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Repetitive transcranial magnetic stimulation (rTMS) improves movement-related cortical potentials in autism spectrum disorders

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Background
Motor impairments are common in autism spectrum disorders (ASD). Electrophysiologic studies reveal abnormalities in the preparation of movement; repetitive transcranial magnetic stimulation (rTMS) to key motor cortical sites may therefore be a useful technique for improving motor function in ASD.

Objective
To examine whether rTMS can improve electrophysiologic and behavioral indices of motor activity.

Methods
Eleven participants with ASD completed three sessions in which they were administered one of three rTMS conditions (left M1, supplementary motor area [SMA], sham) at 1 Hz for 15 minutes. Movement-related cortical potentials (MRCPs) were assessed before and after rTMS.

Results
rTMS to the SMA was associated with a gradient increase to the early component of MRCPs, whereas rTMS to left M1 produced a stronger gradient in the late component.

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Conclusions
rTMS appears to improve movement-related electrophysiologic activity in ASD, perhaps through an influence on cortical inhibitory processes.

Keywords autism; Asperger's disorder; supplementary motor area; EEG; rTMS

Although autism spectrum disorders (ASD) are diagnosed according to social, behavioral, and (in some cases) communicative impairments, motor dysfunction is a commonly associated feature. For example, DSM-IV-TR[1] notes "abnormalities of posture" in autism, and "motor clumsiness and awkwardness" in Asperger's disorder. These impairments have been further established using experimental paradigms (eg, gait analysis[2,3]), whereas a recent metaanalysis confirms the pervasive nature of motor deficits in ASD.[4] The preparation and initiation of movement appears to be particularly affected.[5-7] Although stereotyped and repetitive behaviors are typically the major motor feature of ASD, in many cases these additional motor impairments add to the social isolation experienced by young people with ASD. This might include, for example, limiting or affecting involvement in sports, recreation, and the usual physical activities of childhood.

Cortical processes associated with the preparation and execution of movement can be probed by examining movement-related cortical potentials (MRCPs), which refers to electroencephalogram (EEG) activity preceding and immediately after voluntary motor activity.[8] Typically, there is a steady rise in EEG negativity beginning 1-2 seconds before movement, with a steeper rise in negativity beginning about 500 milliseconds before movement. This early component is maximal over Cz and thought to reflect preparatory processes associated with the impending movement. The latter, steeper component is referred to as the negative slope; the negative slope, which is maximal over the contralateral primary motor cortex (PMC), appears to correspond to the specific execution of the impending movement (eg, precision, complexity).[8] Additional components of MRCPs include a motor potential immediately before movement initiation, and the postpeak slope (reflecting a positive deflection after movement initiation and return to baseline activity).

Abnormalities in MRCPs have been established in movement disorders such as Parkinson's disease (PD),[9] but more recently in ASD[10,11] where there is evidence for Parkinsonian-like dysfunction; for example, individuals with autism demonstrate a reduced early component gradient and reduced peak amplitude of the subsequent motor potential at electrode site Cz. Although MRCP impairments appear most profound in autism, they are still evident in Asperger's disorder, particularly in relation to the early component. Thus, the supplementary motor area (SMA), which lies beneath electrode site Cz, appears a likely site of dysfunction in ASD. Although not necessarily the major cause of motor impairments in ASD, SMA dysfunction may contribute to difficulties in motor function, particularly those associated with the preparation of movement.

