



Add-on rTMS for the acute treatment of depressive symptoms is probably more effective in adolescents than in adults: Evidence from real-world clinical practice

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) is considered as an effective treatment for adults with major depressive disorder. However, it remains unknown whether rTMS has comparable or better efficacy in adolescents.

Objective: The current naturalistic study aimed to investigate the efficacy and clinical outcome of add-on rTMS in a large sample of adolescent patients compared to adult patients.

Methods: This study included 117 patients (42 adolescents vs. 75 adults) with mood or anxiety disorders who were treated with at least 10 sessions of rTMS. rTMS was applied over the left dorsolateral prefrontal cortex (10 Hz). Symptoms of depression and anxiety were measured using the Hamilton Rating Scale for Depression (HAM-D) and the Hamilton Rating Scale for Anxiety (HAM-A) respectively, at baseline and after 2 and 4 weeks of follow-up. Comparisons of clinical improvement and rates of response/remission were made across age groups.

Major findings and conclusions: All the age groups showed significant improvements in clinical symptoms. No safety or tolerability concerns were identified. Symptomatic improvements and response/remission rates were more significant in adolescent patients than in adults. Decrease in HAM-D and HAM-A scores after 2 weeks and 4 weeks of rTMS treatment were positively correlated in adolescents, but not in adults. General linear model repeated measures demonstrated significant effect of time × age group interaction on the HAM-D score, in response to 10 sessions of rTMS. Add-on rTMS is feasible, tolerable, effective and more applicable to adolescents with mood or anxiety disorders. However, double-blinded and sham-controlled trials are needed for validating this conclusion.

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Depression and anxiety disorders are commonly present in adolescents [1,2]. Contemporary pharmaceutical treatment approaches are often ineffective (remission rates are around 30%) [3–5] and/or intolerable [6]. A recent network meta-analysis [7] compared the efficacy and tolerability of antidepressants for major depressive disorder (MDD) in adolescent patients and further concluded that the currently available antidepressants did not offer a clear advantage for adolescents. In contrast, the symptoms of depression and anxiety in adolescents which lead to significant functional impairment [8], increase the risk of suicidality [9] and place a heavy burden and responsibility on caregivers [10].

Currently, selective serotonin reuptake inhibitors (SSRIs) seem to be the only class of antidepressants for pharmacological therapy for adolescents, of which, only Fluoxetine shows evidence indicating benefits that could outweigh the risks [11]. Even worse, the US Food and Drug Administration (FDA) mentioned the possibility that antidepressants might be associated with an increased risk of suicidal behavior in children and adolescents. Besides, the presentation of pharmacotherapy for adolescent anxiety and depression is biased especially when combining anxiety as an indication [12,13]. Medications used in the treatment of the symptoms of depression and anxiety in adolescents are still controversial, therefore, there is an urgent need for better and safer approaches. Significant positive effects of repetitive transcranial magnetic stimulation (rTMS) for MDD among adult patients have been found in several studies [14–17]. Unfortunately, systematic rTMS evidence for adolescents is limited [18]. Currently, only the left unilateral dorsolateral prefrontal cortex (DLPFC) 10 Hz stimulation protocol has been approved by FDA for the management of treatment-resistant depression in adults. However, some existing studies [19–21] suggested that rTMS is a safe and well-tolerated acute treatment in adolescent population. Although it is premature to make definitive recommendations, converging evidences [18,22] hint to the possibility that rTMS may be a promising modality for clinicians to deal with depression and anxiety disorders in the youth in a combinatorial approach with psychotropic medications or psychotherapy.

