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A Double-blind, Randomized Trial of Deep Repetitive Transcranial Magnetic Stimulation (rTMS) for Autism Spectrum Disorder

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ABSTRACT

Background: Biomedical treatment options for autism spectrum disorder (ASD) are extremely limited. Repetitive transcranial magnetic stimulation (rTMS) is a safe and efficacious technique when targeting specific areas of cortical dysfunction in major depressive disorder, and a similar approach could yield therapeutic benefits in ASD, if applied to relevant cortical regions.
Objective: The aim of this study was to examine whether deep rTMS to bilateral dorsomedial prefrontal cortex improves social relating in ASD.
Methods: 28 adults diagnosed with either autistic disorder (high-functioning) or Asperger's disorder completed a prospective, double-blind, randomized, placebo-controlled design with 2 weeks of daily weekday treatment. This involved deep rTMS to bilateral dorsomedial prefrontal cortex (5 Hz, 10-s train duration, 20-s inter-train interval) for 15 min (1500 pulses per session) using a HAUT-Coil. The sham rTMS coil was encased in the same helmet of the active deep rTMS coil, but no effective field was delivered into the brain. Assessments were conducted before, after, and one month following treatment.
Results: Participants in the active condition showed a near significant reduction in self-reported social relating symptoms from pre-treatment to one month follow-up, and a significant reduction in social relating symptoms (relative to sham participants) for both post-treatment assessments. Those in the active condition also showed a reduction in self-oriented anxiety during difficult and emotional social situations from pre-treatment to one month follow-up. There were no changes for those in the sham condition.
Conclusion: Deep rTMS to bilateral dorsomedial prefrontal cortex yielded a reduction in social relating impairment and socially-related anxiety. Further research in this area should employ extended rTMS protocols that approximate those used in depression in an attempt to replicate and amplify the clinical response.

Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a safe and efficacious treatment for major depressive disorder (MDD) [1], where it is generally used to enhance excitability within underactive cortical regions (e.g., left dorsolateral prefrontal cortex; dlPFC) and associated networks. rTMS has potential therapeutic benefits in a range of other psychiatric and neurological disorders, and might be useful in autism spectrum disorder (ASD), a condition for which there is an ample neuroimaging and neurophysiological evidence of abnormal patterns of cortical excitability [2].

A likely neurobiological target for rTMS in ASD is the dorsomedial prefrontal cortex (dmPFC), a region of the brain that has been implicated in 'theory of mind' or 'mentalizing' (i.e., the ability to comprehend other's thought, beliefs, and intentions). While there is evidence for a broad mentalizing network that also involves temporoparietal junction, temporal poles, and posterior cingulate [3], dmPFC is consistently implicated and has been considered to have a unique contribution to mentalizing [4]. Mentalizing deficits have long been theorized as contributing to social relating

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impairments in ASD [5] and neuroimaging studies have found reduced dmPFC activity during mentalizing tasks in ASD [6]. Standard rTMS coils have limited penetrative depth and are unable to directly stimulate a significant portion of dmPFC, but recent developments in "deep" rTMS coil technology allow the direct stimulation of large volumes within the brain such as the dmPFC region.

There are a small number of studies examining therapeutic effects of rTMS in ASD; for example [7], applied low-frequency stimulation to left dlPFC and reported a reduction in repetitive behaviors, although this research did not involve a "sham" or "placebo" control condition. Stimulation of the dmPFC, however, has not been undertaken in ASD. Through a double-blind, placebo-controlled clinical trial, the current study examined the safety and efficacy of a two-week course of deep rTMS to dmPFC among adults with ASD. It was hypothesized that those receiving active deep rTMS would show a reduction in social relating impairment and improvements in mentalizing.

