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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.

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; Strömland, 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