These findings raise the possibility that repetitive transcranial magnetic stimulation (rTMS) of motor cortical regions (including the SMA) could be used to improve motor function in ASD. This is an approach that has previously been used in PD, with sites of stimulation including the PMC and SMA.[12] Results to date have been somewhat inconsistent (eg, rTMS has been found in some studies to worsen movement in PD[13,14]), but generally support the use of both low-frequency (inhibitory) and high-frequency (excitatory) rTMS. For example, low-frequency (1 Hz) rTMS to the SMA in PD has been associated with ameliorated dyskinesia,[15,16] whereas high-frequency rTMS (5-10 Hz) has been associated with improved clinical ratings[17] and improved bradykinesia.[18] For those studies involving stimulation of the PMC, results again support the use of low- and high-frequency rTMS. For example, in a study using both techniques, Lefaucheur et al.[19] found that low-frequency rTMS (0.5 Hz) to the PMC produced improved gait and reduced bilateral upper limb rigidity, whereas high-frequency rTMS (10 Hz) to the PMC was associated with reduced bradykinesia and unilateral (contralateral to stimulation) upper limb rigidity. Beyond PD, low-frequency rTMS to the SMA has been associated with a reduction in clinical symptoms in adults with obsessive compulsive disorder and/or Tourette's syndrome, and normalized cortical hyperexcitability in adults with obsessive compulsive disorder.[20] Among healthy individuals, Rossi et al.[21] demonstrated a reduced negative slope amplitude after low-frequency rTMS (1 Hz) of M1. This was thought to reflect an influence on "cortical inhibitory networks," but interestingly there were no associated behavioral changes. A more recent study of healthy individuals demonstrated that "inhibitory" theta burst TMS can modulate MRCPs; in this study, stimulation of M1 reduced the negative slope amplitude and shortened the duration of the early component.[22] Theta burst stimulation of the premotor cortex has also been found to assist movement preparation,[23] whereas there is evidence to indicate that high-frequency rTMS to the PMC can enhance premovement (ie, preparatory) EEG amplitude in healthy individuals.[24] Thus, there is ample evidence to support the clinical use of rTMS in relation to motor dysfunction, and the use of rTMS to motor cortical sites to affect MRCPs.

Using the MRCP paradigm used by Rinehart et al.,[11] the current study investigated whether low-frequency rTMS can improve motor function in young people with ASD. The rationale for this investigation was that previous EEG

studies of ASD reveal similarities with PD (eg, reduced premovement negativity over SMA), and rTMS has been used successfully in the treatment of motor dysfunction in PD. On the basis of previous findings concerning likely sites of impairment in ASD, and rTMS studies of healthy and clinical populations, it was hypothesized that stimulation of the SMA would be associated with gains in motor function.

Materials and methods

Participants

Participants were 11 individuals with ASD. Six had been diagnosed with high-functioning autism (all male), whereas five had been diagnosed with Asperger's disorder (four male). Participants were aged between 14 and 26 years (mean = 17.55, standard deviation [SD] = 4.06). All were diagnosed by an experienced group of clinicians according to DSM-IV criteria. Diagnostic information was gathered using the revised Autism Diagnostic Interview.[25] This involved structured interviews with parents, direct observation of the young person's behavior and interactions, and information from external sources (eg, teachers). Participants were screened according to TMS safety guidelines (ie, no history of seizures or serious head injury, no metal in head[26]), and excluded on the basis of comorbid psychiatric or neurologic disorder (including epilepsy). All adult participants (18+ years) provided informed consent, whereas a parent provided informed consent for child participants. This project was approved by the human research ethics committees of Monash University, Southern Health, and the Alfred, and conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007) (National Health and Medical Research Council, Australia) and the Declaration of Helsinki.

Design

This was a within-subjects study in which participants completed three separate sessions that were 1 week apart. In each session, rTMS was administered at 100% of resting motor threshold (RMT) at 1 Hz for 15 minutes (900 pulses). There were three rTMS conditions: stimulation of the left PMC (defined as the site that produces a maximal EMG response in the contralateral abductor pollicis brevis muscle), stimulation of the SMA (defined as the site 15% of the distance between nasion and inion anterior to Cz[20]), and sham stimulation of the left PMC (TMS coil placed against the scalp but angled 45% away from scalp, a commonly used sham procedure). Although the use of 100% RMT stimulation introduces an element of variability across the three conditions (ie, stimulation of the PMC will likely produce a discernable muscle twitch with each pulse, whereas the other two will have no effect on peripheral muscle), threshold (rather than subthreshold) stimulation was chosen as it is more reliably associated with changes to cortical excitability,[27] and therefore maximizes the chances of detecting an effect. The use of 900 pulses was also based on previous literature concerning significant effects of 1 Hz rTMS. The order of rTMS conditions was randomized across participants. Several measures of motor function were administered pre- and post-rTMS in each session, and these are described below. Each session was identical, except for the site of rTMS.

