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ORIGINAL RESEARCH

Evaluating the Therapeutic Efficacy of rTMS Combined with Low-Dose Antipsychotic Medication in Somatic Symptom Disorder

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Objective: We aim to evaluate the therapeutic efficacy of repetitive transcranial magnetic stimulation (rTMS) combined with low-dose antipsychotic medication in somatic symptom disorder (SSD) and its effects on neurotransmitters and inflammatory factors.

Methods: This was a retrospective study. According to different treatment regimens, 90 patients with SSD were divided into a medication group (n = 45) and a combination group (n = 45). The medication group received low-dose antipsychotic medication, while the combination group received low-dose antipsychotic medication combined with rTMS. The primary outcomes were to compare the scores of the Hamilton Anxiety Rating Scale (HAMA) and the Hamilton Rating Scale for Depression (HAMD) between the two groups before and after intervention. The secondary outcomes involved assessing the quality of life of the two groups using the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36). Neurotransmitters and inflammatory factors were measured using enzyme-linked immunosorbent assay. Clinical efficacy and adverse reaction rates were also compared.

Results: After treatment, the combination group showed greater improvements in HAMA and HAMD scores, higher SF-36 scores across physical, social, psychological, and daily living dimensions, with increased levels of γ-aminobutyric acid and 5-hydroxytryptamine, decreased dopamine, lower levels of C-reactive protein and interleukin-1β, higher interleukin-10 levels (all $P < 0.05$). The total effective rate of the combination group was 97.78%, higher than that of the medication group at 84.44% ($P = 0.024$). There was no significant difference in the incidence of adverse reactions between the two groups ($P > 0.05$).

Conclusion: rTMS combined with low-dose antipsychotic medication for SSD shows superiority over medication alone in improving anxiety and depression, enhancing quality of life, regulating neurotransmitter levels, and reducing inflammatory factors, with fewer side effects and significant clinical efficacy. However, due to the small sample size of this study, further prospective, randomized controlled studies with larger samples are needed.

Plain Language Summary: Given the limited efficacy of existing treatments for schizophrenia spectrum disorders (SSD), this study aimed to assess whether combining repetitive transcranial magnetic stimulation (rTMS) with low-dose antipsychotic medication could enhance therapeutic outcomes. By analyzing symptom relief, neuromediator regulation, inflammatory response reduction, and quality-of-life improvements in SSD patients, the results demonstrated that this combined approach outperformed antipsychotic monotherapy. These findings imply that rTMS-antipsychotic combination therapy may represent a viable, innovative treatment option for clinical practice, potentially addressing unmet needs in SSD management.

Keywords: somatic symptom disorder, repetitive transcranial magnetic stimulation, antipsychotic medication, clinical efficacy, neurotransmitters, inflammatory factors

Introduction

Somatic symptom disorder (SSD) refers to a psychiatric condition marked by an intense preoccupation with bodily symptoms.[1] These symptoms cause significant distress or disruption to daily life, evident through exaggerated and

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maladaptive cognitive, emotional, and behavioral reactions. For instance, an individual with SSD might exhibit chronic pain, gastrointestinal disturbances, or fatigue, alongside anxiety, catastrophizing thoughts, and avoidance behaviors.[2] Estimates of the prevalence of SSD in the general population range from 6.7% to 17.4%, with an average frequency of 12.9%.[1] Despite SSD's elevated prevalence and strong association with detrimental functional consequences, such as diminished quality of life and increased healthcare utilization, research on interventions for its treatment and management remains sparse.[3] As a result, healthcare providers continue to face challenges in providing adequate treatment for SSD.

