6-26-2015

Aberrant Development of Post-Movement Beta Rebound in Young Adults with Fetal Alcohol Spectrum Disorders

Andrei Vakhtin

Andrei A. Vakhtin

Candidate

Psychology

Department

This thesis is approved, and it is acceptable in quality and form for publication:

Approved by the Thesis Committee:

Dr. Claudia Tesche, Chairperson

Dr. Derek Hamilton

Dr. James Cavanagh

Aberrant Development of Post-Movement Beta Rebound in Young Adults with Fetal Alcohol Spectrum Disorders

Andrei A. Vakhtin

B.S., Biology; University of New Mexico, 2009

B.S., Psychology; University of New Mexico, 2009

THESIS

Submitted in Partial Fulfillment of the Requirements for the Degree of

Master of Science in Psychology

The University of New Mexico

Albuquerque, New Mexico

April, 2015

ACKNOWLEDGMENTS

I would like to thank my advisor, Claudia Tesche, for challenging me in my work and studies, and providing support throughout my graduate academic career. I'd also like to thank my parents, Andrei and Irina, for always valuing education above all, and providing me with opportunities to excel in areas of my interest. Additionally, I extend my gratitude to my master's committee members, Derek Hamilton and James Cavanagh, for their time and guidance throughout the project. Finally, I would like to thank Sephira Ryman for inspiring me to pursue graduate studies in neuroscience.

Aberrant Development of Post-Movement Beta Rebound in Young Adults with Fetal Alcohol Spectrum Disorders

by

Andrei A. Vakhtin

B.S., Biology, University of New Mexico, 2009

B.S., Psychology, University of New Mexico, 2009

M.S., Psychology, University of New Mexico, 2015

ABSTRACT

Prenatal alcohol exposure results in cognitive and physical impairments in children, which are collectively defined as fetal alcohol spectrum disorders (FASDs). The disorders account for the largest proportion of intellectual disabilities in the US. While few functional findings exist today that shed light on the mechanisms responsible for the observed impairments in individuals with FASD, animal models consistently report deleterious effects of early alcohol exposure on GABA-ergic inhibitory pathways. The post-motor beta rebound (PMBR), a transient increase of 15-30 Hz beta power in the motor cortex that follows the termination of movement, has been implicated as a neural signature of GABA-ergic inhibitory activity. Further, PMBR has been shown to be a reliable predictor of age in adolescents. The present study sought to investigate any differences in the development of PMBR between FASD and control groups. Twenty-two subjects with FASD and 22 age and sex-matched controls

underwent magnetoencephalography scans while performing an auditory oddball task, which required a button press in response to select target stimuli. The data surrounding the button presses ([-1.5 2 s] interval) were localized to the participants' motor cortices, and the time courses from the locations of the maximally evoked PMBR were subjected to wavelet analyses. In addition to age and group, early (0.5-1 s after button press) and late (1-1.5 s after button press) evoked PMBR measures were contrasted. The PMBR evoked values were analyzed with a 2 x 2 x 2 ANOVA (group, age, PMBR latency). The results revealed a significant interaction between group and age. While age had a significant effect on PMBR in the controls, no simple effects of age were detected in the FASD group. The described findings provide further evidence for broad impairments in inhibitory processes in adolescents with FASD, possibly related to aberrant development of GABA-ergic pathways.

TABLE OF CONTENTS

LIST OF FIGURES vii

INTRODUCTION 1

Background 1

Inhibitory Control in Children with FASDs 3

Post-Movement Beta Rebound 4

Proposed Study and Hypotheses 5

METHODS 6

Participants 6

Task 6

Data Collection and Preprocessing 7

PMBR Localization in the Motor Cortex 8

Data Analysis 10

RESULTS 12

Behavioral Measures 12

PMBR Localization in the Motor Cortex 12

Interactions, Main, and Simple Effects 13

Examination of TFR and Beta Time Courses 14

DISCUSSION 16

REFERENCES 20

LIST OF FIGURES

Figure 1. Post-movement Beta Rebound Localization 26

Figure 2. Significant Interactions and Main Effects 27

Figure 3. Time-Frequency Maps for Main Effects 28

Figure 4. Simple Effects of Group Within Different Levels of Age 29

Supplementary Figure 1. MEG Data Co-registration and Transformation to MNI-152 space 30

Supplementary Figure 2. Behavioral Data 32

Introduction

Background

Prenatal alcohol exposure produces a variety of developmental problems in children that have life-long implications. The physical and mental manifestations of early ethanol exposure are collectively defined as fetal alcohol spectrum disorders (FASDs). The disorders account for the largest proportion of preventable causes of intellectual disability in the United States (May et al. 2009). With about 130,000 pregnant mothers exposing their unborn children to dangerously high levels of alcohol annually, and the lifetime cost of the disease approaching 3 million USD per person, research on symptom mitigation, treatment, and diagnosis of FASD carries substantial social and economic incentives (Abel, 1998; Lupton et al., 2004).

Neuropsychological studies have demonstrated a variety of attentional, perceptual, cognitive, and executive control impairments in children with FASDs (Meyer 1998; Strömland 2004; Franklin et al. 2008; Mattson et al. 2011; Paolozza et al. 2014). Neurophysiological correlates of these deficits have the potential to serve as biomarkers for diagnosis and severity assessment. Few neuroimaging measures on FASD samples exist today, largely due to the difficulties involved in scanning young clinical populations. While comparatively non-invasive methods such as electroencephalography (EEG) have been successfully implicated in studying children with FASDs (Kaneko et al. 1996; Burden et al. 2009; Hemington and Reynolds 2014), the use of imaging tools with higher spatial resolutions, functional magnetic resonance imaging (fMRI) in particular, poses significant challenges due to loud and potentially

claustrophobia-inducing scanner environments. The use of magnetoencephalography (MEG) to image children's brain function, on the other hand, has shown great potential for such applications due to its quiet, non-invasive nature (Minassian et al. 1999; Ciesielski and Stephen 2014), and has been implicated in numerous experiments studying young populations (Paetau et al. 1995; Lewine et al. 1999; Otsubo and Snead 2001). Importantly, utilizing MEG source localization algorithms offers spatial resolution that exceeds that of EEG, while maintaining temporal resolution on the order of milliseconds.

