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Repetitive Transcranial Magnetic Stimulation and Exercise as Rehabilitation Methods for Adolescent Depression: A Narrative Review of Current Evidence and Future Potential

Michalis Kodounis[1], Theodoros S. Constantinidis[2], Maya Louvardi[3], Antonios Kodounis[4], Dilara Onan[5, 6]

1. National and Kapodistrian University of Athens, First Neurology Department, Eginitio Hospital, School of Medicine, Athens, Greece.

2. Hellenic Clinical Neurophysiology Society, Independent Researcher, Corinth, Greece.

3. National and Kapodistrian University of Athens, 1st Department of Psychiatry, Eginition Hospital, School of Medicine, Athens, Greece.

4. Hellenic Clinical Neurophysiology Society, Independent Researcher, Athens, Greece.

5. Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Yozgat Bozok University, Yozgat Turkey.

6. Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila Italy.

Abstract

Introduction: Adolescent depression is a prevalent disorder with significant physiological and psychological consequences that often persist into adulthood. Despite the use of pharmacological and psychological treatments, these interventions may be limited in their efficacy for some individuals. Therefore, researchers and clinicians are actively investigating novel, safe, and low-side-effect therapies. Repetitive transcranial magnetic stimulation (rTMS) and exercise are emerging as synergistic rehabilitation methods targeting neuroplasticity in adolescents. This narrative review aims to examine the current evidence on the use of rTMS and exercise as rehabilitation approaches for adolescent depression and to explore their combined potential in targeting neuroplasticity as a theoretical model.

Methods: A comprehensive search was conducted on PubMed (MEDLINE) using specific keywords to identify studies exploring rTMS and exercise interventions, both individually and in combination, for adolescents with depression. Systematic reviews and meta-analyses were included to examine the mechanisms targeted by these therapeutic approaches, their efficacy, safety, and feasibility. Additionally, studies in adult populations were reviewed to explore the combined intervention model.

Results: Both rTMS and exercise modulate neuroplasticity-related mechanisms such as Brain-Derived Neurotrophic Factor, Insulin-Like Growth Factor 1, Vascular Endothelial Growth Factor, and other neurotrophic factors, leading to antidepressant effects. rTMS is an effective, safe, and adaptable method for improving depressive symptoms in adolescents, while exercise improves depressive symptoms through physiological and psychosocial pathways. However, there is a notable lack of studies combining these interventions. Limited studies in adults suggest that the combined use of rTMS and exercise, targeting neuroplasticity, is feasible, safe, and may enhance clinical outcomes compared to either intervention alone.

Conclusion: rTMS and exercise appear to be promising approaches for alleviating depressive symptoms in adolescents, particularly in cases where pharmacological and psychological treatments are insufficient. Their synergistic effect on neuroplasticity supports the need for further studies combining these interventions. Future research should focus on randomized controlled trials to assess the efficacy, safety, compliance, side effects, and protocol requirements tailored to this developmentally sensitive population within ethical and legal frameworks.

Keywords

adolescent depression, rTMS, exercise, neuroplasticity, Brain-Derived Neurotrophic Factor, neurotrophic factors, rehabilitation

Corresponding author: Michalis Kodounis: kodounis@gmail.com, https://orcid.org/0000-0003-4549-7607 +306973600069, National and Kapodistrian University of Athens, First Neurology Department, Eginitio Hospital, School of Medicine, Athens, Greece.

Introduction

Depressive disorders are common among both adolescents and adults. A systematic review and meta-analysis reported an increase in the global point prevalence of depressive symptoms in adolescents (aged 10-19) from 24% to 34% between 2001 and 2020. [1]. A separate meta-analysis revealed that adolescents with depression are approximately 2.5 times more likely to experience depression in adulthood (odds ratio = 2.50; 95% confidence interval 1.97, 3.93) [2]. Adolescent depression presents a major public health problem due to its early onset, high prevalence, long-term consequences, and economic and social burdens [3,4]. Furthermore, depressive disorders in adolescence are linked to recurrent depressive episodes, substance use disorders, academic failure, and an increased risk of suicide. [5-7]. The neurodevelopmental vulnerabilities of this period, coupled with the risk of ongoing transmission of depressive symptoms, further exacerbate the consequences, highlighting the urgent need for effective interventions [2,8].

