BRIEF REPORT

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The Early Start Denver Model Intervention and Mu Rhythm Attenuation in Autism Spectrum Disorders

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Abstract

We examined the relationship between the Early start Denver model (ESDM) intervention and mu rhythm attenuation, an EEG paradigm reflecting neural processes associated with action perception and social information processing. Children were assigned to either receive comprehensive ESDM intervention for two years, or were encouraged to pursue resources in the community. Two years after intervention, EEG was collected during the execution and observation of grasping actions performed by familiar and unfamiliar agents. The ESDM group showed significantly greater attenuation when viewing a parent or caregiver executing a grasping action, compared with an unfamiliar individual executing the same action. Our findings suggest that the ESDM may have a unique impact on neural circuitry underlying social cognition and familiarity.

Keywords Mu rhythm · Autism spectrum disorders · Early start denver model · EEG

Introduction

The attenuation of the mu rhythm in the human brain has been demonstrated during the observation and execution of motor actions, and has been characterized as an observationexecution matching system (Muthukumaraswamy & Johnson, 2004) Mu attenuation is theorized to play an integral role in action interpretation along with more advanced elements of social cognition (for review, see Kilner & Lemon, 2013; Rizzolatti & Craighero, 2004). There has been significant interest spanning over two decades in this neural system, including multi-modal experimental investigations and complex theoretical models (Heyes & Catmur, 2020). While there has been some concerns expressed regarding

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the interpretation of the EEG mu rhythm in particular (Coll et al., 2017; Hobson & Bishop, 2016, 2017), others have continued to defend it as useful index of neural activity (Bowman et al., 2017; Vanderwert et al., 2013).

Oberman and colleagues (2005) investigated mu attenuation in a sample of individuals ages 6-47 (mean age = 16.6) with a clinical diagnosis of ASD and corresponding sample of age and gender-matched controls. They found that although the ASD group displayed mu attenuation during the execution of motor actions, mu attenuation was not exhibited during the observation of motor actions (Oberman et al., 2005). Later studies replicated this finding (Bernier et al., 2007; Martineau et al., 2008) and demonstrated a correlation between mu attenuation and imitation ability in a sample of adults (mean age = 25.15) with ASD (Bernier et al., 2007). Further studies failed to show differences between diagnostic groups (Fan et al., 2010; Raymaekers et al., 2009), although a subsequent study in children (mean age = 6.65) demonstrated that mu attenuation correlated with imitation ability, independent of diagnosis (Bernier et al., 2013), noting that since imitation deficits are commonly associated with ASD but are not part of the diagnostic criteria, ASD groups may inconsistently demonstrate mu attenuation depending on imitation and social cognitive abilities. Other studies have not supported a correlation with imitation abilities (Fan et al., 2010; Ruysschaert et al., 2014),

though imitation was assessed through various and potentially less rigorous methods (for a critical review, see Hobson & Bishop, 2017). A review of 4 EEG studies found a significant relationship between mu attenuation and age, irrespective of diagnosis (Oberman et al., 2013).

Familiarity may be a significant factor in modulating neural functioning. For example, face processing differences have been well documented in ASD (Dawson et al., 2005; McPartland et al., 2004; Pierce, 2001; Schultz et al., 2000; for review see Campatelli et al., 2013). However, familiarity with the face seems to alleviate the observed differences (Pierce & Redcay, 2008; Pierce et al., 2004). Similar results were found using eye-tracking to observe differential gaze patterns (Gillespie-Smith et al., 2014). Familiarity and attentional engagement have also been shown to modulate ERPs to faces (Dawson et al., 2002).

