



Aberrant development of post-movement beta rebound in adolescents and young adults with fetal alcohol spectrum disorders



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ABSTRACT

Dependent on maternal (e.g. genetic, age) and exposure (frequency, quantity, and timing) variables, the effects of prenatal alcohol exposure on the developing fetus are known to vary widely, producing a broad range of morphological anomalies and neurocognitive deficits in offspring, referred to as fetal alcohol spectrum disorders (FASD). Maternal drinking during pregnancy remains a leading risk factor for the development 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. Beta event-related de-synchronization (ERD) and movement-related gamma synchronization (MRGS), although not clearly linked to brain maturation, were also examined. Twenty-two participants with FASD and 22 age and sex-matched controls (12–22 years old) 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 were localized to the participants' motor cortices, and the time courses from the locations of the maximally evoked PMBR were subjected to wavelet analyses. The subsequent analysis of PMBR, ERD, and MRGS revealed a significant interaction between group and age in their effects on PMBR. While age had a significant effect on PMBR in the controls, no simple effects of age were detected in the FASD group. The FASD group additionally displayed decreased overall ERD levels. No group or age effects on MRGS were detected. 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.

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1. Introduction

1.1. Fetal alcohol spectrum disorders

Prenatal alcohol exposure produces a variety of developmental problems in adolescents that have life-long implications. The physical and mental manifestations of the effects of prenatal ethanol exposure are collectively referred to as fetal alcohol spectrum disorders (FASDs). Prenatal alcohol exposure is held to be the leading preventable cause 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 this disorder 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 broad range of attentional, perceptual, cognitive, and executive control impairments in adolescents with FASDs (Franklin et al., 2008; Mattson et al., 2011; Meyer, 1998; Paolozza et al., 2014; Strömmland, 2004). Neurophysiological correlates of these deficits have the potential to serve as functional biomarkers to aid in diagnosing FASD and assessing the severity of exposure effects. 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 employed in the study of adolescents with FASDs (Burden et al., 2009; Hemington and Reynolds, 2014; Kaneko et al., 1996), 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

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magnetoencephalography (MEG) to image adolescent's brain functions, on the other hand, has shown great potential due to its quiet, non-invasive nature (Ciesielski and Stephen, 2014; Minassian et al., 1999), and has been implicated in numerous experiments studying young populations (Lewine et al., 1999; Otsubo and Snead, 2001; Paetau et al., 1995). Importantly, the utilization of 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 (Coffman et al., 2013; Kaneko et al., 1996; Stephen et al., 2012). 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), 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, adolescents 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, adolescents 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.

1.2. Inhibitory control in adolescents with FASDs

One explanation for the impairments in motor control lies in 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 (Hall et al., 2011; Muthukumaraswamy et al., 2009). 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 neurophysiological manifestations of GABA-ergic activity exist in human participants with FASDs.

1.3. 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 (Pfurtscheller et al., 1996), during which beta activity undergoes event-related de-synchronization (ERD). The power increase briefly exceeds the levels observed prior to the movement and, while maximal in the motor cortex contralateral

to the movement, is often detected in the ipsilateral motor cortex and nearby regions as well. 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; Gaetz and Cheyne, 2006; Muthukumaraswamy and Johnson, 2004; Neuper et al., 2006). In the context of a task, whether 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 may 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.

Another movement-related component in the gamma range has consistently been reported alongside beta ERD and PMBR (Gaetz et al., 2011, 2010). Specifically, movement-related gamma synchrony (MRGS) in the [70–80 Hz] range appears to shortly follow movement initiation. While no linear relationship between age and MRGS has been established, the frequency of peak MRGS has been shown to decrease with age (Gaetz et al., 2011, 2010), and may serve as a useful marker of functional brain maturation. As such, we included the MRGS component in our investigation.

