Personalized repetitive transcranial magnetic stimulation with dual-target in cerebellem and rDLPFC for the treatment of negative symptoms of schizophrenia: A multicenter, randomized, double-blinded, placebo-controlled trial

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Background:

Negative symptoms have a detrimental impact on functional outcomes and quality of life in schizophrenia. Recent studies have shown that a connectivity breakdown between the cerebellum and the right dorsolateral prefrontal cortex is associated with negative symptoms. The present study aimed to explore the efficacy and possible brain mechanism of cerebellar-right prefrontal dual target neuronavigated rTMS intervention in the treatment of negative symptoms of schizophrenia.

Methods:

A multicenter randomized, double-blind, sham-controlled study were conducted from 2021 to 2023(NCT04853485). Seventy-five patients were randomly assigned to either a real or sham group under MRI-guided neuronavigation, targeting right dorsolateral prefrontal cortex (rDLPFC) with 1Hz at 100% motor threshold (MT), cerebellar with intermittent theta burst stimulation (iTBS) at 120% MT for 20 consecutive days. Assessments were conducted at baseline (T0), 10-session (T1), 20-session (T2) and one month after the intervention (T3). Cognition and MRI were evaluated at T0 and T2. The primary outcome was change of negative score of PANSS, while the secondary outcomes included the reduction of PANSS subscale scores of positive, general symptoms and total score, and the resting-state functional connectivity of frontal-cerebellar connectivity.

Results:

Thirty-six in the real group and thirty-nine in the sham group were recruited. The ITT analysis showed that the real group had better improvements in Positive, Negative, General and PANSS total score both at T1($p<0.05$) and T2 ($t=3.47$, $p<0.05$). The response rate of positive ($\chi2 =3.80$, $p =0.051$) and negative ($\chi2 =9.5$, $p=0.002$) symptoms in the real group was significantly higher than that in the sham group after 20 sessions of rTMS.

Resting state functional connectivity showed a significant group*time interaction between cerebellar and the right middle temporal gyrus, the right parahippocampus, the left caudate , the right parietal operculum cortex. Meanwhile there is a significant positive correlation between reduction of PANSS negative subscale and functional connectivity of cerebella and the left caudate ($R=0.33$, $p=0.026$).

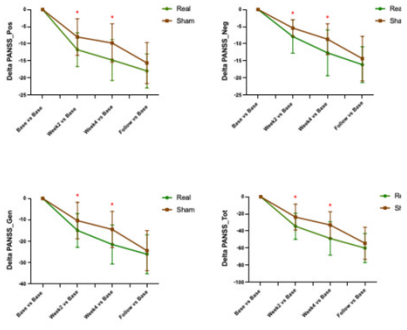

Fig1. Symptom changeof positive symptom, negative symptom, general symptoms, and PANSS total scores at different intervention time points in the real and sham stimulation group.

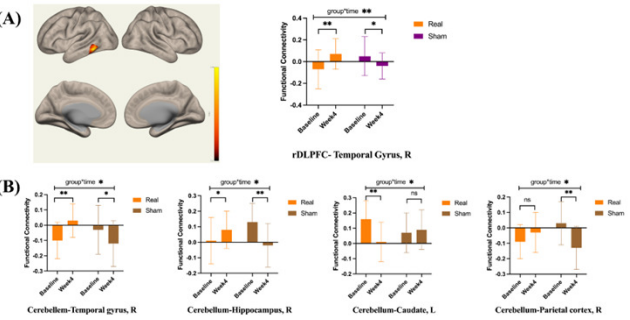

*Fig2. Brain regions with functional connectivity that showed a group*time interaction effect using the cerebellum and rDLPFC as seed point.*

Conclusion:

The study suggest that neuronavigated cerebellar-rDLPFC rTMS has a potential effect for negative symptom as well as general and positive symptoms of schizophrenia. Further studies with longer phase of treatment to explore the maintenance effect are needed

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Key References:

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