Running Head: AUTISM MU RHYTHM DEVELOPMENT

Developmental changes in mu suppression to observed and executed actions in autism spectrum disorders

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Abstract

Disruptions in the mirror neuron system (MNS) have been suggested to play a key role in the core social deficits observed in autism spectrum disorders (ASD). EEG mu rhythm suppression during the observation of biological actions is believed to reflect MNS functioning but understanding of the developmental progression of the MNS and EEG mu rhythm in both typical and atypical development is lacking. To provide a more thorough and direct exploration of the development of mu suppression with age in individuals with ASD, a sample of 66 individuals with ASD and 51 typically developing individuals from 6 to 17 years of age was pooled from four previously published studies employing similar EEG methodology. We found a significant correlation between age and mu suppression in response to the observation of actions, both for individuals with ASD and typical individuals. This relationship was not seen during the execution of actions. Additionally, the strength of the correlation during the observation of actions did not significantly differ between groups. These results suggest that developmental changes to the systems underlying mu suppression in response to observation of actions are independent of diagnosis. The results provide evidence against the argument that mirror neuron dysfunction improves with age in individuals with ASD and suggest, instead, that a diagnosis-independent developmental change may be at the root of the correlation of age and mu suppression.

Key Words: Autism, Mu Supression, Mirror Neuron System, Development

Total Words in Main Text: 3,498

1. Introduction

Autism Spectrum Disorders (ASDs) are behaviorally defined disorders affecting an estimated 1 in 110 individuals (Baird, et al., 2006; Baron-Cohen, et al., 2009), and characterized by qualitative impairments in language and social skills as well as the presence of restricted, repetitive, and stereotyped patterns of behaviors, interests, and activities. Converging methodologies have suggested that a specific neural system, the mirror neuron system, may play a key proximal role in these core behavioral deficits (Oberman and Ramachandran, 2007; Perkins et al., 2010, Williams et al., 2001).

Mirror neurons, first discovered in the macaque, are unique in that they respond to both the observation and execution of actions (Di Pellegrino et al., 1992). The existence of an analogous system in humans has been supported by population-level measures, including transcranial magnetic stimulation (TMS; Fadiga et al., 1995), positron emission tomography (PET; Parsons et al., 1995), electroencephalography (EEG; Altschuler et al., 1997), and functional magnetic resonance imaging (fMRI; Iacoboni et al., 1999).

Even prior to the discovery of mirror neurons, Gastaut and Bert (1954) reported that the so-called rolandic *en arceau rhythm* (now more commonly referred to as the mu rhythm) was reduced when stationary subjects identified themselves with an active person represented on a screen. Despite having relatively poor spatial resolution, the functional similarities between EEG mu rhythm and the mirror neuron system has led several researchers to suggest that suppression of the mu rhythm can be considered an index of MNS functioning (Pineda, 2005; Cochin et al., 1998; Cochin et al., 1999; Cochin et al., 2001; Martineau & Cochin, 2003; Muthukumaraswamy & Johnson, 2004;

Muthukumaraswamy, Johnson, & McNair, 2004; Perry and Bentin, 2009). Consistent with this, Keuken et al (2011) recently showed that using TMS to disrupt activity in the inferior frontal gyrus (the primary locus of mirror neurons in the frontal cortex) directly affects the modulation of mu rhythms over sensorimotor cortex.

In addition to action observation and production, the MNS has been implicated in higher-level cognitive processes that are known to be impacted in ASD, including imitation, language, theory of mind, and empathy leading many to suggest that individuals with ASD may have abnormalities in the functioning of the MNS (Oberman and Ramachandran, 2007; Perkins et al., 2010; and Williams et al., 2001). Consistent with this proposal, evidence from magnetoencephalography (MEG), (Nishitani et al., 2004), TMS, (Theoret et al., 2005), fMRI (Dapretto et al., 2006, Hadjikhani et al., 2006; Martineau et al., 2010; Williams et al., 2006) and EEG (Altschuler et al., 2000; Bernier et al., 2007; Oberman et al., 2005; Martineau et al, 2008) have supported abnormalities in the MNS in individuals with ASD.

