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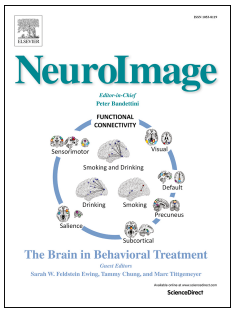

Evaluating motor cortical oscillations and age-related change in autism spectrum disorder

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Original Science Article – For NeuroImage

Running Title: Evaluating motor cortical oscillations and age-related change in autism spectrum disorder

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Keywords and Abbreviations

Magnetoencephalography (MEG); Typical Development (TD); Autism spectrum disorder (ASD); mu event-related desynchronization (Mu-ERD); Beta event-related desynchronization (Beta-ERD); movement-related gamma synchrony (MRGS), post-movement Beta rebound (PMBR)

Abstract

Autism spectrum disorder (ASD) is primarily characterized by impairments in social communication and the appearance of repetitive behaviors with restricted interests. Increasingly, evidence also points to a general deficit of motor tone and coordination in children and adults with ASD; yet the neural basis of motor functional impairment in ASD remains poorly characterized. In this study we used magnetoencephalography (MEG) to (1) assess potential group differences between typically developing (TD) and ASD participants in motor cortical oscillatory activity observed on a simple button-press task and (2) to do so over a sufficiently broad age-range so as to capture age-dependent changes associated with development. Event-related desynchronization was evaluated in Mu (8-13 Hz) and Beta (15-30 Hz) frequency bands (Mu-ERD, Beta-ERD). In addition, post-movement Beta rebound (PMBR), and movement-related gamma (60-90 Hz) synchrony (MRGS) were also assessed in a cohort of 123 participants (63 typically developing (TD) and 59 with ASD) ranging in age from 8-24.9 years.

We observed significant age-dependent linear trends in Beta-ERD and MRGS power with age for both TD and ASD groups; which did not differ significantly between groups. However, for PMBR, in addition to a significant effect of age, we also observed a significant reduction in PMBR power in the ASD group ($p < 0.05$). Post-hoc tests showed that this omnibus group difference was driven by the older cohort of children >13.2 years ($p<0.001$) and this group difference was not observed when assessing PMBR activity for the younger PMBR groups (ages 8 to 13.2 years; $p=0.48$). Moreover, for the older ASD cohort, hierarchical regression showed a significant relationship between PMBR activity and clinical scores of ASD severity (SRS-T scores), after regressing out the effect of age ($p<0.05$).

Our results show substantial age-dependent changes in motor cortical oscillations (Beta-ERD and MRGS) occur for both TD and ASD children and diverge only for PMBR, and most significantly for older adolescents and adults with ASD. While the functional significance of

PMBR and reduced PMBR signaling remains to be fully elucidated, these results underscore the importance of considering age as a factor when assessing motor cortical oscillations and group differences in children with ASD.

Introduction

Despite being largely characterized as a social-cognitive disorder, considerable evidence indicates the presence of significant motor impairments in children and adults with autism spectrum disorder (ASD)[1]. Present estimates suggest approximately 80-90% of children with ASD show some variety of *motor-specific* abnormality [2-5]. These findings have led some investigators to conclude that motor impairment represents a core characteristic of ASD [6-8]. Whereas the link between motor function and social communication impairments in ASD remains to be elucidated, it has been suggested that early motor impairments in children with ASD may directly limit social-communication opportunities which subsequently impairs social development [7, 8].

In his original article on 'infantile autism', Kanner (1943) listed low muscle-tone as a common feature of Autism Spectrum Disorder [9], and hypotonia has since been reported in numerous clinical studies of children with ASD [2, 10-12], occurring alongside hyporeflexia in approximately 77% of patients [13]. Children with ASD often present with poor motor coordination: abnormal limb movements, shortened steps, persistent 'toe walking', as well as problems with balance and posture [14-21]. In addition to gross motor impairment, fine motor skill, including manual dexterity, hand-eye coordination and graphomotor skills are commonly

[1] *Individuals on the autism spectrum, their parents, and professionals in the field have unique and overlapping opinions regarding the use of person-first (e.g., children with ASD) or identity first (e.g., autistic child) language 1. Kenny, L., et al., Which terms should be used to describe autism? Perspectives from the UK autism community. Autism, 2015.* ***20****(4): p. 442-62.. With respect for divided opinions, we use both approaches to terminology in this paper.*

impaired in children with ASD [4, 22-24]. In more severely affected cases, motor stereotypies (e.g., hand flapping, body rocking, etc.) are also common [25-27].

Beyond issues with weak muscle tone, poor dexterity and atypical repetitive movements, *higher order* impairments of motor imitation and gesture have also been a focus of interest in autism research, as these impairments may possibly stem from the more *core* social and communication impairment exhibited in ASD [21, 28-31]. While there does appear to be extensive behavioral evidence of weak imitation skills in ASD (see Williams et al., 2004 for a review [32]) the degree to which these impairments are specific to imitation is controversial. Some researchers, for example, contend that these imitation impairments in ASD do not reflect impaired action observation and mirror neuron circuitry but rather a deficit of skilled motor gestures or *developmental dyspraxia* [21].

To date, the majority of electroencephalographic (EEG) studies exploring the question of motor impairment in ASD have largely centered on tasks involving action observation modulations of the sensorimotor mu rhythm (~8-13 Hz). Overall, however, the results of action observation studies in ASD are largely equivocal, with some studies showing that mu ERD is increased [33], decreased [34-40], or equivalent to typically developing (TD) controls [41-44]. These varying outcomes may ultimately be due to the inherent variability of mu activity observed in adults [45-48] or possibly the failure to control for age-related differences that naturally occur with development. For example, an age-related increase in mu-ERD during action observation tasks, previously interpreted as decreased reactivity of the mirror neuron network, was later attributed to a diagnosis-independent developmental change in resting mu oscillations [49].

While basic and higher-order motor responses are increasingly a focus of interest, there remains a paucity of brain imaging studies (e.g., MEG, fMRI) designed to assess group level differences in motor function in ASD within the broader context of development - spanning early

childhood and adulthood. Unlike mu, the Rolandic Beta (15-30 Hz) rhythm is robust and has been well characterized across the TD lifespan. Recent magnetoencephalographic (MEG) studies have consistently shown marked developmental (i.e., age-dependent) increases in power associated with resting Beta power as well as Beta-band event-related desynchrony (ERD) and post-movement Beta rebound (PMBR) [50-52]. Thus, evaluation of motor cortical oscillation differences between children who have ASD and TD must also control for the dramatic influence of development on these sensorimotor cortical oscillatory measures. For example, a recent MEG study observed significantly reduced PMBR in children who have ASD performing an action observation motor task [53]. While the demonstration of clear PMBR differences in adolescents who have ASD is interesting, it remains unclear whether this difference is due to (i) developmental delay, (ii) impaired social action observation dysfunction, or rather (iii) a fundamental impairment in motor cortical signaling (i.e., independent and unrelated to any potential social action observation dysfunction).

Another candidate motor cortical signal which might be associated with atypical motor function in ASD is movement-related gamma synchrony (MRGS), the increase in gamma (~60-90Hz) synchrony associated with movement onset [50, 54, 55]. MRGS likely reflects function pertaining to motor execution [51, 56], as MRGS is transiently elicited during active, but not passive, movement of a limb [56]. Recently, Trevarrow and colleagues (2018), [57] found an age-dependency in MRGS power, decreasing in power from childhood into adolescence in typically developing children. While studies have shown increased spontaneous midline gamma in ASD (see Wang 2013 for a review), age-related changes in MRGS in ASD have not been reported previously.

Characterizing the neural responses associated with the observed actions of others (including interactions with development) presents theoretical and technical challenges. Given the controversy surrounding this approach, the aim of the current study was to assess, in a

broad range of ages spanning development (8 to 24 years), whether children and young adults with ASD exhibit differences in movement related oscillatory signatures compared with TD controls. Specifically, we aimed to characterize Mu-ERD, Beta-ERD, PMBR and MRGS, on a simple visually cued button-press motor task. Given the evidence that GABA appears to be downregulated in sensorimotor brain areas in ASD [58, 59], and PMBR has been associated with GABAergic inhibition [60], we predicted that PMBR will be significantly reduced in children and adults with ASD compared to age-matched typically developing peers.

Methods

Participants

The Children's Hospital of Philadelphia Institutional Review Board approved this study, and written parental informed consent and child assent was obtained for all children in this study under 18 years of age. Adult participants provided their informed consent in writing. In total, 142 participants were recruited for this study, consisting of 70 ASD and 72 TD subjects.

ASD Inclusion Criteria: Fifty-nine children and young adults with ASD (ranging in age from 8.2 to 24.6 years; mean 14.1 years, SD 4.49 years; 6 female) were recruited from CHOP's Regional Autism Center (RAC) and from CHOP's Recruitment Enhancement Core (REC), which allows recruitment of children with ASD seen throughout the CHOP system. Adult participants were recruited from the Adult Autism Spectrum Program in the Penn Medicine Department of Psychiatry, as well as from cohorts of participants from prior studies by the current investigators and investigators at the Center for Autism Research at CHOP. Diagnostic and neurocognitive testing was performed to confirm ASD diagnosis, as described below, to ensure subjects met study inclusion/exclusion criteria, and to provide phenotypic characterization of the ASD group.

