransmitter/receptor type, the corresponding maps were averaged to derive its regional distribution density profile across AAL3 regions. Finally, correlation analysis was employed to explore the relationships between functional connectivity (FC) and these neurotransmitter/receptor density profiles, with results corrected

for multiple comparisons using the false discovery rate (FDR; $p < 0.01$).

Statistical Analysis

Statistical analyses were performed using R 4.3 software. Continuous variables are presented as mean (standard deviation) or median (interquartile range), and categorical variables as number (percentage). Baseline characteristics were compared between patients with schizophrenia and healthy controls using independent-samples t tests, Mann - Whitney U tests, or chi-square tests, as appropriate. Pre- and post-MST PANSS and MCCB scores in the longitudinal imaging sample were compared using paired-samples t tests. Cohen's d was calculated to estimate the effect size of paired comparisons. All tests were two-sided, with statistical significance set at $p < 0.05$.

RESULTS

Demographic, clinical, and cognitive data

A total of 53 patients with schizophrenia and 40 healthy controls were included in the baseline analysis. The two groups did not differ significantly in age, sex distribution, or years of education (all $p > 0.05$). Demographic, clinical, and MST treatment characteristics are summarized in **Table 1**.

The longitudinal imaging analysis included 33 patients with available and usable pre- and post-MST MRI data. Within this imaging subsample, PANSS total, positive, negative, and general psychopathology scores were significantly reduced after MST (all $p < 0.001$). The MCCB overall composite score and speed of processing also improved significantly ($p = 0.016$ and $p = 0.001$, respectively), whereas no significant changes were observed in the remaining cognitive domains (all $p > 0.05$; **Table 2**).

Treatment-related functional connectivity changes

Compared to the baseline state, after 2 weeks of treatment, we found that the functional connections of the inferior frontal gyrus, hippocampus, lingual gyrus, and precuneus cortex connected by the fronto-occipital fasciculus in the left hemisphere were significantly enhanced after treatment. Within this circuit, all connections were weakened at baseline compared with healthy controls (Table 3, Fig. 1A). In addition, we also found that the functional connectivity of the bilateral corona radiata mediated by the corpus callosum, left thalamus, and anterior cingulate gyrus decreased. Although there was no significant difference in these functional connections at baseline compared with healthy controls, patients showed enhanced functional connections between gray matter and white matter regions in this circuit (Table 3, Fig. 1B). It is worth noting that the enhanced and weakened circuits were mainly located in the left hemisphere, and treatment-related changes were mainly concentrated in connections between gray matter and white matter, while no significant differences were found in connections between gray matter and gray matter.

Correlation between FC changes and clinical or cognitive changes

Clinical and cognitive changes within the longitudinal imaging sample are summarized in Table 2. To further explore the relationship between alterations in brain functional connectivity and clinical symptoms, we conducted a partial correlation analysis between the changes in functional connectivity and changes in clinical symptoms, while controlling for covariates such as gender and age. The correlation analysis revealed that, the decreased functional connection between bilateral corona radiata and thalamus positively correlated with schizophrenia-related symptoms, such as T (left: $r = 0.440$, $p =$

0.013; right: r = 0.441, p = 0.013) and N (left: r = 0.428, p = 0.016; right: r = 0.387, p = 0.032), while negatively correlated with cognitive scores (left: r = -0.406, p = 0.023; right: r = -0.441, p = 0.013). Besides, we also found negative correlation between functional connectivity with left inferior frontal gyrus and left and schizophrenia-related symptom G (r = -0.398, p = 0.027), while positive correlation with cognitive scores (r = 0.417, p = 0.020). However, only the results within schizophrenia-related symptom T and cognitive scores remain significant after FDR corrections. (Fig. 2).

Changes in Neurotransmitter

Considering the role of neurotransmitters in functional connectivity, we further analyzed the relationship between functional connectivity networks and neurotransmitters in patients and healthy individuals at baseline, as well as the relationship between functional networks and neurotransmitters in patients after MST treatment. Research has found that histamine and serotonin T4 are mainly involved after treatment. Prior to treatment, the gray-white matter functional connectivity network showed a significant negative correlation with these two neurotransmitters, but after treatment, the functional network showed a significant positive correlation with these two neurotransmitters. Although the associations between other neurotransmitter receptors and functional networks showed the same correlation direction as baseline after treatment, we found a decrease in the correlation weights of serotonin, and dopamine receptors with functional networks after treatment.(Fig. 3).