Methods and materials

Participants

Thirty adults who had received a primary diagnosis of autistic disorder (high-functioning) or Asperger's disorder were recruited via advertisement or clinician referral between June 2009 and June 2012. All participants had been diagnosed with DSM-IV autistic disorder (high-functioning) or Asperger's disorder by a qualified psychiatrist, pediatrician, or psychologist. This was verified by either diagnostic report or direct communication with the diagnosing clinician. Diagnostic procedures involved detailed clinical interview and observation with the patient and relevant family members, although standardized assessments were not universally implemented among clinicians. Differentiation between Asperger's disorder and autistic disorder was made on the basis of DSM-IV criteria (e.g., early language impairments in the former but not the latter). There were many more participants with Asperger's disorder; while the reason for this is unclear, it may relate it part to recruitment methods (e.g., community groups specifically targeting Asperger's disorder). As is common in these conditions, 50% of participants also reported secondary diagnoses of depression and/or anxiety, although rates were similar across both treatment groups (active: 53%; sham: 46%). Participants who were medicated were not withdrawn from medication, but were required to have a consistent medication regime for at least one month prior to enrollment in the study, and throughout the duration of the trial. 39% of participants were taking psychotropic medication (active: 40% [1 venlafaxine, 1 fluoxetine, 1 lorazepam, 1 escitalopram, 1 haloperidol, 1 duloxetine]; sham: 39% [1 fluoxetine, 1 sertraline, 1 propranolol, 1 venlafaxine, 1 sertraline/risperidone/lorazepam]). Exclusion criteria were related to safety aspects of rTMS, and included a history of seizures, the presence of metal in the cranium, a history of serious head injury, pregnancy, and the presence of an implanted medical device (e.g., cardiac pacemaker).

Unlabeled envelopes containing treatment information (active or sham/placebo) were prepared prior to the study, and then randomly selected for each participant. Thus, participants were randomly allocated to receive either active deep rTMS, or a sham/placebo form of deep rTMS. These procedures were completed by the first author. One participant (sham) withdrew from the study after 4 deep rTMS treatments due to ongoing health concerns unrelated to deep rTMS, while another participant (active) refused to complete post-rTMS assessments. As we only had pre-treatment data for these individuals, they are not included in the final sample. Participant information is presented in Table 1.

Table 1
Participant demographics.

	Active	Sham
n	15	13
Gender (m:f)	13:2	10:3
Diagnosis (autism:Asperger's)	3:12	1:12
Age (SD, range)	33.87 (13.07) (18–59)	30.54 (9.83) (19–54)

This study was approved by the Human Research Ethics Committees of Monash University, Alfred Health, and Southern Health. After complete description of the study to the participants, written informed consent was obtained. The study was registered at clinicaltrials.gov (NCT00808782, http://clinicaltrials.gov/ct2/show/NCT00808782)

Materials

Participants were administered deep rTMS through a HAUT-coil (Brainsway Ltd., Israel) that was connected to a Magstim Rapid stimulator (Magstim Co, Wales, UK). During treatment, the anterior edge of the coil was positioned over the bilateral dmPFC according to landmark procedures that are recommended by the developers of the coil (centered and 7 cm anterior to M1, typically 3–4 cm from the nasion). This coil is designed to stimulate bilateral dmPFC to a depth of 4–5 cm below the scalp (as verified by field modeling performed by the coil manufacturers see Fig. 1).

Each deep rTMS treatment session involved 30 10 s trains at 5 Hz, with a 20 s inter-train interval. This was chosen to provide conservative excitatory stimulation to dmPFC that was within standard safety guidelines outlined by Wasserman et al. [8]. Deep rTMS was delivered at the individual's resting motor threshold (i.e., minimum stimulation intensity required to elicit a discernible hand muscle response in at least 3 of 5 consecutive pulses). Sham stimulation involved a simulation, whereby the sound and vibration of the coil was simulated by a sham coil encased in the same helmet but no effective magnetic pulses were delivered into the brain. This sham method is described in detail by Isserles et al. [9].