All ASD children had a prior diagnosis, typically made by an expert clinician in CHOP's Regional Autism Center (RAC) or, more rarely, by community providers according to DSM-IV or DSM-5 criteria. Adult participants had a diagnosis confirmed by an expert clinician in the Adult Autism Spectrum Program in the Penn Medicine Department of Psychiatry at the Hospital of the University of Pennsylvania or during previous ASD research participation. In addition to the extensive clinical evaluations upon which original ASD diagnosis was made, the diagnostic battery confirmed the original ASD diagnosis using the Autism Diagnostic Observation Schedule (ADOS/ADOS-2) and parent report on the Social Communication Questionnaire (SCQ) [61-63]. Symptom severity indices were obtained by parent report (or other informant report (spouse, caregiver, etc.) for adults) on the Social Responsiveness Scale (SRS/SRS-2; [64]) and from the ADOS Calibrated Severity Score metric (ADOS CSS; [65]). The parent-completed Autism Diagnostic Interview-Revised (ADI-R; [66]) was administered for any participants who entered the study without a formal ASD diagnosis made by an expert clinician (e.g., ASD educational classification only) and for any child with a prior ASD diagnosis for whom a diagnostic discordance existed (e.g. a child who exceeded ADOS diagnostic cut-offs but was below SCQ and SRS-2 cut-offs). Adult participants for whom informant report was not available were included in the ASD group if they had a documented prior diagnosis of ASD and exceeded established cut-offs on the ADOS-2 as well as on both the SRS-2 Adult-Self Report and Broad Autism Phenotype Questionnaire [15]

"TD Clinical" Inclusion Criteria: Forty-four TD participants (mean age 13.4 years (7F), range of 8.16 years to 23.75 years) were initially recruited for participation in this study, through REC and the pediatric practices of the CHOP primary care network. Adult TD participants were recruited through local newspaper advertisements, social media, and CHOP Clinical Trials Seeking Volunteers webpage, as well as from participation in prior studies.

We refer to this group as "TD_Clinical" due to the availability of ASD specific Clinical and IQ measures observed for all of our ASD participants. The inclusion criteria for TD_Clinical participant children included scoring below the cut-off for ASD on the ADOS-2 and parent questionnaires, as well as performance above the 16th percentile (SS>85) on an index of language ability, the Clinical Evaluation of Language Fundamentals-4th or 5th Editions (CELF-4 or CELF-5; [67, 68]. TD adults were required to score below the cut-off for ASD on all domains of the ADOS-2 and below cut-offs on informant and self-report questionnaires (including the SRS-2 adult informant and self-reports and the Broad Autism Phenotype Questionnaire self-report [BAPQ] [69]). To ensure a TD sample without developmental language disorders, TD participants also demonstrated performance above the 16th percentile on the Clinical Evaluation of Language Fundamentals - Fourth Edition (CELF-4) [18] (if within age-range for this measure), the Verbal Comprehension Index of Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II) [70], and an average of the Peabody Picture Vocabulary Test-4 (PPVT-4; Dunn & Dunn 2007) [71] and Expressive Vocabulary Test-2 (EVT-2; Williams 2007) [72]. Per parent or adult-participant self-report, TD subjects had no first degree relatives with ASD and also had never been diagnosed with the following: intellectual disability, speech/language disorder, learning disability, ADHD, or psychiatric conditions including bipolar disorder, obsessive compulsive disorder, schizophrenia, conduct disorder, depression, or anxiety disorder.

Additional inclusion/exclusion criteria for ASD and TD: All subjects were native English speakers with no known genetic syndromes, neurological disorders (e.g. epilepsy, cerebral palsy, traumatic brain injury (TBI)) or sensory impairments (somatosensory, hearing, visual). To rule out global cognitive delay, all subjects scored at or above the 2nd percentile (SS > 70) on at least one index of verbal or nonverbal intellectual functioning on a standard intellectual assessment (Wechsler Intelligence Scale for Children-4th or 5th editions (WISC-IV/WISC; [73], Wechsler Abbreviated Scale of Intelligence-2nd edition (WASI-II) [70], or Differential Ability Scales-2nd

Edition) [74]. Estimated Full Scale IQ was obtained from the WISC General Ability Index (GAI) or from the DAS-II General Conceptual Ability composite.

TD Supplemental Control Group: To enhance any possible age-dependent features of our TD cohort, we included an additional 19 TD participants screened for neurologic or ophthalmologic conditions (see Table 1) who performed the same MEG and MRI imaging protocols, but received none of the clinical testing (no GAI or SRS-T) scores. This Supplemental Control Group was screened to be neurologically normal (via self/parent report) including 'no history of ever receiving a medical diagnosis involving a neurological disorder ("such as epilepsy or Autism") nor a past-history of concussion(s)'. Thus, the MEG related imaging results will be based on a pooled group of 63 TDs (44 TD_Clinical + 19 TD_Supplemental) in total (mean age 14.7 years, 17F, range of 8.2 to 24.7 years).

MEG Data Acquisition

All MEG recordings were performed at the Lurie Family Foundations' MEG Imaging Center, Department of Radiology, at the Children's Hospital of Philadelphia. MEG recordings were taken in a magnetically shielded room using a whole-cortex 275-channel MEG system (CTF Inc., Coquitlam, BC). Three head-position indicator coils were attached to the scalp to provide continuous specification of the position and orientation of the MEG sensors relative to the head. For younger participants, foam wedges were inserted between the side of the head and the inside of the dewar to ensure immobility. To identify eye-blink activity, an electrooculogram (EOG) was collected. Electrodes were also applied over the left and right clavicles for electrocardiogram (ECG) recording. All recorded signals (EOG, ECG, and MEG) were digitized at 1200 Hz with 3rd order gradiometer environmental noise reduction applied to the MEG data. All participants were recorded in a seated, upright position with eyes open. MEG

was recorded for 400 s resulting in approximately 100 presentations of the visual cue. MEG data were epoched off-line into 100 trials of 4 s duration (−2 s to +2 s) with the button-press at time zero (4 s epochs, 2 s pre-response). The stimulus was varied in duration ~1.5–2 s to reduce the anticipation regarding stimulus offset.

Brain MR images were obtained for each subject on a 3 Tesla Siemens Verio (TM) scanner using a 32-channel receive only head RF coil. For each participant we recorded a 3D Magnetization-Prepared Rapid Acquisition Gradient-Echo (MPRAGE) scan in an axial orientation, with field of view =256 × 256× 192 and matrix =256 × 256× 192 to yield 1 mm isotropic voxel resolution (TR/ TE =1900/2.87 ms; inversion time = 1100 ms; flip angle =9 degrees).

Visual Stimulus

Following previously published methods [75-77], a visual stimulus was presented consisting of a vertical, stationary, maximum contrast, three cycles per degree, square-wave grating, presented on a mean luminance background. Stimuli were presented in the lower left visual field and subtended 4 deg. both horizontally and vertically, with the upper right corner of the stimulus located 0.5^0 horizontally and vertically from a small red fixation cross [75, 77]. Participants were instructed to fixate and to press a response key with the right index finger at the disappearance of the visual grating stimulus. To ensure that participant attended to each trial, the response was required to occur within 700 ms in order for the next stimulus to occur. Failure to respond resulted in a prompt that the response was ‘‘too slow”, whereupon the experiment resumed. All stimulus presentations were controlled by Presentation software (Neurobehavioral Systems Inc.).

Beamformer Data Analysis

Head motion was evaluated off line by first calculating the average head coordinates over the 400 s of MEG, and then removing any trials where any coil exceeded a maximum of 1.0 cm from its average coil location. Participants for whom <70 trials remained after this procedure were excluded from subsequent analysis. In addition, EOG/ECG artifacts were also manually rejected per trial off-line by removing all trials with excessive >1pT artefacts.

Following previously published methods [50, 54, 78] movement-related oscillatory changes for mu (8-13 Hz), Beta (15 to 30 Hz) and gamma (60 to 90 Hz) frequency bands were assessed using synthetic aperture magnetometry (SAM) differential beamformer analysis [79, 80]. The SAM algorithm was then used to create differential images of differential source power (pseudo-T statistics) for baseline versus active conditions for each frequency band of interest. We used in-house Matlab software to call SAMcov and SAMsrc (released by the MEG vendor CTF ver 5.3). Specifics of differential beamformer methods have been described in detail elsewhere [80, 81]). Estimates of the three-dimensional distribution of differential source power were derived using 4 mm isotropic voxels for the entire brain volume. See Figure 1 to see each motor cortical oscillation response of interest, including baseline and active time windows used in this study.