Although there is peer-reviewed research describing the efficacy of rTMS in randomized control trials [16,23–25] and replications of positive findings [26], these trials often only included adults. This does not help answer the question whether rTMS has comparable or even better efficacy in the treatment of symptoms of depression and anxiety in adolescents compared to adults. Thus, such data from naturalistic studies are important as they permit the inclusion of subjects with a wider range of age than those found in controlled trials. To our knowledge, the effects of rTMS on the symptoms of depression and anxiety have not yet been compared between adults and adolescents. Therefore, the present real-world, naturalistic and observational study was done to investigate whether add-on rTMS could improve the symptoms of depression and anxiety more efficiently in adolescent patients than in adults.

Methods

Overview

The current study included inpatients with mood or anxiety disorders across a wide range of age, who were enrolled at one site, the Shanghai Mental Health Center (SMHC), the largest mental health service in China. The Research Ethics Committees at the SMHC approved the study in 2015 and the study was conducted according to the Declaration of Helsinki. A key element of this study was that all the patients were drug-free (at least 2 weeks) prior to admission to the hospital.

Sample and study design

All participants provided written informed consent at the recruitment stage of the study. Subjects younger than 18 years of age had their consent forms signed by their parents and the adolescents gave assent. In total, 171 subjects from the ages of 10–80 years, were included in the study if they met the criteria for mood or anxiety disorders defined in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), and experienced an acute exacerbation of the symptoms of depression or anxiety, or had a baseline score of at least 14 points on the 17-items

Hamilton Rating Scale for Depression (HAMD) or at least 10 points on the 14-items Hamilton Rating Scale for Anxiety (HAMA). Each subject was asked to spend 1 week as an inpatient for clinical assessment and screening procedures (including physical examination, electrocardiography, and clinical laboratory investigations) before receiving rTMS treatment. Other inclusion criteria were: having only one type of antidepressant during the rTMS treatment; willing to and being capable of completing at least 10 sessions. Patients were excluded from the study if they had received past treatment with rTMS or other electromagnetic stimulations such as, ex. electroconvulsive therapy, ferromagnetic metallic implants, pacemakers, had previous neurosurgery, seizures, head trauma, substance abuse or dependence, any psychiatric or neurological disorder other than depression and anxiety, psychotic depression, and suicidal propensities. The costs of rTMS sessions and associated clinical treatment were borne entirely by the patient or their insurer.

The disposition of samples across the acute treatment course is shown in Fig. 1. The pooled data represent 117 inpatients who were of ages 10 to 80 years, were in a depressive and/or anxiety episode, and had a baseline HAMD score of greater than 14 and/or a baseline HAMA score of greater than 10. The treating psychiatrists and a study psychiatrist assigned them a DSM-IV diagnosis. Ninety-two patients had a diagnosis of MDD; 8, of bipolar II disorder; 6, of dysthymia; 6, of general anxiety disorder; 3, of eating disorder; and 2, of obsessive-compulsive disorder. All the patients were taking one type of antidepressant during the rTMS treatment: 80 of them were taking a SSRI (54 of them took sertraline); 14, venlafaxine; 12, duloxetine; and 11, mirtazapine. Antidepressant was used for the acute treatment for a depressive and/or anxiety episode and was not changed during the rTMS treatment.

rTMS treatment

All rTMS treatment was administered by trained medical doctors. All patients were seated in a comfortable chair while TMS stimuli were delivered to the left prefrontal cortex (using the 5-cm rule) with a figure-of-eight coil and a MagPro X100 magnetic stimulator (Medtronic Co., Denmark). Patients were stimulated at a frequency of 10 Hz, the position of DLPFC, power (intensity) level of 120% of motor threshold (MT), 80 trains, 30 pulses per train, 12 s intertrain-interval, 2400 pulses per session and 5 sessions per week.

Clinical assessment

The primary outcome measure for the study was the scores on the 17-items version of the HAMD and the 14-items version of the HAMA. The outcome measures (HAMD/HAMA) were administered at baseline (before rTMS treatment), mid-treatment (after 10 sessions), at the end of the treatment (after 11–20 sessions), 2 weeks and 4 weeks after the completion of rTMS. Response to rTMS was defined as a $\geq 50\%$ decrease in HAMD/HAMA. Remission was defined as a HAMD/HAMA score of 7 or below. These measures and the cut points for therapeutic evaluation of depression and anxiety disorders had been widely used in Chinese clinical routine and related studies for over 30 years.

