Deep Repetitive Transcranial Magnetic Stimulation Associated With Improved Social Functioning in a Young Woman With an Autism Spectrum Disorder

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Objectives: There are currently no biomedical treatments targeting the core symptoms of autism spectrum disorders (ASDs). Considering evidence for cortical dysfunction in ASD, repetitive transcranial magnetic stimulation (rTMS) has been discussed as a potential therapeutic technique.

Methods: We describe the application of a new type of rTMS, deep rTMS, to the bilateral medial prefrontal cortex in a young woman with a high-functioning ASD. High-frequency rTMS was applied for 15 minutes each consecutive weekday for an 11-day period (9 treatments in total). Self-reported assessments were conducted before the first rTMS session, immediately after the last rTMS session, and 1-month after the last rTMS session.

Results: Self-reported assessments revealed a number of improvements after deep rTMS. These were primarily in the domain of social relating and interpersonal understanding and were corroborated by family members.

Conclusions: Deep rTMS in ASD may serve to remediate aspects of cortical dysfunction (as standard rTMS seems to do in depression and schizophrenia) and provides a potential new avenue for the development of a biomedical treatment of impaired social relating in ASD.

Key Words: autism spectrum disorder, repetitive transcranial magnetic stimulation, theory of mind, social relating, medial prefrontal cortex

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High-functioning autism spectrum disorders (ASDs) are primarily characterized by significant impairments in social relating and interpersonal communication. This includes a lack of emotional reciprocity and a reduced ability to understand other people's mental states.[1] There are currently no biomedical treatments that are available for treating ASD.

Repetitive transcranial magnetic stimulation (rTMS), which involves the administration of magnetic pulses to the scalp that stimulate underlying cortical neurons, can be used to either excite underactive cortical regions (via high-frequency stimulation, typically ≥5 Hz) or inhibit overactive cortical regions (via low-frequency stimulation, typically ≤1 Hz).[2] It has been used with success in the treatment of refractory depression, where stimulation is typically designed to excite the underactive left dorsolateral prefrontal cortex.[3] In high-functioning ASD, functional neuroimaging has revealed that a region within the bilateral medial prefrontal cortex (mPFC) is underactive when performing tasks requiring social relating and the inference of mental states.[4] Standard rTMS coils are only able to stimulate to a depth of 1 to 2 cm, preventing stimulation of deeper cortical structures such as mPFC. A new development in coil technology, however, now allows stimulation of structures further away from the scalp via deep rTMS (Brainsway Ltd, Jerusalem, Israel).[5] The potential therapeutic value of this has not been explored to date. Later, we describe deep rTMS treatment of a young woman with high-functioning ASD.

MATERIALS AND METHODS

Ms D is a 20-year-old woman who had a diagnosis of high-functioning ASD (Asperger disorder) at age 4 years. Her early childhood was characterized by impaired social relating and delays in language acquisition. Cognitive assessment revealed that she was within the mean range of intellectual functioning. She was educated in a mainstream school setting (with part-time integration aide assistance throughout most of her schooling) and is currently pursuing tertiary studies. She lives at home with her mother, father, and 2 younger siblings. Ms D reports no other medical conditions and is not taking any medications. Ms D had previously undergone speech therapy (ages 3–13 years) and occupational therapy (ages 13–18 years) and has undergone psychological intervention from the age of 4 years. She has infrequent consultations with her current psychologist. Current concerns related to Ms D's diagnosis of ASD included difficulties in social interactions (including the establishment and the maintenance of interpersonal relationships) and a risk of social isolation.

As part of her involvement in a double-blind, randomized clinical trial (aimed at improving social relating among adults with ASD), Ms D was administered 15 minutes of high-frequency (5 Hz) deep rTMS at 100% of resting motor threshold (54% of the stimulator's capacity) each consecutive weekday for an 11-day period (9 treatments in total). As noted, unlike standard TMS, deep TMS involves deeper penetration of the magnetic pulse, allowing stimulation of cortical structures that are further away from the scalp. Each session involved 30 10-second rTMS trains, each separated by 20 seconds. Stimulation was administered via a deep rTMS HAUT-coil (Brainsway Ltd) connected to a Magstim Rapid stimulator (Magstim Co, Wales, UK). The anterior edge of the coil was positioned over the bilateral mPFC according to landmark procedures recommended by the coil manufacturer (7 cm anterior to M1). For Ms D, the anterior edge of the helmet in which the coil was embedded was positioned along the midline and 4.5 cm from the nasion.

The treatment was well tolerated, and the participant had no difficulty attending each session. Ms D did not report any

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PF has previously received support for participation in a research study from Neuronetics Ltd and equipment for research from MagVenture A/S. Part of the equipment used to provide deep repetitive transcranial magnetic stimulation was provided to PF by Brainsway Inc (Jerusalem, Israel), a company that develops nonsurgical equipment for deep transcranial magnetic stimulation. AZ has financial interest in Brainsway Inc.

