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Spatial Working Memory in Children with FASD: A Multimodal Imaging Approach

A dissertation submitted in partial satisfaction of the requirements for the degree of Doctor in Philosophy

in

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by

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PUBLICATIONS

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Infante, M. A., Moore, E. M., Nguyen, T. T., Fourligas, N., Mattson, S. N., & Riley, E. P. (2015). Objective assessment of ADHD core symptoms in children with heavy prenatal alcohol exposure. *Physiology & Behavior*, *148*, 45-50. doi:10.1016/j.physbeh.2014.10.014

Jacobus, J., Squeglia, L. M., **Infante, M. A**., Castro, N., Brumback, T., Meruelo, A. D., & Tapert, S. F. (2015). Neuropsychological performance in adolescent marijuana users with co-occurring alcohol use: A three-year longitudinal study. *Neuropsychology, 29,* 829-843. doi:10.1037/neu0000203.

Migliorini, R., Moore, E. M., Glass, L., **Infante, M. A**., Tapert, S. F., Jones, K. L., Mattson, S. N., & Riley, E. P. (2015). Anterior cingulate cortex surface area relates to behavioral inhibition in adolescents with and without heavy prenatal alcohol exposure. *Behavioral Brain Research, 292,* 26-35. doi:10.1016/j.bbr.2015.05.037

Ware. A. L., **Infante, M. A**., O'Brien, J. W., Tapert, S. F., Riley, E. P., & Mattson, S. N. (2015). An fMRI study of behavioral response inhibition in adolescents with and without histories of heavy prenatal alcohol exposure. *Behavioral Brain Research*, *278*, 137-146. doi:10.1016/j.bbr.2014.09.037

Cardenas, V. A., Price, M. M., **Infante, M. A**., Moore, E. M., Mattson, S. N., Riley, E. P., & Fein, G. (2014). Automated cerebellar segmentation: Validation and application to detect smaller volumes in children prenatally exposed to alcohol. *NeuroImage: Clinical*, *4*, 295-301. doi:10.1016/j.nicl.2014.01.002

Moore, E. M., Migliorini, R., **Infante, M. A**., & Riley, E. P. (2014). Fetal Alcohol Spectrum Disorders: Recent neuroimaging findings. *Current Developmental Disorders Reports*, *1*, 161-172. doi:10.1007/s40474-014-0020-8

Jacobus, J., Squeglia, L. M., **Infante, M. A**., Bava, S., & Tapert, S. F. (2013). White matter integrity pre- and post marijuana and alcohol initiation in adolescence. *Brain Sciences*, *3*, 396-414. doi:10.3390/brainsci3010396

Riley, E. P., **Infante, M. A**., & Warren, K. R. (2011). Fetal Alcohol Spectrum Disorders: An overview. *Neuropsychology Review*, *21*, 73-80. doi:10.1007/s11065-011-9166-x

Squeglia, L. M., Spadoni, A. D., **Infante, M. A.**, Myers, M. G., & Tapert, S. F. (2009). Initiating moderate to heavy alcohol use predicts changes in neuropsychological functioning for adolescent girls and boys. *Psychology of Addictive Behaviors*, *23*, 715-722. doi:10.1037/a0016516

ABSTRACT OF THE DISSERTATION

Spatial Working Memory in Children with FASD: A Multimodal Imaging Approach

by

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Rationale. Individuals prenatally exposed to alcohol often have impaired working memory. Neuropsychological studies have further suggested that spatial working memory (SWM) may be significantly affected in this group. Studies of the neural correlates of working memory have consistently shown the involvement of a fronto-parietal network. Despite evidence for microstructural and functional abnormalities in frontal and parietal regions in individuals prenatally exposed to alcohol, the relation and contribution of these

abnormalities to SWM deficits remain unclear. The main goal of this study was to expand on previous research by using a multimodal imaging approach to examine brain structure and function associated with SWM deficits in children prenatally exposed to alcohol.

Design. Children ages 10 to 16 with histories of heavy prenatal alcohol exposure (AE group; $n = 18$) and non-exposed controls (CON group; $n = 19$) underwent functional magnetic resonance imaging while performing a SWM task and diffusion tensor imaging. Whole-brain blood oxygen level dependent (BOLD) response to SWM relative to vigilance trials (SWM – vigilance contrast) was computed for each participant. Whole brain task-related functional connectivity of bilateral dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC) seed regions were estimated for each participant using a psychophysiological interaction approach. Fractional anisotropy and mean diffusivity were used as indices of white matter integrity. Independent samples *t*-tests were used to examine group differences in BOLD response contrast, task-based functional connectivity, and white matter integrity of the superior longitudinal fasciculus (SLF) and genu of the corpus callosum (GCC).

Results. Children in the AE group were less accurate than children in the CON group when performing the SWM task ($p = .008$). Group differences in neural activity to the SWM – vigilance contrast were found primarily in frontal, parietal, and cingulate regions. In all regions, the CON group showed greater BOLD response contrast compared to the AE group. Results from the functional connectivity analyses revealed positive coupling between bilateral DLPFC seeds and regions within the fronto-parietal network in the CON group, whereas the AE group showed negative connectivity. In contrast to the CON group, the AE group showed positive connectivity between PPC

seeds and frontal lobe regions. Across seeds, weaker negative coupling with regions outside the fronto-parietal network (e.g., left middle occipital gyrus) were observed in the AE group relative to the CON group. Functional data clusters were considered significant at $p < .05$ (with an uncorrected voxelwise threshold: $p < .05$; minimum cluster volume: 63 voxels). No significant groups differences were noted with respect to white matter integrity in the SLF and GCC.

Conclusions. Overall findings suggest that localized alterations in neural activity, aberrant fronto-parietal network synchrony, and poor coordination of neural responses with regions outside of this network may help explain SWM deficits in individuals with a history of heavy prenatal alcohol exposure. Greater understanding of the neural mechanism underlying cognitive deficits in children prenatally exposed to alcohol may contribute to the development of targeted interventions, and may serve as a potential neurobiological marker of treatment outcomes.

CHAPTER 1: INTRODUCTION

Alcohol use during pregnancy is a leading preventable cause of birth defects, intellectual disabilities, and neurodevelopmental disorders (American Academy of Pediatrics, 2000; Pulsifer, 1996). According to the U.S. Surgeon General's Advisory on alcohol use in pregnancy there is no amount of alcohol that has been identified as safe to consume during pregnancy. The advisory urges women who are pregnant or who may become pregnant to abstain from drinking alcohol because of the potential harmful effects on the developing embryo and fetus. However, despite increasing public awareness of alcohol's teratogenic (i.e., damaging to the developing embryo or fetus) effects, an estimated 10.2% of women in the United States report drinking alcohol during pregnancy, and 3.1% of these women report binge drinking, or consuming four or more drinks on one occasion (Centers for Disease Control and Prevention, 2015). Maternal binge drinking can be especially harmful to the developing embryo and fetus because it results in exposure to higher blood alcohol concentration levels (Flak et al., 2014; Maier & West, 2001; Pierce & West, 1986; Thomas, Wasserman, West, & Goodlett, 1996). Heavy prenatal alcohol exposure has been associated with cognitive and behavioral impairments across several domains, including general intelligence, memory, language, attention, executive function, visuospatial ability, fine and gross motor skills, and social and adaptive functioning (for reviews, see Glass, Ware, & Mattson, 2014b; Mattson, Crocker, & Nguyen, 2011). Moreover, many factors, including timing, dose, and frequency of alcohol exposure, nutrition, socioeconomic status, and maternal characteristics such as age, gravidity, and parity, can contribute to the severity of the possible consequences associated with prenatal alcohol exposure (May & Gossage, 2011;

May et al., 2005). The cognitive and behavioral deficits associated with prenatal alcohol exposure can persist into adulthood and may result in adverse outcomes such as disrupted education, trouble with the law, and substance abuse (Spohr, Willms, & Steinhausen, 2007; Streissguth et al., 2004; Streissguth, Sampson, & Barr, 1989). Research that explores these deficits is crucial for improving diagnosis, treatment, and overall quality of life for those affected by prenatal alcohol exposure. For example, increased knowledge of the mechanisms underlying the cognitive and behavioral impairments commonly seen among individuals who have been prenatally exposed to alcohol may lead to the development of targeted treatments that could not only remediate these deficits, but also prevent associated secondary disabilities.

One of the most severe and widely known consequences associated with heavy prenatal alcohol exposure is fetal alcohol syndrome (FAS), which was first introduced in the medical literature over 40 years ago (Jones & Smith, 1973; Jones, Smith, Ulleland, & Streissguth, 1973; Lemoine, Harousseau, Borteyru, & Menuet, 1968). Since the original description of FAS, diagnostic criteria have remained largely consistent over time. These criteria are based on three features: prenatal and/or postnatal growth deficiency, a unique pattern of facial anomalies, and central nervous system dysfunction. Although the physical features of FAS are often the most noticeable aspect of the syndrome, alcohol's effect on the developing central nervous system can be one of the most devastating. Importantly, individuals who lack the characteristic facial features or growth retardation associated with FAS may exhibit similar cognitive and/or behavioral deficits as compared to those who meet full diagnostic criteria for the syndrome (Mattson et al., 2011; Mattson, Riley, Gramling, Delis, & Jones, 1998) Thus, the non-diagnostic umbrella term

Fetal Alcohol Spectrum Disorder(s) (FASD) has been adopted to encompass the range of potential outcomes associated with prenatal alcohol exposure (Bertrand, 2004). In a recent study based on a randomly selected group of first grade students from a representative Midwestern U.S. community, the prevalence of FAS was estimated at 0.6-0.9% while the total prevalence of FASD was estimated at 2.4% to 4.8% (May et al., 2014). This is consistent with previous reports on the prevalence of FASD, which has been shown to be as high as 2% to 5% in the U.S. and some Western European countries (May et al., 2009). These rates highlight the public health concern that prenatal alcohol exposure represents.

In the absence of the physical features, particularly the facial dysmorphism associated with FAS, identifying individuals who have been prenatally exposed to alcohol presents a major challenge. Obtaining accurate histories of maternal alcohol consumption is difficult due to mothers' denial, recall bias, and/or reluctance to disclose true levels of alcohol consumption during pregnancy (Clarren, Carmichael-Olson, Clarren, & Astley, 2000; McNamara, Orav, Wilkins-Haug, & Chang, 2005). The discovery of biomarkers of prenatal alcohol exposure would be a major step forward in helping to identify these nondysmorphic cases, particularly when maternal exposure data are not available. Neuroimaging techniques have the potential to identify brain biomarkers of prenatal alcohol exposure, rather than emphasizing the physical characteristics of FAS. Such biomarkers might also be able to indicate the severity of exposure, and could be used to assess treatment outcomes, at the neural system level. Thus, continued research in this area is critical. In particular, the application of multiple imaging modalities, such as structural magnetic resonance imaging (MRI), functional

MRI (fMRI), and diffusion tensor imaging (DTI) would allow for a comprehensive evaluation of the effects that prenatal alcohol exposure has on brain structure and function.