Pharmacotherapy is one of the important approaches in the treatment of SSD. Pharmacological treatment for SSD includes non-psychotropic medications (such as β-blockers, non-steroidal anti-inflammatory drugs, and muscle relaxants for alleviating somatic symptoms), psychotropic medications, and herbal remedies (such as St. John's wort). Psychotropic medications have been proven effective in treating some somatic symptoms, including selective serotonin reuptake inhibitors (SSRI) (eg, escitalopram, fluoxetine), serotonin and norepinephrine reuptake inhibitors (SNRI) (eg, venlafaxine), atypical antidepressants (eg, mirtazapine), and tricyclic antidepressants (eg, amitriptyline).[4] However, a significant number of individuals suffering from SSD do not attain a treatment response, which is characterized by a reduction in severity exceeding 50%, following treatment with antidepressant monotherapy administered at adequate doses and for an adequate duration.[5] Additionally, antidepressants mainly improve mood and relieve somatic symptoms by regulating neurotransmitters such as 5-hydroxytryptamine (5-HT) and norepinephrine.[5,6] However, patients with SSD may have more extensive neurotransmitter imbalances, including the dopamine (DA) system.[7] Antipsychotic medications can regulate DA.[8] Typical antipsychotic medications include chlorpromazine, trifluoperazine, and pimozide. These drugs, among the earliest developed in the field of antipsychotic medications, primarily exert their effects by targeting DA D2 receptors but may also interact with other receptors.[9] In the 1990s, new antipsychotic medications are developed, known as second-generation or "atypical" antipsychotic medications, such as quetiapine, aripiprazole, and risperidone.[10] Risperidone, classified as an atypical antipsychotic, exhibits robust antagonistic effects on DA D2, 5-HT2A, 5-HT2C, 5-HT1D, α1-, and α2-adrenergic receptors. It serves as an effective augmenting therapy for SSRI-resistant major depressive disorder. Furthermore, risperidone has the capability to counteract the SSRI-induced suppression of norepinephrine activity through its 5-HT2A antagonism.[5] Paliperidone, which is the principal metabolite of risperidone, has demonstrated notable therapeutic benefits when used as an adjunctive treatment alongside citalopram in patients diagnosed with somatoform disorder.[5] Compared with other second-generation antipsychotic medications, risperidone has relatively fewer adverse reactions.[5] However, currently, antipsychotic medications are usually not used as monotherapy for SSD but are part of combination therapy, combined with other treatment methods to improve therapeutic efficacy.[5]

In recent years, the combined application of neuromodulation techniques and pharmacotherapy has provided new ideas for the treatment of SSD.[11] Repetitive transcranial magnetic stimulation (rTMS), a form of noninvasive brain stimulation, has the capability to modulate the neural excitability of specific brain regions, which has been applied in the treatment of various neurological and psychiatric disorders.[12] It has few side effects and is considered a promising intervention for improving symptoms in patients with SSD.[13] rTMS has good efficacy in modulating targeted neural activity and further alleviating symptoms, so an increasing number of studies are focusing on examining the effects of rTMS on negative symptoms and cognitive deficits in patients with SSD.[13] Xue Li et al report that rTMS combined with family intervention and risperidone has a synergistic effect in the treatment of schizophrenia, especially in improving positive symptoms, negative symptoms, and cognitive function.[14] Additionally, data from Rui Li et al show that rTMS combined with risperidone treatment may affect the brain-gut-microbiota axis by regulating the gut microbiota in patients with chronic schizophrenia, thereby participating in the therapeutic effect.[11] Given this, this study aimed to explore the application effect of rTMS combined with low-dose antipsychotic medication (risperidone) in SSD.

It is worth noting that patients with SSD often have comorbid symptoms such as anxiety and depression and may have central nervous system dysfunction.[2,15] Neurotransmitter imbalance may be one of the mechanisms leading to symptoms and requires further study. It is well known that DA receptors are widely expressed in the body and function in both peripheral and central nervous systems.[16] Their dysfunction is associated with anxiety and obsessive-compulsive symptoms.[17] Furthermore, high levels of γ-aminobutyric acid (GABA) in the medial prefrontal cortex play an important pathophysiological role in the generation of somatic symptom disorders.[18] Meanwhile, 5-HT abnormalities are also considered a key biological cause of somatic symptoms.[5] On the other hand, data from Bumhee et al showed that patients with SSD have higher levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) compared with healthy

controls, and hypersensitive C-reactive protein (hs-CRP) and IL-6 have a complete mediating inhibitory effect on the relationship between the functional connectivity strength of the default mode network and depression levels.[19] Against this background, we included studies on neurotransmitters and inflammatory markers to comprehensively evaluate the biological effects of rTMS combined with risperidone on SSD. By analyzing changes in neurotransmitters such as DA, GABA, 5-HT, and inflammatory markers, we can reveal the potential mechanisms of combination therapy and provide a scientific basis for the treatment of SSD.

