HHS Public Access

Author manuscript

Autism Res. Author manuscript; available in PMC 2023 May 01.

Published in final edited form as:

Autism Res. 2020 March ; 13(3): 346–351. doi:10.1002/aur.2266.

Treatment of Adults with Autism and Major Depressive Disorder using Transcranial Magnetic Stimulation: An Open Label Pilot Study

McLeod Frampton Gwynette[1], **Danielle W Lowe**[1], **Erin A Henneberry**[1,*], **Melanie Gail Wiley**[1], **Hussam Alsarraf**[1,†], **Sarah Brice Russo**[1], **Jane E. Joseph**[3], **Philipp M. Summers**[1], **Laura Lohnes**[3], **Gregory L. Sahlem**[1], **Mark S. George**[1,2]

[1]Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, United States

[2]Ralph H. Johnson VA Medical Center, Charleston, SC, USA

[3]Department of Neuroscience, Medical University of South Carolina, Charleston, SC, United States

Abstract

Patients with Autism Spectrum Disorder (ASD) are at high risk for co-morbid major depressive disorder (MDD), which can severely impair functioning and quality of life. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that is FDA-approved for treatment of MDD. Despite demonstrated efficacy in the treatment of depression, there is limited data for the use of rTMS in patients with ASD and co-morbid MDD. We hypothesized a standard rTMS protocol for MDD would reduce depressive symptoms for adults with ASD and MDD. Secondarily, we investigated whether this treatment would also reduce core ASD symptoms. Participants 18-65 years old with ASD and MDD without any medication changes in the last month were eligible for this open label trial. Participants underwent 25 sessions of rTMS (figure-of-eight coil, 100-120% rMT,10 Hz, 3000 pulses per session) applied to the left dorsolateral prefrontal cortex (L-DLPFC). Thirteen participants enrolled in the study, with two withdrawing due to tolerability, and one excluded from analysis. Overall, side effects were mild and rTMS was well tolerated. The Hamilton rating scale for depression ($HAM\text{-}D_{17}$) improved 13.5 points (IQR 5-15), and 40% of participants achieved remission ($HAM\text{-}D_{17} \leq 7$) after rTMS treatment. Informant clinical scales of core symptoms of autism also suggested improvement with rTMS, though no change was observed by the participants themselves. Thus, this open label trial suggests high-frequency rTMS is well-tolerated by adults with autism and MDD, with improvement in depressive symptoms and possible effects on core autism symptoms.

Lay Summary:

Corresponding Author: McLeod Frampton Gwynette, MD, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, 67 President Street, 5th Floor, South Tower, Room 509, Charleston, SC, 29425, United States, Phone: 1-843-792-9162, Fax: 1-843-792-4190, gwynette@musc.edu.

*Medical College of Georgia, Augusta, GA, USA

†Duke University School of Medicine, Durham, NC

This study evaluated the safety and effects of repetitive transcranial magnetic stimulation (rTMS) on depression and autism symptoms in individuals with both Major Depressive Disorder and Autism Spectrum Disorder (ASD). rTMS was well tolerated by the participants, depression improved with treatment, and family members' assessment of autism symptoms improved as well. This study supports the need for further work to evaluate rTMS in individuals who have both autism and depression.

Keywords

adults with autism spectrum disorder; autism spectrum disorder; major depressive disorder; mood; psychiatric comorbidity; transcranial stimulation; treatment research

Introduction:

Despite the rising prevalence of Autism Spectrum Disorder (ASD) (Kogan et al., 2018; Xu et al., 2019) there remain no evidence-based biological treatments for core ASD symptoms. Patients with ASD have high rates of comorbid psychiatric symptoms and conditions, including major depressive disorder (MDD), which affects an estimated 26% of adults with ASD (Croen et al., 2015). MDD appears to have a more pernicious course in adults with ASD compared to typically-developing (TD) adults (Charlot et al., 2008), including higher rates of suicidal ideation and suicide attempts (De-la-Iglesia & Olivar, 2015). There is currently limited data showing efficacy and tolerability of standard pharmacological treatments in adults with ASD and co-morbid MDD (Williams, Wheeler, Silove, & Hazell, 2010), and some studies have reported that antidepressant medications may exacerbate core symptoms of ASD (Kolevzon, Mathewson, & Hollander, 2006; Williams et al., 2010) or trigger irritability. Since MDD is both more difficult to treat and tends to be more severe in adults with ASD, the need for different treatment modalities is critical.

ASD is widely theorized to involve an imbalance between excitatory and inhibitory signaling and altered functional connectivity within and between different brain regions. Specifically, evidence suggests that ASD is associated with patterns of local hyper-connectivity and global or long-distance hypo-connectivity (Maximo, Cadena, & Kana, 2014). There is compromised functional connectivity between different brain regions, in which distant regions typically function together in higher level processing of stimulus input and regulation/modulation of stimulus response (i.e. top-down processing) (Just, Keller, Malave, Kana, & Varma, 2012). This aberrant connectivity has been shown to contribute to a vast array of deficits seen in autism, including visual imagery and language (Kana, Keller, Cherkassky, Minshew, & Just, 2006), working memory (Koshino et al., 2008), social and emotional tasks (Rudie et al., 2012), problem solving (Just, Cherkassky, Keller, Kana, & Minshew, 2007), response inhibition (Kana, Keller, Minshew, & Just, 2007), and theory of mind (Kana, Keller, Cherkassky, Minshew, & Just, 2009).

