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# FRONTAL PARIETAL NETWORK FUNCTION DURING A VISUOMOTOR TASK IN FETAL ALCOHOL SPECTRUM DISORDER: A MAGNETOENCEPHALOGRAPHY STUDY

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by

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## ABSTRACT

Exposure to alcohol in utero produces a range of morphological and functional outcomes called fetal alcohol spectrum disorders (FASD). Children with FASD exhibit a broad range of cognitive disabilities. We utilized an isochronous, visuomotor, finger tapping task to probe differences in brain dynamics in adolescents, 23 diagnosed with FASD and 25 control (12-19 years of age). Data were recorded with a 306-channel magnetoencephalographic (MEG) array. A finger tapping task of 100 trains of 6 – 8 visually presented cues were presented for 350 milliseconds with interstimulus intervals of 750 milliseconds. The FASD group showed greater reaction times and reaction time variability relative to controls. Patterns of activation were extracted from the sub regions of the frontal parietal network in response locked data. Amplitude, peak onset, and peak latency differences were observed. Correlations detected between peak onsets and latencies with behavioral data reveal details about the processes occurring during the task.

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## CHAPTER 1 INTRODUCTION

### Fetal Alcohol Spectrum Disorder

The term fetal alcohol spectrum disorders (FASD) refers to a broad range of morphological and functional anomalies observed in individuals exposed to alcohol prenatally. The central nervous system is particularly sensitive and vulnerable to the deleterious effects of alcohol. Exposure to alcohol in utero is considered the leading preventable cause of intellectual disabilities (Riley, Infante, & Warren, 2011).

There have been references to the detrimental effects of alcohol to the unborn fetus from as far back as Biblical times(Riley *et al*., 2011). However, it was believed that drinking during conception, not during pregnancy, led to the "birth of a damaged child". In the 1700's, children of alcoholics were described as being "weak, feable, and distempered" (Calhoun & Warren, 2007). In the late 19th century, Sullivan (1899), observed that imprisoned alcoholic mothers giving birth to children with aberrant behaviors or having increased number of miscarriages. As these children aged, they did not become productive members of society. It was also noted that the infants of alcoholic women were healthier when the gestation occurred in prison, indicating that alcohol was responsible for their aberrant behavior (Hoyme *et al*., 2005; Riley *et al*., 2011; Sullivan, 1899). The first medical article reporting the behavioral and physical patterns associated with heavy drinking during pregnancy was not published until 1968, by Lemoine and colleagues in France. In 1973, Jones and colleagues published 2 papers that led to the recognition of fetal alcohol syndrome and a more definitive diagnostic criteria (Calhoun & Warren, 2007).

Since 1973, thousands of papers have been published on the teratogenic effects of alcohol. Four main conclusions can be drawn from this large body of literature: 1) As a teratogen alcohol has devastating effects on the CNS; 2) the deleterious effects of prenatal alcohol exposure are mediated and moderated by a broad range of factors, producing significantly variable developmental outcomes; 3) cognitive and behavioral outcomes of prenatal alcohol rather than morphological outcomes are of clinical concerns; 4) the economic cost of FASD to the society is considerable, with the lifetime cost for caring for an individual with FASD being estimated at estimated at millions of dollars (Olson *et al*., 2009). The incidence of FASD has been estimated as high as 2 - 5 in 100 live births . Despite the large number of publications, there still remain many unanswered questions (Riley *et al*., 2011).

## Diagnosis

There are currently 4 diagnostic methods used to diagnose FASD. They are: 1) 4-Digit Code, 2) National Task Force/CDC criteria, 3) Canadian Guidelines, and 4) Revised IOM (Paintner, Williams, & Burd, 2012; Riley *et al*., 2011). Although there are 4 different diagnostic methods, there is considerable overlap in criteria. There have been no comparison studies on the 4 methods. Although researchers have sought to identify biomarkers of prenatal alcohol exposure and to identify anomalies associated with alcohol exposure on ultrasound, prenatal diagnosis of FASD is not currently possible (Paintner *et al*., 2012).

Diagnosis of FASD is performed by a clinician or a team of clinicians. Children usually present with delays, birth defects and behavioral issues. The children also present with a history of being placed in foster or adoptive homes, while their mother has been

incarcerated or receiving substance abuse treatment. The optimal time window for diagnosis is between 2 and 16 years of age. An early diagnosis is optimal as the child can be entered into an intervention program as soon possible, which is associated with improved outcomes. Only the most severe cases of FASD, (FAS) can be diagnosed at birth or infancy. Clinicians will look for growth impairments, central nervous system damage, and at least 2 characteristic facial features (Paintner *et al*., 2012). The facial phenotype of FASD include short palpebral fissures, a thin vermillion border of the upper lip, and indistinct or smooth philtrum. Those diagnosed with fetal alcohol syndrome display growth restrictions, with height or weight being below the 10$^{th}$ percentile. Microcephaly is taken as an index of a central nervous system anomaly. The confirmed prenatal exposure of alcohol is an optimal selection criterion (Hoyme *et al*., 2005).

Cognitively, there are many problems seen with this disorder. These individuals also have a lower than normal Intelligence Quotient. Alcohol-affected children often display attention deficits, executive dysfunction, motor delay, visual constructional difficulties and math problems (P. W. Kodituwakku, 2010; P.W. Kodituwakku, 2007). These cognitive and motor problems are known to produce a range of secondary disabilities including mental health problems, disrupted school experiences, trouble with the law, inappropriate sexual behavior, alcohol and drug abuse problems (Streissguth *et al*., 2004). Children with FASD also present with neurological problems. These include hearing and vision abnormalities, and seizures (Hoyme *et al*., 2005). Most of these can be correlated to the many physical brain malformations found with this group.

## CHAPTER 2 REVIEW OF RELATED LITERATURE

### Neuroimaging

Magnetic Resonance Imaging (MRI) has long been employed to study the structural anomalies resulting from prenatal alcohol exposure. The cerebellum has been shown to have a thinner than normal vermis (Cardenas *et al*., 2014). There is also malformation of the corpus callosum (Yang *et al*., 2012). Some areas are thinner than normal or not fully formed. There are also numerous abnormalities in multiple other regions including, basal ganglia (Joseph *et al*., 2014), hippocampus(Joseph *et al*., 2014; Treit *et al*., 2013), grey and white matter distribution and density (Malisza, 2007). However, a substantial proportion of individuals with prenatal alcohol exposure have no measurable CNS dysfunction and/or structural abnormalities (Astley *et al*., 2009).

There also exists a growing body of literature on functional differences associated with prenatal alcohol exposure. These include functional Magnetic Resonance Imaging (fMRI), Magnetoencephalography (MEG), Electroencephalography (EEG) and Magnetic Resonance Spectroscopy (MRS) studies (Eileen M. Moore, 2014; Norman, Crocker, Mattson, & Riley, 2009; Riley *et al*., 2011). In comparison to fMRI, MEG and EEG have finer temporal resolution, ideal for studying brain dynamics in FASD. D'Angiulli *et al*, conducted a review of EEG studies conducted prior to 2005 (D'Angiulli, Grunau, Maggi, & Herdman, 2006). These authors looked at sensory processes and attention and cognition among other things. For sensory processes, the authors reviewed 5 studies, three of which probing electrophysiological signals associated with the processing of auditory stimuli. The first one looked at auditory evoked potentials (AEP's) in the auditory cortex and auditory brain structures in children with FAS. Their findings

showed that 79% of the children were abnormal. The auditory brainstem response (ABR) was consistent with a conductive hearing disorder with low amplitude wave in 69% of the FAS children. There was not a correlation between peripheral hearing loss and craniofacial dysmorphism (Rössig, Wässer, & Oppermann, 1994). In the second study, an abnormal ABR was found in FAS infants. The third study was going to assess ABR thresholds, but very little analysis was conducted on the ABR (Church & Gerkin, 1988; D'Angiulli *et al*., 2006).

Two studies examined visual evoked potentials (VEP) in infants with FAS (D'Angiulli *et al*., 2006). Scher *et al*., (1998) employed a binocular flash or pattern to elicit electrophysiological responses. Exposure to alcohol in the first trimester was associated with prolongation of N100 and P100 wave latencies at 1 month of age. At 18 months of age, the N100 and P100 wave latencies decreased. Second and third trimester alcohol exposure was associated with a N200 latency prolongation and an increase in N100 and P100 amplitude at 4 months age. Olegard *et al*., (1979) used VEP and somatosensory evoked potentials (median nerve stimulation). In 70% of the infants, there were abnormal somatosensory evoked potentials. In 35% of the infants, there were abnormal VEP's. In 35% of the infants there were large side differences (contralateral and ipsilateral) in the somatosensory evoked potentials (D'Angiulli *et al*., 2006).

For attention and cognition, D'Angulli *et al*, looked at 4 EEG studies. The first study involved an auditory oddball task. There was a longer P300 wave latency in the parietal cortical region in the FAS children. The N100 wave, which is linked to attention, was not different between groups (Kaneko, Phillips, Riley, & Ehlers, 1996b). A reanalysis of this data was preformed and 50% of the EEG's for the FAS subjects were

found to be borderline abnormal to abnormal. This included low amplitude and decrease alpha activity in the left hemisphere (Kaneko, Ehlers, Philips, & Riley, 1996a).

Another study looked at contingent negative variation (CNV). This is an anticipatory response, which is a long negative wave, to an expected stimulus. In the control group, 8 of 10 children had negative CNV slopes. In the FAS group, 4 of 10 children had negative CNV slopes. This was not statistically significant, but perhaps with a larger sample it could have been (Buffington, Martin, Streissguth, & Smith, 1980).

The next study D'Angulli *et al*, reviewed was a longitudinal study by Spohr and Steinhausen (1987) on the long-term effects of prenatal exposure to alcohol. These children (72) did numerous assessments as well as EEG. Based on the results of the tests, rehabilitative measures were prescribed. Of the 72 children, 54 were able to do follow up testing 3 – 4 years later; 45 did a follow up EEG. EEG abnormalities were shown to have decreased at follow up (more normal activity). However, behavioral problems persisted such as hyperactivity and distractibility (Spohr & Steinhausen, 1987).

Burden *et al*., (2009) recently observed ERP differences in the FASD group relative to the Control group on a visual Go/No Go task. The FASD group had slower latency to P2 compared to the Control group. The Control group showed a larger P2 to the Go vs. No Go, which was absent in the FASD group, suggesting a facilitation effect for the Control group. On the other hand, the FASD group not having this may reduce their ability to efficiently process the stimulus meaning, leading to a slower processing speed. This is consistent with previous findings. For N2, there was no difference by group. In the Control group, the No Go N2 was larger than Go at the central electrodes. This may reflect frontal inhibition activation or a cognitive control process related to

response decision. The generator is located within the Anterior Cingulate Cortex, which is important for action monitoring and decision making. The FASD group did not have this effect. Lack of a group difference in latency may have been due to the lack of a well defined N2 peak in the FASD group. For P3, there was no difference by group. Even though both groups showed the expected larger P3 amplitude during the No Go trials, there was a larger Late Slow Wave in the left hemisphere of the FASD group during No Go trials. This suggests increased neural activation that persists beyond the P3, a pattern that has been associated with increased cognitive effort. This is an interesting study, but has an extremely low number of participants (Burden *et al*., 2009).

MEG has been a useful tool in studying sensory and motor characteristics in FASD. Relative to EEG, MEG has a much greater spatial resolution. For sensory processing, both auditory and visual processing has been studied in FASD using MEG. In one study, the FASD group was found to have an auditory processing delay relative to controls. During the presentation of auditory stimuli, the FASD group had an approximately 10 millisecond delay in M100 and M200 latencies (Stephen *et al*., 2012). In another study, sex differences were found in brain activation and dynamics during an auditory oddball task. Differences were found in frontal, medial, and temporal cortex compared to controls (Tesche, Kodituwakku, Garcia, & Houck, 2015). MEG has also been used to study visual processing, which has been found to also be delayed in FASD. In a study using a prosaccade task, the FASD group demonstrated a delay in visual M100 response latency relative to controls (Coffman *et al*., 2012).

Fine motor dysfunction, and gross motor problems are present in FASD (Barr, Streissguth, Darby, & Sampson, 1990). MEG has been used to probe motor issues.

During a visual prosaccade task, gamma oscillations during saccade responses were altered in the FASD group compared to controls, suggesting sensory and motor control impairments (Stephen, Coffman, Stone, & Kodituwakku, 2013). In another MEG study, Post-Movement Beta Rebound (PMBR) and Event-Related De-synchronization (ERD) were investigated in FASD. PMBR is a transient increase in power after a voluntary movement, followed by ERD. PMBR is believed to be related to a participant's perceived response accuracy. The study found impairments in PMBR for the FASD group relative to healthy controls (Vakhtin, Kodituwakku, Garcia, & Tesche, 2015).

**Frontal Parietal Network**

Attention is defined as the "mental ability to select stimuli, responses, memories, or thoughts that are behaviorally relevant, among the many others that are behaviorally irrelevant" (Corbetta M, 1998). Research on attention focuses on understanding levels of performance, computations, and neural systems. One form of attention is sustained attention, which is the ability to mindfully and consciously sustain cognitive processing of stimuli when they are repetitive and non-arousing (Robertson, 1997). Sustained attention can be described by 2 qualities: endogenous modulation of alertness and exogenous controlled alertness (influenced by novelty, salience, and stimulus change).

Early studies using positron emission tomography (PET) found frontal and parietal activation during measures of sustained attention (Pardo, Fox, & Raichle, 1991). This line of research gave rise to the Frontal Parietal Network (FPN). The FPN is comprised of the following bilateral areas: anterior prefrontal cortex (aPFC), anterior cingulate cortex (ACC), anterior inferior parietal lobe (IPL), dorsolateral prefrontal cortex (dlPFC) and insular cortex. These brain regions roles in cognitive control have

been observed in many studies (Gao & Lin, 2012). The FPN is described as a network as many of the sub regions within it are activated during attentionally demanding tasks (Vincent, Kahn, Snyder, Raichle, & Buckner, 2008; Woldorff *et al*., 2004). Research into the FPN has suggested different functional roles for the sub regions of this network (Coull, Frith, Büchel, & Nobre, 2000; Vincent *et al*., 2008; Woldorff *et al*., 2004). Due to these different functional roles, we will look at each sub region individually.

**Anterior Cingulate Cortex**

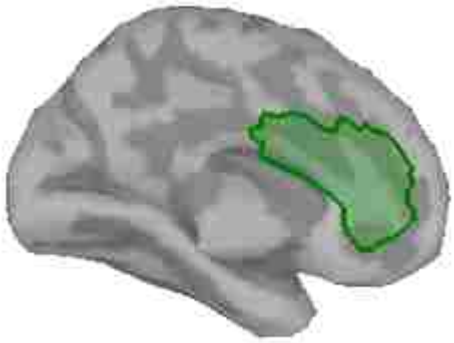


**Figure 1. Anterior Cingulate Cortex (ACC). This figure is a reconstructed MRI, which depicts the medial cortical surface of the right hemisphere of the brain. The ACC is highlighted in green, as described by the Brainvisa Tzourio-Mazoyer cortical atlas. This area was used in Brainstorm for the ACC, group-averaged waveforms.**

The ACC (Figure 1) is involved in conflict monitoring, error monitoring and detection, response selection, arousal, and attention control. It has extensive bidirectional connections with dorsolateral, orbitofrontal, primary and secondary motor, and insular regions of the cerebral cortex. (Torta & Cauda, 2011). Evidence suggests that the ACC is involved with sustained attention (Migliorini *et al*., 2015). Response anticipation has also been shown to engage the ACC (Fan *et al*., 2007). The ACC has been shown to be active in trials where there is no response conflict, which has been thought to show that the ACC is involved in preparatory control (Aarts, Roelofs, & Turennout, 2008). In

FASD individuals, structural damage to the cingulate may be a factor contributing to dysregulated behavior (Bjorkquist, Fryer, Reiss, Mattson, & Riley, 2010). There seems to be very little known on the functional differences of the ACC in FASD outside of studies probing inhibition. One FASD study found a relationship between the surface area of the ACC with inhibition and processing speed (Migliorini *et al*., 2015).

**Anterior Prefrontal Cortex**

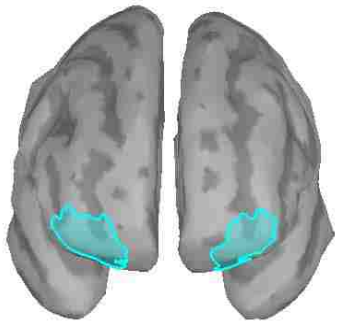


**Figure 2. Anterior Prefrontal Cortex (aPFC). This figure is a reconstructed MRI, which depicts the anterior cortical surface of the brain. The middle frontal orbital cortex is highlighted in light blue, as described by the Brainvisa Tzourio-Mazoyer cortical atlas. This area was used in Brainstorm for the aPFC, group averaged waveforms.**

The aPFC (Figure 2) is considered the apex of cognitive control. Studies have shown how important the aPFC is for adapting attention to external and internal information (Burgess, Gilbert, & Dumontheil, 2007; Pollmann, 2004). Attention may be modulated through task set rules. The right aPFC enables task set rules to be placed in a readiness state for easy retrieval and execution (Koechlin & Hyafil, 2007). The right aPFC has been associated with working memory (Ramnani & Owen, 2004). As a task unfolds, dependent on its complexity, cognitive control mechanisms prepare the brain for events that are coming up to optimize performance (Chiu & Yantis, 2009). This area has extensive bilateral connections with the ACC. The ACC is associated with conflict, error

monitoring and detection. The aPFC controls adaptive behavior. When the ACC detects conflict or errors, it signals the aPFC to resolve the incongruency (Torta & Cauda, 2011). This is accomplished through left aPFC, which has been associated with attentional reallocation (Ramnani & Owen, 2004).

FASD patients present with behavioral and intellectual impairments that indicate frontal lobe dysfunction, however, neuroimaging studies have failed to elucidate the extent of damage (Burke, Palmour, Ervin, & Ptito, 2009). Anatomically, significant surface deformations to anterior and orbital frontal regions have been observed. Increases in cortical thickness have been revealed in several frontal regions that are involved in response inhibition, attention, social cognition, and executive functioning. Thicker frontal cortex suggests that this region is especially vulnerable to alcohol neurotoxicity, leading to the functional impairments observed in FASD (Yang *et al*., 2012).

Studies have also found the aPFC to be functionally altered in prenatally alcohol exposed children and adults. Functional MRI studies have shown excessive activation in the frontal cortex during spatial and verbal working memory, number processing, and response inhibition compared to healthy controls (Burden *et al*., 2009; Nuñez, Roussotte, & Sowell, 2011; Yang *et al*., 2012).

**Dorsolateral Prefrontal Cortex**

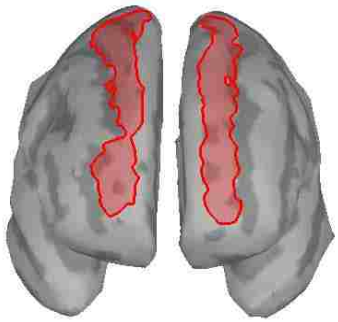


**Figure 3. Dorsolateral Prefrontal Cortex (dlPFC). This figure is a reconstructed MRI, which depicts the anterior cortical surface of the brain. The superior frontal cortex is highlighted in red, as described by the Brainvisa Tzourio-Mazoyer cortical atlas. This area was used in Brainstorm for the dlPFC, group averaged waveforms.**

In general, the dlPFC (Figure 3) is associated with processing and maintenance of cognitive control (Barber & Carter, 2005). Neuroimaging studies have found that the dlPFC is active when relevant information must be maintained. This activity also increases with working memory load when information must be maintained (Cohen *et al*., 1997). The dlPFC not only increases with working memory load, but is also implicated in allocating attentional resources (MacDonald, Cohen, Stenger, & Carter, 2000), response selection when there is a conflict (Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000), and overcoming residual inhibition (Dreher & Berman, 2002).