Oberman and colleagues (2008) examined mu attenuation in children ages 8-12 (mean age = 10.23) with ASD in response to the observation of familiar and unfamiliar actors. They found that the children with ASD showed greater activation in response to the observation of familiar actors compared with unfamiliar actors (Oberman et al., 2008). However, in this paradigm, the unfamiliar condition contained only a video of a hand without a person visible in the screen, whereas the familiar condition contained both the familiar individual and hand. This requires an inference as to the presence of an unfamiliar person. Given documented deficits in holistic processing in ASD (Behrmann et al., 2006; Dawson et al., 2005; Nakahachi et al., 2008), this may have influenced the lack of attenuation to the unfamiliar condition in the ASD group (Oberman et al., 2008). It is also not clear whether the familiarity effect is evident in younger individuals with ASD or whether it may be enhanced through interventions that promote social learning and development.

The early start Denver model (ESDM; Dawson et al.,2010, 2012), a naturalistic developmental behavioral intervention (Schreibman et al., 2015), focuses on building foundational cognitive, social, communication, motor, and adaptive skills, using evidence-based teaching practices. It incorporates principles of applied behavior analysis and developmental science to inform a developmental curriculum that targets goals across key domains. Caregivers receive training in basic ESDM strategies facilitating implementation across environments. There is a specific emphasis on facilitating caregiver-child engagement and interaction, with a focus on foundational social affective processes. A randomized-control trial examining the efficacy of the ESDM demonstrated significant gains in IQ, language development, social, and adaptive skills (Dawson et al., 2010) and these gains were generally maintained 2 years after treatment ended (Estes et al., 2015). There have since been further extensions (Rogers et al., 2019a) and replications (Rogers et al., 2019b) examining the clinical impact of ESDM.

In a follow-up study of this ESDM sample, changes in brain activity attributed to ESDM intervention were identified (Dawson et al., 2012). EEG activity (event-related potentials and spectral power) was measured during the presentation of faces versus objects. The ESDM group and chronological-age-matched typical children showed a shorter Nc latency and increased cortical activation (decreased alpha power and increased theta power) when viewing faces, whereas the community group showed the opposite pattern (shorter latency event-related potential and greater cortical activation when viewing objects). Greater cortical activation while viewing faces was associated with improved social behavior (Dawson et al., 2012). Additional studies have shown changes in brain activity in response to pivotal response treatment using fMRI. A study examining the effects of 4 months of pivotal response treatment indicated greater activation in the right posterior superior temporal sulcus, fusiform gyrus, dorsolateral and ventrolateral prefrontal cortex, key brain areas related to biological motion (Voos et al., 2013). A further study of pivotal response treatment demonstrated reduced activation in thalamus, amygdala, and hippocampus post treatment in a group that displayed hyperactivation at baseline, and increased activation in the ventral striatum and putamen in a group that displayed hypoactivation at baseline (Ventola et al., 2015).

Given ESDM's presumptive impact on IQ, language development, and adaptive skills, with a focus on foundational social affective processes, mu attenuation may be an appropriate marker of treatment change given its role as an index of neural activity related social cognition.

Purpose and Hypotheses

Our primary aim was to investigate the relationship between ESDM intervention and neural activity underlying social cognitive abilities, as assessed by EEG mu attenuation. The current study capitalizes on the rigorous design of the ESDM intervention study (Dawson et al., 2010), and applies a carefully defined and established social neuroscience paradigm of mu rhythm attenuation. Given the evidence that ESDM impacts neural functioning (Dawson et al., 2012), that the intervention targets social cognitive behaviors such as imitation (Dawson et al., 2010; Rogers et al., 2012), and that mu attenuation is linked to imitation ability (Bernier et al., 2007, 2013), we hypothesized greater mu attenuation in response to the observation of motor actions would be found in the ESDM group as compared with the community group. A further aim was to examine the impact of familiarity on this neural index. We hypothesized that greater mu attenuation would be observed across both groups in response to viewing familiar actors compared with unfamiliar actors.

Methods

All procedures were reviewed and approved by our Institutional review board (IRB).