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that alters cortical excitability via the use of magnetic fields. High-frequency rTMS is defined as greater than or equal to a frequency of 5 Hz and is generally considered to be excitatory stimulation, while low-frequency rTMS is between 0.5-1 Hz and is

considered to be inhibitory. High-frequency rTMS has been FDA-approved for patients with treatment-resistant depression since 2008, with demonstrated efficacy and effectiveness (Dunner et al., 2014; George et al., 2010; Levkovitz et al., 2015; O'Reardon et al., 2007). There are currently three rTMS paradigms that are FDA-cleared for the treatment of major depressive disorder, including the original paradigm, which utilizes a figure-of-eight coil to deliver pulses at a high frequency (10 Hz) while placed at a scalp estimate of the left dorsolateral prefrontal cortex (DLPFC), a standard treatment location for rTMS treatment of depression. Daily (weekday) sessions are recommended for four to six weeks (Perera et al., 2016). No studies to date have investigated using this protocol in either adults or children with ASD, or specifically evaluated the treatment of MDD using rTMS in patients with comorbid ASD.

There is an emerging body of literature suggesting that rTMS may be beneficial for treating the core ASD symptoms (Barahona-Correa, Velosa, Chainho, Lopes, & Oliveira-Maia, 2018; Enticott et al., 2014; Oberman, Rotenberg, & Pascual-Leone, 2015). Various rTMS protocols have been investigated in ASD, the majority of which used low-frequency stimulation (0.5-1Hz). Studies utilizing low-frequency, subthreshold rTMS paradigms applied to the DLPFC (either left-sided or sequential bilateral) have reported that treatment reduced irritability and repetitive behaviors, and enhanced autonomic balance (Casanova et al., 2014; Wang et al., 2016). A recent meta-analysis concluded that rTMS treatment results in a significant reduction of repetitive behaviors, with a medium effect size, but with concern for publication bias. The same meta-analysis showed modest and inconsistent evidence for any reduction in social interaction deficits, with the majority of the data for these conclusions coming from studies applying low-frequency stimulation (Barahona-Correa et al., 2018).

The high prevalence of co-morbid depression in adults with ASD, and data suggesting that rTMS applied to the DLPFC may impact core ASD symptoms make experimentation with anti-depressant rTMS paradigms intriguing. However, the safety and efficacy of standard high-frequency rTMS has not been studied in patients with comorbid ASD and MDD, limiting the utilization of rTMS as a therapeutic option for these patients. Given the theorized abnormalities in neuronal connectivity in ASD, it is not clear that the same protocol, which is well tolerated, effective, and safe in treating depression in TD adults would also be safe and effective in treating depression in adults with comorbid ASD. Major concerns include the increased risk for seizure, intolerance of the procedure, including sensory sensitivity, and potential worsening of ASD symptoms in the setting of atypical neuroanatomical brain structure.

We subsequently took the first step in developing this promising treatment technique by applying a standard anti-depressant high-frequency rTMS protocol in a cohort of participants with ASD and MDD to determine the safety and feasibility of this paradigm.

Methods:

Recruitment and Enrollment Criteria

This prospective, open label, single arm study was approved by the Internal Review Board at the Medical University of South Carolina, and pre-registered at clinicaltrials.gov (NCT02939560, https://clinicaltrials.gov/ct2/show/NCT02939560). Participants were given a complete description of the study and written consent was obtained by participants (and legal guardians where appropriate). Adults 18 to 65 years old who had previously been diagnosed with ASD or Asperger's disorder and who also reported symptoms of depression were recruited via clinician referral, community outreach, and advertisement.

Prior diagnoses of ASD/Asperger's and current major depressive disorder (MDD) were confirmed via structured clinical interview based on DSM-5 criteria performed by qualified clinicians. IQ testing was performed via the Wechsler Abbreviated Scale of Intelligence Second Edition for Adults– Two Subtest form (WASI-II, published by Pearson) and those with IQ < 60 were excluded. Participants on pharmacological regimens, including bupropion, targeting either ASD or MDD were eligible provided the regimen was stable for at least one month prior to and throughout the study. Exclusion criteria included certain comorbid psychiatric conditions - bipolar disorder, schizophrenia, MDD with psychotic features, active substance use disorder, and ASD or intellectual disabilities secondary to genetic syndromes. Remaining exclusion criteria pertained to safety for rTMS, including uncontrolled seizure disorder (seizure within last 6 months on an antiepileptic or within one year while unmedicated), presence of metal in the head or neck, presence of an implanted medical device, history of serious head injury, or pregnancy. Compensation for time was provided to all participants.

Study Design

Prospective participants completed an initial assessment via a structured psychiatric clinical interview, IQ testing, and review of documentation of prior diagnostic testing for ASD, MDD, or intellectual disabilities. Female participants were given a pregnancy test. Once eligibility was confirmed and consent given, participants and designated informants (usually a parent) filled out standardized clinical scales for the participant's baseline MDD and ASD symptom burden. Participants were then treated with twenty-five sessions of rTMS as described below. Allowances were made for missed appointments or holidays, in order for each person to receive 25 treatment sessions within 6 calendar weeks. After completion of the rTMS sessions, post-treatment clinical scales were completed. One-month and three-month follow-up clinical scales were sought from participants and their informants.