Despite the aforementioned support, there is much disagreement over the direction of the abnormality in the MNS in ASD with some groups reporting a reduction in activity (Nishitani et al., 2004, Dapretto et al., 2006, Hadjikhani et al., 2006, Williams et al., 2006, Altschuler et al., 2000; Bernier et al., 2007; Oberman et al., 2005; Martineau et al, 2008), while others report an increase in activity (Martineau et al., 2010) and others show a difference in selectivity (Theoret et al., 2005). Still others have reported no apparent abnormality in the system (Avikainen et al., 1999, Dinstein et al., 2010, Oberman et al., 2008; Raymaekers et al., 2009; Fan et al, 2010). Though it is tempting to interpret the absence of significant differences as evidence for normal functioning, it is

plausible that abnormalities in this system were not detected in these studies for a number of reasons (population heterogeneity, differences in age, lack of power, particular stimuli used etc.).

Recently, Raymaekers and colleagues (2009) reported no significant difference in mu suppression between 20 high-functioning children with ASD and 20 matched control participants during observation of actions. The authors propose that heterogeneity of the sample could account for the findings. Specifically, they highlight that they find a "nearly significant" ($p = 0.05$) correlation with age in the ASD sample, that was not present in the control group. Based on this, these authors suggest that age has an influence on MNS functioning in ASD, with more suppression being linked to increasing age.

A similar conclusion was reached in a recent fMRI study (Bastiaansen et al., in press) that found reduced activation in the inferior frontal gyrus in an ASD group during early adulthood (ages 18-35), compared to a neurotypical control group. However, this reduction normalizes and then surpasses the activation in the control group in late adulthood (ages 35-54). Results, therefore, suggest that mirror neuron system activity increases with age in ASD, but decreases with age in neurotypical development. Additionally, the increased activity in inferior frontal gyrus in the ASD group correlated with changes in gaze behavior and improved social functioning. The authors claim that increased motor simulation may contribute to the amelioration in social functioning documented in adolescence and adulthood.

Given the discrepant findings in the literature and the importance both clinically and theoretically to understand factors mediating the functioning or dysfunction of the mirror

neuron system in ASD, we conducted a direct exploration of the development of mu rhythm suppression with age in individuals with ASD in ages 6-17 by pooling data across four previously published studies. Each of the studies included in our analysis used the same methodology. Specifically, each study included a biological action observation and a nonbiological control or resting baseline condition. Each study 1) defined mu power as power in the 8-13 Hz band 2) recorded EEG power over central electrodes (C3, Cz, and C4), 3) recorded EEG data across the scalp to ensure that the results are specific to rolandic mu rhythm and not generalized to alpha power fluctuations from other scalp locations and 4) included both typically developing control participants and those with ASD. Finally, 5) the authors of each study analyzed their data using highly similar methodologies to compute power and suppression in the mu band.

2. Results

As ratio data sometimes deviates from normality, the goodness of fit for the normal curve was estimated based on the Kolmogorov-Smirnov test and was deemed to be not significantly different from normal for both the observation values ($p=0.36$) and execution values ($p=0.93$). Thus, parametric tests were used for analysis. There was a significant difference in mu suppression between the ASD ($M=0.94$, $SD=0.27$) and the control group ($M=0.84$, $SD=0.24$) ($t=2.09$, $p<0.05$) for the observation condition, but no significant difference between groups for the execution condition ($t=.203$, $p=0.84$).

The regression analysis resulted in a significant negative correlation between mu suppression and age during action observation ($R=-0.281$, $p<0.05$), indicating a greater degree of suppression (lower ratio of power during observation or execution with respect to the baseline condition) with increasing age (Figure 1). This relationship was not

present during action execution where no significant correlation existed ($R = 0.054$, $p=.63$). When the correlation coefficients for the observation condition were calculated separately for the two groups, both samples reached significance individually (ASD $R=-0.269$, $p<0.05$ and control $R=-0.287$, $p<0.05$), while neither reached significance in the execution condition (ASD $R=0.173$, $p=0.286$ and control $R=-0.113$, $p=0.49$). Additionally, there was no significant difference in the degree of correlation between the two groups during action observation ($z = 0.102$, $p=0.92$) . Error variance and the covariance matrices across both groups during observation and execution were examined and no differences were observed (observe condition: Levene's $F =0.62$, $p =0.43$; execute condition: Levene's $F = 0.553$, $p= 0.46$; Box's $M = 6.7$, $p=.09$), suggesting that this lack of difference between groups is not due to differences in error variance in one group compared with the other.

