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The Emerging Role for rTMS in Optimizing the Treatment of Adolescent Depression

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Abstract

Major depressive disorder (MDD) in adolescents is a common illness and significant public health problem. Treatment is challenging due to recurrences and limited modalities. Selective serotonin reuptake inhibitors (SSRIs) and Cognitive Behavioral Therapy (CBT) are considered the standard of care in severe or treatment resistant MDD in this age group. However, responses to these interventions are often suboptimal. A growing body of research supports the efficacy of repetitive transcranial magnetic stimulation for the treatment of MDD in adults. Induced seizures are a primary safety concern, although this is rare with appropriate precautions. There is, however, limited experience with rTMS as a therapeutic intervention for adolescent psychiatric disturbances. This review will summarize the rTMS efficacy and safety data in adults and describe all published experience with adolescent MDD. Applications in other adolescent psychiatric illnesses such as schizophrenia and attention-deficit/hyperactivity disorder (ADHD) are reviewed. Safety and ethical issues are paramount with investigational treatments in adolescent psychiatric illnesses. However, further research with rTMS in adolescent MDD is imperative to establish

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standards for optimal stimulation site, treatment parameters, and its role in treatment algorithms. These may diverge from adult data. Early intervention with neuromodulation could also hold the promise of addressing the developmental course of dysfunctional neurocircuitry.

Keywords

transcranial magnetic stimulation; adolescents; major depressive disorder

Introduction

Treatment options for adolescents with major depressive disorder (MDD) remain relatively limited. Thus far, standard of care for the treatment of adolescent depression as defined by the American Academy of Child and Adolescent Psychiatry (AACAP) utilizes pharmacotherapies and psychotherapies,¹ with combination therapy generally deemed most effective.² A third treatment option is electroconvulsive therapy (ECT). However, ECT is used sparingly due to its potential significant side effects and limited availability due to geographic and legal constraints.³ Unfortunately, many depressed adolescents remain suboptimally treated, with significant resultant morbidity which includes ineffective polypharmacy, inpatient psychiatric hospitalization, psychosocial maldevelopment, and suicide. Thus, newer therapeutic modalities for the treatment of adolescent depression are essential. Repetitive transcranial magnetic stimulation (rTMS) is a well-tolerated, safe and potentially effective treatment approach for depression. Currently, its role as a treatment option in adolescent depression is under investigation.^{4,5}

TMS is a non-invasive tool that uses brief magnetic pulses for cortical stimulation. The magnetic field penetrates the scalp and skull with virtually no impedance, thereby producing electrical currents in underlying cortical tissue. Repetitive transcranial magnetic stimulation (rTMS) involves trains of magnetic pulses for neuromodulation which can be applied as a therapeutic treatment. Thus far, the vast majority of data supporting a therapeutic effect of rTMS has been demonstrated in adults with depression.^{6–9} Researchers have also utilized this modality for pediatric populations.^{4,5,10} The objectives of this paper are to review the existing literature related to the use of rTMS in adults with depression, as well as in child and adolescent psychiatry. Given that there are limited options for adolescents with depression that do not respond to traditional treatments,¹¹ future research in this area is critical. Additional published therapeutic trials for other psychiatric disorders in adolescents will be discussed. Safety and ethical issues related to the use of rTMS in adolescent populations will also be addressed.

Therapeutic use of rTMS in adults with Major Depressive Disorder

There are over thirty controlled trials of rTMS¹² and seven meta-analysis studies that support the use of prefrontal rTMS for the treatment of MDD in adult patients.^{6–9, 13–15} It is important to note that only one of these meta-analysis studies¹⁵ included the largest rTMS trial for major depressive disorder to date.¹⁶ However, one recent meta-analysis did not support its efficacy.¹⁴ The majority of these studies utilized high frequency rTMS (>1 Hz) over the left dorsolateral prefrontal cortex (DLPFC) with the assumption that high frequency rTMS would enhance cortical excitability in that region. Other trials have targeted the right DLPFC with the idea that it is overactive in depressed patients and may be normalized with low frequency stimulation (<1 Hz).^{17–19} Yet another novel approach involves sequential bilateral low and high frequency stimulation.^{20,21} Collectively, studies involving rTMS applied to the left and right DLPFC are promising but also pose limitations. This includes heterogeneous subjects and rTMS dosing parameters. The interpretation of results is also

often challenging due to inadequate study masking, short treatment duration and small sample sizes. It does appear that patients with minimum treatment resistance and shorter courses of illness may reap the most benefit more from rTMS.²² Other analyses have suggested that increasing age may also be a negative predictor of response to rTMS due to increased cortical atrophy with age and increased coil to cortex distance.²³ Prospective investigations will assist in characterizing the optimal treatment parameters including stimulation site, TMS stimulus intensity, and treatment duration.²⁴

