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Childhood trauma mediates repetitive transcranial magnetic stimulation efficacy in major depressive disorder

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Abstract

Childhood trauma is one of the most prominent risk factors in developing major depressive disorder (MDD) and may lead to unfavorable outcomes of pharmacotherapy and psychotherapy in MDD. While how it modulates the treatment outcome of the repetitive transcranial magnetic stimulation (rTMS) and how sex difference may play a role in mediating this relationship remain unknown. To evaluate this question, 51 (37 women) MDD patients were treated with 10 Hz rTMS to the left dorsolateral prefrontal cortex (lDLPFC). The experience of childhood trauma was quantified by the Childhood Traumatic Questionnaire (CTQ). The depressive severity was assessed by Hamilton Depression Scale (HAMD) and Beck Depression Inventory (BDI) as the primary and secondary assessments. Beck Hopelessness Scale (BHS) and Hamilton Anxiety Scale (HAMA) were also assessed for further confirmation. Thirty-six (70.6%) participants showed a response including 17 (33.3%) achieving remission to the rTMS treatment. The alleviation of depressive symptoms was negatively correlated with the CTQ scores, specifically in women but not men, in subjective BDI and BHS, but not objective HAMD or HAMA. We demonstrate that childhood trauma negatively affects the subjective perception of rTMS-lDLPFC treatment outcomes in female MDD patients. This highlights the importance of measuring childhood trauma-related symptoms in routine clinical rTMS treatment, as they may impact perceived efficacy.

Keywords Major depressive disorder · Childhood trauma · Repetitive transcranial magnetic stimulation · Sex difference

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Introduction

Childhood trauma and maltreatment are widely acknowledged as one of the major public health problems [1]. A variety of studies have documented that childhood traumatic experiences have a life-long impact on adulthood mental and physical health [2–4], and are strongly associated with depressive disorders which have been proven in both retrospective [5, 6] and prospective studies [7]. For instance, patients with major depressive disorder (MDD) show significantly more severe childhood abuse and neglect than healthy control subjects [8], while subjects who had childhood trauma show greater risk to develop MDD in later adulthood [9, 10].

MDD is a multifaceted mental disorder and characterized by various symptoms including depressed mood, loss of interest, feelings of worthlessness or excessive/inappropriate guilt, sleep disturbance, and even cognitive disturbances in memory and attention [11]. These symptoms impair daily life functions which make MDD one of the leading causes of disability worldwide [12]. MDD affects one in six adults

in their lifetime [13] and is associated with a high degree of mortality [14]. Conventional treatment for MDD includes pharmacotherapy and psychotherapy, or the combination of both; for severe MDD patients, electroconvulsive therapy (ECT) may also be needed [15–18]. In recent decades, the non-invasive repetitive transcranial magnetic stimulation (rTMS) using 10 Hz stimulation on the left dorsolateral prefrontal cortex (lDLPFC) has been approved by the Food and Drug Administration (FDA) and widely recognized as a clinical treatment for depression [19].

Recent evidence suggests that childhood maltreatment may lead to an unfavorable clinical treatment outcome of either pharmacotherapy or psychotherapy in MDD [20]. This raises the question of whether childhood traumatic experiences also impact the therapeutic effect of rTMS-lDLPFC in MDD patients. To address this yet open question is the goal of our present study. In addition, the sex disparities that women having a higher risk, prevalence, and severity of MDD [21], have attracted researchers' attention to the pharmacological treatment effects [22, 23]. Therefore, sex differences may also play a role in mediating the relationship between childhood trauma and rTMS-lDLPFC therapeutic effects. In this present study, we conduct an investigation of how childhood trauma and sex differences modulate the efficacy of clinical rTMS-lDLPFC treatment in MDD patients.

Materials and methods

Participants

Participants were recruited from in- and out-patients of the, Zhejiang University School of Medicine, China. All the participants provided written informed consent for the TMS treatment and for the use of their clinical information for research purposes. All procedures have been approved by the Institutional Review Board, and comply with the ethical standards of the Hangzhou Seventh People's Hospital.