Standardized Clinical Scales

To evaluate depressive symptoms, the Hamilton Rating Scale for Depression-17 (HAM-D_{17}) was administered by a trained clinician prior to starting TMS and immediately after last TMS treatment was delivered (Hamilton, 1960). The HAM-D_{17} was used for participants both with and without intellectual disability, as its use in patients with mild to moderate ID is generally accepted and considered accurate (McBrien, 2003). To evaluate ASD symptoms, participants filled out two self-reporting questionnaires: the Social Responsiveness Scale,

Second Edition –Adult (SRS-2) (Constantino, 2012) and the Ritvo Autism Aspergers Diagnostic Scale – Revised (RAADS-R) (Ritvo et al., 2008). Additionally, two informant-based questionnaires were completed by close family members or care providers: the Aberrant Behavior Checklist (ABC) (Aman MG, 1985) and the Repetitive Behavior Scale—Revised (RBS-R) (Bodfish, 1999). All four questionnaires were completed prior to the participant starting rTMS, and again within two weeks after completing rTMS and at one month and three months after completing rTMS.

rTMS Treatment

Participants received a total of 25 sessions of rTMS, performed daily on weekdays within a six-week period via a figure-of-eight coil (Neotonus NeoPulse) that was powered via a Neotonus NeoPulse Model 3600 stimulator. A standard resting motor threshold (rMT) was determined in order to calculate the appropriate TMS dose (Borckardt, Nahas, Koola, & George, 2006). Treatment was delivered at a goal of 120% MT. If 120% of MT was not tolerable for the participant, treatments were delivered at a minimum of 100% MT. During the first week, treatment was allowed to be less than the ideal, down to 80% MT if needed. Each active rTMS treatment consisted of a total of 3000 pulses of 10Hz stimulation (5s-on, 10s-off) per treatment, lasting 15 minutes total. Treatments were delivered at the EEG coordinate for F3 (which approximates the left DLPFC), found using the Beam-F3 method (Beam, Borckardt, Reeves, & George, 2009). Participants were allowed to watch videos, play handheld games, or listen to music of their choice to help alleviate any stress or discomfort experienced during the treatment.

Statistical Methods

Study data were collected and managed using REDCap and exported to SPSS v.24 for statistical analysis. Given the small sample and non-parametric distributions, data are presented as medians (interquartile range) and analyzed with non-parametric statistical methods including Mann-Whitney, Wilcoxon signed ranked test, and generalized mixed models for repeated measure analyses as appropriate.

Results:

Demographics and Baseline Characteristics

Thirteen participants were enrolled in the study (92% males). Two participants withdrew from the study due to intolerability and one participant was removed from the analysis a priori because of significant delays in his treatment course due to hurricane evacuations. The final analysis included ten participants (90% male) with a median age of 25.5. One of these participants did not complete the post-treatment questionnaires, so some analyses only have nine participants. Two informants and three participants were lost to follow-up for one- and three-month questionnaires, thus the analyses are limited to n=7-8 for these timepoints. Baseline characteristics for clinical measures for participants included in the analysis are seen in Table 1, which characterizes the study population as young adults, mostly male with moderate depression and autism symptom burden. The minimum number of antidepressants tried were 2, and over half of the population had tried at least 4 different antidepressants.

Safety and Tolerability of rTMS in Autistic Adults with Depression

One participant withdrew from the study after three rTMS treatments due to anticipatory anxiety surrounding coming to the daily treatments; this anxiety was not perceived to be causally related to the rTMS. One participant withdrew from the study after eight rTMS treatments due to increased irritability. The irritability resolved within a week of their withdrawal from the study. One participant had transient muscle spasms, which resolved instantly after removal of the coil, and did not recur when we reattempted with a modified protocol that started rTMS at 70% MT and slowly titrated up to 100% MT over the course of one week. Other adverse events included mild scalp discomfort, mild headache, and fatigue, mostly within the first week of treatment. There was no significant difference in baseline characteristics between participants that were able to tolerate rTMS and those who could not. All participants who tolerated rTMS reached at least 100% MT during the study protocol.

One subject inadvertently received approximately 10 seconds of pulses at 171% MT due to a programing error on the instrument, resulting in a provoked seizure. The subject was evaluated in the emergency department, was debriefed on the incident afterwards with full disclosure of the error, and ultimately decided to complete the study without further incident. An adverse event report was submitted to the institutional review board and additional safeguards were introduced to prevent future reoccurrences of the error. No major adverse events occurred at intended treatment levels.

Treatment effects on Clinical Measures

Participants were given a clinical depression interview before and after completing the rTMS treatments. All participants who completed the study showed a decrease in HAM-D_{17} depression scale score (Figure 1A) with median decrease of 13.5 points (IQR 5-15, Wilcoxon signed ranked test, p=0.005). Seventy percent of participants had a response to treatment (≥50% decrease in HAM-D_{17} score), and 40% of all participants were considered in remission after rTMS treatment (HAM-D_{17} ≤7). Compared to responders, those that reached remission had a significantly lower HAM-D_{17} score prior to and after treatment (Mann-Whitney U, p=0.048 and 0.031, Figure 1B) but not in the change in HAM-D_{17} scores (Mann-Whitney U, p=1.0). Together these data suggest that individuals that reached remission had milder depression at baseline but an equally good response to treatment as those who did not obtain remission but still responded. When analyzed by number of antidepressants tried in the past, there was no difference in baseline HAM-D_{17} or improvement in HAM-D_{17} (Mann-Whitney U, p≥0.69), suggesting that response to rTMS treatment for depression was independent of prior medication trials.