1.1 Working Memory Deficits in Individuals with FASD

Working memory is an essential component of executive function. It refers to the process of temporarily storing and manipulating information, and is necessary for a wide range of cognitive tasks (Baddeley, 1986, 1992). In 1974, Baddeley and Hitch proposed the highly influential and enduring multi-component model of working memory. Their original model consisted of three components: the central executive, and two subsidiary systems, the phonological loop, and the visuospatial sketchpad. The model was later updated by Baddeley (2000) to include a fourth component, the episodic buffer. The central executive component is assumed to act as an attention control system responsible for directing the actions of the other components. The phonological loop is responsible for the temporary storage and manipulation of verbal information. Similarly, the visuospatial sketchpad is used for the temporary storage and manipulation of visuospatial information. The episodic buffer is comprised of a limited-capacity temporary storage system, which is capable of integrating information from the subsidiary systems of working memory (i.e., the phonological loop and the visuospatial sketchpad) and from long-term memory.

Findings from neuropsychological studies generally indicate deficits in children and adolescents who have been prenatally exposed to alcohol, in comparison to non-exposed controls, in both verbal (Aragon et al., 2008; Burden, Jacobson, Sokol, & Jacobson, 2005b; Carmichael Olson, Feldman, Streissguth, Sampson, & Bookstein, 1998;

Jacobson, Jacobson, Sokol, & Ager, 1998; Paolozza et al., 2014; Quattlebaum & O'Connor, 2013) and non-verbal (Green et al., 2009; Hemington & Reynolds, 2014; Paolozza et al., 2014; Quattlebaum & O'Connor, 2013; Rasmussen, Soleimani, & Pei, 2011) working memory tasks. While most of the studies examining neurobehavioral deficits associated with prenatal alcohol exposure have focused on children and adolescents, some evidence suggests that working memory deficits may also persist into adulthood (Connor, Sampson, Bookstein, Barr, & Streissguth, 2000; Kerns, Don, Mateer, & Streissguth, 1997).

It has also been suggested that spatial working memory (SWM), the temporary storage of spatial locations for further manipulation (Baddeley, 1986) may be significantly impaired in individuals with prenatal alcohol exposure (Green et al., 2009; Rasmussen et al., 2011). Green and colleagues (2009) found that, across a series of executive function measures, the effect size for SWM deficits was the largest, suggesting that prenatal alcohol exposure may affect SWM to a greater degree than it does other executive function domains. Another study used eight subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) to examine executive function, visual memory, and attention in children prenatally exposed to alcohol (Rasmussen et al., 2011). Using an alpha level of $\leq .01$ to correct for multiple comparisons, findings revealed that, relative to non-exposed controls, children prenatally exposed to alcohol scored significantly lower on the Reaction Time, Spatial Working Memory, and Rapid Visual Information Processing subtests. Children prenatally exposed to alcohol also appeared more impaired than control participants on the Spatial Span subtest, although this difference only trended toward significance. Notably, out of four executive function

subtests (Spatial Span, Stockings of Cambridge, Intra-Extra Dimensional Set Shift, and Spatial Working Memory) children prenatally exposed to alcohol were only impaired on the two that depend heavily on SWM (Spatial Span and Spatial Working Memory). The authors also found that the Spatial Span subtest was the only one that differentiated children who met criteria for an FASD-related diagnosis from those who were prenatally exposed to alcohol but did not meet diagnostic criteria according to the Four-Digit Diagnostic Code (Astley, 2004). Children with an FASD related diagnosis performed worse on the CANTAB Spatial Span subtest, a measure that depends heavily on intact SWM, than did the non-diagnosed children with prenatal alcohol exposure. Similarly to the study by Green and colleagues (2009), Rasmussen et al. (2011) concluded that SWM appears to be specifically impaired in children with FASD. The authors also hypothesized that the SWM impairment observed in FASD is related to Baddeley's subsidiary visuospatial sketchpad system. In an attempt to further define a neurobehavioral profile of FASD, a previous study found that measures of executive function and spatial processing are among the most sensitive to prenatal alcohol exposure (Mattson et al., 2010b). Thus, it is not surprising that deficits in these areas are likely to result in significant SWM impairments.

In addition to neuropsychological studies, neuroimaging techniques have allowed researchers to examine the neural correlates of cognitive dysfunction associated with prenatal alcohol exposure. Within the past decade, four fMRI studies have investigated the neural correlates of SWM in individuals with FASD (Malisza et al., 2005; Malisza et al., 2012; Norman et al., 2013; Spadoni et al., 2009). These studies will be discussed in further detail in subsequent sections. It is important to note that while differences in

methodology and subject characteristics make direct comparison of these studies challenging, these studies together identify aberrant brain activity that contributes to SWM impairment in individuals who have been prenatally exposed to alcohol compared to their non-exposed peers. In an attempt to clarify and expand on previous findings, the present study will further characterize the neural substrates underlying SWM deficits in youth with histories of heavy prenatal alcohol exposure using a multimodal imaging approach.

1.2 Neural Underpinnings of Spatial Working Memory

Neuroimaging techniques such as fMRI have led to new insights into the neural correlates of human cognition. Studies of the neural correlates of working memory have consistently shown the involvement of a fronto-parietal network (Owen, McMillan, Laird, & Bullmore, 2005; Rottschy et al., 2012; Wager & Smith, 2003). Prefrontal and posterior parietal brain regions, including the dorsolateral prefrontal cortex (DLPFC) and the posterior parietal cortex (PPC), are key regions involved in SWM (Koch et al., 2005; Nee & D'Esposito, 2015; van Asselen et al., 2006). While the majority of studies examining the neural underpinnings of SWM have focused on adults, it appears that similar brain regions are recruited in children and adolescents (Nelson et al., 2000; Thomas et al., 1999). However, children and adolescents show a more widespread neural response pattern than adults, suggesting that the neural circuits involved in SWM continue to refine as the brain develops (Geier, Garver, Terwilliger, & Luna, 2009; Kwon, Reiss, & Menon, 2002; Scherf, Sweeney, & Luna, 2006). Furthermore, children and adolescents generally show greater activation in bilateral prefrontal and parietal regions during SWM tasks with increasing age (Geier et al., 2009; Klingberg, Forssberg,

& Westerberg, 2002; Kwon et al., 2002; Nagel, Herting, Maxwell, Bruno, & Fair, 2013; Schweinsburg, Nagel, & Tapert, 2005; Spencer-Smith et al., 2013). Consistent with these findings, previous studies have shown a positive correlation between white matter structure of the pathways between the frontal and parietal lobes, including the superior longitudinal fasciculus (SLF), and working memory capacity during childhood and adolescence (Darki & Klingberg, 2015; Ostby, Tamnes, Fjell, & Walhovd, 2011; Peters et al., 2012; van Asselen et al., 2006).

1.3 Effects of Prenatal Alcohol Exposure on Brain Structure and Function in Relation to Spatial Working Memory: Review of Structural MRI and fMRI Studies

Structural brain abnormalities have been documented in individuals with FASD (for reviews, see Lebel, Roussotte, & Sowell, 2011; Moore, Migliorini, Infante, & Riley, 2014), such as disproportionate volumetric reductions of the frontal (Astley et al., 2009) and parietal lobes (Archibald et al., 2001; Sowell et al., 2002). Previous studies have also found increased cortical thickness in large areas of frontal and parietal cortices (Sowell et al., 2008b; Yang et al., 2012) as well as increased gray matter and decreased white matter density in bilateral inferior parietal regions (Sowell et al., 2002). Although less research has been published in this area, more recent longitudinal MRI studies have suggested that there are alterations in the developmental trajectories of regional brain volume in children prenatally exposed to alcohol. One study found aberrant developmental trajectories of cortical brain volume in posterior areas, particularly the parietal cortex, in children with heavy prenatal alcohol exposure compared to non-exposed control subjects (Lebel et al., 2012). Children prenatally exposed to alcohol showed a more linear decline in volume across childhood and adolescence in comparison to demographically similar non-exposed

controls, who showed an inverted U-shaped growth trajectory consistent with the expected developmental trajectory. The atypical neurodevelopmental trajectory in alcohol-exposed youth may indicate reduced neuroplasticity in brain regions important for SWM. In contrast, similar rates of white matter (Gautam et al., 2015; Gautam, Nunez, Narr, Kan, & Sowell, 2014) and subcortical gray matter growth (i.e., a similar developmental trajectory) between subjects prenatally exposed to alcohol and non-exposed subjects have been observed (Treit et al., 2013).

In addition to structural neuroimaging studies, over the past decade several studies have examined brain function in FASD using primarily fMRI techniques (for reviews, see Coles & Li, 2011; Moore et al., 2014). Non-invasive measurement and localization of brain activity can be achieved with fMRI, which detects fluctuations in blood flow and oxygenation levels. These fluctuations are referred to as the blood oxygen level dependent (BOLD) signal. The underlying mechanism of BOLD signal relates to the magnetic susceptibility arising from deoxyhemoglobin concentration in the brain (Kwong et al., 1992; Ogawa, Lee, Kay, & Tank, 1990). It has been well established that BOLD response measured by fMRI represents an indirect, yet valid measure of neural activation (Logothetis, 2008).

Previous fMRI studies of individuals prenatally exposed to alcohol have found aberrant patterns of neural activation associated with SWM; however, findings have been somewhat inconsistent. The first fMRI study to examine the neural correlates of SWM in FASD evaluated children and adults with prenatal alcohol exposure compared to age-and sex-matched controls (Malisza et al., 2005). In this study, different conditions of an *n-back* task, which is commonly used to investigate working memory, were administered

during the fMRI session. The results showed increased activation in inferior and middle frontal brain regions for the low manipulation condition of the *n-back* task in both children and adults prenatally exposed to alcohol, relative to controls. Conversely, control participants showed significantly greater activity in superior frontal and parietal brain regions. In addition to increased activation patterns, alcohol-exposed children also exhibited decreased activity in the frontal lobe with increasing task difficulty, while the opposite pattern was observed among control children. However, failure to account for between-group differences in task performance, and a lack of between-group statistical comparisons make interpretation of these findings difficult (Bookheimer & Sowell, 2005). A subsequent study by Spadoni et al. (2009) examined neural activation during a SWM task in youth with heavy prenatal alcohol exposure compared to a group of non-exposed controls. Though there were no statistically significant group differences in task performance, the alcohol-exposed participants showed greater BOLD response to SWM relative to vigilance trials in frontal, insular, superior and middle temporal, occipital, and subcortical regions. Over the past few years, two additional fMRI studies have examined the impact of prenatal alcohol exposure on neural correlates of SWM. Malisza et al. (2012) compared brain activation patterns during a SWM task in children with alcohol-related neurodevelopmental disorder (ARND), children with attention-deficit/hyperactivity disorder (ADHD), and non-exposed controls. Children with ARND had greater activation in the DLPFC and PPC in comparison to children with ADHD and non-exposed controls. Similar to a previous study by Malisza et al. (2005), the authors found differences in task performance between the groups. Children with ARND performed similarly to non-exposed children with ADHD, but both of these groups were

less accurate and had greater response time variability during the SWM component of the task as compared to typically developing non-exposed controls. Of note, differences in task performance between groups are not an ideal outcome in fMRI experiments because these differences make interpretation of BOLD response challenging. For example, one could argue that differences in brain activity are related to the differences in task performance. A more recent study examined the neural correlates of SWM in children with heavy prenatal alcohol exposure, non-exposed children with a confirmed family history of alcohol use disorders, and non-exposed controls (Norman et al., 2013). In comparison to non-exposed control children, children prenatally exposed to alcohol had increased activation in four clusters that included areas of the left middle and superior frontal gyrus, lingual gyrus and cuneus, lentiform nucleus and insula, and the right middle frontal gyrus. Although the authors reported group differences in task performance, a post-hoc analysis indicated that these differences in activation patterns remained significant after accounting for differences in task performance.