Relevant to the present study, the dlPFC has been associated with temporal processing. There are connections with the parietal and premotor cortices that are involved in visuomotor control of actions. Studies have shown that the dlPFC plays a crucial role in cognitive control of motor behavior (Hoshi, 2006). There is evidence of a right cortical timing network, involving parietal and dlPFC areas. TMS to the right dlPFC affected timing, while TMS to left dlPFC did not (Jones, Rosenkranz, Rothwell, & Jahanshahi, 2004). Further, in finger tapping tasks, right dlPFC is more active during

internally generated movements versus movements to auditory pacing cues. Unlike auditory paced finger tapping, right dlPFC is also found to be more active in visual cued finger tapping. Left dlPFC is also found to be active, but could not be explained. This area is involved in motor preparation for imitative tasks, as well as new motor tasks. The finger tapping tasks are neither imitative nor novel (Buccino *et al*., 2004). It is possible that the left dlPFC activation may be due to salience of the stimuli (Seeley *et al*., 2007).

Previous fMRI studies of working memory have found increased activation in dlPFC in individuals with FASD compared to controls. This is attributed to functional recruitment abnormalities, concluding that despite this area being structurally "normal" in FASD individuals, it appears to be functionally abnormal (O'Hare *et al*., 2009).

**Insular Cortex**

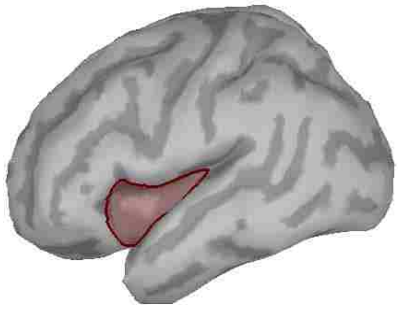


**Figure 4. Insular Cortex. This figure is a reconstructed MRI, which depicts the lateral cortical surface of the left hemisphere of the brain. The insular cortex is highlighted in purple, as described by the Brainvisa Tzourio-Mazoyer cortical atlas. This area was used in Brainstorm for the insular cortex, group averaged waveforms.**

The insular cortex (Figure 4) is a distinct, but entirely hidden area of the brain, situated in the depth of the Sylvian fissure. Insular cortex activation is involved in a wide array of functional situations, including sensory perception, vestibulo-proprioceptive processing, interoception, somesthesis, somatic control (regulation of cardioregulatory,

vasomotor and visceromotor function), motor function (speech), emotion (empathy and disgust), and cognition (attention and language processing) (Kelly *et al*., 2012). Its role in movement timing is not completely known. This region is implicated in timing tasks that involve interval sequence encoding and sensorimotor synchronization (Schubotz, Friederici, & Von Cramon, 2000) . Cerasa, Hagberg, Bianciardi, & Sabatini (2004), proposed that the insular cortex may be involved in processing interval duration. This hypothesis is supported by studies using auditory and visually cued timing tasks(Witt, Laird, & Meyerand, 2008). The researchers did not look at this in terms of left and right insular cortex, which deserves further investigation.

While most studies mention the activation of left insular cortex in attention tasks (specifically temporal attention), they fail to explain this areas role. Given its strong connectivity with aPFC and ACC, this pattern may be due to the saliency of the interval duration or the switching from exogenous to endogenous attention (Menon & Uddin, 2010). The right insular cortex is functionally connected to many regions associated with executive functions and appears to play a role in the monitoring of task performance and flexibility (Doyle-Thomas *et al*., 2013). The right insular cortex has been found to be involved in switching between brain networks across task paradigms and stimulus modalities(Menon & Uddin, 2010). The right insular cortex is also associated with regulating arousal. In other clinical populations it is believed that too little right insular cortex activity fails to entrain the dlPFC, resulting in careless mistakes. On the other hand, too much right insular cortex activity limits dlPFC function, which also limits the selection of optimal responses (Eckert *et al*., 2009).

There are few studies of FASD and insular cortex. One study used fMRI to compare Control and FASD groups on a Stop Signal Task. The researchers found during response inhibition that the FASD group had a greater BOLD response in the insular cortex relative to controls which they believed was due to abnormal auditory stimulus processing in the FASD group (Ware *et al*., 2015).

**Inferior Parietal Cortex**

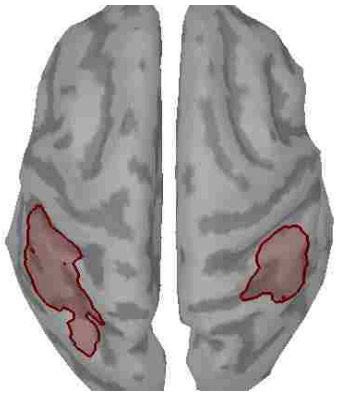


**Figure 5. Inferior Parietal Cortex. This figure is a reconstructed MRI, which depicts the dorsal cortical surface of the brain. The inferior parietal cortex is highlighted in purple, as described by the Brainvisa Tzourio-Mazoyer cortical atlas. This area was used in Brainstorm for the inferior parietal cortex, group averaged waveforms.**

The inferior parietal lobes (Figure 5) are involved in arousal, attention and attentional control, decision making, visuomotor control, movement control, and the representation of time. In FASD, the parietal lobe is affected by prenatal alcohol exposure. The roles of left and right IPL in finger tapping tasks are not quite understood. The left IPL is believed to process aspects of temporal processing such as rhythm or temporal processing (Assmus *et al*., 2003). It may play a role in converting timing cues to timed finger movements (Sakai, Ramnani, & Passingham, 2002). The right IPL has been associated with controlling sequence production and performance, and controlling sensorimotor integration and general movement production (Witt *et al*., 2008).

In FASD, the parietal lobes have been found to be both structurally and functionally abnormal relative to typically developing individuals (Lebel, Rasmussen, Wyper, Andrew, & Beaulieu, 2010; O'Hare *et al*., 2009; Sowell *et al*., 2008). Fagerlund *et al*., (2006), found altered brain metabolism. Sowell *et al*., (2002), reported that in FASD individuals, there is increased grey matter density and decreased white matter compared to typically developing individuals.

As described in the previous sections, the sub regions of the frontal parietal network have been found to be active in finger tapping. To probe the function of these areas in FASD adolescents, we used a finger tapping task.

**Visuomotor Finger Tapping Task**

This study employs a finger tapping task, which is a type of sensorimotor synchronization. In sensorimotor synchronization, an action is temporally coordinated with an external pacing stimuli. The action and external pacing stimuli are paired, so that the timing of the external pacing stimuli becomes predictable (Repp BH, 2005; Witt *et al*., 2008). Sensorimotor synchronization is crucial to human daily activities. It relies on the ability to predict external events (Ruspantini, D'Ausilio, Mäki, & Ilmoniemi, 2011). The finger tapping task is simple enough that it can be used to study both normal controls and clinical populations (Repp BH, 2005; Witt *et al*., 2008). For example, it has often been employed to assess patients with Huntington's Disease (Antoniades *et al*., 2012).

The finger tapping task is also a flexible task that can accommodate multiple modifications. A literature review of finger tapping tasks reveal a variety of different modifications (Repp BH, 2005; Witt *et al*., 2008). Tasks range from utilizing single finger motor responses, to those that utilize complex, multi-finger, or bimanual motor

responses. There are also those tasks that are self pacing, or employ auditory or visual pacing stimuli. Self-pace finger tapping that is performed with the absence of pacing stimuli is considered internally guided or internally generated (Witt *et al*., 2008).

Most of the finger tapping studies to date employ finger tapping cued by auditory stimuli. Models suggest that finger tapping to auditory cues is processed in a very direct manner. Auditory rhythms are computed from the auditory cues in the auditory pathway. These are coded and sent through the auditory nerve to cortical and sub cortical motor areas for auditory-motor coupling, as well as rhythm perception (Cerasa *et al*., 2004; Repp & Su, 2013). This facilitates rapid entrainment to the auditory cues. Rapid entrainment is observed even when the Inter-stimulus Interval (ISI) are changed periodically, indicting behavioral automaticity (behavioral performance achieved with small demand on attentional resources) (Cerasa *et al*., 2004).

Although there is some concordance in brain area activation (primary sensorimotor cortex, supplementary motor area, and anterior cerebellum), visually cued finger tapping tasks influence the brain differently from auditory cued finger tapping tasks (Cerasa *et al*., 2004). In some ways, visually cued finger tapping tasks appear to have more concordance with self pacing finger tapping tasks, then auditory paced finger tapping. For instance, the right dorsolateral prefrontal cortex is often linked to self-paced movements, which is also active during visually cued finger tapping. However, there are some distinct areas active during visually paced finger tapping tasks that are not observed in auditory or self pacing finger tapping tasks. They include bilateral insular cortex, right inferior frontal gyrus, Broadmann's areas 18 and 37, and left posterior cerebellum (Witt *et al*., 2008). A reason for this disparity may be due to the visually cued

finger tapping tasks creating a larger cognitive load compared to auditory cued tasks. The use of visual stimuli yields more variability, which engages attentional control to monitor and adjust responses to isochronic cues (Cerasa *et al*., 2004).

## CHAPTER 3 HYPOTHESIS

Finger tapping tasks have been studied in neurologic diseases such as autism spectrum disorders, attention-deficit/hyperactivity disorder (ADHD), schizophrenia, and alcoholism. In a bimanual, self-paced, sequential finger tapping study, children with autism had slower tapping in the left hand, and decreased functional connectivity (Mostofsky *et al*., 2009). Utilizing the same task in children with ADHD, there were no differences in performance, however differences in the contralateral primary motor cortex and right superior posterior parietal cortex were observed (Mostofsky *et al*., 2006). In a left hand, self-paced, sequential finger tapping study, significant effects on brain activation were found in schizophrenic patients based on treatment and psychotic condition (Müller, Röder, Schuierer, & Klein, 2002). In a self-paced finger tapping study, alcohol dependent individuals were found to have a slower tapping rate and higher fMRI activation in ROI's compared to the controls (Parks *et al*., 2003).

Finger tapping has not been effectively studied in FASD. A literature search found one study published in 2015 (du Plessis L, 2015). The authors performed an fMRI study probing cerebellum timing and accuracy using an auditory cued finger tapping task on children ranging in age from 9.5 to 12 years of age. The researchers found differences in BOLD signal during rhythmic and non-rhythmic tapping, but not on performance.

Granted the lack of studies utilizing both MEG and visually cued finger tapping in FASD, we utilized these tools to investigate brain dynamics and how they relate to behavior. Specifically, to characterize frontal parietal network function in prenatally alcohol exposed adolescents and how it relates to speed and variability in a visuomotor finger tapping task. Given previous studies and the structural and functional abnormalities found in FASD individuals, it is predicted they would have differences in

behavioral data, and altered function in the frontal parietal network relative to typically developing individuals.

## CHAPTER 4 METHODS

### Participants

Forty eight adolescents and young adults, aged 12 to 22 years, participated in this study. Twenty-three of these participants (10 male, mean age = 15.837 years, standard deviation [SD] = 3.06) were identified as having a fetal alcohol diagnosis (9 FASand 11 ARND) according to the modified Institute of Medicine criteria (Stratton, Howe, & Battaglia, 1996). Twenty-five individuals (14 male, mean age = 16.384 years, SD = 3.03) with no history of prenatal alcohol exposure, developmental delays, seizure disorder, head trauma, significant psychiatric or neurological problems served as controls. All participants were right- handed (Edinburgh Handedness Inventory: Oldfield, 1971) and none had significant sensory problems (e.g. poor vision or hearing) or difficulty understanding the task. Participants with FASD were recruited through the University of New Mexico Fetal Alcohol Diagnostic and Evaluation Clinic and healthy controls, through flyers and word of mouth.

This study was approved by the University of New Mexico Health Sciences Center Institutional Review Board and was in full compliance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent was obtained from the parents/legal guardians and/or participants dependent on the age and assent from minors in accord with the Institutional Review Board guideline of the University of New Mexico. Participants were compensated for their time and travel expenses.

**Finger Tapping Visuomotor Task**

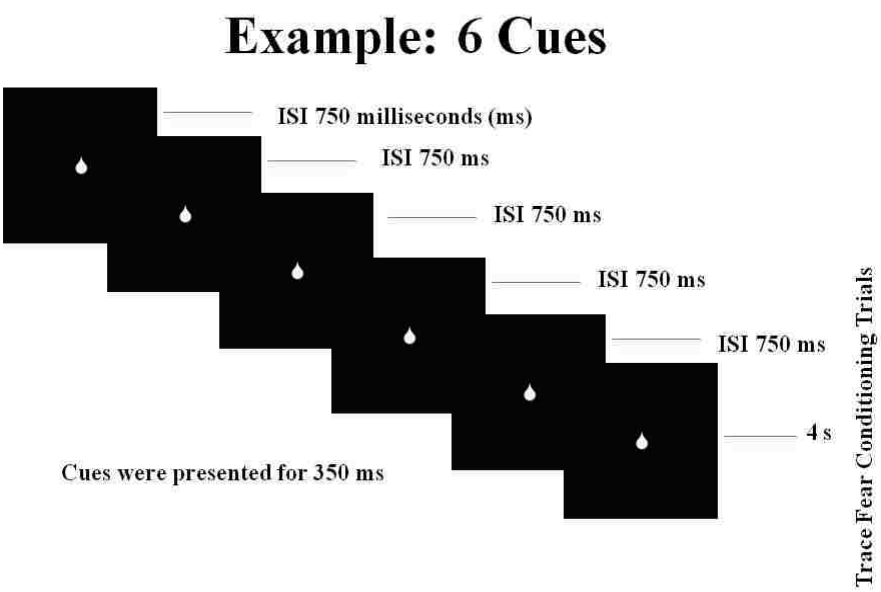



**Figure 6. Example of a 6 cued finger tapping trial to illustrate the task and timing.**

The isochronous finger tapping visuomotor task was administered using 100 trials of 6 – 8 visually presented cues. The visual stimuli were presented for 350 milliseconds with an interstimulus interval of 750 milliseconds (See Figure 6 for illustration). Three, randomly-ordered, trace fear conditioning trials were presented after every finger tapping trial. These consisted of a 1) conditioned picture paired with an aversive sound, 2) conditioned picture without the aversive sound, and 3) a conditioned picture, which is never paired with the aversive sound. Visual stimuli were projected onto the back of a translucent screen placed at a distance of 1 meter from the nasion of each participant. The stimuli were white objects with a black background and measured 5 centimeters (Figure 6). The visual angle of the stimuli was 2.864˚. The visual stimuli were presented using a Panasonic PT-D7700 projector with a visual delay of 35.1 milliseconds + 0.2

milliseconds. This delay was taken into account for all reported latency statistics. Presentation software (www.neurobs.com) was used to deliver the stimuli and record motor responses to them. Participants were instructed to respond with the right index finger to each cue. A practice run consisting of 5 presented cues and one trace fear conditioning trial was completed prior to starting the scan to make sure participants understood the task. Reaction times were recorded during the task.

**MEG Data Acquisition**

MEG scans were conducted at the Mind Research Network in Albuquerque, New Mexico using a 306-channel whole-head array (Elekta Neuromag). The scanner was located in a magnetically shielded room (Vacuumschmelze – Ak3B). Prior to data acquisition, four Head Position Indicator (HPI) coils were affixed on each participant: one each on the left and right mastoid bone and two on the forehead. The HPI coils detect and monitor the location and orientation of the participant's head with respect to the MEG sensor array during the scan. The coil locations were registered, along with a 3 dimensional model of the head shape/size and the location of the participants' nasion and preauricular points using digitization equipment (Polhemus). Eye movements were recorded continuously throughout the scan using bipolar horizontal and vertical electro-oculograms. Participants were seated upright under the MEG array during the task and were monitored at all times by an audio and video link between the magnetically shielded room and control room. MEG and eye-movement data were band-pass filtered at 0.1-330 Hz and sampled at 1 kHz.

## Analysis

### Behavioral data analysis

Seven participants (3 FASD, 4 Controls) were excluded from analysis. Three FASD participants were excluded due to a revision to the timing paradigm. Four control participants were excluded for the following reasons: 2 control participants had too much noise in the data; 1 control participant had a psychiatric issue; and 1 control participant had a previous diagnosis of ADHD. The Wechsler Abbreviated Scale of Intelligence™ (WASI™) was utilized to assess general cognitive ability. A brief measure of IQ was obtained from each participant by administering the Vocabulary and Matrix Reasoning subtests of this test. The FASD group scored significantly lower than the control group on the Vocabulary subtest (FASD: mean = 30.68, SD = 7.28; Control: mean 40.65, SD = 8.63, $t(37) = 7.01$, $p < 0.001$), but not on the Matrix Reasoning subtests (FASD: mean = 44.53, SD = 9.12; Control: mean 49.85, SD = 8.2; $t(37) = 1.92$, $p = 0.063$). The two groups differed with respect to composite IQ scores (FASD: mean = 80.9, SD = 9.89; Control: mean 99.65, SD = 9.84; $t(37) = 6.01$, $p < 0.001$).

Behavioral differences in the finger tapping task were explored between the two groups (FASD and Controls). We tested two behavioral outcomes from this task: mean reaction time and reaction time variability. Reaction times were extracted from logfiles generated by Presentation. The display delay was removed from each reaction time (35.1 milliseconds). The reaction times were averaged for each Cue. A grand average and standard deviations for each Cue were computed for each participant across all trials. These values were entered into SPSS (IBM Statistical Package for the Social Sciences, version 19.0) to compute independent samples T tests to compare the 2 groups on

reaction times. Levene's test of equality of variances were also computed which revealed significant differences in the data. The adjusted T statistic was used in those cases. The results of Levene's test of equality of variances are also reported in this paper, given the number and amount of reaction time variability observed. We also used SPSS to compute Pearson's correlations to reveal relationships between reaction times and reaction time variability with age and IQ. A Chi Squared test was performed to further explore differences in the number of positive and negative correlations between reaction times, peak latencies, and peak onsets between the 2 groups. On all of these analyses, the critical value for rejecting the null hypotheses was defined at $p \leq 0.05$.

**MEG Analysis**

Elekta Neuromag Maxfilter™ software was used to compensate for head movement and to remove artifacts originating outside the cranial volume (Taulu & Simola, 2006). The data was downsampled at 600 Hz, filtered at 40 Hz and averaged time-locked to the motor response for epochs of 500 milliseconds before to 500 milliseconds after the individual motor response. The data were baseline corrected from -500 milliseconds to -350 milliseconds before the motor response. The unaveraged data was utilized to create signal-space projectors to suppress blink and cardiac signals for each individual participant (Uusitalo & Ilmoniemi, 1997).

Surface tessellation of the cerebral and of the cerebellar cortex was extracted from each participant's MR images using BrainSuite (http://brainsuite.org). Each surface was approximated by a grid of 7,000 points. The cerebral tessellations formed a brain-based source space for MEG data inversion. A similar cerebral tessellation was constructed

from MR images for the Collin 27 adult brain (Collins *et al*., 1998) which was used as a common source space for all between-subject analyses.

Brainstorm (Tadel, Baillet, Mosher, Pantazis, & Leahy, 2011) was used to compute average sensor plots from the MEG sensor data and to extract brain-based waveforms for specific brain regions. Brainstorm is a documented and free software package downloaded online under a GNU general public license (http://neuroimage.usc.edu/brainstorm/). The MEG data were co-localized with the structural MRI for each individual participant. Source space waveforms were computed for each participant from all sensor evoked-response data (utilizing both gradiometer and magnetometer sensor data) and the individual brain surface tessellation using a weighted minimum norm estimate (wMNE). The data were normalized with the baseline standard deviation.

Group-averaged brain activation patterns were determined by projection of each participant's source-space data onto a common surface derived from the Collin 27 brain. Averages of individual activation patterns within this source space were determined for the first four stimuli for the FASD and control groups. One participant did not have a MRI. MEG data for this subject were projected directly onto the Collin 27 brain using the Polhemus digitization of the participant's face and scalp.