Active window for the Mu band was based on pilot data which showed that the most robust Mu band activity occurred post-movement (0.2 to 0.7 s post button-press), and thus we used a 500 ms active time window from 0.2 to 0.7 s to evaluate Mu-ERD (see Figure 1). Peri-movement Beta-ERD was assessed using a 500 ms active window (-0.3 to 0.2 s). Both Mu-ERD and Beta-ERD were assessed relative to a 500 ms pre-movement baseline time-period locked to the button-press response (-1.8 s to -1.3 s). To assess the expected synchronization of Beta-band power following transient movements, (i.e., post-movement Beta-rebound; PMBR) a 0.5 to 1.0 s active time window was compared to the same pre-movement baseline (-1.8 to -1.3 s). Movement-related gamma-band synchrony (MRGS) was assessed using a 300 ms active

window (-0.1 to 0.2 s), relative to the button-press and referenced to a 300 ms (-1.8 to -1.5 s) pre-movement baseline period (see Figure 1). For each subject, Mu, Beta-ERD, MRGS and PMBR noise normalized differential power values were calculated (integrated across a spectrotemporal "active" window compared to a "baseline" window) and expressed as a pseudo-t statistic, (and hereafter abbreviated as "source power"). Both Mu-ERD and Beta-ERD responses included consistently robust ipsilateral peak activity, and so these peak amplitudes were also reported (specifics to follow).

MRI structural images and the individual differential beamformer results for Mu-ERD, Beta-ERD, PMBR MRGS analysis were first normalized to the Montreal Neurologic Institute (MNI) 151 template using a non-linear FNIRT[82] transform (Andersson et al., 2008) and averaged separately within group and frequency band of interest. Peak MNI locations and associated Talairach labels are listed separately on Figure 2. Using FSL, each warped SAM image was then interrogated at the group averaged peak location for all Controls and ASD Groups separately, and for each peak location observed as noted in Figure 2.

Time–frequency analysis was conducted by first transforming the MNI peak locations back to each individuals MRI and thus generate a source waveform based on the group averaged peak locations. Time–frequency analysis of the single trial source waveform data from these locations was convolved with a Hilbert transform between 1 and 100 Hz at 0.5 Hz frequency step intervals (as shown in Figure 1). The resulting time–frequency plot represents changes in the total power of both phase-locked and non-phase-locked oscillations over the duration of the recording epoch and the entire frequency range of 1 to 100 Hz. Differential source power is plotted as percentage change above baseline (as defined above) to account for non-linear decreases in power with increasing frequency, and to normalize any existing age / group specific differences in baseline power.

Insert Figure 1 about here

Statistical Analysis

Peak contralateral (left hemisphere) Mu-ERD, Beta-ERD, PMBR and MRGS power values were assessed independent of the effects of diagnostic group using General Linear Models (GLMs) with group as a fixed effect and age as a covariate. A full factorial model was constructed with age by group interactions considered in each case.

Results

Eleven ASD subjects and 8 TD controls were excluded retrospectively because of excessive head motion (resulting in too few trial numbers). One TD child was excluded due to a score above clinical cut-off on the ADOS and clinician concerns for presence of a psychiatric condition. Of the remaining 59 ASD and 63 TD participants, no statistical differences in trial numbers between groups (TD; 87.9 trials; ASD; 84.9 trials) was observed ($p > 0.05$; 2 sample t-test (see Table 1)).

There was no significant difference in age, trial number, reaction time, handedness or Wechsler General Ability Index (GAI-IQ) between groups (See Table 1). As expected, Autism

Social Responsiveness Scale T-Scores was significantly different at the group level; TD (mean, ± S.D.) 43.2 ± 6.1, ASD 71.4 ± 11.6, ($p<0.001$ (see Table 1)).

The number of females was also observed to be significantly higher in our larger sample of TD cases ($p=0.02$; chi-square). The inclusion of more females than typically expected by ASD sex ratio ~4:1 was done to optimally resolve the age dependent TD curves. Sex was however balanced within the TD_Clinical and ASD groups (n.s.).

Table 1

Grand averaged differential beamformer plots (pooling all ages) were constructed to assess overall group differences between all TD (N=63) and ASD (N=59) individuals (see Figure 2). Overall, the visually-cued button-press response produced the expected Mu-ERD, and Beta-ERD desynchrony which did not differ significantly between groups. Similarly, peak MRGS synchronization was not different at the group level, however, peak PMBR activity was observed to be significantly weaker in the ASD group (see below).

Insert Figure 2 about here

Next, the relation of developmental age on Mu-ERD, Beta-ERD, MRGS and PMBR differential power for each group, was tested using General Linear Models; specifically,

Mu-ERD (Contralateral): GLM showed no significant main effect of age, group or group by age interaction.

Mu-ERD (Ipsilateral): GLM showed no significant main effect of age, group or group by age interaction.

Beta-ERD (Contralateral): GLM showed a significant main effect of age ($p<0.001$) with no main effect of group on Beta ERD power (TD = -1.41 ± 0.11 SEM, ASD = -1.55 ± 0.11 SEM; $p=0.35$) and no interaction of group by age (TD = -0.078 / year, ASD = -0.73 / year; $p=0.94$).

Beta-ERD (Ipsilateral): GLM showed a significant main effect of age ($p<0.003$) with no main effect of group (TD -0.880 ± 0.10 SEM, ASD -0.68 ± 0.10 SEM; $p=0.15$) with no interaction of diagnosis by age (TD = -0.08 / year, ASD = -0.04 / year; $p=0.26$).

Movement-related Gamma Synchrony: MRGS is an index of synchronization, and thus typically positive (measured as an increase in gamma power above baseline). Unlike Mu-ERD and Beta-ERD which is stronger (more negative) with age, MRGS was observed to significantly decrease (i.e., get weaker) with age for both groups. GLM showed a significant main effect of

age ($p<0.001$) and no main effect of group (TD = 1.87 ± 0.18 SEM, ASD = 2.11 ± 0.19 SEM, $p=0.37$) and no significant group by age interaction (TD -0.11 / year, ASD -0.13 / year; $p=0.70$).

PMBR: In contradistinction to the above non-significant group level contrasts, when considering PMBR as the dependent variable, not only was there a significant increase with age, but there was also both a significant main effect of diagnostic group as well as a significant difference in maturational rate between diagnostic groups (i.e. a significant diagnosis by age interaction). The GLM showed a significant effect of age ($p<0.001$), significant main effect of diagnosis (TD = 0.81 ± 0.13 SEM, ASD = 0.30 ± 0.13 SEM; $p < 0.01$) and a significant interaction of diagnosis by age (TD = 0.23 / year, ASD = 0.11 / year; $p=0.004$). A post-hoc test of sex as a main effect in our linear mixed model showed no significant main effect of participant's sex on PMBR activity ($p > 0.05$).

Figure 3A, B, C, D shows Mu-ERD, Beta-ERD, MRGS and PMBR differential power plotted by age comparing TD and ASD groups. As noted, significant developmental changes occur for each measure, however, only PMBR differs between groups.

Insert Figure 3 A-D about here

Next, we plotted a 5 point (2 pre & 2 post) moving average for TD PMBR power with increasing age. A clear increase in PMBR power emerges at ~13.2 years (see Figure 4), and thus we concluded that for ages less than 13.2 years, due to normal development [50, 51, 57], there

should be little or no PMBR at the group level while at ages greater than 13.2 years, PMBR should be present at the group level. Thus, we conducted post-hoc tests where we split our groups at age 13.2 years and tested for group differences separately for younger and older sub-cohorts.

Insert Figure 4 about here

Young_PMBR (< 13.2; TD, N=32; ASD, N=34): As expected, for the Young_PMBR group, there is no significant change with age (p=0.32), no main effect of diagnosis (TD= -0.19 ± 0.13 SEM; ASD= -0.06 ± 0.13 SEM; p=0.48) and no significant diagnosis by age interaction (p=0.14).

Old_PMBR (> 13.2; TD, N=31; ASD N=25): As expected, for the Old_PMBR group, there is a significant increase with age (p=0.003) and a highly significant main effect of diagnosis (TD=1.96 ± 0.22 SEM, ASD = 0.72 ± 0.25; p< 0.001). In addition, there was no significant diagnosis by age interaction (TD = 0.16 / year, ASD = 0.14 / year; p=0.86) (Figure 5A).

Insert Figure 5A and 5B about here

Considering only the ASD group with age>13.2 years, we used hierarchical regression to test the influence of (first) age and then (second) age and SRS on PMBR activity. Within the ASD group, age alone accounts for significant variance (R^2 = 17.2%, p<0.05). Additional regression of Age + SRS accounts for significant additional variance (R^2 = 32.6%, ΔR^2 = 15.4%, p<0.05; see Figure 5B). For neither group did GAI IQ or RT account for significant variance (both p's > 0.05).