3. Discussion

The current study reflects the first large-scale examination of the development of the neural mechanisms that underlie body action observation through examination of mu suppression as a putative index for mirror neuron functioning across childhood and adolescence in typically developing individuals and individuals with autism spectrum disorders. The current study pooled data across several published reports resulting in a much larger sample size than any other individual study. Additionally, we directly compared the size of the relationship between age and mu suppression in both ASD and control groups to establish whether this relationship was unique to ASD.

Understanding the developmental course of mu suppression in ASD is critically important. If differences in mu suppression between individuals with ASD and typically developing individuals are only present early in life but people with ASD exhibit pervasive difficulties throughout the lifespan, this would have clear implications for theoretical models of the role of body action processing and MNS dysfunction in the social and communication difficulties experienced by people with ASD. Similarly, if mu suppression normalizes with age, then this would suggest that any interventions targeting the normalization of the mirror neuron system should be focused on younger individuals.

The results of the current analysis indicate that mirror neuron dysfunction in autism does not improve with age. Although the mu suppression in response to action observation values show a negative correlation with age when data are collapsed across diagnosis, this trend is not specific to ASD. Therefore, although it is tempting to interpret the finding that mu rhythm during body action observation becomes more suppressed with age reflecting a "normalization" of the mirror neuron system over time in autism, this does not appear to be the case. Instead, the current results quite clearly show that this increased suppression in mu rhythm is not different between individuals with autism and controls.

One potential explanation for these findings is that mu frequency is more selective for action observation in older childhood and adulthood as compared to younger children. Martineau and Cochin (2003) found that children age 5-8 show greater suppression in the theta frequency during action observation as compared to the mu frequency in adulthood. Southgate and colleagues (2009) similarly found attenuation in a 6-9 Hz frequency band in nine month old infants. Additionally, Hagne (1968) noted that the resting rhythm

associated with motor activity oscillates at approximately 4-7 Hz in infants increasing to approximately 7 Hz at one year of age, 8 Hz by 18 months and 9 Hz by 4 years. In fact, this effect only appears to stabilize to the standard 8-13 Hz range in mid-adolescence. Interestingly, similar shifts in the specific EEG frequency bands that are sensitive to other types of stimuli or states have also been found to exhibit clear shifts with development (e.g., Marshall et al., 2002). Thus, examining frequencies outside of the 8-13 Hz range (perhaps in the theta range as has been found in younger children) in the youngest of children or defining person specific EEG ranges (as in Muthukumaraswamy & Johnson, 2004) may be a more accurate index.

Finally, though the mu rhythm is thought to originate in primary motor cortex, its suppression could be influenced by activity in primary motor cortex, premotor regions such as IFG or other regions earlier in processing such as the posterior parietal cortex. Thus, it is possible that the greater mu suppression with age reflects a general change either in the extended motor system or in the relationship between motor functioning and mu suppression over the lifespan (as discussed above), independent of diagnosis.

The current results are inconsistent with recent reports by Raymaekers and colleagues (2009) and Bastiaansen and colleagues (in press). Unlike previous studies, the current study, we pooled data across several studies (ASD n = 66, Control n = 51), considered the specificity of developmental changes to action observation versus action execution, and also conducted the first direct comparison of the developmental trajectory of mu rhythm modulation in individuals with ASD to the developmental trajectory of mu rhythm modulation in controls. We found no evidence for differential changes in mirror neuron functioning with age in autism compared to a typically developing control group

as indicated by nearly parallel regression lines. Our more detailed analysis of the relationship of mu rhythm suppression in ASD and controls suggests that Raymaekers and colleagues' "nearly significant" finding of a negative correlation between mu rhythm suppression with age in individuals with ASD may, in fact, reflect more generic developmental process in the mu rhythm as opposed to normalization of the mirror neuron system, *per se*. Our findings are also inconsistent with Bastiaansen's results. Bastiaansen and colleagues, however, studied adults, while our study focuses on childhood and adolescence. So, perhaps the relationship is different in adulthood. Additionally, it is possible that the differences in mu suppression we report represent changes in activity in other regions of the motor system outside of IFG (that Bastiaansen studied) such as in primary motor cortex or posterior parietal regions.