Self-reported autism questionnaires by participants (SRS-2 and RAADS-R) had no change with rTMS treatment (Figure 2A, 2B). On informant questionnaire RBS-R, there is a combination of scale responses (0-100 severity) and categorical responses (never, mild, moderate, severe) to quantify the frequency and impact of repetitive behaviors. On the scale responses, informant global impression of repetitive behaviors was improved and maintained three months after rTMS (Figure 2D, generalized mixed model p=0.014; post-hoc p≤0.007 compared to baseline). In the sub-scores of ritualistic, sameness, and restricted behaviors,

informants reported decreased frequency, decreased interference of these behaviors on ongoing activities, and improved participants' response to be being interrupted that was maintained at least one month after rTMS (data not shown, generalized mixed models $p \leq 0.031$). However, informants did not identify similar improvements in stereotyped, self-injurious, or compulsive behaviors.

On the RBS-R categorical questions total score, all but one informant identified improvements in overall repetitive behaviors immediately after treatment (Wilcoxon Signed Ranks Test, $p=0.015$), however the effect failed to reach significance over time (Figure 2C, generalized mixed model $p=0.217$). There was also no improvement noted on the RBS-R individual categorical response sub-scores over time (stereotyped, self-injurious, compulsive, ritualistic, sameness, and restricted behavior). The inconsistency between the scale responses and the categorical responses may be partially explained by the difficulty to change between the four categorical responses on the questionnaire, particularly from mild to never and that the scale responses may be more prone to observer bias.

Informants also reported improvement on the ABC questionnaire that was maintained at least one month after rTMS (Figure 3A generalized mixed model $p=0.034$). Post-hoc analysis reveals ABC scores were significantly lower post treatment and at one month follow up, but the effect waned at 3 months ($p= 0.008$, 0.008 and 0.096 respectfully). In a secondary analysis of ABC sub-scores, there were significant reductions in the irritability and hyperactivity sub-scores (Figure 3B, 3C generalized mixed model $p=0.011$ and $p=0.027$ respectfully), but not lethargy, stereotypy, or inappropriate speech sub-scores (Figure 3D, 3E, 3F). As with the total ABC score, these effects were observed post treatment and at one month follow-up, but waned at 3 months (irritability: $p= 0.002$, 0.004 and 0.056 respectfully; hyperactivity: $p= 0.004$, 0.015 and 0.283 respectfully). There was no relationship between depression improvement measured by HAM-D_{17} and informant reported ABC or RBS-R response.

Discussion:

This is the first study to use 10Hz rTMS in individuals with ASD, and also has a greater number of total sessions (25) and a greater number of pulses per session (3000) than the majority of published studies to date. The protocol used was based on the FDA-approved protocol for treatment-resistant depression, which had not been examined specifically among adults with co-morbid ASD and MDD. As expected, we did notice some attrition due to treatment intolerance. Two participants, or 15%, withdrew from the trial due to irritability (1) or treatment emergent anxiety (1). This is more than the 5.4% who withdrew in the active arm in the George et. al. multicenter, randomized control trial in TD adults with MDD, and it should be noted that most of those participants withdrew after the first treatment for pain or headache (George et al., 2010). First line treatments for depression are known to potentially worsen ASD symptoms and irritability, though there is not enough data to provide clear incidences of these side effects (Kolevzon et al., 2006; Williams et al., 2010). The present study using rTMS showed similar worsening in those participants who withdrew, and further studies are necessary to better characterize the incidence of these side effects in this population. As described above, one of our participants suffered a

provoked seizure during the study, however this was the result of instrument programming error and the participant had no provoked seizures throughout the remainder of the study. No participants had a seizure under the approved treatment protocol which follows the safety recommendations endorsed by International Federation for Clinical Neurophysiology (Rossi, Hallett, Rossini, Pascual-Leone, & Safety of, 2009).

In regard to efficacy, 70% of participants had a clinical response for depressive symptoms as defined as at least 50% improvement in their HAM-D_{17} score. 40% of the population reached remission criteria, which is similar to the 30% remission rate of open-label follow-up treatment of participants enrolled in the George et. al. trial (George et al., 2010). There were no self-identified improvements in ASD core symptoms. However, informants identified sustained improvements in hyperactivity and irritability as well as potential improvements in ritualistic, sameness, and restricted behaviors.

The main limitations of the study are the open-label, single arm design and the small sample size. Due to the lack of randomization with a control group and blinding, it is impossible to account for how much of the response was due to placebo effect or observer bias, and how much was true response to the treatment. In this study, we included multiple self-reporting and informant-based questionnaires to improve the likelihood of gathering relevant and meaningful data on any changes in symptom burden, but that data remains subjective. In future studies, other objective measures could include neuroimaging, cognitive laboratory tasks, and biomarkers, which could be correlated with any changes seen on subjective assessments.

In conclusion, this study supports the safety and tolerability of high-ea rTMS for major depressive disorder in adults with autism. Larger, blinded and randomized control trials are needed to confirm efficacy of this rTMS protocol in treating both MDD and core ASD symptoms. Given that current standard first-line treatments for depression in the general population are often less effective and poorly tolerated in individuals with ASD, these initial results using an FDA-approved protocol for MDD are encouraging. Furthermore, the results suggest that this particular rTMS protocol may be effective for core autism symptoms. As with all rTMS patients, clinicians should still proceed with caution if they choose to treat their patients due to the increased risk of seizures. Furthermore, patients with ASD undergoing any rTMS treatment should be carefully monitored for any increased irritability or anxiety, and pre-emptive measures such as earplugs and distracting techniques should be taken to minimize distress for patients during treatment. As evidence-based biological treatments for core autism symptoms remain elusive, rTMS warrants further study in this growing patient population.