Pharmacological treatments for adolescent depression remain limited, with only fluoxetine and escitalopram currently approved by the FDA for treating major depressive disorder in adolescents [9,10]. However, the efficacy of these selective serotonin reuptake inhibitors (SSRIs) is modest, with meta-analyses revealing only small reductions in symptoms compared to placebo [11]. Additionally, concerns regarding the safety and tolerability of antidepressant medications, particularly in relation to suicidal ideation during treatment initiation, underscore the necessity for non-pharmacological alternatives [11,12]. Despite the combination of psychotherapy and pharmacological treatments being a recommended approach, barriers such as stigma and limited access to psychotherapy can hinder treatment uptake [13,14].

Non-invasive interventions such as rTMS and exercise represent promising options for treating adolescent depression, offering favorable safety profiles and complementary mechanisms [15]. rTMS, which induces action potentials in neurons via electromagnetic induction, has demonstrated effects on synaptic plasticity, such as long-term potentiation (LTP) and long-term depression (LTD) with repeated application [16]. rTMS is FDA-approved for treatment-resistant depression in adults and has shown promising safety and applicability in adolescents [17-21]. Similarly, exercise has been shown to alleviate depressive symptoms by increasing levels of BDNF, maintaining neurotransmitter balance, and enhancing neuroplasticity [22-24]. Exercise also elevates other neurotrophic factors such as glial cell-derived neurotrophic factor (GDNF), nerve growth factor (NGF), and VEGF, which are known to promote neurogenesis and mood regulation [25-29]. Increases in GDNF, NT-3 and VEGF with exercise increase hippocampal neurogenesis [25,26]. Increases in NGF, which is important for mood regulation, contribute positively to the cognitive processes of mood in depression [27]. Increases in IGF-1 contribute to synaptic plasticity by increasing neuronal survival and mediate recovery in antidepressant action [28,29].

Both aerobic and resistance exercises have demonstrated positive effects on depressive symptoms in adolescents [30,31]. The combination of exercise and rTMS may offer direct benefits for restoring neuroplasticity in individuals with depression, potentially leading to enhanced outcomes compared to each intervention individually [32].

This narrative review aims to evaluate the use of rTMS and exercise separately in the treatment of adolescent depression, while also discussing the theoretical foundation and future potential for their combined application. Although preliminary studies have explored the synergy of rTMS and exercise in adults, there remains a notable gap in the adolescent literature, presenting an opportunity for future research.

Multiple rTMS Protocols for Depression: Key Parameters and Evidence

rTMS has gained prominence as therapeutic option for major depressive disorder, especially in patients resistant to available pharmacological treatments. In fact, it is worth noting that, together with neuropathic pain and motor stroke, it has evidence level A (definitely effective) [33]. Various rTMS protocols have been developed, reflecting both advancements in technology and differing approaches to neuromodulation in brain circuits involved in depression.

The most established and widely investigated rTMS protocol involves high-frequency stimulation (10 Hz) applied to the left dorsolateral prefrontal cortex (DLPFC), typically delivering around 3,000 pulses per session. This protocol targets the hypoactivity of the left prefrontal cortex, commonly seen in depressed individuals. It has been FDA approved for treating treatment-resistant depression in adults and has been shown in clinical studies to improve symptoms and promote synaptic plasticity [34].

Alternative therapeutic protocols include low-frequency rTMS (1 Hz) applied over the right dorsolateral prefrontal cortex (DLPFC), which aims to reduce hyperactivity in right prefrontal circuits, associated with negative affect and emotional dysregulation. Although less frequently used, accumulating evidence suggests that right-sided low-frequency rTMS can be equally effective and has a favorable safety profile, making it an attractive option for adolescents and other vulnerable populations [35,36].