Visual inspection of the scatter plot of Old_PMBR vs. age (Figure 5A) also identifies two clusters: those with positive PMBR (lying approximately within the range of the TD trajectory) and a sub-cohort exhibiting absent (in fact, negative) PMBR (N=8; 1 TD and 7 ASD). Importantly, eliminating these cases (all remaining cases > 13.2 years and negative PMBR), the GLM still shows a significant main effect of age (p=0.01) and diagnosis (TD = 2.06 ± 0.21 SEM, ASD 1.29 ± 0.27 years; p<0.05) with no diagnosis by age interaction (p=0.96). Developmental trajectories of PMBR in these two cohorts was TD =0.13 / year, ASD = 0.13 / year. Furthermore, the regression of PMBR with SRS in ASD remained intact and indeed more profound (ΔR^2=31.9%, p=0.002).

Insert Figure 6A, 6B and 6C TFRs about here

Source waveform time courses from grand-averaged (omnibus) peak locations (considering all participants for TD and ASD separately) were projected back to each individual's brain MRI. TFR's are shown in Figure 6 for young vs older TD and ASD

participants. Fig 6C depicts the older ASD cohort split by the presence/absence of positive PMBR. The source activity time course of Beta band activity (capturing both ERD and subsequent PMBR) was then grand-averaged for the older TD and ASD PMBR groups separately and plotted in Figure 7. Figure 7 also shows the Beta-band timecourses for ASD sub-cohorts split according to the presence or absence of positive PMBR, as above and in Fig 6C. As anticipated, TD participants show more PMBR than the ASD participants, an effect which is in large part, but not entirely, attributable to the sub-cohort of ASD participants with absent PMBR.

Insert Figure 7 Virtual Sensors about here

Discussion

The aim of the present study was to assess TD and ASD group differences in motor cortical oscillations on a visually-cued button-press response task, and to do so in a broad sample of ages sufficient to capture age-dependent changes for each of the measured motor cortical signals. We observed significant maturational changes for Beta-ERD and MRGS which were not different between ASD and TD groups, while Mu-ERD showed neither age-dependence nor group differences. In contrast, and in accord with our main hypothesis, not only was a significant maturational change observed for PMBR for both ASD and TD, but we also observed an age by group interaction driven by age-related increases in PMBR power in TD which was significantly lower in our ASD participants. Furthermore, these differences become apparent only when positive PMBR begins to emerge at approximately 13 years of age. In younger subjects (both TD and ASD), PMBR values are below the noise floor. In the older ASD

subjects, the magnitude of PMBR was shown to significantly correlate (negatively) with a measure of ASD symptom severity (SRS T-score). That is, in more severely affected participants, PMBR values were more abnormal (lower). While a direct association between (rather specific) cortical oscillatory activity of primary motor cortex and a (rather general) parent report of ASD symptom severity might, at first, be surprising, we speculate the aberrant cortical responsiveness, indicated in our study by PMBR, points to a more generalized cortical circuitry imbalance, underlying atypical phenotypic behaviors. Alternatively, the atypical cortical excitability/reactivity indexed by aberrant PMBR in ASD may underlie subtle (perhaps sub-clinical) motor impairments, which might nonetheless have social sequelae and therapeutic ramifications.

The current study shows that Beta-ERD power increases significantly in power with age (i.e., Beta-ERD power becomes more negative) and does so for both contralateral and ipsilateral motor sources, and equally for both TD and ASD participants. The current results are consistent with prior MEG studies evaluating cortical motor oscillations in typical developing children and adults which have also shown that Mu and Beta-ERD power generally increases with age [50, 51]. However, this association was not replicated in a recent MEG study by Trevarrow, et al. (2019) who reported a relatively flat (r=0.11) positive association of Beta-ERD power and age from 83 typically developing children (8 to 15 years of age) on a simple motor response task. To explore this issue further, we replicated our analysis of the Beta-ERD vs. age plots for TD and ASD, but restricted the analysis to the 8-15 year age range. Interestingly, the resulting correlations became non-significant trends (TD=37, r=0.226; p=.178; ASD=40, r= 0.237 p=0.141) yet maintained negative slopes for both TD and ASD. Thus, we interpret the inconsistent findings between the current Beta-ERD vs. age results and those reported in the Trevarrow, et al. (2019) paper to be potentially due to the relatively narrow age range (and particularly the low 15 years age-limit) of their sample. In general, and like the PMBR finding, we

surmise that Beta-ERD becomes increasingly conspicuous with development into adulthood and is non-linearly affected by the inclusion of older (post-adolescent) children and young adults [52, 83].

Trevarrow, et al. (2019) also measured the effect of age on MRGS and PMBR activity, and reported that PMBR increases with age whereas MRGS decreases with age. The present results are consistent with these findings and we now extend these findings to an ASD sample of children who show the same inverse correlation of MRGS activity vs. age observed in TDs. Moreover, we provide novel physiological evidence of a distinct functional deficit in PMBR motor cortical oscillations in children and young adults with ASD, which becomes visibly conspicuous (after the zero-crossing of the TD_PMBR moving average; see Figure 4) after approximately 13.2 years of age.

Given the parallel nature of the PMBR trajectory in older individuals who have ASD (compared to older TD individuals), it is tempting to speculate that low PMBR activity reflects a delay in maturation. To establish this conclusively, asymptotic levels of PMBR in both this subset of individuals with ASD and TD would need to be equivalent. It is beyond the statistical power and age-range of the present study to confirm or refute this hypothesis. In any case, there remains the sub-cohort of individuals with ASD who showed no evidence of positive PMBR despite their age. This could possibly reflect a more extreme maturational delay or a categorically-distinct subgroup. In the latter case, we speculate that such biologically-based stratification (present vs absent PMBR, Figure 5A) might provide a basis for selective patient management / therapeutic intervention.

More generally, our findings underscore the importance of considering development as a factor when assessing cortical oscillations between groups in general. For example, Buard et al., (2018) has recently shown that PMBR is reduced in adolescent children with ASD where

they are asked to copy finger movements observed on a video screen [53]. Here, we speculate that similar measures applied to young children (<~13 years) with ASD may not show a group difference (because of absent PMBR in both groups). Interestingly, Buard et al., (2018) also reported that children with ASD exhibited significantly greater Beta-ERD on action observation tasks. Thus, it is intriguing that Beta-ERD in this context may be additionally sensitive to features associated with social aspects of the observed motor response. Of note, though not significant, we also saw greater Beta-ERD in ASD compared to TD with our visually-cued response task (see Figure 7).

The mechanism underlying the observed PMBR differences remains unclear. However, prior studies have reported that PMBR activity correlates with concentration of the inhibitory neurotransmitter GABA in TD adults [60]. Recent magnetic resonance spectroscopy studies from our group and others have shown decreased GABA levels from voxels aligned with somatosensory and motor brain area in ASD [58, 59]. Thus a potential association between reduced GABA levels in sensorimotor cortex and reduced PMBR could point to PMBR as an index of cortical circuitry “health”. The link between decreased GABA levels and reduced PMBR has in fact been seen in other patient populations. A previous study conducted by Vakhtin et al., (2015) investigated the development of PMBR in patients with fetal alcohol syndrome disorders (FASDs) [84]. One possible reason that FASD patients suffer from motor deficits is that early alcohol exposure has been shown to lead to impairments in GABA-specific inhibitory pathways. Much like the findings of the present study, Vakhtin et al. (2015) found no significant difference in PMBR power in their younger adolescent participants (age 12-15 years), however, assessment of PMBR in older participants (16-22 years) showed a significant difference in PMBR amplitudes between FASD patients and age-matched controls, largely driven by an increase in PMBR power in the older control group [84].

To assess the *functional* significance of the transient burst of Beta band synchrony (such as that observed in PMBR), prior work has used Transcranial Magnetic Stimulation (TMS) to directly assess whether motor cortex excitability is affected by the presence of synchronous Beta oscillations. For example, Chen et al., (1994) modulated resting sensorimotor rhythms using median nerve electrical stimulation, and then assessed cortical excitability of the motor cortex at different time points around SEF response. Cortical excitability was assessed by delivering a TMS pulse to the contralateral motor cortex [85], producing a motor evoked potential (MEPs) from the TMS associated with thumb response, with the thumb MEP amplitude serving as an index of cortical excitability. Chen et al., (1999) observed that MEPs amplitudes were larger when the TMS pulse occurred around the onset of median nerve stimulation (a period with relatively low Beta rhythms) and was significantly attenuated when the TMS pulse occurred ~ 500-1000 ms post-stimulus; corresponding to the approximate time-point of maximum post-stimulus beta synchrony. While not direct evidence, PMBR activity here does seem directly associated with reduced motor cortical excitability. Analogously, fronto-central beta synchronization has been shown to increase following successfully inhibited 'No Go' cues in a Go/No-Go paradigm, corresponding to the subject's decision to withhold a response [86]. Again, the increase in beta synchrony is thought to index a reduced excitatory state that allows for a prepared response to be inhibited. Indeed, a prior MEG study has also shown that PMBR activity is related to the forced termination (i.e., inhibition) of on-going motor output [87]. This association between response inhibition and PMBR is further supported by the observation of weaker MEP amplitudes (indexing reduced excitability) on 'No Go' vs 'Go' trials [88, 89]. It remains an open question how responses to 'No Go' cues would be affected by developmental increases in PMBR. We speculate that the known response inhibition impairments in ASD [88, 89], would be predicted by relatively low PMBR.