Dependent measures

Movement-related cortical potentials

MRCPs were recorded while participants performed an externally cued, right-handed sequential button-pressing task (identical to that described in ref. 11). This involved a pathway of 12 illuminated (red light-emitting diode [LED]) buttons embedded within a wooden board; moving from right to left, participants were required to use their index finger to hold down each button until it extinguished (4 seconds after extinction of the previous LED in the sequence), and then move to depress the next button in the sequence as quickly as possible. To ensure generation of the early component, participants were instructed to internally time the duration of each LED, and to anticipate each movement (thus introducing an internally driven, voluntary component to the task). They were also instructed to keep the rest of their body as still as possible (including mouth/facial muscles), and were reminded of this requirement any time the experimenters noticed any such movement. Once participants reached the end of the sequence, they were instructed to return to the beginning and start again.

EEG recordings were acquired using a Synamps[2] EEG system (Compumedics Neuroscan, Charlotte, NC). Single Ag/AgCl surface electrodes were used to record activity at Cz, as determined by the international 10-20 system of electrode placement. EEG was recorded in DC at a sampling rate of 1000 Hz. Impedance was kept below 5 kΩ. Each participant completed at least 100 sweeps (ie, button depressions/movements) on the tapping board while EEG was recorded. A trigger was sent to the EEG recording on release of each button (indicating movement initiation).

EEG recordings were processed offline. Data were low pass filtered at 30 Hz, and artefact rejection was applied to data ± 50 μV. This was intended to ensure exclusion of those trials contaminated by ocularmotor activity. Data were then epoched from −3000 to 1000 milliseconds (ie, 3000 milliseconds before movement to 1000 milliseconds after movement), averaged across all accepted trials, and baseline corrected according to the average of the period −3000 to −2000 milliseconds.

The following five variables were extracted from the MRCPs: early component (gradient of the period −2000 to

−500 milliseconds), negative slope (gradient of the period −500 to −200 milliseconds), peak amplitude (maximal μV amplitude from −100 to 100 milliseconds), peak time (millisecond time from the beginning of the epoch at which peak amplitude occurred, with movement occurring at 3000 milliseconds), and postpeak slope (gradient of the 300 milliseconds period after peak time).

Cortical excitability

Motor-evoked potentials (MEPs) after suprathreshold (115% RMT) single-pulse TMS to left M1 were recorded from the right abductor pollicis brevis muscle. Ten pulses were administered at an interstimulus interval of 4 seconds. EMG signals were amplified and filtered (bandpass 10 Hz-2 kHz), and recorded using PowerLab/4SP (AD instruments, Colorado Springs, CO).

Reaction time and movement time

Behavioral data were collected for the button task used to generate MRCPs. This consisted of downtime (ie, total length of time [millisecond] buttons were depressed during an entire sequence), which corresponds to a measure of reaction time (ie, response after LED extinction), and movement time (ie, total length of time taken to move from one button to the next during an entire sequence).

Procedure

Participants were seated in a comfortable recliner chair. Disposable adhesive snap electrodes were attached to their right hand to measure abductor pollicis brevis EMG activity. Single-pulse TMS was then administered to the left PMC to determine the site of M1 (ie, site at which MEPs to TMS are maximal) and the RMT (ie, lowest stimulation intensity at M1 that produces an MEP of at least 50 μV in three of five consecutive trials). Measures of cortical excitability (ie, MEPs) were then recorded.

Before the button board task, surface electrodes were placed at Cz (according to 10-20 system of electrode placement), the left mastoid (reference), and the forehead (ground) to record EEG activity. Participants then completed the button board task (which took approximately 8-10 minutes to complete) while EEG was recorded.

rTMS was then administered via a Magstim-200 stimulator (Magstim Company Ltd, Whitland, Carmarthenshire, Wales) and using a hand-held, 70 mm figure-of-eight coil that was positioned over the scalp. During left PMC stimulation and sham stimulation the coil handle was oriented 45° away from the midsagittal plane, whereas during SMA stimulation, the coil handle was oriented along the midsagittal plane.

Immediately after rTMS, the participant was again administered TMS measures of cortical excitability, followed by the completion of the button board task while EEG was recorded.