An even newer approach, intermittent Theta Burst Stimulation (iTBS), delivers pulse trains at frequencies mimicking the normal brain rhythms, offering comparable clinical efficacy to traditional 10 Hz rTMS but in much shorter sessions (3 to 5 minutes). iTBS has been FDA approved for treatment-resistant depression in adults, and its brevity and efficiency make it particularly suitable for younger populations, where cooperation and session duration can be challenging [37]. Moreover, accelerated forms of iTBS, such as the SAINT protocol, further optimize neuroplasticity-related outcomes in shorter timeframes without compromising safety [38].

Finally, stimulation parameters such as intensity (typically expressed as a percentage of the resting motor threshold), treatment duration (commonly spanning 4 to 6 weeks), and the total number of pulses per session significantly influence

both the efficacy and tolerability of rTMS interventions. Higher cumulative pulse doses have been associated with better clinical responses without an increase in adverse effects [39]. The comparative efficacy of different TMS protocols remains under investigation, especially in adolescents, where empirical data is still limited. Nevertheless, the variety of available protocols offers flexibility in tailoring treatments to individual clinical profiles, paving the way for personalized neuromodulatory interventions in adolescent depression.

Searching Methodology

The search strategy of the study was conducted using keywords from the PubMED database, searching for reviews, systematic reviews, and meta-analyses up to June 27, 2025, without any restriction on the start date. In this way, the articles with the best level of evidence in the evidence pyramid were examined and the results of current reviews, systematic reviews and meta-analyses on rTMS and exercise studies in adolescent individuals with depressive disorder were included. The keywords used were listed in Table 1.

Table 1. Searching strategy of the keywords on PubMED

Keywords of rTMS	(repetitive transcranial magnetic stimulation) AND (depression) AND (adolescent)
	(rTMS) AND (depression) AND (adolescent)
Keywords of exercise	(exercise) AND (depression) AND (adolescent)
	(physical activity) AND (depression) AND (adolescent)
Keywords of rTMS and exercise	(repetitive transcranial magnetic stimulation) AND (exercise) AND depression
	(rTMS) AND (exercise) AND (depression)
	(repetitive transcranial magnetic stimulation) AND physical activity AND (depression)
	(rTMS) AND (physical activity) AND (depression)

rTMS: Repetitive transcranial magnetic stimulation

The rTMS in Adolescent Depression

The use of rTMS in adolescents remains underexplored, primarily due to the challenges of conducting clinical studies in this sensitive population. Specifically, obtaining informed consent for randomized controlled trials (RCTs) in adolescents is complicated, and ethical and legal concerns arise due to ongoing brain development, particularly in the prefrontal cortex [40,41]. Furthermore, long-term safety data on neuromodulation in adolescents are limited, making it essential to investigate potential impacts on brain development. Despite these challenges, the existing evidence suggests that rTMS is generally well-tolerated in adolescents, with transient headache and mild scalp discomfort being the most common adverse effects, and no significant effects on cognitive function reported [42,43].

However, it is important to note that children and adolescents may exhibit different responses to rTMS compared to adults, as they tend to be more hyperexcitable, recover more quickly, and show unimpaired cortical responses to repeated stimuli. These differences in neurophysiological responses imply that adult rTMS parameters may not be directly applicable to adolescents [44,45]. Therefore, the parameters used in adults may not be appropriate for this sensitive group [45]. Studies indicate that longer treatment durations and individualized rTMS protocols may enhance effectiveness in adolescent populations [15,45].