Acknowledgements:

The authors would like to thank the Medical University of South Carolina Brain Stimulation Lab and the Center for Biomedical Imaging for making this project possible. We would also like to thank the participants of this study and their families who graciously volunteered. The authors have no conflicts of interest to report.

References:

Aman MG SN, Stewart AW, Field CJ. (1985). The aberrant behavior checklist: a behavior rating scale for the assessment of treatment effects. Am J Ment Defic, 89(5)(Mar), 485–491. [PubMed: 3993694]

Barahona-Correa JB, Velosa A, Chainho A, Lopes R, & Oliveira-Maia AJ (2018). Repetitive Transcranial Magnetic Stimulation for Treatment of Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. Front Integr Neurosci, 12, 27. [PubMed: 30038561]

Beam W, Borckardt JJ, Reeves ST, & George MS (2009). An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. Brain Stimul, 2(1), 50–54. [PubMed: 20539835]

Bodfish JW, Symons FJ, & Lewis MH . (1999). Repetitive Behavior Scale. Western Carolina Center Research Reports.

Borckardt JJ, Nahas Z, Koola J, & George MS (2006). Estimating resting motor thresholds in transcranial magnetic stimulation research and practice: a computer simulation evaluation of best methods. J ect, 22(3), 169–175. [PubMed: 16957531]

Casanova MF, Hensley MK, Sokhadze EM, El-Baz AS, Wang Y, Li X, & Sears L (2014). Effects of weekly low-frequency rTMS on autonomic measures in children with autism spectrum disorder. Front Hum Neurosci, 8, 851. [PubMed: 25374530]

Charlot L, Deutsch CK, Albert A, Hunt A, Connor DF, & McIlvane WJ Jr. (2008). Mood and Anxiety Symptoms in Psychiatric Inpatients with Autism Spectrum Disorder and Depression. J Ment Health Res Intellect Disabil, 1(4), 238–253. [PubMed: 24009649]

Christensen DL, Baio J, Braun KV, Bilder D, Charles J, Constantino JN, … Yeargin-Allsopp M (2016). Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. MMWR Surveill Summ, 65(3), 1–23.

Constantino JN (2012). The Social Responsiveness Scale Manual, Second Edition (SRS-2). Los Angeles: Western Psychological Services.

Croen LA, Zerbo O, Qian Y, Massolo ML, Rich S, Sidney S, & Kripke C (2015). The health status of adults on the autism spectrum. Autism, 19(7), 814–823. [PubMed: 25911091]

De-la-Iglesia M, & Olivar JS (2015). Risk Factors for Depression in Children and Adolescents with High Functioning Autism Spectrum Disorders. ScientificWorldJournal, 2015, 127853. [PubMed: 26413564]

Dunner DL, Aaronson ST, Sackeim HA, Janicak PG, Carpenter LL, Boyadjis T, … Demitrack MA (2014). A Multisite, Naturalistic, Observational Study of Transcranial Magnetic Stimulation for Patients With Pharmacoresistant Major Depressive Disorder. J Clin Psychiatry.

Enticott PG, Fitzgibbon BM, Kennedy HA, Arnold SL, Elliot D, Peachey A, .Fitzgerald PB (2014). A double-blind, randomized trial of deep repetitive transcranial magnetic stimulation (rTMS) for autism spectrum disorder. Brain Stimul, 7(2), 206–211. [PubMed: 24280031]

George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, … Sackeim HA (2010). Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry, 67(5), 507–516. [PubMed: 20439832]

Hamilton M (1960). A rating scale for depression. J Neurol Neurosurg Psychiatry, 23, 56–62. [PubMed: 14399272]

Just MA, Cherkassky VL, Keller TA, Kana RK, & Minshew NJ (2007). Functional and anatomical cortical underconnectivity in autism: evidence from an FMRI study of an executive function task and corpus callosum morphometry. Cereb Cortex, 17(4), 951–961. [PubMed: 16772313]

Just MA, Keller TA, Malave VL, Kana RK, & Varma S (2012). Autism as a neural systems disorder: a theory of frontal-posterior underconnectivity. Neurosci Biobehav Rev, 36(4), 1292–1313. [PubMed: 22353426]

Kana RK, Keller TA, Cherkassky VL, Minshew NJ, & Just MA (2006). Sentence comprehension in autism: thinking in pictures with decreased functional connectivity. Brain, 129(Pt 9), 2484–2493. [PubMed: 16835247]

Kana RK, Keller TA, Cherkassky VL, Minshew NJ, & Just MA (2009). Atypical frontal-posterior synchronization of Theory of Mind regions in autism during mental state attribution. Soc Neurosci, 4(2), 135–152. [PubMed: 18633829]

Kana RK, Keller TA, Minshew NJ, & Just MA (2007). Inhibitory control in high-functioning autism: decreased activation and underconnectivity in inhibition networks. Biol Psychiatry, 62(3), 198–206. [PubMed: 17137558]

Kogan MD, Vladutiu CJ, Schieve LA, Ghandour RM, Blumberg SJ, Zablotsky B, … Lu MC (2018). The Prevalence of Parent-Reported Autism Spectrum Disorder Among US Children. Pediatrics, 142(6).