Waveforms of brain activity were computed within Brainstorm from group averages of the source activation data. The following regions were selected: middle frontal orbital cortex, insular cortex, superior frontal cortex, anterior cingulate cortex, and inferior parietal cortex, as described in the Brainvisa Tzourio-Mazoyer cortical atlas (Tzourio-Mazoyer *et al*., 2002). Significant amplitude differences were determined by running T tests within Brainstorm. Amplitude values were extracted from the

waveforms. The peak onset was ascertained as the lowest point prior to the motor response, approximately -0.1 seconds prior to time 0). The peak latency was determined to be the highest peak near the motor response (time 0). These values were extracted using Brainstorm and placed into SPSS (IBM Statistical Package for the Social Sciences, version 19.0) in order to compute independent samples T tests to compare the 2 groups. We also used SPSS to compute Pearson's correlations to reveal relationships between the peak latency and onset values with behavioral measures. The critical value for rejecting the null hypotheses was defined at $p \leq 0.05$, for all analyses.

## CHAPTER 5 RESULTS

### Behavioral Data Results

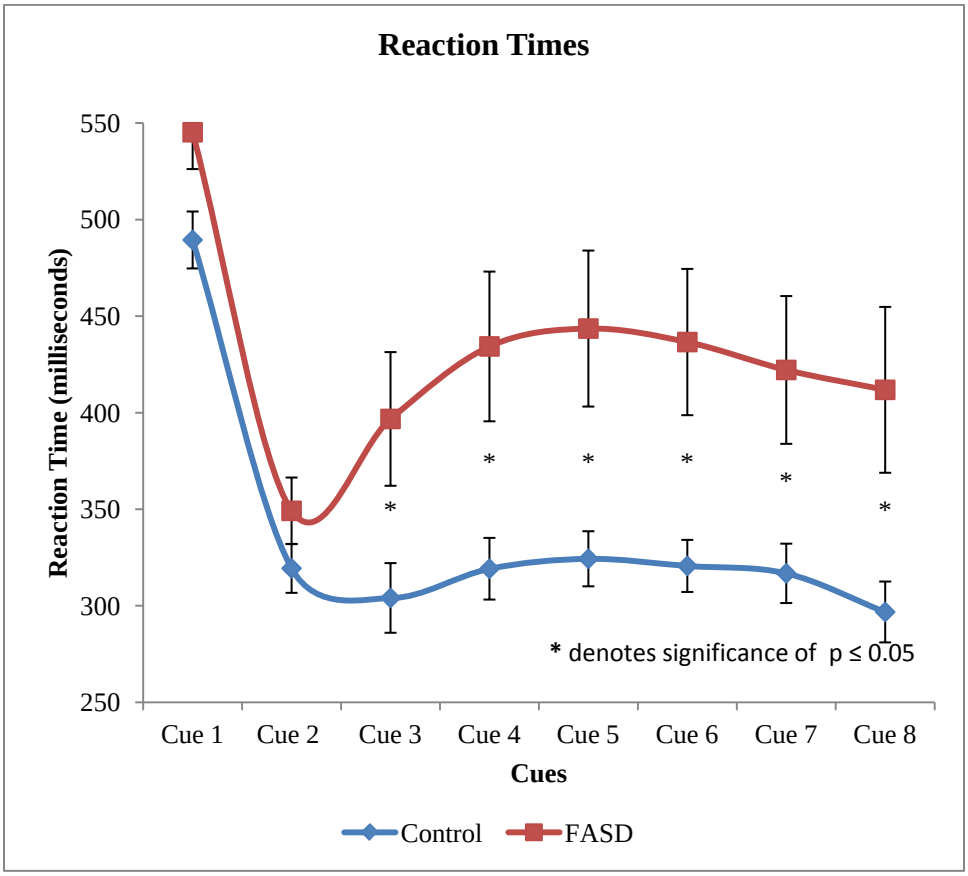



**Figure 7. Group comparison of reaction times to cues.**

An analysis of the motor response to cues revealed significant differences between the FASD group and Control group. Independent- Samples T Tests were computed to test the differences between the FASD group and Control groups. Averages and statistics are presented in Figure 7. For all cues, the FASD group has a slower response reaction time compared to the Control group. Differences in Cue 1 and Cue 2 did not reach statistical significance. However, differences in Cues 3 through 8 reach significance at an alpha level of 0.05.

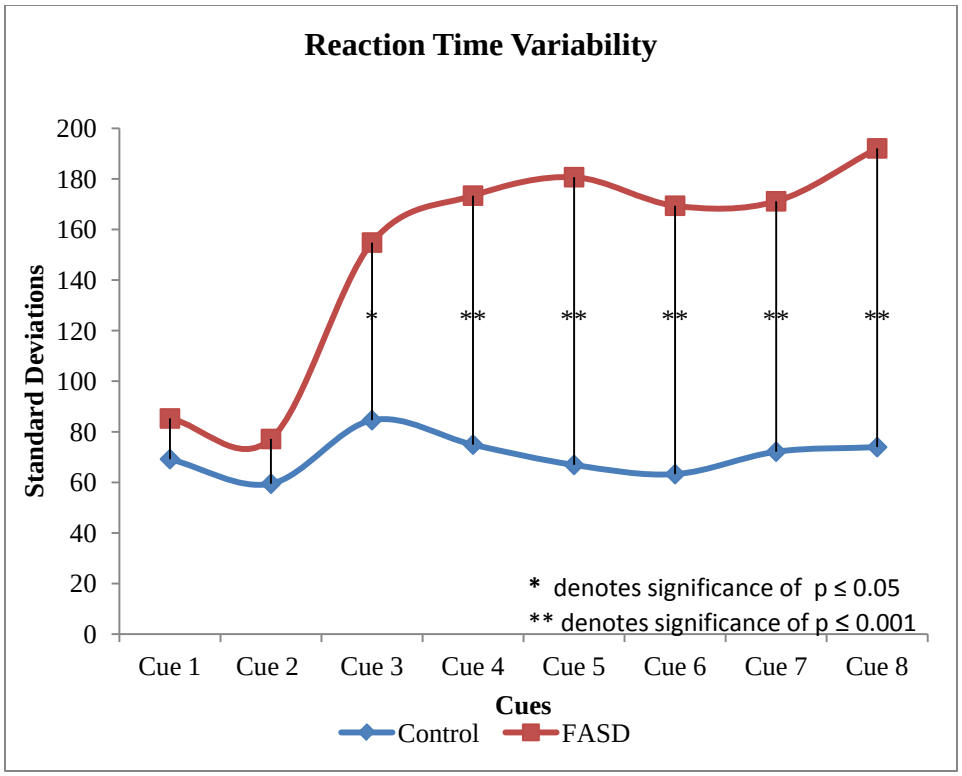



**Figure 8. Group comparison of reaction time variability to cues.**

Differences are also present in the reaction time variability. The reaction time variability is found to be statistically different using Levene's Test of Equality of Variance. These differences are found in Cues 3 through 8, and the corrected *t* statistic is used in those cases. The reaction time variability and statistics are presented in Figure 8. In Cues 3 through 8, the reaction time variability for the FASD group are quite large, hovering around 2X or more the size of the Control group.

**Table 1. Control group reaction times correlates with age.**

| Correlate | Statistic |
|---|---|
| Cue 1 Reaction Time | r = -0.391, p = 0.072 |
| Cue 2 Reaction Time | r = -0.42, p = 0.051 |
| Cue 3 Reaction Time | r = -0.418, p = 0.053 |
| Cue 4 Reaction Time | r = -0.536, p = 0.01 |
| Cue 5 Reaction Time | r = -0.577, p = 0.005 |
| Cue 6 Reaction Time | r = -0.583, p = 0.004 |
| Cue 7 Reaction Time | r = -0.397, p = 0.067 |

**Table 2. Control group reaction time variability correlates with age.**

| Correlate | Statistic |
|---|---|
| Cue 1 Reaction Time Variability | r = -0.414, p = 0.055 |
| Cue 2 Reaction Time Variability | r = -0.456, p = 0.033 |
| Cue 3 Reaction Time Variability | r = -0.384, p = 0.078 |
| Cue 4 Reaction Time Variability | r = -0.422, p = 0.051 |
| Cue 5 Reaction Time Variability | r = -0.46, p = 0.031 |
| Cue 6 Reaction Time Variability | r = -0.567, p = 0.006 |
| Cue 7 Reaction Time Variability | r = -0.53, p = 0.011 |
| Cue 8 Reaction Time Variability | r = -0.479, p = 0.024 |

For the Control group, the best predictor for performance on the finger tapping task is age. Age is a significant predictor with most of the cue reaction time and their reaction time variability (Table 1 and 2). Reaction times for Cues 2 - 6 negatively correlate with age. Younger Control group participants have slower reaction times compared to older participants. All reaction time variability negatively correlates with age. Surprisingly, none of these correlations are present in the FASD group.

**Table 3. Control group reaction time variability correlates with IQ.**

| Cue | IQ Correlate | Statistic |
|---|---|---|
| Cue 7 | IQ Score | r = -0.469, p = 0.037 |
| Cue 1 | Vocabulary subtest | r = -0.463, p = 0.04 |
| Cue 2 | Vocabulary subtest | r = -0.511, p = 0.021 |
| Cue 5 | Vocabulary subtest | r = -0.508, p = 0.022 |
| Cue 6 | Vocabulary subtest | r = -0.497, p = 0.026 |
| Cue 7 | Vocabulary subtest | r = -0.668, p = 0.001 |
| Cue 8 | Vocabulary subtest | r = -0.473, p = 0.035 |

In the Control group, IQ and the Vocabulary subtest scores also predict performance (Table 3). Cue 7 reaction time variability negatively correlates with IQ scores. Reaction time variability for Cues 1, 2, 5 - 8 negatively correlate with IQ Vocabulary subtest scores. These correlations are also not present in the FASD group.

## Anterior Cingulate Cortex Results

### Cue 1 Motor Response

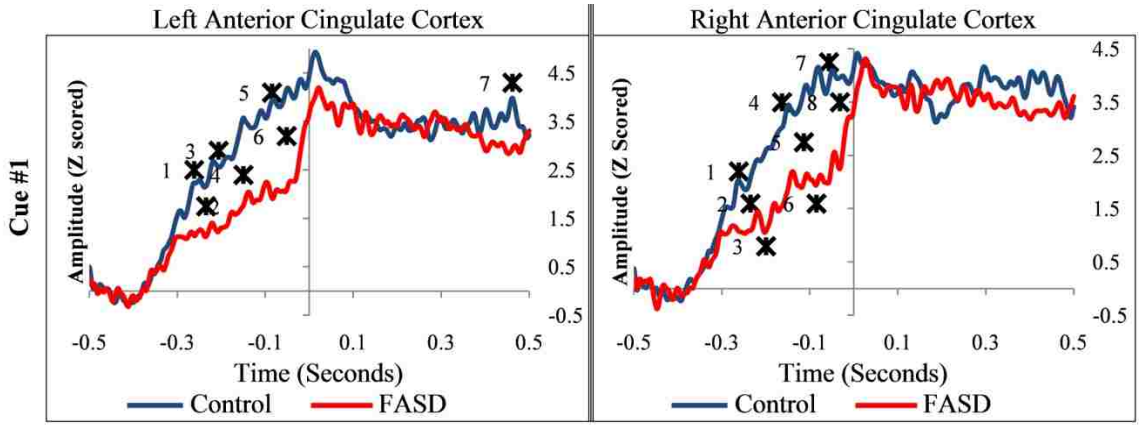



**Figure 9. Left and right Anterior Cingulate Cortex: Cue 1. Evoked response waveforms are time-locked to the motor response. * denotes significant differences between groups in amplitude ($p \leq 0.05$).**

**Table 4. Anterior Cingulate Cortex (ACC) Cue 1 Amplitude differences.**

| Left | | | Right | | |
|---|---|---|---|---|---|
| # | Seconds | Statistic | # | Seconds | Statistic |
| 1 | -0.2617 | t (40) = 2.635, p = 0.01 | 1 | -0.2617 | t (40) = 2.565, p = 0.01 |
| 2 | -0.235 | t (40) = 2.378, p = 0.02 | 2 | -0.235 | t (40) = 2.224, p = 0.03 |
| 3 | -0.2067 | t (40) = 2.936, p = 0.005 | 3 | -0.2 | t (40) = 3.473, p = 0.001 |
| 4 | -0.15 | t (40) = 3.21, p = 0.003 | 4 | -0.1633 | t (40) = 2.82, p = 0.007 |
| 5 | -0.085 | t (40) = 3.758, p = 0.001 | 5 | -0.1133 | t (40) = 3.504, p = 0.001 |
| 6 | -0.0517 | t (40) = 3.917, p = 0.0003 | 6 | -0.085 | t (40) = 3.954, p < 0.001 |
| 7 | 0.4617 | t (40) = 2.304, P = 0.02 | 7 | -0.0567 | t (40) = 3.188, p = 0.003 |
| | | | 8 | -0.0317 | t (40) = 2.793, p = 0.008 |

In left and right Anterior Cingulate Cortex (ACC), the amplitude is significantly different prior to the motor response, with the Control group leading with higher amplitude (See Figure 9 and Table 4). Amplitudes diverge approximately -0.3 seconds prior to the response and reconverge after time 0. In left and right ACC, the differences reach significance at -0.2617 seconds; in left ACC, t (40) = 2.635, p = 0.01, and in right t (40) = 2.565, p = 0.01. In left ACC, amplitudes diverge and reach significance after the

button response, with the Control group having increased amplitude versus the FASD group. Amplitudes diverge at around 0.4 seconds, reaching significance at 0.4617 seconds [t (40) = 2.304, p = 0.02]. Peak latencies are also significantly different in left and right ACC. In left ACC, the Control group response peak is at 0.0133 seconds, whereas the FASD group response peak is at 0.0217 seconds [t (40), -2.895, p = 0.006]. In right ACC, latencies are similar to left, with the Control group response peak at 0.0083 seconds, and at 0.0267 seconds for the FASD group [t (40), -6.505, p < 0.001].

**Cue 2 Motor Response**

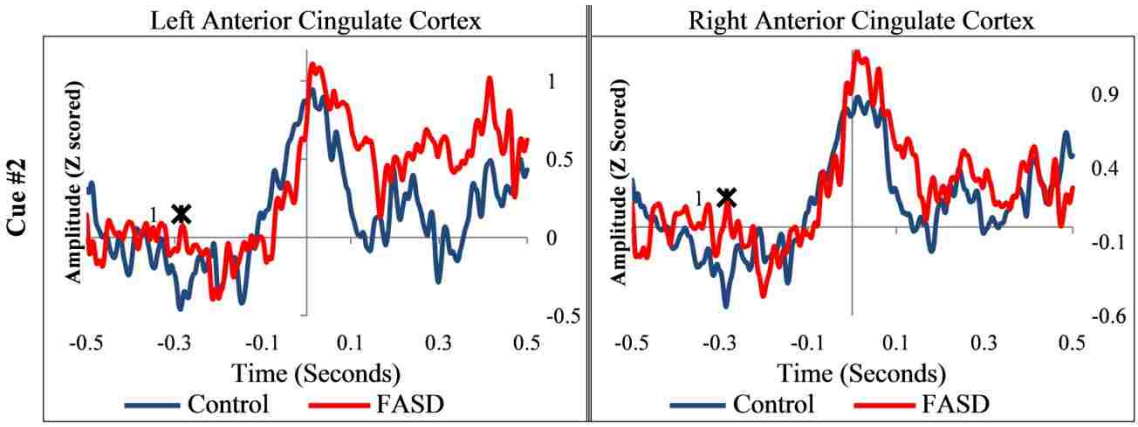



**Figure 10. Left and right Anterior Cingulate Cortex: Cue 2. Evoked response waveforms are time-locked to the motor response. * denotes significant differences between groups in amplitude ($p \leq 0.05$).**

In left and right ACC, there are significant differences in amplitude prior to the motor response at -0.285 seconds; t (40) = -2.132, p = 0.03 and t (40) = -2.951, p = 0.005, respectively (Figure 10). In both cases, the FASD group has larger amplitude then the Control group. There are differences in peak onsets for left ACC, but not right. In left ACC, peak onsets for the Control group appears to start earlier, at -0.12 seconds, whereas peak onsets for the FASD group starts at -0.078 seconds [t (40) = -9.885, p < 0.001].

**Cue 3 Motor Response**

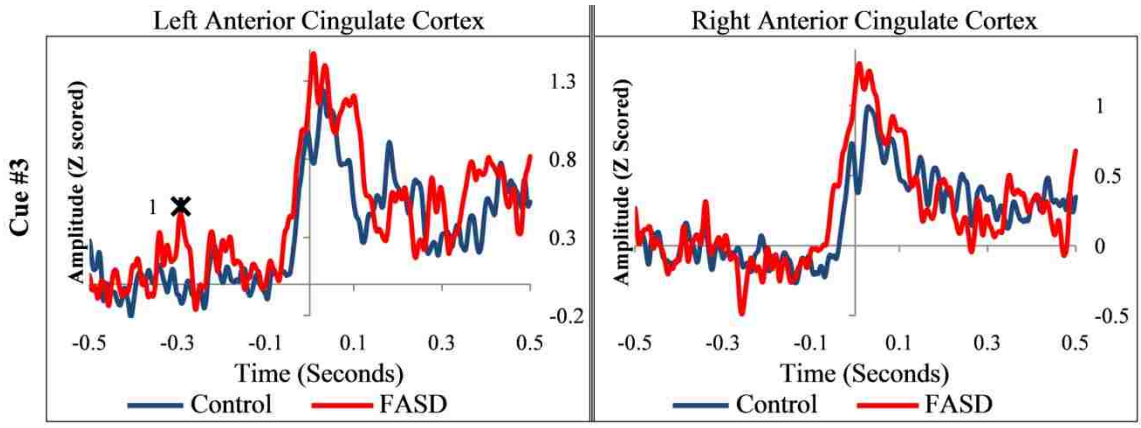



**Figure 11. Left and right Anterior Cingulate Cortex: Cue 3. Evoked response waveforms are time-locked to the motor response. * denotes significant differences between groups in amplitude ($p \leq 0.05$).**

In right ACC, there are no differences in amplitude. In left ACC, there is a difference in amplitude at -0.2933 seconds [$t(40) = -2.243$, $p < 0.001$], with the FASD group having a higher amplitude (Figure 11). Also, in left and right ACC, there are some differences present in peak latencies and onsets near time 0. In left and right ACC, the FASD group had the earlier peak latencies and onsets. In left ACC, peak onsets for the FASD group starts at -0.0467 seconds and peak onsets for the Control group starts at -0.0717 seconds [$t(40) = 9.246$, $p < 0.001$]. This leads to a difference in peak latencies with the FASD group leading at 0.0083 seconds, followed by the Control group at 0.025 seconds [$t(40) = 4.871$, $p < 0.001$]. Peak onsets and latencies are very similar in right ACC. In right ACC, peak onsets for the FASD group starts at -0.0667 seconds and at -0.0417 seconds for the Control group [$t(40) = 9.69$, $p < 0.001$]. The FASD group reaches a peak sooner at 0.0083 seconds, followed by the Control group at 0.0283 seconds [$t(35.025) = 8.735$, $p < 0.001$].