Participants were assessed at three time points: immediately before the first deep rTMS treatment ('pre'), immediately after the last deep rTMS treatment ('post'), and one month after the last deep rTMS treatment ('month'). Participants and assessors (the latter of which were not involved with rTMS treatments) remained blinded until after the 'month' assessment. The assessments involved a 1.5–2 h session featuring self-report clinical scales with good psychometric properties (Ritvo Autism-Aspergers Diagnostic Scale [RAADS] [10], Autism Spectrum Quotient [AQ] [11], Interpersonal Reactivity Index [IRI] [12]), and experimental measures of mentalizing (reading the mind in the eyes test [13] and animations mentalizing test [6]). The clinical measures were administered at the post and month time points with explicit instructions that participants should complete them only in relation to the period since the last assessment. Items on the RAADS are typically rated as either 'true now and when I was young,' 'true only now,' 'true only when I was young,' or 'never true,' but the administration of the RAADS was further altered at the 'post' and 'month' time points so that participants could simply indicate whether each item was true [1] or not true (0), with reverse coding as usual.

Procedure

Participants attended eleven sessions at the Monash Alfred Psychiatry Research Centre (Melbourne, Australia). During the first session, participants were consented and then completed the pre assessment. Immediately after this they underwent the resting

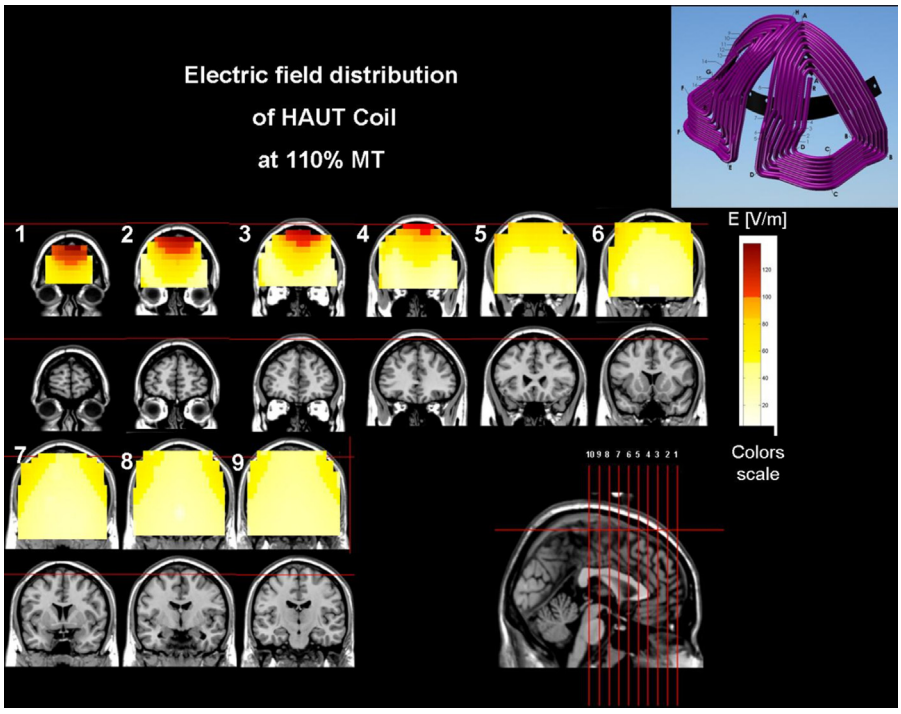

Figure 1. Colored field maps for the HAUT-coil indicating the electrical field absolute magnitude in each pixel, for 9 coronal slices 1 cm apart. The red colors indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m. The field maps are adjusted for stimulator power output of 47%, which was the level required to obtain 110% of the threshold (110 V/m), at a depth of 1.5 cm from coil center. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

motor threshold procedure with the HAUT-coil (active mean = 50.80%, SD = 7.66, sham mean = 50.62%, SD = 7.41; $F[1,26] = .004$, $P = .949$), then were administered the first deep rTMS treatment. Treatment was administered every consecutive weekday for a total of ten treatments. Immediately after the last treatment, participants completed the post assessment. Participants attended again one