DISCUSSION

This fMRI study sought to elucidate the neurophysiological substrates through which MST confers symptomatic and cognitive benefits in schizophrenia. Following MST, patients exhibited marked

symptomatic remission, alongside enhancements in processing speed. Neuroimaging revealed that MST-related effects were predominantly localized to GM-WM connectivity, manifesting as two dissociable, opposite circuit patterns significantly correlated with clinical outcomes. Post-treatment reductions in thalamus-corona radiata-cingulate connectivity were specifically associated with symptom improvement, whereas increased left IFOF connectivity correlated with cognitive gains. Notably, at baseline, these circuits displayed reversed connectivity profiles relative to post-treatment states: patients showed diminished IFOF-related connectivity but elevated thalamus-corona radiata connectivity compared with healthy controls. Collectively, these findings indicate that MST-induced symptomatic and cognitive improvements may be underpinned by partially separable GM-WM circuit mechanisms.

The clinical and cognitive findings of the present study were broadly consistent with our previous findings, which showed marked symptom improvement following MST together with relative preservation of cognitive function, particularly in speed of processing[10]. Importantly, although the coil was positioned over the vertex, MST is a seizure-based neuromodulation treatment, and its effects are unlikely to be confined to the cortex immediately beneath the coil. This interpretation is supported by a previous fMRI study of MST in major depressive disorder, in which stimulation delivered over the vertex was associated with altered functional connectivity involving distributed regions, including the subgenual anterior cingulate, parietal cortex, hippocampus, and prefrontal cortex, beyond the immediate stimulation site[25, 26]. In the present study, MST-related changes were concentrated in two GM-WM circuits that showed different associations with symptom and cognitive improvement. This pattern suggests that symptomatic and cognitive changes following MST may involve partly distinct circuit mechanisms.

An important implication of the present findings is that symptom improvement after MST appears to be preferentially linked to a thalamus-corona radiata-cingulate circuit. This interpretation is broadly consistent with current models of thalamocortical dysconnectivity in schizophrenia. Under normal conditions, the thalamus functions as a central integrative hub that coordinates sensory gating, cortico-cortical communication, and cortico-subcortical information transfer through reciprocal loops with prefrontal, cingulate, sensory, and motor systems[27–29]. In schizophrenia, these thalamocortical interactions appear to be spatially reorganized rather than uniformly disrupted, with selective weakening of higher-order associative connectivity and relative overengagement of sensorimotor-related thalamic pathways[30–33]. Importantly, such abnormalities are detectable across the course of illness, including near illness onset, suggesting that thalamic dysconnectivity is a relatively early and persistent feature of the disorder[34, 35]. Against this background, connectivity linking the left thalamus and anterior cingulate cortex with the bilateral corona radiata decreased after MST, while this circuit showed relatively higher connectivity in patients than in healthy controls at baseline. These findings suggest that MST may modulate an elevated pattern of thalamus-centered functional coupling. Previous intervention studies have similarly shown that seizure-based treatment can alter thalamic functional connectivity in schizophrenia[36, 37]. Importantly, greater reductions in corona radiata-thalamus connectivity were associated with greater PANSS improvement, further supporting the clinical relevance of this circuit-level modulation.

The involvement of the corona radiata also provides an important white matter context for these findings. The corona radiata contains major reciprocal thalamocortical projection fibers connecting the thalamus with frontal and other cortical regions, while the anterior corona radiata and corpus callosum are among the WM pathways consistently implicated in schizophrenia[38–40]. Moreover, magnetic

306 stimulation effects may be shaped by WM architecture and propagate through anatomically connected
307 pathways[41]. Thus, MST-related symptom improvement may involve reorganization of thalamic
308 signaling through major white matter projection pathways supporting cortical-subcortical
309 communication.

310 Another important finding is that cognitive improvement after MST was more closely associated
311 with a long-range integrative circuit involving the IFOF. Cognitive impairment in schizophrenia has
312 been consistently linked to dysfunction of prefrontal and frontoparietal control systems, particularly in
313 domains such as executive function, working memory, and processing speed[42–44]. Previous studies
314 have also shown that impaired functional integration within these networks is associated with poorer
315 cognitive performance[45].