A recent, multicenter, double-blind, sham-controlled trial involving 301 subjects provided additional data that rTMS is an efficacious treatment for adult MDD. Active treatment was administered to the left DLPFC, five times per week, with ten pulses per second (3,000 pulses per session) at 120% motor threshold for four to six weeks. Response rates were significantly higher for patients receiving active treatment at weeks four and six with a number needed to treat (NNT) of 11 and 9 respectively. At 4 weeks patients receiving active rTMS had a response rate of 20.6% (compared to 11.6% with sham treatment) and a remission rate of 7.1% compared to 6.2% with sham treatment. After 6 weeks the response rate was 24.5% and 13.7% with sham treatment. At this point the remission rate was 15.5% with rTMS and 8.9% with sham treatment.¹⁶ In October, 2008 data from this trial led to the United States Food and Drug Administration (FDA) clearance for rTMS treatment for adults with MDD who have failed one prior medication trial at an adequate dose and duration.

Given that the safety of any new antidepressant treatment in adolescents is a paramount concern, it is encouraging that adult studies with rTMS indicate that it is a safe and well-tolerated procedure. Major side effects and safety concerns included the risk for possible cognitive or structural changes, pain, headaches, hormonal changes, and hearing loss. Although seizures have occurred in healthy participants during TMS and rTMS there have been no known lasting sequelae.^{25,26} Seizures are much more likely to occur in patients with significant neurological morbidity (i.e., a history of stroke, cortical structural lesions, epilepsy), or when existing safety guidelines for stimulation parameters are exceeded.^{27–29} The incidence of seizures with rTMS in depressed patients who are healthy otherwise has been estimated to be no higher than 0.1–0.6%.³⁰ Studies of cognitive functioning before and after rTMS have found no clinically significant impairment in exposed patients.^{31,32} Most commonly, patients suffer from mild headaches, neck pain, and scalp pain which respond well to analgesics. There is no evidence that rTMS exposure induces temporary or permanent hearing loss in adults when earplugs are worn.^{33,34} Ear plugs are provided for comfort and added safety uniformly in rTMS studies. Experts agree that patients with metal hardware near the area of the rTMS coil (for example cochlear implants, pulse generators, or medication pumps) should not be exposed to rTMS as there is the risk that these devices will malfunction.²⁸ Patients with baclofen pumps and deep brain stimulation implants have been safely exposed to TMS, but this is still considered a relative contraindication.^{35,36} A recent large, multicenter trial also supports the argument that rTMS is safe as it was administered to subjects in over 10,000 sessions with no seizures or deaths and a dropout rate of 4.5% for adverse events. In this trial side effects were mild to moderate and most commonly involved transient headaches and scalp pain.³⁷ Patient preference and comfort are paramount in treatment planning. It is noteworthy that systematic studies regarding the attitudes of patients who have received rTMS demonstrate that the majority of recipients characterize it as helpful and preferable to treatment with ECT.³⁸

The treatment of major depressive disorder in adolescents

Major depression is a common and recurrent illness in adolescents, frequently resulting in negative psychosocial consequences and increased risk of suicide and substance abuse.^{1,3} The prevalence of MDD is estimated to be 4% to 8% in adolescence, with a male-female

ratio of 1:2.⁴⁰ By age 18, the cumulative incidence of MDD is approximately 20% in community samples.¹ Several studies have suggested that successive generations since 1940 are at greater risk for developing MDD, and this disorder is now being recognized at younger ages.⁴¹ Suicide is the third leading cause of death in adolescents, and depressive disorders are strongly correlated with suicide attempts. Although adolescents must meet DSM-IV-TR diagnostic criteria for MDD, the clinical picture of depression in adolescents varies considerably across developmental stages and diverse ethnic groups, making them unique and different from an adult population when implementing successful treatment interventions.⁴²