Materials and Methods

Ethics Statement

All experimental procedures were approved by the Medical Ethics Committee of The First Affiliated Hospital of Harbin Medical University, and patients or their families provided informed consent and signed an informed consent form. This study adhered to the Declaration of Helsinki.

Subjects and Grouping

Ninety patients with SSD admitted to The First Affiliated Hospital of Harbin Medical University from May 2023 to May 2024 were selected as the study subjects. Inclusion criteria: Patients who met the diagnostic criteria for SSD in the International Classification of Diseases, 10th Edition[20] and the Chinese Classification and Diagnostic Criteria for Mental Disorders, 3rd Edition, and had a Patient Health Questionnaire-15 score ≥ 5; patients aged 18–75 years; patients who had not received antipsychotic medication or rTMS within the past 6 months; patients on the 17-Item Hamilton Rating Scale for Depression (HAMD)[21] score ≥ 17 points before treatment. Exclusion criteria: Patients with severe physical diseases (including stroke, malignant tumors, chronic obstructive pulmonary disease, end-stage renal disease, liver cirrhosis, myocardial infarction, etc) or brain organic diseases; patients with a history of schizophrenia, mania, and depression associated with various types of organic lesions; patients with epilepsy, acute-phase cerebrovascular accidents, intracranial infections, and intracranial presence of metal or other foreign bodies; patients with suicidal behavior or suicidal ideation; patients with allergies or sensitivities to all the medications used in the study; and women who were pregnant or breastfeeding.

Depending on the treatment regimen, the enrolled patients were divided into the medication and combination groups, with 45 cases each. The medication group was treated with low-dose antipsychotic medication, while the combination group received low-dose antipsychotic medication combined with rTMS.

Treatments

Patients in the medication group were treated with low-dose antipsychotic medication, specifically risperidone (Janssen Pharmaceutical Co., Ltd., Xi ‘an, China; State Drug Administration H20010309), administered orally at an initial dose of 0.5 mg twice daily, with the dose adjustable to 1.5 mg within one week, for a treatment cycle of 8 weeks. The combination group received low-dose antipsychotic medication combined with rTMS. Specific methods: The antipsychotic medication regimen was identical to that of the medication group. YRDCCY-1 transcranial magnetic stimulator (Yi Ruide Medical Equipment New Technology Co., Ltd., Wuhan, China) was used for the treatment, with an output pulse frequency range of 0–100 Hz and a peak stimulation intensity range of 1.5–6 Tesla. Specific operations: The patient was laid on the magnetic therapy bed, relaxed systemically, with the “8”-shaped coil placed on the right dorsolateral prefrontal cortex. The treatment was stimulated with an intensity of 1Hz frequency and 80% motor threshold, delivering 800 pulses per session, lasting 20 minutes per session, once daily for 5 consecutive days, followed by a 2-day break. This cycle was continued for 8 weeks.

Observation Parameters

General data: General demographic information such as gender, age, years of education, ethnicity, marital occupation, and place of residence of the study subjects were collected through a retrospective case system.

Anxiety and depression: The Hamilton Anxiety Rating Scale (HAMA)[22] was used to assess patients’ psychological states. The scale includes 14 items, such as anxious mood, fear, and cognitive function, scored on a 0–4 scale (0 = none, 1

= mild, 2 = moderate, 3 = severe, 4 = very severe), with a maximum score of 56. The HAMD-17 scale was used to assess the depressive symptoms in both groups of patients. This scale consists of 17 items covering aspects such as depressed mood, guilt, and suicidal thoughts, and is divided into five factors: anxiety somatization, weight, cognitive disturbance, retardation, and sleep disturbances. Each question has a different scoring standard, and the corresponding score is selected based on the patient's response. The total score is then calculated.

