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Repetitive transcranial magnetic stimulation combined with imaginal exposure therapy for adolescents with acute stress disorder: case report

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Acute stress disorder (ASD) is a transient psychiatric disorder that may arise subsequent to abrupt, extreme trauma exposure, and serves as a reliable indicator for the subsequent development of posttraumatic stress disorder (PTSD) (Bryant, 2011; Battle, 2013). It exhibits rapid progression in the aftermath of trauma and persists for a duration of days or weeks (not exceeding one month), manifesting symptoms of dissociation, re-experiencing, avoidance, and hyperarousal (Bielas et al., 2018). In the absence of efficacious and prompt intervention, ASD is linked to substantial morbidity and functional impairment (McLean et al., 2022). However, there is a deficiency in terms of providing sensitive diagnosis and effective treatment for adolescents diagnosed with ASD, with the majority of current approaches being derived from PTSD treatment. The prevailing strategies for addressing PTSD in children and young individuals primarily involve psychological intervention and pharmaceuticals, including selective serotonin reuptake inhibitors (SSRIs) (Smith et al., 2013). Nevertheless, the efficacy of SSRIs in adolescents with ASD remains suboptimal (Robb et al., 2010; Locher et al., 2017; Boaden et al., 2020).

Psychotherapy continues to be the preferred and efficacious intervention for adolescents suffering from PTSD. Recent research has indicated that cognitive behavioral therapy (CBT) administered during the acute phase can effectively mitigate the development of subsequent PTSD (Bryant, 2018). Consequently, early intervention in the aftermath of trauma is imperative, and the dearth of treatment options for ASD and PTSD necessitates immediate resolution.

Successful application of exposure therapy in treating PTSD has demonstrated the potential for symptom amelioration (McLean et al., 2022). This trauma-focused treatment modality encompasses imaginal exposure (McLean et al., 2022). In a controlled environment, patients were subjected to imaginal exposure, wherein memories of traumatic events were intentionally recalled, resulting in desensitization to the events and the subjects' realization that they were no longer at risk (Kaczkurkin and Foa, 2015). Consequently, the patients experienced relaxation and a gradual improvement in their anxiety and/or fear associated with the traumatic memories. This trauma-focused treatment has been deemed secure, efficacious, and highly viable for children and adolescents diagnosed with PTSD, offering the potential for early intervention (Smith et al., 2013).

Repetitive transcranial magnetic stimulation (rTMS), a non-invasive neurostimulation technique based on electromagnetic induction, is employed in this context; it is widely used in treating psychiatric disorders, especially major depressive disorder (George et al., 2010; Gaynes et al., 2014). Several studies in functional neuroimaging have found an elevation in oxygen perfusion within the right prefrontal cortex

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when individuals with PTSD were exposed to reminders of their traumatic experiences (Herringa, 2017). This finding has led to a prevailing interpretation that heightened activity in the right hemisphere of PTSD patients is associated with involvement of the right hemisphere in anxiety and other negative emotional experiences (Simmons et al., 2004; Milad et al., 2006). Moreover, most investigations on rTMS for PTSD have targeted the right prefrontal cortex (Kozel, 2018), specifically the right dorsolateral prefrontal cortex (DLPFC), which is known to be sensitive to non-verbal affective content and has been implicated in anxiety disorders, fear, and PTSD (White et al., 2023). Previous research has indicated that low- and high-frequency rTMS yield contrasting outcomes, with low-frequency rTMS exhibiting a propensity to reduce cortical excitability, thereby potentially serving as a more efficacious intervention for PTSD (George et al., 2000; Hoffman and Cavus, 2002; Huang et al., 2004). Nevertheless, it has also been reported that high-frequency stimulation demonstrated greater effectiveness (Iglesias, 2020). Furthermore, an additional study elucidated that the therapeutic benefits of low-frequency stimulation were observed as a result of the partial inhibition of lateralized right-sided hyperactivity within the DLPFC (Berlim and van den Eynde, 2014). Numerous recent clinical trials have indicated that rTMS holds promise as an intervention for alleviating symptoms associated with PTSD, including anxiety and fear memory (Osuch et al., 2009; Kozel et al., 2019; Philip et al., 2019), but further research is necessary to establish precise treatment parameters, duration, and potential side effects. It is worth noting that several studies have only employed rTMS treatment, which typically spans a duration of 4–6 weeks (Osuch et al., 2009; Kozel et al., 2019; Philip et al., 2019). Therefore, the efficacy and rationality of employing low-frequency rTMS for treating PTSD are recognized. However, utilization of rTMS in the context of ASD has received limited attention in the existing literature.