The treatment of MDD in this age group is challenging due to difficulty in diagnosis, limited therapeutic modalities, paucity of evidence based clinical practice, and research with discordant conclusions. Psychosocial interventions are generally considered first for uncomplicated, mild to moderate MDD. One meta-analysis of thirty-five randomized controlled trials of psychotherapy for the acute treatment of MDD in children indicated that while some studies have large effects, overall results are meager.⁴³ Of the psychotherapies such as cognitive behavior therapy (CBT) and interpersonal psychotherapy (IPT) have received significant investigation. Meta-analysis studies^{44,45} support the efficacy of CBT for the treatment of MDD in teenagers, but a recent, large scale, randomized, controlled trial found it to be no different than placebo.⁴⁶ Relative to pharmacotherapy, long-term effectiveness data indicated that after thirty-six weeks of treatment with CBT alone, fluoxetine alone or combined treatment with fluoxetine and CBT, response rates between all three modalities were similar. However, CBT was found to protect against suicidal events in the course of treatment with fluoxetine.² IPT is another evidence-based psychotherapy for adolescent MDD which has been found to be superior to other supportive psychotherapeutic interventions^{47,48} and equal in efficacy to CBT.⁴⁹ Family therapy and psychodynamic psychotherapy are two other options for clinicians but both have a paucity of data on efficacy.

Based on the available data, selective serotonin reuptake inhibitors (SSRIs) continue to be an effective treatment for moderate to severe MDD in adolescents and are considered the first line medication approach for this population.⁵⁰ Tricyclic antidepressants are no longer considered to be an effective treatment option in this age group.^{51,52} Fluoxetine and escitalopram are the only FDA approved medications for this indication. One recent meta-analysis of fifteen separate trials of antidepressants in patients under the age of eighteen revealed a NNT= 10 (number needed to treat) and NNH=125 (number needed to harm). These authors concluded that SSRIs are safe and efficacious in the treatment of MDD in this population.⁵⁰ Since 2004, when the FDA issued a black box warning for patients under the age of eighteen treated with antidepressants relating an increased risk for clinical worsening and suicidality, there has been ongoing controversy regarding the efficacy and safety of antidepressant medications. In adolescent trials of SSRIs for the treatment of MDD, remission rates range from 30 to 40% and even with optimal treatment involving combined psychotherapy and pharmacotherapy at least 40% of patients treated do not show a significant clinical response.^{11, 53, 54} This information substantiates the necessity for novel, safe, and efficacious somatic treatment alternatives or adjuncts in this population.

The AACAP Practice Parameter officially endorses the use of ECT in adolescents for severe, major depression, mania, schizoaffective disorder, schizophrenia, catatonia, and neuroleptic malignant syndrome. Although limited, there have been reports of adolescents with treatment resistant depression who responded to electroconvulsive therapy (ECT).⁵⁵ In a study of seventy-two adolescents, age 14–18 years, who underwent a total of 84 courses of ECT from 1990 to 1999, Walter, et. al found the changes in ECT practice for adolescents to be consistent with the ECT practice in general over this survey period. These investigators

concluded that overall safety and effectiveness supports the use of ECT in children and adolescents. However, the study relied on retrospective data which could have limited the systematic collection of ECT associated adverse effects.⁵⁶ The main negative effects of ECT revolve around neurocognitive sequelae. Possible ECT iatrogenically induced cognitive adverse effects include disorientation and anterograde and retrograde amnesia. As with adults, ECT techniques can be modified to mitigate these risks by the use of right unilateral electrode placement and ultrabrief pulse width stimulation. Other safety concerns include tardive or prolonged seizures and the risks associated with receiving general anesthesia.⁵⁵ Although Cohen et al. showed no significant cognitive deficits in adolescents receiving ECT, this study had several limitations, including a small sample size and lack of sophisticated neurocognitive measures of retrograde amnesia.⁵⁷ Adolescents are not believed to be at additional risk than adults from ECT or anesthesia-related complications; however, hospitalization is usually recommended for adolescents receiving ECT to allow for comprehensive monitoring of recovery after anesthesia and treatment response. Adolescents may have lower seizure thresholds and more prolonged seizures with ECT than adults.⁵⁵ Prior research suggested that most adolescents who have been treated with ECT view the treatment as less aversive than the illness itself;⁵⁸ however, both adolescents and parents have expressed fear associated with ECT, and in one study, parents found it difficult to provide consent.⁵⁹ There is also no data to guide the practice of maintenance ECT for patients under the age of eighteen.⁵⁵ Generally, ECT is still viewed as a treatment option only after multiple psychotropic and psychotherapeutic interventions have been exhausted.

rTMS for MDD in Children and Adolescents

Data regarding the treatment of adult MDD with rTMS is accruing, but there is relatively little information regarding the use of this modality in children and adolescents with MDD. Current literature includes a few case studies with varied results (see Table 1).