Adults (1) aged 18–65 years; (2) who had a diagnosis of MDD confirmed by a Mini-International Neuropsychiatric Interview; (3) whose current episode of MDD showed a 17-item Hamilton Depression Scale (HAMD) score ≥ 18 were included in the study. All patients were medication-free or unchanged at least 1-week preceding rTMS treatment, which continued unchanged during treatment. The exclusion criteria included (1) pregnancy; (2) bipolar affective disorder; (3) schizophrenia spectrum disorders or any other psychiatric comorbidities; (4) previous TMS or modified ECT (MECT) in the past 6 months; (5) severe somatic diseases including neurological or immunological illness, acute myocardial ischemia and etc.; (6) the presence of a cardiac pacemaker, intracranial implant or metal in the body. In addition, patient's previous status to pharmacotherapies were listed in

Table S1, and no participants received psychotherapy during the whole study course.

rTMS procedures

Based on the evidence-based guidelines on rTMS by Lefaucheur et al. [24], we applied a shorter twice daily TMS treatment design to improve clinical utility. Participants all received a 5-day rTMS treatment by targeting the left dorsolateral prefrontal cortex (lDLPFC). TMS was delivered with a Rapid2 stimulator equipped with a figure-of-eight D70 Air Film Coil (Magstim, UK). The resting motor threshold (RMT) was determined for each participant prior to the initial TMS session. In brief: participants were seated in a comfortable chair with armrests and maintained relaxation. The coil was positioned tangentially to the head and approximately 45° to the midline. Surface electromyography was used to record the motor evoked potential (MEP) from the right abductor pollicus brevis (APB) muscle. RMT was defined as the intensity of a single TMS pulse that was able to elicit at least five MEPs, with an amplitude of at least 50 μV, in ten consecutive trials [25, 26]. DLPFC was defined as a site 5 cm anterior to the position that elicited maximal MEPs in the APB muscle according to the widely used clinical method. The present TMS parameters were: 90% RMT intensity for safety, 10 Hz frequency, 5 s on and 20 s off, 2000 pulses per session. The whole treatment comprised ten sessions in total, i.e., two sessions per day with an interval of 3–6 h for 5 consecutive days (from Day 1 to Day 5). The rTMS procedure was performed by a trained specialist for all of the participants.

Clinical assessments

The Childhood Trauma Questionnaire (CTQ) is an internationally accepted retrospective self-reported measure of childhood trauma that investigates the history of maltreatment before the age of 16, it covers five respects, i.e., physical, emotional, and sexual abuse, as well as physical and emotional neglect [27]. Before the TMS treatment, all participants filled out the Chinese version of the 28-item CTQ-Short Form (CTQ-SF) which has shown good reliability and validity among patients with depression [28]. The HAMD [29], 14-item Hamilton Anxiety Scale (HAMA) [30], 21-item Beck Depression Inventory-2nd edition (BDI-II) [31], and 20-item Beck Hopelessness Scale (BHS) [32] were obtained at baseline (Day 0) and at the end of the study (Day 5). The primary outcome was the reduction of HAMD scores after 5-day TMS treatment from the baseline. HAMD score reduction $\geq 50\%$ was defined as a response; HAMD score < 8 was defined as remission [33]. Like HAMD, BDI was used for assessing the presence and severity of depressive symptoms and regarded as the secondary assessment

of the depression severity in this study. Besides, we also assessed with the HAMA and BHS as further confirmation. BDI and BHS are subjective scales as they are self-reported questionnaires, while HAMD and HAMA are more objective scales administered by a board-certified psychiatrist. Side effects were assessed after each day of rTMS treatment by asking the participants the items of the Treatment Emergent Symptom Scale [34]. We focused on the most TMS-related side effects, such as seizures, headache, and dizziness. Other self-reported discomforts were also recorded. Participants' basic physical checkups and inquiries were performed daily.