Actually, many studies have suggested that combination therapy is more effective in psychiatric disorders (O'Neal and Baslet, 2018; Pan et al., 2019). Several recent studies have shown that rTMS is effective in the treatment of PTSD after stroke and can be accelerated by adding a brief exposure program (Jiang et al., 2023). Repeated ultra-short exposure therapy combined with deep transcranial magnetic stimulation may be an effective treatment for PTSD, and repeated stimulation of medial prefrontal cortex (mPFC) by magnetic coils may interfere with traumatic memory-mediated regression (Isserles et al., 2021). Thus, there is increasing evidence that magnetic stimulation combined with exposure therapy for PTSD fills the treatment gap while yielding favourable outcomes. On account of the severe consequences and specifics of adolescent ASD (March, 2003), various obstacles hinder treatment, such as parents' concerns about side effects, potential developmental impacts, and slow effect. Therefore, there is urgent demand for prompt, secure, and efficacious interventions.

Here, we present a preliminary experiment involving 5 d of twice-a-day low-frequency (1 Hz) rTMS performed in the DLPFC, in conjunction with imaginal exposure, for the treatment of ASD in adolescents. Based on the principle that rTMS stimulation of the DLPFC can reduce cortical excitability (Simmons et al., 2004; Milad et al., 2006; Kozel, 2018; White et al., 2023) and thus improve PTSD anxiety behaviour, we hypothesize that anxiety behaviour in ASD can also be improved by the same stimulation pattern, so that the first low-frequency stimulation per day in DLPFC can improve and control existing symptoms. Based on the principle of gradually desensitizing patients to traumatic stimuli through imaginative exposure therapy, incorporation of a second low-frequency stimulation in daily treatment, along with imaginative exposure, has the potential to elicit anxiety and fear associated with trauma. This induced anxiety can subsequently be addressed through daily application of a second low-frequency stimulation. After a 5-d treatment period, notable improvements in patient anxiety and fear levels were observed. This approach may also serve to mitigate the likelihood of ASD progressing into PTSD.

Patient 1, a 16-year-old female high-school student of Han ethnicity, received a diagnosis of ASD following a severe traumatic event. Specifically, she was subjected to sexual assault by her geography teacher during after-school lessons. Upon returning to school, the patient experienced distressing recollections of the incident while attending geography class, often resulting in emotional outbursts. Notably, the patient had no familial history of mental illness, prior occurrences of mental disorders, or any other medical

conditions. There was also no evidence of alcohol or substance abuse, nor any significant medical comorbidities. As a result of the apprehension expressed by the parents regarding the potential adverse effects of the recommended medication, the patient was not administered medication prior to undergoing combination therapy. The initial assessment using the Children's Revised Impact of Event Scale version 8 (CRIES-8) yielded a cumulative score of 23, with intrusion and avoidance subscale scores of 3 and 20, respectively. The patient's baseline scores on the Hamilton Depression Rating Scale 24 Items (HAMD-24), Hamilton Anxiety Rating Scale (HAMA), and Baker Scale for Suicidal Ideation-Chinese Version (BSI-CV) were 31, 13, and 10, respectively. We performed follow-up visits of 7 d and one month. By the end of the treatment, her total scores on the HAMD-24, HAMA, and BSI-CV were 5 (83.87% improvement), 6 (53.85% improvement), and 6 (40.00% improvement), respectively (Fig. 1; Table 1). Strikingly, the patient reported no subjective side effects after any rTMS session.

Patient 2, a 17-year-old male high-school student of Han ethnicity, unfortunately witnessed his father's death in a car accident. Subsequently, the patient consistently displayed resistance towards recollecting the incident or acknowledging the veracity of his father's passing. His aunt perceived him as excessively apathetic. The patient's family history did not indicate any instances of mental illness, prior episodes of mental disorders, or other medical conditions. There was also no evidence of alcohol or substance abuse, nor any significant medical ailments. Prior to the commencement of combination therapy, the patient exhibited reluctance to take medication. Low-frequency rTMS combined with imaginal exposure rapidly ameliorated mental symptoms and maintained the effect for at least one month post treatment (with no other treatment). The patient's baseline total scores on the HAMD-24, HAMA, and BSI-CV were 12, 7, and 0, respectively. We performed follow-up visits of 7 d and one month after treatment. By the end of the treatment, his total scores on the HAMD-24 and HAMA were 2 (83.33% improvement) and 2 (71.43% improvement), respectively (Fig. 1; Table 1).