Walter et al.¹⁰ described the antidepressant treatment of four teenagers with rTMS. Over two weeks, one seventeen-year-old male received daily sessions (for 10 days) of 10 Hz rTMS over the left DLPFC at 90% above motor threshold. This patient's depression was recalcitrant to medication and he had received maintenance ECT prior to this rTMS course. He improved with rTMS, but did have a tension headache during two of the treatment sessions. Also, a sixteen-year-old male with treatment-resistant MDD received a similar course of rTMS treatment. His prior treatment included two courses of ECT. This patient's depression improved with rTMS and there were no reported side effects or complications. The third patient, a seventeen-year-old patient with refractory MDD, mild mental retardation, and ADHD, received the same course of rTMS, except it was administered at 110% above motor threshold. Unlike the other two adolescents, no clinical improvement was found. No side effects or complications were reported. Finally, one other eighteen-year-old patient with bipolar depression was treated with 14 sessions of 1 Hz rTMS to the RDLPFC at 110% motor threshold. She had no improvement and no side effects.¹⁰

In another case series, Loo et al.⁴ reported on two sixteen-year-old females with MDD that were enrolled in a double-blind, sham-controlled study of 10 Hz rTMS at 110% motor threshold for depressed adolescents. Both of these patients were assigned to active treatment. The first female received twenty-nine rTMS sessions during six weeks. She responded to this treatment with minimal depressive symptoms or functional impairment four months after the last session. The other patient with MDD missed one session per week during the treatment and then had almost a two week period with no rTMS sessions. She later returned for twenty sessions over five weeks on an open-label basis. During the rTMS course, the patient also took venlafaxine and methylphenidate. This patient had a slower response to rTMS but three months after this treatment course had maintained improvement.

Neither of these patients had significant side effects from the treatment, and formal neuropsychological assessments failed to show any adverse effects in cognitive functioning.⁴

A recent open-label study of rTMS involved nine teenagers (ages 16–18) with treatment resistant depression who were treated with 20 sessions of 10 Hz rTMS applied to the left DLPFC at 80% motor threshold for 20 minutes over two weeks. A few of the patients had been treated with ECT previously and all were taking psychotropic medications concurrently with the rTMS treatments. Treatment parameters for rTMS were likely suboptimal in this pilot trial due to safety concerns, though three of nine patients showed a clinical response. Regarding adverse effects, one patient stopped treatment early due to anxiety and mood lability, another had hypomania, and one attempted suicide 3-weeks after rTMS. Also, aside from five patients who reported a mild headache, no other side effects or adverse events were found.⁵

Collectively, this literature demonstrates that at this time there are no definitive guidelines for the application of rTMS to adolescent MDD. Although it is premature to make definitive recommendations, current information suggests that high frequency stimulation applied to the left DLPFC over six or more weeks may be an optimal strategy for the treatment of adolescent MDD. Moreover, rTMS does appear to be safe and well tolerated in this population even in conjunction with psychotropic medications.

Additional trials and applications of rTMS in adolescents

Other studies with psychiatric patients under the age of eighteen can inform clinicians and researchers of the safety and possible utility of rTMS. One such area where this treatment modality has been found promising is childhood and adolescent schizophrenia. Published cases include three teenagers with schizophrenia treated with ten daily sessions over two weeks with 20 Hz rTMS applied to the right frontal cortex. Two of these patients were eighteen-year-old males that showed significant improvements in rating scales of positive and negative symptoms. The third patient reported subjective improvement in hallucinations, agitation, and global functioning. In all three cases, no side effects or adverse events were reported.¹⁰

A separate case described by Fitzgerald et al.¹⁸ involved an eighteen-year-old female with longstanding schizophrenia (since age 9) with recalcitrant symptoms on multiple medications. Clozapine at 400 mg daily had improved her positive symptoms and disorganized thought processes. However, she continued to experience auditory hallucinations. This patient was ultimately treated with ten sessions of rTMS on consecutive weekdays. One Hz rTMS at 90% resting motor threshold was applied to the left temporoparietal cortex for 15-minutes. This resulted in a reduction of hallucinatory severity based on the Hallucinations Change Scale (HCS)⁶⁰ and the Positive and Negative Syndrome Scale (PANSS).⁶¹ Her clozapine dosage was maintained during and after the treatment course. She did relatively well for six months but then ten identical rTMS sessions were repeated for a relapse in auditory hallucinations. Clinical improvement was temporary and required a third course of rTMS three months later. With the acute and continuation courses combined, thirty rTMS sessions with the aforementioned treatment parameters were administered successfully.⁶²