Data analysis

Data were summarized using standard descriptive statistics in SPSS version 16.0 (SPSS, Inc., Chicago, IL, USA) statistical software. Samples were grouped according to age at the point when the study was initiated, such that the adolescents group included patients from those younger than 18 years of age ($n = 42$), the adults

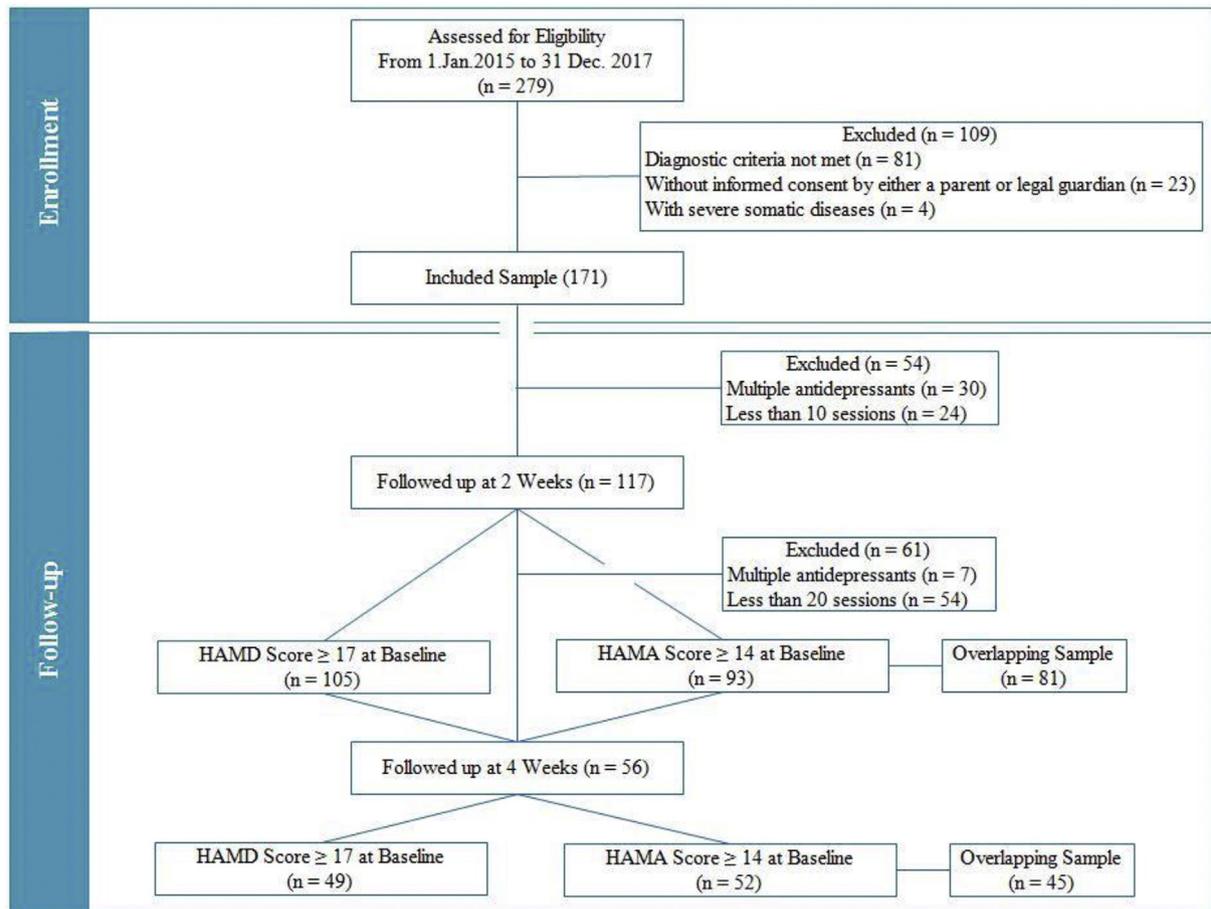


Fig. 1. Sample flow diagram of the study.