316 This interpretation is broadly consistent with intervention studies suggesting that long-range WM
317 pathways may contribute to cognitive plasticity in schizophrenia. For example, WM integrity within
318 the fronto-occipital fasciculus has been shown to predict cognitive training-induced improvement in
319 attention/vigilance in patients with schizophrenia[46]. In addition, previous ECT-related network
320 studies have shown that seizure-based treatment can induce functional reorganization across distributed
321 brain networks, including prefrontal and cingulate systems[25, 47]. The IFOF, as a major association
322 pathway linking frontal regions with posterior cortical areas, may provide an anatomical and functional
323 substrate for such long-range integration[48]. Thus, our findings extend previous network-level
324 observations by suggesting that MST-related cognitive improvement may involve enhanced GM-WM
325 functional integration along long-range association pathways.

326 Taken together, symptom and cognitive improvement following MST may not be supported by a
327 single unified neural pathway. In the present study, symptom improvement was preferentially

associated with modulation of the thalamus-corona radiata-cingulate circuit, whereas cognitive improvement was more closely related to increased connectivity within an IFOF-related long-range integrative circuit. This dissociation is consistent with the multidimensional nature of schizophrenia, in which different clinical domains may involve partly distinct neural substrates. Notably, both treatment-related patterns predominantly involved GM-WM connectivity rather than GM-GM or WM-WM connectivity. Given growing evidence that WM contributes to long-range information transfer and functional coordination across distributed brain systems[20, 49, 50], these findings suggest that GM-WM coupling may provide an important functional substrate for symptom- and cognition-related network reorganization following MST.

Baseline functional connectivity abnormalities in schizophrenia were associated with multiple neurotransmitter systems, including serotonin, dopamine, glutamate, GABA, acetylcholine, and opioid systems[23, 51]. The prominent 5-HT4-related change may be particularly relevant to MST-related functional reorganization. 5-HT4 signaling has been implicated in synaptic plasticity, learning, and memory[52, 53], and pharmacological activation of 5-HT4 receptors has been shown to modulate resting-state functional connectivity in humans. More recently, 5-HT4 receptor activation was also reported to improve memory deficits and restore disrupted hippocampal-prefrontal neural dynamics in a schizophrenia model[54]. Following MST, the most prominent changes involved histamine and serotonin 5-HT4 receptor maps, whose associations with the GM-WM functional connectivity network shifted from negative before treatment to positive after treatment. Meanwhile, the correlation weights of several serotonin- and dopamine-related receptors were reduced after MST. These findings suggest that MST-related circuit remodeling may be accompanied by a reorganization of the spatial relationship between GM-WM functional connectivity and the underlying neurochemical architecture. Together,

these findings provide a biologically plausible context for the marked shift in 5-HT4-related associations observed after MST and identify 5-HT4 as a candidate neurochemical system for future mechanistic investigation. As the receptor maps were derived from normative atlases, these findings reflect spatial correspondence rather than direct changes in neurotransmitter levels or receptor availability.

Several limitations should be acknowledged. First, the sample size was modest, and the stability of the identified treatment-responsive circuits should be tested in larger cohorts. Second, the neurotransmitter analyses were atlas-based and therefore provide indirect neurochemical inference rather than subject-specific measurement. Third, the current brain-behavior and brain-neurochemical associations are correlational, so causal interpretations remain premature. Even with these limitations, the present findings support a model in which MST acts not merely through diffuse seizure induction, but through selective remodeling of gray-white matter circuits, with symptom-related and cognition-related improvements linked to partly dissociable pathways. In this sense, the mechanism of MST in schizophrenia may be better understood within a multilevel framework that integrates circuit dynamics, white matter-mediated information transfer, and neurochemical organization.

In conclusion, symptom and cognitive improvements following MST were associated with changes in GM–WM functional connectivity in schizophrenia. Exploratory receptor mapping provided a neurochemical context for these functional patterns. Larger controlled longitudinal studies incorporating patient-specific molecular imaging are needed to establish the specificity and biological basis of these associations.

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AUTHOR CONTRIBUTIONS

F.Z. and S.L. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. X.C.W., Z.L. and S.L. conceived and designed the study. All authors contributed to the acquisition, analysis or interpretation of the data. F.Z., Z.G. and S.L. drafted the manuscript. W.Z., X.D., Y.G., X.W., J.P., J.H.L., J.Y.L., X.L., C.Y., X.C., N.S., X.C.W. and Z.L. critically reviewed and revised the manuscript for important intellectual content. F.Z. and Z.G. performed the statistical analyses. S.L. obtained funding and provided administrative, technical and material support. X.C.W., Z.L. and S.L. supervised the study. All authors reviewed and approved the final version of the manuscript.