A systematic review and meta-analysis of 165 individuals with a mean age of 10-25 years demonstrated that rTMS significantly improved symptoms of depression across 13 studies (Hedges' g 1.37, 95% CI 0.85-1.90, p=0.001). All 13 included protocols applied unilateral or bilateral rTMS to the dorsolateral prefrontal cortex at 10 Hz, 10-30 sessions, 2-8 weeks of treatment, and 80-120% Resting Motor Threshold (RMT), for a total of 24,000-90,000 pulses. Six of the studies reported follow-up results ranging from 4-144 weeks (4 at 24 weeks), and the effects of rTMS treatment were particularly evident after 24 weeks. Although a low rate of 4% of participants discontinued treatment due to adverse effects such as headache, eye pain, mood swings, fear, and suicidal thoughts, rTMS was reported to be relatively safe and beneficial in improving symptoms of depression in children and adolescents, and could be used in clinical practice [45]. Another noteworthy point in this meta-analysis was that the authors emphasized that children and adolescents were less likely to discontinue treatment due to pain when given stimulation below 100% RMT, and that individualized parameters could be used [45].

Sigrist et al.'s meta-analysis reported a strong improvement in symptoms after rTMS applications (pooled SMCC=2.04, 95% CI [1.46; 2.61], p<0.001) and a treatment response rate of 41.3% [15]. They also noted that the effect of rTMS treatment was better in younger individuals with more severe depression and that this improvement could be enhanced by a higher number of treatment sessions, a longer treatment duration, and unilateral or bilateral applications [15].

In a comprehensive study examining real-world data on 1,257 young people aged 11-21, deep Transcranial Magnetic Stimulation (dTMS) treatment was administered in 56 clinics for an average of 30-36 sessions. Up to 75% improvement in depression and anxiety questionnaires was observed in 36-session protocols, and a linear relationship was reported between treatment duration and improvement [46].

In summary, while further investigation is required to refine treatment protocols and address ethical concerns, rTMS has demonstrated positive results in adolescent depression and could be a viable treatment option.

The Exercise in Adolescent Depression

Exercise has long been recognized as an effective treatment for adolescent depression through both physiological and psychosocial mechanisms [47]. The physiological effects of exercise improve depressive symptoms by enhancing neuroplasticity, the brain's ability to structurally and functionally adapt, particularly in brain regions associated with depression, such as the hippocampus and prefrontal cortex [48]. Depression has been shown to impair neuroplasticity, with the hippocampus-crucial for stress and emotional regulation-being particularly affected [49,50]. Increased levels of BDNF, a key marker of neuroplasticity, are associated with improved cognitive and psychological health and are often found to be deficient in individuals with depression [51,52]. Exercise strengthens synaptic plasticity and supports the restructuring of neuronal connections, especially by increasing BDNF, GDNF, NT-3, VEGF and IGF-1 levels [53]. This increase has been shown in different studies with both adult [54-59] and adolescent [60,61] individuals, and it has been emphasized that exercise causes a significant increase in BDNF levels and that this has a reducing effect on depression symptoms [51]. The increase in BDNF also contributes to the improvement of processes such as learning, memory and emotional regulation [62]. Increases in GDNF, NGF, NT-3, and VEGF with exercise increase hippocampal neurogenesis, providing a positive effect on mood and cognitive processes [25-27]. Additionally, an increase in IGF-1 levels improves synaptic plasticity through neuronal survival and provides improvements in psychological status [28,29]. The decrease in neuroplasticity associated with depression can lead to impairments in emotional and cognitive functions. In this context, exercise-induced neuroplasticity provides a mood-regulating effect on individuals [62]. It is stated that chronic inflammation contributes to the pathophysiology of depression by increasing the levels of pro-inflammatory markers such as CRP, IL-6, and TNF-α [63,64]. Exercise reduces systemic inflammation levels by suppressing pro-inflammatory markers such as CRP, IL-6, and TNF-α [65,66]. It also contributes to the reduction of depressive symptoms by supporting synaptic functions, attention, mood and motivation functions by increasing the release of neurotransmitters such as dopamine, serotonin and noradrenaline, which are reduced with depression [67-69]. This effect is considered an important mechanism in reducing depressive symptoms [70].