Participants

Participants were recruited from the original 48 participants in the ESDM randomized controlled trial (Dawson et al., 2010). As described in that trial, forty-eight children between 18 and 30 months with a documented diagnosis of an autism spectrum disorder were randomized into two groups using a stratified randomization procedure based on gender and IQ. The intervention (ESDM) group received two years of comprehensive behavioral intervention by trained ESDM therapists in children's homes for 15.2 h per week. The community (COM) control group received regular assessment and monitoring and was encouraged to pursue services available in the community. Measures of IQ, ASD symptoms, adaptive behavior, and repetitive behavior were collected at one-year post-entry and two years post-entry into the study by clinicians who were blind to subject status. These findings have been previously reported (Dawson et al., 2010).

In the current study, participants were recruited to participate in a follow-up study when the children were 6 years of age, approximately 2 years post-experimental intervention. Of the original sample, 39 children participated in the follow-up study. Clinicians who were naive to intervention group status collected measures of IQ (Differential Abilities Scales), adaptive behavior (Vineland Adaptive Behavior Scales), and ASD symptoms using the Autism diagnostic observation schedule (ADOS; Lord et al., 2000). These results have also been previously reported (Estes et al., 2015).

Of the 39 children who participated at the 6-year old time point, 27 participants agreed to participate in the EEG assessment within 4 weeks of their 6th birthday. Twenty participants (10 ESDM, 10 COM group) completed the EEG assessment successfully and produced usable EEG data. Seven participants did not produce usable data. In the ESDM group, 3 did not produce artifact free rest data, and 1 did not complete the paradigm. In the COM group, 1 did not produce artifact free rest data, and 2 did not complete the paradigm. The group of 20 that participated in the EEG demonstrated higher IQ than the 19 that did not participate in the EEG t(37) = 3.60, p < 0.05. This is consistent with other ASD imaging research, which often features children with higher IQ due to the constraints of participation. The intervention and community groups that participated in the EEG did not differ significantly in age, gender, verbal IQ, nonverbal IQ, adaptive behavior, or autism symptoms. Results of these comparisons are listed in Table 1. Thus the EEG assessment was conducted on well-matched groups.

EEG Assessment

Brain activity was recorded at rest and during the observation and execution of motor actions using a 128-electrode EEG system (Electrical Geodesics, Eugene OR). The electrical brain activity was analog filtered (01. Hz high-pass, 100 Hz elliptical low-pass), amplified, and digitized at 500 samples per second. Impedances were below 50 k Ω with signals referenced to the vertex at acquisition. EEG and video were recorded simultaneously using NetStation 4.3. This allows for subsequent video inspection of the session to ensure the participant was attending to the presented stimuli,

ESDM COM Measures t р n = 10n = 10М (SD)М (SD)IQ Verbal IQ 103.80 97.00 1.08 .297 (10.36)(17.11)Non-verbal IO 98.80 96.70 0.44 (11.67)(9.63).666 GCA 101.80 (11.48)94.30 (15.17)1.24 .232 Vineland ABC 86.25 (10.91)79.00 (12.01)1.30 .214 Socialization 84.88 (13.29)76.78 (10.85)1.38 .187 Autism symptoms ADOS - CSS 5.20 (2.53)7.20 (3.19)- 1.55 .138

GCA general conceptual ability, ABC adaptive behavior composite, ADOS CSS autism diagnostic observation schedule - calibrated severity score

*p < .05 when adjusted for multiple comparisons using Bonferroni (controlling familywise by construct). Observed unadjusted *p*-values also given

Table 1 Comparison of
measures collected at age
six: ESDM and community
subsamples with EEG data

and assists with identifying eye blink and other movement artifacts.

EEG Paradigm

The paradigm included an observe condition, an execute condition, and a rest condition to evaluate baseline activity, adapted from an established procedure designed to assess mu attenuation via EEG (Muthukumaraswamy & Johnson, 2004). In the observe condition, participants watched a 6-s clip on a video monitor displaying a person grasping a block of wood. Within the observe condition, participants observed videos of their parent or guardian conducting a grasping motion, as well as an unfamiliar person executing the same grasping motion. This allowed for the examination of potential differential brain responses to the observation of actions performed by familiar versus unfamiliar actors. A photocell installed on the video monitor allowed the EEG recording to be time-locked to the display of the grasping motion. In the execute condition, participants grasped a block of wood identical to the one displayed in the video clip. A sensor on the block of wood allowed the EEG recording to be time-locked to the participant's grasping motion. In the rest condition, participants sat with eyes opened and watched a plus sign on the monitor.