**Cue 4 Motor Response**

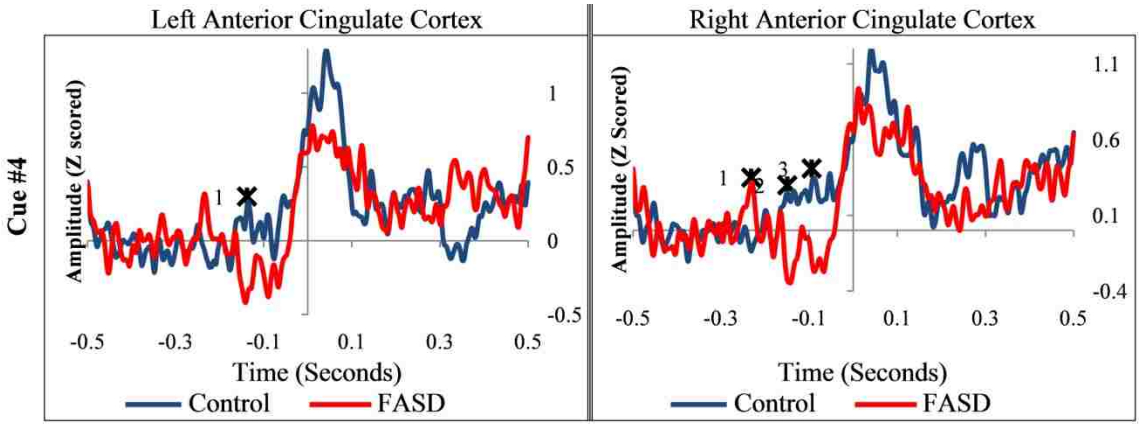



**Figure 12. Left and right Anterior Cingulate Cortex: Cue 4. Evoked response waveforms are time-locked to the motor response. * denotes significant differences between groups in amplitude ($p \leq 0.05$).**

In left and right ACC, amplitude is significantly different prior to the motor response (Figure 12). In left ACC, this occurs at -0.1383 seconds, with the Control group having higher amplitude. In right ACC, significance occurs at -0.2317 seconds, -0.15 seconds, and -0.095 seconds. The FASD group has higher amplitude at -0.2317 seconds, and the Control group has a higher amplitude at -0.150 seconds and -0.095 seconds. Peak onsets are also significantly different in left and right ACC. In left ACC, the Control group peak onsets begin at -0.08 seconds, and at -0.0683 seconds for the FASD group [t (40), -2.408, p = 0.02]. In right ACC, the Control group peak onsets begin at -0.0417 seconds and at -0.0683 seconds for the FASD group [t (40), 10.14, p < 0.001].

**Behavioral Correlates**

In right ACC, correlations are found between onsets, latencies, and behavioral data. In the FASD group, Cue 4 peak onsets correlate to Cue 2 reaction time variability [r = 0.503, p = 0.024], Cue 3 reaction time variability [r = 0.525, p = 0.017], and Cue 7 reaction time variability [r = 0.456, p = 0.043]. Also, Cue 1 peak latencies correlate with

IQ [r = 0.566, p = 0.014], Vocabulary subtest [r = 0.518, p = 0.033], and Matrix Reasoning subtest [r = 0.47, p = 0.057]. Lastly, Cue 3 peak onsets correlate with age [r = 0.421, p = 0.065]. In the Control group, Cue 1 peak latencies correlate with Matrix Reasoning subtest [r = 0.458, p = 0.042]. Cue 3 peak onsets negatively correlate with Cue 4 peak onsets [r = -0.471, p = 0.027]. Cue 4 peak onsets correlate with age [r = 0.49, p = 0.02]. Lastly, Cue 3 peak latencies correlate with Cue 8 reaction time variability [r = 0.526, p = 0.012].

**Table 5. Left Anterior Cingulate Cortex (ACC) Control group correlations.**

| Correlate 1 | Correlate 2 | Statistic |
|---|---|---|
| Cue 2 Reaction Time | Cue 3 Peak Latencies | r = -0.425, p = 0.048 |
| Cue 3 Peak Latencies | Cue 3 Reaction Time | r = 0.492, p = 0.02 |
| Cue 3 Peak Latencies | Cue 4 Reaction Time | r = 0.528, p = 0.011 |
| Cue 3 Peak Onsets | Cue 5 Reaction Time | r = -0.604, p = 0.003 |
| Cue 3 Peak Onsets | Cue 6 Reaction Time | r = -0.604, p = 0.003 |
| Cue 3 Peak Onsets | Cue 7 Reaction Time | r = -0.653, p = 0.001 |
| Cue 3 Peak Onsets | Cue 8 Reaction Time | r = -0.588, p = 0.004 |
| Cue 4 Peak Onsets | Cue 4 Reaction Time Variability | r = 0.462, p = 0.03 |
| Cue 4 Peak Onsets | Cue 5 Reaction Time Variability | r = 0.423, p = 0.05 |
| Cue 1 Peak Latencies | IQ (Vocabulary) | r = -0.471, p = 0.036 |
| Cue 3 Peak Latencies | IQ (Vocabulary) | r = -0.44, p = 0.052 |

**Table 6. Left Anterior Cingulate Cortex (ACC) FASD group correlations.**

| Correlate 1 | Correlate 2 | Statistic |
|---|---|---|
| Cue 1 Peak Latencies | Cue 3 Reaction Time | r = 0.542, p = 0.013 |
| Cue 1 Peak Latencies | Cue 4 Reaction Time | r = 0.654, p = 0.002 |
| Cue 1 Peak Latencies | Cue 5 Reaction Time | r = 0.684, p = 0.001 |
| Cue 1 Peak Latencies | Cue 6 Reaction Time | r = 0.508, p = 0.022 |
| Cue 1 Peak Latencies | Cue 7 Reaction Time | r = 0.469, p = 0.037 |
| Cue 1 Peak Latencies | Cue 2 Reaction Time Variability | r = 0.489, p = 0.029 |
| Cue 2 Peak Onsets | Cue 3 Reaction Time Variability | r = 0.519, p = 0.019 |
| Cue 3 Peak Onsets | Cue 3 Reaction Time | r = -0.585, p = 0.007 |
| Cue 3 Peak Onsets | Cue 7 Reaction Time | r = -0.45, p = 0.047 |
| Cue 3 Peak Onsets | Cue 8 Reaction Time | r = 0.469, p = 0.037 |

In left ACC, many correlations are found between onsets, latencies, and behavioral data in both groups. These are presented in Table 5 and 6.

## Anterior Prefrontal Cortex Results

### Cue 1 Motor Response

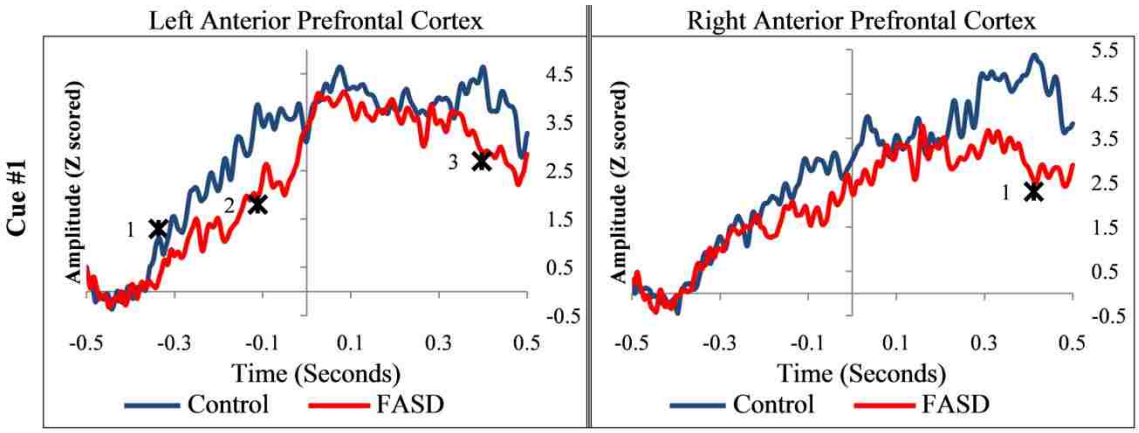



**Figure 13. Left and right Anterior Prefrontal Cortex: Cue 1. Evoked response waveforms are time-locked to the motor response. * denotes significant differences between groups in amplitude ($p \leq 0.05$).**

**Table 7. Anterior Prefrontal Cortex (aPFC) Cue 1 amplitude differences.**

| Left | | | Right | | |
|---|---|---|---|---|---|
| # | Seconds | Statistic | # | Seconds | Statistic |
| 1 | -0.3367 | t (40) = 2.915, p = 0.006 | 1 | 0.4117 | t(29.92) = 2.532, p = 0.01 |
| 2 | -0.1117 | t (40) = 2.634, p = 0.01 | | | |
| 3 | -0.3983 | t (40) = 2.155, p = 0.03 | | | |

In left anterior prefrontal cortex (aPFC), the amplitude is significantly different both prior to and after the response. The amplitudes diverge at approximately -0.35 seconds prior to the response and reconverge at around time 0. Differences reach significance at -0.3367 seconds [t (40) = 2.915, p = 0.006] and -0.1117 seconds [t (40) = 2.634, p = 0.01]. In right aPFC, amplitude differences do not reach significance prior to the button response. In left and right aPFC, amplitudes diverge and reach significance after the button response, with the Control group having increased amplitude versus the FASD group (Figure 13 and Table 7). In left aPFC, the amplitudes diverge at 0.21 seconds, reaching significance at 0.3967 seconds [t (40) = 2.155, p = 0.03]. In right

aPFC, the amplitudes diverge near 0.32 seconds, reaching significance at 0.4117 seconds [t (29.92) = 2.532, p = 0.01].

### Cue 2 Motor Response

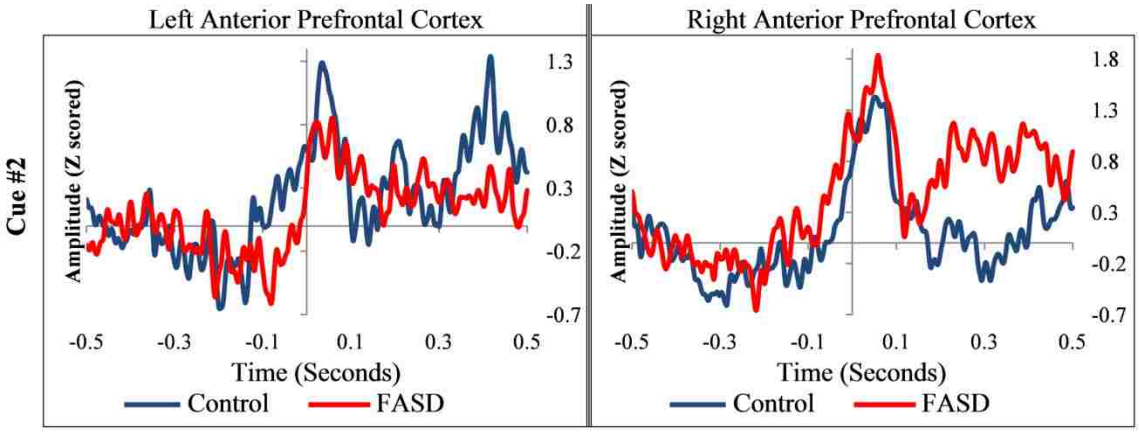



**Figure 14. Left and right Anterior Prefrontal Cortex: Cue 2. Evoked response waveforms are time-locked to the motor response.**

In left and right aPFC, there are no differences in amplitude (Figure 14). There are differences in peak onsets for left and right aPFC. In left aPFC, peak onsets for the Control group appear to start earlier, at -0.1417 seconds, and at -0.0817 seconds for the FASD group [t (40) = -22.002, p < 0.001]. The opposite occurs in right aPFC, with peak onsets of the FASD group starting earlier at -0.0883 seconds and at -0.0717 seconds for the Control group [t (40) = 5.298, p < 0.001].

**Cue 3 Motor Response**

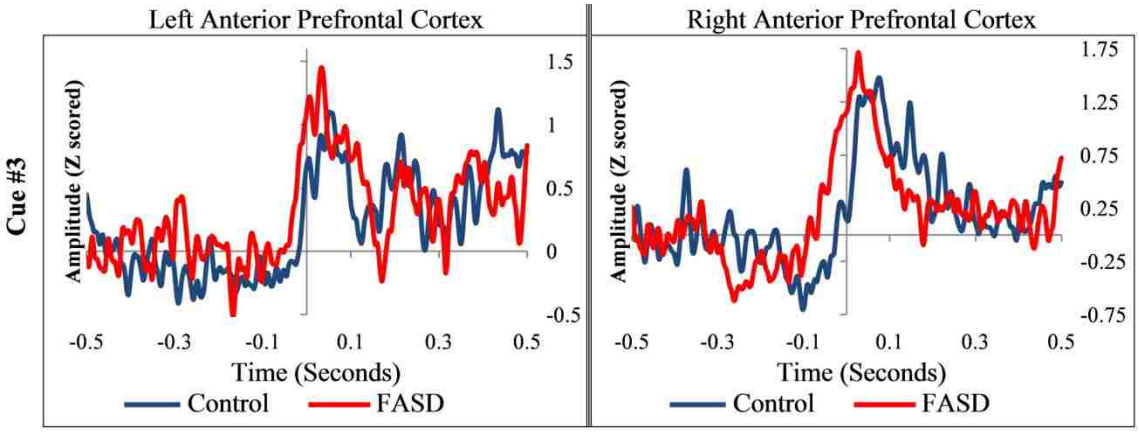



**Figure 15. Left and right Anterior Prefrontal Cortex: Cue 3. Evoked response waveforms are time-locked to the motor response.**

In left and right aPFC, there are no differences in amplitude (Figure 15). In left and right PFC, the FASD group has the earlier peak onsets. In left aPFC, peak onsets for the FASD group start at -0.0417 seconds and at -0.025 seconds for the Control group [t (40) = 6.468, $p < 0.001$]. In right aPFC, peak onsets for the FASD group start at -0.0717 seconds and at -0.045 seconds for the Control group [t (40) = 10.22, $p < 0.001$].

**Cue 4 Motor Response**

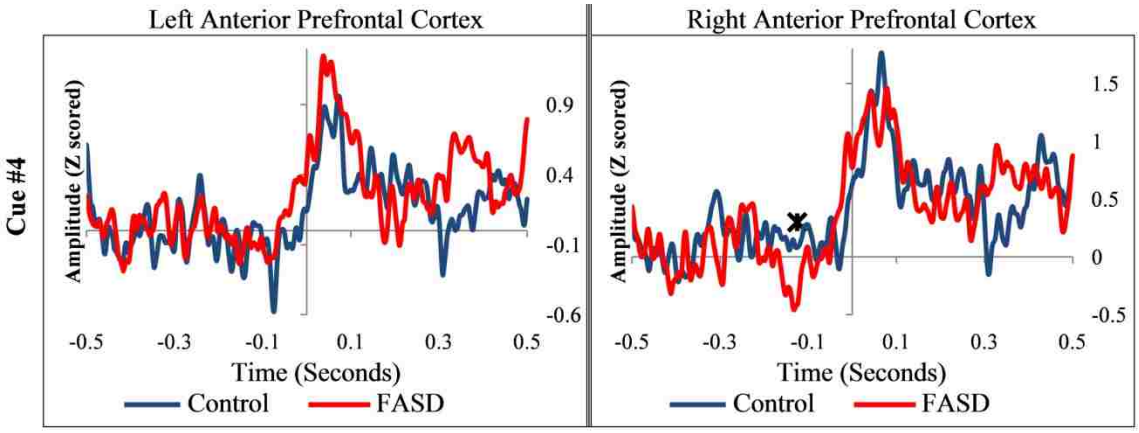



**Figure 16. Left and right Anterior Prefrontal Cortex: Cue 4. Evoked response waveforms are time-locked to the motor response. * denotes significant differences between groups in amplitude ($p \leq 0.05$).**

In left aPFC, there is no difference in amplitude. In right aPFC, there is an amplitude difference prior to the button press at -0.125 seconds [t (33.734) = 2.466, p = 0.01] (Figure 16). Differences in peak onsets are also present in left and right aPFC. In left and right PFC, the FASD group had the earlier peak onsets. In left aPFC, peak onsets for the FASD group starts at -0.0417 seconds and at -0.03 seconds for the Control group [t (40) = -4.01, p < 0.001]. In right aPFC, peak onsets for the FASD group starts at -0.0517 seconds and at -0.0317 seconds for the Control group [t (40) = 9.487, p < 0.001].

**Behavioral Correlates**

In left aPFC, only one correlation is present between onsets, latencies, and behavioral data. In the Control group, Cue 1 reaction times negatively correlate with Cue 2 peak latencies [r = -0.513, p = 0.015]. In left aPFC, no correlations are present for the FASD group.

**Table 8. Right Anterior Prefrontal Cortex (aPFC) FASD group correlations.**

| Correlate 1 | Correlate 2 | Statistic |
|---|---|---|
| Cue 3 Peak Latencies | Cue 6 Reaction Time Variability | r = 0.444, p = 0.05 |
| Cue 3 Peak Latencies | Cue 7 Reaction Time Variability | r = 0.454, p = 0.045 |
| Cue 1 Reaction Time | Cue 4 Peak Latencies | r = 0.554, p = 0.011 |
| Cue 1 Reaction Time Variability | Cue 4 Peak Latencies | r = 0.515, p = 0.02 |
| Cue 4 Peak Latencies | Cue 7 Reaction Time | r = 0.444, p = 0.05 |
| Cue 4 Peak Latencies | Cue 8 Reaction Time | r = 0.445, p = 0.049 |
| Cue 4 Peak Latencies | Cue 8 Reaction Time Variability | r = 0.619, p = 0.004 |

In right aPFC, only a few correlations are found between onsets, latencies, and behavioral data in the Control group. Cue 2 peak latencies negatively correlate with: Cue 2 reaction time [r = -0.522, p = 0.013]; Cue 5 reaction time [r = -0.498, p = 0.018]; Cue 7 reaction time [r = -0.459, p = 0.032]; and Cue 8 reaction time[r = -0.461, p = 0.031]. The correlations are numerous in the FASD group. These are presented in Table 8.