From a psychosocial perspective, exercise improves adolescents' sense of self/efficacy and supports social interaction [71,72]. Group-based, enjoyable, and voluntary physical activities, in particular, have been reported to have positive effects on depressive symptoms [73]. Group exercise may increase young individuals' motivation to continue exercising and their social support [73].

Regarding exercise prescription, although the evidence in the literature may offer varying parameters, there is strong evidence that exercise is effective in reducing depressive symptoms in adolescent depression. In a meta-analysis by Zhang et al., they recommended a moderate-to-vigorous-intensity mixed-intensity group exercise program with a high effect size, consisting of at least three sessions per week, lasting 40–50 minutes per session, for 12 weeks or more, for improving symptoms of depression in adolescents [74]. They also noted that the positive effects of exercise on depression can persist for up to 40 weeks after exercise [74]. In a meta-analysis by Wang et al., they concluded that aerobic exercise (AE) for 6 weeks, four sessions per week, lasting 30 minutes per session, is the most effective program for reducing depressive symptoms in adolescents with mild to moderate depression [30]. On the other hand, for a subgroup with depressive symptoms, they emphasized that AE lasting 75-120 minutes, 3 sessions per week for 8 weeks, yielded optimal results, and consequently, they suggested that moderate-intensity physical exercise is an optimal approach for adolescents with depression and depressive symptoms. The results of a network meta-analysis indicated that AE lasting 12 weeks, 3 sessions per week, 40-50 minutes is an optimal program for improving depression [31]. Consequently, AE starting from six weeks may be recommended for 12 weeks or more to improve symptoms of depression, depending on the adolescent's condition. Aiming for 30-40 minutes of sessions, at least three days a week, can be used as a basis for structuring the program.

rTMS and Exercise Combination: A Theoretical Model

rTMS and physical exercise both target neuroplasticity, and their combined use could offer a synergistic effect in treating depression. Both interventions share common neurobiological targets, such as BDNF, and modulate similar neurotransmitter systems involved in mood regulation [32]. Combining rTMS and exercise may enhance the effects of each approach, leading to greater improvements in neuroplasticity and clinical outcomes compared to either intervention alone.

Finding treatments that increase synaptic connections and neuroplasticity in adolescent depression and minimize the cognitive factors or emotional symptoms that cause the disorder are key points [32,75]. The enhancement of plasticity by stimulating neurotrophins and neurogenesis with exercise, the targeting of synaptic efficacy with rTMS, and the combined effects of both on neurotransmitter systems such as BDNF, proinflammatory cytokines, and serotonin, dopamine, and norepinephrine, highlight both methods as synergistic rehabilitative approaches that promote synaptic plasticity. This synergistic basis suggests that combining exercise with rTMS is a biologically plausible approach. The combined use of different techniques with complementary neural mechanisms and similar effects can significantly increase the combined therapeutic benefits compared to either approach used alone. Given the broad neuroplasticity-enhancing effects of AE, increased neurogenesis in the hippocampus with AE alters neuronal excitability [76,77] and increases neuronal survival [78]. On the other hand, the increase in morphological effect mechanisms, such as BDNF effects, facilitates synaptic neuroplasticity [79]. The fact that TMS also acts by generating action potentials in cortical interneurons and projection neu-

rons through repetitive stimulation of neuroplasticity-targeted neural pathways and plays a role in the BDNF effect mechanism makes this assumption plausible [32,80].