Researchers from France recently published a case that involved an eleven-year-old boy with medication-resistant schizophrenia. This inpatient had struggled with aggression and psychotic symptoms (delusions and hallucinations) for two years. Neuroleptics were ineffective and lead to a dystonia. A comprehensive evaluation included functional magnetic resonance imaging (fMRI) which displayed increased auditory cortex activity with

concurrent auditory hallucinations. He received ten sessions of 1 Hz, fMRI-guided, rTMS applied to the left temporal-parietal cortex. This decreased the auditory hallucinations by 50% as rated on the Auditory Hallucinations Rating Scale.⁶² This gain was maintained by repeating sessions every five weeks. This patient also had significant improvement in his adaptive functioning based on the Children's Global Assessment (CGI) Scale.⁶³ The patient was discharged home and was able to attend school. No side effects or adverse events were reported.⁶⁴

Weaver et al. recently reported preliminary results from a double-blind, sham-controlled trial of 10 Hz rTMS at 100% motor threshold, 2000 pulses per session, applied to the right DLPFC for 10 sessions over two weeks in patients ages 17–21 with ADHD. Seven subjects completed the study with no seizures, adverse cognitive effects or shifts in auditory thresholds. There was also a mean improvement based on clinical global improvement (CGI) and ADHD-IV scales.^{65,66}

Other work has examined the therapeutic effects of rTMS for status epilepticus in children. For example, rTMS was applied in two patients with intractable epilepsy partialis continua⁶⁷ and in another case of a child with intractable seizures due to Rasmussen's encephalitis. The foundation of this approach relies on the ability of low frequency (1 Hz) stimulation to suppress neuronal activity and cortical excitability.⁶⁸

Safety of rTMS in Children and Adolescents

Single and paired-pulse TMS has been utilized safely in children to assess brain maturation, neurophysiologic parameters, and motor development.^{69,70} No adverse events were reported in seventy-five TMS studies including more than 2000 children.^{71,72} Experts have argued that single and paired-pulse studies confer only minimal risk to children.⁷³ However, there is much less experience with rTMS in children and adolescents. As with adults, concerns for rTMS exposure include: seizure risk, hearing damage, pain, and neurocognitive effects. Despite the concern that children have lower seizure thresholds, to date, there have been no reported seizures in children and adolescent exposed to TMS. However, caution is warranted as while no seizures have occurred in this age range, the total number of subjects exposed to rTMS is far less than adult studies. Also, one evaluation of eighteen children with numerous TMS exposures did not detect decreases in auditory functioning.⁷⁴ A theoretical concern is that TMS could cause structural changes when administered to developing brains. However, imaging^{75–77} and histological studies⁷⁸ failed to find significant changes in adults exposed to rTMS. Differences in brain size in developing patients could impact the extent and focality of stimulation in pediatric populations. As with medications, dose finding studies for rTMS treatments in children and adolescents would be indispensable in guiding future clinical practice. Experts contend that safety guidelines for the use of TMS in pediatric patients should be developed.⁷⁹

Ethics

In considering the ethics involved with utilizing rTMS in the pediatric population, a myriad of factors must be considered. One important factor includes the likelihood of efficacy in this population. In adult studies, rTMS has shown acceptable response rates and effect sizes.⁸⁰ These results are similar to other augmentation strategies for antidepressant treatment. A review of previous rTMS studies in depressed adolescent cases showed a total of 15 adolescents with major depression who were treated with a variety of rTMS treatment parameters (see Table 1). This limited data is promising, and will require further research using rTMS in this population. Support for ongoing, pediatric specific research comes from Rowell and Zlotkin who argued that, ultimately, improved clinical care of children depends on their participation in pediatric research. For a physician to fulfill a responsibility to

provide the best care possible, research is necessary. Furthermore, in the absence of relevant research, harm to children can result. For example, a reluctance to carry out studies to evaluate the uses of drugs in pediatric populations has resulted sometimes in children being deprived of optimal care, and in other cases exposure to untested interventions resulting in severe toxic effects, including death.⁸¹ Their assertion logically extends to the research and use of rTMS in the treatment of pediatric and adolescent neuropsychiatric disturbances. Ongoing research of rTMS as a potentially safe, effective and optimal treatment modality in depressed adolescents is imperative based upon the available literature.