## Dorsolateral Prefrontal Cortex Results

### Cue 1 Motor Response

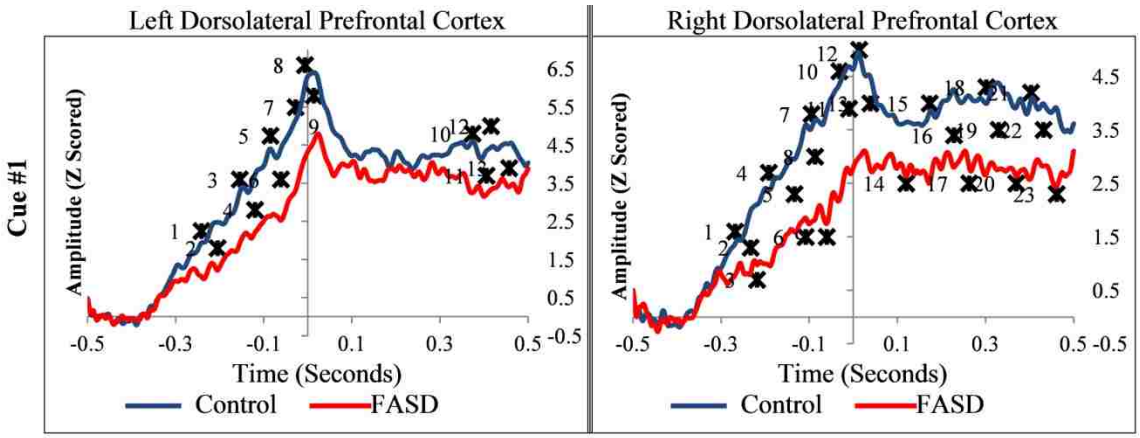



**Figure 17. Left and right Dorsolateral Prefrontal Cortex: Cue 1. Evoked response waveforms are time-locked to the motor response. * denotes significant differences between groups in amplitude ($p \leq 0.05$).**

**Table 9. Dorsolateral Prefrontal Cortex (dlPFC) Cue 1 amplitude differences.**

| Left | | | Right | | |
|---|---|---|---|---|---|
| # | Seconds | Statistic | # | Seconds | Statistic |
| 1 | -0.2417 | t (40) = 2.842, p = 0.007 | 1 | -0.2683 | t (40) = 2.205, p = 0.03 |
| 2 | -0.205 | t (40) = 3.144, p = 0.003 | 2 | -0.2333 | t (40) = 3.099, p = 0.004 |
| 3 | -0.155 | t (40) = 2.992, p = 0.005 | 3 | -0.2183 | t (40) = 2.586, p = 0.01 |
| 4 | -0.12 | t (33.79) = 3.41, p = 0.002 | 4 | -0.1917 | t (40) = 3.671, p = 0.001 |
| 5 | -0.085 | t (40) = 3.373, p = 0.002 | 5 | -0.1333 | t (40) = 2.884, p = 0.006 |
| 6 | -0.0617 | t (40) = 3.163, p = 0.003 | 6 | -0.1083 | t (40) = 3.73, p = 0.001 |
| 7 | -0.0283 | t (40) = 2.786, p = 0.008 | 7 | -0.095 | t (40) = 3.621, p = 0.001 |
| 8 | -0.0067 | t (40) = 2.517, p = 0.016 | 8 | -0.0867 | t (40) = 3.474, p = 0.001 |
| 9 | 0.0133 | t (40) = 2.108, p = 0.04 | 9 | -0.06 | t (40) = 3.871, p > 0.001 |
| 10 | 0.3717 | t (40) = 2.236, p = 0.03 | 10 | -0.0317 | t (40) = 3.595, p = 0.001 |
| 11 | 0.405 | t (40) = 2.095, p = 0.04 | 11 | -0.01 | t (40) = 3.246, p = 0.002 |
| 12 | 0.415 | t (40) = 2.029, p = 0.049 | 12 | 0.0133 | t (40) = 3.153, p = 0.003 |
| 13 | 0.4567 | t (40) = 2.111, p = 0.04 | 13 | 0.0383 | t (40) = 3.081, p = 0.004 |
| | | | 14 | 0.12 | t (40) = 2.102, p = 0.04 |
| | | | 15 | 0.1733 | t (40) = 2.58, p = 0.01 |
| | | | 16 | 0.2283 | t (40) = 2.276, p = 0.02 |
| | | | 17 | 0.2633 | t (40) = 2.364, p = 0.02 |
| | | | 18 | 0.3017 | t (40) = 2.603, p = 0.01 |
| | | | 19 | 0.33 | t (40) = 2.942, p = 0.005 |
| | | | 20 | 0.37 | t (40) = 2.43, p = 0.02 |

| | | | | | |
|---|---|---|---|---|---|
| | | | 21 | 0.4033 | t (40) = 2.732, p = 0.009 |
| | | | 22 | 0.4317 | t (40) = 2.734, p = 0.009 |
| | | | 23 | 0.4617 | t (40) = 3.212, p = 0.003 |

In left and right dorsolatereral Prefrontal Cortex (dlPFC), the amplitude is significantly different both prior to and after the response (Figure 17). Amplitudes diverge roughly 0.3 seconds prior to the response and do not reconverge. Differences reach significance at -0.2417 seconds [t (40) = 2.915, p = 0.006] in left dlPFC and -0.2683 seconds [t (40) = 2.634, p = 0.01] in right dlPFC and continue throughout (see Table 9). Left and right dlPFC in the Control group have greater amplitude than the FASD group. Peak latencies are significantly different in left and right dlPFC. In left dlPFC, the Control group response peaks at 0.015 seconds, and at 0.0233 seconds for the FASD group [t (40) = -2.528, p = 0.016]. Right dlPFC latencies are similar to left, with the Control group response peaks at 0.0117 seconds, and at 0.0267 seconds for the FASD group [t (40) = -7.798, p < 0.001].

**Cue 2 Motor Response**

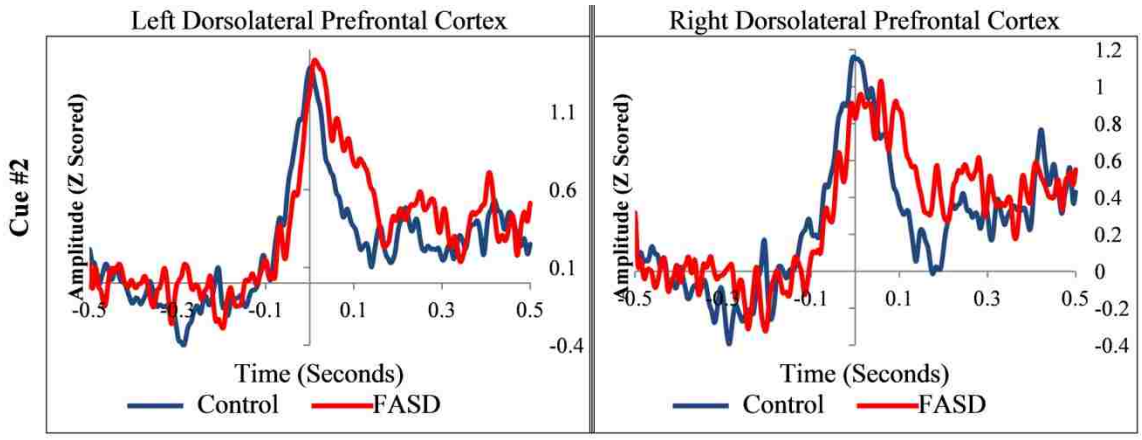



**Figure 18. Left and right Dorsolateral Prefrontal Cortex: Cue 2. Evoked response waveforms are time-locked to the motor response.**

In left and right dlPFC, there are no amplitude differences (Figure 18). There are differences in peak onsets and latencies for left and right dlPFC. In left dlPFC, peak onsets for the Control group start, at -0.08 seconds and at -0.0883 seconds for the FASD group [t (40) = 3.129, p = 0.003]. The response peaks occur at significantly different times. The Control group response peaks at 0.0017 seconds, and at 0.0117 seconds for the FASD group [t (40) = -4.875, p < 0.001]. In right dlPFC, the response for the Control group peaks at -0.005 seconds and at 0.0117 seconds for the FASD group [t (40) = -7.859, p < 0.001].

**Cue 3 Motor Response**

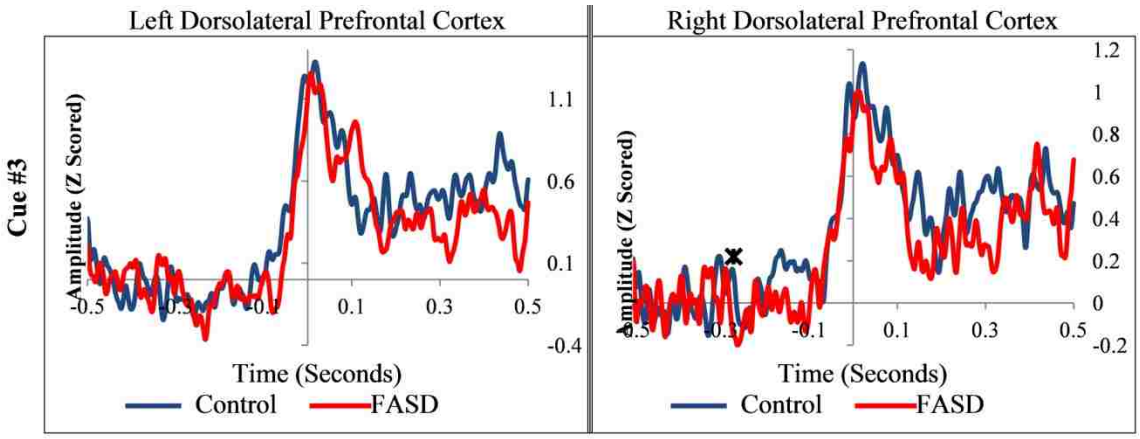



**Figure 19. Left and right Dorsolateral Prefrontal Cortex: Cue 3. Evoked response waveforms are time-locked to the motor response. * denotes significant differences between groups in amplitude ($p \leq 0.05$).**

In left and right dlPFC, there are no differences in amplitude (Figure 19). In left dlPFC, the Control group had earlier peak onsets. Peak onsets for the FASD group start at -0.07 seconds and at -0.0983 seconds for the Control group [t (40) = -11.016, p < 0.001]. The response for the Control group peaks at -0.0083 seconds, whereas this occurs at 0.0067 seconds for the FASD group [t (40) = -7.585, p < 0.001]. In right dlPFC, the FASD group had earlier peak onsets. Peak onsets for the FASD group start at -0.0767

seconds and at -0.0683 seconds for the Control group [t (40) = 3.766, p = 0.001]. The response for the Control group peaks at 0.0217 seconds, and at 0.0133 seconds for the FASD group [t (40) = 4.079, p < 0.001].

**Cue 4 Motor Response**

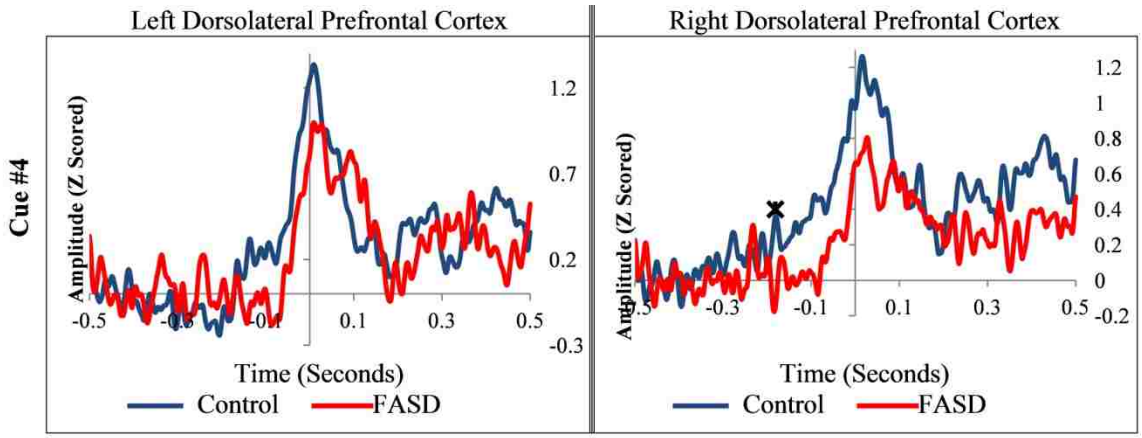



**Figure 20. Left and right Dorsolateral Prefrontal Cortex: Cue 4. . Evoked response waveforms are time-locked to the motor response. * denotes significant differences between groups in amplitude ($p \leq 0.05$).**

In left dlPFC, there is no difference in amplitude. In right dlPFC, there is an amplitude difference prior to the motor response at -0.1817 seconds [t (29.978) = 2.125, p = 0.04] (Figure 20). Differences in peak onsets are also present in left and right dlPFC. In left and right dlPFC, the Control group had the earlier peak onsets. In left dlPFC, peak onsets for the FASD group start at -0.0467 seconds and at -0.0783 seconds for the Control group [t (40) = -16.991, p < 0.001]. However, the peak response is not significantly different. In right dlPFC, peak onsets for the FASD group start at -0.0233 seconds and at -0.0533 seconds for the Control group [t t (40) = -12.706, p < 0.001]. The response for the Control group peaks at 0.0167 seconds, whereas this occurs at 0.0267 seconds for the FASD group [t (40) = -6.125, p < 0.001].

**Behavioral Correlates**

In left dlPFC, only a few correlations are found between onsets, latencies, and behavioral data. In the FASD group, Cue 2 peak latencies correlate with Cue 3 reaction time variability [r = 0.449, p = 0.049]. Also, Cue 2 reaction times negatively correlate with Cue 3 peak latencies [r = -0.474, p = 0.035]. In the Control group, Cue 2 peak onsets correlate with Cue 3 reaction times [r = 0.471, p = 0.027]. Cue 2 peak onsets also correlate with Cue 4 reaction times [r = 0.434, p = 0.044]. Lastly, Cue 3 peak latencies correlate with Cue 3 reaction time variability [r = 0.424, p = 0.049].

**Table 10. Right Dorsolateral Prefrontal Cortex (dlPFC) Control group correlations.**

| Correlate 1 | Correlate 2 | Statistic |
|---|---|---|
| Cue 1 Peak Latencies | Cue 4 Reaction Time | r = 0.455, p = 0.033 |
| Cue 3 Peak Onsets | Cue 2 Reaction Time | r = 0.423, p = 0.05 |
| Cue 3 Peak Onsets | Cue 5 Reaction Time | r = 0.456, p = 0.033 |
| Cue 3 Peak Onsets | Cue 6 Reaction Time | r = 0.494, p = 0.019 |
| Cue 3 Peak Onsets | Cue 7 Reaction Time | r = 0.498, p = 0.018 |
| Cue 4 Peak Latencies | Cue 4 Reaction Time | r = 0.427, p = 0.047 |
| Cue 4 Peak Latencies | Cue 5 Reaction Time | r = 0.444, p = 0.038 |
| Cue 4 Peak Latencies | Cue 7 Reaction Time | r = 0.501, p = 0.017 |
| Cue 4 Peak Latencies | Cue 8 Reaction Time | r = 0.481, p = 0.023 |

In right dlPFC, only a few correlations are found between onsets, latencies, and behavioral data in the FASD group. Cue 2 peak latencies negatively correlate with Cue 4 peak latencies [r = -0.523, p = 0.018]. Cue 3 peak onsets negatively correlate with Cue 3 peak latencies [r = -0.533, p = 0.015]. The correlations are numerous in the Control group. These are presented in Table 10.

## Insular Cortex Results

### Cue 1 Motor Response

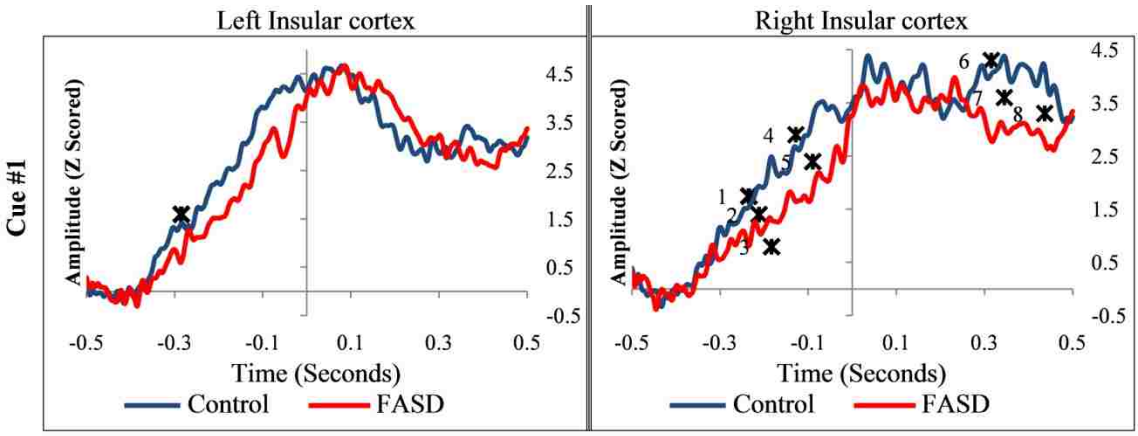



**Figure 21. Left and right Insular Cortex: Cue 1. Evoked response waveforms are time-locked to the motor response. * denotes significant differences between groups in amplitude ($p \leq 0.05$).**

**Table 11. Insular Cortex Cue 1 amplitude differences.**

| Left | | | Right | | |
|---|---|---|---|---|---|
| # | Seconds | Statistic | # | Seconds | Statistic |
| | -0.285 | t (40) = 2.453, p = 0.019 | 1 | -0.235 | t (40) = 2.453, p = 0.019 |
| | | | 2 | -0.2117 | t (40) = 2.645, p = 0.012 |
| | | | 3 | -0.1833 | t (40) = 3.133, p = 0.003 |
| | | | 4 | -0.1283 | t (40) = 2.189, p = 0.034 |
| | | | 5 | -0.09 | t (40) = 2.727, p = 0.009 |
| | | | 6 | 0.315 | t (40) = 2.092, p = 0.043 |
| | | | 7 | 0.345 | t (40) = 2.361, p = 0.023 |
| | | | 8 | 0.4367 | t (40) = 2.859, p = 0.007 |

In left and right insular cortex, the amplitude is significantly different prior to the motor response, with the Control group leading with higher amplitude (Figure 21 and Table 11). In left insular cortex, the amplitudes diverge approximately -0.366 seconds prior to the response and reconverge after time 0. The only significant difference in amplitude occurs at -0.285 seconds. In right insular cortex, amplitudes diverge at approximately -0.311 seconds and reconverge after time 0. Differences reach significance at -0.235 seconds [t (40) = 2.453, p = 0.019]. Amplitudes continue to reach

significance (Table 12) until time 0, when the amplitudes reconverge. Amplitudes rediverge at approximately 0.285 seconds, with points reaching significance starting at 0.315 seconds (#6 - #8, Table 12). In right Insular cortex, peak latencies for the FASD group occurs at 0.0233 seconds and at 0.035 seconds for the Control group [t (40) = 4.717, $p < 0.001$]. Peak latencies in left insular cortex are not significantly different. Interestingly, left and right insular cortex peak latencies of the Control group correlates with IQ subtests. The left peak latencies correlate with Vocabulary [r = 0.474, p = 0.026]. The right peak latencies correlate with Matrix Reasoning [r = 0.428, p = 0.047]. These correlations are not found in the FASD group.

**Cue 2 Motor Response**

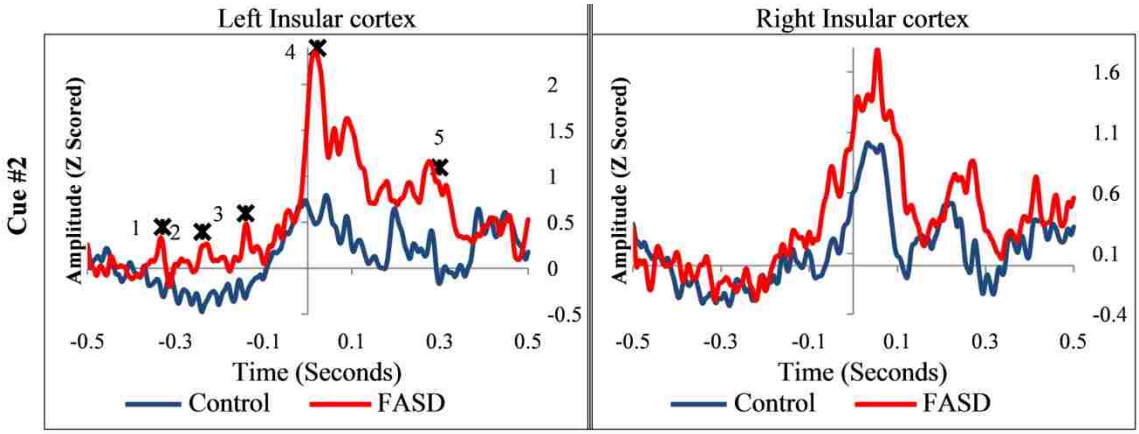



**Figure 22. Left and right Insular Cortex: Cue 2. Evoked response waveforms are time-locked to the motor response. * denotes significant differences between groups in amplitude ($p \leq 0.05$).**

**Table 12. Insular Cortex Cue 2 amplitude differences.**

| Left | | |
|---|---|---|
| **#** | **Seconds** | **Statistic** |
| 1 | -0.330 | t (40) = -2.147, p = 0.038 |
| 2 | -0.24 | t (40) = -2.462, p = 0.018 |
| 3 | -0.1417 | t (40) = -2.288, p = 0.027 |
| 4 | 0.0217 | t (40) = -2.178, p = 0.035 |
| 5 | 0.2983 | t (40) = -2.033, p = 0.049 |

In left and right insular cortex, the FASD group have larger amplitudes (Figure 22), reaching significance in left insular cortex, both before and after the motor response (Table 12). There are differences in peak onsets for left insular cortex, but not right. In left insular cortex, peak onsets for the Control group appear to start earlier, at -0.1017 seconds and at -0.0317 seconds for the FASD group [t (40) = -22.36, p < 0.001]. This leads to a difference in peak latencies with the Control group ahead at -0.0067 seconds, followed by the FASD group at 0.0167 seconds [t (40) =- 7.397, p < 0.001]. There is a significant difference in peak latencies in right insular cortex, with the Control group peak occurring at 0.0317 seconds, and 0.0533 seconds for the FASD group [t (31.184) = -9.266, p < 0.001]. Interestingly, left insular cortex peak onsets in the Control group negatively correlate with IQ [r = -0.446, p = 0.037] and Matrix Reasoning subtest [r = -0.468, p = 0.028]. Lastly, for the Control group, left insular cortex peak latencies correlate with Cue 3 peak latencies [r = 0.524, p = 0.012]. In the FASD group, Cue 2 peak latencies negatively correlate with Cue 4 peak latencies [r = -0.458, p = 0.042].