Previously described functional brain impairments in individuals with FASD, observed using MEG, include delays in primary auditory and visual processing (Stephen et al. 2012; Coffman et al. 2013). While such findings are consistent with reports of widespread deficiencies in sensory processing and motor control in this clinical population (Franklin et al. 2008; Jirikowic et al. 2008, 2013; Tesche et al. 2015), the mechanisms underlying the observed patterns remain unknown. Further complicating these findings is evidence that sensory impairments observed in very young children with FASD may not generalize to older individuals. Specifically, studies examining auditory processing in older FASD samples have demonstrated a lack of delays in 4-15 year old children (Kaneko et al. 1996) and shorter processing times in adolescents (Tesche et al. 2015).

In addition to impaired sensory processing, children with FASDs have been reported to display aberrant oscillatory activity in the right parieto-frontal network during a prosaccade task, particularly in the gamma frequency range

(Stephen et al. 2013), suggesting impairments in motor control. Indeed, children with FASDs appear to have difficulties executing tasks involving complex fine motor skills (Doney et al. 2014) as well as exertion of isometric force (Simmons et al. 2012). Analogously to the reported sensory impairments in this clinical population, few explanations exist for the observed broad deficiencies in motor control.

Inhibitory Control in Children with FASDs

One explanation for the impairments in motor control implements inhibitory control processes, specifically ones involving GABA neurotransmitter, as the primary factors driving the neurophysiological findings in FASD. Making this a compelling theory is the apparent specificity of recently-reported FASD findings to the gamma and beta power bands (Stephen et al. 2013; Tesche et al. 2015), frequencies associated with GABA-ergic activity in visual and motor areas (Muthukumaraswamy et al. 2009; Hall et al. 2011). In addition, animal FASD models have demonstrated the GABA-ergic inhibitory pathways as being particularly sensitive to early alcohol exposure. Specifically, impairments in expression of GABA-α have been reported (Toso et al. 2006). Further, ethanol appears to inhibit long-term post-synaptic potentiation and facilitate long term depression via GABA-α and NMDA modulation in the hippocampus, possibly contributing to learning difficulties experienced by FASD patients (Zucca and Valenzuela 2010). While histological and animal *in vivo* studies have shed light on prenatal alcohol exposure's potential structural and chemical effects on the brain, no study to date has examined the neurophysiological markers of such

inhibitory GABA-ergic alterations in individuals with FASDs. The present study thus aimed to investigate whether any abnormalities in the functional manifestations of GABA-ergic activity exist in human subjects with FASDs.

Post-Movement Beta Rebound

The post-movement beta rebound (PMBR) is defined as a transient increase in beta power (15-30 Hz) in the motor cortex following termination of voluntary movement, during which beta activity is suppressed (Pfurtscheller et al. 1996). This power increase briefly exceeds the levels observed prior to the movement. While the PMBR response is a reliable and widely described phenomenon, relatively little is known about its specific mechanisms. Confounding our understanding of this response is the fact that it also occurs during tactile stimulation experiments, passive movements, and even observation of movements executed by others (Alegre et al. 2002; Muthukumaraswamy and Johnson 2004; Gaetz and Cheyne 2006; Neuper et al. 2006). In the context of a task, performed or observed, the beta rebound appears to be modulated by the participant's perceived accuracy of the provided response, increasing when an incorrect response is provided (Koelewijn et al. 2008). Further, PMBR has previously been investigated in this context in a group of participants with autism spectrum disorders, whose beta activity was found to be lower than controls' during observation of motor actions (Honaga et al. 2010). These results suggest that motor cortical beta rhythm appears to be involved in top-down inhibitory processes.

Importantly, PMBR has been shown to represent a marker of functional brain development, increasing in power as a function of age in healthy individuals (Gaetz et al. 2010). The authors suggested that the findings reflected activity of the GABA-ergic inhibitory system, the development of which may parallel that of the PMBR. Indeed, the beta oscillations in the motor cortex have been shown to rely on the GABA-ergic interneurons in deep cortical layers (Hall et al. 2011). The PMBR may thus offer a fundamental developmental measure of the inhibitory GABA-ergic system in the brain, making it an appealing investigation target in individuals with developmental disorders such as FASDs.

Proposed Study and Hypotheses

Given the possible relationship between the PMBR and GABA-ergic inhibitory processes in the brain (Hall et al. 2011), we sought out to investigate whether the beta rebound can be utilized as a neurophysiological marker of FASD. The present study examines the extent to which, if any, the PMBR is affected by FASDs in terms of its development between childhood and adolescence. In light of the reported negative effects of ethanol exposure on GABA-ergic processes, we hypothesize that individuals with FASD would have diminished PMBR when compared to controls, and that age would affect the development of this response differently in the FASD and control groups. Specifically, our prediction is that the FASD group would exhibit diminished PMBR power increases as a function of age relative to healthy controls.

Methods

Participants

Twenty-one children with FASDs (10 males, 12 females; 15.6 ± 2.9 y. o.) were recruited from the University of New Mexico (UNM) Fetal Alcohol Diagnostic and Evaluation Clinic in Albuquerque, NM, USA. Eleven participants were diagnosed with alcohol-related neurodevelopmental disorder (ARND), while 11 had fetal alcohol syndrome (FAS) diagnoses. Twenty-two age-matched control subjects (10 males, 12 females; 16.3 ± 3.0 y. o.) were recruited via flyers posted around campus. Control subjects were selected on the criteria of having no history of prenatal alcohol exposure, as well as developmental, neurological, or psychiatric disorders. All participants were right-handed, had corrected vision and good hearing. Prior to participation in the study, the participants or legal guardians, depending on age, reviewed and signed the informed consent form, which was approved by the UNM Institutional Review Board.

Task

The data analyzed in the present study were collected as a part of an auditory oddball paradigm. Standard stimuli consisted of 1 kHz tones presented for 200 ms with a randomized onset asynchrony between 1 and 3 seconds. The standard stimuli were grouped in clusters of 3-5 consecutive presentations in between novel or target stimuli. Target stimuli consisted of 1.5 kHz tones presented for 200 ms, to which participants were instructed to respond to by pressing a button with the right index finger. Previously-unused digital sounds comprised the novel cues. The stimuli were presented bilaterally using plastic

tubes inserted into the participants' ears. All subjects completed 4 scans, with a total of 784 standard, 98 target, and 98 novel stimuli being presented to each participant.