While previous studies have examined the neural correlates of SWM in individuals with FASD, methodological and sampling differences have made it difficult to draw conclusions regarding the impact of prenatal alcohol exposure on the neural mechanisms of this cognitive domain. Nevertheless, findings do suggest aberrant activation patterns in alcohol-exposed individuals in comparisons to non-exposed controls. Therefore, further research examining this domain is warranted. This dissertation project aims to expand on previous studies using a multimodal imaging approach to examine the impact of prenatal alcohol exposure on the functional connectivity and underlying white matter integrity associated with SWM.

1.4 Effects of Prenatal Alcohol Exposure on Functional Network Connectivity

The majority of the functional neuroimaging research (e.g., fMRI research) that has been conducted to date has focused on the localization of brain regions that are active during specific tasks. However, identifying patterns of functional interaction between brain regions is critical given that no specific brain region works in isolation (Fox et al., 2005; McIntosh, 2000). Functional connectivity methods examine the degree to which distinct brain regions form functional networks by measuring temporal correlations in BOLD signal fluctuations (Biswal, Yetkin, Haughton, & Hyde, 1995). These correlations enable the investigation of resting state (Biswal et al., 1995; Deco, Jirsa, & McIntosh, 2011; Lowe, Mock, & Sorenson, 1998) and task specific (Arfanakis et al., 2000; Friston et al., 1997; Lowe, Dzemidzic, Lurito, Mathews, & Phillips, 2000) neural networks.

Previous studies have examined patterns of functional connectivity at rest in children prenatally exposed to alcohol (Wozniak et al., 2013; Wozniak et al., 2011) and adults (Santhanam et al., 2011). Wozniak et al. (2011) examined inter-hemispheric functional connectivity in children prenatally exposed to alcohol in comparison to demographically similar controls with no history of prenatal alcohol exposure. Specifically, the authors focused on brain regions known to have white matter alterations at the microstructural level. Findings indicated lower inter-hemispheric connectivity in paracentral regions in the alcohol-exposed group as compared to the non-exposed control group (i.e., the correlations between contralateral paracentral BOLD response were lower in the FASD group than in the control group). Another study examined resting state functional connectivity of the default-mode network in adults with prenatal alcohol exposure compared to healthy controls (Santhanam et al., 2011). Results of this study

showed that alcohol-exposed adults displayed reduced connectivity between the middle prefrontal cortex and posterior cingulate cortex as compared to control participants. A more recent resting state functional connectivity study examined global cortical connectivity in children prenatally exposed to alcohol relative to non-alcohol exposed controls (Wozniak et al., 2013). The results revealed altered network connectivity in children with prenatal alcohol exposure that indicated overall less efficient brain circuitry.

Unlike resting state functional connectivity, task-based functional connectivity can provide new insights into the functional organization of brain networks during different cognitive tasks. Psychophysiological Interaction (PPI) analysis is a statistical technique that provides a measure of task-based functional interactions between different brain regions' activity (Friston et al., 1997). This approach can enhance our understanding of the pathophysiological mechanisms of cognitive dysfunction in individuals with FASD. For example, a study by Roussotte and colleagues (2012) using simple correlational analysis between BOLD signal fluctuations found that, compared to a group of control children, children with prenatal alcohol exposure showed greater connectivity between putamen seeds and frontal areas, but decreased connectivity with caudate seeds. While these findings suggest altered corticostriatal connectivity, the methodological approach used does not allow for the possibility that the correlation of neural activity in different brain regions may change as a function of task. That is to say that the correlations observed by Roussotte and colleagues (2012) may actually have been a function of non-task-related spontaneous BOLD signal activity. To address this, PPI provides a useful exploratory technique that allows for examination of connectivity

between two brain regions as a specific function of the task of interest. No studies to date have used this approach to examine task-based functional connectivity in FASD.

1.5 Effects of Prenatal Alcohol Exposure on White Matter Microstructure

DTI is a MRI-based technique that allows for the examination of white matter microstructure in a way that is not possible with traditional structural MRI. More specifically, DTI assesses the direction and integrity of white matter fibers by measuring the Brownian motion of water molecules (Basser & Jones, 2002; Basser & Pierpaoli, 1996; Le Bihan et al., 2001). Fractional anisotropy (FA) and mean diffusivity (MD) are two widely used measures of white matter integrity. FA is a scalar measure of the degree of anisotropy (i.e., directional variation) and is calculated from the diffusion rates across all three principal axes of the diffusion ellipsoid (Pierpaoli & Basser, 1996). FA ranges from 0 to 1, with 0 indicating completely random diffusion (i.e., isotropic diffusion) and 1 indicating completely directional diffusion (i.e., anisotropic diffusion), such as that seen in densely packed, myelinated axonal fiber bundles. Mean diffusivity refers to the average diffusion over all directions, with possible values ranging from 0 to 1. Values closer to 1 denote an increased rate of diffusion, while values approaching 0 indicate reduced water movement (Basser & Pierpaoli, 1996). These metrics are thought to be indicative of different biological properties, such as myelination, axonal diameter, and cellular densities (Alexander, Lee, Lazar, & Field, 2007). Disruptions in white matter integrity may disrupt signal transmission between brain regions, resulting in altered functional network organization. For example, axon myelination increases the speed of signal propagation. Increased myelination or packing density has been associated with decreased radial diffusivity and increased FA (Sen & Basser, 2005). An appropriate

degree of myelination is necessary for the smooth, efficient, and integrated connections between white matter fiber pathways.

DTI studies have revealed white matter abnormalities in several brain regions among individuals prenatally exposed to alcohol (for review, see Wozniak & Muetzel, 2011). One of the most consistent findings resulting from DTI studies in FASD is altered white matter integrity in the corpus callosum (Fryer et al., 2009; Lebel et al., 2008; Li, Coles, Lynch, & Hu, 2009; Ma et al., 2005; O'Conaill et al., 2015; Sowell et al., 2008a; Wozniak et al., 2006; Wozniak et al., 2009). Abnormalities in white matter fibers innervating frontal, temporal, and occipital regions of the brain have also been reported in youth with heavy prenatal alcohol exposure (Fryer et al., 2009; Lebel et al., 2008; O'Conaill et al., 2015; Sowell et al., 2008a). Findings from a longitudinal study by Treit et al. (2013) showed alterations in the developmental trajectory of white matter integrity in frontal association fibers in children prenatally exposed to alcohol as compared to non-exposed controls. Specifically, compared to non-exposed controls, children with FASD showed greater reductions in MD with age. According to the authors, the greater age-related reductions in MD suggest delayed compensatory mechanisms of underlying cellular events than what would be expected in typically developing children. More recent studies suggest that abnormalities in white matter integrity following prenatal exposure to alcohol are evident in the early neonatal period (Donald et al., 2015; Taylor et al., 2015).

White matter integrity is critical for high-level cognitive processes such as attention, executive functioning, non-verbal visuospatial processing, and processing speed (for review, see Filley, 2010). Aberrant white matter integrity as a result of prenatal

alcohol exposure may contribute to many of the cognitive deficits characteristic of individuals with FASD. For example, Sowell and colleagues (2008a) found that among a group of children and adolescents with FASD, lower FA in bilateral splenium was associated with poorer performance on visuomotor integration tests.

1.6 Purpose of the Current Study

One deficit often found in individuals with FASD is impaired working memory (Connor et al., 2000; Gautam et al., 2014; Green et al., 2009; Paolozza et al., 2014; Rasmussen et al., 2011). More specifically, SWM may be particularly deficient in youth prenatally exposed to alcohol (Green et al., 2009; Rasmussen et al., 2011). A fronto-parietal network has consistently been shown to activate during working memory tasks (Owen et al., 2005; Rottschy et al., 2012; Wager & Smith, 2003). Despite evidence for microstructural and functional abnormalities in frontal and parietal brain regions in individuals prenatally exposed to alcohol, the relation and contribution of these abnormalities to SWM deficits remain unclear. An increasing number of studies are combining measures of white matter microstructure and functional connectivity to explore the anatomical substrates of the functional organization in the brain (for review, see Rykhlevskaia, Gratton, & Fabiani, 2008). The main goal of the current study was to expand on previous research by examining the brain structure and function underlying SWM deficits in children with FASD using a multimodal imaging approach. Specially, task-based fMRI and DTI were used to delineate the effects of prenatal alcohol exposure on the neural substrates underlying SWM. Identification of the brain abnormalities in individuals with FASD may yield brain biomarkers, which have the potential to aid in the identification of individuals who experience cognitive deficits associated with FASD in

the absence of facial dysmorphism. It will also enable assessment of the severity of deficiencies associated with prenatal alcohol exposure. Moreover, such knowledge can inform the development of treatment approaches designed to improve the efficiency of neural networks underlying the cognitive deficits associated with prenatal alcohol exposure.

1.7 Specific Aims and Hypotheses

Aim 1: Examine brain activation associated with SWM in children with heavy prenatal alcohol exposure compared to non-exposed controls. Using fMRI response to a SWM paradigm previously shown to be sensitive to the effects of heavy prenatal alcohol exposure (Norman et al., 2013; Spadoni et al., 2009), whole-brain between group differences in BOLD response (expressed as a percent signal change) to SWM relative to vigilance trials (SWM – vigilance contrast) were assessed.

Hypothesis 1. Based on previous findings showing that individuals with FASD display functional abnormalities during SWM (Malisza et al., 2005; Malisza et al., 2012; Norman et al., 2013; Spadoni et al., 2009), it was hypothesized that children with heavy prenatal alcohol exposure would show greater BOLD response to the SWM – vigilance contrast in expected frontal and parietal brain regions in comparison to non-exposed controls. It was also hypothesized that these children would show more widespread neural activity in comparison to non-exposed controls**,** despite equivalent task performance.