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headaches or discomfort due to muscle contractions, and accordingly, there did not seem to be any factors present that would suggest to her that she was in the active condition. Ms D was assessed using standardized self-reported measures of autism symptoms before the first treatment, immediately after the last treatment, and 1-month after the last treatment (at which point the participant and her family were unblinded to their treatment condition). The measures chosen were the Interpersonal Reactivity Index (IRI),[6] the Autism Spectrum Quotient,[7] and the Ritvo Autism Asperger Diagnostic Scale.[8] These measures were selected for their relevance to autistic symptoms/social relatings and their strong psychometric properties. Importantly, each of these measures can effectively differentiate individuals with ASD from individuals without ASD.[7–9] Both she and her mother were also interviewed approximately 6 months after the treatment; this was not part of the usual study protocol but rather an assessment undertaken on the basis of her positive response at 1-month follow-up.

RESULTS

Self-reported measures administered after the treatment and at 1-month follow-up all revealed a lessening of symptoms and symptom intensity. These are presented in Table 1.

Ms D was interviewed approximately 6 months after the last deep rTMS treatment. She felt that deep rTMS had been associated with a number of improvements to her social functioning. Ms D felt that she could now more easily make eye contact (describing it as "less uncomfortable"), was more aware of other's feeling (eg, recognition of a faux pas and the effect on other people), and was more comfortable in social situations. Ms D stated that social situations had become "more natural" for her, that she "did not have to think so much of what to say," and that she was more aware of instances when she might be making someone uncomfortable. Ms D felt that she was now able to recognize and set social "boundaries." Indeed, Ms D reported that before the treatment, she was more likely to spend time alone because she was worried about saying the wrong thing in the presence of other people but now she is more comfortable interacting with others. Another pronounced change reported by Ms D was greater consideration for, and affection toward, family members. This included displays of physical affection, including hugs. When asked why she was now displaying this behavior, Ms D replied that she "thinks about it more and wants to show physical affection."

Ms D also reported an increased capacity for empathy and perspective taking, even for incidents that had occurred many years before. For example, where she had previously been angry at a school classmate's behavior, she felt that she was now able to understand this behavior and appreciate the classmate's perspective. Ms D said that now she had been feeling sorry for this individual.

These improvements were corroborated by family members, who reported noticing marked changes beginning around 2 weeks after the end of treatment. After the treatment, Ms D's mother described her as more considerate of others (eg, offering her sister food and drinks while the sister was studying, wishing her sister luck before examinations, asking family members how their day had been) and more affectionate (eg, expressing a desire for physical contact including hugs). It was also reported that Ms D made more eye contact, including looking toward the lens when a photo was taken (which previously required several attempts), and had reportedly told her mother that eye contact was "less painful" since the deep rTMS treatment. Ms D's mother indicated that she had displayed an interest in interpersonal relationships and social situations; for example, she had joined a social group and formed new friendships. Overall, Ms D's mother felt that she was more confident, happier, and more tolerant of other people. Extended family members reported that Ms D was more affectionate (eg, expressing a desire to hold hands, inquiring for the first time as to their well-being) and more talkative. Importantly, these were all reported as new behaviors, rather than an increased frequency or intensity of previously displayed behaviors. There was also no suggestion of behavioral regression, with Ms D's mother reporting that Ms D continued to improve.

TABLE 1. Assessment Results Before and After Deep rTMS and 1-Month Follow-Up

	Before Deep rTMS	After Deep rTMS*	1-Month Follow-Up*
IRI†	39	48	49
Autism Spectrum Quotient	28	12	7
Ritvo Autism-Asperger Diagnostic Scale	111	91	84

*For the posttreatment and 1-month follow-up assessments, these measures were administered in relation to the period since the last assessment.

†Unlike the other scales reported, a higher score on the IRI is associated with greater social functioning.

DISCUSSION

This case study demonstrates improvements in social functioning in a young woman with a high-functioning ASD after a 2-week course of high-frequency deep rTMS to the bilateral mPFC. Neuroimaging evidence suggests that this region is underactive in ASD.[4] We speculate that high-frequency stimulation of this region increases cortical excitability and activity within the mPFC and associated neural networks, thereby enhancing an individual's capacity for understanding others' mental states (a fundamental skill for effective social relating). This is an encouraging finding, particularly given that there are no biomedical treatments that target core symptoms of ASD, but one that requires validation via a placebo-controlled, double-blind clinical trial of deep rTMS in ASD, which our group is currently undertaking. At the time of writing, 14 participants have completed the study; although several other participants also seem to have responded to the active treatment (ie, reduction in self-reported clinical symptoms), the participant described in this case study has shown the most pronounced response. Beyond the obvious shortcomings of a case report, an additional limitation was a reliance on only self-reported measures at pretreatment, posttreatment, and 1-month follow-up assessments (although there is a lack of appropriate third-party rating scales for adults with ASD).

It was particularly interesting that a positive response was only noticed 2 weeks after the last treatment. This may simply reveal a delayed response to TMS (which has been reported anecdotally in relation to rTMS depression treatments), the neurophysiological mechanism of which is unclear. Alternatively, it might reflect that a social outcome takes longer to either consolidate or be noticed (ie, requires the participant to be exposed to a range of social environments, which may not occur immediately).

An important consideration that this case has illustrated is the potential need for psychological services after biomedical

intervention in ASD. Because of Ms D's improvements, she is now likely to be exposed to a range of social environments and situations, some of which she may not have previously encountered, and will likely benefit from assistance provided by psychologists in the form of interventions targeting social and emotional functioning.

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