Data Collection and Preprocessing

The data were collected using a 306-channel Elekta Neuromag system (Elekta NeuroMag, Elekta AB, Stockholm, Sweden), located inside a magnetically shielded room at the Mind Research Network, Albuquerque, NM, USA. Prior to the scan, the shapes of participants' heads were traced using a Polhemus system for co-registration purposes. Four head position indicator (HPI) coils were attached to the subjects' heads (2 forehead, 2 mastoids) for continuous tracking of the head position inside the sensor array throughout the scan. The subjects' eye movements and heart rates were recorded using bipolar electrooculogram (horizontal and vertical) and electrocardiogram electrodes, respectively. Participants were placed into the scanner in a sitting position, and had the response device, a "claw" with buttons underneath each finger, attached to the right arm with Velcro tape. The raw MEG scans were preprocessed using MaxFilter software (Elekta NeuroMag, Elekta AB, Stockholm, Sweden), which utilizes spatial filters to eliminate non-head-originating signals from the data and corrects it for motion using the information provided by the HPI coils, re-positioning the functional recordings to a default static location within the MEG sensor helmet. The continuous data were additionally down-sampled to a rate of 600 Hz.

The resulting scans were reduced to their functional constituents using independent component analysis in MNE, which utilizes blind source separation algorithms to decompose the observed aggregate, linearly-mixed signal into components with high intrinsic levels of coherence and maximal spatial independence. The obtained spatial network distributions were qualitatively examined for known EOG and ECG component features, such as bilateral prefrontal and bilateral posterior edge artifacts, respectively. Components were also examined in terms of their correlations with the data recorded from the ECG and EOG channels. Those components with significant EOG/ECG correlations and features were removed, and the data were reconstituted back to its aggregate format. Since planar gradiometers used in the described MEG sensor array have been shown to provide more accurate representations of superficial local source activity than magnetometers, magnetometer channels were excluded from further analyses.

PMBR Localization in the Motor Cortex

All but 4 subjects underwent a structural MRI scan to be used for source localization. An MNI-152 template structural volume was segmented and used to compute the brain volume model. Analogous brain models were created for all subjects using individual structural MRI scans. A 7 mm resolution grid was then fit within the segmented template brain volume, resulting in a matrix with 5027 points. The grid points were subsequently nonlinearly fit to each subject's brain volume model, resulting in brain grids that can be aligned to MNI-152 space via reverse transforms. Since the subject-aligned grids were not linearly spaced, it

was imperative to transform the individual data to the template volume after beamforming and prior to interpolation. Each subject's grid was used to compute the leadfield prior to source localization. The co-registration process is summarized in Supplementary Figure 1.

In order to detect beta time-locked activity, the preprocessed continuous runs were band-pass filtered in the 15-30 Hz range for source localization purposes. The data were epoched 5 s before and 5 s after button presses, excluding those that followed non-target stimuli, leaving only correct response trials. This measure was taken due to reports that the PMBR is modulated by the subjects' perceived accuracy on the task at hand, increasing in power following subjectively erroneous motor responses (Koelewijn et al. 2008). Although the time interval of interest in this study is [-1.5 2 s] relative to the button press, we utilized the longer, padded trials in order to increase the precision of beamformer filters and pad the time-frequency wavelet-based analyses. The resulting segments were scanned for jump artifacts in the [-1.5 2 s] period of interest, and bad trials were removed. The full 10 s epochs were then used to compute the average linearly constrained minimum variance (LCMV) spatial filter, producing a common beamforming filter to be used for individual localizations of separate conditions. The use of a common filter removes any potential differences in within-trial comparisons that can arise due to the use of filters that are computed separately for each data segment. Using the obtained common filter, source localization was performed on the [-1.5 -1 s] "baseline" and [1 1.5 s] "active" segments of each trial. The two datasets were then entered into a t-test,

producing a whole-head spatial t-map for each participant. The t-maps were transformed to the MNI template volumes for interpolation and anatomical inferences.

Given that the purpose of this study was to investigate a fundamental neurophysiological developmental marker, we sought to identify the location where it is most robust, and constrain further analyses to that area. As PMBR has been consistently reported in the hemisphere ipsilateral to the movement, and beta increases may be present in areas other than the motor cortices, the search for maximum activation was restricted to clusters in the left hemispheric motor area. This was achieved by identifying the indices of the motor region of interest in the MNI template grid, transforming each subject's individual whole-head t-map to the MNI coordinate space, identifying the grid point indices corresponding to the left motor cortex, and restricting the search for the maximum activation to these grid indices. Data from a single source with the highest time-locked beta activation was selected form each participant for further analyses.

Data Analysis

Time courses from the locations of the maximum t-map values obtained in the previous step were transformed to time frequency domain on a trial-wise basis using a 7-cycle wavelet convolution. Power maps were obtained for the [-1.5 2 s] time period and frequencies in the range of [1 50 Hz]. Individual beta [15 30 Hz] time courses were then extracted and baseline corrected using a pseudo-z statistic, which applied a pseudo-z transform at each data point using the [-1.5 -

1 s] baseline mean and standard deviation. Beta time courses were entered into a series of t-tests contrasting the [-1.5 -1 s] and [1 1.5 s] time periods to obtain the evoked beta power values. Since the range used for the calculation of evoked beta power was primarily selected for localization purposes and may not have captured the full activation range of the PMBR, an analogous procedure was also utilized to obtain the beta evoked power values during the [0.5 1 s] range, resulting in two levels of PMBR latency in the analysis.

Adolescent and young adult groups were created by splitting control and FASD cohorts down the mean age, producing 12-15 and 16-22 year old data sets within each group. The obtained PMBR values were subsequently entered into a 3-way (group x PMBR latency x age) ANOVA. Full [1 50 Hz] time-frequency maps were decibel baseline corrected using the [-1.5 -1 s] time interval, and one sample t-tests were performed on them for result interpretations and presentation purposes. To aid the inferences from any potential interactions of main effects detected in the previous steps, the maps were contrasted between different levels of age and group, including simple effects.

Results

Behavioral Measures

An analysis of variance in target identification accuracy (control adolescents: 93.6 ± 2.2 %; control young adults: 96.7 ± 1.2 %; FASD adolescents: 90.9 ± 2.9; FASD young adults: 80.3 ± 10.4) detected a significant interaction between group (FASD, controls) and age (adolescents, young adults) ($p < 0.05$). Further examination of performance within each group revealed a low-performing 16 year-old outlier in the FASD cohort (Supplementary Figure 2). While the interaction lost significance upon removal of the outlier's data, we kept the imaging data from the participant in the analysis, as only correct trials were examined. An analogous analysis of variance in participants' response times (control adolescents: 490 ± 22 ms; control young adults: 480 ± 28 ms; FASD adolescents: 511 ± 22 ms; FASD young adults: 484 ± 37 ms) indicated no significant main effects of age or group. Further, the interaction between age and group was not significant.