Future research should continue to utilize multiple neuroscientific techniques, as brain imaging tools and neurophysiological frequency analysis can provide complementary information. It will be important to continue to explore the neurological underpinnings of ASDs, fully taking into account that the behavioral and likely neurological phenotypes are extremely heterogeneous and, thus, group means may not be representative. It is also critical to explore all potential mediating factors that may influence the degree of dysfunction. Finally, careful clinical phenotyping of individuals with autism and other developmental disorders, including measures of severity in various domains of functioning, will be critically important for quantifying the contribution of various mediating factors in the observed variability of neurological indices, including mirror neuron dysfunction.

4. Experimental Procedure

4.1 Participants

Data from a total of 66 individuals with ASD and 51 typically developing individuals were included in the current analysis. The participants in the ASD group ranged in age from 6 years to 17 years (M = 10.28, SD = 2.44). The typically developing participants were age matched and ranged in age from 6 years to 17 years (M = 10.54, SD = 2.22). All participants with ASD were considered high functioning and had a diagnosis of Autistic Disorder (n=37), Aspergers Disorder (n=26), or Pervasive Developmental Disorder – Not Otherwise Specified (n=3) based on DSM-IVTR criteria and confirmed with an independent administration of the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000) in 58 participants and by independent clinical evaluation in 8 participants (Oberman et al., 2005).

INSERT TABLE ONE HERE

4.2 Procedure

Data were obtained with permission from the corresponding authors of four published datasets (Oberman et al., 2005; Oberman et al., 2008; Pineda et al., 2008; and Raymaekers et al., 2009). Although the exact stimuli and display parameters differed across studies, there were sufficient methodological similarities that justified merging the datasets. For detailed methods for each of the studies, see the original published papers.

All of the studies in this analysis collected power in the 8-13 Hz (“mu”) frequency band sampled over central electrodes (i.e., C3 and C4) during a baseline condition of

either rest or the observation of a nonbiological motion stimulus that did not itself show any mu suppression compared to rest, and during an observed hand action condition with a stranger. All studies included also examined other frequency bands, across the whole scalp, in order to ensure that the effect was specific to both this frequency and this scalp location. In all studies the hand action condition was a continuous opening and closing of a stranger's hand for a period of over one minute. The EEG response to this continuous movement was then broken into 2 second epochs for analysis. All four studies used similar analysis techniques to derive power in the mu frequency for these conditions. All studies involved required participants in both groups to engage in a continuous performance task which required the participant to maintain attention to the experimental stimuli. All studies reported near perfect performance on this task in both ASD and control groups.

Three of the studies also included an action execution condition, which was also analyzed for this subgroup of studies (ASD: n = 41, M = 10.63 years, SD = 2.07 years, range 6-16 years; controls: n = 40, M = 10.47 years, SD = 1.58 years, range 6-16 years). Although one of the datasets utilized was collected as part of an intervention study (Pineda et al., 2008), the data used in the current analysis were collected prior to the intervention. Additionally, one of the datasets (Oberman et al., 2008) included other conditions where the hand stimulus was that of a familiar individual. This condition was not included in the analysis; only the condition which included a stranger (stimulus identical to Oberman et al., 2005) was included. Oberman et al., 2005 also included two adult participants. However, these data were not included in the analysis as no other study included adult participants.

Mu suppression, as indexed by the ratio of mu power during action observation or execution divided by mu power during baseline, was calculated for each individual participant. Values greater than one indicate greater power during the experimental condition compared to baseline and values less than one indicate "mu suppression", that is, less power in the experimental condition compared to the baseline condition. Normalizing power in the observation and execution conditions to a baseline condition was done in the original studies to control for any potential differences in overall power across participants due to factors such as differences in skull thickness and electrode impedance. However, this also allowed us to control for differences across studies based on differences in acquisition systems, or other across-study differences. Once these normalized values were obtained for the observation and execution conditions, an outlier analysis was performed. A Cook's distance analysis was performed and one ASD individual's data in the execute condition was identified as an outlier based on having a Cook's Distance (D) value of greater than 4/n and removed from analysis.