Statistical analysis

Mann–Whitney test was used to compare non-normally distributed BDI, BHS, HAMD, and HAMA scores between Day 0 and Day 5, as well as non-normally distributed CTQ scores between sexes. Student's *t*-test was used to compare the normally distributed reduction rates, i.e., % (Day 0–Day 5), of BDI, BHS, HAMD, and HAMA between sexes. Correlation analyses between CTQ scores and reduction rate of BDI, BHS, HAMD, and HAMA were performed with the Spearman test. Statistical analyses were performed with GraphPad Prism 5.0 and Matlab R2012a. $P < 0.05$ was considered to be significant. Significances with multiple comparisons were further tested with FDR correction.

Results

Eighty-two patients with MDD were enrolled. Thirty-one (37.8%) discontinued the treatment. Among these dropouts, 16 could not adhere to the treatment schedule, three could not bear the treatment (2 complained about the noise, 1 was dissatisfied with the mild headache), 3 got interrupted due to the other necessary treatments (1 had a toothache, 1 had skin itch, the other received MECT), 2 discontinued due to lack of perceived benefit, one withdrew due to the concerns about the medical costs for the treatment (which had to be paid privately), and six were unwilling to fill out questionnaires after the TMS treatment. Fifty-one participants completed the 5-day rTMS-lDLPFC treatment and were included in the following analysis. See detailed baseline demographic characteristics and medication use during the treatment of the study participants in Table 1.

rTMS-lDLPFC significantly alleviates depressive symptoms in MDD

After the 5-day TMS treatment, BDI, BHS, HAMD, and HAMA scores were all decreased in the total sample with significant *P* values that were all less than 0.0001

**Table 1** Demographic and clinical characteristics of participants

	Mean (SD)/Number (%)	Comparison between sexes (*P*-value)
Women	37 (72.5%)	
Age (years)	28.29 (9.8)	0.25
Education years	13.80 (2.7)	0.20
CTQ scores	34.98 (14.1)	0.48
Emotional abuse	8.39 (3.5)	0.58
Physical abuse	6.69 (3.1)	0.91
Sexual abuse	5.96 (2.4)	0.99
Emotional neglect	7.39 (5.3)	0.61
Physical neglect	6.55 (3.7)	0.20
Baseline scores		
BDI	29.43 (10.3)	0.10
BHS	12.21 (3.8)	0.99
HAMD	26.16 (4.9)	0.07
HAMA	19.94 (6.1)	0.05
Medication	47 (92.2%)	0.27[#]
Antidepressant	42 (82.4%)	
Antianxiolytic	33 (64.7%)	
Antipsychotic	33 (64.7%)	
Mood stabilizer	5 (9.8%)	
Hypnotics	4 (7.8%)	

Note: Data were presented as mean (SD) or number of patients in each group (%). Mann–Whitney test was used to compare the differences between sexes

[#]The numbers of patients were counted for each combination of medication use and compared. $P < 0.05$ was considered to be significant

(Fig. 1). The reduction rates were 55.4%, 35.0%, 59.3%, and 58.7%, respectively. Thirty-six (70.6%) participants showed response including 17 (33.3%) achieving remission based on HAMD. There were no seizures, and no participants showed problems with memory or attention. The reported side effects were very mild: 20 (38.5%) participants reported dizziness, 8 (15.4%) felt a headache, and 5 (9.6%) felt nausea, 4 (7.7%) and 3 (5.8%) reported agitation and anxiety, respectively, and only 1 (1.9%) experienced tinnitus. The baseline scores of all depressive severity scales were similar in women and men ($P \geq 0.05$, Table 1). No significant difference of reduction rate of depressive symptoms was found between sexes in either BDI ($52.5\% \pm 33.0\%$ and $63.3\% \pm 32.4\%$, respectively, $P = 0.30$) or HAMD ($59.8\% \pm 19.8\%$ and $57.9\% \pm 22.6\%$, respectively, $P = 0.78$). Consistent results were also observed in the reduction rate of BHS ($31.3\% \pm 39.2\%$ and $44.6\% \pm 37.9\%$, respectively, $P = 0.28$) and HAMA ($59.2\% \pm 23.3\%$ and $57.1\% \pm 22.0\%$, respectively, $P = 0.77$).