**Cue 3 Motor Response**

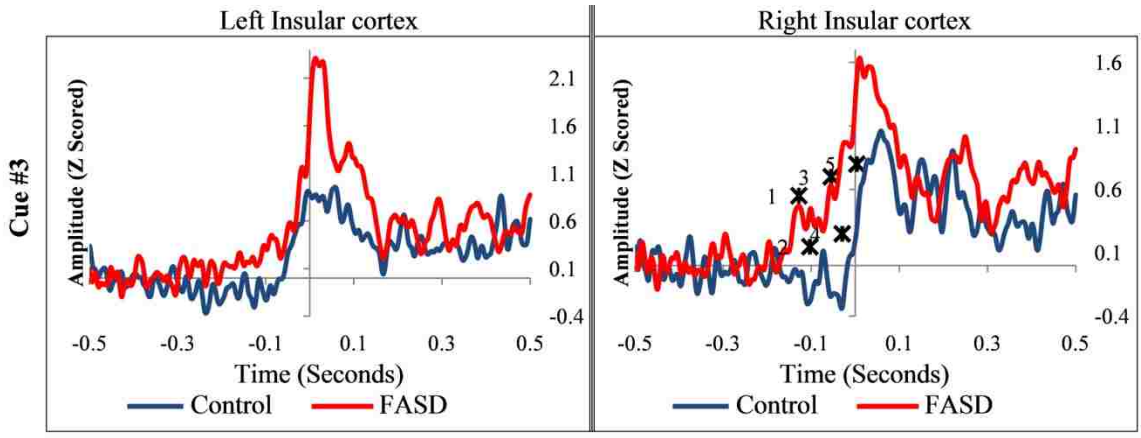



**Figure 23. Left and right Insular Cortex: Cue 3. Evoked response waveforms are time-locked to the motor response. * denotes significant differences between groups in amplitude ($p \leq 0.05$).**

**Table 13. Insular Cortex Cue 3 amplitude differences.**

| Right | | |
|---|---|---|
| # | Seconds | Statistic |
| 1 | -0.1283 | t (40) = -2.138, p = 0.039 |
| 2 | -0.1033 | t (40) = -2.522, p = 0.016 |
| 3 | -0.055 | t (40) = -2.098, p = 0.042 |
| 4 | -0.03 | t (28.935) = -2.642, p = 0.013 |
| 5 | 0.0033 | t (25.785) = -2.14, p = 0.042 |

In left insular cortex, there are no differences in amplitude. In right insular cortex, there are numerous differences in amplitude leading up to and around the time of the motor response (Figure 23 and Table 13). The amplitudes diverge at approximately -0.1733 seconds and reach significance at -0.1283 seconds, with the FASD group having higher amplitude. Also, in left and right insular cortex, there are differences present in peak latencies and onsets near time 0. In left insular cortex, the Control group had earlier peak latencies and onsets. Peak onsets for the Control group start at -0.0817 seconds and start at -0.0667 seconds for the FASD group [t (32.846) = -6.89, $p < 0.001$]. This leads to a difference in peak latencies with the Control group leading at -0.005 seconds, followed by the FASD group at 0.0117 seconds [t (40) = -6.793, $p < 0.001$]. In right insular cortex, peak onsets and latencies are the opposite, with the FASD group with the earlier peak onsets and peak latencies. In right insular cortex, peak onsets for the FASD group start at -0.0733 seconds and at -0.0317 for the Control group [t (40) = 4.852, $p < 0.001$]. The FASD group reaches a peak sooner at 0.01 seconds, followed by the Control group at 0.0583 seconds [t (40) = -13.648, $p < 0.001$]. For the Control group, left insular cortex peak onsets correlate with Cue 4 peak onsets [r = 0.485, p = 0.022]. Surprisingly, for the FASD group in right insular cortex, age correlates with peak onsets [r = 0.554, p = 0.011], and negatively correlate with peak latencies [r = -0.583, p = 0.007].

**Cue 4 Motor Response**

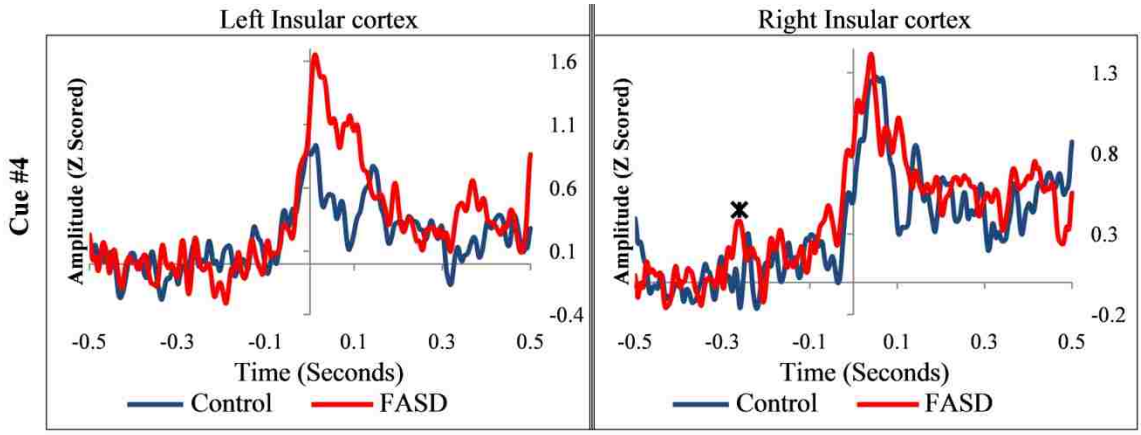



**Figure 24. Left and right Insular Cortex: Cue 4. Evoked response waveforms are time-locked to the motor response. * denotes significant differences between groups in amplitude ($p \leq 0.05$).**

In left insular cortex, there are no differences in amplitude. In right insular cortex, there is a difference in amplitude, which occurs at -0.2617 seconds [t (34.812) = -2.277, p = 0.029], with the FASD group having a higher amplitude (Figure 24). Also, in left and right insular cortex, there are some differences present in peak latencies and onsets near time 0. In left insular cortex, the Control group peak onsets begin at -0.0767 seconds, whereas this begins at -0.04 seconds for the FASD group [t (40) = -13.845, p < 0.001]. Surprisingly, there are no significant differences in peak latencies. In right insular cortex, peak onsets are not significantly different. Peak latencies are significantly different though. The Control group peak occurs at 0.05 seconds, whereas this happens at 0.04 seconds for the FASD group [t (40) = 3.116, p = 0.003].

**Behavioral Correlates**

In left and right insular cortex, many correlations are found between onsets, latencies, and behavioral data. In the FASD group, only one correlation is present in left insular cortex. Cue 1 peak latencies correlate with Cue 7 reaction time variability [r =

0.452, p = 0.045]. For the Control group, there are more numerous correlations present in left insular cortex. Cue 2 peak latencies correlate with Cue 8 reaction time variability [r = 0.47, p = 0.027]. Cue 3 peak latencies also correlate with Cue 8 reaction time variability [r = 0.504, p = 0.017]. Also, Cue 4 peak latencies negatively correlate with Cue 4 reaction time variability [r = -0.418, p = 0.053], Cue 5 reaction time variability [r = -0.498, p = 0.018], Cue 6 reaction time variability [r = -0.447, p = 0.037], and Cue 7 reaction time variability [r = -0.725, p < 0.001].

In right insular cortex, many correlations are found between onsets, latencies, and behavioral data. In the Control group, Cue 1 reaction time variability [r = 0.597, p = 0.003] and Cue 2 reaction time variability [r = 0.451, p = 0.035] correlate with Cue 3 peak onsets. Cue 3 peak onsets then correlate with Cue 3 reaction time [r = 0.539, p = 0.01], and Cue 4 reaction time [r = 0.539, p = 0.01]. Lastly, Cue 4 peak onsets correlate with Cue 7 reaction time variability [r = 0.539, p = 0.01]. In the FASD group, Cue 1 reaction time variability negatively correlates with Cue 1 peak latencies [r = -0.461, p = 0.041] and Cue 4 peak onsets [r = -0.575, p = 0.008]. Cue 2 peak latencies correlate with Cue 2 reaction time [r = 0.513, p = 0.021]. Also, Cue 2 peak latencies negatively correlate with Cue 3 reaction time variability [r = -0.473, p = 0.035], Cue 4 reaction time variability [r = -0.469, p = 0.037], and Cue 5 reaction time variability [r = -0.562, p = 0.01]. Cue 3 peak onsets correlate with Cue 7 reaction time variability [r = 0.496, p = 0.026]. Lastly, Cue 4 peak onsets negatively correlate with Cue 8 reaction time variability [r = -0.541, p = 0.014].

## Inferior Parietal Cortex Results

### Cue 1 Motor Response

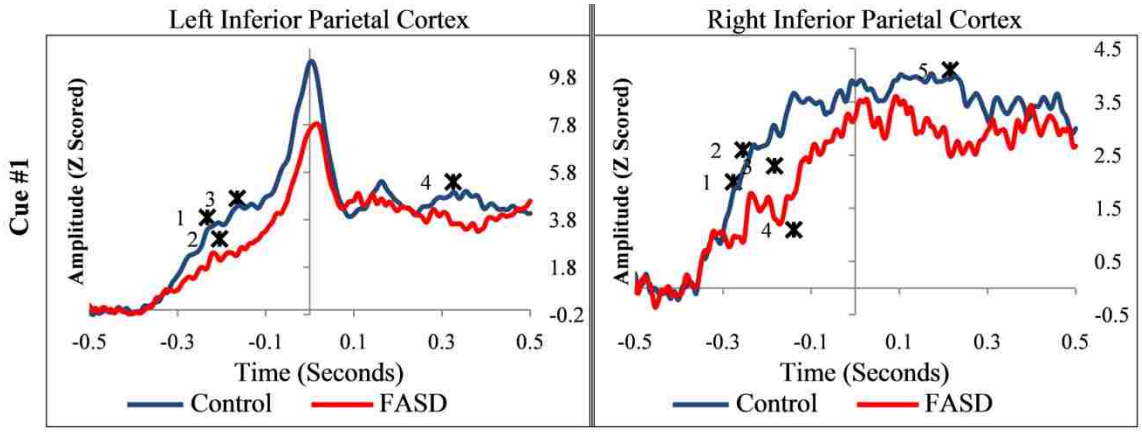



**Figure 25. Left and right Inferior Parietal Cortex: Cue 1. Evoked response waveforms are time-locked to the motor response. * denotes significant differences between groups in amplitude ($p \leq 0.05$).**

**Table 14. Inferior Parietal Cortex Cue 1 amplitude differences.**

| Left | | | Right | | |
|---|---|---|---|---|---|
| # | Seconds | Statistic | # | Seconds | Statistic |
| 1 | -0.2333 | t (37.209) = 2.847, p = 0.007 | 1 | -0.2767 | t (40) = 2.113, p = 0.04 |
| 2 | -0.205 | t(40) = 2.42, p = 0.02 | 2 | -0.255 | t (40) = 2.281, p = 0.028 |
| 3 | -0.165 | t(40) = 2.9, p = 0.006 | 3 | -0.1833 | t (40) = 2.197, p = 0.03 |
| 4 | 0.325 | t(40) = 2.129, p = 0.03 | 4 | -0.14 | t (40) = 2.485, p = 0.017 |
| | | | 5 | 0.215 | t (40) = 2.067, p = 0.045 |

In left inferior Parietal Lobe (lIPL) and right inferior Parietal Lobe (rILP), amplitude is significantly different prior to the motor response, with the Control group leading with a higher amplitude (Figure 25 and Table 14). In lIPL, amplitudes diverge approximately -0.315 and reconverge after the motor response at approximately 0.075 seconds. Differences reach significance starting at -0.2333 seconds. Multiple amplitudes continue to reach significance (Table 15) until time 0, where amplitudes reconverge. Amplitudes diverge after the motor response at approximately 0.275 seconds, reaching significance at 0.325 seconds. In lIPL, peak latencies for the FASD group occurs at

0.0183 seconds and at 0.005 seconds for the Control group [t (40) = -4.777, p < 0.001]. In rIPL, amplitudes diverge around -0.3 seconds prior to the response and converging again after the motor response at approximately 0.3883 seconds. Differences reach significance starting at -0.2767 seconds. Amplitudes again reach significance after the motor response at 0.215 seconds. In lIPL, the Control group peak latencies correlate with Cue 3 peak latencies [r = 0.751, p < 0.001]. For the FASD group in lIPL, peak latencies negatively correlate with age [r = -0.462, p = 0.04].

**Cue 2 Motor Response**

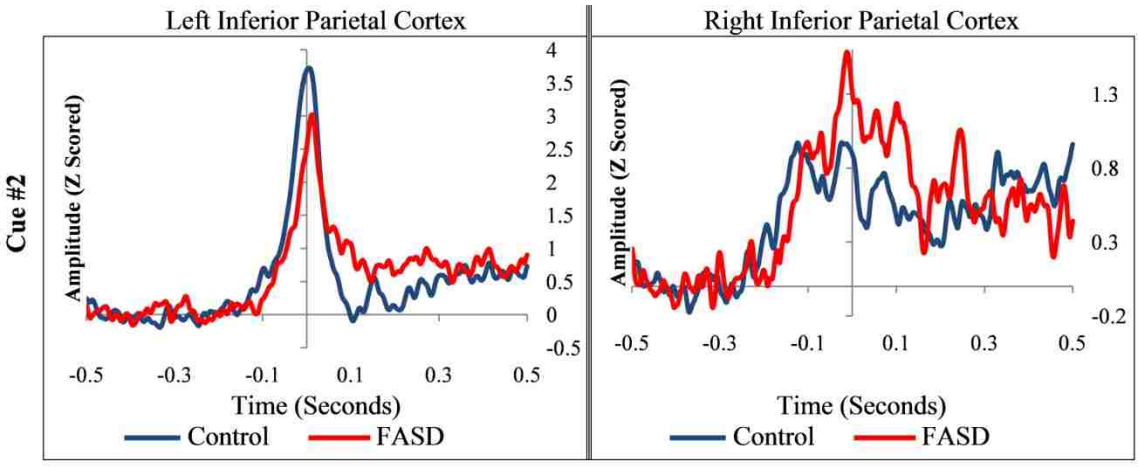



**Figure 26. Left and right Inferior Parietal Cortex: Cue 2. Evoked response waveforms are time-locked to the motor response.**

In lIPL and rIPL, there are no significant differences in amplitude (Figure 26). There are differences in peak onsets and latencies for lIPL and rIPL. In lIPL, peak onsets for the Control group start earlier, at -0.16 seconds, and at -0.1167 seconds for the FASD group [t (40) = -17.34, p < 0.001]. This leads to a difference in peak latencies with the Control group leading at 0.005 seconds, followed by the FASD group at 0.0117 seconds [t (28.36) = -2.478, p = 0.01]. In rIPL, peak onsets for the Control group start earlier, at -0.2233 seconds, and at -0.1933 seconds for the FASD group [t (40) = -12.503, p < 0.001].

This leads to a difference in peak latencies with the Control group leading at -0.125 seconds, followed by the FASD group at -0.1033 seconds [t (40) = -6.807, p < 0.001]. For the Control group in rIPL, peak onsets negatively correlate with peak latencies [r = -0.487, p = 0.022]. For the FASD group in rIPL, peak onsets negatively correlate with Cue 3 peak onsets [r = -0.525, p = 0.018].

**Cue 3 Motor Response**

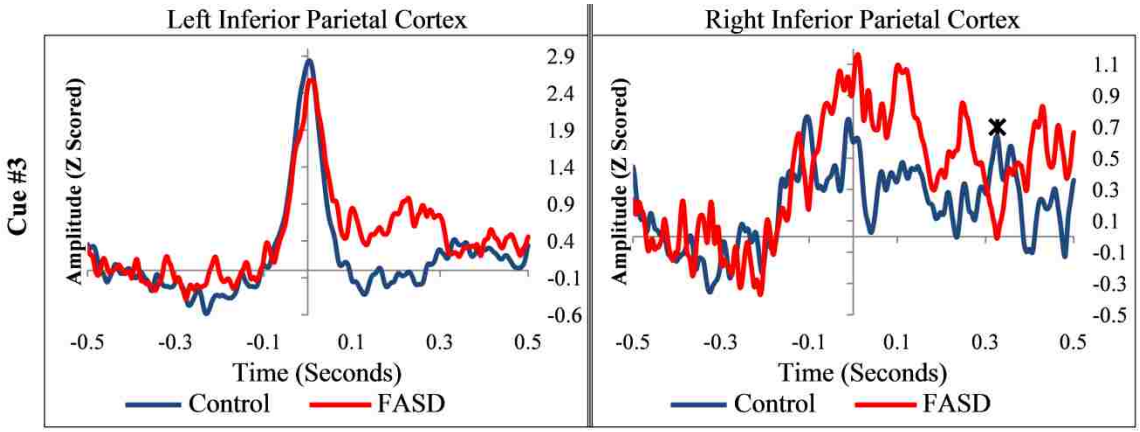



**Figure 27. Left and right Inferior Parietal Cortex: Cue 3. Evoked response waveforms are time-locked to the motor response. * denotes significant differences between groups in amplitude ($p \leq 0.05$).**

In lIPL, there are no differences in amplitude. In rIPL, there is a difference in amplitude at 0.3267 seconds [t (26.525) = 2.077, p = 0.048], with the Control group having a higher amplitude (Figure 27). In lIPL and rIPL, there are differences present in peak onsets. In lIPL, the Control group had the earlier peak onsets. Peak onsets for the FASD group start at -0.0783 seconds and at -0.0917 seconds for the Control group [t (40) = -6.235, p < 0.001]. In rIPL, peak onsets for the FASD group start at -0.15 seconds and at -0.1267 seconds for the Control group [t (34.607) = 11.165, p < 0.001]. The FASD group reaches a peak sooner at -0.125 seconds, followed by the Control group at -0.105

seconds [t (40) = 9.308, p < 0.001]. For the FASD group in rIPL, peak onsets negatively correlate with age [r = -0.47, p = 0.037].