Somewhat less intuitive are the observations that PMBR can also be driven solely by proprioception (PMBR observed following passive movement disappears with sensory nerve block [90]) or simply observing movement and movement-related *errors* [91]. This suggests a role for both somatosensory proprioception and top-down expectation (without afferent input) producing significant PMBR. A recent series of experiments from Tan et al. (2016) demonstrated that the amplitude of the PMBR also correlates negatively with estimation uncertainty [92]. Related commentary by Cao and Hu (2016) [93] suggest that PMBR might (due to its occurrence after a planned movement has occurred) reflect an updating process of the forward model (and thereby indexing processes governing movement expectations) [93]. Importantly, these theories are compelling in adult populations but entirely fail to account for the relative absence of PMBR in children, who (even in early adolescence) can simultaneously demonstrate weak or absent PMBR yet also exhibit comparable motor planning and performance (and presumably formulate expectations about movement outcome) like adults. It is also worth noting here that the absence of PMBR in children may only be quantitative (present but not detected). Alternatively, the emergence of a PMBR response with development may reflect a qualitative change in cortical signaling – possibly reflecting inhibitory circuits coming on-line after about age 13 years.

Finally, it is tempting to speculate that reduced PMBR power in ASD is somehow related to the known motor abnormalities associated with the disorder (i.e., weakness, repetitive and stereotyped behavior [3, 4, 94]), or the social communication deficits inherent in ASD, which include the failure to suppress inappropriate social reactions, especially in children and adolescents [89, 94]. Indeed, we observed that the magnitude of PMBR was shown to significantly correlate (negatively) with a measure of ASD symptom severity (SRS T-score). However, reduced PMBR has also been reported in adults with Schizophrenia [95], schizotypal personality disorder (SPD) [96], and Parkinson's disease [97]. In addition, PMBR 'time to peak'

is delayed for both adults with Multiple Sclerosis (MS) [98] and adults with amyotrophic lateral sclerosis (ALS) [99]. The current study is somewhat distinctive in that the group differences in PMBR are considered in relation to the emergence of PMBR activity with typical development – similar to Vakhtin et al,'s (2015) observation of reduced PMBR power in Fetal Alcohol Spectrum Disorders (FASD), [84]. Further study is warranted to reveal the functional significance of PMBR as it emerges during typical development and the behavioral consequence of reduced PMBR in clinical populations such as individuals with ASD.

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Table 1: Summary of all group level mean values level measures ± S.D. for Age, Sex, Trials, Reaction Times, Handedness, Wechsler General Ability Index, (GAI-IQ) and Autism Social Responsiveness Scale T-Score (SRS-T). A total T-score of 76 or higher is considered severe and strongly associated with clinical diagnosis of Autistic Disorder [70, 73]. Grey shading indicates which column measures are considered when reporting the corresponding significance values (far right column). *N.B. We included sex as a main effect in our linear mixed model, and observed no significant effect of participant sex (p=0.17) on PMBR amplitude.

Figure 1. Grand averaged (N = 63) TD PMBR peak location (Talairach coordinate **(**-31.1 -17.1 63.0; left pre-central gyrus) was projected back to each individual's MRI. The associated source waveform was then evaluated using time-frequency analysis, with the average TFR plotted here. The Mu-ERD, Beta-ERD, PMBR and MRGS active and baseline time windows are shown.

Figure 2. Grand average (all TD (N63) and ASD (N59) participants) beamformer responses to task induced button-press responses for Mu-ERD, Beta-ERD, MRGS and PMBR, and PMBR. Only PMBR amplitude is significantly different at the group level (see GLM results). Each oscillation category shares the same max and min cut-offs, with the exception of the display threshold of the PMBR images which used the same maximum values, however the PMBR minimum was lowered for the ASD group average to show the reduced levels of PMBR power observed.

Figure 3. Figure 3A, B, C, D shows Mu-ERD, Beta-ERD, MRGS and PMBR power respectively. Peak values are plotted by age comparing TD and ASD groups. As noted, significant developmental changes occur for each measure, however, only PMBR differs between groups (3D), diverging in mean PMBR power with increasing age.

Figure 4. To estimate a non-arbitrary threshold for PMBR power vs. Age, a 5 point (2 pre & 2 post) moving average was calculated for TD PMBR power with increasing age. A clear increase in PMBR power emerges at ~13.2 years. Thus, we used 13.2 years as an age-limit for age-specific post-hoc statistical tests defining Young_PMBR and Old_PMBR sub-groups.

Figure 5A. Consideration of PMBR differential power vs. Age was evaluated between TD and ASD groups. The main finding of a significant effect of Age and group is recapitulated without including these outliers (p=0.039). While speculative, the complete lack of PMBR power in these ASD participants (despite their increasing age) might represent a biological basis for

stratification. **5B**. Hierarchical regression shows a significant effect of PMBR activity with SRS-T score after regressing out the effect of age ($p<0.05$).

Figure 6. Time-frequency plots based on PMBR peak locations (TD and ASD group peak locations considered separately) are shown. Time-frequency plots show nearly identical responses in Mu-ERD, Beta-ERD, and MRGS responses in children < 13.2 years (upper left and upper middle panels). For these younger TD and ASD participants, the absence of PMBR power would be predicted from prior studies. However, the lower left and lower middle TFR plots shows a significant decrease in PMBR in older ASD PMBR participants relative to older TD controls. The Old_PMBR ASD group was further separated into a group of subjects who showed negative PMBR activity (N=7; see triangles that fall below the black horizontal line in Figure 5A) from those Old_PMBR adults with positive values (triangles above the black line in Figure 5A).

Figure 7. Source waveforms for the TD and ASD Old_PMBR groups show significantly more PMBR activity for the TD group (blue) vs the ASD group (red) as a whole as well as vs the ASD Respondersgroup (the (N=18) sub-cohort with positive PMBR). A subset of ASD non-responders (N=7) can be defined by the absence of measurable post-movement rebound in beta band activity (see Figure 5A). Of note, the ASD groups appear to exhibit slightly deeper ERD (at ~0 s) than the TD group. This was not statistically significant. Nonetheless the greater magnitude of PMBR in TD vs ASD at ~ 0.5 s cannot be attributed to this offset, as the significant difference in PMBR amplitude between groups is substantially larger.

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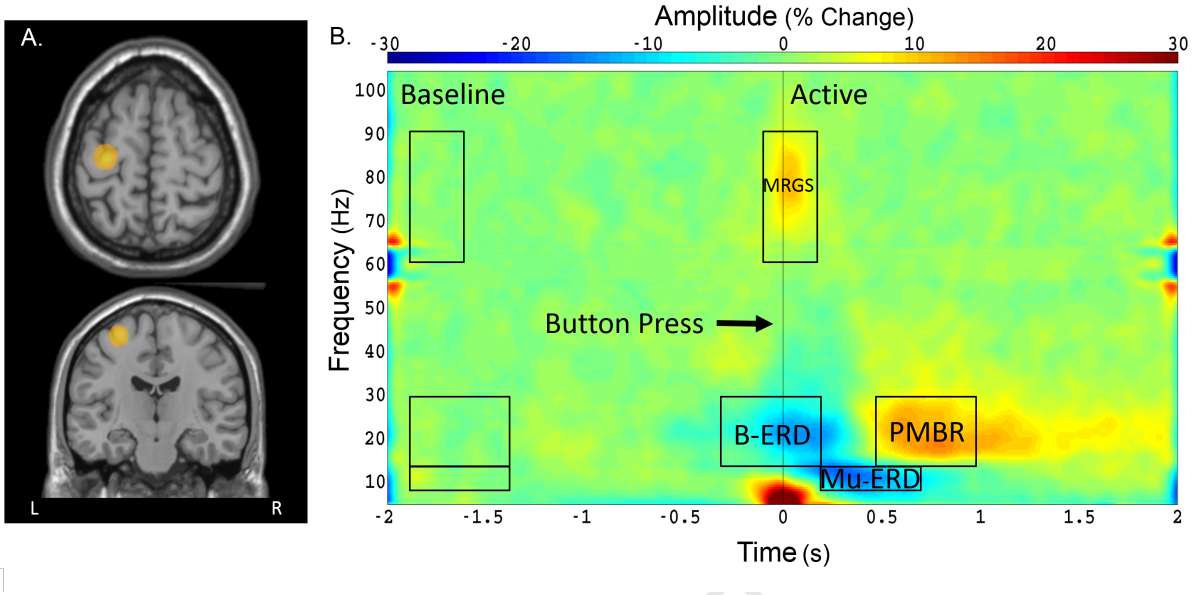
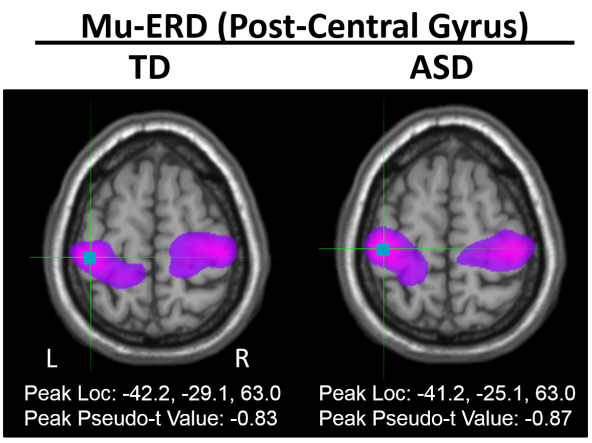
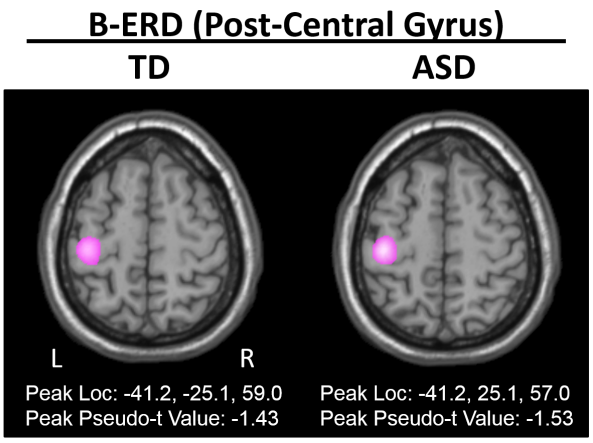
	TD Total
Count	63
Mean Age (StDev)	14.7 (4.9)
Male / Female	47/17