Clinical efficacy: HAMD-17 was utilized to evaluate the treatment response. A reduction rate of ≥ 75% before and after treatment was considered clinical remission, 25–74% was considered effective, and < 25% was considered ineffective. The total effective rate was calculated as [(number of clinical remissions + effective cases) / total number of cases × 100%]. The reduction rate was calculated as [(pre-treatment HAMD-17 score - post-treatment HAMD-17 score) / pre-treatment HAMD-17 score × 100%].

Quality of life: The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) (SF-36)[23] was used for assessment. The survey included four functional domains: physical, social, psychological, and daily living. Each domain is scored out of 100, with higher scores indicating better quality of life for the patient.

Adverse reactions: The occurrence of adverse reactions including fatigue, drowsiness, anorexia, nausea, xerostomia, and dizziness, were compared.

Neurotransmitters levels: Before treatment (admission day 2) and after treatment (8 weeks of treatment), 5 mL of cubital vein blood was collected with an EDTA blood collection tube. Blood samples should be processed within 2 hours; otherwise, they must be stored at −80°C, with strict avoidance of multiple freeze–thaw cycles. The levels of GABA, 5-HT, and DA were measured using the enzyme-linked immunosorbent assay (ELISA).[24] ELISA kits for GABA (CB10292-Hu), 5-HT (CB10030-Hu), and DA (CB10524-Hu) were purchased from Coibo Biotechnology (Shanghai, China).

Inflammatory factor levels: Levels of CRP, IL-1β, and IL-10 were measured using ELISA. ELISA kits for CRP (CB10116-Hu), IL-1β (CB10347-Hu), and IL-10 (CB13566-Hu) were available from Coibo.

Statistical Processing

Data were processed using SPSS 26.0 software. The normality of measurement data was tested using the Shapiro–Wilk method, and all data conformed to a normal distribution. Additionally, the measurement data were expressed as mean ± standard deviation (Mean ± SD). Comparisons between groups used independent sample t-tests, and within-group comparisons used paired sample t-tests. Numeration data were expressed as [number of cases (n)], and analyzed using chi-square tests, with Yates' correction applied to small sample sizes. A P-value < 0.05 was considered statistically significant.

Results

General Data

Baseline data differences between the two groups were analyzed, revealing no statistically significant differences in age, gender, disease duration, marital status, ethnicity, residence, or education level ($P > 0.05$), indicating comparability (Table 1).

Table 1 Comparison of General Data in the Two Groups

Information		Medication Group (n = 45)	Combination Group (n = 45)	χ^2/t	P
Age		40.31 ± 7.83	40.96 ± 7.60	−0.396	0.693
Disease duration (years)		5.11 ± 2.12	4.85 ± 2.23	0.561	0.576
Gender	Male	15	19	0.756	0.384
	Female	30	26		

(*Continued*)

Table 1 (Continued).

Information		Medication Group (n = 45)	Combination Group (n = 45)	χ^2/t	*P*
Marital status	Unmarried	8	11	1.042	0.594
	Married	36	32		
	Divorce	1	2		
Ethnicity	Han nationality	41	43	0.714	0.398
	Ethnic minority	4	2		
Residence	Rural	18	22	1.131	0.288
	Urban	27	23		
Education level	Primary school	9	12	1.209	0.751
	Middle school	16	19		
	High school	10	7		
	College degree or above	10	7		

HAMA and HAMD Scores

There was no notable difference in HAMA and HAMD scores between the two groups before treatment ($P > 0.05$). After treatment, HAMA and HAMD scores in both groups decreased compared to pre-treatment levels ($P < 0.05$). Post-treatment improvements in HAMA and HAMD scores were better in the combination group than in the medication group (Table 2).

SF-36 Scores

There was no significant difference in SF-36 scores between the two groups before treatment ($P > 0.05$). After treatment, SF-36 dimension scores in both groups increased ($P < 0.05$), with the combination group's scores higher than the control group's ($P < 0.05$) (Table 3).