Both subjects met the criteria for ASD in the Diagnostic and Statistical Manual of Mental Disorders,

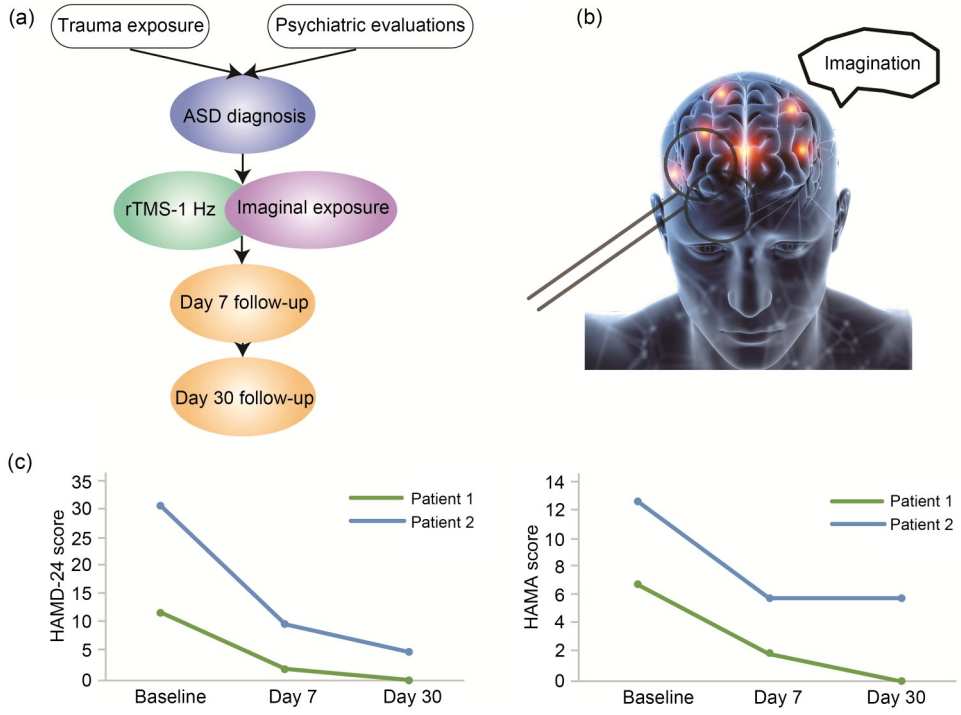

Fig. 1 Results of depression assessment after 5 d of treatment. (a) Program flowchart of acute stress disorder (ASD) treatment. (b) Schematic diagram of repetitive transcranial magnetic stimulation (rTMS) combined with imaginal exposure for ASD. The picture of the three-dimensional (3D) brain was taken from the freepik website (https://www.freepik.com). (c) Changes in depression assessments for ASD. HAMD-24: Hamilton Depression Rating Scale 24 Items; HAMA: Hamilton Anxiety Rating Scale.

Table 1 Clinical characteristics of the patients with acute stress disorder (ASD)

Scales	Baseline	Day 7	Day 30
Patient 1			
HAMD-24	31	10	5
HAMA	13	6	6
BSI-CV	10	7	6
Patient 2			
HAMD-24	12	2	
HAMA	7	2	
BSI-CV	0	0	0

HAMD-24: Hamilton Depression Scale 24 Items; HAMA: Hamilton Anxiety Scale; BSI-CV: Beck Scale for Suicide Ideation-Chinese Version.

fifth Edition (DSM-V). This was assessed using structured clinical interviews based on the DSM-V (SCID), conducted by two professional psychiatrists. Both patients scored ⩾30 on the trauma score at baseline and met the criteria for current major depression. Neither patient used drugs before or after receiving the combination therapy because their parents showed concern about the occurrence and development of side effects. As mentioned, upon study entry, both subjects had had intermittent, disturbing flashbacks and trauma exposure history for less than one month. Primary outcomes at baseline were measured by means of the HAMD-24 and HAMA on Day 7 and Day 30.