Kolevzon A, Mathewson KA, & Hollander E (2006). Selective serotonin reuptake inhibitors in autism: a review of efficacy and tolerability. J Clin Psychiatry, 67(3), 407–414. [PubMed: 16649827]

Koshino H, Kana RK, Keller TA, Cherkassky VL, Minshew NJ, & Just MA (2008). fMRI investigation of working memory for faces in autism: visual coding and underconnectivity with frontal areas. Cereb Cortex, 18(2), 289–300. [PubMed: 17517680]

Levkovitz Y, Isserles M, Padberg F, Lisanby SH, Bystritsky A, Xia G, … Zangen A (2015). Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. World Psychiatry, 14(1), 64–73. [PubMed: 25655160]

Maximo JO, Cadena EJ, & Kana RK (2014). The implications of brain connectivity in the neuropsychology of autism. Neuropsychol Rev, 24(1), 16–31. [PubMed: 24496901]

McBrien JA (2003). Assessment and diagnosis of depression in people with intellectual disability. J Intellect Disabil Res, 47(Pt 1), 1–13. [PubMed: 12558690]

O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, Sackeim HA (2007). Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry, 62(11), 1208–1216. [PubMed: 17573044]

Oberman LM, Rotenberg A, & Pascual-Leone A (2015). Use of transcranial magnetic stimulation in autism spectrum disorders. J Autism Dev Disord, 45(2), 524–536. [PubMed: 24127165]

Perera T, George MS, Grammer G, Janicak PG, Pascual-Leone A, & Wirecki TS (2016). The Clinical TMS Society Consensus Review and Treatment Recommendations for TMS Therapy for Major Depressive Disorder. Brain Stimul, 9(3), 336–346. [PubMed: 27090022]

Ritvo RA, Ritvo ER, Guthrie D, Yuwiler A, Ritvo MJ, & Weisbender L (2008). A scale to assist the diagnosis of autism and Asperger's disorder in adults (RAADS): a pilot study. J Autism Dev Disord, 38(2), 213–223. [PubMed: 17610152]

Rossi S, Hallett M, Rossini PM, Pascual-Leone A, & Safety of T. M. S. C. G. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol, 120(12), 2008–2039. [PubMed: 19833552]

Rudie JD, Shehzad Z, Hernandez LM, Colich NL, Bookheimer SY, Iacoboni M, & Dapretto M (2012). Reduced functional integration and segregation of distributed neural systems underlying social and emotional information processing in autism spectrum disorders. Cereb Cortex, 22(5), 1025–1037. [PubMed: 21784971]

Wang Y, Hensley MK, Tasman A, Sears L, Casanova MF, & Sokhadze EM (2016). Heart Rate Variability and Skin Conductance During Repetitive TMS Course in Children with Autism. Appl Psychophysiol Biofeedback, 41(1), 47–60. [PubMed: 26341093]

Williams K, Wheeler DM, Silove N, & Hazell P (2010). Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). Cochrane Database Syst Rev(8), Cd004677. [PubMed: 20687077]

Xu G, Strathearn L, Liu B, O'Brien M, Kopelman TG, Zhu J, … Bao W (2019). Prevalence and Treatment Patterns of Autism Spectrum Disorder in the United States, 2016. JAMA Pediatr, 173(2), 153–159. [PubMed: 30508021]