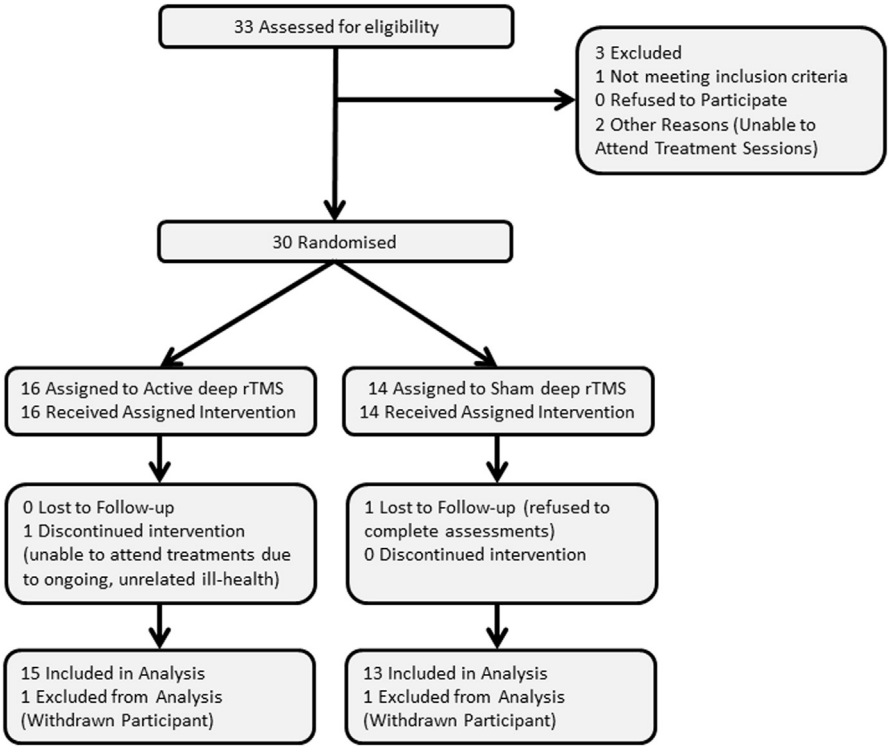

Figure 2. CONSORT flow diagram.

month after the last treatment session for the month assessment, after which they were unblinded. Those in the sham condition were offered the opportunity to receive the active treatment. Both participants and the assessor were blind to the treatment condition. A CONSORT flow diagram is shown in Fig. 2.

Statistical analysis

The social relatedness subscale of the RAADS was considered our primary outcome measure due to its clinical relevance and theoretical relationship to dmPFC function. 'Pre' ratings for the RAADS were converted to be consistent with 'post' and 'month' ratings (i.e., items classed as true or not true at the time of assessment). Where appropriate, two-way mixed-model ANOVAs examining time (pre vs. post vs. month) and condition (active deep rTMS vs. sham deep rTMS) were used to evaluate effects on the clinical and experimental dependent measures. In several cases, data violated the assumptions of ANOVA, and non-parametric tests (Friedman's 2-way ANOVA by ranks and Wilcoxon signed rank test) were used. This was the case for both experimental measures of mentalizing, and for the 'fantasy' and 'empathic concern' subscales of the IRI. Simple Bonferroni adjustments were performed for all follow-up analyses on each dependent measure.

Results

There were no serious adverse events reported. With respect to non-serious adverse events, one participant reported "lightheadedness" for approximately 5 min following treatment, while another two participants reported minor facial discomfort during rTMS treatment.