**Cue 4 Motor Response**

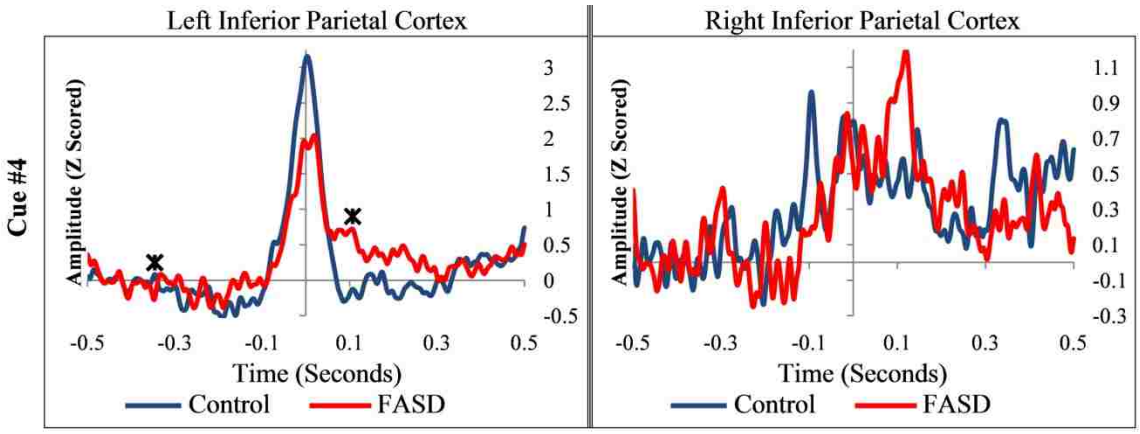



**Figure 28. Left and right Inferior Parietal Cortex: Cue 4. Evoked response waveforms are time-locked to the motor response. * denotes significant differences between groups in amplitude ($p \leq 0.05$).**

In lIPL, amplitude is significantly different prior to and after the motor response, but not rIPL (Figure 28). In lIPL, this occurs at -0.3467 seconds, with the Control group having a higher amplitude [t (40) = -2.411, p = 0.02] and again at 0.1067 seconds with the FASD group having a higher amplitude [t (23.637) = -2.19, p = 0.03]. Peak onsets and latencies are both significantly different in lIPL and rIPL. In lIPL, peak onsets for the FASD group start at -0.095 seconds and -0.11 seconds for the Control group [t (40) = -6.39, p < 0.001]. The Control group reaches a peak sooner at 0.005 seconds, followed by the FASD group at 0.0183 seconds [t (40) = -4.448, p < 0.001]. In rIPL, peak onsets for the FASD group start at -0.0567 seconds and at -0.0617seconds for the Control group [t (32.817) = -2.252, p = 0.031]. The Control group reaches a peak sooner at -0.0217 seconds, followed by the FASD group at 0.0133 seconds [t (40) = -2.866, p = 0.007]. For the FASD group, age correlates with lIPL peak latencies [r = 0.471, p = 0.036], and rIPL

peak latencies [r = 0.644, p = 0.002]. For the Control group, age correlates with lIPL peak onsets [r = 0.589, p = 0.004].

**Behavioral Correlates**

In lIPL and rIPL, many correlations are found between onsets, latencies, and behavioral data. In the FASD group, no behavioral correlations are present in lIPL. For the Control group, there are a few correlations present in lIPL. Cue 1 reaction time negatively correlates with Cue 2 peak onsets [r = -0.462, p = 0.03]. Cue 2 peak onsets negatively correlates with Cue 6 reaction time [r = -0.511, p = 0.015], Cue 7 reaction time [r = -0.427, p = 0.048], and Cue 8 reaction time [r = -0.462, p = 0.03].

In rIPL, many correlations are also found between onsets, latencies, and behavioral data. In the Control group, Cue 2 peak onsets correlates with Cue 8 reaction time variability [r = 0.44, p = 0.04]. Cue 3 peak latencies negatively correlate with Cue 7 reaction time variability [r = -0.559, p = 0.007], and Cue 8 reaction time variability [r = -0.505, p = 0.017]. In the FASD group, Cue 2 reaction time correlates with Cue 3 peak latencies [r = 0.447, p = 0.048]. Cue 3 reaction time variability correlates with Cue 4 peak latencies [r = 0.519, p = 0.019]. Cue 4 peak latencies correlate with Cue 5 reaction time [r = 0.445, p = 0.049] and Cue 6 reaction time [r = 0.443, p = 0.05]. Also, Cue 4 peak latencies correlate with Cue 6 reaction time variability [r = 0.493, p =0.027], Cue 7 reaction time variability [r = 0.554, p = 0.011], and Cue 8 reaction time variability [r = 0.631, p = 0.003].

## Number of Correlations

**Table 15. Chi squared analysis of the number of correlations between peak onsets and latencies with reaction times.**

| | | Correlations | | |
|---|---|---|---|---|
| | | Positive | Negative | Total |
| Group | Control | 14 | 13 | 27 |
| | FASD | 12 | 3 | 15 |
| | Total | 26 | 16 | 42 |

It was observed that the number of correlations between peak onsets and latencies with reaction times are different for the groups. Most notable is the difference in the quantity of negative correlations between groups (See Table 15). The Control group has 13 negative correlations, whereas the FASD group only have 3 negative correlations. A $X^2$ (Chi Squared) test was performed to test the difference in correlations. There was not a significant difference, but there was definitely a trend [$X^2(1) = 3.24$, $p = 0.072$].

# CHAPTER 6 DISCUSSION

## Behavioral Data

In this study, the reaction times are found to be significantly different in all the cues except for Cue 2, with the FASD group having a longer reaction time compared to the Control group. The reaction time variability is also significantly different, with the FASD group having a greater reaction time variability between Cues 3 through 8. After Cue 2, the reaction times and reaction time variability increase in the FASD group. Children with FASD present with reduced reaction time of information processing, caused by reduced efficiency in information processing, which leads to delays in responding. They are also sensitive to the increasing complexity of a task, which leads to a decline in performance (P.W. Kodituwakku, 2007).

Reaction times are a very telling in regards to development. Typically, reaction times decrease throughout childhood, peak during the second decade of life, and progressively increase after. In motor response selection, children with FASD show evidence of developmental delay, through elevated reaction times (Simmons, Thomas, Levy, & Riley, 2006). In this study, the FASD group had significantly slower or elevated reaction times to most of the cues. Also, most of the reaction time variability observed in the FASD is significantly different from the Control group.

Interestingly, the reaction times and the reaction time variability in the Control group negatively correlate with age. This follows typical development, contrary to the FASD group, which have no correlations with reaction times or reaction time variability and age.

Noted are the negative correlations with IQ/Vocabulary subtests and the reaction time variability found in the Control group. These correlations are not present in the FASD group. This has been observed in studies involving motor response selection. The authors did not have a reason for the correlation. However, they do note that this indicates that the FASD group reaction times are sensitive to decreases in reaction time without the potential confound of IQ (Simmons *et al*., 2006). Interestingly, most of these negative correlations are between the reaction time variability and the IQ Vocabulary subtest. This may be due to the sub vocalization of the timing of the cues by the Control group. In other studies, it has been hypothesized that the activation of the insular cortex during visually cued finger tapping tasks is due to the sub vocalization of timing (Cerasa *et al*., 2004).

**Anterior Cingulate Cortex**

For Cue 1, the Control group has higher amplitude compared to the FASD group in left and right ACC building up to the motor response. This may be related to the selection of the motor response to Cue 1. Differences later in the waveform may reflect the cognitive processes of conflict detection and/or resolution within the ACC, specifically with resolving the timing of the Cues. In both groups, Cue 1 peak latencies correlate with IQ and IQ subtests. For the Control group, this occurs in left and right ACC. In left ACC, Cue 1 peak latencies correlate with the Vocabulary subtest. In right ACC, Cue 1 peak latencies correlate with the Matrix Reasoning subtest. In the FASD group, correlations are only found in right ACC. Cue 1 peak latencies correlate with IQ, Vocabulary subtest, and Matrix Reasoning subtest. This observation points to an altered lateralization of function in FASD. Lastly, the FASD group has a correlation between

left ACC Cue 1 latencies and Cue 3 through 8 reaction time. ACC is known to contribute to arousal. I believe these correlations in the FASD group are related to arousal or the allocation of attention.

The ACC is well known for its influence in conflict detection and resolution (Torta & Cauda, 2011). This pattern is present in both groups in left ACC. In the Control group Cue 2 peak onsets negatively correlate with Cue 3 reaction time and Cue 1 and 7 reaction time variability. Interestingly, this appears to show the conflict detection and resolution of the ACC. It appears that Cue 1 reaction time variability influenced Cue 2 peak onsets, which influenced Cue 3 reaction time. This pattern is observed in the FASD group, but appears to be altered and delayed. For the FASD group, Cue 2 reaction time variability influenced Cue 3 peak onsets, which influenced Cue 3 reaction time. For the Control group, this appears to influence future performance as peak onsets for Cue 3 and 4 continue to influence performance on future cues. This future influence is absent in the FASD group.

For Cue 2 -4, in both left and right ACC, the Control group has an amplitude spike around 300 ms prior to the button response. T tests reveal that amplitude differences are statistically different to the FASD group. This corresponds to the presentation of the visual cues, which may be the ACC responding to the salience of the stimuli. It has been hypothesized that the ACC contributes to behavior modification by monitoring the emotional salience of stimuli and modulating cognitive activity (Torta & Cauda, 2011).

There are a couple of observations that cannot be explained at this time. First, prior to the motor response to Cue 4, in left and right ACC, the FASD group has some

significant amplitude differences compared to the Control group. This may be related to the ACC modulating cognitive control, either through arousal or control of attention (Torta & Cauda, 2011). Another possibility is that this activity may also be an attempt to adjust to an error in the previous Cue response (Womelsdorf, Johnston, Vinck, & Everling, 2010). Secondly, there are unexplained correlations between age and Cue peak responses in both groups. These are observed in the right ACC. The Cue 3 peak onsets correlate with age in the FASD group. In the Control group, the Cue 4 peak onsets negatively correlate with age. This points to a maturational relationship, however, it cannot be fully explained.

**Anterior Prefrontal Cortex**

After the motor response to Cue 1, amplitude differences are present in left and right aPFC. The Control group has increased activation, while the FASD group activation is waning. This may represent an adaptive process associated with Cue 1 performance in preparation for future events. Functional MRI studies have shown excessive activation in the frontal cortex during spatial and verbal working memory, number processing, and response inhibition in prenatally alcohol exposed children and adults (Burden *et al*., 2009; Nuñez *et al*., 2011; Yang *et al*., 2012). Much like these fMRI studies, the FASD group had altered aPFC activation. This is demonstrated by the earlier peak onsets and latencies with Cue 2, 3 and 4. This did not result in a behavioral advantage, as demonstrated by the correlations. In right aPFC, Cue 2 latencies had negative correlations with reaction times on Cues 5, 7, and 8 (4 & 6 just missed significance), which denotes an adaptive behavior. In the FASD group, the correlations between latencies and performance happened later. The latencies involved Cue 3 & 4

reaction times and Cues 6, 7, and 8 reaction time variability. Contrary to the Controls, the FASD correlations are all positive.

### Dorsolateral Prefrontal Cortex

Contrary to previously mentioned working memory studies, in left and right dlPFC the FASD group has significantly diminished amplitude prior to, during, and after the Cue 1 motor response. There are more differences in right dlPFC, which is implicated in temporal learning. Subsequent Cues did not have as many amplitude differences. However, differences are found in peak latencies and onsets. Peak latencies and onsets did correlate with the reaction times. In the Control group, correlations between right dlPFC peak latencies, onsets, and reaction time are found. Interestingly, the latencies and onsets correlated with average cue reaction times further down in the sequence. This pattern is absent from the FASD group. In left dlPFC, both the FASD group and Control group had few correlations. Cue 2 peak latencies correlate with Cue 3 reaction time in the Control group. In the FASD group, Cue 2 peak latencies correlate with Cue 3 reaction time variability. Behaviorally, the reaction times in Cue 2 are still high. Cue 3 is where the reaction times level off, and has the lowest reaction time variability in both groups.

### Insular Cortex

The left insular cortex is often associated with language. In fact, in the Control group left insular cortex, Cue 1 peak latencies are correlated with the Vocabulary subtest. Further, Cue 2 onsets negatively correlate with IQ and Matrix Reasoning subtest. These are not present in the FASD group. There are amplitude differences between the groups

prior to, during, and after the motor response, with the FASD group having the higher amplitudes. Also interesting is the linear pattern found in peaks and onsets in the Control group. After Cue1, it is observed that Cue 2 peak latencies correlate with Cue 3 peak latencies and Cue 3 peak onsets correlate with Cue 4 peak onsets. This type of pattern is not present in the other ROI's. Given its strong connectivity with aPFC and ACC, I speculate that this pattern is first due to the saliency of the interval duration and then the switching from exogenous to endogenous attention (Menon & Uddin, 2010). Once the interval duration is encoded, the future stimuli can be predicted, reducing error. The prediction of the stimuli can be seen in the Control group, as Cue 4 latencies negatively correlate with Cue 4 through 7 reaction time variability. This pattern is absent from the FASD group.

The right insular cortex is often associated with dynamic switching and regulating arousal. In the Control group, Cue 1 peak latencies are correlated with the Matrix Reasoning subtest. This is, in all probability, related to the processing of the switch from the trace fear conditioning trials to the visuomotor task. The right insular cortex is involved in switching between brain networks across task paradigms and stimulus modalities (Menon & Uddin, 2010). This correlation is not present in the FASD group. The right insular cortex is also associated with regulating arousal. Between the two groups, there is a difference in amplitudes for Cue 1, with the Control group having the higher amplitude prior to and after the motor response. These amplitude differences prior to the motor response are most likely the modulation of arousal for the start of the task. The amplitude differences after the motor response are in all likelihood the modulation of arousal in preparation for the next Cue. In the Control group, Cue 1 and 2 reaction time

variability correlate with Cue 3 peak onsets. In the FASD group, this also occurs except it is delayed until the Cue 4 peak onsets and is a negative correlation. In the Control group, peak onsets correlate with more immediate Cue reaction times (Cue 3 peak onsets with Cue 3 reaction times and Cue 3 peak onsets with Cue 4 reaction times). In other words, the affect is more immediate. Interestingly, in the FASD group, age correlates with the Cue 3 peak onsets, and negatively correlates with the Cue 3 peak latencies. This is not present in the Control group. The reason for this pattern is unknown.

Further, in right insular cortex, the FASD group have higher amplitudes in both Cue 2 and Cue 3 (statistically significant prior to the motor response). Cue 2 latencies correlate with Cue 2 reaction times and negatively correlate with Cues 3 through 5 reaction time variability. In other clinical populations it is believed that too little right insular cortex activity fails to entrain the dlPFC, resulting in careless mistakes. On the other hand, too much right insular cortex activity limits dlPFC function, which also limits the selection of optimal responses (Eckert *et al*., 2009). The dlPFC in the FASD group had decreased amplitude in Cue 1 and Cue 4. Compared to the Control group, the FASD group has significantly higher reaction time variability across the Cues.

**Inferior Parietal Cortex**

Amplitude differences are present in lIPL prior to and after the motor response for Cue 1. In both cases, the Control group has the higher amplitude. The differences prior to the motor response are mostly likely related to the allotment of motor attention and selection (Rushworth, Johansen-Berg, Göbel, & Devlin, 2003). The amplitude differences found in Cue 4 are mostly likely due to temporal processing. For all 4 Cue peak onsets and peak latencies (except the Cue 3 peak onsets), the FASD group is

significantly delayed. Further, in the Control group, Cue 1 reaction times negatively correlate with Cue 2 peak onsets. Cue 2 peak onsets in turn negatively correlate with Cue 6 through 8 reaction times. Left parietal cortex has been shown to be associated with temporal processing (Assmus *et al*., 2003). Lastly, there appears to be some adaption to the task occurring in the Control group. Cue 1 reaction time negatively correlates with Cue 2 peak onsets. This also repeats as Cue 3 reaction times negatively correlate with Cue 4 peak latencies. This does not occur in the FASD group.

Amplitude differences are also present in rIPL. This occurs prior to and after the motor response for Cue 1. In both cases, the Control group has the higher amplitude. For Cue 2 and 3, there appears to be amplitude differences, with the FASD group having the higher amplitude. However, these differences do not reach statistical significance. Also, for Cue 2 through 4, there are differences in peak onsets and latencies with the FASD group being delayed. There are not many correlations present for the Control group. Cue 2 peak onsets correlate with Cue 2 reaction time variability. Also, Cue 3 peak latencies negatively correlate with Cue 7 and 8 reaction time variability. Interestingly, the FASD have many more correlations present. There is a pattern of continuity in the rIPL with the FASD group. Cue 2 peak onsets negatively correlate with Cue 3 peak onsets, which in turn negatively correlate with Cue 4 peak latencies. Most of the correlations occur with Cue 4 peak latencies. Cue 4 peak latencies correlate with Cue 5 and 6 reaction times. Also, Cue 4 peak latencies correlate with Cue 6, 7, and 8 reaction time variability. This may be due an increase in attentional demands. Increased activation in the rIPL has been observed in previous studies using visually paced stimuli. This phenomena has been

hypothesized to be the result of increased attentional demands (Debaere, Wenderoth, Sunaert, Van Hecke, & Swinnen, 2003).

Present in both groups, age correlates with waveform components. Interestingly, for the FASD group in lIPL, age negatively correlates with Cue 1 peak latencies. In rIPL, the Control group does not have any correlations with age. There are age correlations present in the FASD group in the rIPL. Age negatively correlates with Cue 3 peak onsets and correlates with Cue 4 peak latencies. These correlations may be related to functional maturation, however the reason for these correlations are unknown. Previous studies have shown increased functional maturation with age in lIPL (Rivera, Reiss, Eckert, & Menon, 2005). No publications have studied functional maturation in FASD group.

**Limitations**

It may be difficult to generalize these findings. These findings may be confounded by the small N. The small N may have increased the probability of type 2 error. Many correlations between brain and behavior were borderline significant, and may have been found significant with a larger N. Another confound may be age (maturational differences). With the large age range, group maturational differences may be difficult to detect and interpret.

Another limitation to this study may involve a concept known as ego depletion. Ego depletion is the notion that the "self's acts of volition" draws upon a limited resource (energy or strength), so when one act is performed, it has negative effects on subsequent acts. Another way to explain it is a temporary reduction in the self's capacity to engage in acts of volition caused by prior acts of volition. Malfunction in self-regulation fits the model of ego depletion (Baumeister, Bratslavsky, Muraven, & Tice, 1998). Given the

breakdown in self-regulation FASD individuals present with (e.g., inappropriate sexual behavior, alcohol and drug abuse), it can by hypothesized that they have an even more diminished resource for self regulation. In this study, blocks alternated between finger tapping entrainment trials and trace fear conditioning trials, which may create a confound. It cannot be ascertained how much of an effect this had on the FASD group. In a self-regulation study using normal participants, it was found that inhibition in the cognitive domain lead to an increase in amygdala response to negative emotional material. This effect was not present in response to neutral or positive emotional material (Wagner & Heatherton, 2012).

An analysis of the evoked responses provided some elucidation into the differences in FASD brain dynamics. However, time-frequency analysis may provide more information not available in the evoked responses. Future studies should utilize time-frequency analysis to further investigate information processing in the brain.

## Conclusion

In this study, we used MEG and a visuomotor finger tapping task to examine millisecond effects of prenatal alcohol exposure on frontal parietal network function. Processing of motor response to cues in frontal parietal network areas were found to be altered in FASD. Reaction times revealed speed and variability differences between groups. We were able to caste some illumination onto the relationship between millisecond brain dynamics by cue and the reaction time behavioral data in FASD. These results suggest timing deficits, specifically in temporal attention, prediction, and learning in this population, due to inefficient frontal parietal processing.