group included patients with ages between 18 and 60 years ($n = 27$) and the old people group included patients who were 60 years or older ($n = 48$). Analyses of variance (ANOVAs) and χ^2 tests were used to investigate differences between the age groups on demographics, clinical variables and treatment parameters. The percentage decrease in HAMD and HAMA scores after rTMS treatment for the age groups were displayed using histograms. Microsoft Excel was used to make the histogram graphs. Comparisons between outcome groups were made by ANOVAs and Bonferroni adjustments were used for all post hoc multiple-group comparisons. To further graphically display the feature of the relationship between the decrease of HAMD and HAMA scores among groups, a scatter plot with a set of linear trend lines was drawn. Finally, a general linear model repeated measure was used to evaluate time \times age interaction.

Results

Demographics, clinical characteristics, and treatment parameters

As shown in Table 1, the distribution of sex did not differ between age groups. Education and course of disease differed as expected, such that the adolescent group had significantly lower educational level and less length of course. The old people group had significantly higher baseline depression and anxiety severity scores on the HAMD17 and HAMA14, as well as the follow-up points after rTMS treatment. The proportion of patients who completed 4-weeks follow-up did not significantly differ between age groups. Patients were not found to differ by age groups in terms

of the number of rTMS sessions, but the adolescent group had lower stimulation intensity compared with adult and old people groups.

Safety

There were no seizures, syncope or other significant adverse events in the entire sample during the rTMS treatment. Only 5 patients (2 from the adolescents group, 2 from the old people group, and 1 from the adult group) reported non-serious adverse events (3 with transient headaches, 2 with musculoskeletal discomfort during rTMS treatment).

Effectiveness of rTMS: continuous data

There was a significant improvement in both depression and anxiety symptomatology in three age groups (Fig. 2.). All the age groups had significant reductions in total HAMD and HAMA scores. In both the 2 weeks and 4 weeks follow-up point of the trial, a mean percentage decrease in HAMD and HAMA scores were significantly greater in the adolescents group than in the adult and the old people group.

Effectiveness of rTMS: categorical data

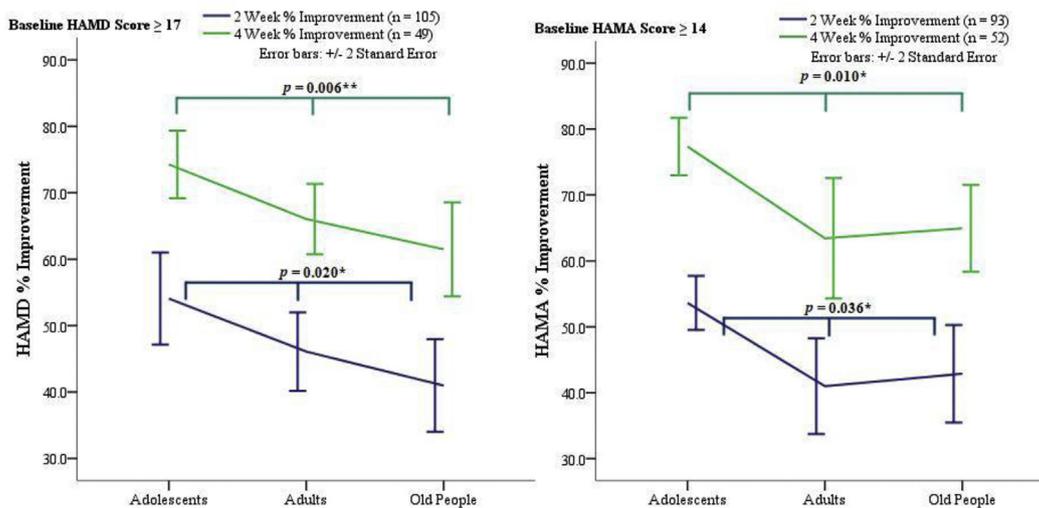
For symptoms of depression, a significantly higher number of patients met the remission criteria (HAMD scores < 8) in the adolescents group than in the adult and the old people group at week 2 and remained significant at week 4 in comparison with the old