Summary data and interaction effects for the clinical measures are presented in Table 2. There was a significant reduction on the social relatedness subscale of the RAADS in the active but not the sham group (A reduction on the RAADS reflects less impairment or reduced symptomatology.). There was a significant *time* × *condition* interaction and one-way repeated measures ANOVAs showed a significant effect of time for the active condition, $F(2,28) = 4.31$, $P = .023$, but not for the sham condition, $F(2,24) = .86$, $P = .434$. Employing a corrected alpha value ($\alpha = .017$), in the active condition there was a near significant reduction in social relating symptoms from 'pre' to 'month,' $F(1,14) = 7.08$, $P = .019$, $d = .58$. The difference between 'pre' to 'post' did not reach significance, $F(1,14) = 3.84$, $P = .070$, $d = .45$, while there was no difference between 'post' and 'month,' $F(1,14) = .075$, $P = .403$, $d = .15$. In addition, when comparing group differences at each timepoint, while there was no significant between-group difference at baseline, $F(1,26) = 3.78$, $P = .063$, $d = .73$, active was significantly lower than sham for both 'post,' $F(1,26) = 9.86$, $P = .004$, $d = 1.18$, and 'month' follow-ups, $F(1,26) = 14.05$, $P = .001$, $d = 1.41$ (see Fig. 3). While it is difficult to define a clinical "response" using the RAADS in this manner, Fig. 4 presents boxplots by group demonstrating the difference in score between 'pre' and 'month' for RAADS social relating (where a greater score indicates a greater symptom reduction). There were no interaction effects for either the communication and language subscale or the sensorimotor subscale, suggesting that the effects of deep rTMS on ASD were specific to the social relating domain.

There was a near significant *time* × *condition* interaction for the personal distress subscale of the IRI, which broadly measures self-oriented anxiety in difficult and emotional social situations. Follow-up analyses showed a reduction for the active condition, $F(2,28) = 4.16$, $P = .026$, but not for the sham condition, $F(2,24) = .92$, $P = .412$. Again using a corrected alpha value ($\alpha = .017$), for those in the active condition there was a reduction from 'pre' to 'month' in the active group, $F(1,14) = 11.61$, $P = .004$, $d = .41$. There was no difference between 'pre' and 'post,' $F(1,14) = 1.06$, $P = .321$, $d = .17$, and no difference between 'post' and 'month,' $F(1,14) = 2.93$, $P = .109$, $d = .21$. There were, however, no significant between-group differences at any of the time points.

There was also a significant reduction on the fantasy subscale for the active condition but not for sham condition, which provides a measure of the tendency to imagine oneself as a fictional character in a book being read or a movie/play being watched. For the active condition, follow-up Wilcoxon signed rank tests revealed a near significant reduction from 'pre' to 'month' ($P = .026$), but no change from 'pre' to 'post' ($P = .580$) or 'post' to 'month' ($P = .079$).

Table 2
Summary data for clinical measures.