In addition, a significant positive correlation between the reduction rate of BDI and HAMD scores was observed in the entire group of participants ($\rho = 0.79$, $P < 0.0001$) and in each
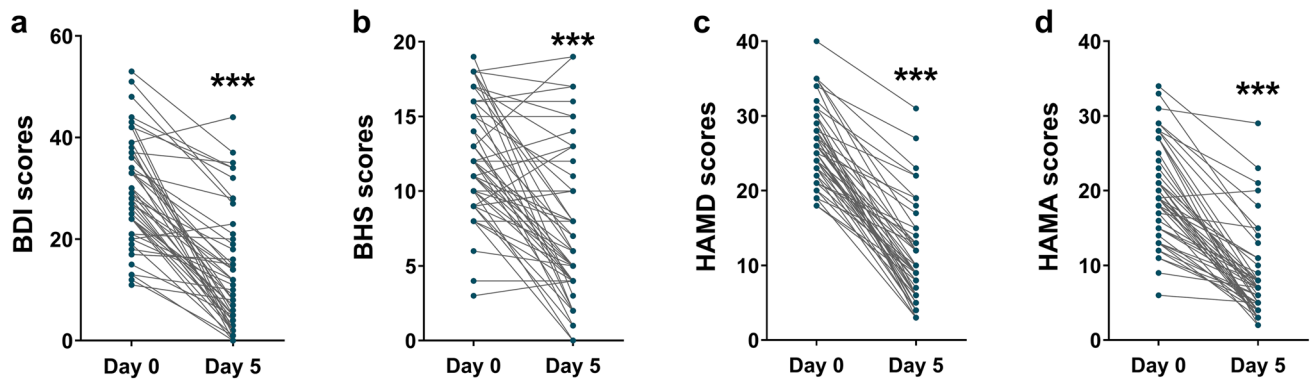
Fig. 1 Changes in depression severity scores after 5-day rTMS-lDLPFC treatment from the baseline. The scores of **a** BDI, **b** BHS, **c** HAMD and **d** HAMA after treatment (Day 5) were significantly decreased from the baseline scores (Day 0). *BDI* Beck Depression Inventory, *BHS* Beck Hopelessness Scale, *HAMD* Hamilton Depression Scale, *HAMA* Hamilton Anxiety Scale. Each dot presents the score of one participant. $P < 0.05$ was considered to be significant. ***$P < 0.0001$

sex (women: $\rho = 0.77$, $P < 0.0001$; men: $\rho = 0.85$, $P = 0.0002$); this indicates good agreement between subjective (BDI) and objective (HAMD) scales in our present study. It should be noted that none of the reduction rates of our depressive severity scales shows a significant correlation with medication use during the course of TMS treatment ($P \geq 0.20$); therefore, drug-related effects on symptom reduction, complementing those of rTMS-lDLPFC, were not considered to be crucially effective in our sample. This is supported by the recommendation from Lefaucheur et al. that there is possibly no differential antidepressant efficacy between rTMS therapy performed alone versus combined with antidepressants [35].

CTQ scores mediate rTMS-lDLPFC treatment effects

The total CTQ scores showed no significant correlation with baseline BDI, BHS, HAMD, and HAMD scores in the total sample ($P \geq 0.23$). Significant correlations were observed between the CTQ subscale emotional abuse and BDI ($\rho = 0.30$, $P = 0.33$), and between sexual abuse and HAMD ($\rho = 0.30$, $P = 0.03$), and HAMA ($\rho = 0.34$, $P = 0.02$); nevertheless, these correlations were no longer significant after FDR correction ($P \geq 0.22$).