Aim 2: Examine group differences in task-based functional connectivity with frontal and parietal seed regions subserving working memory for spatial information. Four seed regions within the bilateral DLFPC and PPC were selected.

Group differences in task-based functional connectivity between each of the selected seeds and every voxel in the brain were examined for the SWM – vigilance contrast using a PPI approach.

***Hypothesis 2*.** Based on previous findings of inefficient network connectivity in individuals prenatally exposed to alcohol (Santhanam et al., 2011; Wozniak et al., 2013; Wozniak et al., 2011), it was hypothesized that, relative to non-exposed controls, children prenatally exposed to alcohol would show reduced functional connectivity of the DLPFC and PPC seed regions with other task-related brain regions.

Aim 3: Examine group differences in white matter integrity underlying the fronto-parietal network implicated in SWM. Group differences in white matter integrity, as measured by FA and MD, for the superior longitudinal fasciculus (SLF) and the genu of the corpus callosum (GCC) were examined. These white matter tracts subserve frontal and parietal seed regions discussed in Hypothesis 2.

***Hypothesis 3*.** Previous DTI studies have shown atypical white matter integrity of these regions associated with prenatal alcohol exposure (Fryer et al., 2009; Lebel et al., 2008; Ma et al., 2005). Based on prior research, it was hypothesized that children prenatally exposed to alcohol would show altered white matter integrity in the SLF and GCC as compared to non-exposed controls, as evidenced by reductions in FA and/or increases in MD.

CHAPTER 2: METHODS

2.1 Participants

Study participants were recruited through the Center for Behavioral Teratology (CBT) at San Diego State University (SDSU) as part of a larger, ongoing study on the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD). A multifaceted recruitment strategy was employed, including referrals from diagnostic clinics and other professionals, and community outreach via advertising at various child-related agencies and venues. Primary caregivers completed questionnaires and participated in interviews about their children to determine study eligibility. A total of 40 eligible (criteria described below) children between the ages of 10 and 16 ultimately participated: 21 children with histories of heavy prenatal alcohol exposure (AE group), and 19 demographically similar non-exposed controls (CON group). Data from three participants in the AE group were excluded from the analyses due to excessive head motion during scanning, resulting in a total sample of 37 participants.

Inclusion/Exclusion Criteria and Group Characterization. To participate in the present study, children must have: (1) been between the ages of 10:0 and 16:11, (2) been fluent in English, and (3) met the requirements for one of the groups detailed below. General exclusion criteria included the following: (1) history of significant head injury with loss of consciousness for more than 30 minutes, (2) evidence of any other known causes of mental deficiency, or significant physical, neurological, or psychiatric disability that would prevent participation in the study, (3) adopted from abroad after the age of five or less than two years before the assessment, and (4) any contraindication for MRI procedure (e.g., metallic implants). Participants were excluded from the CON group if

they met diagnostic criteria for a psychiatric illness based on the NIMH Diagnostic Interview Schedule for Children Version IV (C-DISC-4.0; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). The inclusion/exclusion criteria used in this study were identical to those used in the CIFASD project. Thus, children eligible for the neuroimaging component of the CIFASD project were considered for participation in the current study.

AE group. Participants in the AE group were evaluated by Dr. Kenneth Lyons Jones, a pediatric dysmorphologist with expertise in alcohol teratogenesis, who determined the presence of FAS diagnosis using standardized criteria defined by the Dysmorphology Core of the CIFASD project. A diagnosis of FAS was sufficient to meet study criteria for inclusion in the AE group. FAS diagnosis was based on the presence of two or more key facial features (short palpebral fissures, smooth philtrum, and thin vermilion border of the upper lip) and either evidence of growth deficiency (height and/or weight $\leq 10^{th}$ percentile) or microcephaly (head circumference $\leq 10^{th}$ percentile) (for details, see Jones et al., 2006; Mattson et al., 2010a). Three subjects met these criteria for a diagnosis of FAS. When maternal self-report was available, heavy prenatal alcohol exposure was defined as maternal consumption of ≥ 4 drinks per occasion at least once per week or ≥ 13 drinks per week several times during pregnancy. For the remaining subjects in the AE group, mothers were reported to be "alcoholic" or to have had alcohol abuse or dependence during pregnancy. Of note, direct maternal self-report was generally unavailable, as many children with heavy prenatal alcohol exposure were no longer residing with their biological families at the time of study participation. While prospective measures of alcohol consumption are valuable as they allow for consideration

of alcohol dose and timing, such data were not available for the majority of participants in the AE group.

CON group. Participants in the CON group had minimal to no prenatal alcohol exposure, defined as no more than one drink per week on average and never more than two drinks on a single occasion during pregnancy. Because the majority of participants in the CON group resided with their biological mothers, unlike the children in the AE group, screening for exposure to alcohol or other teratogens was determined through direct maternal self-report in most cases.

2.2 Study Procedures

General study procedures. Written informed parental consent and participant assent were obtained prior to participation. The Institutional Review Boards of SDSU and the University of California San Diego (UC San Diego) approved all study procedures. Participants received a financial incentive for participation in the study. As part of this larger study, a general conceptual ability (GCA) score from the Differential Ability Scales–Second Edition (DAS–II) (Elliott, 2007), which is a composite score related to general reasoning and conceptual abilities that is similar to a Full Scale IQ score, was computed. Socioeconomic status (SES), as measured by the Hollingshead Four Factor Index of Social Status (Hollingshead, 1975), was also determined for all study participants.

Familiarization with scanner environment. All participants habituated to the scanning environment using a mock scanner located at the CBT. The mock scanner simulates the actual scanner experience in the absence of a magnetic field. During this session participants practiced staying still while lying in the mock scanner. All

procedures to be used at the actual neuroimaging session were replicated, including placement of the participant's head into the head coil, stabilization with padding and tape, and movement into the magnet bore. Completion time for the mock scanning procedure was approximately 30-45 minutes**.**

Scan session. Participants were scanned at the UC San Diego Center for Functional Magnetic Resonance Imaging (CfMRI) on a General Electric Discovery MR750 3.0 Tesla whole body magnet using an 8-channel gradient head coil. Upon arrival to the CfMRI, participants were re-screened for contraindications for MRI scanning and inspected for metal on their person using a hand-held metal detector. Immediately before the scan session, participants were provided with instructions and a practice session of the fMRI experimental task to ensure they understood the task demands, and to alleviate task-related confusion during scanning. Upon entering the scanner room, the scan operator reminded participants of the scanning procedures. Participants were instructed to lie supine on the scanner bed. The participant's head was then adjusted within the head coil and stabilized with padding and tape to minimize head motion. All participants wore earplugs to further attenuate scanner noise, and padding was placed inside the head coil to restrict head movement. After localizing the head position and ensuring that the participant was comfortable and had a full view of the display screen, the operator left the room and initiated image acquisition. The total time in the scanner was approximately 45 minutes per participant.

Localizer. A localizer (13 s) was obtained at the beginning of each scan session to ensure good head placement and slice selection covering the whole brain.

Anatomical scan. A high-resolution T1-weighted anatomical scan was acquired

in the sagittal plane using a three-dimensional inversion recovery spoiled echo (IR-SPGR) pulse sequence [repetition time (TR) = 8.1 ms, echo time (TE) = min full, inversion time = 640 ms, flip angle = 8 degrees, field of view (FOV) = 24 cm, frequency =256, phase =192, slice thickness 1.2 mm, number of slices = 170, acquisition time = 8 min, 33 s)]. All T1-weighted anatomical scans were collected using real time prospective motion correction (PROMO) (White et al., 2010).

DTI. Diffusion weighted images were acquired in the axial plane along 30 diffusion directions (b value = 1000, TR = 12000 ms, TE = minimum, frequency = 96, phase = 96, slice thickness = 2.5 mm, acquisition time = 7 min, 36 s).

Field maps. Two B0 field maps were collected to correct for echo planar imaging (EPI) distortions caused by the static-field-inhomogeneity.

Task-based fMRI. A T2-weighted functional scan was acquired in the axial plane using gradient echo EPI (TR = 3000 ms, TE = 30 ms, flip angle = 90 degrees, FOV = 24 cm, frequency = 64, phase = 64, number of slices = 32, slice thickness = 3.8 mm, in plane resolution = 3.75 mm x 3.75 mm, repetitions = 156, acquisition time = 7 min 48 s). Task stimuli were back-projected from a laptop onto a screen at the foot of the scanner bed, and were visible via an angled mirror mounted to the head coil. During fMRI acquisition, participants were administered a task designed to probe brain regions subserving SWM (Kindermann, Brown, Zorrilla, Olsen, & Jeste, 2004; Tapert et al., 2001). The SWM task (see Figure 1), originally adapated from McCarthy et al. (1994), consisted of three blocks of rest, during which a fixation cross appeared in the center of the projection screen, and 18 experimental blocks (20 s in duration) that alternated between baseline (vigilance) and experimental (SWM) conditions. A 1 s cue word (‘LOOK,’ ‘DOTS,’ or ‘WHERE’)

appeared at the center of the screen immediately before each block to indicate the beginning and type of condition. Rest blocks, prefaced by the word 'LOOK,' were followed by 20 s of viewing a cross. Figures presented during the vigilance and SWM conditions consisted of abstract Kimura line drawings (Kimura, 1963). The baseline vigilance condition began with the word 'DOTS,' which cued the participant to press the button every time a dot appeared above a figure, approximately 30% of the time. The vigilance condition allowed for control of visual attention and simple motor processes involved during SWM. In the SWM condition, figures were individually presented in one of eight locations. The SWM began with the word 'WHERE,' cueing participants to press the button every time a figure appeared in the same location as a previous figure within that block. Of the ten stimuli presented in each block, an average of three were target trials, or figures that were presented in the same location as the figure presented two trials ago (2-back). For each condition, stimuli were presented on the screen for 1000 ms with an inter-trial stimulus interval of 1000 ms. Accuracy and reaction time (RT) data were logged using a response box designed for MRI studies.

2.3 Data Processing and Statistical Analyses

Continuous variables were tested for normality using the Shapiro-Wilk test, skewness and kurtosis statistics, and visual inspection of outliers via Q-Q plots. In instances where the assumption of normality was not met after removal of potential outliers, the non-parametric Mann-Whitney U test was used.

Demographic and fMRI behavioral data. Analyses were conducted using IBM Statistical Package for Social Sciences (SPSS) version 22. Group differences in demographic characteristics (i.e., sex, race, ethnicity, handedness, age, SES, and GCA)

were examined using independent samples *t*-tests and chi-squared tests. A total accuracy cut-off of 69% was set for both task conditions (vigilance and SWM), so that only participants who were engaged during cognitive task performance were included in the analyses. Total accuracy was calculated as the percentage of correct responses for all trials belonging to the same condition. Similar criteria have been used in prior studies of youth with heavy prenatal alcohol exposure using the same SWM task (Norman et al., 2013; Spadoni et al., 2009). Group differences in vigilance and SWM total accuracy and RT were examined using independent samples *t*-tests.