We pooled the data across these four studies and calculated Pearson correlation coefficients in order to quantify the relationship between mu suppression and age across all subjects as well as for each group individually. Correlation coefficients were also directly compared between the two groups using the calculation for the test of the difference between two independent correlation coefficients (Preacher, 2002) in order to evaluate whether or not the relationship between age and mu suppression differed between the ASD and control groups.

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Table 1. Sample sizes and Age ranges for studies included in this analysis.

Study	Number of ASD Participants	Number of Control Participants	Ages
Oberman et al., 2005	8	8	6-16 (M = 10.00, SD = 3.70)
Oberman et al., 2008	13	13	8-12 (M = 10.23, SD = 1.37)
Pineda et al., 2008	25	11	6-17 (M = 10.04, SD = 3.21
Raymaekers et al., 2009	20	19	8-13 (M = 10.94, SD = 1.36
Total	66	51	6-16 (M = 10.40, SD = 2.34)

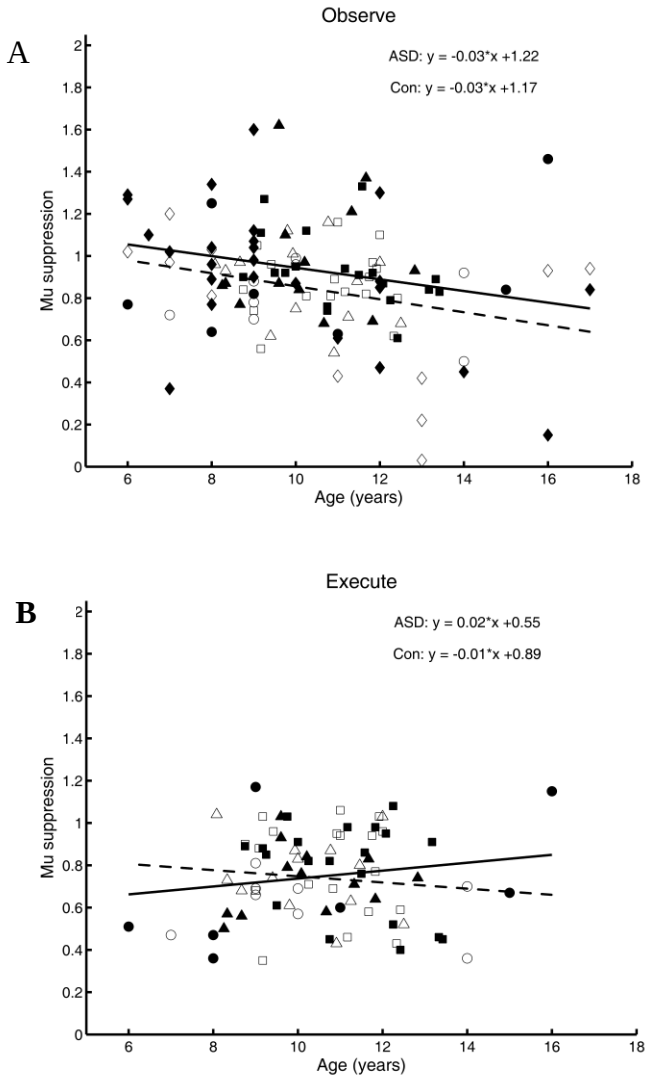

Fig 1. Correlation between age and mu-suppression for the Observe (A) and Execute (B) conditions. In both graphs, solid symbols represent the ASD participants while open symbols represent control participants. The data from the four studies are differentiated by the shape of the symbols. Data from Raymaekers et al., 2009 are represented by squares, Oberman et al., 2005 are represented by circles, Oberman et al., 2008 are represented by triangles and Pineda et al., 2008 are represented by diamonds. The solid regression lines indicate the correlation between age and suppression for individuals with ASD and the dotted line indicates the correlation between age and suppression for control participants.