Intermittent theta-burst stimulation ameliorates synaptic pathology in antidepressant-resistant depression rat model

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Introduction

Treatment-resistant depression (TRD) which is defined as major depression with poor or unsatisfactory response to two different classes of antidepressants, such as fluoxetine. Previous studies demonstrated that traumatic stress plays a critical role in the development of TRD. Moreover, dysregulated synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD), and decreased spine density in the prefrontal cortex (PFC) were identified in TRD. Clinical studies have shown that high frequency (HF)-repetitive transcranial magnetic stimulation (rTMS), a non-invasive method of stimulation, is an effective therapy in treating TRD. Another form of rTMS, called intermittent theta-burst stimulation (iTBS), has long been known as an effective method inducing LTP-like plasticity in humans. Although iTBS was recently found to elicit more rapid and powerful effects than traditional rTMS protocols, the mechanism of iTBS for the treatment of TRD is still unclear.

Materials and Methods

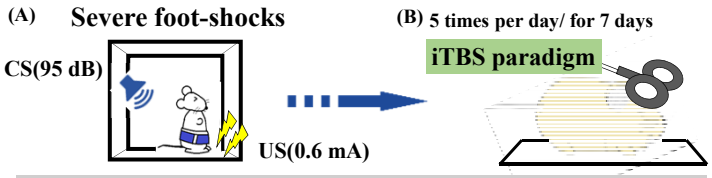

Figure 1 | The TRD animal model and treatment course.
(A) The fear conditioning training with 10 times CS-US pairing (B) The rats received 5 times per day of iTBS for 7 days.

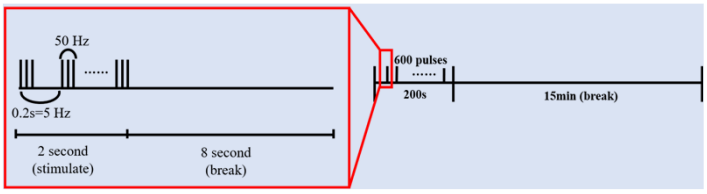

Figure 2 | The iTBS paradigm.
The TBS protocol consisted of burst of three pulses stimulated at 50 Hz and repeated every 0.2 second. For iTBS, a 2 second train of TBS was repeated with 10 second intervals in 200 second (600 pulses with one train). The iTBS was applied with five trains (3000 pulses)

Neuronal activity: ➢ Immunofluorescence

Depressive-like behavior:
➢ Tail suspension test (TST) ➢ Forced swim test (FST)

Electrophysiology: ➢ Long-term potentiation (LTP) ➢ Long-term depression (LTD)

Spine morphology: ➢ Golgi staining

Results

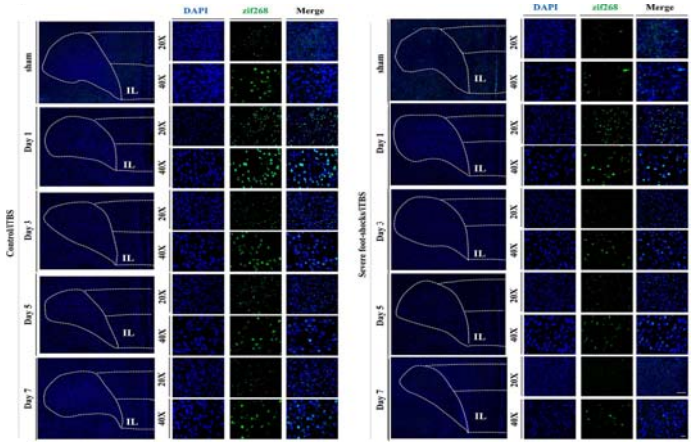

Figure 3 | The neuronal activity was increased by 7 days of iTBS treatment.
Representative images of immunofluorescence showing Hoechst (blue) and zif268 (green) in layer V of PFC sections from the control and severe foot-shocks groups following iTBS treatment for 1, 3, 5 and 7 days (scale bar indicates 200 μm).