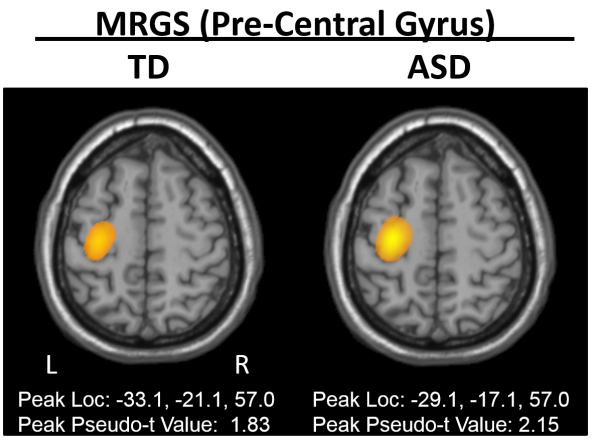




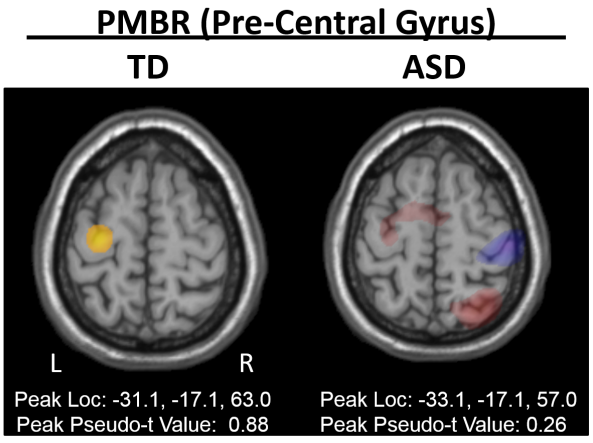
TD (N=63) vs ASD (N=59) peak Mu-ERD (n.s.)



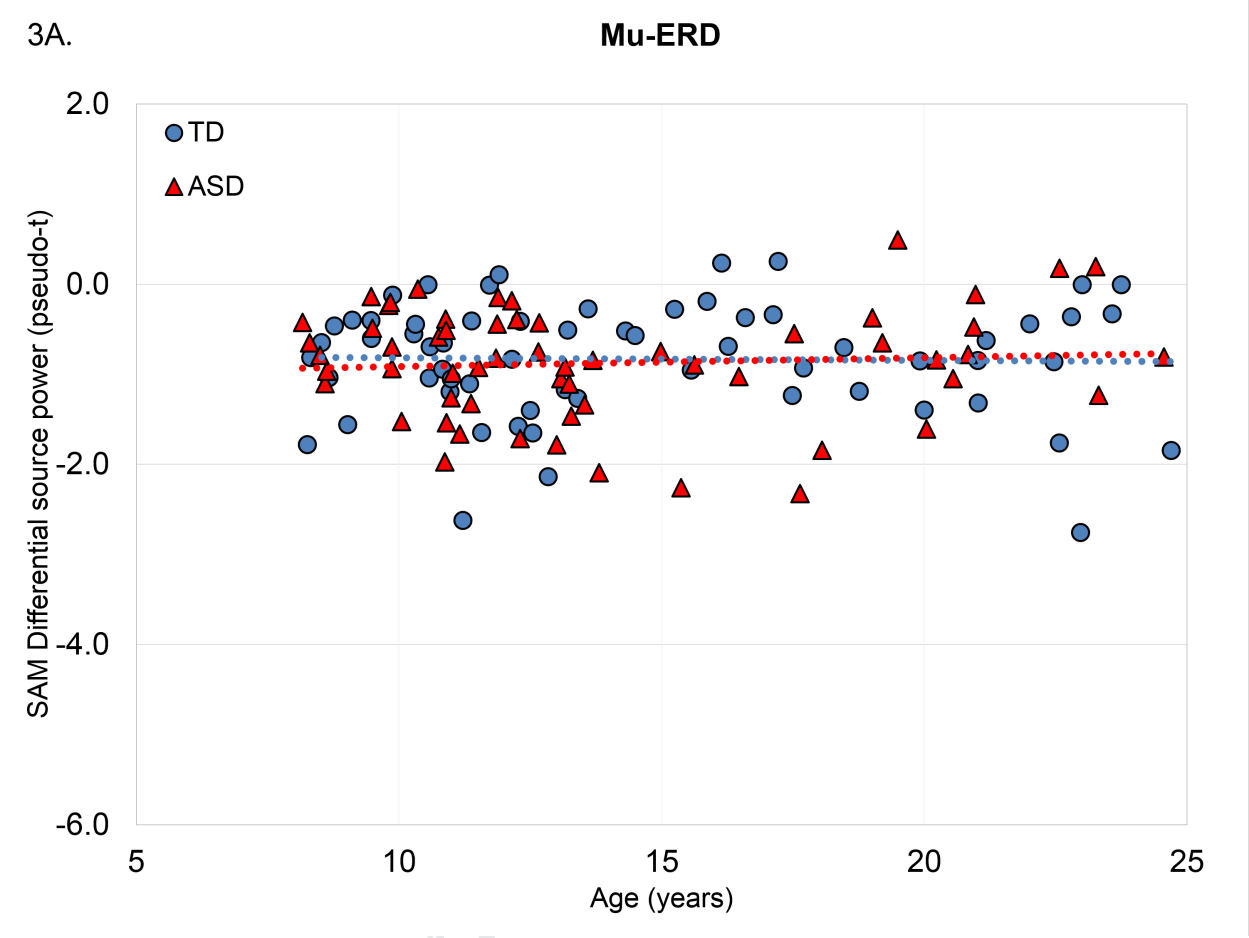
TD (N=63) vs ASD (N=59) peak B-ERD (n.s.)