COMPETING INTERESTS

The authors report no competing financial interests in relation to the work described.

ARTICLE INFORMATION

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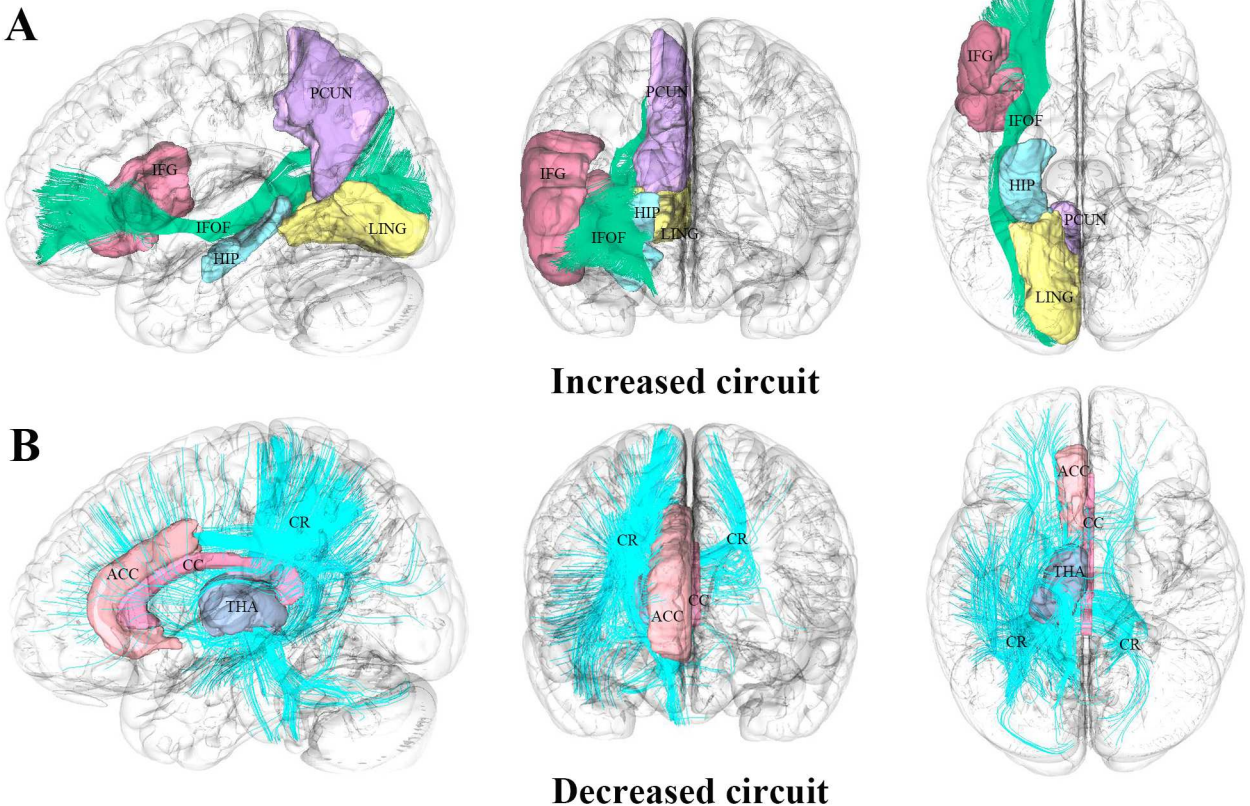
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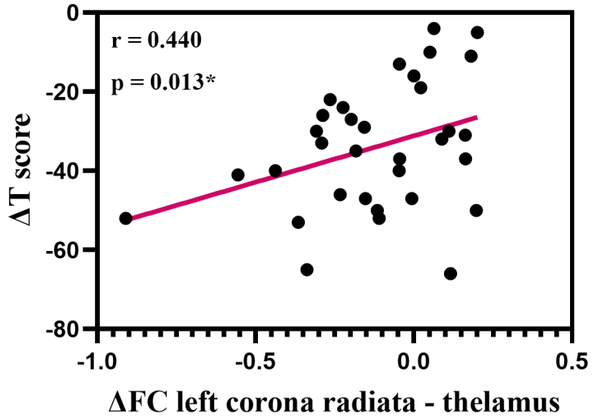
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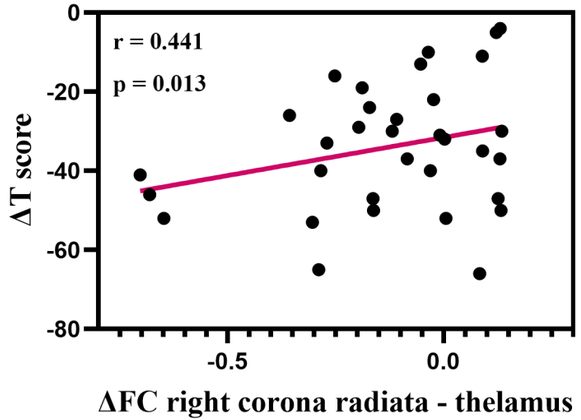
Fig. 1: Functional connectivity alterations of gray-white matter circuits in patients before and after treatment. (A) Significant enhancement was detected in functional connections of the left-hemispheric inferior frontal gyrus, hippocampus, lingual gyrus and precuneus cortex linked by the fronto-occipital fasciculus in patients. (B) patients exhibited decreased functional connectivity in the corpus callosum-, left thalamus-, and anterior cingulate cortex-mediated bilateral corona radiata circuits after 2-week treatment. IFG, inferior frontal gyrus; PCUN, precuneus cortex; LING = lingual gyrus; HIP, hippocampus; IFOF, inferior fronto-occipital fasciculus; ACC, anterior cingulate cortex; THA, thalamus; CC, corpus callosum; CR, corona radiata.