PMBR Localization in the Motor Cortex

All subjects had beta activity clusters localized to their left hemispheric motor cortices. Nearly all participants also displayed evoked beta power in the motor areas ipsilateral to the movement side as well. Further, activations were observed in the anterior and posterior cingulate areas of some subjects, an expected pattern during engagement in a cognitive task. Localization results for representative individuals from each group are presented in Figure 1. The time courses extracted from the points of maximum PMBR were visually examined,

with all showing clear time-locked beta activities. The four subjects who did not complete MRI scans had their volume models replaced by those from age and sex-matched controls. While this raised concerns regarding localization accuracies, as children with FASD have been shown to have lower mean brain volumes relative to controls, individual examinations of evoked PMBR t-maps in substituted volumes revealed them to be consistent with non-substituted source distributions.

Interactions and Main Effects

The ANOVA detected significant main effects of age ($F(1, 6096) = 51.06$, $p < 0.001$), group ($F(1, 6096) = 24.67$, $p < 0.001$), and latency ($F(1, 6096) = 12.29$, $p < 0.001$), which are presented in Figure 2. No significant interactions between age, group, and latency, between age and latency, or between group and latency were observed. The interaction between age and group, however, was significant ($F(1, 6096) = 19.69$, $p < 0.001$), and is also shown in Figure 2. Although the main effects of group, age, and latency are presented to the reader, we caution that few meaningful inferences can be made from these effects since the group-by-age interaction was significant. In order to examine the interaction between age and group, the FASD and control groups were contrasted within each level of age. While no significant effect of group was detected in adolescents ($MD = 0.43 \pm 0.10$, $p = 0.7$), the young adult controls had significantly higher levels of PMBR than young adults with FASDs ($MD = 7.55 \pm 1.17$, $p < 0.001$).

Examination of TFR and Beta Time Courses

The time-frequency map comparisons between the FASD and control groups revealed significantly lower levels of [15 30 Hz] power in the FASD (Figure 3) group between 0.5 and 1 s following the button press (FDR corrected $p < 0.001$). Additionally, the control group exhibited lower power levels in the same range just prior to the button press (Figure 3). Consistent with the time-frequency maps, beta power time course comparisons suggested that the beta desynchronization during the movement was lower in FASD subjects than controls on average. Further, the average PMBR following the desynchronization was also lower in the FASD group relative to controls. The time-frequency map comparison between adolescents and young adults indicated that the main effect of age occupied nearly the entire PMBR time-frequency range, with significant power increases observed throughout the [0.5 1.5 s] period after the button press (Figure 3). The beta time course comparisons showed that young adults displayed significantly higher PMBR than adolescents during nearly the entire examined period after the button press.

The time-frequency map comparisons between groups within each level of age were used to further elaborate on the simple effects detected by the ANOVA. The comparison between control and FASD adolescents found no significant differences at the FDR corrected $p = 0.001$ threshold. The group beta time course contrast within young adults, however, did detect an increased averaged beta desynchronization in controls relative to adolescents with FASDs (Figure 4). A significant group effect was observed in the young adult cohort, with controls'

PMBR levels in the [0.5 1 s] range exceeding those evoked in the FASD group (Figure 4). Beta time courses indicated not only that the young adult controls' PMBR had a higher power than the FASD group, but that the desynchronization latency appeared to be delayed in the FASD group.

Discussion

In the described study, we isolated a PMBR response following cued finger movement, and detected a pattern of PMBR development throughout adolescence that is consistent with previous reports of PMBR maturation in healthy individuals (Gaetz et al. 2010). We detected significant increases in PMBR power in typically developing controls between 12-15 and 16-22 year age ranges, with the differences spanning a wide time-frequency range that encompasses nearly all of the PMBR. These results validate the use of the PMBR as a suitable measure of functional brain development in the described study. As such, PMBR group differences between FASD and control subjects were consistent with our hypothesis, with significant rebound impairments detected in the young adult FASD group. Finally, the late [1 1.5 s] beta power was found to have higher rebound values than the early [0.5 1 s] activity, implying that the "active" time window used for PMBR localization was appropriate and accounted for most of the rebound power.

The age-by-group interaction suggested that the development of inhibitory processes in the motor cortex may be compromised in individuals with FASD. The lack of PMBR differences between groups in young children is consistent with the inhibition hypothesis of PMBR function, given that cognitive and sensorimotor inhibitory systems are largely undeveloped in healthy young children (Brainerd and Dempster 1995). The low PMBR power levels in young adults with FASDs may thus be representative of broader impairments in other inhibitory pathways that develop throughout adolescence. As the group analysis

utilized herein did not allow for the examination of the specific nuances in PMBR developmental trajectories, we cannot extrapolate the reported findings to individuals with FASDs who are younger or older than the analyzed cohorts. Specifically, we cannot speculate on whether the observed PMBR impairments in individuals with FASDs are static, or merely represent a protracted developmental trajectory of the beta rebound. Given the positive trend in PMBR power in the FASD cohort as a function of age, however, the latter explanation appears plausible.

The pattern in the time-frequency map comparison between FASD and control groups is suggestive of group latency differences in beta desynchronization and rebound (Figure 3). Indeed, the examination of beta time courses demonstrated group discrepancies in the time of beta desynchronization onset just prior to the button press (Figure 3). In addition, the latency of resynchronization after the movement also appears to lag behind that of controls. In summary, subjects with FASDs displayed a slower beta power decrease leading up to the button press and a slower increase in power after. A possible explanation for this finding is varying finger movement speed between groups, with FASD participants taking more time to press the button. Since no measures of finger movement initiation and termination were recorded, we cannot readily test this speculation. However, given that the response times did not vary significantly between groups, we are reluctant to attribute the difference in PMBR onset to a movement speed discrepancy. In addition, although beta power clearly decreased below baseline levels during the button press, the inferences made

about this time course may not be accurate in the context of the present study, as beta desynchronization during movement and its post-movement rebound appear to be spatially separated in the brain (Jurkiewicz et al. 2006). As such, future studies seeking to examine the full time-locked range of beta activity in the FASD patients' motor cortex will need to localize the beta power decrease separately from the PMBR.

The reported findings suggest that inhibitory modulation of the motor cortex in FASD patients is not only impaired at the stage of imposing the inhibition after the movement, but could also be altered in its ability to lift inhibition to allow movement initiation. Correlating such delays in event-related beta desynchronization and rebound with response times is of interest for future investigations. Of additional interest are examinations of the degrees of beta connectivity that the motor cortex exhibits with other brain areas, such as the lateral prefrontal cortices, which are thought to be primarily responsible for imposing inhibitive control over other brain areas (Berkman et al. 2009; Aron et al. 2014). Further, techniques such as magnetic resonance spectroscopy (MRS) can be used to establish a link between motor beta activity and GABA-ergic inhibitory processes in adolescents with FASDs.