The blocks proceeded as follows: Unfamiliar Observe (10 trials), Familiar Observe (10 trials), Execute (10 trials), Rest (30 s), Unfamiliar Observe (10 trials), Familiar Observe (10 trials), Execute (10 trials), Rest (30 s). Block order was counterbalanced for familiarity to eliminate order effects.

EEG Analysis

While signals are referenced to the vertex at acquisition, signals were re-referenced to an average reference offline. Artifact detection was conducted using an automated algorithm in NetStation 4.3 to remove eye-blinks and movement artifacts, defined as and fast average amplitudes exceeding 200 μ Vs, differential average amplitudes exceeding 100 µVs, and zero variance across trials. Manual video inspection using NetStation 4.3 ensured subjects were attending to the stimuli, and further visual inspection of each trial to eliminate eye-blinks was conducted, identifying any large power changes across frontal electrodes in the 1-4 Hz band. Matlab was also used to identify trials with movement artifacts indicated by large power fluctuations within a trial to be excluded from analysis. The rejection rate did not differ across groups, with an average rejection rate of 53.38% (intervention 52.50%, community 54.25%).

Following procedures outlined by Muthukumaraswamy and colleagues (2004), a group of eight electrodes in each hemisphere surrounding the standardized positions for C3 and C4 respectively were selected for analysis. A photocell

was used to identify the culmination of the grasping motion during the observe condition, and 1 s of data preceding and succeeding the grasp was selected for analysis. The output from each condition was divided into 2-s epochs and a fast Fourier transform (FFT) was performed. Similar to previously described methods focused on the mu (8-13 Hz) range (Babiloni et al., 1999; Muthukumaraswamy et al., 2004; Muthukumaraswamy & Johnson, 2004; Pfurtscheller et al., 1997), individual spectral plots were generated for each subject, and the Hz band yielding the maximum difference in power between the execute condition and rest condition was selected as the subject's specific Hz band, instead of averaging across the entire range (Coll et al., 2017; Marshall & Meltzoff, 2011; Wang et al., 2012). The mean identified peak frequency was 8.55 (SD = 1.26) for the ESDM group and for the COM group was 8.00 (SD = 0.913). The mean did not differ across groups t(18) = 1.21, p = 0.28. Power was averaged across trials within conditions and across blocks, and these values were then exported to Matlab in order to provide a single numerical value representing the average power for a given condition.

This paradigm yields a score representing a scale-dependent variable of mu attenuation. This was calculated by computing the log of the ratio between the observe and rest condition. The dependent variables of interest are the log of the ratio of the observe-familiar over the rest condition, and the log of the ratio of the observe-unfamiliar over the rest condition. This yields a single numerical value representing mu attenuation for a given subject in a given condition, which can be compared across conditions and across subjects.

Results

An examination of studentized residuals revealed no outliers $(>\pm 3)$. Shapiro–Wilk's test (p > 0.05) and visual inspection of Q-Q Plot indicated the data was normally distributed. Levene's test showed homogeneity of variance (p > 0.05) and Box's test of equality of covariance matrices showed homogeneity of covariances (p=0.750). *t*-Tests revealed no significant differences in overall power between groups during the observe familiar t(18)=0.38, p > 0.05, observe unfamiliar t(18)=.96, p > 0.05, and rest t(18)=1.42, p > 0.05 conditions, indicating consistent recording and analysis across groups. Values by individual subject are represented in Fig. 1 and listed in Table 2.