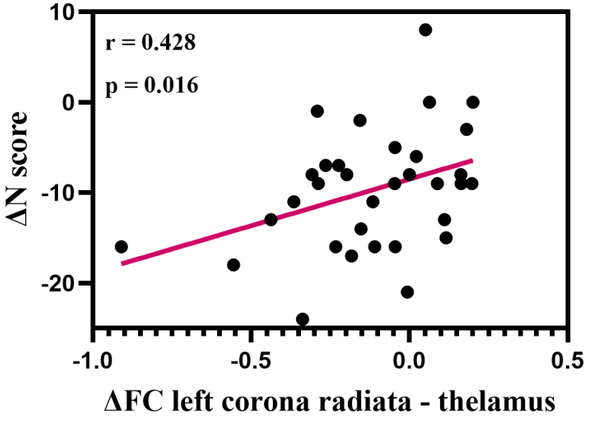
Fig. 2: Correlation between treatment-related functional connectivity changes and clinical or cognitive changes. Scatterplots show partial correlations between changes in selected gray matter-white matter connections and changes in PANSS or MCCB scores after adjustment for age and sex. Each point represents one patient; solid lines indicate fitted regression lines. * Only associations with PANSS total scores and cognitive changes remained significant after false discovery rate correction. FC, functional connectivity; IFG, inferior frontal cortex.

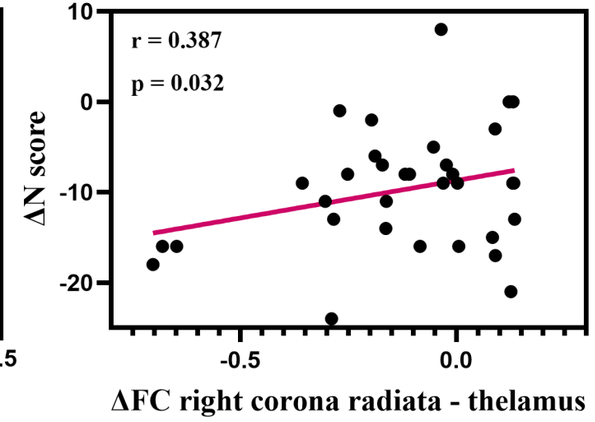
Fig. 3: Spatial associations between functional connectivity patterns and normative neurotransmitter receptor distributions. The ring chart summarizes the correlation weights of neurotransmitter receptors and transporters in patients before and after magnetic seizure therapy. Red and blue represent the associations before and after treatment, respectively. The receptor profile is derived from an independent standardized positron emission tomography dataset. # Indicates a negative association.