The total CTQ scores were significantly correlated with the reduction rate of all our four depressive severity scales after FDR correction (Fig. 2): BDI ($\rho = -0.31$, $P = 0.03$), BHS ($\rho = -0.43$, $P = 0.004$), HAMD ($\rho = -0.30$, $P = 0.03$), and HAMA ($\rho = -0.33$, $P = 0.03$), i.e., the higher the total CTQ scores, the lower the degree of depressive severity reduction. In addition, significant correlations were also observed between BDI reduction rate and CTQ subscale emotional abuse ($\rho = -0.29$, $P = 0.04$), and physical abuse $\rho = -0.32$, $P = 0.02$); between BHS reduction rate and emotional abuse ($P = -0.29$, $P = 0.04$), physical abuse ($\rho = -0.30$, $P = 0.03$), and physical neglect ($\rho = -0.48$, $P < 0.001$); between HAMD reduction rate and emotional abuse ($\rho = -0.28$, $P = 0.04$); between HAMA reduction rate and emotional abuse($\rho = -0.28$, $P < 0.05$), and physical abuse ($\rho = -0.35$, $P = 0.01$). While only the significance between BHS reduction rate and physical neglect survived
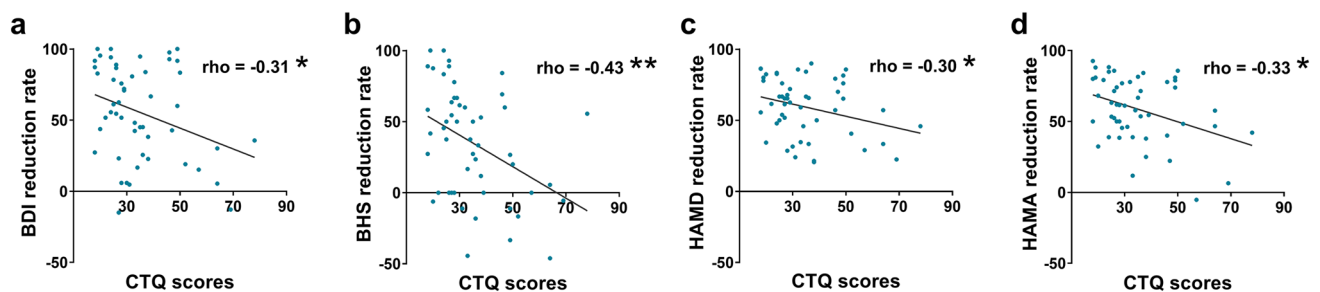
Fig. 2 Correlations between CTQ and the reduction rate of depression severity scores. Total CTQ scores showed significant correlations with the reduction rate of **a** BDI, **b** BHS, **c** HAMD, and **d** HAMA. *CT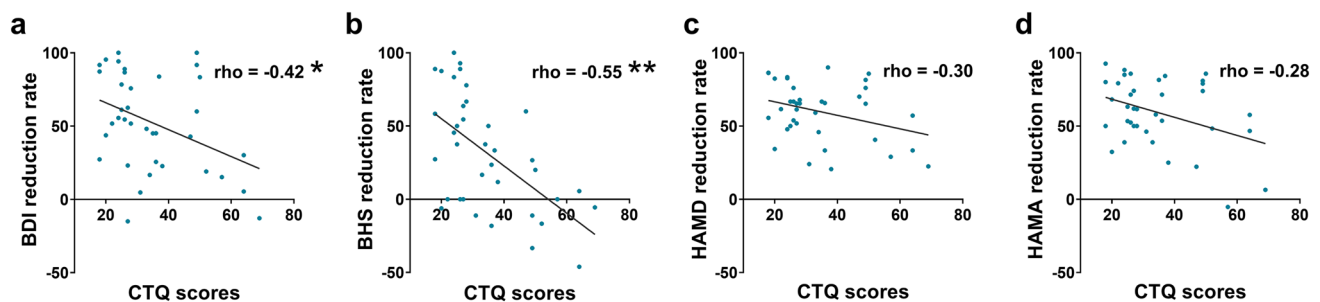Q* Childhood Trauma Questionnaire, *BDI* Beck Depression Inventory, *BHS* Beck Hopelessness Scale, *HAMD* Hamilton Depression Scale, *HAMA* Hamilton Anxiety Scale. $P < 0.05$ after FDR correction was considered to be significant. *$P < 0.05$, **$P < 0.01$

the FDR correction ($P = 0.008$), the rest P values were equal to or higher than 0.11. We further examined the differences in CTQ scores between response and non-response groups for confirmation. The total CTQ scores were significantly lower in the participants who showed response to the rTMS treatment (Mann–Whitney test, $P = 0.03$). The scores of all CTQ subscales were lower in the response group as well, among which the significance was only shown in subscale physical neglect (Mann–Whitney test, $P = 0.04$).