The rTMS treatment was delivered by a Magstim® magnetic stimulator with an eight-figured coil (The Magstim Co., Ltd., Whitland, UK). We defined the right DLPFC target using the International Electroencephalogram (EEG) 10-20 standard positioning system. The rTMS protocol involved applying 1-Hz frequency for five consecutive days. Each daily rTMS session comprised two stimulations: 800 and 1600 pulses. The interval between the two stimuli was 30 min. Each day, the first treatment was 800 pulses, and the second (1600 pulses) was accompanied by imaginal exposure (recalling the traumatic event). The stimulus intensity was 100% of the resting motor threshold (MT) based on participant tolerance. The MT was defined as the lowest intensity of TMS required to induce a motor response in the contralateral resting abductor pollicis brevis muscle.

Imaginal exposure exposes patients to previous traumatic event(s) in a controlled setting. Our patients were asked to provide a list of eight events or clues that would be used for systematic exposure during rTMS. These lists started with item 0, which was chosen by the subject as a calming or soothing experience. The next item (#1) was a neutral experience. Items 2 to 7 were various aspects of the event related to their traumatic experience that would trigger increasing distress. These personalized lists were then used during exposure as a means of activating brain circuits associated with the patients' invasive flashback symptoms.

In our study, the combination of rTMS and imaginal exposure proved to be a safe and effective therapeutic approach for adolescents with ASD. Notably, the symptoms of both patients showed significant improvement following a total of five sessions of low-frequency rTMS, each session comprising one stimulation with and one without imaginal exposure, at different frequencies. These findings align with a previous study on rTMS treatment in adults, which demonstrated the efficacy of rTMS administered over a two-week period (3–5 sessions per week) for the treatment of refractory PTSD (Osuch et al., 2009). Based on the difference in function of the main regulation between the left and right cerebral cortices, the right DLPFC is generally recognized as the main stimulus target for rTMS in the treatment of PTSD (Iglesias, 2020). Low-frequency stimulation can also reduce cortical excitability (Klomjai et al., 2015) and alter synaptic strength (Iglesias, 2020). It is not fully understood how low-frequency rTMS produces favourable changes to PTSD symptoms; however, one model explains that therapeutic effects are observed due to partial inhibition of lateralized right-sided hyperactivity of the DLPFC (Berlim and van den Eynde, 2014). Neurobiological evidence seems to show that low-frequency stimulation can induce long-term depression (LTD) (Klomjai et al., 2015). A gradual, slight increase in calcium concentration after prolonged low-frequency stimulation promotes LTD and produces various changes to synapses (Klomjai et al., 2015). These findings illustrate how the setting of rTMS can alter memory and plasticity; this has clinical applications in PTSD, where individuals are severely impaired by miscoded invasive memories (Iglesias, 2020).

We hypothesized that the first treatment in a day with one rTMS session would stabilize acute symptoms, and the second one, which included imaginal exposure, may activate the anxious and depressive symptoms, which would then be inhibited by the

second rTMS. This study is the first to report adolescents with ASD who responded to rTMS combined with imaginal exposure. Both patients showed surprising results after treatment, at the 7-d follow-up and one-month follow-up, and the efficacy of the combined treatment continued for at least one month in both patients without medication before or after treatment. However, there are several limitations to the study. The sample size was very small, and we did not have a longer follow-up period to determine whether the treatment could prevent progression to PTSD or recrudescence of the original symptoms. However, our finding that the effect lasted at least one month without any other intervention is highly valuable for patients, especially adolescents. Importantly, rTMS combined with imaginative exposure appears to be a promising therapy to rapidly ameliorate ASD in adolescents. Overall, the clinically significant improvement in these cases supports the combination of physical and psychological therapies in adolescents with ASD.

In summary, rTMS combined with imaginal exposure could be used to rapidly and significantly ameliorate depressive and anxious symptoms of adolescents with ASD. The effect lasts for one month in the absence of other interventions. Further well-designed, sham-controlled studies and more participants are needed to test the efficacy and safety of this therapy in adolescents with ASD.

Data availability statement

All data generated and analyzed during this study are available from the corresponding author upon reasonable request.

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Author contributions

Miaomiao ZHAO performed the study design and acquisition, analysis, and interpretation of data, drafted and revised the article. Ying LI contributed to the analysis and interpretation of data and revised the article critically for important intellectual content. Haoyang ZHAO and Chaonan JIANG revised the article critically for important intellectual content. Manli HUANG contributed to study design, acquisition of data, and critical revision of the article for important intellectual content. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Miaomiao ZHAO, Ying LI, Haoyang ZHAO, Chaonan JIANG, and Manli HUANG declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. Informed consent was obtained from all patients for being included in the study. Additional informed consent was obtained from all patients for whom identifying information is included in this article.

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