Data analysis

The 2 (time: pre versus post) × 3 (rTMS: PMC versus SMA versus sham) repeated measures analysis of variances (ANOVAs) were used to determine whether there was an effect of rTMS condition for each of the dependent measures (MRCP variables, MEPs, movement time, and downtime). Follow-up one-way repeated measures ANOVAs (comparing pre and post) were performed for each condition where interaction effects were significant ($P < .05$) or indicated a trend ($P < .10$).

Results

MRCPs

Results are presented in Figure 1. There was a significant interaction effect between time and rTMS on the early component gradient, $F(2,20) = 6.06$, $P = .009$. Subsequent analyses revealed a significant increase in early component gradient (ie, more positive gradient) after stimulation of the SMA, $F(1,10) = 5.98$, $P = .034$, but no change after PMC stimulation, $F(1,10) = 3.21$, $P = .103$. Early component gradient, by contrast, was significantly reduced (ie, less positive gradient) after sham stimulation, $F(1,10) = 5.88$, $P = .036$.

The interaction between time and rTMS on negative slope gradient failed to reach significance, $F(2,20) = 3.21$, $P = .062$. Follow-up comparisons, however, revealed a significant increase in negative slope gradient (ie, more positive gradient) after PMC stimulation, $F(1,10) = 6.13$, $P = .033$, but no difference after SMA stimulation, $F(1,10) = 0.44$, $P = .524$ or sham stimulation, $F(1,10) = 0.43$, $P = .526$.

There was no interaction effect for peak amplitude, $F(2,20) = 1.28$, $P = .300$, peak time, $F(2,20) = 0.96$, $P = .402$, or postpeak slope, $F(2,20) = 1.76$, $P = .197$.

Cortical excitability

Results are presented in Figure 1. The interaction effect between time and rTMS on MEP amplitude failed to reach significance, $F(2,20) = 3.27$, $P = .059$. Follow-up analyses also revealed nonsignificant differences between pre and post on each of the rTMS conditions.

Response time and movement time

Results are presented in Figure 2. There was no significant interaction between time and rTMS for either down time, $F(2,20) = 0.19$, $P = .827$, or movement time, $F(2,20) = 2.74$, $P = .089$. Follow-up analyses revealed a significant reduction in movement time after sham stimulation, $F(1,10) = 6.14$, $P = .033$.