CTQ scores mediate rTMS-lDLPFC treatment effects in women but not in men

By comparing between sexes, no significant difference was found in the scores of either total CTQ ($P = 0.48$) or any of its subscales ($P \geq 0.20$, Table 1). And no significance was observed in either of the sexes when correlating baseline BDI, BHS, HAMD, and HAMD scores with the scores of either the total CTQ (women: $P \geq 0.07$, men: $P \geq 0.13$) or its subscales (women: $P \geq 0.27$, FDR correction; men: $P \geq 0.06$).

However, a clear sex difference was observed in the correlations between CTQ and the depression severity reduction rates. In women, the total CTQ scores were significantly correlated with both BDI ($\rho = -0.42$, $P = 0.02$) and BHS ($\rho = -0.55$, $P = 0.002$) reduction rates after FDR correction, but not with HAMD ($\rho = -0.30$, $P = 0.10$) and HAMA ($\rho = -0.28$, $P = 0.10$) (Fig. 3). In contrast, no significant correlation was observed in men ($P \geq 0.17$, figure not shown). In the CTQ subscales of women, after FDR correction, emotional abuse ($\rho = -0.42$, $P = 0.03$) and physical abuse ($\rho = -0.45$, $P < 0.05$) scores were significantly correlated with BDI reduction rate (Fig. 4a, b); and BHS reduction rate was significantly correlated with all the CTQ subscales: emotional abuse ($\rho = -0.46$, $P = 0.03$), physical abuse ($\rho = -0.40$, $P < 0.05$), sexual abuse ($\rho = -0.47$, $P = 0.03$), emotional neglect ($\rho = -0.43$, $P = 0.03$) and physical neglect ($\rho = -0.60$, $P = 0.002$) (Fig. 4c–g). In contrast, in men, no significance was found ($P \geq 0.06$).

Discussion

In the present study, we investigated the relationship between childhood traumatic experiences and the efficacy of rTMS-lDLPFC treatment in MDD participants. In addition, we preliminarily explored sex differences. We showed good response and remission in our protocol that extend beyond the ones of standard rTMS. Our most novel finding is that (1) the CTQ scores were significantly negatively correlated with the treatment-related depressive symptom reduction, (2) specifically in women but not men; (3) female CTQ scores significantly correlated with the reduction in subjective scales, i.e., BDI and BHS, but not with objective scales, i.e., HAMD or HAMA. This suggests that the experience of childhood trauma and maltreatment among MDD patients, specifically women, may negatively affect their subjective perception of rTMS-lDLPFC treatment outcomes.

Therapeutic effects of the rTMS-lDPFC treatment

Our rTMS-lDLPFC results with a response rate of 70.6% and a remission rate of 33.3% replicate previous studies showing favorable treatment results [36, 37]. We aware that these previous studies were randomized double-blinded trials using the conventional FDA-approved rTMS (120% RMT intensity, 10 Hz, 4 s on and 26 s off, 3000 pulses per session), which requires a period of 4 weeks (one session per day on weekdays, i.e., five sessions a week) [36, 37]. To shorten the duration while at the same time ensure the doses, we therefore applied a shorter 5-day protocol, reduced stimulation intensity to 90% RMT for safety, and conducted 2000 pulses twice per day. Although our present study was single-armed and single-blinded, due to the shorter duration, such protocol is more feasible to be carried in both clinical-inpatient and especially ambulatory-outpatient settings. It should be noticed that the higher discontinue rate in our study was not due to the side effects, but other uncontrollable