A two-way repeated measures ANOVA was computed to examine main effects of group and familiarity on mu attenuation, as well as the interaction between the two. As shown in Fig. 2, results indicated no main effect for group $(F(1,19) = 1.23, p > 0.05, \text{ partial } \eta^2 = 0.000)$ and no significant difference between mu attenuation to familiar and unfamiliar actions within subjects, F(1,18) = 2.35, p > 0.05,

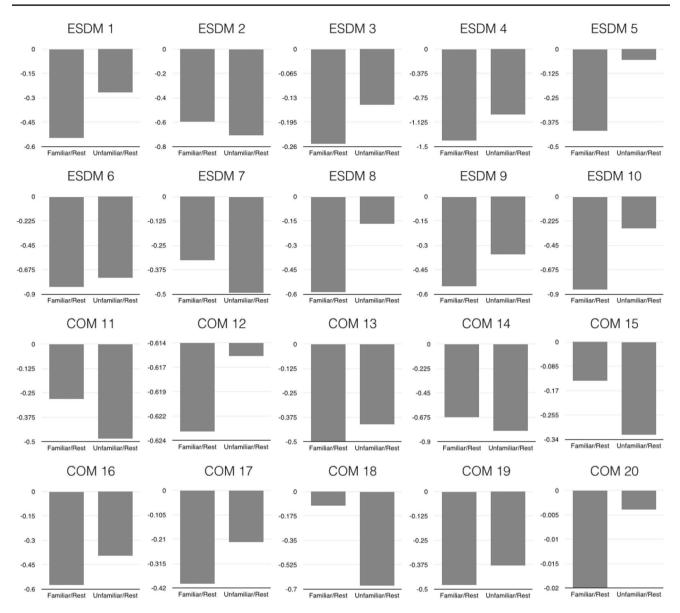


Fig. 1 Attenuation of mu rhythm in response the observation of a motor action, by individual subject, divided by familiar or unfamiliar actor over rest condition

partial $\eta^2 = 0.115$. However, there was a significant familiarity by group interaction, F(1,18) = 6.405, p < 0.05, partial $\eta^2 = 0.262$, with the intervention group showing significantly greater mu attenuation during familiar observation (Fig. 2).

Correlational analyses of mu attenuation with measures of Global conceptual ability (GCA) as assessed by the Differential abilities scale II (DAS-II; Elliot, 2007), hand and face imitation as assessed by the Mature Imitation Task (Rogers et al., 2005), and autism symptoms based on the ADOS (Lord et al., 2000) calibrated severity score are displayed in Table 3. There was no significant correlation between mu attenuation and global conceptual ability, hand or face imitation, or autism symptom severity (Table 3).

Discussion

The primary aim of this study was to further examine neural functioning in young children with ASD who received intensive early comprehensive intervention based on the ESDM or services in the community. We found that mu attenuation during the observation of grasping actions did not differ between the intervention (ESDM) and community (COM) groups, as both groups displayed attenuation to the observation of motor actions. However, there was a significant group by treatment interaction in which mu attenuation was greater within the ESDM group when viewing a parent or caregiver versus an unfamiliar individual executing identical actions.

Table 2Attenuation of mu rhythm values in response the observa-tion of a motor action, by individual subject, the log transform of thefamiliar or unfamiliar condition over rest condition

	Fam/Rest	Unfam/Rest	
ESDM 1	- 0.545344	- 0.267628	
ESDM 2	- 0.595952	- 0.706332	
ESDM 3	- 0.25255	- 0.1491	
ESDM 4	- 1.40263	- 1.006261	
ESDM 5	- 0.41936	- 0.056478	
ESDM 6	- 0.833425	- 0.747447	
ESDM 7	- 0.325708	- 0.492652	
ESDM 8	- 0.587256	- 0.169914	
ESDM 9	- 0.550415	- 0.356417	
ESDM 10	- 0.85611	- 0.292363	
COM 11	- 0.281792	- 0.483899	
COM 12	- 0.623051	- 0.61536	
COM 13	- 0.499026	- 0.412485	
COM 14	- 0.673415	- 0.802769	
COM 15	- 0.135408	- 0.324267	
COM 16	- 0.576126	- 0.394285	
COM 17	- 0.402416	- 0.221742	
COM 18	- 0.100604	- 0.676819	
COM 19	- 0.480141	- 0.378821	
COM 20	- 0.019974	- 0.003919	