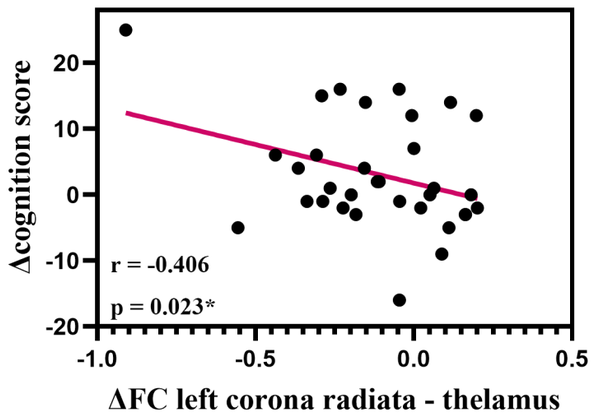

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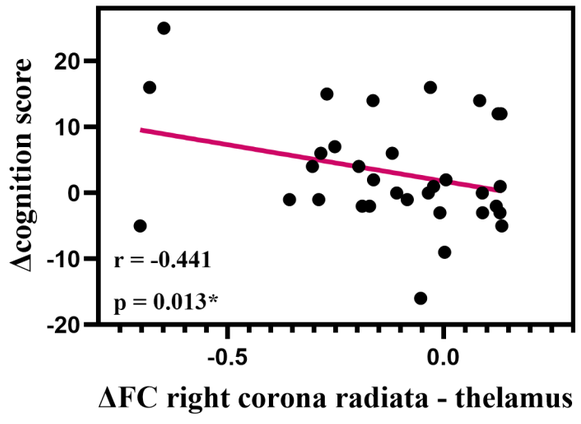