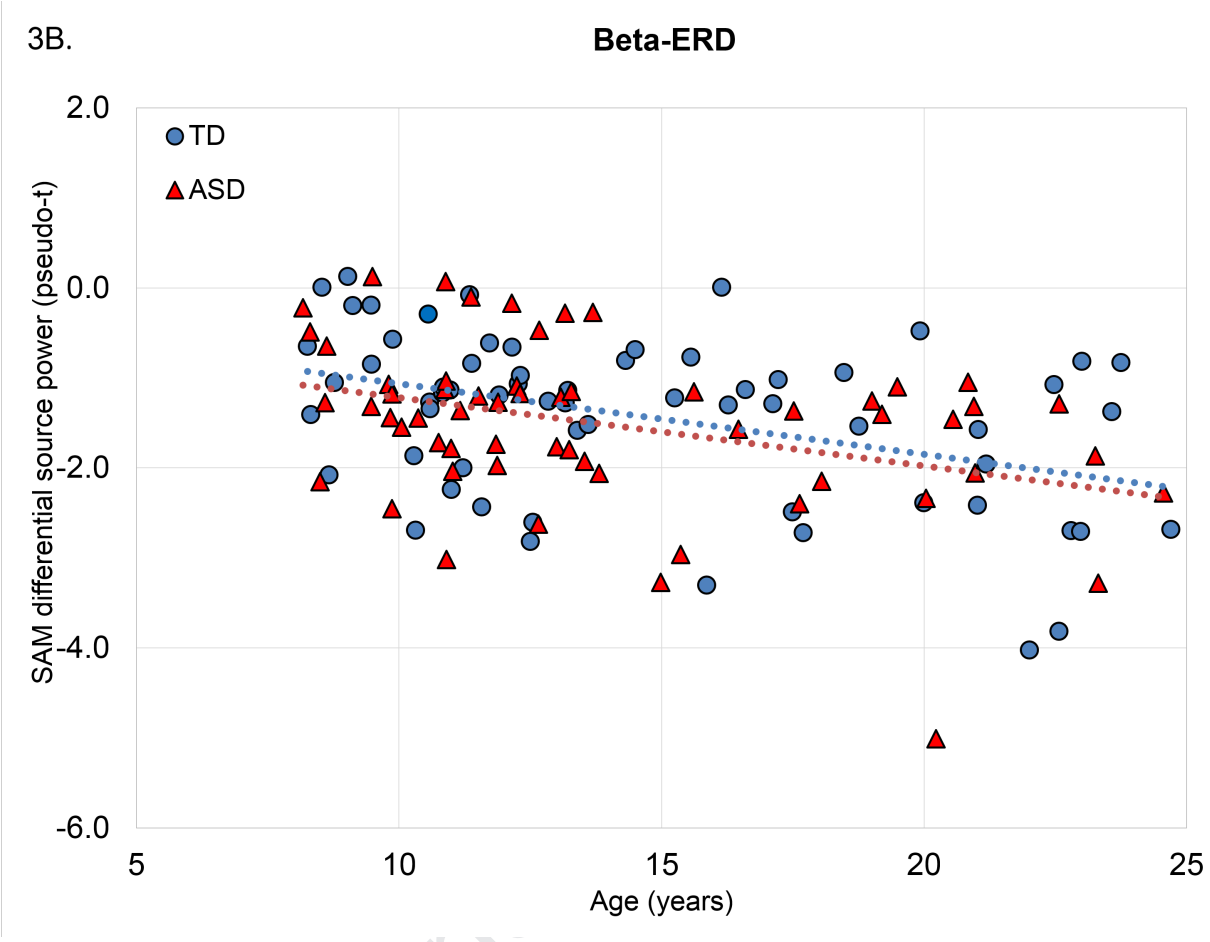


TD (N=63) vs ASD (N=59) peak MRGS (n.s.)



TD (N=63) vs ASD (N=59) peak PMBR (sig. p<0.05).


3A.
Mu-ERD
TD
ASD
SAM Differential source power (pseudo-t)
2.0
0.0
-2.0
-4.0
-6.0
5
10
15
20
25
Age (years)


3B.
Beta-ERD
TD
ASD
SAM differential source power (pseudo-t)
2.0
0.0
-2.0
-4.0
-6.0
5
10
15
20
25
Age (years)

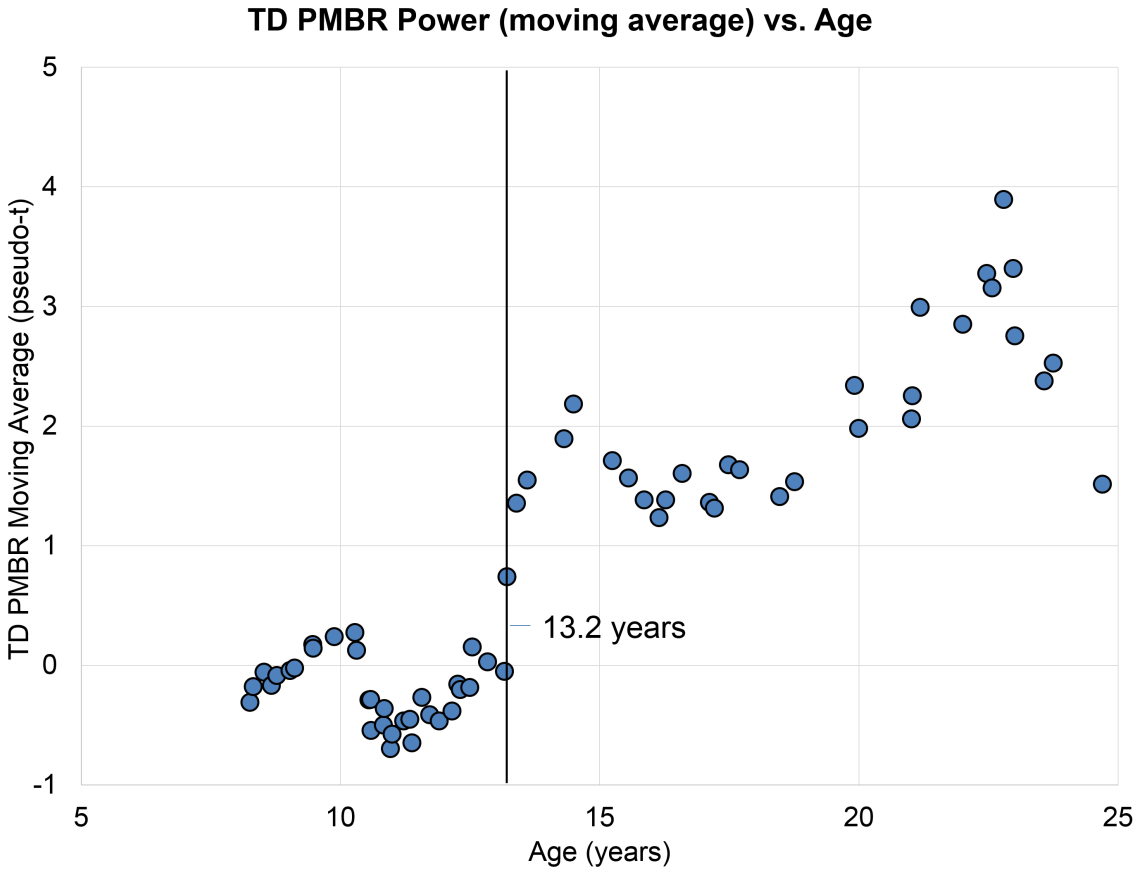
3C.


MRGS
TD
ASD
SAM differential source power (pseudo-t)
8.0
6.0
4.0
2.0
0.0
-2.0
5
10
15
20
25
Age (years)

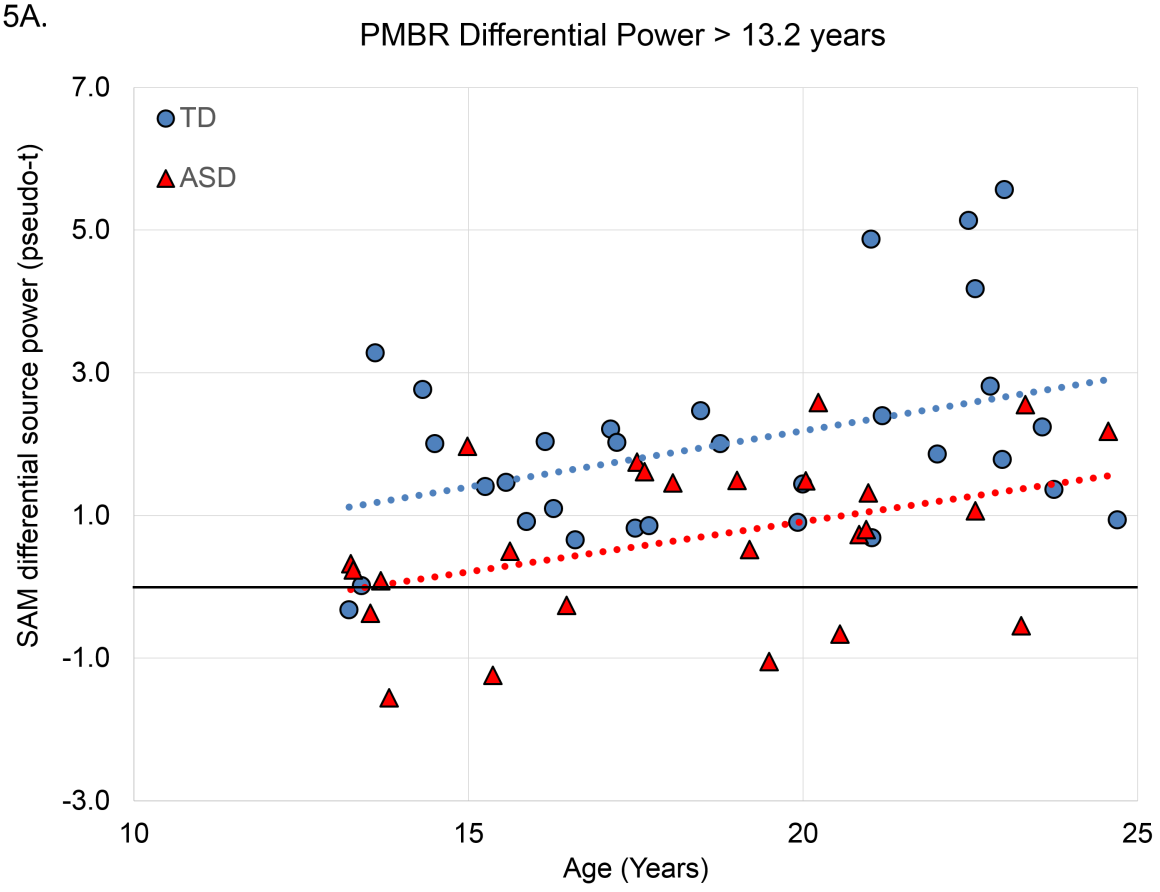
3D.