The COM group showed no difference in mu attenuation when viewing familiar versus unfamiliar individuals. Our findings suggest a potential relationship between the ESDM and neural development in a carefully designed paradigm. Our study provides evidence indicating a potential effect of the ESDM on neural activity underlying social-cognitive processes.

Overall, the presence of a familiarity effect is consistent with existing literature. Our findings may indicate unique neural responsiveness to familiarity. Previous research has demonstrated sensitivity within neural circuitry associated with social cognition to context (Iacoboni, 1999), intention (Iacoboni et al., 2005), and even experience with the action being performed (Calvo-Merino et al., 2006). However, the observed difference may also be the result of modulation from other brain regions sensitive to familiarity (Perkins et al., 2010). With connections to the limbic system (Carr et al., 2003), empathy and emotional valence may influence neural activation, as well as attentional, perceptual, and motivational factors. For example, the anterior cingulate cortex has been implicated in both personal familiarity (Donix et al., 2010; Shah et al., 2001) and vicarious responses to pain (Morrison et al., 2004), supporting the notion of multiple systems involved in human action perception (Filimon et al., 2007). The differential response observed may be

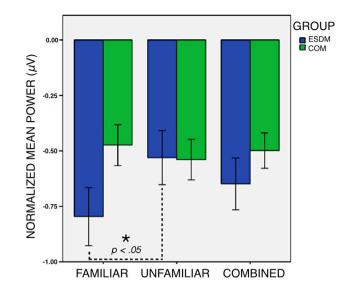


Fig. 2 Attenuation of mu rhythm in response the observation of a motor action executed by a familiar actor, unfamiliar actor, and both combined. The ESDM group showed significantly greater attenuation in response to a familiar actor

specific to the circuitry of the execution-observation matching system, or a system to connected to this network.

Our results are consistent with the possibility that specific features of the ESDM intervention program may influence the development of neural circuitry. The ESDM includes a strong focus on promoting social relationships, including joint attention and shared engagement, imitating and being imitated, positive social affect, adult responsiveness, and verbal and non-verbal communication. Caregivers are taught specific strategies and asked to implement these strategies across many activities daily (Dawson et al., 2010). These factors may increase the number of specific types of social interactions that children with ASD have with parents and other caregivers. This may in turn modulate attention and motivation, and early training and experience may alter the child's neural responsiveness to familiar individuals. Future studies are needed to evaluate the active ingredients of efficacious early ASD interventions such as the ESDM.

Previous research using multiple modalities demonstrates differential responses to familiarity across samples of children and adults with ASD and typical development (Key & Stone, 2012; Taylor et al., 2009; Webb et al., 2010). Several regions have been implicated in this differentiation, including the posterior cingulate, amygdala, and medial frontal lobes, the posterior cingulate cortex (Shah et al., 2001), and the inferior parietal lobule (Liew et al., 2011). Research has shown that individuals with ASD demonstrated an expected pattern of face processing to their mother or other children, but attenuated responses to unfamiliar adults (Pierce & Redcay, 2008). Although simultaneous eye-tracking was not

Observe/Rest	Pearson correlation Sig. (2-tailed)	Observe/Rest	GCA	Face imitation	Hand imitation	Complex hand
GCA	Pearson correlation	- 0.334				
	Sig. (2-tailed)	0.149				
Single face total	Pearson correlation	0.021	0.019			
	Sig. (2-tailed)	0.931	0.938			
Single hand total	Pearson correlation	- 0.251	0.151	.614**		
	Sig. (2-tailed)	0.286	0.525	0.004		
Complex hand total	Pearson correlation	- 0.115	0.128	.600**	.767**	
	Sig. (2-tailed)	0.629	0.59	0.005	<.0001	
ADOS calibrated severity score	Pearson correlation	- 0.193	0.092	- 0.215	0.008	0.003
	Sig. (2-tailed)	0.416	0.701	0.363	0.973	0.989