# APPENDICES

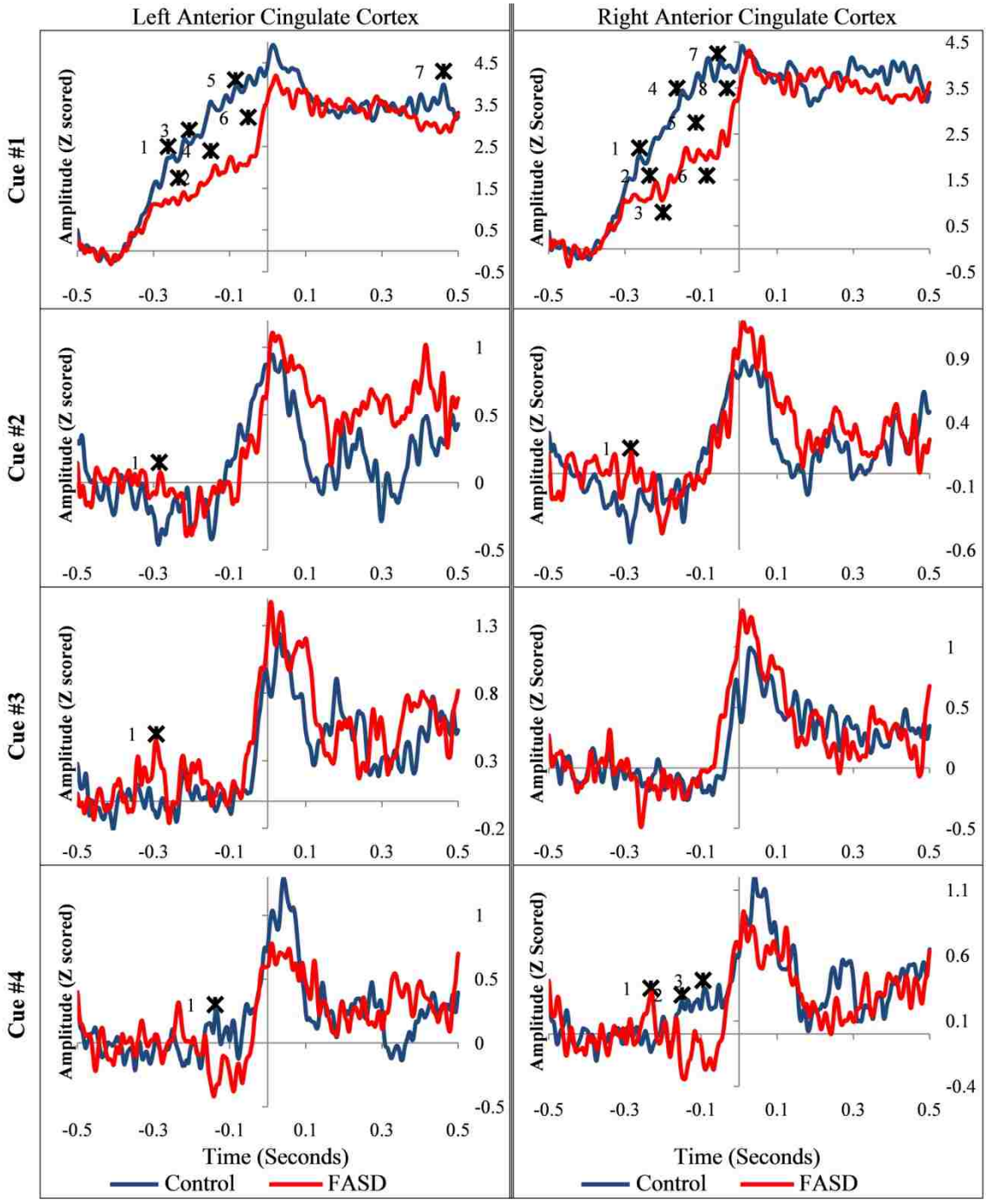
## APPENDIX A REACTION TIME TO CUES

| Statistics: Reaction Time to Cues | | | |
|---|---|---|---|
| **Cue** | **Control Average** | **FASD Average** | **Statistic** |
| Cue 1 | 489.406 | 545.186 | t (40) = -2.314, p = 0.025 |
| Cue 2 | 319.34 | 349.136 | t (40) = -1.409, p = 0.167 |
| Cue 3 | 304.025 | 396.719 | t (28.794) = -2.374, p = 0.024 |
| Cue 4 | 319.149 | 434.265 | t (25.337) = -2.745, p = 0.011 |
| Cue 5 | 324.305 | 443.53 | t (23.701) = -2.783, p = 0.01 |
| Cue 6 | 320.609 | 436.543 | t (23.778) = -2.884, p = 0.008 |
| Cue 7 | 316.758 | 422.089 | t (25.039) = -2.554, p = 0.017 |
| Cue 8 | 296.757 | 411.792 | t (24.07) = -2.515, p = 0.019 |

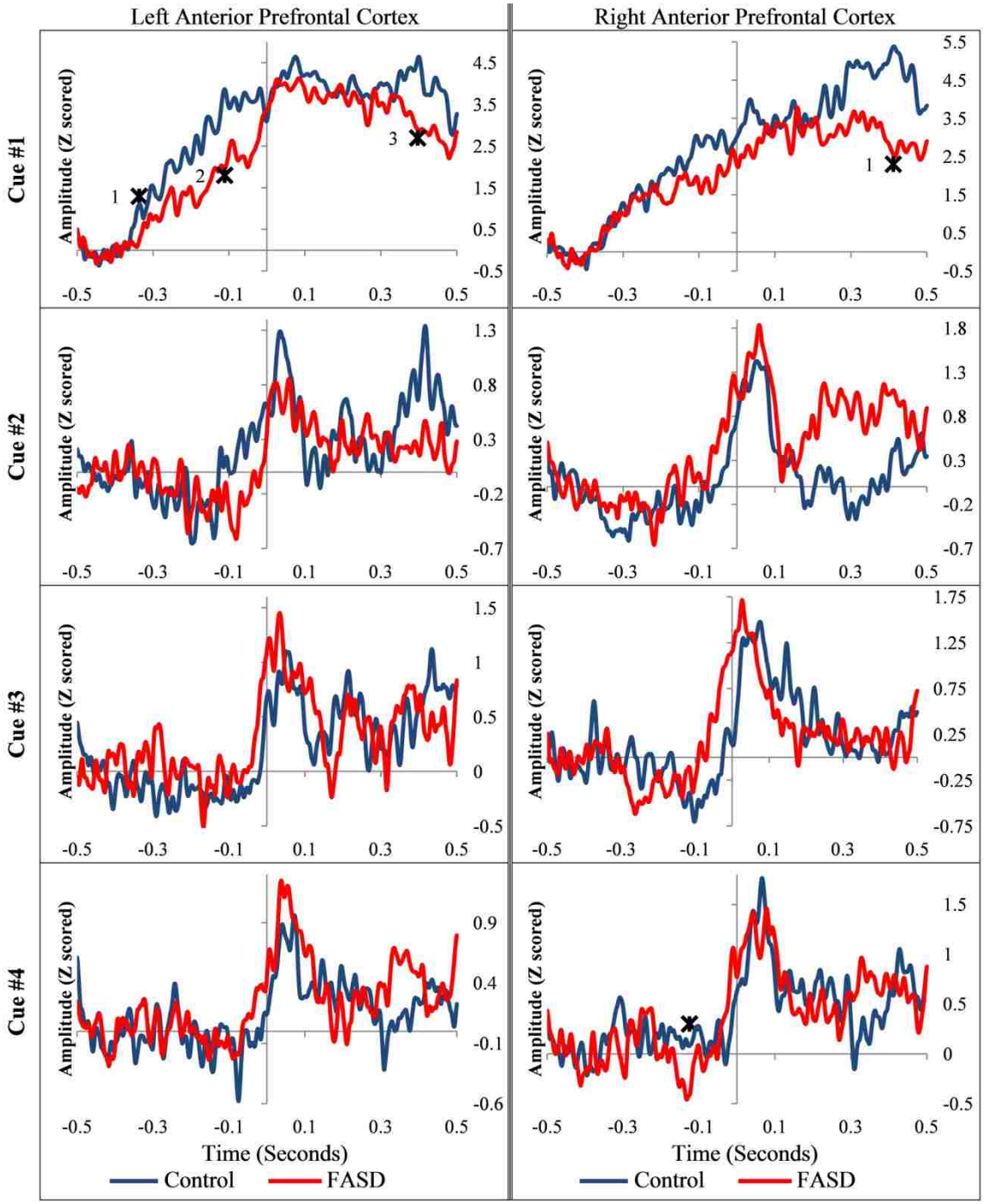
## APPENDIX B LEVENE'S TEST COMPARING STANDARD DEVIATIONS

| Statistics: Levene's Test Comparing Standard Deviations | | | |
|---|---|---|---|
| **Cue** | **Control Standard Deviation** | **FASD Standard Deviation** | **Statistic** |
| Cue 1 | 69.184 | 85.273 | F (1,40) = 0.577, p = 0.452 |
| Cue 2 | 59.473 | 77.161 | F (1,40) = 0.501, p = 0.483 |
| Cue 3 | 84.6 | 154.829 | F (1,40) = 6.539, p = 0.014 |
| Cue 4 | 74.918 | 173.381 | F (1,40) =20.412, p < 0.001 |
| Cue 5 | 66.92 | 180.681 | F (1,40) =24.478, p < 0.001 |
| Cue 6 | 63.261 | 169.388 | F (1,40) =21.442, p < 0.001 |
| Cue 7 | 72.12 | 171.15 | F (1,40) =15.149, p < 0.001 |
| Cue 8 | 73.942 | 192.064 | F (1,40) =14.214, p = 0.001 |

## APPENDIX C ANTERIOR CINGULATE CORTEX CUE 1 - 4 WAVEFORMS

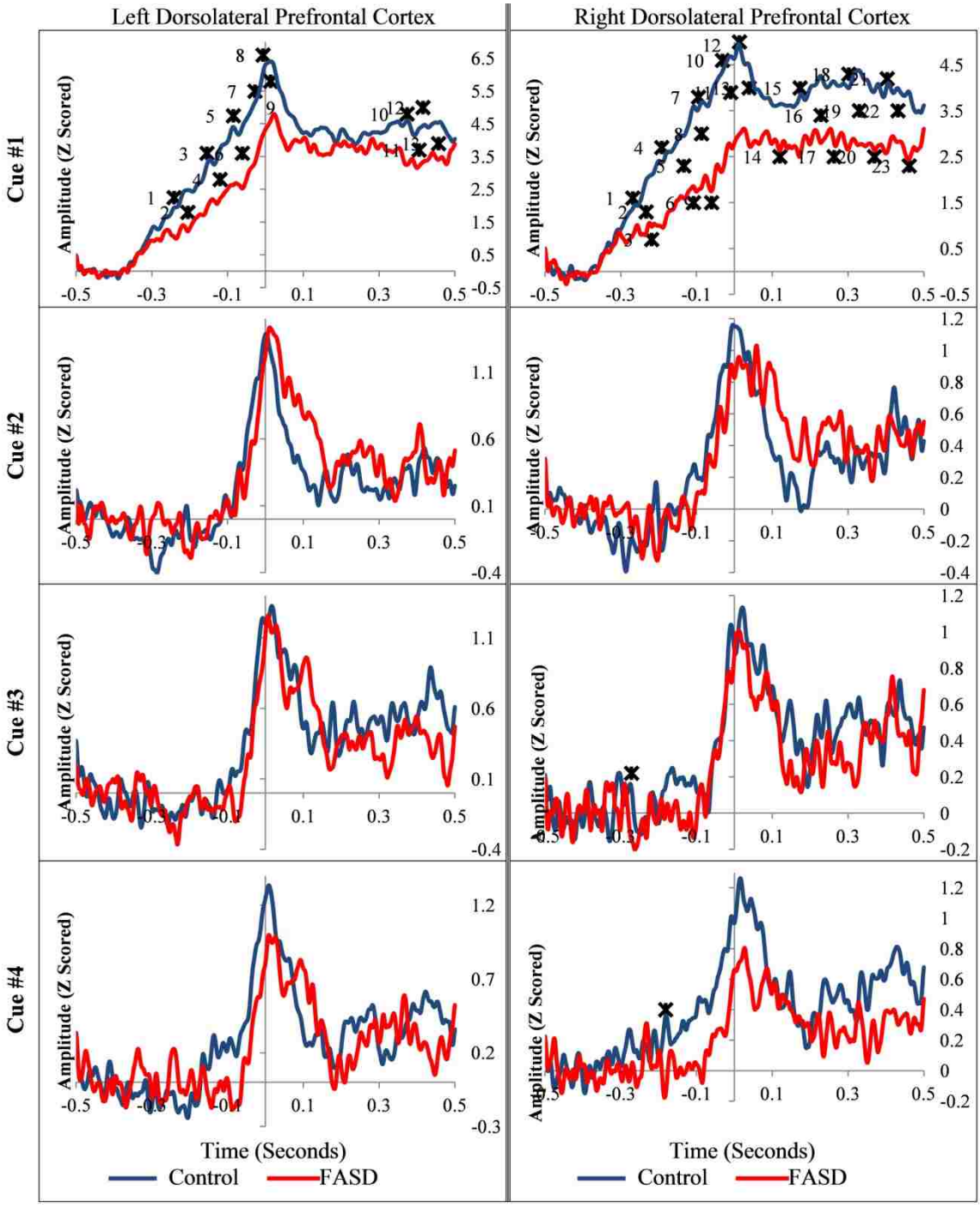


## APPENDIX D ANTERIOR PREFRONTAL CORTEX CUE 1 - 4 WAVEFORMS

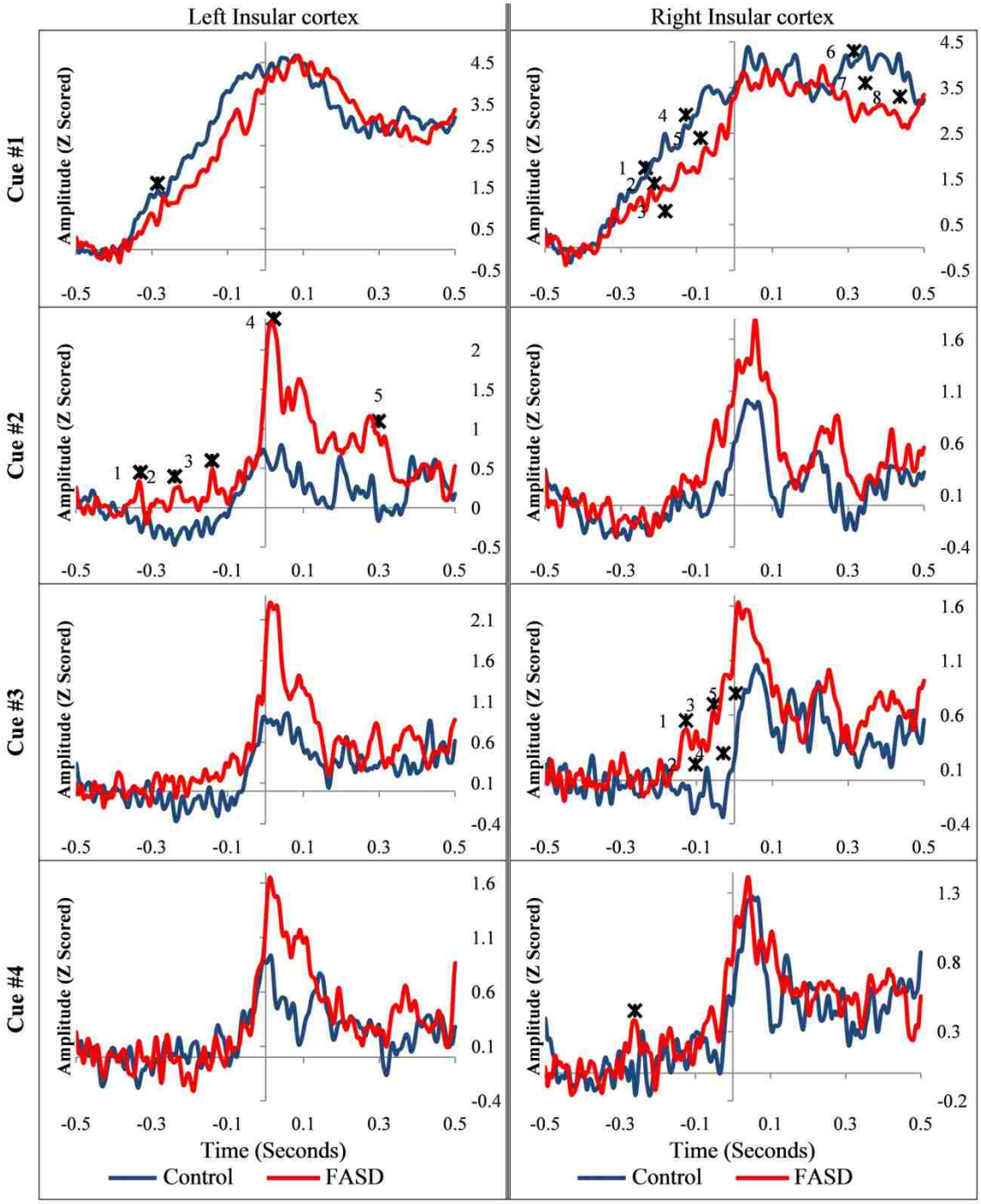


## APPENDIX E DORSOLATERAL PREFRONTAL CORTEX CUE 1 - 4

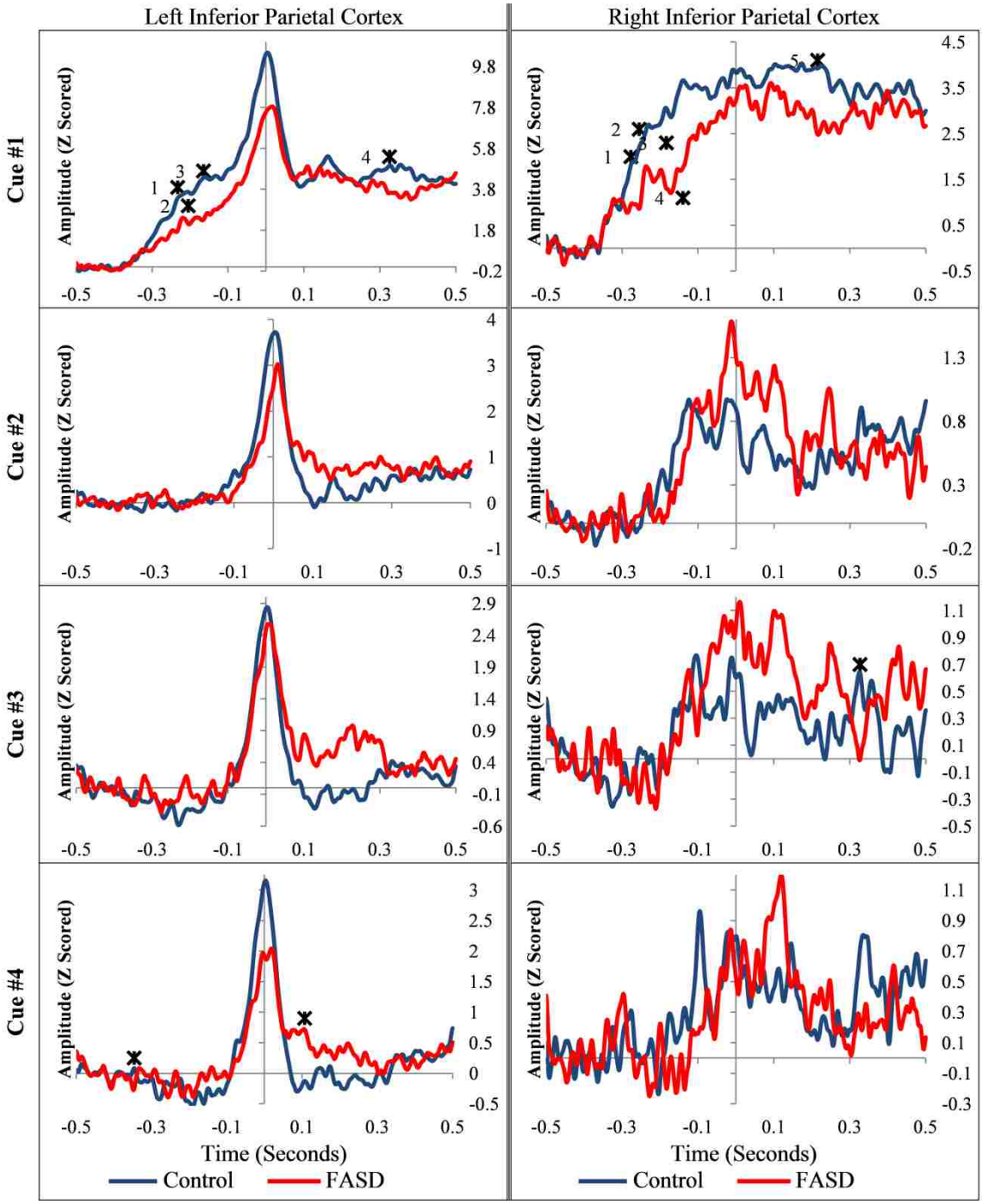
## WAVEFORMS



## APPENDIX F INSULAR CORTEX CUE 1 - 4 WAVEFORMS



## APPENDIX G INFERIOR PARIETAL CORTEX CUE 1 - 4 WAVEFORMS



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