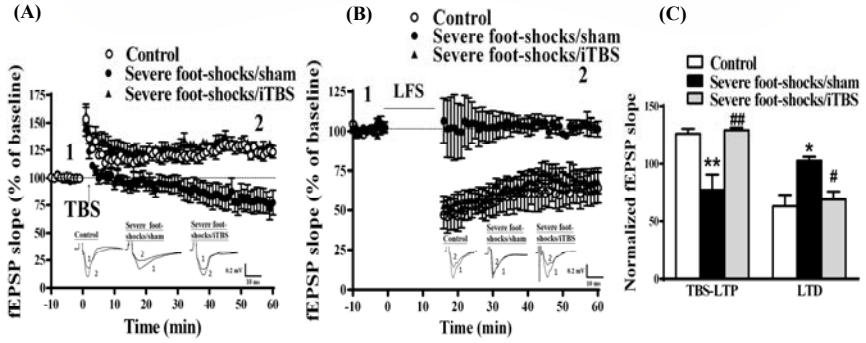

Figure 5 | The aberrant LTP and LTD were reversed by 7 days of iTBS treatment.
(A) LTP induced by theta-burst stimulation in the control, sham and iTBS treatment groups. (B) LTP induced by low-frequency stimulation in the control, sham and iTBS treatment groups. (C) Bar chart comparing the normalized fEPSP amplitude during LTP and LTD expression in the control, sham and iTBS treatment groups over the last 10 minutes. Data represent means ± SEM in each experiment. *p < 0.05, **p < 0.01 versus control group; #p < 0.05, ##p < 0.01 versus severe foot-shocks group.

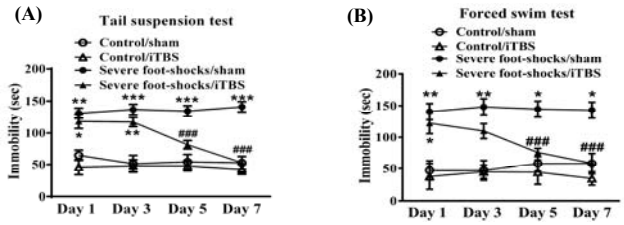

Figure 4 | The depressive-like behavior and active coping behavior were improved by 7 days of iTBS treatment. (A) Immobility duration following iTBS treatment in the TST (B) Immobility duration following iTBS treatment in the FST. Data represent means ± SEM in each experiment. *p < 0.05, **p < 0.01, ***p < 0.001 versus control/sham group; #p < 0.05, ###p < 0.001 versus severe foot-shocks/sham group.

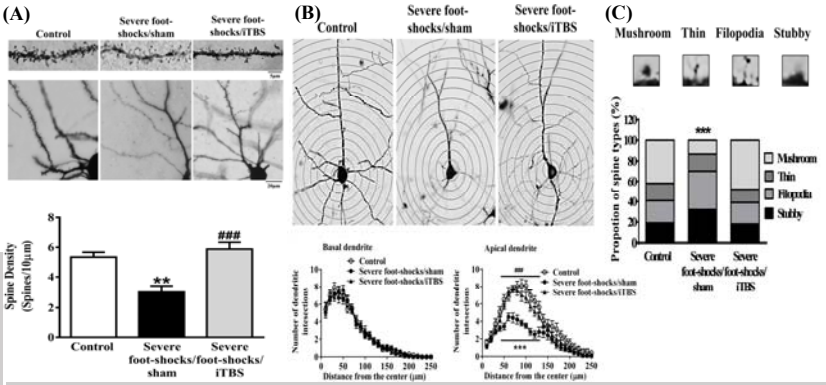

Figure 6 | the density of dendritic spines, complexity of dendritic trees and proportions of dendritic spine types were improve by 7 days of iTBS treatment. (A) Representative Golgi-stained sections showing spine density in layer V of the PFC (upper scale bar indicates 5 μm; lower scale bar indicates 20 μm). (B) Sholl analysis of basal dendrites of pyramidal neurons and apical dendrites of pyramidal neurons in layer V of the PFC. (C) Summary graph depicting the number of dendritic spines of each type, including mushroom, filopodia, thin and stubby spines, in layer V of the PFC. Data represent means ± SEM in each experiment. *p < 0.05, **p < 0.01, ***p < 0.001 versus control group; ###p < 0.001 versus sham group.

Conclusion

This study demonstrated that iTBS paradigm can cure TRD in 1 week in our rat model. Interestingly, the 1 week of iTBS treatment improved not only LTP but also LTD in TRD rat model, suggesting that the mechanism of iTBS paradigm in treating TRD may be more complicated than traditional HF-rTMS.