1.4. 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 to investigate whether the beta rebound could 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 hypothesized 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 was that the FASD group would exhibit diminished PMBR power increases as a function of age relative to healthy controls. Given the evidence that PMBR, beta ERD, and MRGS may rely on separate neurotransmitter systems (Muthukumaraswamy et al., 2013), we did not expect the ERD or MRGS components to display differences between FASD and controls.

2. Methods

2.1. Participants

Twenty-two adolescents and young adults 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 participants (10 males, 12 females; 16.3 ± 3.0 y. o.) were recruited via flyers posted in the community. Controls were selected on the criteria of having no history of prenatal alcohol exposure, as well as lack of 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.

2.2. 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 s. 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. Digital sounds distinct from the standard and target tones comprised the novel cues. The stimuli were presented bilaterally using plastic tubes inserted into the participants' ears. All participants completed 4 sessions of equal duration (about 10 min) with breaks between scans (1–5 min), totaling 784 standard, 98 target, and 98 novel stimuli being presented to each participant.

2.3. Data collection and preprocessing

The data were continuously sampled at 1200 Hz 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 coregistration purposes. Four head position indicator (HPI) coils were attached to the participants' heads (2 forehead, 2 mastoids) for continuous tracking of the head position inside the sensor array throughout the scan. The participants' 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 spatial independent component analysis via MNE-suite software package, 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.

2.4. PMBR localization in the motor cortex

All but 4 participants 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 participants 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 individual's brain volume model, resulting in brain grids that can be aligned to MNI-152 space via reverse transforms. Since the participant-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 individual's grid was used to compute the lead field prior to source localization.

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 segmented from 5 s before to 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 participants' 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 $[-1.5 \text{ s}]$ relative to the button press, we utilized the longer, padded trials in order to increase the precision of beamformer filters and wavelet-based analyses. The resulting segments were scanned for jump artifacts in the $[-1.5 \text{ s}]$ 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 $[-1.5 -1 \text{ s}]$ "baseline" and $[1 \text{ s}]$ "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 (PMBR), we sought to identify the location where it is most robust, and constrain further analyses to that area. As post-movement beta increases has been reported in the hemisphere ipsilateral as well as contralateral to the movement, the search for maximum activation was restricted to clusters in the left (contralateral to the movement) hemispheric motor area. This was achieved by identifying the indices of the motor region of interest in the MNI template grid, transforming each participant'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 for each participant for further analyses.

2.5. 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 $[-1.5 \text{ s}]$ time period and frequencies in the range of $[1 \text{ } 50 \text{ Hz}]$. Individual beta $[15 \text{ } 30 \text{ Hz}]$ 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 $[-1.5 -1 \text{ s}]$ 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. The extent of beta event-related de-synchronization (ERD) was assessed by contrasting the [−1.5 −1 s] baseline data with the [−0.25 0.25 s] period, which was centered on the button press.

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 × PMBR latency × age) ANOVA. Beta ERD values were analyzed using a 2-way (group × 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.

Using an approach analogous to the PMBR analysis, the time courses from the site of maximum evoked PMBR were also convolved with a 7-cycle wavelet family in the [50 100 Hz] range. Similarly to the PMBR and ERD analyses, the power time courses were pseudo-z transformed using a [−1.5 −1 s] baseline period, and trial-wise power values from the maximum MRGS time–frequency bin were entered into a t-test to obtain the evoked MRGS value for each participant. The resulting MRGS values were entered into an analysis of variance with MRGS evoked power as dependent variable, and group (FASD and controls) and age (adolescents and young adults) as fixed factors.

3. Results

3.1. Behavioral measures

An analysis of variance in target identification accuracy (control adolescents: $93.6 \pm 2.2\%$; control young adults: $96.7 \pm 1.2\%$; FASD adolescents: $90.9 \pm 2.9\%$; FASD young adults: $80.3 \pm 10.4\%$) 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. 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.

3.2. PMBR localization in the motor cortex

All participants 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 participants, an expected pattern during engagement in a cognitive task. Localization results for representative individuals from each group are presented in Fig. 1. The time courses extracted from the points of maximum PMBR were visually examined, with all showing clear time-locked beta activities. The four participants 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 adolescents 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.