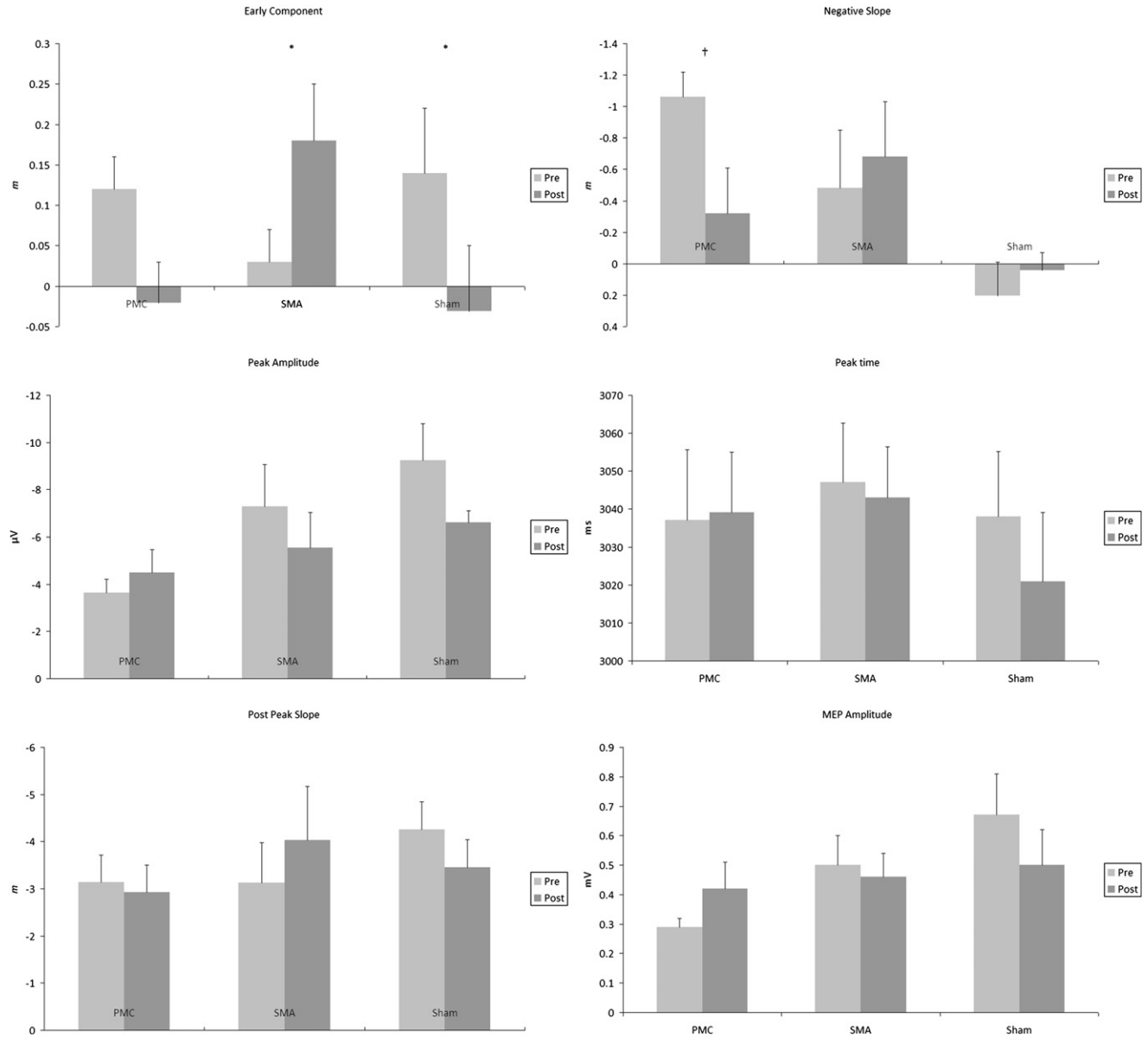

Figure 1 Results pre- and post-rTMS (PMC, SMA, Sham) for the EEG and EMG measures (+ standard error [SE]) (*$P < .05$, †$P < .07$).

Discussion

Low-frequency rTMS was associated with improvements to components of MRCPs in ASD. Specifically, stimulation of the SMA resulted in an improved gradient of the early component, which is thought to reflect neural processes associated with the preparation of movement (with an increased gradient suggesting enhanced preparatory activity at that site[8]). Unexpectedly, early component gradient was reduced after sham stimulation. Stimulation of the PMC was associated with an improved gradient of the late component of MRCPs (ie, negative slope), which immediately precedes motor activity and appears to relate to the execution of movement. By contrast, rTMS had no impact on motor cortical excitability, nor did it result in any discernable behavioral change (ie, downtime, movement time).

Cortical abnormalities related to motor processes in ASD are reasonably well established, and these findings provide initial support for the use of rTMS in improving electrophysiologic correlates of motor function in ASD. They are also somewhat consistent with the use of low-frequency rTMS in PD, a movement disorder that, from both clinical and neurophysiologic perspectives, appears to share motor features with ASD.[28-30] Low-frequency rTMS to SMA in PD has been associated with reduced bradykinesia,[15,16] which may relate to the initiation of movement and premovement electrophysiologic measures in the current