Imaging data. All image processing and analyses were conducted using the Analysis of Functional NeuroImages (AFNI) software (Cox, 1996), the University of Oxford's Center for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) software (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Smith et al., 2004), and SPSS. Researchers conducting the image preprocessing were blinded to participants' group classification.

fMRI. Each T1-weighted anatomical scan was first transformed to Montreal Neurological Institute 152 (MNI152) standard space by first using FSL's linear image registration, FLIRT (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001), followed by FSL's FNIRT for non-linear registration (Andersson, Jenkinson, & Smith, 2007a, 2007b). Next, functional data were visually inspected for scanner artifacts (e.g., spikes, ghosting). Distortions caused by inhomogeneities of the magnetic field were corrected using field maps. Post-corrected images were examined and compared to the non-corrected images to ensure that the application of the field map correction did not introduce any artifact. To correct for small movements over time, image repetitions were

registered to a selected base volume using a three-dimensional algorithm implemented via AFNI's 3dvolreg (Cox & Jesmanowicz, 1999). The time series of the motion parameters were used in the linear regression analysis of individual data to control for spin history effects (Friston, Williams, Howard, Frackowiak, & Turner, 1996). Participants were excluded from the analysis if more than 15% of repetitions were discarded due to excessive motion. In addition, series data were visually inspected for gross movement artifacts by examining plots of estimated head motion and functional images. Participants with excessive motion, operationalized as greater than 4 mm movement (the size of one voxel), within the run were excluded from group analyses. Next, functional data were resampled into 4 mm^3 isometric voxels and transformed into the subject's anatomical space. This was followed by transformation into standard space using the previously computed anatomical to MNI152 standard space transformation matrix. Images were spatially smoothed by a Gaussian filter with 6 mm full-width half maximum using AFNI program 3dBlurInMask. Next, AFNI's 3dDeconvolve algorithm was used to estimate the general linear model (GLM) through deconvolution of the time series. The GLM used reference vectors for the SWM and vigilance conditions convolved with the hemodynamic response function. Estimated motion and linear trends were also included as nuisance variables. The resulting model generated scaled beta coefficient maps representing the mean percent BOLD signal change for each condition of the task relative to fixation trials and for SWM relative to vigilance trials.

Functional connectivity. Task-based functional connectivity analyses were conducted in AFNI using a generalized psychophysiological interaction (gPPI) approach (McLaren, Ries, Xu, & Johnson, 2012), with seed regions in bilateral DLPFC and PPC.

PPI analysis evaluates the degree to which brain activity in one seed region can be explained by an interaction between an experimental factor and activity in another part of the brain (Friston et al., 1997). Using the standard PPI approach, the different task conditions are multiplied and then convolved with the hemodynamic response function for the psychological regressor in the GLM, whereas in the gPPI each condition of the task (e.g., SWM and vigilance) is separately convolved with the hemodynamic response to form separate psychological regressors, allowing for improved model fit at the single subject level (McLaren et al., 2012). The selection of seed regions within the bilateral DLPFC and PPC (i.e. regions of the fronto-parietal network) was based on activation to the SWM – vigilance contrast collapsing across all participants, and *a priori* knowledge of the involvement of these regions in SWM (Glahn et al., 2002; Koch et al., 2005; Owen et al., 2005; van Asselen et al., 2006). For all participants combined as one sample, activation to the SWM – vigilance contrast was determined using a one-sample *t*-test with AFNI's 3dttest++ program. Correction for multiple comparisons using a cluster threshold based on Monte Carlo simulations was implemented via AFNI program 3dClustSim (Forman et al., 1995). A corrected significance level of $p < .05$ (with an uncorrected voxelwise threshold: $p < .05$; minimum cluster volume: 63 voxels) was used for all analyses. Because the *t*-test results yielded large clusters of activation covering multiple regions, AFNI's 3dExtrema program was used to identify the local maxima within bilateral DLPFC and PPC from which corresponding seeds were selected. Specifically, activation peaks were located in bilateral middle frontal gyri (right: x = 35.50, y = 28.50, z = 34.50; left: x = -32.50, y = 4.50, z = 54.50), and bilateral superior parietal lobes (right: x = 27.50, y = -51.50, z = 50.50; left: x = -36.50, y = -47.50, z = 58.50).

Functional seeds were defined as spheres (5 mm radius) around the local maxima within each region. For each participant, the average time series of the BOLD signal was extracted for the four seeds, and trends were removed with 3dDetrend. A deconvolution of the seed's time series, using a gamma function, was calculated with AFNI's 3dTfitter program. PPI regressors (interaction terms) for each condition (SWM, vigilance) were computed by multiplying the mean time series of the deconvolved seed with the condition vector of interest, and then convolved with a gamma basis function using AFNI program Waver. Separate voxelwise GLMs were conducted for each seed at the individual subject level. Each GLM contained the PPI regressors, the physiological regressor (seed time series), the psychological regressors (i.e. task condition regressors), and nuisance variables (i.e., the motion regressors from the prior fMRI analysis). A total of four gPPI analyses corresponding to each seed were performed at the single subject level, and the resulting contrast images were transformed into a z-score using Fisher's z transformation for subsequent group level analyses.

DTI. In order to correct for head motion, each diffusion image was registered to a reference volume via affine registration. Next FSL's topup (Andersson, Skare, & Ashburner, 2003) and eddy-correct tools were applied to correct for susceptibility-induced distortions and eddy currents induced artifacts by gradient coils, respectively. Images were visually inspected for quality, followed by skull stripping using FSL's Brain Extraction Tool (BET) (Smith, 2002). FSL Diffusion Toolbox (FDT) DTIfit was then used to fit a diffusion tensor model at each voxel and to compute the scalar FA and MD maps derived from the tensor's eigenvalues (Behrens et al., 2003). The next steps implemented for data processing were obtained using FSL's Tract-Based Spatial

Statistics (TBSS) pipeline (Smith et al., 2006). Briefly, the first step was to slightly erode FA images and zero end slices in order to remove any outliers from the diffusion tensor fitting. Next, every FA image was aligned to every other one using nonlinear registration. The former step was conducted in order to identify the most representative image as the target. The target image was then affine-aligned into MNI152 standard space. Subsequently, each participant's FA image was transformed into 1 × 1× 1 mm MNI152 space using the previously estimated nonlinear and affine transformations. The resulting images were averaged to create a mean FA image, which was then thinned to create a mean FA skeleton. A threshold (> 0.2) was applied to the mean skeleton prior to any statistical analyses. The same non-linear transformations were applied to the corresponding MD maps. Both analyses of FA and MD used the same mean skeleton.

Given the involvement of the frontal and parietal regions in SWM, this study used a region of interest (ROI) approach to examine white matter integrity of tracts known to subserve these cortical regions. Tract-based ROI analyses focused on the bilateral SLF and GCC. Predefined masks for the selected ROIs were obtained from the ICBM-DTI-81 stereotaxic white matter parcellation map within FSL (Mori et al., 2008). Masks were subsequently restricted to voxels only within the mean skeleton to avoid including voxels located outside the tracts in averages. Mean FA and MD values were extracted for each participant within each ROI along the mean skeleton using fslmeants. These values were exported for subsequent group analyses.

Hypotheses testing.

***Hypothesis 1*.** It was hypothesized that children with heavy prenatal alcohol exposure would show greater BOLD response to the SWM – vigilance contrast in

expected frontal and parietal brain regions in comparison to non-exposed controls. It was also hypothesized that these children would show more widespread neural activity in comparison to non-exposed controls**,** despite equivalent task performance.

Between group differences in BOLD response to the SWM – vigilance contrast were examined across the whole brain using an independent samples *t*-test with AFNI's 3dttest++ command. Correction for multiple comparisons were applied using AFNI 3dClustSim at a corrected significance level of $p < .05$ (with an uncorrected voxelwise threshold: $p < .05$; minimum cluster volume: 63 voxels). To further clarify the directionality of significant group differences, the mean percent BOLD signal change for the SWM relative to fixation, and vigilance relative to fixation, within each significant cluster was extracted for each participant. Within group analyses of BOLD response to the SWM – vigilance contrast were also examined to further characterize and explain group differences in brain activation using one-sample *t*-tests.

Hypothesis 2. It was hypothesized that, relative to non-exposed controls, children prenatally exposed to alcohol would show reduced functional connectivity of the DLPFC and PPC seed regions with other task-related brain regions.

Four previously defined seeds (bilateral DLPFC and PPC) were used in these analyses. Each seed's connectivity with other brain areas was examined separately. The z-transformed contrast image was used to denote the strength of the functional connectivity between regions whose task-dependent connectivity with the specific seed changed as a function of SWM. Whole-brain between group differences in functional connectivity were estimated using an independent samples *t*-test via AFNI 3dttest++. To correct for multiple comparisons, the same correction applied to the original BOLD

analyses (see Hypothesis 1) was used for the functional connectivity analyses.

Hypothesis 3. It was hypothesized that alcohol-exposed youth would show reduced white matter integrity in the SLF and GCC compared to non-exposed youth.

An ROI approach was used to examine white matter integrity (measured by FA and MD) for the right and left SLF and GCC. Group differences in FA and MD for these regions were examined using independent samples *t*-tests. To correct for multiple comparisons, a Bonferroni correction was applied. Results were considered significant at $p < .017$ ($\alpha = .05/3$ ROIs).

Exploratory analyses.

Effect of age as a covariate. During childhood and adolescence the brain undergoes significant changes in brain structure and function (Barnea-Goraly et al., 2005; Casey, Giedd, & Thomas, 2000; Spear, 2000). Among other cognitive processes, working memory continues to improve throughout childhood and adolescence (Demetriou, Christou, Spanoudis, & Platsidou, 2002; Klingberg et al., 2002; Luna, Garver, Urban, Lazar, & Sweeney, 2004). In a previous fMRI study using a SWM task identical to the one used in the present study, findings indicated age-related changes in fronto-parietal neural networks involved in SWM in a group of typically developing adolescents (Schweinsburg et al., 2005). Therefore, to examine the potential contribution of age on brain activation, functional connectivity, and white matter integrity, all analyses were repeated with age included as a covariate.

Relationship between functional and structural data. Pearson's product-moment correlations were used to examine the association between white matter integrity measured by FA and MD in each of the selected ROIs (i.e., right SLF, left SLF, and

GCC), and the BOLD response extracted from clusters showing significant group differences in activation to the SWM – vigilance contrast. Correlations were examined within each group separately. Only clusters of anatomical correspondence to the white matter tract(s) were examined. These analyses were exploratory in nature; therefore, corrections for multiple comparisons were not applied.