Clinical Efficacy

The total effective rate in the medication group was 84.44% (38/45), while the total effective rate in the combination group was 97.78% (44/45). According to the chi-square test, the total effective rate in the combination group was higher than that in the medication group ($P = 0.026$) (Table 4).

Occurrence of Adverse Reactions

The medication group and the combination group showed no significant difference in the incidence of adverse reactions such as fatigue, drowsiness, anorexia, xerostomia, nausea, and dizziness (all $P > 0.05$) (Table 5).

Table 2 Comparison of HAMA and HAMD Scores Before and After Treatment in the Two Groups

Group	HAMA (Score)		HAMD (Score)	
	Before Treatment	After Treatment	Before Treatment	After Treatment
Medication group (n = 45)	21.22 ± 5.12	13.22 ± 3.27 [a]	23.73 ± 4.12	12.76 ± 3.58 [a]
Combination group (n = 45)	20.84 ± 5.26	9.20 ± 2.07 [a]	23.76 ± 3.76	9.09 ± 2.84 [a]
t	0.345	6.962	−0.027	5.379
P	0.731	<0.001	0.979	< 0.001

Note: [a] $P < 0.05$ compared to pre-treatment in the same group.

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Table 3 Comparison of SF-36 Scores Before and After Treatment Between the Two Groups

Group	Physical		Social	
	Before Treatment	**After Treatment**	**Before Treatment**	**After Treatment**
Medication group (n = 45)	60.24 ± 6.21	73.24 ± 4.55 [a]	52.22 ± 5.19	69.27 ± 6.78 [a]
Combination group (n = 45)	61.29 ± 6.12	84.29 ± 5.31 [a]	51.60 ± 4.90	78.27 ± 6.24 [a]
t	−0.804	−10.595	0.584	−6.553
P	0.423	< 0.001	0.56	< 0.001
Group	**Psychological**		**Daily living**	
	Before treatment	**After treatment**	**Before treatment**	**After treatment**
Medication group (n = 45)	50.13 ± 4.46	67.69 ± 3.28 [a]	56.53 ± 5.32	70.18 ± 4.41 [a]
Combination group (n = 45)	50.89 ± 5.34	75.58 ± 4.89 [a]	57.13 ± 6.18	81.27 ± 3.76 [a]
t	−0.729	−8.984	−0.494	−12.846
P	0.468	< 0.001	0.623	< 0.001

Note: [a] $P < 0.05$ compared to pre-treatment in the same group.

Table 4 Comparison of Clinical Efficacy Between the Two Groups

Group	Clinical Remission	Effective	Ineffective	Total Effective Rate
Medication group (n = 45)	5	33	7	38 (84.44%)
Combination group (n = 45)	9	35	1	44 (97.78%)
χ^2	–	–	–	4.939
P	–	–	–	0.026

Table 5 Comparison of the Incidence of Adverse Reactions Between the Two Groups

Group	Fatigue and Drowsiness	Xerostomia	Anorexia	Nausea	Dizziness
Medication group (n = 45)	6	5	4	2	3
Combination group (n = 45)	4	4	2	3	5
χ^2	0.450	0.123	0.714	0.212	0.549
P	0.502	0.725	0.398	0.645	0.459

Neurotransmitters Levels

There was no significant difference in GABA, 5-HT, and DA levels between the two groups before treatment ($P > 0.05$). After treatment, GABA and 5-HT levels in both groups increased compared to pre-treatment levels, while DA levels decreased, with the combination group's levels higher/lower than the medication group's (Table 6).

Inflammatory Factor Levels

There was no remarkable difference between the pre-treatment levels of CRP, IL-1β, and IL-10 between the two groups ($P > 0.05$). After treatment, CRP and IL-1β levels in both groups decreased compared to pre-treatment levels, while IL-10 levels increased, with the combination group's levels lower/higher than the medication group's (Table 7).