A limited pilot study in adults indicates that AE combined with rTMS is safe, feasible, and well tolerated. In a study on post-stroke depression, 24 participants were assigned to receive AE, rTMS, AE+rTMS, or AE without depression. The AE group received 40-minute walks (50–70% heart rate reserve) 3 times a week for 8 weeks. rTMS was applied to the left dorsolateral prefrontal cortex at 10 Hz for 5,000 pulses/session (5 seconds on, 10 seconds off), for a total of 100 stimulation cycles, at an intensity of 120% of the resting motor threshold (RMT), 3 days a week for 8 weeks. After 24 sessions, the compliance rate was 97% in the rTMS group and a clinical reduction of 10.5 in PHQ-9 scores was found. In the combined group, the participation rate was 98% and there was an improvement in depressive symptoms with an average decrease of 6.2 points in the Patient Health Questionnaire-9 (PHQ-9) score [81]. Therefore, the combination of rTMS and aerobic exercise was found to be safe, feasible, and highly tolerable [81]. In a case report of treatment-resistant depression, a 34-year-old male patient received rTMS (18 Hz, 2 seconds on, 18 seconds off, 1980 pulses, 36 treatment sessions, 5 days per week, 6 weeks, and then tapered to 2 days per week, 3 weeks) and AE (initiated at the fifth rTMS treatment session to allow time for adaptation and tapered to 3 days per week (15 sessions) for 5 weeks). At the end of treatment, a reduction in depressive symptoms was observed, with an 81% reduction in PHQ-9 (Before: 16; After: 3) and an 83% reduction in HRSD-17 (Before: 18; After: 3), and no adverse effects were observed. The combination of these two treatment approaches was deemed feasible for the patient [82].

While separate studies exist on the effectiveness of exercise or rTMS in the adolescent population, no clinical trials have yet examined the combined use of rTMS and exercise in adolescents with depression. This highlights a significant scientific gap in the field. This gap presents a significant opportunity for future intervention protocols. In particular, the combined application of physical exercise and rTMS in interventions for adolescent depression carries the potential for increased symptom improvement and impact, both physiologically (synaptic plasticity, neurotransmitter modulation) and psychosocially (motivation, participation, social support). Therefore, pilot randomized controlled trials testing the combination of these two powerful approaches in adolescent depression could be an innovative step that will increase both treatment efficacy and intervention diversity.

Clinical Implications and Future Directions

The use of rTMS and exercise in treating adolescent depression holds great promise, with both interventions offering unique physiological and psychosocial benefits. The combined use of rTMS and exercise, two synergistic approaches targeting neuroplasticity, offers promise as complementary approaches to the treatment of adolescents with depressive disorders. As pharmacological treatments may not always be suitable or sufficient for adolescent patients, non-invasive, non-pharmacological treatments like rTMS and exercise offer a viable alternative or adjunct to standard therapies. However, the lack of high-quality evidence, particularly regarding the combined use of rTMS and exercise, underscores the need for further research. Future studies should focus on randomized controlled trials with tailored protocols for adolescents, assessing treatment efficacy, safety, compliance, and long-term outcomes. Research into the neurodevelopmental aspects of adolescent depression and the impact of rTMS and exercise on brain development is also essential.

Additionally, age-specific protocols, treatment adherence, and satisfaction with treatment should be examined to optimize therapeutic strategies for this vulnerable population. As the field progresses, the combination of rTMS and exercise could lead to more personalized, effective treatment options for adolescent depression.

Limitations

This narrative review has several limitations. The theoretical model of combining rTMS and exercise was based on existing studies in adults, and direct evidence in adolescents is scarce. Furthermore, the lack of standardized rTMS and exercise protocols for adolescents prevented a systematic analysis, limiting the strength of our conclusions. The absence of randomized controlled trials focusing on the combined use of these two interventions in adolescent depression presents another significant gap in the literature.

Conclusion

Adolescent depression represents a critical public health challenge, and traditional pharmacological treatments may not always be sufficient. rTMS and exercise are promising non-pharmacological approaches that target neuroplasticity, offering potential benefits in treating depression in adolescents. While studies on their combined use are currently lacking, the theoretical basis for their synergy suggests that such an approach could lead to improved therapeutic outcomes. Future research should prioritize well-designed clinical trials to explore the efficacy, safety, and long-term effects of combining rTMS and exercise for adolescent depression, ultimately contributing to more personalized, effective interventions for this vulnerable population.

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