3.3. Interactions and main effects

Analysis of beta de-synchronization revealed significant main effects of group ($F(1, 3434) = 6.55, p = 0.011$) and age ($F(1, 3434) = 5.77, p = 0.016$). Specifically, overall beta ERD increased in strength with age, but the FASD group displayed significantly weaker de-synchronization than the controls. Both cohorts exhibited ERD increases in the young adult groups relative to their respective adolescent comparisons, with the FASD group appearing to undergo a particularly prominent change (Fig. 2). The interaction between group and age, however, was not significant ($F(1, 3434) = 1.76, p = 0.185$).

The ANOVA detected significant main effects of age ($F(1, 6868) = 51.06, p < 0.001$), group ($F(1, 6868) = 24.67, p < 0.001$), and latency ($F(1, 6868) = 12.29, p < 0.001$) on PMBR, which are presented in Fig. 3. 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 ($F(1, 6868) = 19.69, p < 0.001$), and is also shown in Fig. 3. 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 ($MD = 7.55 \pm 1.17, p < 0.001$).

The multivariate analysis of variance of MRGS revealed no significant main effects of either age (adolescents and young adults) or group (FASD and controls) on MRGS latency (age: $F(1, 40) = 0.68, p = 0.415$; group: $F(1, 40) = 0.65, p = 0.426$), frequency (age: $F(1, 40) = 0.02, p = 0.880$; group: $F(1, 40) = 0.10, p = 0.753$), or power (age: $F(1, 40) = 0.11, p = 0.746$; group: $F(1, 40) = 0.34, p = 0.561$). Further, the interaction between age and group was not significant for any of the dependent variables. While no significant effects were observed, the evoked group MRGS levels are summarized in Fig. 4, and gamma time–frequency representations are presented in Fig. 5.

3.4. Examination of time–frequency representations 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 group between 0.5 and 1 s following the button press (FDR corrected $p < 0.001$; Fig. 6). Additionally, the control group exhibited lower de-synchronization in the same frequency range just prior to the button press, reflecting the main effect of group on beta ERD. The time–frequency map comparison between adolescents and young adults indicated that the main effect of age was present across nearly the entire PMBR time–frequency range, with significant power increases observed throughout the [0.5 1.5 s] period after the button press (Fig. 6). Beta ERD differences were additionally detected by the time–frequency map age comparison, revealing significant main effects of age in multiple time–frequency bins immediately prior to and after the button press (FDR corrected $p < 0.001$; Fig. 6).

The time–frequency map comparisons between groups within each level of age were used to further elaborate on any 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. 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 (Fig. 7).