Discussion

SSD is common in primary health care institutions, and diagnosis and treatment are often challenging.[1] Therefore, this study evaluated the therapeutic effects of rTMS combined with low-dose antipsychotic medication in patients with SSD. The results showed that rTMS combined with low-dose antipsychotic medication has significant advantages in improving anxiety and depression, enhancing quality of life, and regulating neurotransmitter levels, and inflammatory factors in the treatment of SSD.

Table 6 Comparison of Neurotransmitters Levels Between the Two Groups Before and After Treatment

Group	GABA (ng/L)		5-HT (μg/L)		DA (ng/mL)	
	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Medication group (n = 45)	5.72 ± 1.33	9.33 ± 2.34 [a]	198.45 ± 30.23	241.23 ± [23.57] [a]	16.72 ± 2.01	13.62 ± 1.54 [a]
Combination group (n = 45)	5.62 ± 1.42	11.72 ± 3.14 [a]	193.23 ± 29.22	275.56 ± 20.56 [a]	16.34 ± 2.13	10.73 ± 1.26 [a]
t	0.348	−4.093	0.833	−7.363	0.867	9.743
P	0.729	< 0.001	0.407	< 0.001	0.388	< 0.001

Note: [a] $P < 0.05$ compared to pre-treatment in the same group.

Table 7 Comparison of Inflammatory Factor Levels Between the Two Groups Before and After Treatment

Group	CRP (mg/L)		IL-1β (ng/L)		IL-10 (pg/mL)	
	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Medication group (n = 45)	19.33 ± 4.12	13.38 ± 2.23 [a]	83.23 ± 9.76	65.42 ± 5.27 [a]	7.36 ± 2.21	13.33 ± 3.23 [a]
Combination group (n = 45)	19.52 ± 4.33	10.05 ± 2.07 [a]	82.29 ± 10.06	52.34 ± 4.61 v	7.72 ± 2.10	17.52 ± 2.87 [a]
t	−0.213	7.34	0.451	12.531	−0.794	−6.504
P	0.831	< 0.001	0.653	< 0.001	0.429	< 0.001

Note: [a] $P < 0.05$ compared to pre-treatment in the same group.

Specifically, the improvement in HAMA and HAMD scores in the combination group was better than that in the medication group, indicating that rTMS combined with low-dose antipsychotic medication is more effective in improving anxiety and depressive symptoms. Additionally, the SF-36 scores in the combination group were higher than those in the medication group, indicating that combination therapy is more effective in improving quality of life. Meanwhile, the total effective rate in the combination group was higher than that in the medication group, and there was no significant difference in the incidence of adverse reactions between the two groups, revealing that rTMS combined with low-dose antipsychotic medication is superior to monotherapy in overall efficacy and does not increase the risk of adverse reactions. Studies have reported that rTMS leads to a greater reduction in depressive symptoms than medication, which is further reflected in higher rates of response and remission. Additionally, rTMS results in a more substantial decrease in anxiety and anhedonia symptoms compared to switching antidepressants.[25] Furthermore, in the study of Ren et al, intermittent theta burst-rTMS (iTBS-rTMS) demonstrates a favorable therapeutic effect in patients with methamphetamine use disorder, with improvements in both depression and impulsivity. These enhancements are strongly associated with the therapeutic efficacy of iTBS-rTMS.[26]

In addition, this study highlighted that the levels of GABA and 5-HT in the combination group were higher than those in the medication group, and the level of DA was lower than that in the medication group, indicating that rTMS combined with low-dose antipsychotic medication is more effective in regulating neurotransmitter levels. According to previous results, the serum levels of 5-HT in both the acupuncture + rTMS combination group and the rTMS-only group are found to be higher post-treatment compared to their pre-treatment levels.[27] In the study by Feng et al, after rTMS treatment, the GABA levels are notably elevated.[28] A study reveals that antipsychotic medications such as risperidone may regulate N-methyl-D-aspartate receptors through the glycogen synthase kinase 3β-β-catenin signaling pathway and/or the activation of cyclic adenosine monophosphate response element-binding protein 1, and the regulation of $GABA_aR$ may also be related to these signaling pathways.[29] Thomas et al's study shows that risperidone affects motor activity and neural