CHAPTER 3: RESULTS

3.1 Sample Characteristics

The final sample consisted of 37 participants (18 AE and 19 CON) with a mean age of 13.70 years (SD = 2.09). Demographic characteristics of study participants are presented in Table 1. There were no significant group differences in terms of sex, $\chi^2(1)$ = .02, p = .886, race, $\chi^2(4) = 4.92$, p = .295, ethnicity, $\chi^2(2) = 3.96$, p = .138, handedness, $\chi^2(2) = 2.81$, p = .246, age, $t(35) = .49$, p = .63, or SES, $t(35) = -1.02$, p = .313. As expected, children with heavy prenatal alcohol exposure had significantly lower GCA scores on the DAS-II than non-exposed controls, $t(35) = -5.92$, $p < .001$.

3.2 Task Performance

All participants with usable imaging data (N = 37) performed with greater than 70% total accuracy for the vigilance and SWM condition, demonstrating that participants performed better than chance. The Shapiro-Wilk test revealed a non-normal distribution of vigilance accuracy scores in both the AE (W = .83, p = .005) and CON (W = .81, p = .002) groups, as well as a non-normal distribution of SWM accuracy scores in the CON group (W = .82, p = .005). For vigilance accuracy, two outliers were identified in the AE group. For SWM accuracy, two outliers were found in the CON group. While removal of outliers improved the normality of the data, doing so did not change the overall findings. Therefore, these subjects were not excluded from the analyses in an effort to increase power. Given these findings, data were analyzed using the non-parametric Mann-Whitney U test. These analyses yielded the same results in terms of significance as those obtained from the independent samples t-test. Thus for ease of interpretation, the parametric test results are provided. Group differences were found on SWM total

accuracy, $t(35) = -2.82$, $p = .008$, such that the CON group was more accurate ($M = 90.56$, $SD = 6.18$) than the AE group ($M = 83.41$, $SD = 9.05$). Groups did not differ with respect to vigilance total accuracy. The mean RT for correct response for trials in the vigilance and SWM conditions did not differ between groups. Task performance by group is displayed in Figure 2.

3.3 fMRI

Between group differences in BOLD response. Significant between group differences in BOLD response to the SWM – vigilance contrast were found in four clusters, located primarily in frontal, parietal, and cingulate regions (see Table 2 and Figure 3). In all clusters, the CON group had greater BOLD response than the AE group. The largest cluster, which had a peak in the right posterior cingulate cortex, also extended to the right precuneus and middle temporal gyrus. Additional differences in activation were found in a right hemisphere cluster with a peak in the inferior parietal lobule extending to the precuneus and sensorimotor cortex (including the paracentral lobule and postcentral gyrus), a left hemisphere cluster with a peak in the precuneus extending to the inferior parietal lobule, and a bilateral cluster encompassing the medial frontal gyri and anterior cingulate cortex, extending into the right middle frontal gyrus. The peak activation for this final cluster was located in the left medial frontal gyrus. Effect sizes estimated using Cohen's *d*, reflecting differences between groups in BOLD response to the SWM – vigilance contrast, were medium to large.

To further assess the nature of these group differences, the mean percent signal change for the SWM trials (SWM – fixation) and vigilance trials (vigilance – fixation) were separately extracted for each significant cluster identified from the between group

analysis (see Figure 4). In all four clusters, children in the CON group showed greater BOLD response to SWM trials in comparison to vigilance trials. Children in the AE group did not show consistent activation across clusters. In the right posterior cingulate cluster, this group showed increased BOLD response to vigilance trials compared to SWM trials. For the right inferior parietal lobule cluster and the left medial frontal gyrus cluster, children in the AE group showed similar activation pattern to both SWM and vigilance trials. Similar to the CON group, the AE group showed greater BOLD response to SWM trials relative to vigilance trials in the left precuneus cluster; however, the difference in activation between these conditions was greater in the CON group.

Within group BOLD response. One-sample *t*-tests revealed largely similar patterns of activation during the SWM – vigilance contrast in the AE and CON group (see Figure 5). Both groups showed significant activation in expected frontal and parietal regions associated with SWM. In addition, both groups showed activation in occipital regions (middle occipital, lingual, cuneus), as well as bilaterally in the insula. The AE group also showed bilateral activation in the middle temporal gyri. Bilateral caudate activation was only observed in the CON group.

3.4 Functional Connectivity

Clusters showing significant group differences in functional connectivity in response to the SWM –vigilance contrast (examined via gPPI) using bilateral DLPFC and PPC seeds are described below. The peak activation coordinates and additional information for each significant cluster are presented in Table 3.

Right DLPFC seed. Significant group differences in functional connectivity with respect to the right DLPFC were found in five clusters (see Figure 6). Compared to the

CON group, the AE group showed weaker negative connectivity between the right DLPFC seed and clusters encompassing bilateral superior frontal gyri, left inferior temporal gyrus (extending to the fusiform), and left middle occipital gyrus. The CON group showed positive connectivity between the right DLPFC and a cluster with peak connectivity within the right inferior parietal lobule extending to the superior parietal lobule, postcentral gyrus, and medially to the precuneus and paracentral lobule, as well as a cluster encompassing bilateral middle frontal gyri and medial regions (bilateral medial frontal gyri and right cingulate). In contrast, the AE group showed negative connectivity between the seed and these regions.

Left DLPFC seed. In comparison to the CON group, the AE group showed weaker negative connectivity between the left DLPFC and one cluster encompassing bilateral superior frontal gyri, and a cluster in the left middle occipital gyrus. Relative to the AE group, the CON group showed greater connectivity between the left DLPFC and three clusters. These included a right hemisphere cluster with peak connectivity within the inferior parietal lobule, extending to the paracentral lobule, and precuneus, a cluster encompassing the left middle frontal gyrus and medial frontal gyrus, and a cluster in the temporal gyrus extending to the supramarginal gyrus. Regions of significant group differences in connectivity with the left DLPFC are depicted in Figure 7.

Right PPC seed. In comparison to the CON group, the AE group showed weaker negative connectivity between the right PPC seed and a cluster encompassing bilateral middle occipital gyri and cuneus. Positive connectivity between the seed and a cluster encompassing bilateral superior frontal gyri (see Figure 8) was observed in the AE group

relative to the CON group. There were no clusters in which the CON group showed positive connectivity with the right PPC seed.

Left PPC seed. Weaker negative functional connectivity between the left PPC seed and four clusters (see Figure 9) was observed in the AE group as compared to the CON group. The largest cluster encompassed bilateral superior frontal gyri extending into middle frontal gyri. Additional clusters were seen in the left middle occipital gyrus extending bilaterally into the cuneus, the right insula and middle frontal gyrus, and the left paracentral lobule and cingulate. Children in the AE group showed increased connectivity between the seed and cluster encompassing the left inferior and middle frontal gyri. There were no clusters in which children in the CON group showed positive connectivity with the seed.

3.5 DTI

Between group differences in DTI indices: FA and MD. Group comparisons with respect to FA and MD indices were examined for each of the predefined ROIs (right and left SLF and GCC). For the AE group, FA in the right SLF was not normally distributed ($W = .83$, $p = .004$). For this tract, an outlier in the AE group was detected and removed, which resulted in normal distribution of the data ($W = .96$, $p = .711$). After Bonferroni correction ($\alpha = .017$), no significant group differences in FA or MD were found in any of the selected white matter ROIs. A nominally significant group difference was observed with regards to FA in the right SLF at the unadjusted $\alpha = .05$. The AE group showed increased FA ($M = .49$, $SD = .02$) in comparison to the CON group ($M = .47$, $SD = .03$).

3.6 Results from Exploratory Analyses

Effect of age as a covariate. Analyses of BOLD response, functional connectivity, and DTI metrics were repeated controlling for age. Results yielded the same pattern of significance as those without age as a covariate. Thus, results from the more parsimonious model are presented.

Correlations between BOLD response and white matter integrity. For the AE group, there was a significant negative correlation between BOLD signal from a cluster with a peak in the right inferior parietal lobule (peak coordinates = 48, -40, 54) and FA in the right SLF (r = -.55, p = .022). This association was not significant for the CON group (p = .637). Correlations between FA in the left SLF and an anatomically associated cluster with a peak in the left precuneus (peak coordinates = -12, -68, 50) were not significant for either the AE group (p = .259) or the CON group (p = .211). Similarly, no significant correlations were found between FA in the GCC and a cluster with a peak in the left medial frontal gyrus (peak coordinates = -0, -0, 58) for the AE group (p = .164) or for the CON group (p = .160). There were no significant correlations between BOLD response contrast and MD for any of the tracts examined (all ps > .05).

CHAPTER 4: DISCUSSION

Using a multimodal imaging approach, this study examined brain function and structure associated with SWM in children with FASD. Specifically, the study examined brain activation and functional connectivity during a SWM task, as well as white matter microstructure of the SLF and GCC. The first aim of the study was to compare BOLD response to SWM (relative to a baseline vigilance condition of the task) in children with prenatal alcohol exposure (the AE group) and children with no history of prenatal alcohol exposure (the CON group). The second aim of the study was to examine group differences in task-related functional connectivity between seeds in the fronto-parietal network that have previously been consistently implicated in SWM tasks (Owen et al., 2005; Rottschy et al., 2012; Wager & Smith, 2003), and the rest of the brain. For this second aim, bilateral DLPFC and PPC seed regions were selected based on clusters showing significant BOLD response to the SWM – vigilance contrast across all participants combined. The third aim of the study was to examine group differences in white matter microstructure of the right and left SLF and GCC. For this aim, FA and MD were used as proxies of white matter microstructure. The SLF, the main fronto-parietal white matter connection, was examined because it has been previously shown to be associated with SWM performance (Darki & Klingberg, 2015; Klingberg, 2006; Vestergaard et al., 2011). The GCC, a midline structure that includes fibers that connect the medial and lateral surfaces of the frontal lobes, was also examined, as it has been previously implicated in tasks of SWM (Nagy, Westerberg, & Klingberg, 2004).

4.1 Behavioral Performance

Children in the CON group performed more accurately on SWM trials than

children in the AE group. This is consistent with SWM deficits frequently reported in FASD (Aragon et al., 2008; Burden et al., 2005b; Green et al., 2009; Hemington & Reynolds, 2014; Mattson et al., 2013; Paolozza et al., 2014; Quattlebaum & O'Connor, 2013; Rasmussen et al., 2011). Overall accuracy in the AE group was relatively high at approximately 83%; however, this may be in part because study participants needed to achieve greater than 69% overall accuracy to be eligible for participation to ensure above chance performance across subjects. There were no differences between groups on vigilance accuracy. This suggests that children prenatally exposed to alcohol were not able to perform at the same level as participants in the CON group during the SWM condition despite being actively engaged in the task. No significant group differences were found with respect to RT on either the SWM condition or the vigilance condition, suggesting that differences in performance accuracy could not be explained by slower processing speed, as is typically observed among children prenatally expose to alcohol (e.g., Burden, Jacobson, & Jacobson, 2005a), but rather indicated deficits in SWM.