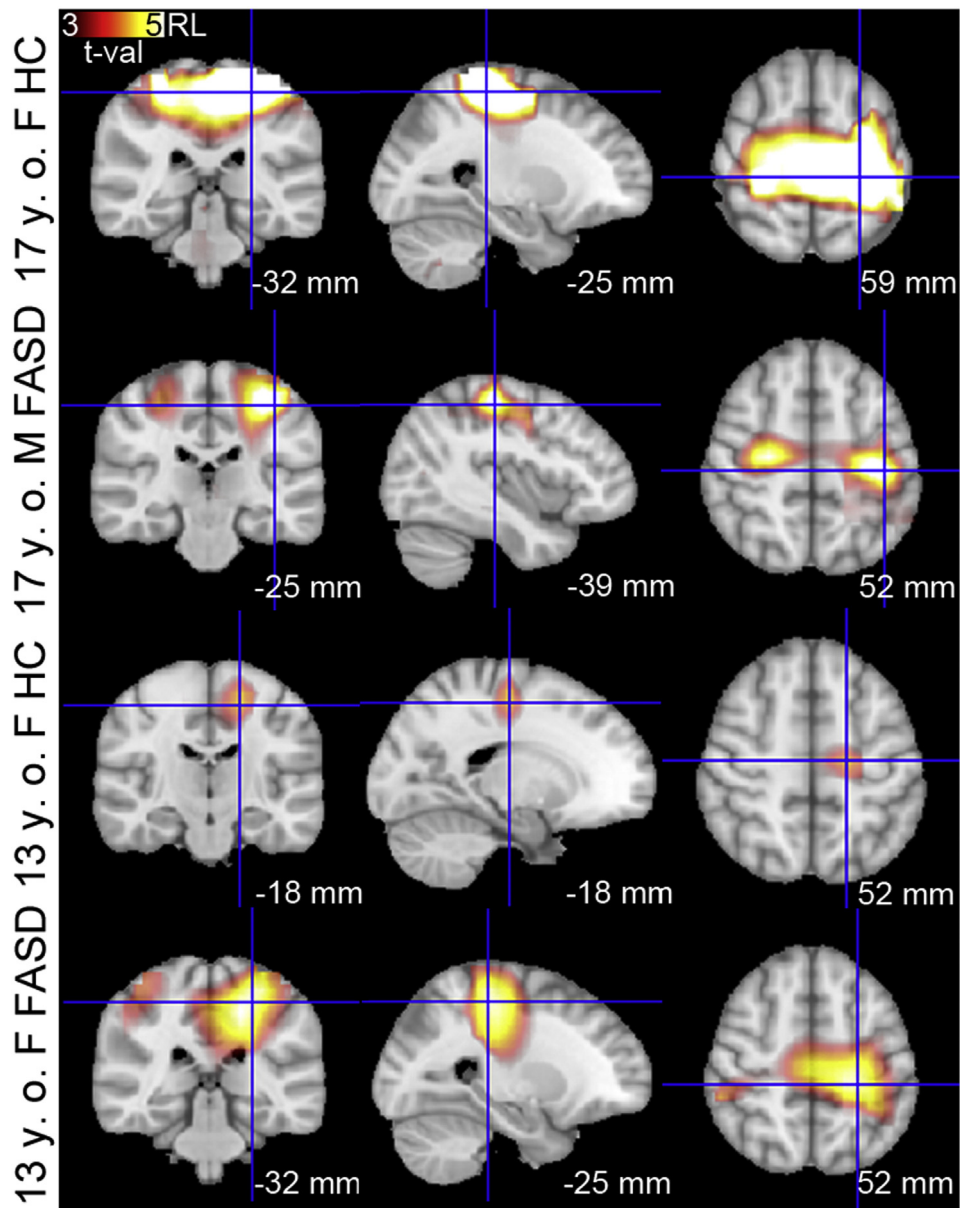


Fig. 1. Post-movement beta rebound localization. Data from representative participants in the young adult healthy control (HC), young adult FASD, adolescent control, and adolescent FASD groups are presented in radiological convention on MNI-152 template volumes. The threshold for the activation maps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

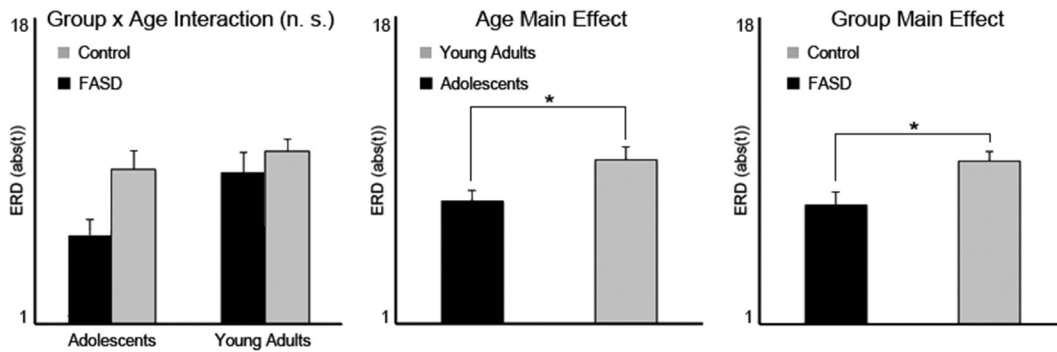


Fig. 2. Interactions and main effects on beta ERD. Main effects of age and group are presented in absolute values of evoked de-synchronization. The main effect of group was significant ($p < 0.05$), with controls displaying higher levels of de-synchronization than the FASD group. Additionally, a significant effect of age was also detected, revealing increased ERD power in the young adult cohort. The group by age interaction was not significant.