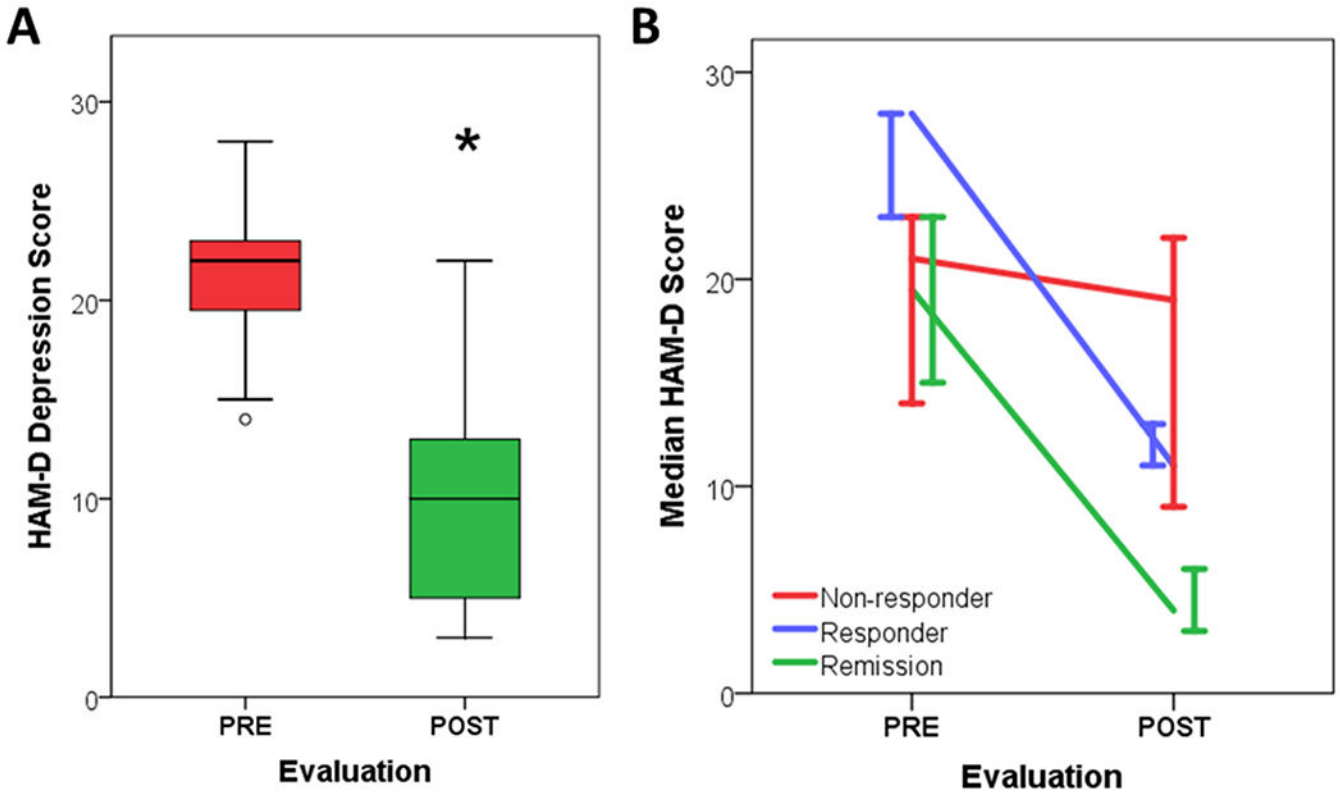

Figure 1.

(A) Box plots of Hamilton Rating Scale for Depression (HAM-D_{17}) pre and post rTMS treatment (*p=0.005). (B) Median HAM-D_{17} and 95% confidence intervals (off-set for ease of viewing) for participants that reached remission (green), responders (blue), and non-responders (red) at pre- and post-treatment.

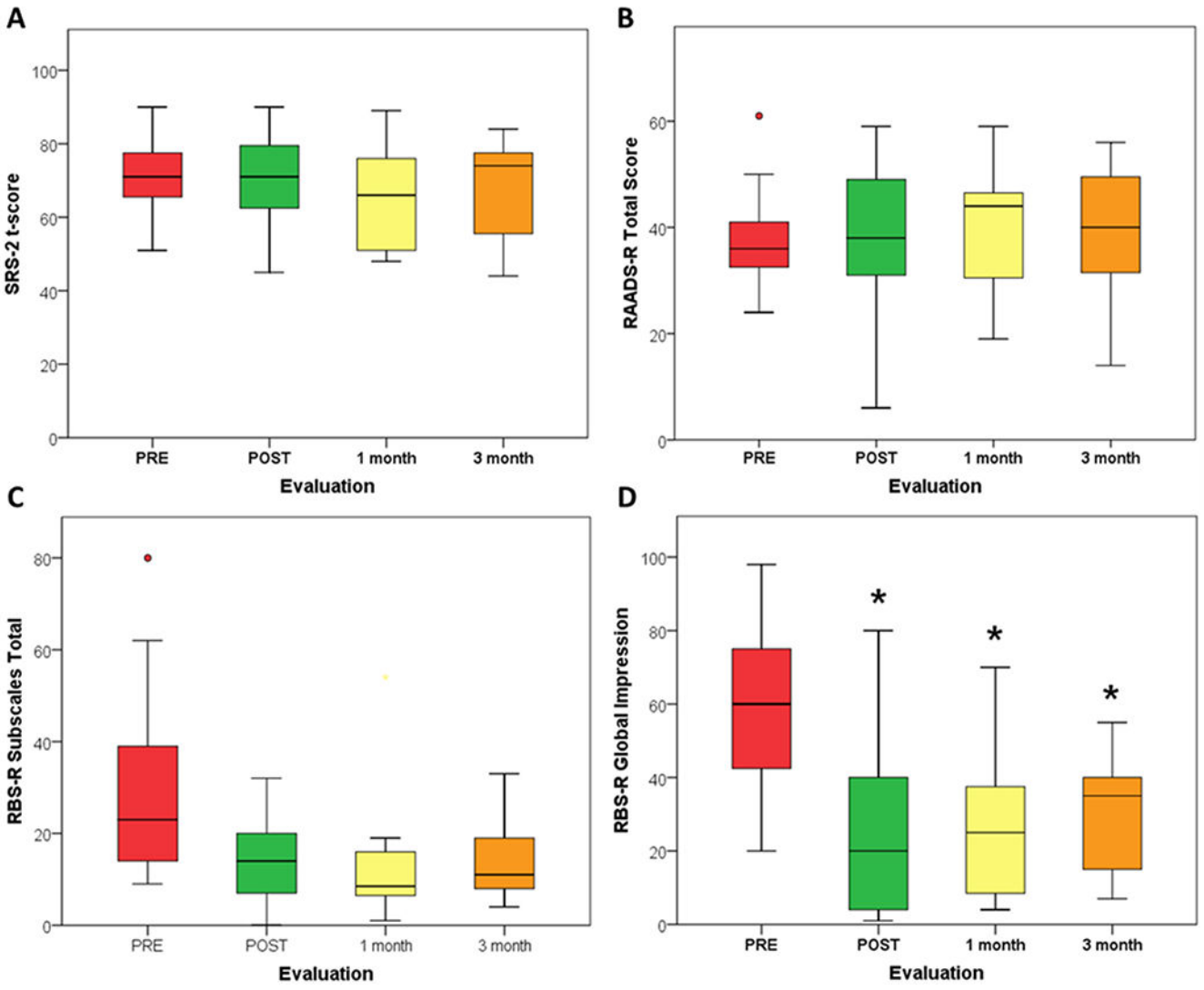

Figure 2.