PMBR
TD
ASD
SAM differential source power (pseudo-t)
5.0
3.0
1.0
-1.0
-3.0
5
10
15
20
25
Age (years)

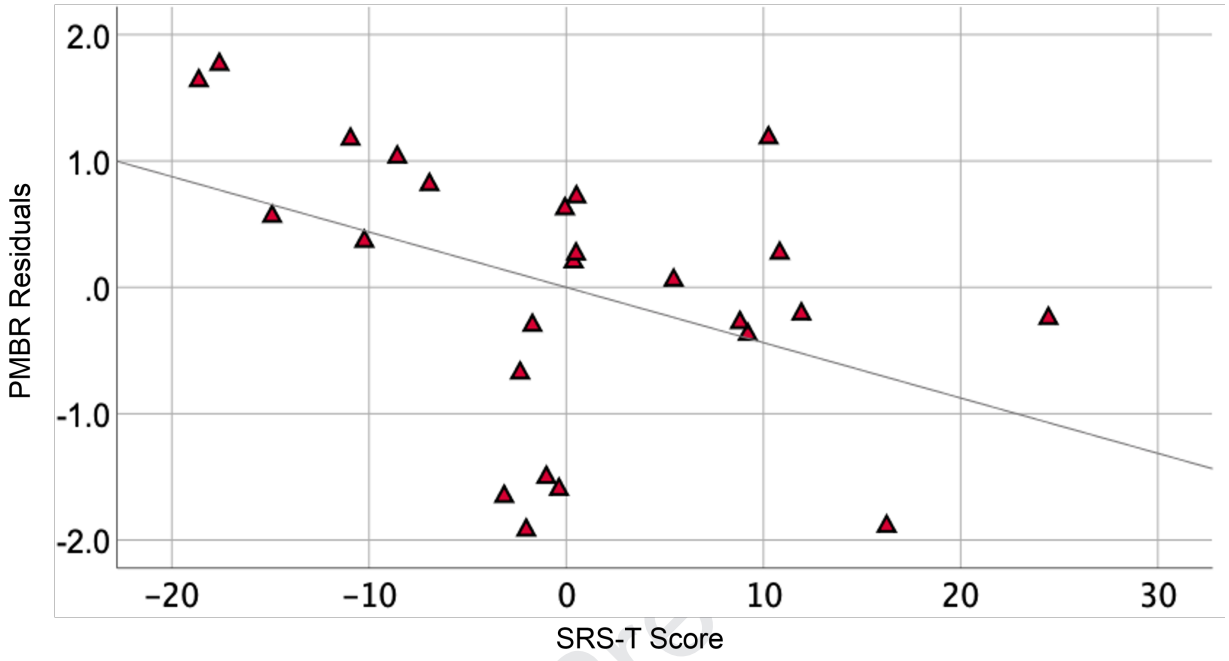
4.

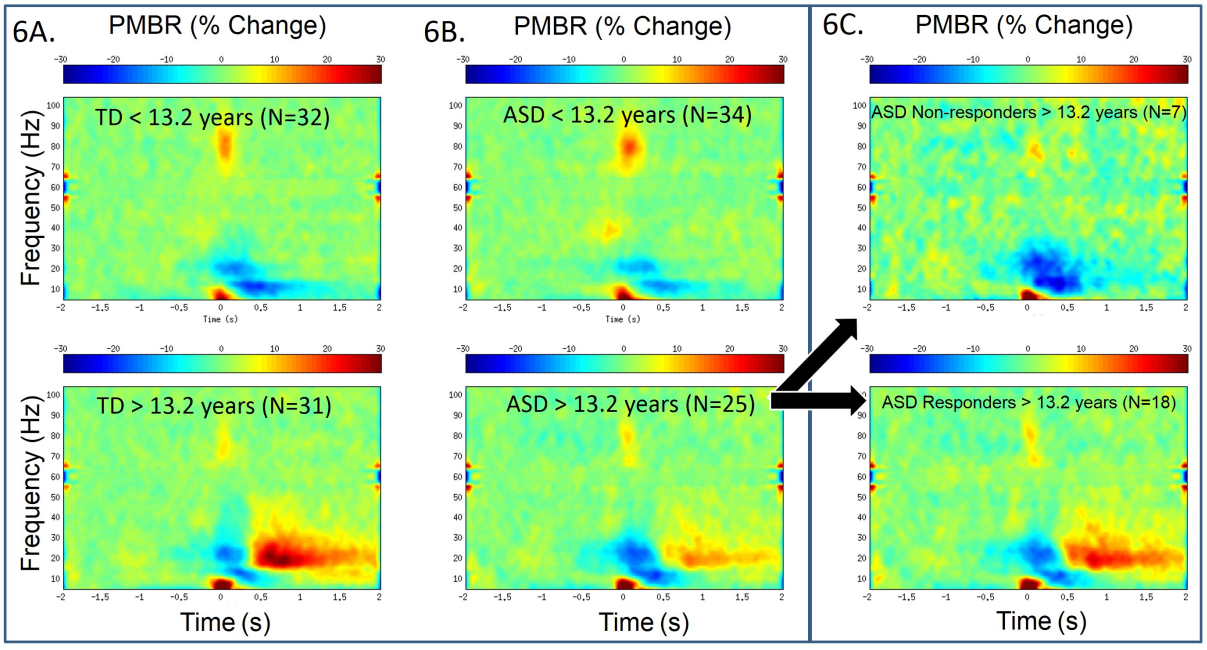

TD PMBR Power (moving average) vs. Age
TD PMBR Moving Average (pseudo-t)
5
4
3
2
1
0
-1
13.2 years
5
10
15
20
25
Age (years)

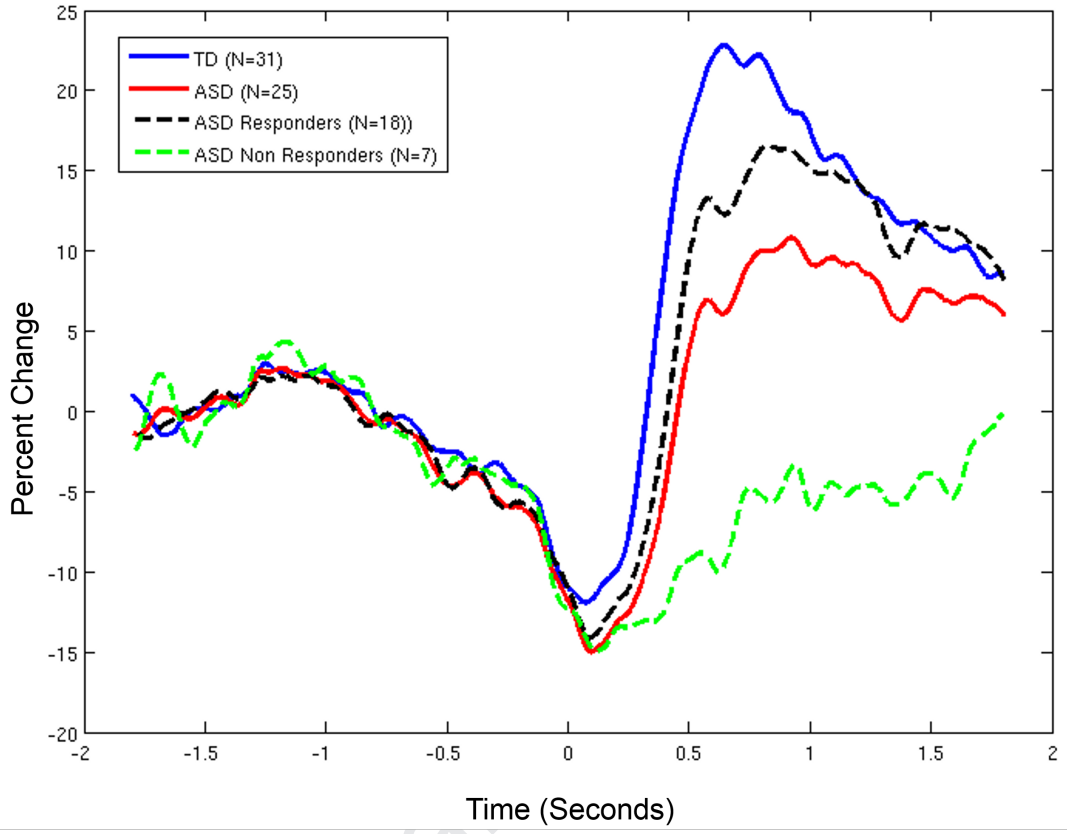
5A.


PMBR Differential Power > 13.2 years
TD
ASD
SAM differential source power (pseudo-t)
7.0
5.0
3.0
1.0
-1.0
-3.0
10
15
20
25
Age (Years)

5B.






TD (N=31)
ASD (N=25)
ASD Responders (N=18))
ASD Non Responders (N=7)
Percent Change
Time (Seconds)
25
20
15
10
5
0
-5
-10
-15
-20
-2
-1.5
-1
-0.5
0
0.5
1
1.5
2