Fig. 3 Correlations between CTQ and the reduction rate of depression severity scores in women. Total CTQ scores showed significant correlations with the reduction rate of **a** BDI and **b** BHS, but not **c** HAMD or **d** HAMA. *CTQ* Childhood Trauma Questionnaire, *BDI* Beck Depression Inventory, *BHS* Beck Hopelessness Scale, *HAMD* Hamilton Depression Scale, *HAMA* Hamilton Anxiety Scale. $P < 0.05$ after FDR correction was considered to be significant. *$P < 0.05$, **$P < 0.01$
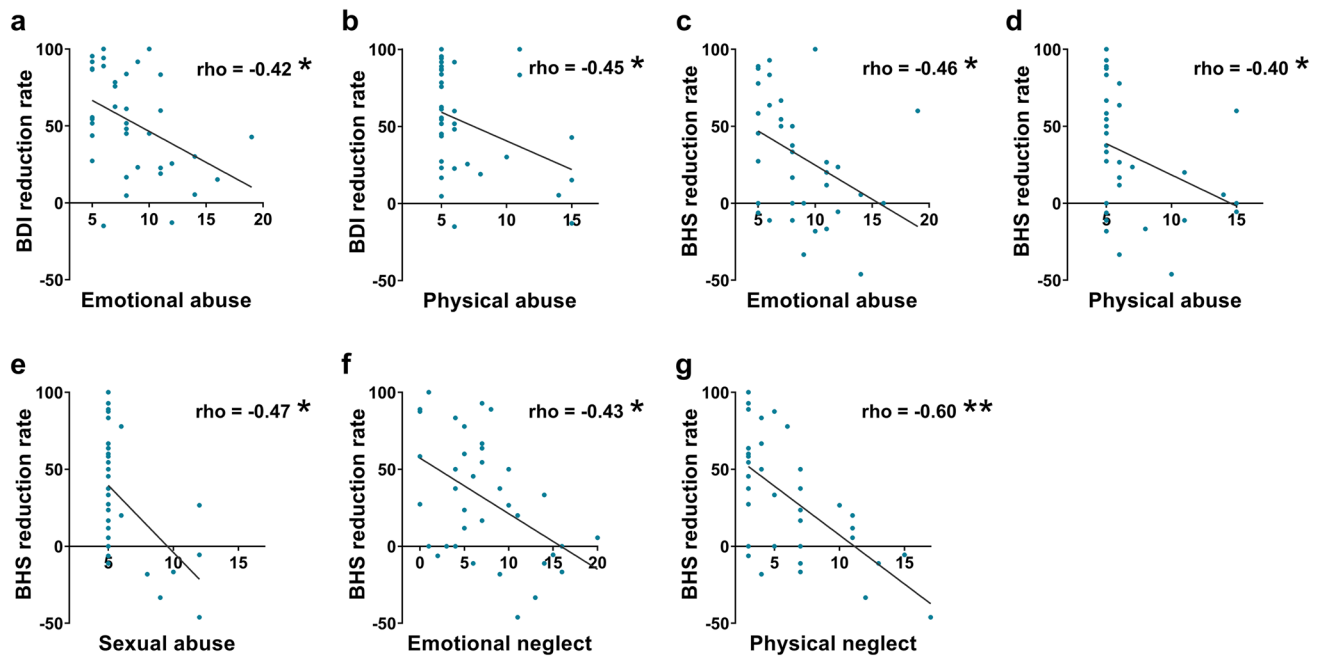
Fig. 4 Significant correlations between CTQ subscales and the reduction rate of BDI and BHS scores in women. BDI reduction rate was significantly correlated with **a** emotional abuse and **b** physical abuse scores; BHS reduction rate was significantly correlated with **c** emotional abuse, **d** physical abuse, **e** sexual abuse, **f** emotional neglect, and **g** physical neglect. *CTQ* Childhood Trauma Questionnaire, *BDI* Beck Depression Inventory, *BHS* Beck Hopelessness Scale. $P < 0.05$ after FDR correction was considered to be significant. $*P < 0.05$, $**P < 0.01$

factors, such as the subjective decisions or treatment needs from the patients. That is further supported by the fact that all participants showed good tolerance, with some reporting slight dizziness or headache.