The presented study further supports the findings that prenatal alcohol exposure has long-lasting consequences that affect development long after birth. Specifically, we have shown that the post-movement beta rebound, a possible measure of GABA-ergic inhibitory processes, failed to properly develop in FASD adolescents. Further studies examining different ranges of the FASD spectrum

are needed to validate the predictive power, if any, PMBR may offer in diagnosing the disorders. In addition, study designs with more accurate temporal control of voluntary movements are needed to replicate the findings described herein, as temporal variability in movement termination may potentially contaminate PMBR measures. Finally, it is imperative for subsequent investigations of PMBR in FASD populations to utilize functional connectivity measures between different brain areas in order to paint a clearer picture of any abnormalities in the beta-reliant inhibitory system.

References

Abel EL. 1998. Fetal Alcohol Abuse Syndrome. Springer Science & Business Media.

Alegre M, Labarga A, Gurtubay IG, Iriarte J, Malanda A, Artieda J. 2002. Beta electroencephalograph changes during passive movements: sensory afferences contribute to beta event-related desynchronization in humans. Neurosci Lett. 331:29–32.

Aron AR, Robbins TW, Poldrack RA. 2014. Inhibition and the right inferior frontal cortex: one decade on. Trends Cogn Sci. 18:177–185.

Berkman ET, Burklund L, Lieberman MD. 2009. Inhibitory spillover: intentional motor inhibition produces incidental limbic inhibition via right inferior frontal cortex. NeuroImage. 47:705–712.

Brainerd CJ, Dempster FN. 1995. Interference and Inhibition in Cognition. Academic Press.

Burden MJ, Andrew C, Saint-Amour D, Meintjes EM, Molteno CD, Hoyme HE, Robinson LK, Khaole N, Nelson CA, Jacobson JL, Jacobson SW. 2009. The effects of fetal alcohol syndrome on response execution and inhibition: an event-related potential study. Alcohol Clin Exp Res. 33:1994–2004.

Ciesielski KR, Stephen JM. 2014. Pediatric MEG: Investigating Spatio-Temporal Connectivity of Developing Networks. In: Supek S, Aine CJ, editors. Magnetoencephalography. Springer Berlin Heidelberg. p. 525–555.

Coffman BA, Kodituwakku P, Kodituwakku EL, Romero L, Sharadamma NM, Stone D, Stephen JM. 2013. Primary visual response (M100) delays in adolescents with FASD as measured with MEG. Hum Brain Mapp. 34:2852–2862.

Doney R, Lucas BR, Jones T, Howat P, Sauer K, Elliott EJ. 2014. Fine motor skills in children with prenatal alcohol exposure or fetal alcohol spectrum disorder. J Dev Behav Pediatr JDBP. 35:598–609.

Franklin L, Deitz J, Jirikowic T, Astley S. 2008. Children with fetal alcohol spectrum disorders: problem behaviors and sensory processing. Am J Occup Ther Off Publ Am Occup Ther Assoc. 62:265–273.

Gaetz W, Cheyne D. 2006. Localization of sensorimotor cortical rhythms induced by tactile stimulation using spatially filtered MEG. NeuroImage. 30:899–908.

Gaetz W, Macdonald M, Cheyne D, Snead OC. 2010. Neuromagnetic imaging of movement-related cortical oscillations in children and adults: age predicts post-movement beta rebound. NeuroImage. 51:792–807.

Hall SD, Stanford IM, Yamawaki N, McAllister CJ, Rönnqvist KC, Woodhall GL, Furlong PL. 2011. The role of GABAergic modulation in motor function related neuronal network activity. NeuroImage. 56:1506–1510.

Hemington KS, Reynolds JN. 2014. Electroencephalographic correlates of working memory deficits in children with Fetal Alcohol Spectrum Disorder using a single-electrode pair recording device. Clin Neurophysiol. 125:2364–2371.

Honaga E, Ishii R, Kurimoto R, Canuet L, Ikezawa K, Takahashi H, Nakahachi T, Iwase M, Mizuta I, Yoshimine T, Takeda M. 2010. Post-movement beta rebound abnormality as indicator of mirror neuron system dysfunction in autistic spectrum disorder: An MEG study. Neurosci Lett. 478:141–145.

Jirikowic TL, McCoy SW, Lubetzky-Vilnai A, Price R, Ciol MA, Kartin D, Hsu L-Y, Gendler B, Astley SJ. 2013. SENSORY CONTROL OF BALANCE: A COMPARISON OF CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS TO CHILDREN WITH TYPICAL DEVELOPMENT. J Popul Ther Clin Pharmacol J Ther Popul Pharamcologie Clin. 20:e212–e228.

Jirikowic T, Olson HC, Kartin D. 2008. Sensory Processing, School Performance, and Adaptive Behavior of Young School-Age Children with Fetal Alcohol Spectrum Disorders. Phys Occup Ther Pediatr. 28:117–136.

Jurkiewicz MT, Gaetz WC, Bostan AC, Cheyne D. 2006. Post-movement beta rebound is generated in motor cortex: evidence from neuromagnetic recordings. NeuroImage. 32:1281–1289.

Kaneko WM, Ehlers CL, Philips EL, Riley EP. 1996. Auditory event-related potentials in fetal alcohol syndrome and Down's syndrome children. Alcohol Clin Exp Res. 20:35–42.

Koelewijn T, van Schie HT, Bekkering H, Oostenveld R, Jensen O. 2008. Motor-cortical beta oscillations are modulated by correctness of observed action. NeuroImage. 40:767–775.

Lewine JD, Andrews R, Chez M, Patil A-A, Devinsky O, Smith M, Kanner A, Davis JT, Funke M, Jones G, Chong B, Provencal S, Weisend M, Lee RR,

Orrison WW, Jr MD. 1999. Magnetoencephalographic Patterns of Epileptiform Activity in Children With Regressive Autism Spectrum Disorders. Pediatrics. 104:405–418.

Lupton C, Burd L, Harwood R. 2004. Cost of fetal alcohol spectrum disorders. Am J Med Genet C Semin Med Genet. 127C:42–50.

Mattson SN, Crocker N, Nguyen TT. 2011. Fetal alcohol spectrum disorders: neuropsychological and behavioral features. Neuropsychol Rev. 21:81–101.

May PA, Gossage JP, Kalberg WO, Robinson LK, Buckley D, Manning M, Hoyme HE. 2009. Prevalence and epidemiologic characteristics of FASD from various research methods with an emphasis on recent in-school studies. Dev Disabil Res Rev. 15:176–192.