4.2 Brain Activation during SWM

Within group analyses of BOLD response during a SWM task revealed largely similar patterns of activation in the expected fronto-parietal network, including clusters encompassing DLPFC and PPC, in both the AE and CON groups. Contrary to the first study hypothesis, levels of activation associated with SWM were lower in the AE group than the CON group. These differing levels of activation were found primarily in the frontal, parietal, and cingulate cortices. Specifically, for all clusters the difference between BOLD response to the more challenging SWM condition and BOLD response to the vigilance condition was greater in the CON group than in the AE group. The

difference in activation between conditions was less marked in the AE group. One possible interpretation for these findings is that children prenatally exposed to alcohol may have needed to exert a greater amount of effort for the simple vigilance condition, and thus may have been unable to exert as much effort for the SWM condition. In other words, children in the AE group may have had to "work" harder than children in the CON group to pay attention during the vigilance condition, leaving fewer neural resources available for the more challenging SWM condition. The fact that accuracy was similar across groups for the vigilance condition, but the AE group performed less accurately on the SWM condition relative to the CON group, further supports this interpretation. These findings suggest impaired neural efficiency in children prenatally exposed to alcohol, and are in line with results from a recent study by O'Conaill and colleagues (2015), which found similar patterns of brain activation during both disjunction and conjunction visual search in children with ARND. The authors concluded that the more challenging conjunction search may require more effort than children with ARND are able to exert, suggesting a neurological limit to the effective utilization of both bottom-up and top-down attention mechanisms.

Converging evidence from more neuroimaging studies of SWM has linked the PPC to the maintenance of spatial information (Curtis, 2006; Nee & D'Esposito, 2015). Within the PPC, the inferior parietal lobule has been implicated in working memory coding of spatial representations (Ackerman & Courtney, 2012), as well as in sustaining attention over time (Adler et al., 2001; Vandenberghe, Gitelman, Parrish, & Mesulam, 2001). Findings of reduced activation in bilateral inferior parietal lobules observed in the AE group (relative to the CON group) suggest that deficits in sustained attention may be

underlying the observed SWM deficits in children prenatally exposed to alcohol. Such deficits in sustained attention have been frequently reported in FASD (Coles, Platzman, Lynch, & Freides, 2002; Glass et al., 2014a; Infante et al., 2015b). Unlike the differences observed with regard to the SWM condition, the AE group performed similarly to the CON group on the vigilance condition of the task. This may be explained by the fact that the vigilance task was not sensitive or challenging enough to detect behavioral performance differences in terms of attention.

Abnormal BOLD response patterns to SWM have been reported previously in children and adolescents prenatally exposed to alcohol (Malisza et al., 2005; Malisza et al., 2012; Norman et al., 2013; Spadoni et al., 2009). In general, previous studies have reported increased activation during SWM (after accounting for the effects of simple attention) in children prenatally exposed to alcohol as compared to non-exposed controls, suggesting compensatory mechanisms. In contrast, the present study found decreased activation in select cortical regions in the AE group relative to the CON group. However, this discrepancy between prior research and the current findings may be explained by differences in statistical approach, sample size/power, sample characteristics, and data processing steps (Barch & Yarkoni, 2013; Thirion et al., 2007).

4.3 Whole Brain Functional Connectivity with Bilateral DLPFC and PPC Seeds as a Function of SWM

The majority of fMRI studies in FASD have focused on the detection of brain activation associated with different cognitive functions (for review, see Moore et al., 2014). Building on this technique, examining task-based functional connectivity may be an important step towards understanding local changes in brain activity during

performance of a task by exploring the neural network in which information is shared and integrated in response to different cognitive processes (Ernst, Torrisi, Balderston, Grillon, & Hale, 2015). This study further explored the brain's functional organization associated with SWM using four seeds within the fronto-parietal network: bilateral DLFPC and bilateral PPC. Group differences in functional connectivity patterns between each seed and all other voxels in the brain were examined using the generalized form of PPI analyses (gPPI; McLaren et al., 2012). In contrast to the more traditional measure of functional connectivity, which is based on correlations among measures of neural activity, PPI provides a measure of the relation or "functional coupling" between two neural regions as a function of the task (Cisler, Bush, & Steele, 2014; Friston et al., 1997). Of note, this is the first study to examine functional connectivity during a SWM task using this type of approach in children with FASD.

As hypothesized, the AE group showed decreased functional connectivity in response to the SWM – vigilance contrast, evidenced by negative coupling between the bilateral DLPFC seeds and clusters encompassing the right inferior parietal lobule. On the contrary, the CON group showed increased connectivity between these regions. Children in the AE group also showed negative connectivity between the DLPFC seed and both ipsilateral and contralateral prefrontal cortex regions, whereas the CON group showed positive connectivity between these regions. Research has shown that functional connectivity between cortical regions is an important marker of cognitive ability (Rychwalska, 2013). A fronto-parietal network has been implicated in top-down control mechanisms required for working memory (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Gazzaley & Nobre, 2012). Alterations in the functional coupling between

the DLPFC and the right inferior parietal lobule may underlie SWM deficits in FASD, and suggest possible deficits in the top-down control mechanisms. The observed negative connectivity between these regions in the AE group may be reflective of activity in one brain region suppressing activity in another region (Fox et al., 2005; Friston et al., 1996). However, it should be noted that PPI is a correlational based type of approach, and therefore does not provide information regarding the causal direction between functional coupled regions (O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012).

Functional connectivity analyses with bilateral PPC as seed regions revealed group differences in connectivity primarily in regions within the DLPFC (superior, middle, and inferior frontal gyri). Children in the AE group showed increased connectivity compared to the CON group. These findings are contrary to the hypothesis that decreased connectivity would be found in the AE group. Of note, the PPC seeds used in the current study were centered on the peak voxel of clusters within the right and left superior parietal lobe. The superior parietal lobe, along with the DLPFC, has been implicated specifically on the manipulation of information on working memory tasks (Koenigs, Barbey, Postle, & Grafman, 2009). Enhanced positive functional connectivity between the PPC seed and DLPFC regions may suggest a compensatory reallocation of cognitive resources, or less efficient communication of neural regions.

Other areas of significant group differences in functional connectivity were noted outside the fronto-parietal network. This is not surprising given that SWM also involves processing of visual information, and thus requires the coordination of visual cortex areas with the prefrontal cortex. In comparison to the CON group, children in the AE group showed weaker negative functional connectivity between each seed and the left middle

occipital gyrus. A possible interpretation concerning SWM deficits in the AE group may be related to the ineffective inhibition of posterior visual processing areas (i.e., the middle occipital gyrus) required for successful task performance. Previous fMRI studies have shown that deficits in neural suppression may be a key component of selective performance deficits (Bressler, Spotswood, & Whitney, 2007; Gazzaley, Cooney, Rissman, & D'Esposito, 2005). This interpretation is supported by the increased activation found during vigilance trials in contrast to the more challenging SWM trials, demonstrating that children prenatally exposed to alcohol may have experienced the SWM component of the task as more cognitively taxing than those in the CON group. They may in turn have necessitated increased recruitment of visual processing regions to complete the task. Other studies also support the possibility that SWM deficits in FASD may be secondary to visual processing, which is consistent with alterations in the bottom-up processing in children with ARND suggested by O'Conaill et al. (2015). For example, a study by Malisza et al. (2012) found decreased occipital activation during a 0-back task in children with ARND relative to controls, indicating inefficient visual processing pathways or compromised visual attention in the ARND group.

4.4 White Matter Integrity of the SLF and GCC is Not Related to SWM BOLD Response

The third aim of this study was to examine the white matter integrity, measured by FA and MD, of a fronto-parietal tract (SLF) and a midline tract (GCC). Contrary to the hypothesis, no significant group differences were found in either FA or MD corresponding to the SLF and GCC. However, it should be noted that children in the AE group had significantly higher FA values than children in the CON group when the

Bonferroni adjustment was not applied. Although higher FA is typically thought to reflect increased directionality of the diffusion or greater white matter integrity, increased FA has been reported in children with neurodevelopmental disorders, such as Williams syndrome (Arlinghaus, Thornton-Wells, Dykens, & Anderson, 2011; Hoeft et al., 2007), attention deficit hyperactivity disorder (Davenport, Karatekin, White, & Lim, 2010), and autism spectrum disorders (Bode et al., 2011; Cheng et al., 2010). It has been argued that this increase in FA may be due to a number of factors, such as increases in myelination or decreases in axonal diameter and fiber packing density (Beaulieu, 2002).

Exploratory correlational analyses examined the relationship between BOLD response extracted from clusters showing significant group differences during the SWM – vigilance contrast and measures of white matter integrity for the selected tracts. With one exception, results showed no significant correlations. Overall, these findings suggest that white matter integrity in these tracts could not explain functional abnormalities during performance of a SMW task. The one significant correlation that was found revealed a significant negative correlation between BOLD response to the SWM – vigilance contrast in a cluster encompassing the right inferior parietal lobule and FA in the right SLF for the AE group. This finding supported a potential association between disrupted neural activity and underlying white matter directional coherence in children prenatally exposed to alcohol that was not observed in the control group. It should be noted; however, that these analyses were exploratory in nature and corrections for multiple comparisons were not applied. Thus, this finding must be interpreted with caution until it is replicated in future research.

It is also possible that the underlying etiology of the functional deficits may be due other white matter alterations, such as volume loss. White matter volumetric reductions of frontal and parietal lobes have been previously reported in FASD (Archibald et al., 2001). Other explanations include potential gray matter abnormalities in the AE group. For example, parietal lobe structural abnormalities have been frequently reported in individuals prenatally exposed to alcohol, including disproportionate volumetric lobar reductions (Archibald et al., 2001; Sowell et al., 2002), decreased cortical folding (Infante et al., 2015a), shape abnormalities (Sowell et al., 2002), increased cortical thickness (Sowell et al., 2008b; Yang et al., 2012), and altered developmental trajectory of posterior parietal regions (Lebel et al. (2012). This reasonably strong evidence of structural abnormalities in the parietal lobe among individuals with FASD may help to explain the aberrant BOLD response in the inferior parietal lobule and disrupted functional connectivity with PPC regions in and outside of the fronto-parietal networks.

4.5 Limitations

Potential limitations of the present study must be noted. The majority of children in the AE group met criteria for at least one psychiatric diagnosis. ADHD was the most common diagnosis in the sample, with 11 (61 %) children meeting diagnostic criteria. It is possible that the abnormal activation and functional connectivity patterns observed in the present study were due to comorbid psychopathology rather than specifically to heavy prenatal alcohol exposure. However, it should also be noted that previous studies have also reported increased rates of psychopathology, such as ADHD, in youth prenatally exposed to alcohol (Fryer, McGee, Matt, Riley, & Mattson, 2007; Ware et al., 2013).