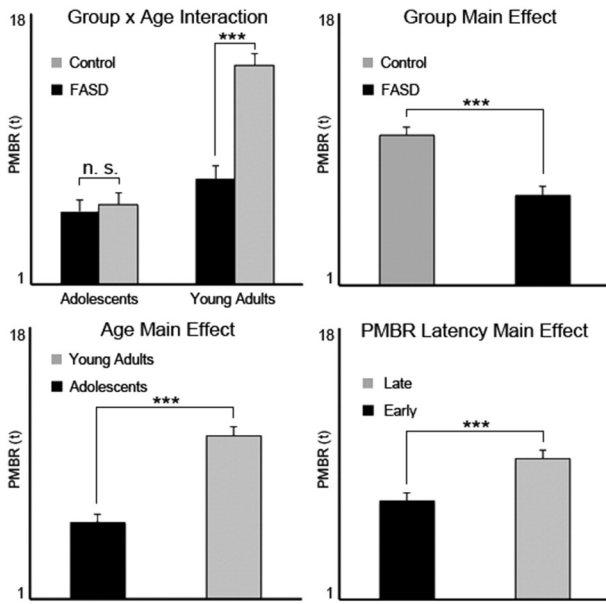


Fig. 3. Significant interactions and main effects on PMBR. Controls displayed significantly higher PMBR than the FASD group ($p < 0.001$). Main effect of age group (12–15 and 16–22 years old) was significant, with higher PMBR in controls than in the FASD group ($p < 0.001$). Relative to the $[-1.5 -1 s]$ 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 ($p = 0.7$).

4. Discussion

In the current 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 participants 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 adolescents 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 observed group difference in ERD power suggest that inhibitory modulation of the motor cortex in FASD patients may not only be impaired at the stage of imposing the inhibition to terminate movement, but may also be altered in its abilities to lift inhibition and initiate movement. While the FASD group displayed lower overall beta de-synchronization during finger movement relative to controls, the two groups exhibited positive relationships between ERD and age. As the specific processes responsible for beta de-synchronization during movement are not yet established, it is difficult to speculate on any implications of the diminished ERD power in individuals with FASDs. Muthukumaraswamy et al. (2013) reported increased beta ERD accompanied by a decreased PMBR in response to stimulated endogenous GABA activity, possibly differentiating the roles of GABA-a and GABA-b in modulating ERD and PMBR, respectively.

Motor deficits are commonly reported in the FASD population (Lucas et al., 2014), possibly implicating altered GABA-ergic concentrations in the cerebellum. The interest in the cerebellum has been driven by its role in fine motor control, impairment of which is a common manifestation of FASD (Doney et al., 2014). In addition to dexterity, motor learning, as measured through eye-blink conditioning paradigms, is also broadly impaired by FASD (Jacobson et al., 2008), and has been linked to cerebellar abnormalities (Fan et al., 2015; Spottiswoode et al., 2011). Indeed, numerous reports of functional and structural alterations in the cerebellum have shed light on the sensitivity of this brain region to prenatal alcohol exposure (du Plessis et al., 2015). Low GABA levels have been implicated in ethanol-induced cerebellar dysfunction (Bao et al., 2002; Luo, 2015), and are capable of modulating motor learning in healthy neural systems (Attwell et al., 2002). These findings suggest that any GABA concentration deficiencies in our FASD cohort, as measured via PMBR in the motor cortex, are likely to be representative of GABA-ergic imbalances elsewhere in the brain.