Meyer MJ. 1998. Perceptual differences in fetal alcohol effect boys performing a modeling task. Percept Mot Skills. 87:784–786.

Minassian BA, Otsubo H, Weiss S, Elliott I, Rutka JT, Snead OC. 1999. Magnetoencephalographic localization in pediatric epilepsy surgery: Comparison with invasive intracranial electroencephalography. Ann Neurol. 46:627–633.

Muthukumaraswamy SD, Edden RAE, Jones DK, Swettenham JB, Singh KD. 2009. Resting GABA concentration predicts peak gamma frequency and fMRI amplitude in response to visual stimulation in humans. Proc Natl Acad Sci. 106:8356–8361.

Muthukumaraswamy SD, Johnson BW. 2004. Primary motor cortex activation during action observation revealed by wavelet analysis of the EEG. Clin Neurophysiol. 115:1760–1766.

Neuper C, Wörtz M, Pfurtscheller G. 2006. ERD/ERS patterns reflecting sensorimotor activation and deactivation. In: Klimesch CN and W, editor. Progress in Brain Research. Event-Related Dynamics of Brain Oscillations. Elsevier. p. 211–222.

Otsubo H, Snead OC. 2001. Topical Review: Magnetoencephalography and Magnetic Source Imaging in Children. J Child Neurol. 16:227–235.

Paetau R, Ahonen A, Salonen O, Sams M. 1995. Auditory evoked magnetic fields to tones and pseudowords in healthy children and adults. J Clin Neurophysiol Off Publ Am Electroencephalogr Soc. 12:177–185.

Paolozza A, Treit S, Beaulieu C, Reynolds JN. 2014. Response inhibition deficits in children with Fetal Alcohol Spectrum Disorder: Relationship between diffusion tensor imaging of the corpus callosum and eye movement control. NeuroImage Clin. 5:53–61.

Pfurtscheller G, Stancák Jr. A, Neuper C. 1996. Post-movement beta synchronization. A correlate of an idling motor area? Electroencephalogr Clin Neurophysiol. 98:281–293.

Simmons RW, Nguyen TT, Levy SS, Thomas JD, Mattson SN, Riley EP. 2012. Children with heavy prenatal alcohol exposure exhibit deficits when regulating isometric force. Alcohol Clin Exp Res. 36:302–309.

Stephen JM, Coffman BA, Stone DB, Kodituwakku P. 2013. Differences in MEG gamma oscillatory power during performance of a prosaccade task in adolescents with FASD. Front Hum Neurosci. 7.

Stephen JM, Kodituwakku PW, Kodituwakku EL, Romero L, Peters AM, Sharadamma NM, Caprihan A, Coffman BA. 2012. Delays in Auditory Processing Identified in Preschool Children with FASD. Alcohol Clin Exp Res. 36:1720–1727.

Strömland K. 2004. Visual impairment and ocular abnormalities in children with fetal alcohol syndrome. Addict Biol. 9:153–157; discussion 159–160.

Tesche CD, Kodituwakku PW, Garcia CM, Houck JM. 2015. Sex-related differences in auditory processing in adolescents with fetal alcohol spectrum disorder: A magnetoencephalographic study. NeuroImage Clin. 7:571–587.

Toso L, Roberson R, Woodard J, Abebe D, Spong CY. 2006. Prenatal alcohol exposure alters GABAAα5 expression: A mechanism of alcohol-induced learning dysfunction. Am J Obstet Gynecol. 195:522–527.

Zucca S, Valenzuela CF. 2010. Low Concentrations of Alcohol Inhibit BDNF-Dependent GABAergic Plasticity via L-type Ca2+ Channel Inhibition in Developing CA3 Hippocampal Pyramidal Neurons. J Neurosci. 30:6776–6781.

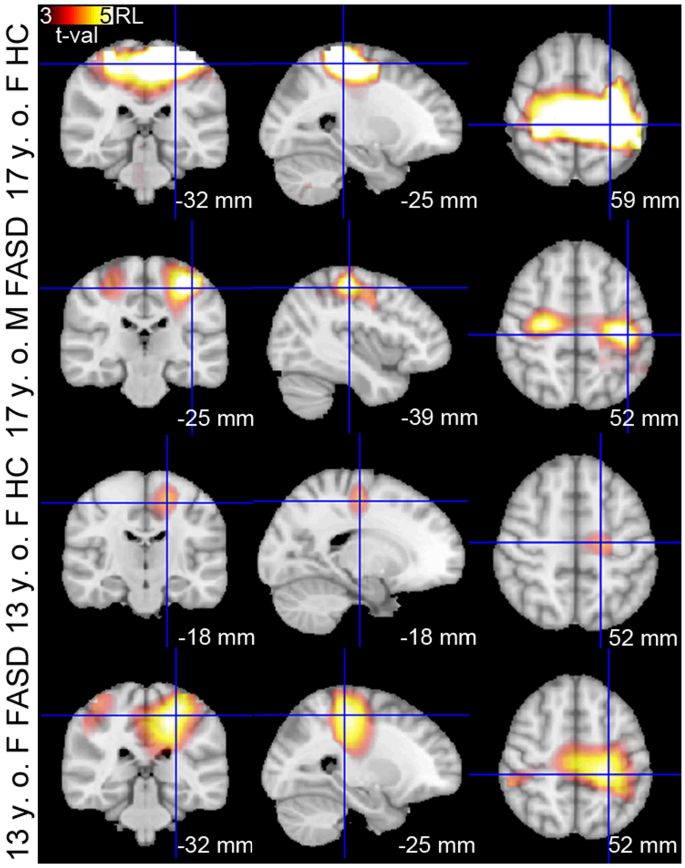


Figure 1. Post-movement Beta Rebound Localization. Data from representative participants in the young adult healthy control (HC), young adult FASD, adolescent control, and adolescent FASD groups are presented in radiological convention on MNI-152 template volumes. The threshold for the activation maps is p = 0.05. The crosshairs are centered on the location of maximum evoked PMBR in each volume.