Feasibility

Several factors are important to consider when implementing rTMS in adolescents including the timing, frequency, and tolerability of the treatments. Typical rTMS treatment protocols require daily treatment during the early phase. The time intensity of this treatment approach can certainly interfere with school requirements, extracurricular activities, and other social functions. However, one must also consider the real impact and suffering endured by adolescents with suboptimally treated depression. Current standard models of care for depression in this population include weekly visits to therapists, psychotherapy groups, and visits with physicians for medication management. Furthermore, if these modalities result in suboptimal treatment, there is an increased risk of suicidality, psychiatric hospitalization, and further deterioration in developmental and biopsychosocial functioning. Antidepressant medication intolerance, side effects and noncompliance in the pediatric population provide another real and important barrier to optimal treatment in the depressed adolescent population. Importantly, children's perceptions of rTMS have been observed. Garvey et al. reported a study of 40 boys and girls – 20 with ADHD and 20 normal controls – who participated in a neurophysiologic TMS investigation. The children ranked TMS as more enjoyable than a long car ride, and 34 of the 40 subjects said they would participate in a TMS study again.⁸² Although this was not a therapeutic trial, it provides important insights into the tolerability of TMS procedures in children. Therefore, early indications from pediatric studies regarding treatment response data, minimal reported side-effect profile, and generally favorable subjective review, position rTMS as a feasible treatment modality.

Conclusion

Depressive disorders in childhood and adolescence are a considerable source of mortality and morbidity. Currently, treatment options for depressive disorders in this population are limited. Adult data supports the use of rTMS in depression as a safe, tolerable, and effective treatment. Currently, treatment of adolescent MDD with rTMS is limited to case reports and open trials. However, extensive experience with TMS in children as a neurophysiological probe suggests that it is safe and well tolerated. Safety, ethical, and feasibility concerns must be considered in applying this modality in the treatment of adolescent MDD and in constructing well-designed trials in the future. Ultimately, the optimal stimulation site, dosing parameters, and treatment choices with rTMS in adolescent depression may vary from that of adults. Brain stimulation techniques such as rTMS may one day play a significant role in shifting the developmental course of pathological neurocircuitry.

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Table 1

Published Case Reports and Case Series: rTMS for MDD in Adolescents^{4,5,10}

Age	Treatment	Number of Treatments	Response	Side Effects
16 F	10 Hz 40 Trains 5s/25s at 110% MT	29	Clinically Significant	None
16 F	10 Hz 40 Trains 5s/25s at 110%MT	38	Clinically Significant	None
16 M	LDLPFC 10 Hz 20 Trains 8s/25s at 90%MT	10	Clinically Significant	Headache
16 M	LDLPFC 10 Hz 20 Trains 8s/25s at 90% MT	10	Clinically Significant	None
17M	LDLPFC 10Hz 40 Trains 2s/58s at 110% MT	10	No Improvement	None
18 F	RDLPEC 1 Hz 1,600 stimuli/26.6 min at 110% MT	10	No Improvement	None
			Of 9 below: 3 patients had clinically significant response	Of 9 below: 5 had headaches, one had "fear and mood swings", one made a suicide attempt 3 weeks after the treatment, one had hypomania
18 M	LDLPFC 10 Hz 20 Trains 2s/58 sec 80% MT	14		
18 F	LDLPFC 10 Hz 20 Trains 2s/58 sec 80% MT	10		
16 F	LDLPFC 10 Hz 20 Trains 2s/58 sec 80% MT	14		
18F	LDLPFC 10 Hz 20 Trains 2s/58 sec 80% MT	14		
16F	LDLPFC 10 Hz 20 Trains 2s/58 sec 80% MT	14		
17F	LDLPFC 10 Hz 20 Trains 2s/58 sec 80% MT	14		
17F	LDLPFC 10 Hz 20 Trains 2s/58 sec 80% MT	14		
18M	LDLPFC 10 Hz 20 Trains 2s/58 sec 80% MT	14		
17F	LDLPFC 10 Hz 20 Trains 2s/58 sec 80% MT	14		

LDLPFC-Left Dorsolateral Prefrontal Cortex

RDLPEC- Right Dorsolateral Prefrontal Cortex

MT-Motor Threshold