activity in mice, especially having a significant impact on neural oscillations in the prefrontal cortex and hippocampus, by blocking DA receptor D_2R and regulating the activity of serotonin receptors (5-HT_1AR and 5-HT_2AR).[30] Based on the results of this study, there is a synergistic mechanism in neurotransmitter regulation when risperidone is combined with rTMS. Risperidone, as a D2 receptor antagonist, can block excessive DA activity in the mesolimbic system to alleviate positive symptoms,[14] while rTMS activates glutamatergic neurons in the prefrontal cortex through high-frequency stimulation, promoting DA release and enhancing prefrontal-striatal circuit function. The combined treatment may partially counteract the inhibitory effect of risperidone on DA, thereby optimizing DA metabolic balance. Additionally, risperidone indirectly increases synaptic 5-HT levels by blocking 5-HT2A receptors, and rTMS stimulates the dorsolateral prefrontal cortex to increase 5-HT release into the limbic system. The synergy of the two may increase 5-HT concentrations in relevant brain regions, thereby improving anxiety and depressive symptoms. On the other hand, rTMS can enhance GABAergic interneuron activity to inhibit prefrontal cortex hyperactivity, and risperidone can indirectly regulate DA-GABA interactions to enhance GABAergic inhibition. The combined treatment can more effectively reduce prefrontal cortex excitability and reduce anxiety and obsessive-compulsive symptoms.

Meanwhile, this study also observed that the levels of CRP and IL-1β in the combination group were lower than those in the medication group, and the level of IL-10 was higher than that in the medication group, indicating that rTMS combined with low-dose antipsychotic medication is more effective in regulating inflammatory marker levels. In line with the results of the present study, in the study of Yang et al, deep rTMS reduced microglial activation at the lesion sites and normalized cytokine levels (IL-1β, IL-6, and IL-10) in regions affected by cuprizone.[31] Based on the results of this study, rTMS may activate the vagus nerve-cholinergic anti-inflammatory pathway, inhibit microglial activation, and reduce the release of pro-inflammatory cytokines (such as IL-1β). Although risperidone does not directly have anti-inflammatory effects, it may inhibit microglial M1 polarization by regulating the DA signaling pathway. When combined, the two may synergistically reduce peripheral blood CRP and IL-1β levels and increase the level of the anti-inflammatory cytokine IL-10.

Limitation

This study preliminarily revealed the efficacy of rTMS combined with risperidone in the treatment of SSD in improving anxiety and depression, enhancing quality of life, regulating neurotransmitter levels, and inflammatory factors. However, this study also has some limitations. For example, we did not perform sample size calculation, and the sample size was small, which may affect the generalizability of the findings. Additionally, the 8-week observation period in this study may not be sufficient to assess the long-term efficacy and potential delayed effects of rTMS combined with risperidone treatment. The lack of long-term follow-up may not allow for the assessment of symptom recurrence rates and drug dependence after treatment.

Conclusion

In conclusion, this study confirms that rTMS combined with low-dose antipsychotic medication is superior to monotherapy in improving anxiety and depression, enhancing the quality of life, regulating neurotransmitter levels, and inflammatory factors in the treatment of somatic symptom disorder, with fewer side effects and significant clinical efficacy. This study provides a new direction for the treatment of SSD, and it is hoped that the treatment regimen can be further optimized to benefit more patients in the future. Importantly, future research should further verify the mechanisms and long-term safety of combination therapy by expanding the sample size, extending the follow-up period, and controlling confounding factors (such as treatment adherence, social support systems, etc). Additionally, the treatment of SSD requires multidisciplinary collaboration, including psychiatry, neurology, and psychology. The multidisciplinary collaborative treatment model can integrate the advantageous resources of various disciplines to provide patients with more personalized and comprehensive treatment plans and improve the overall treatment level of SSD.

Ethical Statement

All experimental procedures were approved by the Medical Ethics Committee of The First Affiliated Hospital of Harbin Medical University, and informed consent was signed by patients' families.

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

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Disclosure

The authors declare that they have no conflicts of interest for this work.

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