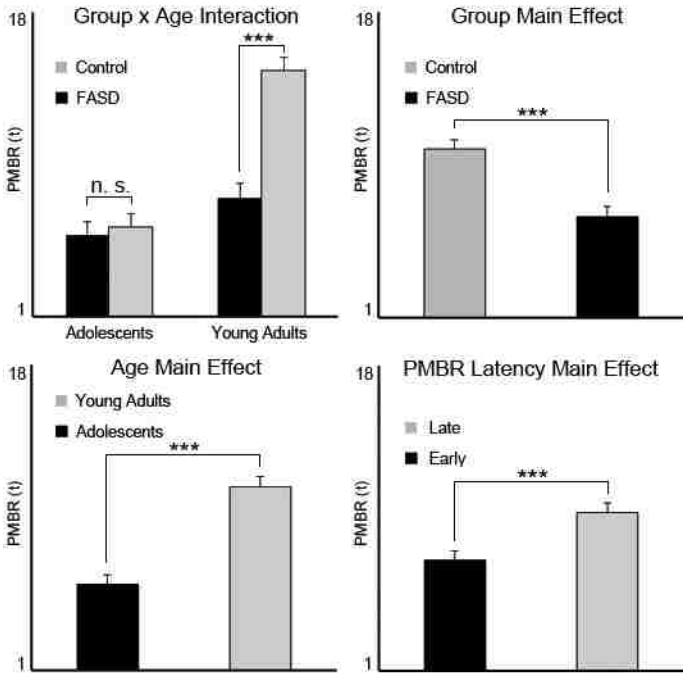


Figure 2. Significant Interactions and Main Effects. Controls displayed significantly higher PMBR than the FASD group ($p < 0.001$). Main effect of age group (12-15 and 16-22 years old) was significant, with higher PMBR in controls than in the FASD group ($p < 0.001$). Relative to the [-1.5 -1 s] baseline period, late [1 1.5] PMBR power was statistically higher than the early [0.5 1 s] PMBR power levels ($p < 0.001$). Group-by-age interaction is presented in terms of simple effects of group (FASD and control) within each level of age (adolescents and young adults). While a significant effect of age was observed in the control group ($p < 0.001$), no such effect was detected in the FASD group ($p = 0.7$).

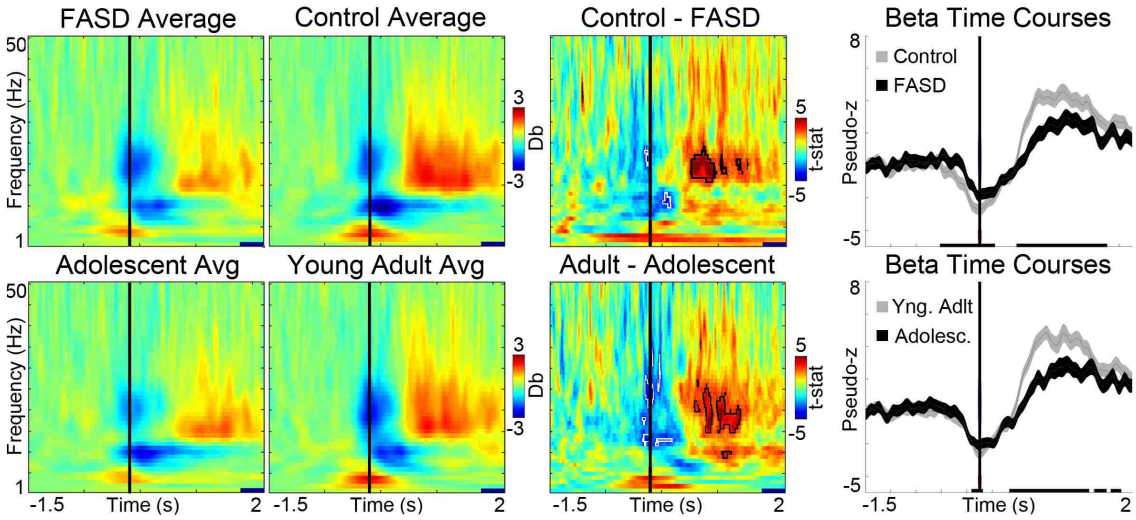


Figure 3. Time-Frequency Maps for Main Effects. Time-frequency maps are presented for the control and FASD groups, as well as the contrast between the two. The main effects of group are outlined (black = control > FASD; white = FASD > control; FDR-corrected p = 0.001). Average beta time courses are shown for both groups, with black bars on the bottom representing the significance of a between-group t-test at each time point (FDR-corrected p = 0.001). Time-frequency maps for the young adult and adolescent groups are also shown, with the main effects of age outlined on the comparison map (black = young adults > adolescents; white = adolescents > young adults; FDR-corrected p = 0.001). Beta time courses are presented for both groups, with black bars on the bottom representing the significance of a between-group t-test at each time point (FDR-corrected p = 0.001).