Table 1
Demographic, clinical characteristics, and treatment parameters, comparison among adolescents, adults and old people.

Variables	Overall	Adolescents	Adults	Old people	Comparisons	
					F/χ^2 ^a	<i>p</i>
Cases [n]	117	42	27	48	–	–
Age (years) [Mean (SD)]	43.7(26.4)	14.6(2.0)	39.3(13.1)	71.7(7.1)	–	–
Age range (years)	10–80	10–17	18–59	60–80	–	–
Female [n(%)]	68(58.1)	29(69.0)	12(44.4)	27(56.3)	$\chi^2 = 4.2$	0.122
Education (years) [Mean (SD)]	10.1(3.7)	8.0(1.9)	13.7(2.3)	10.0(4.0)	$F = 28.8$	<0.001
Course (months) [Mean (SD)]	81.9(105.7)	17.2(13.4)	66.3(65.0)	147.2(129.7)	$F = 24.3$	<0.001
Suicidal Ideation ^b [n(%)]	79(67.5%)	25(59.5%)	17(63.0%)	37(77.1%)	$\chi^2 = 3.482$	0.175
Baseline clinical characteristics						
HAMD [Mean (SD)]	20.2(5.7)	16.4(5.1)	18.9(3.2)	24.2(4.8)	$F = 33.2$	<0.001
HAMA [Mean (SD)]	17.9(5.5)	17.6(5.7)	15.2(4.8)	19.7(5.1)	$F = 6.5$	0.002
rTMS treatment parameters						
Stimulation intensity	42.3(4.9)	39.1(4.5)	46.3(3.8)	42.9(4.0)	$F = 25.9$	<0.001
Number of sessions	15.6(5.7)	16.2(4.8)	16.5(7.5)	14.5(5.2)	$F = 1.5$	0.226
Week 2						
HAMD [Mean (SD)]	9.8(4.6)	6.9(3.4)	9.2(3.0)	12.7(4.6)	$F = 24.9$	<0.001
HAMA [Mean (SD)]	9.3(4.0)	8.2(3.6)	8.6(3.2)	10.8(4.3)	$F = 5.9$	0.004
Week 4						
Cases [n]	56	19	14	23	$\chi^2 = 0.3$	0.866
HAMD [Mean (SD)]	7.0(3.7)	4.3(2.1)	6.8(2.3)	9.4(3.9)	$F = 14.4$	<0.001
HAMA [Mean (SD)]	6.2(3.2)	4.4(2.1)	6.4(2.1)	7.5(3.8)	$F = 5.9$	0.005

^a F/χ^2 : *F* for One-way ANOVA Test, χ^2 for kappa test.

^b Suicidal Ideation defined according to the third item of HAMD. (a baseline HAMD (3-item) score of >1). Significant *P* bold.



Note: HAMD: the 17-item Hamilton Depression Rating Scale; HAMA: the 14-item Hamilton Anxiety Rating Scale; Analyses of variance (ANOVAs) were used to compare the percentage decrease of HAMD and HAMA scores among three age groups.

Fig. 2. Percentage decrease in HAMD and HAMA scores across three age groups.

Note: HAMD: the 17-item Hamilton Depression Rating Scale; HAMA: the 14-item Hamilton Anxiety Rating Scale; Analyses of variance (ANOVAs) were used to compare the percentage decrease of HAMD and HAMA scores among three age groups.

people group. For the anxiety symptoms, there were significantly more number of patients meeting the response criteria (>50% reduction in HAMA score) in the adolescents group than in the adult and the old people group at week 2 (Fig. 3).