The pattern in the time–frequency map comparison between FASD and control groups is suggestive of group latency differences in

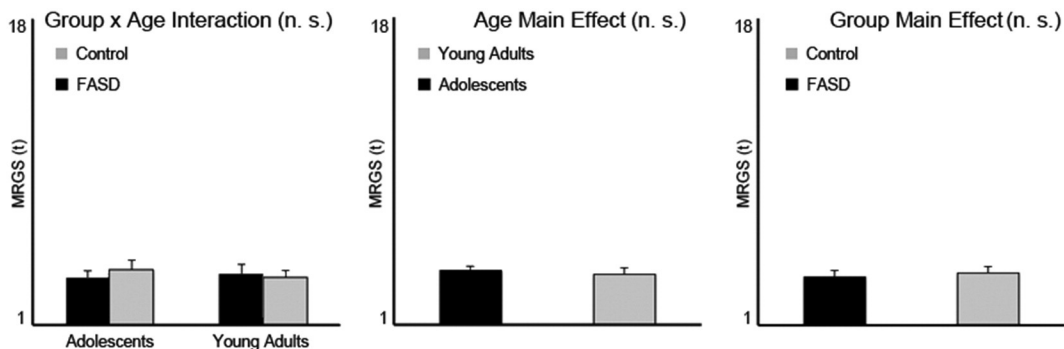


Fig. 4. Interactions and main effects on MRGS. Evoked MRGS values are summarized for each experimental group. No significant effects of age or group were detected on MRGS ($p > 0.05$). The interaction between age and group was also not significant ($p > 0.05$).

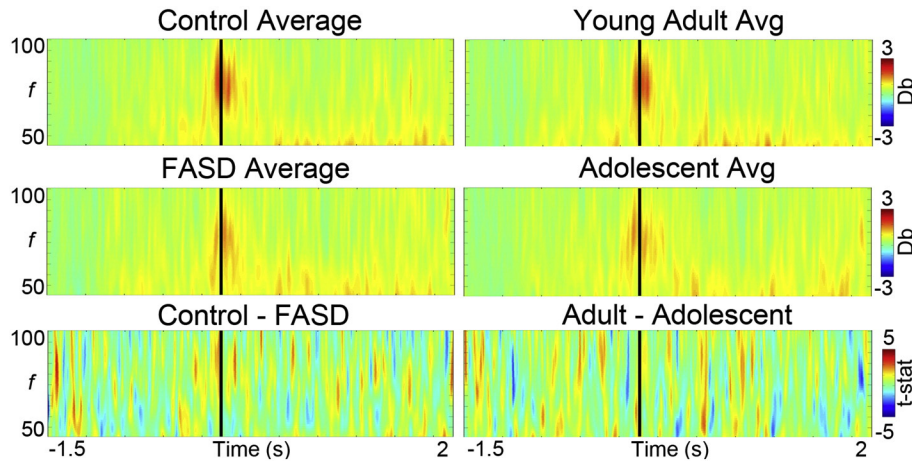


Fig. 5. Time–frequency MRGS representations. Averaged time–frequency maps are presented for the FASD and control groups, as well as the difference between them. Young adult and adolescent cohorts’ time–frequency representations are also presented. The interaction between age and group was not significant ($p > 0.05$). Further, each variable’s main effect on MRGS also failed to reach significance ($p > 0.05$).

ERD onset and rebound (Fig. 6). 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 hypothesis. However, given that the response times did not vary significantly between groups and that maximal ERD power was concurrent in the two groups, we are reluctant to attribute the difference in PMBR onset to any discrepancies in movement speeds.

Future examinations into the degrees of beta connectivity that the motor cortex exhibits with other brain areas, such as the cerebellum and the basal ganglia, are necessary in order to quantify the degree to which the ERD and PMBR may represent this network’s activity. Investigations into task-relative activity in the lateral prefrontal cortices, which are thought to be primarily responsible for imposing inhibitive control over other brain areas (Aron et al., 2014; Berkman et al., 2009), are also of interest. 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.