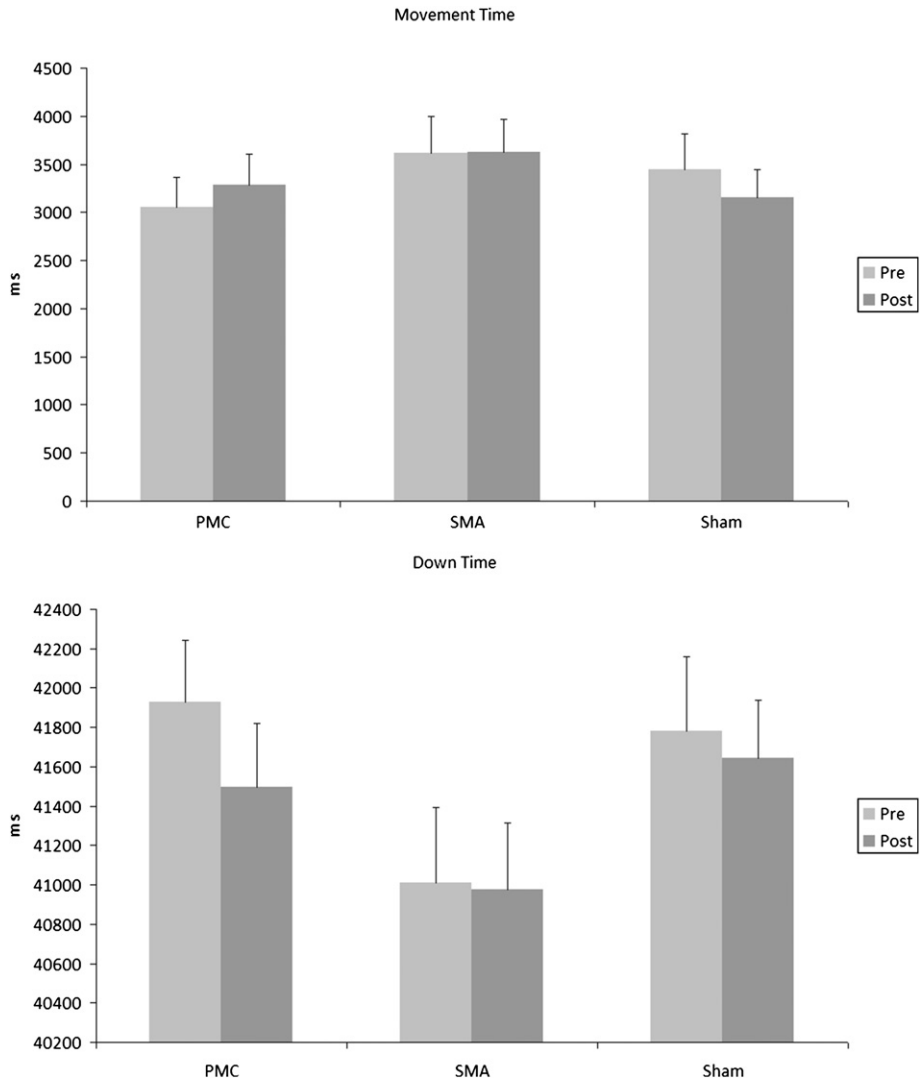

Figure 2 Results pre-and post-rTMS (PMC, SMA, Sham) for the button board behavioral measures (+ standard error [SE]).

study. A clearer characterization of the specific motor impairments in ASD, however, will be required before we are able to determine the extent of overlap in motor-related neurology (and effects of rTMS) in ASD and PD. In relation to MRCPs, the obtained pattern of results is in accordance with the literature concerning premovement neural activity. The early component of MRCPs is thought to be influenced by cognitive processes related to the preparation of the movement, which are recorded maximally over the SMA, whereas the negative slope appears to be associated with features of the actual movement, and primarily reflects PMC activity.[8] It is therefore not unexpected that stimulation of the SMA, an area closely linked to movement preparation, would result in improvements in the early component, whereas stimulation of the PMC, which is involved the execution and performance of that movement, would result in improvements in negative slope. Although a reduction in the early component gradient was seen after sham stimulation (coupled with a nonsignificant reduction after PMC stimulation), this could reflect practice effects that are known to affect the early component (eg, intention, level of preparation required).[8] That is, SMA stimulation may have prevented the typical deterioration that is seen in the early component measure after repeated exposure to the task within a short period. Sham stimulation also appeared to improve movement time, which was unexpected and will require further investigation.