Patterns of improvements in depression and anxiety symptoms

We further analyzed whether the decreased HAMD scores correlated with the decreased HAMA scores. Percentage decrease in

HAMD and HAMA scores after 2 weeks and 4 weeks of rTMS treatment were positively correlated in adults and old people (Fig. 4). However, among the adolescents, this positive correlation trend was not obvious ($p > 0.05$).

Interaction

After 2 weeks and 10 sessions of rTMS treatment, data analyzed using a repeated measures general linear model, showed a

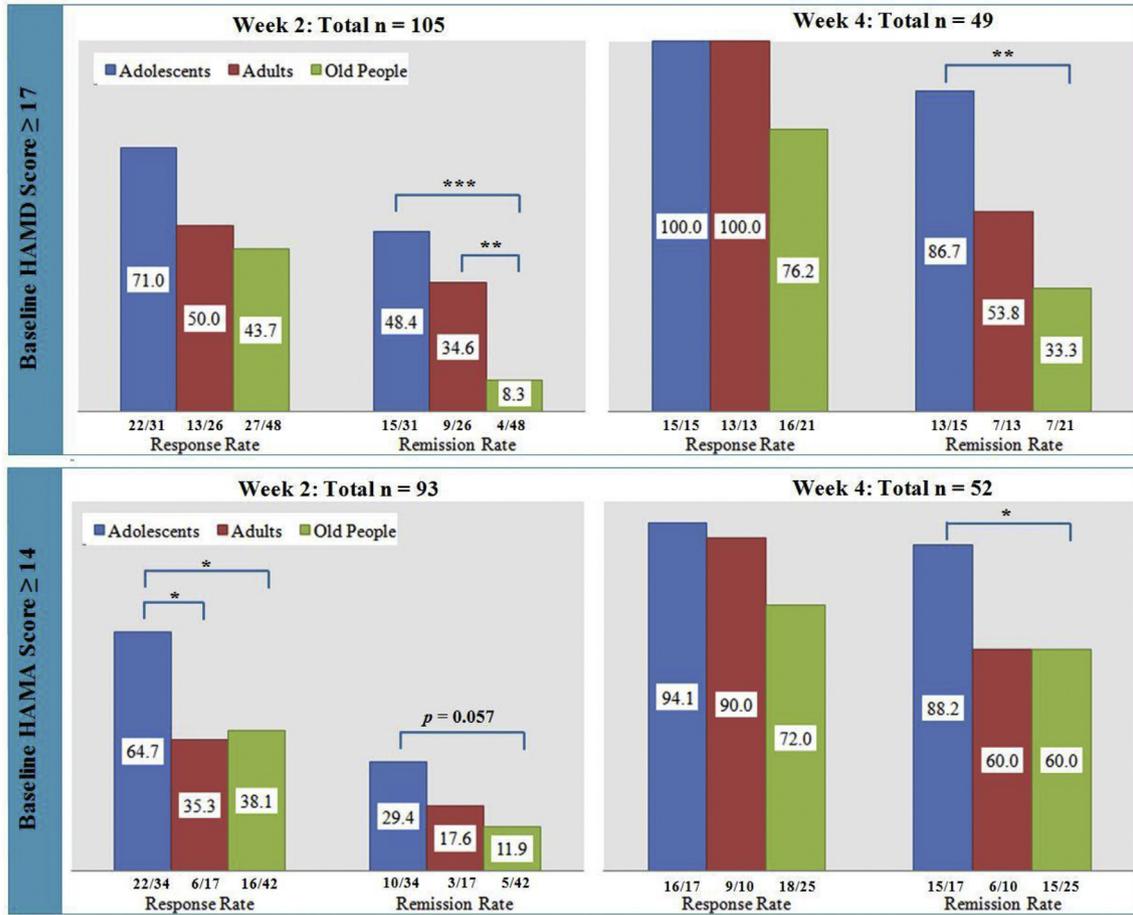


Fig. 3. Histogram of the percentage of patients meeting response and remission criteria across different age groups.