r = 0.440
p = 0.013*
ΔT score
ΔFC left corona radiata - thelamus

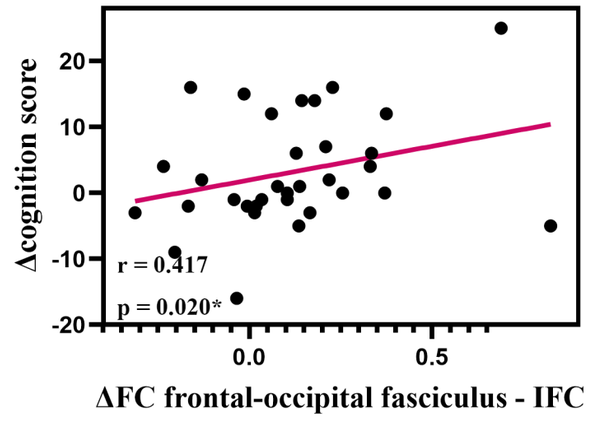

r = 0.441
p = 0.013
ΔT score
ΔFC right corona radiata - thelamus

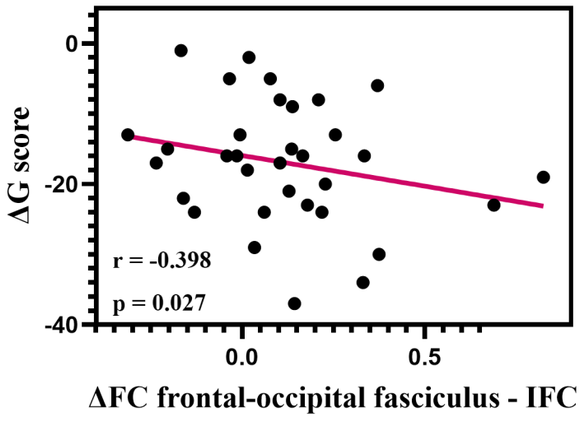

r = 0.428
p = 0.016
ΔN score
ΔFC left corona radiata - thelamus


r = 0.387
p = 0.032
ΔN score
ΔFC right corona radiata - thelamus


r = -0.406
p = 0.023*
Δcognition score
ΔFC left corona radiata - thelamus


r = -0.441
p = 0.013*
Δcognition score
ΔFC right corona radiata - thelamus


r = 0.417
p = 0.020*
Δcognition score
ΔFC frontal-occipital fasciculus - IFC


r = -0.398
p = 0.027
ΔG score
ΔFC frontal-occipital fasciculus - IFC

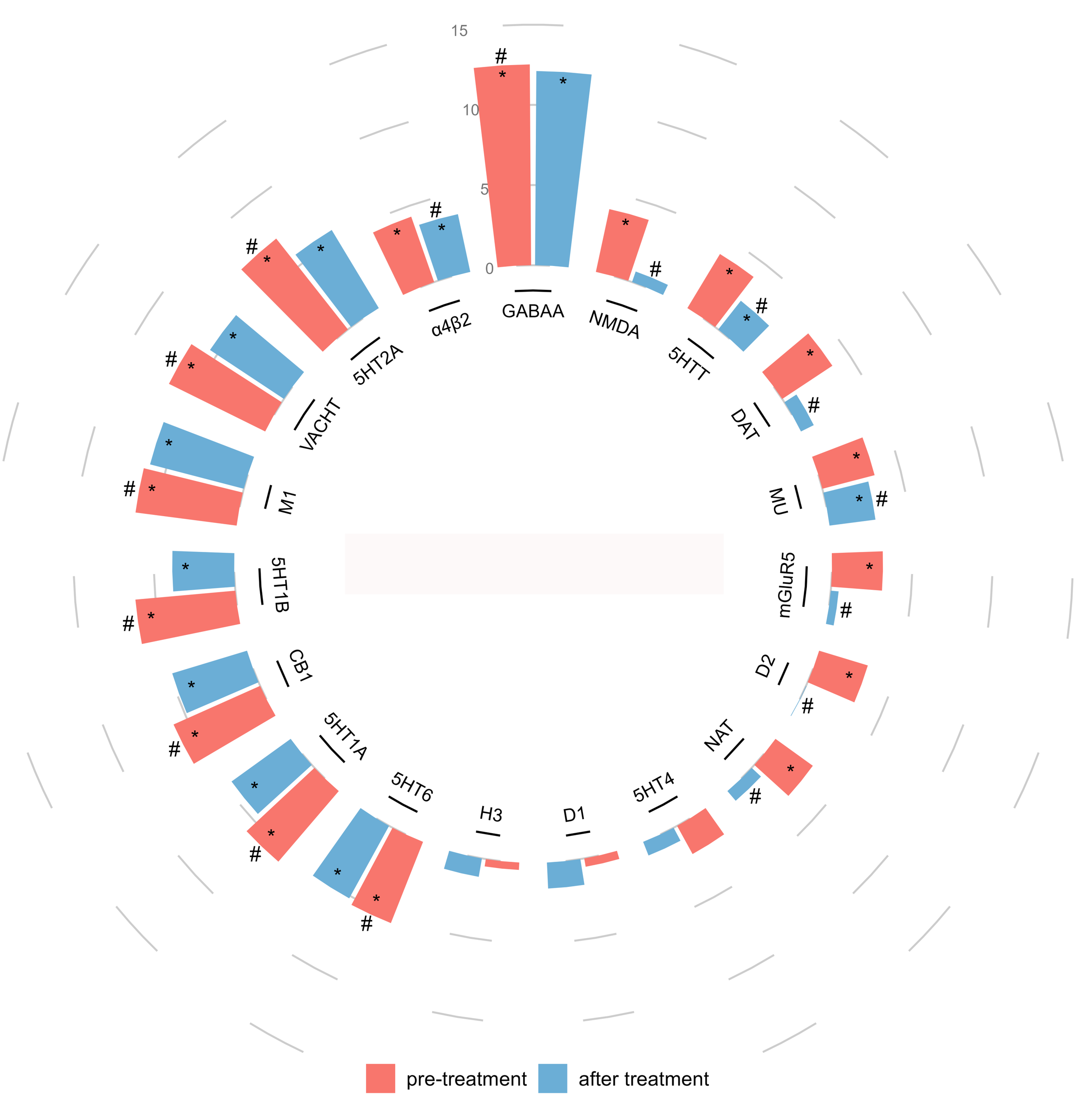

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DAT
5HTT
NMDA
pre-treatment
after treatment