RAADS	Active mean (SD)	Sham mean (SD)	IRI	Active mean (SD)	Sham mean (SD)	AQ	Active mean (SD)	Sham mean (SD)
RAADS social relatedness			IRI perspective taking			AQ social		
Pre	11.27 (5.09)	15.23 (5.70)	Pre	14.60 (3.16)	13.54 (5.03)	Pre	5.47 (2.17)	7.00 (2.24)
Post	9.00 (5.11)	15.69 (6.17)	Post	15.53 (2.72)	14.23 (5.20)	Post	5.20 (1.86)	6.08 (2.96)
Month	8.20 (5.51)	16.39 (6.05)	Month	15.73 (3.35)	14.77 (5.73)	Month	4.80 (2.83)	6.54 (2.70)
Time × *condition*	$F^{2,52} = 4.50$	$P = .016$	*Time* × *condition*	$F^{2,52} = .05$	$P = .954$	*Time* × *condition*	$F^{2,52} = .87$	$P = .425$
RAADS communication			IRI fantasy			AQ attention		
Pre	11.47 (4.07)	11.15 (3.69)	Pre	16.20 (5.52)	13.69 (6.32)	Pre	6.67 (2.41)	8.39 (1.66)
Post	9.07 (4.30)	10.31 (5.01)	Post	15.20 (4.77)	14.54 (6.40)	Post	6.20 (2.96)	8.23 (1.92)
Month	10.00 (5.03)	11.92 (5.01)	Month	12.80 (4.26)	14.69 (6.34)	Month	5.87 (3.16)	8.39 (1.33)
Time × *condition*	$F^{2,52} = 1.29$	$P = .284$	Friedman's by group	$P = .039$	$P = .633$	*Time* × *condition*	$F^{2,52} = .75$	$P = .477$
RAADS sensorimotor			IRI empathic concern			AQ local details		
Pre	9.67 (2.94)	12.69 (6.17)	Pre	19.27 (4.82)	16.54 (4.12)	Pre	6.27 (1.95)	8.23 (1.48)
Post	8.40 (4.12)	11.15 (7.30)	Post	19.87 (4.45)	16.77 (4.57)	Post	5.27 (2.40)	8.00 (1.96)
Month	8.60 (5.88)	11.77 (7.27)	Month	19.27 (3.47)	16.85 (5.29)	Month	5.73 (2.22)	7.23 (2.05)
Time × *condition*	$F^{2,52} = .04$	$P = .961$	Friedman's by group	$P = .684$	$P = .856$	*Time* × *condition*	$F^{2,52} = 2.03$	$P = .141$
			IRI personal distress			AQ communication		
			Pre	14.80 (4.59)	14.00 (3.81)	Pre	6.07 (2.40)	7.92 (1.85)
			Post	13.87 (6.26)	13.00 (3.81)	Post	5.47 (2.70)	6.46 (2.60)
			Month	12.53 (6.33)	14.39 (4.61)	Month	5.47 (3.18)	6.15 (2.30)
			Time × *condition*	$F^{2,52} = 3.03$	$P = .057$	*Time* × *condition*	$F^{2,52} = 1.25$	$P = .295$
						AQ imagination		
						Pre	4.40 (2.06)	5.15 (2.82)
						Post	4.33 (2.09)	4.92 (2.84)
						Month	4.53 (2.10)	4.46 (2.73)
						Time × *condition*	$F^{2,52} = .89$	$P = .417$

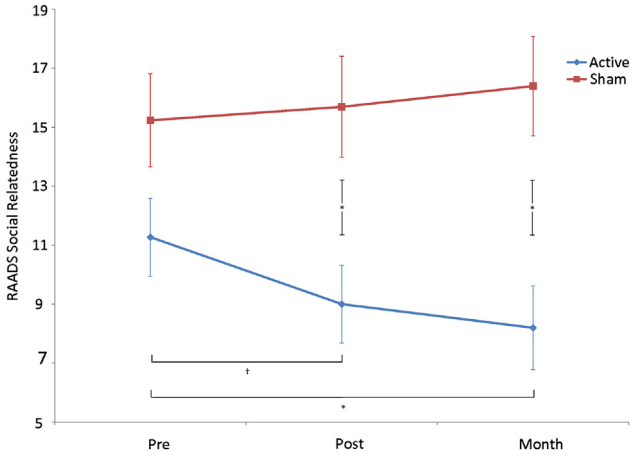

Figure 3. Social relating scores (±SE) from the RAADS for the active and sham groups (*$P < .05$, †$P = .07$).

There was no significant effect for the perspective taking subscale or for the empathic concern subscale for either the active or sham groups.

There was no significant interaction effect for the social relating subscale of the AQ. Interaction effects for all other AQ subscales were also not significant.

Summary data and results of statistical analyses for the experimental mentalizing measures are presented in Table 3. There were no significant effects of condition (active vs. sham) for either of the experimental mentalizing tasks. Practice effects were evident for both groups, but this was only significant for the appropriateness scale of the animations mentalizing test among the sham condition. Follow-up analyses (Wilcoxon) revealed a trend toward a significant increase from pre to month in the sham condition ($P = .048$).