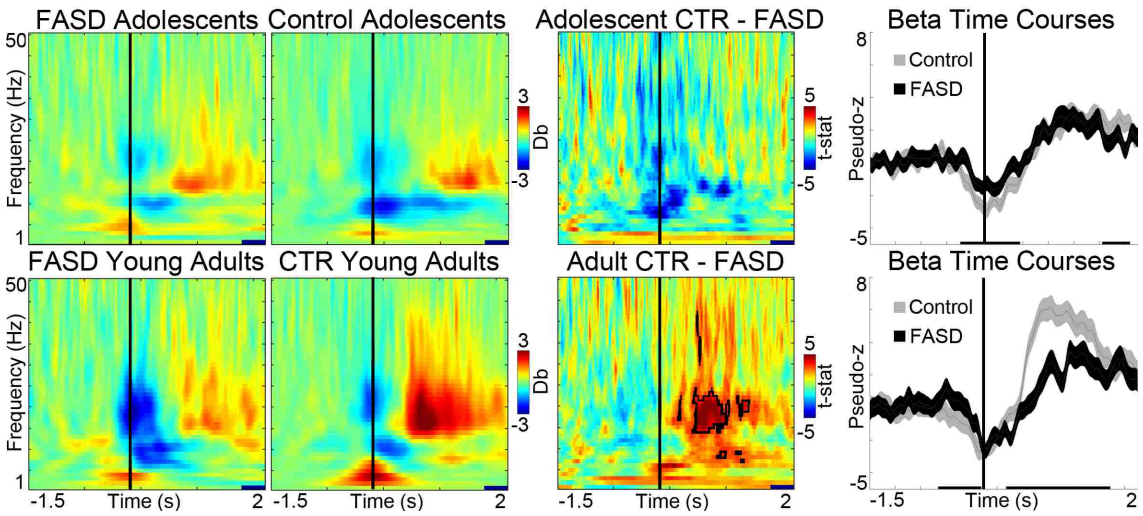
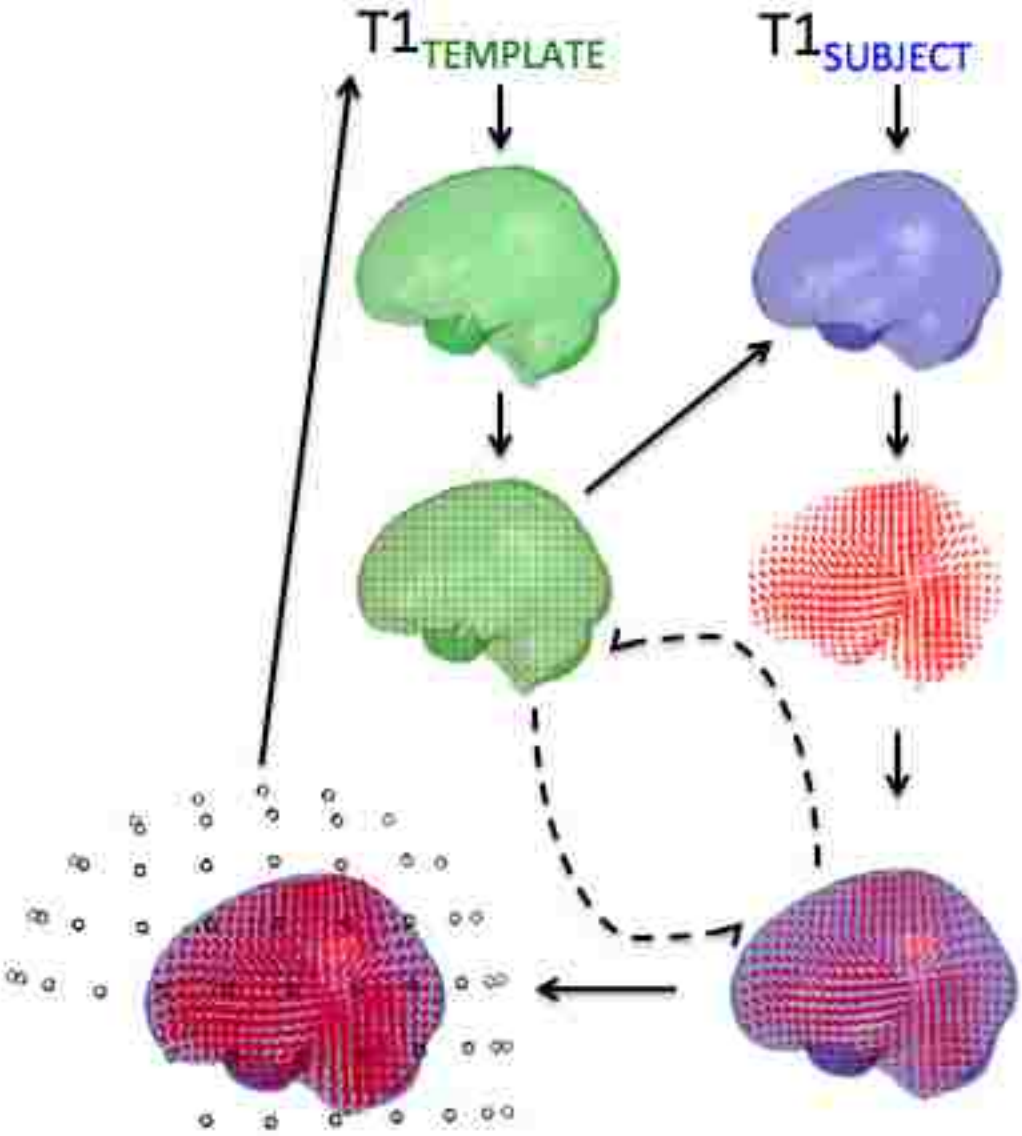
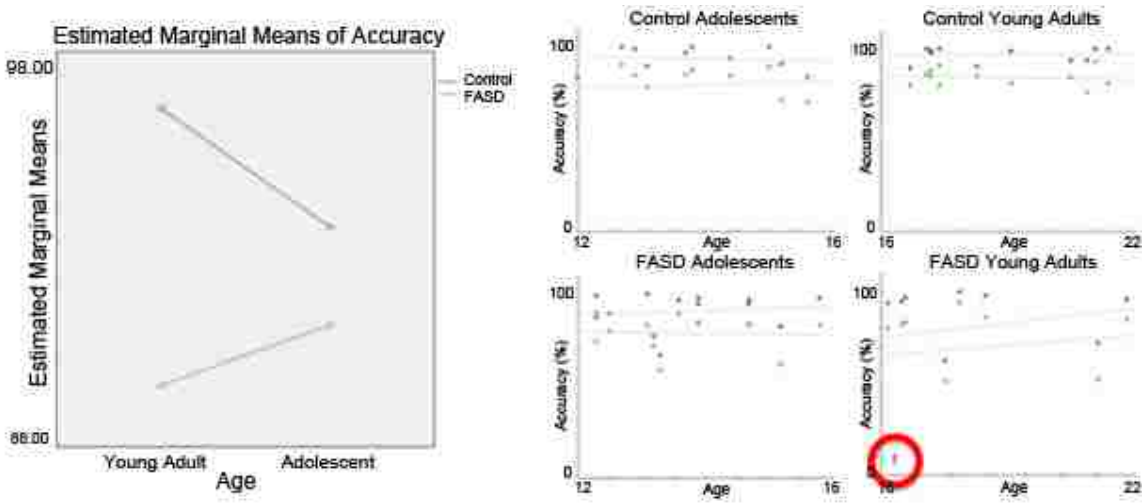


Figure 4. Simple Effects of Group Within Different Levels of Age. Group (FASD, control) did not exhibit a statistically significant simple effect on PMBR within the adolescent cohort. A simple effect of group on PMBR within the young adult cohort was significant (FDR-corrected p = 0.001), with greater rebound power observed in controls than participants with FASDs. Contrast maps are presented, with statistically significant differences outlined (black = control > FASD). Beta time courses are presented as well, with black bars on the bottom representing the significance of a between-group t-test at each time point (FDR-corrected p = 0.001).



Supplementary Figure 1. MEG Data Co-registration and Transformation to MNI-152 space. Subject and template MRI volumes were independently segmented and aligned to the sensor-space using fiducial markers. A grid with a 7 mm resolution was fit to the template volume and registered to individual volumes, producing template-subject transformation matrices. The transformation

matrices were subsequently used to fit each subject's source localized data onto the MNI-152 template volume.



Supplementary Figure 2. Behavioral Data. Scatter plots depicting the relationship between age and correct responses (blue) and accepted clean trials (green), used for detecting potential outliers. While the age x group interaction became non-significant upon the outlier's removal, the correct trials from this participant were included in imaging data analysis.