Additional 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.

5. Conclusions

The described MEG study further supports the findings that prenatal alcohol exposure has long-lasting consequences that affect development long after birth. Specifically, we detected an overall beta desynchronization power decrease in FASD patients relative to controls, possibly due to ethanol-related GABA-b imbalances. Additionally, we showed that the post-movement beta rebound, a transient increase in [15–30 Hz] power that occurs in the motor cortex after termination of voluntary movement, displayed aberrant development in young adults with FASDs. While a significant effect of age on PMBR power was detected in healthy controls, the data from the FASD group did not display this pattern. This finding is suggestive of possible broad impairments in inhibitory processes in adolescents with FASD, possibly related to aberrant development of GABA-ergic pathways.

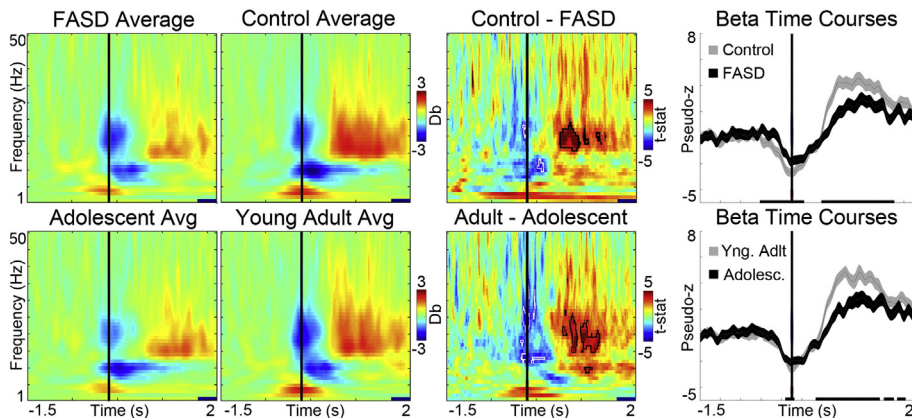


Fig. 6. Time–frequency maps for main effects. Time–frequency maps are presented for the control and FASD groups, as well as the contrast between the two. The main effects of group are outlined (black = control > FASD; white = FASD > control; FDR-corrected $p = 0.001$). Average beta time courses are shown 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 $p = 0.001$).

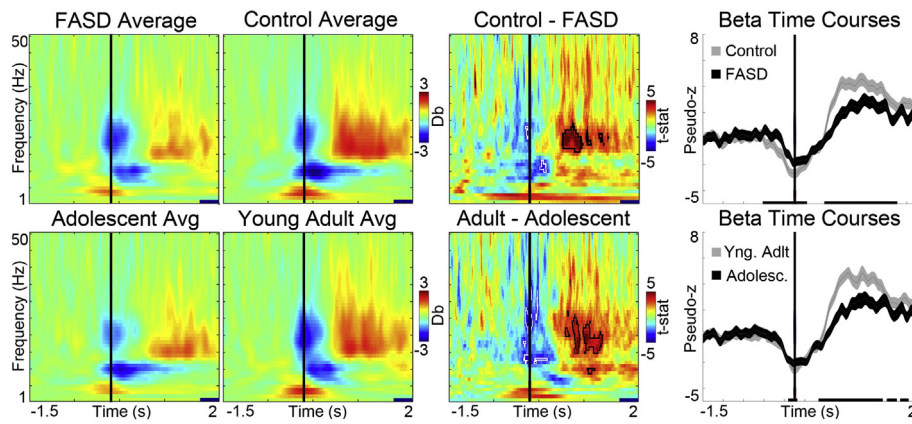


Fig. 7. Simple effects of group within different levels of age. Group (FASD, control) did not exhibit a statistically significant simple effect on PMBR within the adolescent cohort. A simple effect of group on PMBR within the young adult cohort was significant (FDR-corrected $p = 0.001$), with greater 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 $p = 0.001$).

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