Table 3 Correlational analyses of mu attenuation in the observe condition over rest with Global conceptual ability (GCA) as assessed by the Differential abilities scale II, single hand, face, and complex hand imitation as assessed by the Mature imitation task, and autism symptom severity as assessed by the Autism diagnostic observation schedule (ADOS)

*Correlation is significant at the 0.05 level (2-tailed)

**Correlation is significant at the 0.01 level (2-tailed)

recorded in our study, we used behavioral coding and visual inspection via time-locked video to ensure participants were attending to the stimuli during included trials. However, differential responses to familiarity are likely due to differences in neural activation and not attention or gaze patterns (Sterling et al., 2008), diagnosis (Gillespie-Smith et al., 2014), or fixation patterns (Key & Stone, 2012).

While Oberman and colleagues (2008) did find a familiarity effect, their study compared the observation of a familiar person executing a motor action with the observation of an unfamiliar hand with no person attached to it. Their results may thus not reflect a differential response to familiarity, but may rather reflect differences in holistic processing (Behrmann et al., 2006; Dawson et al., 2005; Nakahachi et al., 2008) or context (Iacoboni, 2005; Iacoboni & Dapretto, 2006).

Mu attenuation did not correlate with any of the evaluated behavioral measures, including face and hand imitation, IQ, or autism symptom severity. This stands in contrast to previous findings using a similar paradigm indicating a correlation between imitation and mu attenuation (Bernier et al., 2007; Bernier et al., 2013). These findings are included for transparency, though further investigation is warranted, especially given the small sample size, as to whether there exists a relationship among these factors.

The implications of this study must be considered in the context of existing limitations. Attrition within the sample stands as the most significant limitation. Only a subset of the 48 children who participated in the original trial were included in this study. EEG as a modality presents some inherent limitations to acquiring usable data in children and clinical populations. This limits conclusions that can be drawn from our results. Secondly, there is a lack of baseline mu activity prior to the intervention. Ideally, mu rhythm attenuation would have been assessed pre and post intervention. In this instance, we were forced to rely on data from a single time point. Nonetheless, the careful randomization procedures prior to intervention, and the fact that the groups were similar across measures of IQ, adaptive behavior, and ASD symptoms at the EEG, make the comparison worthy of consideration. Another limitation concerns the nature of the control group. In many intervention studies, the control group receives no intervention or delayed intervention. However, the COM control group in this trial received a similar number of intervention hours to the ESDM intervention group. Without details of the individual interventions received, it is difficult to precisely characterize the COM group. Taken together, this study provides preliminary evidence of a connection between the effects of ESDM and mu attenuation, but replication in a larger prospective study is needed.

This study applied an established cognitive neuroscience paradigm to examine the association between ESDM intervention and neural activity associated with social information processing. Our findings indicate a potential relationship between the ESDM and neural activity underlying responses to social cognition and familiarity.

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Author Contributions All authors contributed to the study conception and design. Programming, data collection, and data analysis were performed by BA with supervision from RB. The first draft of the manuscript was written by BA with supervision from RB, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest Dr. Aaronson, Dr. Estes, and Dr. Bernier declare no competing interests. Dr. Dawson and Dr. Rogers are authors of *The Early Start Denver Model for Young Children with Autism* from which they receive royalties from Guilford Press. Dr. Dawson is on the Scientific Advisory Boards of Janssen Research and Development, Akili, Inc., Roche Pharmaceutical Company, and LabCorp, and has received grant funding from Janssen Research and Development, LLC, and PerkinElmer, speaker fees from ViaCord, and receives royalties from Oxford University Press.

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