Box plots of clinical questionnaires over time with no improvement in self-reported questionnaires SRS-2 (A) and RAADS-R (B), as well as the RBS-R sub-scores total score (C), but sustained improvement in informant global impression of repetitive behaviors on the RBS-R (D). (*$p<0.05$ compared to pretreatment baseline.)

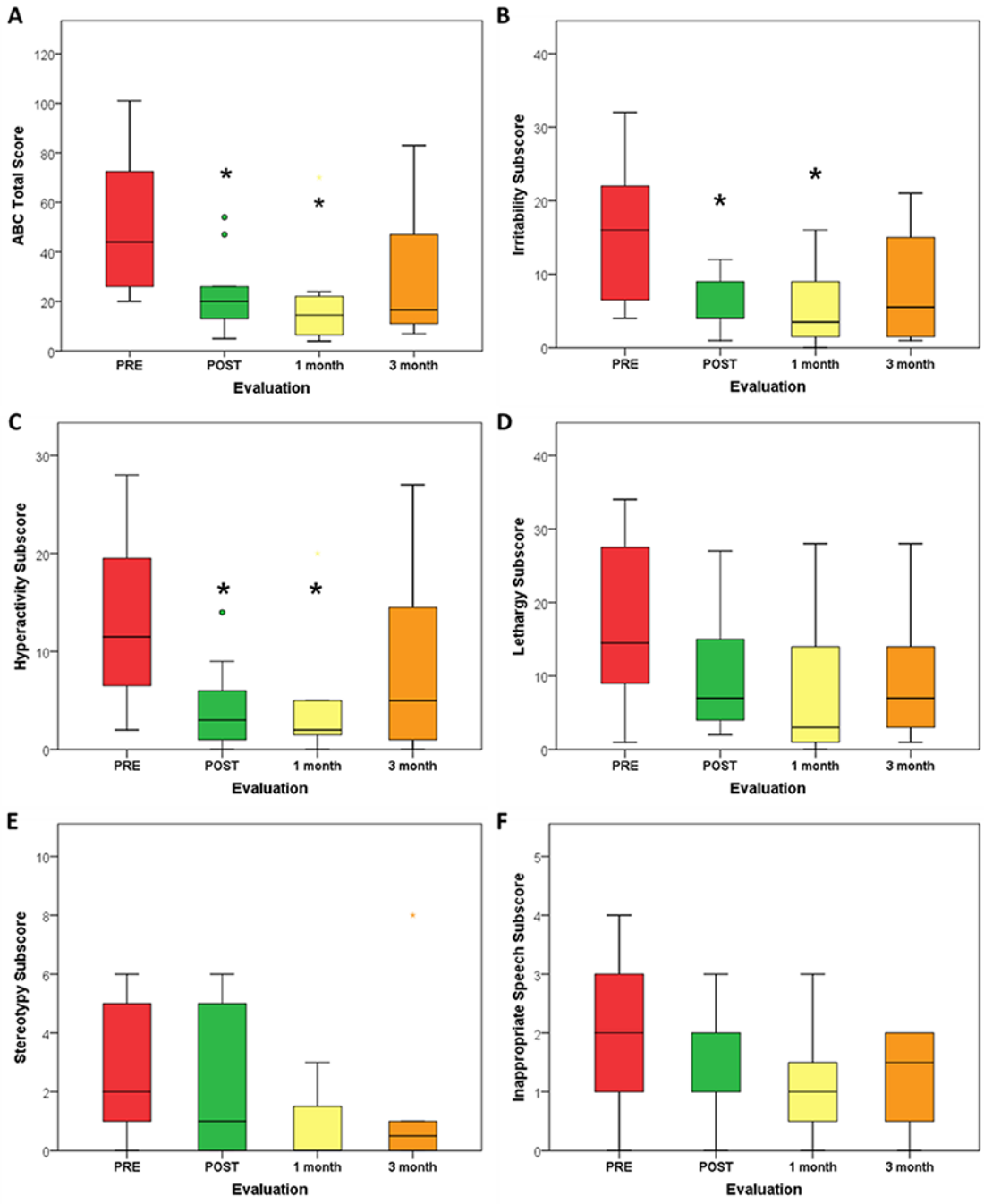

Figure 3.

Box plots of ABC total score and sub-scores over time with improvement in overall score (A) and sub-scores evaluating irritability (B) and hyperactivity (C), but not lethargy (D), stereotypy (E), or inappropriate speech (F). (*p<0.05 compared to pretreatment baseline).

Table 1.

Baseline characteristics of participants included in analysis. Clinical measures are presented as median (interquartile range).

	Baseline Characteristics (n=10)
Male	9 (90%)
Age	25.5 (23-29)
HAM-D_{17} total	22 (18-23)
SRS-2 t-score	73.5 (64-78)
RAADS-R total	36 (35-45)
RBS-R global impression	55 (35-80)
RBS-R total	22 (13-42)
ABC total	56 (26-77)