Childhood trauma modulates the therapeutic effects of rTMS-lDPFC

Childhood maltreatment is an environmental risk factor for developing depressive disorder in later life [9, 10]. Studies have shown that adults with a history of childhood trauma tend to have higher stress sensitivity [38] and elevated levels of inflammation [39], which may predispose the MDD patients to a poor treatment outcome of both pharmacological and psychological therapies [20]. To our knowledge, we for the first time investigated the association between childhood traumatic experiences and the therapeutic effect of TMS on MDD patients. We found that the decrease of depressive severity scores in MDD patients was significantly negatively correlated with their total CTQ scores, indicating that a history of traumatic childhood life events also plays an adverse role in the TMS treatment efficacy on depressive patients.

Childhood traumatic life events can also lead to alterations in brain structure, for instance, reduced hippocampal volume [40, 41], and white matter integrity [42]; as well

as the resting-state brain activity [43], cognitive [44], and emotional [41] functioning. As the most prominent rTMS target in MDD, the lDLPFC has been found to be hypoactive in MDD patients [45]. By stimulating the lDLPFC, TMS was suggested to normalize the functional balance between brain networks: reduced functional connectivity between the subgenual anterior cingulate cortex on the one hand and the default mode network, lDLPFC, and insula on the other [46]. These areas show overlap with the childhood trauma-related network, e.g., the prefrontal-insular-motor cortical network [47]. That may serve as a neural correlate of the here observed modulation of rTMS-lDLPFC treatment effects by childhood trauma [41, 47, 48].

Differences between female and male patients

Sexual dimorphism has been observed in MDD patients not only in lifetime risk, clinical presentation, but also in their response to pharmacotherapy [22, 23], e.g., greater therapeutic response has been observed in men than women for imipramine [49, 50], and women may respond better to serotonergic antidepressants than men [50, 51]. The sex variance in antidepressant efficacy has been attributed to sex-specific biological differences, including hormone levels and metabolic enzymes, which all together lead to different profiles of

pharmacokinetics and pharmacodynamics [22, 52]. However, the reason remains unclear. In our present study, no significant sex difference was found in the efficacy of rTMS treatment based on all four clinical scales (BDI, BHS, HAMD, and HAMA). This finding is in agreement with previously limited evidence, which has found equivalent TMS efficacy in both men and women [53]. In addition, although no significant sex difference was found in the scores of the total CTQ and all its subscales, the correlations between CTQ and the depression severity reductions were of significance only in women, not men; and interestingly, these significances could only be observed when assessed by BDI and BHS, even though women had comparable baseline depression and hopelessness with men, which supports the idea that CTQ is related to subjectively perceived change of depressive symptoms. Together, this speaks for sex differences in specifically the subjective perception of rTMS-lDLPFC treatment effects which may be less perceived in women due to their childhood trauma. One thing that needs to be aware of is the discrepancy of sample size between two sexes, therefore, this result should be considered preliminary.

Limitations

Our present study still has several limitations that should be considered: (1) due to the sex discrepancy of morbidity and clinical consultation rate in MDD patients, the sample size of men was relatively small; (2) out of consideration for patients' benefit, we did not include a sham group, therefore, the alleviation of depressive symptoms might be benefited from the interactions between the psychiatrists and the patients; (3) how long the effects of rTMS-lDLPFC treatment may persist in responders is unavailable in this study, the follow-up study in this sample is ongoing to determine the long-term outcome.

Conclusions

In summary, we demonstrate that a history of childhood traumatic experience negatively influences the subjective perception of rTMS-lDLPFC treatment outcome in specifically female MDD patients. We, therefore, emphasize the importance of measuring childhood trauma-related symptoms in routine clinical rTMS treatment, as they may impact perceived efficacy.

Declarations

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