That low-frequency rTMS should improve neurophysiologic recordings of motor function may reveal more specific information about the brain basis of motor impairments in ASD. As mentioned, low-frequency rTMS to motor regions among healthy adults disrupts MRCPs, presumably through its effect on cortical inhibitory processes.[21] This pattern of findings suggests that reduced cortical inhibition, and perhaps abnormal subcortical (GABAergic) inhibitory projections from the thalamus and basal ganglia, contributes to the clinically significant motor impairments seen in ASD. These findings might even suggest motor cortical hyperexcitability in

ASD. Indeed, this is not the first study to report beneficial effects of low-frequency rTMS in ASD. Sokhadze et al.[31] reported improvement on EEG measures of visual processing in autism after six sessions of subthreshold, low-frequency (0.5 Hz) rTMS to the left dorsolateral prefrontal cortex. This was attributed to improvements in cortical inhibitory deficits in autism that are thought to stem from cytoarchitectural abnormalities ("minicolumn" abnormalities involving a reduction in cortical inhibitory interneurons[32,33]), which would presumably also affect motor cortical sites. Other authors have suggested that autism involves disruption of the brain's excitation/inhibition balance (ie, reduced inhibition and/or increased excitatory processes[34]), and it is therefore conceivable that low-frequency rTMS, by reducing cortical excitability, may contribute toward partially redressing this imbalance. Interestingly, functional magnetic resonance imaging (fMRI) reveals greater SMA activation in autism during motor activity,[35] which might reflect reduced cortical inhibition that disrupts regulatory motor processes. Nevertheless, the specific neurophysiologic effects of low-frequency rTMS (ie, inhibitory versus excitatory) have not been conclusively established, and discussion of these mechanisms should be considered speculative.

These findings, although encouraging, are preliminary and should be interpreted with caution. Although improvements were seen in MRCPs, there is no evidence to suggest that rTMS was able to restore premovement electrophysiologic activity to within neurotypical limits. Although the gradient of the early component was increased after SMA stimulation, the mean value is still well below that reported previously among healthy individuals.[10,11] This was also true for the negative slope after PMC stimulation, which generally only seems to be less impaired rather than restored. Individuals with ASD demonstrate profound impairments in these measures, and although the effects of rTMS appear positive there is still much improvement required to be comparable with healthy individuals. In addition, despite the capacity of rTMS to favorably modulate MRCPs in ASD, there was no effect on motor cortical excitability or behavioral measures. The behavioral measures were relatively crude indices of reaction time and movement time, and may not be sensitive enough to detect any form of functional change after rTMS. Alternatively, the electrophysiologic changes induced by rTMS in the current paradigm may not be sufficient to generate a functional outcome. It should be noted, however, that a failure to detect a behavioral change despite electrophysiologic modulation has also been found among healthy adults.[21] A failure to detect change in cortical excitability, however, was somewhat unexpected, particularly after stimulation of the PMC. Typically, low-frequency rTMS results in a reduction in cortical excitability.[36] The effect of low-frequency stimulation on cortical excitability, however, is intensity dependent, and lower intensities have generally been insufficient to produce this effect.[27] In the current study, stimulation at 100% RMT, or the number of pulses given, may have been inadequate to significantly alter cortical excitability. Alternatively, it might also reflect that significant cortical inhibition cannot be induced in ASD because of the substantial GABAergic deficits (for which there is an emerging literature[37-39]) or simply relate to our limited statistical power. Despite the fact that rTMS in this study resulted in only a partial correction of MRCP deficits, it is encouraging as these improvements were produced with only a single session of stimulation and longer treatment courses may produce greater and more clinically relevant effects.

Limitations to this study include a single EEG recording site (which was intended to reduce the length of time required for the participants) and a small sample size with a relatively large age range. Although it can be very challenging to recruit young people with pervasive developmental disorders for a study such as this, the small sample size raises the possibility of underpowered analyses. A later follow-up assessment would have provided crucial information concerning the lasting effects (if any) of stimulation, whereas MRI-guided localization would be a useful addition in determining the site of stimulation for the SMA. Related to this, although we expect that electrode Cz reflects SMA activity, there may also be contributions from more anterior prefrontal cortical regions. Furthermore, despite a clinical need for improving motor function in ASD, as noted the demonstrated EEG improvements were not associated with functional improvements. It therefore remains to be seen whether rTMS in these populations is sufficient to generate changes that will result in functional improvements and, most importantly, enhanced quality of life. On the basis of the current data, a useful future approach might involve multiple sessions of rTMS, perhaps combining PMC and SMA stimulation (given that we found each improved a different aspect of MRCPs), higher stimulation intensities, and more sensitive outcome measures of motor function (both clinical and experimental). This could include standardized clinical measures together with more sophisticated techniques such as three-dimensional gait analysis and movement-related fMRI.

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