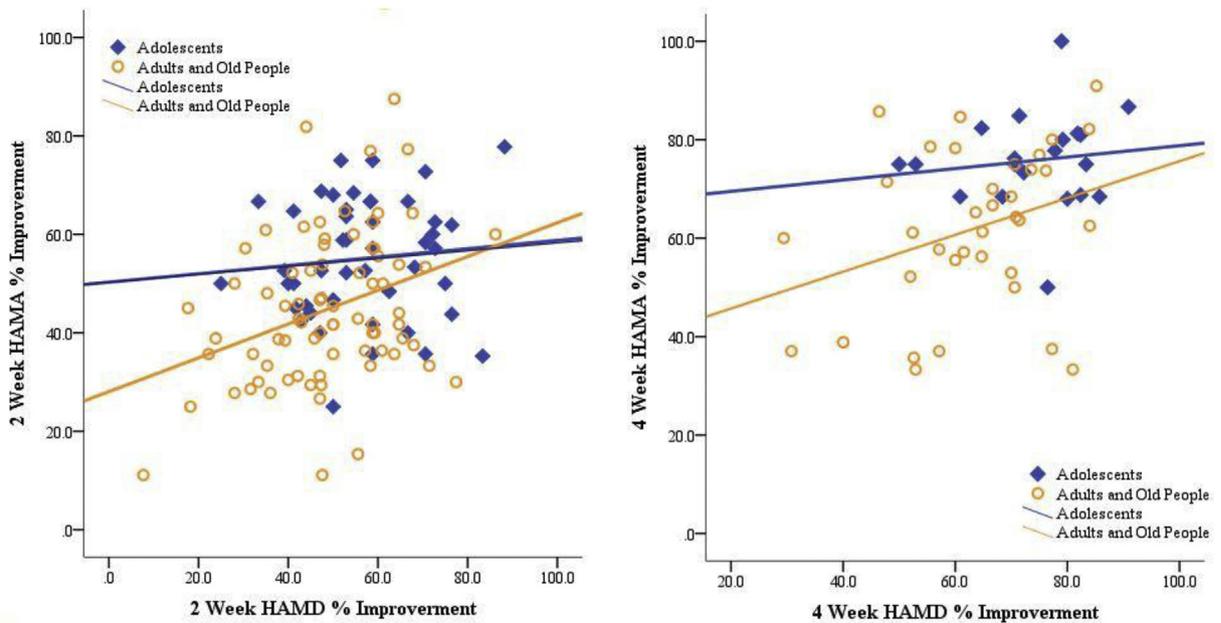


Fig. 4. Correlation characteristics between improvements in depression and anxiety symptoms after rTMS treatment in adolescents, adults and old people.

significant effect of time ($F=12.835$, $p=0.001$) and age-group \times time ($F=5.020$, $p=0.027$) on the HAMD score but no effect of course \times time ($p=0.204$) and stimulation intensity \times time ($p=0.496$). As for the HAMA score, general linear model repeated measures demonstrated significant effect for time ($F=25.657$, $p<0.001$) and stimulation intensity \times time ($F=5.989$, $p=0.016$), but no effect of age-group \times time ($p=0.635$).

Discussion

The main finding of the present study is that there are meaningful differences in add-on rTMS treatments for improvement of symptoms of depression and/or anxiety, based on age groups. Clinical improvement after rTMS significantly increased across the three groups, with best results in the adolescents' group. We regard this finding as a first and preliminary evidence for applying rTMS as an acute treatment method in adolescents with mood or anxiety disorders rather than only for patients featured as treatment-resistant. To our knowledge, this is the first naturalistic study to compare the effects of rTMS on symptoms of depression and/or anxiety in adolescent patients with that of adults and old patients. The data provided in this report suggest that rTMS may be efficient especially when applied for adolescents and it may prove to have value in the treatment of the symptoms of depression and/or anxiety.