Table 3
Summary data and non-parametric analysis results for experimental measures of mentalizing.

	Active mean (SD)	Sham mean (SD)
RMET		
Pre total correct	23.20 (4.35)	23.62 (4.84)
Post total correct	23.20 (5.07)	25.85 (5.13)
Month total correct	24.47 (6.08)	25.46 (5.84)
Friedman's by group	$P = .482$	$P = .067$
Animations mentalizing		
Pre mentalizing intent	11.07 (4.50)	11.92 (5.72)
Post mentalizing intent	12.36 (3.88)	12.00 (5.69)
Month mentalizing intent	11.64 (4.85)	13.08 (6.81)
Friedman's by group	$P = .135$	$P = .337$
Pre mentalizing appropriateness	3.50 (1.61)	4.39 (2.69)
Post mentalizing appropriateness	4.07 (1.33)	5.46 (2.18)
Month mentalizing appropriateness	4.57 (2.14)	5.39 (2.82)
Friedman's by group	$P = .210$	$P = .012$
Pre mentalizing length	11.21 (3.47)	12.77 (3.94)
Post mentalizing length	10.36 (3.39)	13.77 (3.17)
Month mentalizing length	10.93 (3.43)	13.31 (5.06)
Friedman's by group	$P = .290$	$P = .975$

Discussion

These data provide initial support for the safety and efficacy of deep rTMS to the dmPFC to improve social relating in ASD. Specifically, active deep rTMS (relative to sham deep rTMS) significantly reduced social relating impairments as measured by the RAADS, and decreased self-oriented anxiety in difficult social environments as measured by the IRI (while maintaining empathic capacity). There was also a near significant reduction in the fantasy subscale of the IRI, suggesting that deep rTMS may have reduced the tendency to imagine oneself as a fictional character. This is somewhat difficult to interpret in the context of social relating, and this subscale has been suggested to measure other processes (including emotional self-control) [14]. Although relatively small from a clinical perspective, these significant improvements should not be undervalued given the difficulty in adequately treating social relating symptoms in ASD, and the conservative rTMS parameters employed (which were markedly less intensive than those used in rTMS treatments for MDD). The specific mechanism behind these changes will require investigation, and may reflect specific neuroplastic effects associated with high-frequency stimulation.

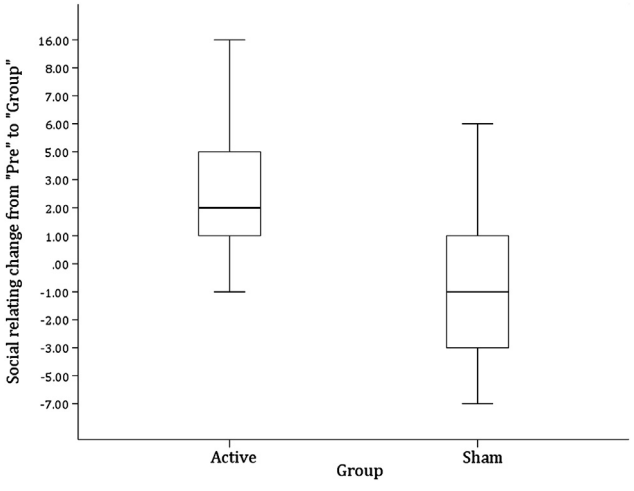

Figure 4. Boxplot demonstrating difference in RAADS social relating score by group from 'pre' to 'month.' A larger score indicates greater symptom reduction.

From a neurobiological perspective, we suggest that these improvements resulted from stimulation of dmPFC regions and associated 'mentalizing' networks that have previously been associated with a reduced BOLD response in ASD, which may be indicative of reduced activity. Stimulation of these networks may induce long-lasting alterations in the excitability of components within the network, especially when stimulation is provided while the relevant circuitry is active during the experimental setup (which necessarily involves social interaction with the experimenters). Such alterations may enhance the capacity for interpreting one's social environment, and it follows that an enhanced understanding would reduce social relating impairments and anxiety related to difficult social situations as seen in the current trial. Alternatively, however, high-frequency stimulation may trigger an inhibitory response, a deficiency in which has been implicated in the neuropathology of ASD [15]. This current study was only concerned with testing therapeutic aspects, and while we can only speculate on the precise underlying mechanism of action, in future it will be important to also collect pre and post neuroimaging and/or neurophysiological data.