Table 1. Demographic and baseline clinical characteristics

Characteristic	MST group (N = 53)	HC group (N = 40)	t/U/χ^2	*p value*
Age, mean(SD), y	31.26 (7.32)	31.95 (7.99)	-0.425[a]	0.672
Gender, No.(%)				
Male	24 (45.3%)	15 (37.5%)	0.292[b]	0.589
Female	29 (54.7%)	25 (62.5%)		
Education, median (IQR), y	12 (10 - 16)	14 (11 - 16)	871.5[c]	0.139
Illness duration, mean(SD), y	7.42 (5.46)		-	
Family history, No.(%)			-	
Yes	14 (26.4%)		-	
No	39 (73.6%)		-	
Age at illness onset, mean(SD), y	25.67 (7.83)		-	
Dosage of CPZ, mean (SD), mg	386.83 (124.96)		-	
Number of MST sessions, mean (SD)	5.82 (0.68)		-	

Abbreviations: MST, magnetic seizure therapy; HC, healthy controls; CPZ, chlorpromazine; [a] Independent-samples t test; [b] Chi-square test; [c] Mann - Whitney U test.

Table 2. Changes in clinical symptoms and cognitive performance following magnetic seizure therapy

Clinical measure	SCZ (N=33)		*t*	*p*	*Cohen's d*
	Pre-MST, mean (SD)	Post-MST, mean (SD)			
Clinical symptoms (PANSS)					
PANSS-P	17.12 (3.73)	9.85 (2.92)	9.086	＜0.001*	-1.582
PANSS-N	20.33 (6.13)	10.61 (3.59)	8.357	＜0.001*	-1.455
PANSS-G	41.03 (5.73)	24.09 (5.37)	11.117	＜0.001*	-1.935
PANSS-T	78.48 (11.01)	44.55 (9.41)	12.039	＜0.001*	−2.096
Cognitive functions (MCCB)					
SoP	35.42 (11.52)	40.33 (10.38)	-3.494	0.001*	0.608
AoV	40.30 (13.26)	43.09 (8.74)	-1.441	0.159	0.251
WM	38.12 (10.67)	41.06 (9.52)	-1.889	0.068	0.329
VeL	37.73 (10.26)	39.91 (9.82)	-1.135	0.265	0.198
ViL	43.42 (12.04)	44.97 (11.97)	-0.803	0.428	0.140
RaPS	41.73 (11.99)	43.15 (9.94)	-0.887	0.382	0.154
SC	45.00 (10.72)	45.24 (12.70)	-0.117	0.908	0.020
OC	35.24 (11.86)	38.61 (10.83)	-2.542	0.016*	0.442

Abbreviations: SCZ, schizophrenia; MST, magnetic seizure therapy; PANSS-T, total scores; PANSS-P, positive scores; PANSS-N, negative scores; PANSS-G, general psychopathology; MCCB,

MATRICS Consensus Cognitive Battery; SoP, Speed of processing; AoV, attention and vigilance; WM, working memory; VeL, verbal learning; ViL, visual learning; RaPS, reasoning and problem solving; SC, social cognition; OC, MCCB overall composite score. *$p < 0.05$.

Table 3. Functional connections showing significant treatment-related changes

White matter	Gray matter	pre- *VS* post-treatment		patient *VS* controls	
		***t*-value**	***p*-value**	***t*-value**	***p*-value**
Superior.corona.radiata.L	Thal_PuM_L	-2.74	0.010	1.06	0.293
Posterior.corona.radiata.R	Thal_PuL_L	-2.79	0.009	1.99	0.050
Posterior.corona.radiata.R	ACC_pre_L	-3.07	0.004	0.86	0.391
Inf.fronto-occipital.fasciculus.L	Frontal_Inf_Tri_L	3.14	0.004	-7.51	<0.001
Inf.fronto-occipital.fasciculus.L	Frontal_Inf_Oper_L	2.77	0.009	-4.53	<0.001
Inf.fronto-occipital.fasciculus.L	Hippocampus_L	3.49	0.001	-5.42	<0.001
Inf.fronto-occipital.fasciculus.L	Lingual_L	2.77	0.009	-3.64	<0.001
Inf.fronto-occipital.fasciculus.L	Precuneus_L	3.09	0.004	-3.15	0.002
Fornix.(cres)./.Stria.terminalis.L	Frontal_Inf_L	2.74	0.010	-4.68	<0.001

Abbreviations: L, left; R, right; ACC_pre, anterior cingulate cortex pregenual; Thal_PuM, medial pulvinar nucleus of the thalamus; Frontal_Inf_Tri, inferior frontal gyrus triangular part; Frontal_Inf_Oper, inferior frontal gyrus opercular Part.