To date, barring a few case reports [27,28], there has been little published research addressing issues relating to the real-world efficacy of rTMS on adolescents versus adults. However, it had been noticed that adult patients in the younger age group respond better. A previously naturalistic study [29] included 307 MDD outpatients (mean age around 48.6 years) received TMS treatment. They found that the cohort of younger age group (≤ 55 years) fared better than the older cohort with rTMS treatment. The present finding of a better outcome for adolescent rTMS patients adds to the growing body of literature which suggests wider clinical applications of rTMS in adolescents with symptoms of depression and/or anxiety [18].

A new contribution from this study to the current research field is that we found significant association between improvement of symptoms of depression and anxiety only in adult patients, but not in adolescents. This result indicates that add-on rTMS improvement effect is characterized by parallel relations in symptoms of both depression and anxiety in adult patients, and with the improvement of symptoms of depression their symptoms of anxiety also improved. However, this phenomenon was not found in adolescent patients [30]. This result provide clinicians an important clue that targeting symptoms of both depression and anxiety as a whole for the treatment of adolescent patients would be the better choice compared to treating the symptoms of just one disorder alone.

As expected, significant time effects were seen for HAMD and HAMA scores, in response to 10 sessions of rTMS treatment. Furthermore, time \times age interaction effect was only observed in the HAMD score, not in the HAMA score. These data further supported the fact that adolescent patients would incur the benefits of rTMS treatment on symptoms of depression compared to the adults. For symptoms of anxiety, no significant time \times age interaction was found. The most likely explanation is that the age effect of rTMS treatment maybe more obvious in treating symptoms of depression than those of anxiety.

Our study has several limitations that should be noted. Firstly, the premise of this study lies in the nature of the assessments conducted in the real world. However, the raters were not informed that the aim of this study was comparison between adolescents and adults. The naturalistic aspect would realistically reflect the impact

of the rTMS treatment of these patients in an unbiased fashion. There are considerable practical impediments in this type of study than in a true double-blind study. The other limitation relates to the short period of follow-up; it remains unknown whether a long-term outcome can replicate our findings. Preliminary evidence [31–33] suggests that adolescent patients may derive long-term benefit from the rTMS course. Besides, the heterogeneity of antidepressant medication treatment that was not controlled between age groups should also be considered. We identified this potential limitation prior to the beginning of this study. To address this problem, we included patients who were receiving only single antidepressant during the rTMS treatment, for comparison. However, even though, there is a possible alternative interpretation of our findings that because of the antidepressants which play the leading role and the TMS was simply an incidental treatment. Another limitation is that we did not systematically measure other outcomes such as daily functions and cognition. The current study relied only on assessment of clinical symptoms which is inadequate. The absence of a standardized assessment tool for making clinical diagnoses which may then result in a clinical heterogeneity of this sample which selected only based on the severity of depressive or anxiety symptoms rather than specific diagnosis. Finally, the baseline characteristics such as education level, course of disease, and severity of symptoms were not well matched between adolescents and adults. Although some factors are due to the inherent nature of age (e. g. years of education and course of disease), it is possible that our results were influenced by these unmatched factors. Further research in this area with a longer study period, comprehensive assessment of outcomes such as general functions and cognitive tests, and multi-site cross-country samples to consider patients with different backgrounds is needed.

Conclusions

In summary, our results support the use of rTMS as an add-on treatment for patients with symptoms of depression and anxiety in the acute phase, and suggest that adolescents have better outcomes compared to adults. Our findings indicate that adolescents benefit more from the rTMS treatment for symptoms of depression, which is the standard rTMS protocol for adult patients.

Declaration/conflict of interest

None.

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