There are possible alternative explanations for the relationship between deep rTMS and the reported improvements. For example, it might be suggested that deep rTMS had an antidepressant effect, and that this drove the socially-related findings. As we did not measure depression, we cannot rule this out, and the sample size precludes a meaningful analysis of participants who do not experience depression. However, the region stimulated was not one that is targeted in rTMS treatments for depression, and the measures used are less focused on motivation for sociability and more on a capacity for social understanding (which would presumably not

be affected by a simple antidepressant response). It will be particularly difficult to disentangle these issues, as depression in ASD is often reactive to social difficulties, and improvements in the former would be expected following improvements in the latter. Nevertheless, it will be important in future studies to attempt to determine whether the impact of deep rTMS on social relating is primary or secondary.

It was unexpected that there were no changes in the mentalizing tasks, particularly when clinical improvements were seen in the social relating measures. While it is possible that social relating improvements were induced via a mechanism unrelated to mentalizing (or at least unrelated to the aspects of mentalizing assessed with these particular measures), it also seems likely that these experimental tasks lacked the necessary sensitivity. Both groups displayed evidence of practice effects (i.e., improved performance over time), and these measures were generally designed for children. Among a high-functioning, adult sample, it may be prudent to utilize tasks that involve reaction time indices and a higher level of mentalizing to provide a more appropriate estimate of mentalizing capacity.

There are a number of limitations to this study, which includes a relatively small sample size (which may have resulted in underpowered analysis and a limited capacity to look at mediating effects of treatment response), a failure to target dmPFC via neuronavigation (which was unfortunately not feasible with this HAUT-coil), and the absence of neuroimaging or neurophysiological outcomes. While diagnosis was applied using DSM-IV criteria, a standardized diagnostic tool was not consistently employed among diagnosing clinicians. The specific area of tissue stimulated also cannot be quantified for each participant. The use of only high-functioning adult participants, while appropriate for an initial study, ensures that generalizability to younger and intellectually disabled individuals with ASD is not clear. The use of only self-report measures might be criticized, but in this instance it was considered appropriate as (a) many participants lived alone and would not necessarily have a third-party to provide a valid assessment, and (b) the perceived benefit to the individual is of utmost importance. The use of third-party ratings scales, however, would be a useful adjunct in future studies. The follow-up period was also relatively short, and it will be necessary to demonstrate that any therapeutic benefits are sufficiently durable. As noted previously, the protocol involved social interaction between participants and experimenters who administered the deep rTMS (and who were therefore not blind to treatment condition). Given that these individuals were broadly aware of the aims of the research, it is possible that this may have added an additional source of bias into the study. Finally, from a safety perspective, rTMS is not recommended for those who have a history of seizure activity. Accordingly, the apparent safety aspects from this study are unlikely to generalize to those with ASD who have a comorbid seizure disorder. This is particularly problematic given the increased rates of epilepsy typically found in autism (although more common in the context of autism and intellectual disability) [16].

Nevertheless, we were able to demonstrate therapeutic effects in a condition that is notoriously difficult to treat, and for individuals (i.e., adults with ASD) who typically have extremely limited access to therapeutic interventions. Furthermore, the rTMS parameters used in this study were deliberately conservative. Given that there is typically a strong dose–response relationship with rTMS [17,18], it will now be critical to examine whether an expanded protocol (e.g., more and longer treatments, higher stimulation intensity) produces enhanced therapeutic effects in this population, but also among younger individuals with ASD and individuals with ASD and intellectual disability.

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