Thus, excluding individuals who met criteria for a psychiatric disorder may have diminished the representativeness of the present sample. Additionally, doing so may have limited the generalizability of the present results to only apply to children who have been least affected by prenatal alcohol exposure. Another limitation to consider is that psychotropic medications may have impacted cerebral blood flow, contributing to the altered BOLD signals that were observed. While primary caregivers were asked to refrain from giving participants any psychoactive medication (e.g., methylphenidate) on the day of scanning, it was not possible or ethical to require abstinence for inclusion in the present investigation. Accordingly, three children in the AE group took psychotropic medication on the same day of their appointment, prior to their scan time. Post hoc analyses indicated that results did not significantly change if data provided by these three children were excluded from analyses; however, it is nonetheless possible that the effect sizes or other statistics may have been impacted.

Interpretation of "negative" percent BOLD signal change must be acknowledged as a potential limitation. There are a number of reasons that could explain the negative BOLD signal, including neural inhibition, vasoconstriction (Devor et al., 2007), and/or non-modeled events contained within the implicit baseline. These potential alternative explanations make interpretation of findings more challenging; however, at this point the mechanisms underlying this finding remain controversial and require further study (Ma et al., 2016).

Another important consideration in the present study is the use of ROIs for the evaluation of white matter integrity. By using ROI-based analyses, results were restricted to the regions chosen based on the a priori hypotheses. As a result, this approach was not

able to detect biologically meaningful differences outside of the predefined ROIs. However, an advantage of this approach is that it reduces the possibility of Type I error by limiting the number of statistical tests. It also increases power to detect group differences. Because the use of multimodal imaging is relatively new and limited in FASD, one of the goals of this study was to take a first step toward determining if there is any relation between the BOLD response to SWM and white matter integrity. Thus, despite the limitations of this approach, ROI-based analysis was nonetheless an ideal strategy for the present investigation.

Finally, although overall accuracy for the SWM trials was relatively high in the AE group (83.41%), this performance was significantly lower than the CON group (90.56%). Thus, it is possible that performance differences may have impacted the fMRI results. However, the clusters that showed significant differences in activation between groups remained significant after accounting for behavioral performance in post hoc analyses.

4.6 Future Research Directions

Replication of these findings with a larger sample size would increase the generalizability of the results. Future studies with a larger sample size should examine the potential role that psychiatric disorders (e.g., ADHD) may play in the brain mechanisms of children prenatally exposed to alcohol. The multimodal imaging approach and data analyses used in the current study were appropriate given its exploratory nature and available sample size. However, given recent advances in multimodal imaging techniques, future research with a larger sample size should use more precise techniques to study brain function and structure relations in individuals with heavy prenatal alcohol

exposure. For example, future studies could use fMRI in combination with DTI probabilistic tractography to study the functional and structural integrity of the fronto-parietal network in children affected by gestational exposure to alcohol. Multimodal fusion applications may also be a promising avenue for future research (Sui, Huster, Yu, Segall, & Calhoun, 2014). Furthermore, dividing the SLF into smaller subcomponents in future studies may lead to an increased understanding of how this large white matter tract is impacted by prenatal alcohol exposure (Schmahmann et al., 2007). Future work may also investigate white matter integrity in the subcomponents of this tract.

4.7 Summary and Conclusions

Overall findings suggest that both localized alterations in neural activity, aberrant fronto-parietal network synchrony, and poor coordination of neural responses with regions outside of this network may help explain SWM deficits in individuals with a history of heavy prenatal alcohol exposure. The present study extends prior work reporting spatial working memory deficits in FASD. Although behavioral data suggested that participants understood the task and were engaged, children in the AE group performed worse than children in the CON group in the SWM condition. Beyond the behavioral performance, results from this study revealed differences in neural activity in response to the demands of SWM. These differences may have been the result of increased neural recruitment by the AE group when performing the less challenging vigilance condition of the task. This interpretation is consistent with sustained attention deficits previously reported in FASD (Coles et al., 2002; Glass et al., 2014a; Infante et al., 2015b). The current study also expands on previous findings by examining functional connectivity during a SWM task. This is the first known study to use PPI to examine

task-based functional connectivity in children with FASD. Results showed altered fronto-parietal network connectivity during SWM, and suggested that children prenatally exposed to alcohol may have struggled to update spatial information necessary for successful completion of the task. This may have been driven by a reliance on posterior regions involving the parietal and occipital cortices. Disruption in the functional connectivity between task-related regions may have been related to alterations in top-down control mechanisms and/or ineffective inhibition of posterior visual processing areas required for successful task performance. No significant groups differences were noted with respect to white matter integrity in the SLF or the GNN. These findings suggest that the integrity of fronto-parietal white matter pathways cannot explain functional abnormalities during performance of a SMW task.

In conclusion, the present study adds to the growing body of research on the neurobiological impact of gestational exposure to alcohol, and advances understanding of the mechanisms underlying cognitive deficits in FASD. Additionally, although further research is needed in this area, this study may help identify potential neurobiological markers of intervention effectiveness. Further research in this population using multimodal imaging is now needed to better understand the pathophysiology of cognitive deficits as result of prenatal alcohol exposure. A better understanding of the neural mechanisms that lead to working memory impairments in children with FASD could lead to the development of targeted, and more effective interventions to ameliorate these deficits.

REFERENCES

Ackerman, C. M., & Courtney, S. M. (2012). Spatial relations and spatial locations are dissociated within prefrontal and parietal cortex. *Journal of Neurophysiology, 108*(9), 2419-2429. doi:10.1152/jn.01024.2011

Adler, C. M., Sax, K. W., Holland, S. K., Schmithorst, V., Rosenberg, L., & Strakowski, S. M. (2001). Changes in neuronal activation with increasing attention demand in healthy volunteers: an fMRI study. *Synapse, 42*(4), 266-272. doi:10.1002/syn.1112

Alexander, A. L., Lee, J. E., Lazar, M., & Field, A. S. (2007). Diffusion tensor imaging of the brain. *Neurotherapeutics, 4*(3), 316-329. doi:10.1016/j.nurt.2007.05.011

American Academy of Pediatrics, Committee on Substance Abuse and Committee on Children With Disabilities. (2000). Fetal alcohol syndrome and alcohol-related neurodevelopmental disorders. *Pediatrics, 106*(2 Pt 1), 358-361.

Andersson, J. L., Jenkinson, M., & Smith, S. (2007a). *Non-linear optimisation*. Retrieved from http://fsl.fmrib.ox.ac.uk/analysis/techrep/tr07ja1/tr07ja1.pdf

Andersson, J. L., Jenkinson, M., & Smith, S. (2007b). *Non-linear registration, aka Spatial normalization*. Retrieved from https://www.fmrib.ox.ac.uk/analysis/techrep/tr07ja2/tr07ja2.pdf

Andersson, J. L., Skare, S., & Ashburner, J. (2003). How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. *Neuroimage, 20*(2), 870-888. doi:10.1016/S1053-8119(03)00336-7

Aragon, A. S., Kalberg, W. O., Buckley, D., Barela-Scott, L. M., Tabachnick, B. G., & May, P. A. (2008). Neuropsychological study of FASD in a sample of American Indian children: processing simple versus complex information. *Alcoholism: Clinical and Experimental Research, 32*(12), 2136-2148. doi:10.1111/j.1530-0277.2008.00802.x

Archibald, S. L., Fennema-Notestine, C., Gamst, A., Riley, E. P., Mattson, S. N., & Jernigan, T. L. (2001). Brain dysmorphology in individuals with severe prenatal alcohol exposure. *Developmental Medicine and Child Neurology, 43*(3), 148-154.

Arfanakis, K., Cordes, D., Haughton, V. M., Moritz, C. H., Quigley, M. A., & Meyerand, M. E. (2000). Combining independent component analysis and correlation analysis to probe interregional connectivity in fMRI task activation datasets. *Magnetic Resonance Imaging, 18*(8), 921-930.

Arlinghaus, L. R., Thornton-Wells, T. A., Dykens, E. M., & Anderson, A. W. (2011). Alterations in diffusion properties of white matter in Williams syndrome. *Magnetic Resonance Imaging, 29*(9), 1165-1174. doi:10.1016/j.mri.2011.07.012

Astley, S. J. (2004). *Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit diagnostic code*. Retrieved from: https://depts.washington.edu/fasdpn/htmls/4-digit-code.htm

Astley, S. J., Aylward, E. H., Olson, H. C., Kerns, K., Brooks, A., Coggins, T. E., Davies, J., Dorn, S., Gendler, B., Jirikowic, T., Kraegel, P., Maravilla, K., & Richards, T. (2009). Magnetic resonance imaging outcomes from a comprehensive magnetic resonance study of children with fetal alcohol spectrum disorders. *Alcoholism: Clinical and Experimental Research, 33*(10), 1671-1689. doi:10.1111/j.1530-0277.2009.01004.x

Baddeley, A. (1986). *Working memory*. Oxford, UK: Oxford University Press.

Baddeley, A. (1992). Working memory. *Science, 255*(5044), 556-559.

Baddeley, A. (2000). The episodic buffer: a new component of working memory? *Trends in Cognitive Sciences, 4*(11), 417-423. doi:10.1016/S1364-6613(00)01538-2

Baddeley, A., & Hitch, G. (1974). Working Memory. In G. H. Bower (Ed.), *The psychology of learning and motivation: Advances in research and theory* (Vol. 8, pp. 47-89). New York: Academic Press.

Barch, D. M., & Yarkoni, T. (2013). Introduction to the special issue on reliability and replication in cognitive and affective neuroscience research. *Cognitive, Affective & Behavioral Neuroscience, 13*(4), 687-689. doi:10.3758/s13415-013-0201-7

Barnea-Goraly, N., Menon, V., Eckert, M., Tamm, L., Bammer, R., Karchemskiy, A., Dant, C. C., & Reiss, A. L. (2005). White matter development during childhood and adolescence: a cross-sectional diffusion tensor imaging study. *Cerebral Cortex, 15*(12), 1848-1854. doi:10.1093/cercor/bhi062

Basser, P. J., & Jones, D. K. (2002). Diffusion-tensor MRI: theory, experimental design and data analysis - a technical review. *NMR in Biomedicine, 15*(7-8), 456-467. doi:10.1002/nbm.783

Basser, P. J., & Pierpaoli, C. (1996). Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *Journal of Magnetic Resonance. Series B, 111*(3), 209-219. doi: 10.1016/j.jmr.2011.09.022

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR in Biomedicine, 15*(7-8), 435-455. doi:10.1002/nbm.782

Behrens, T. E., Woolrich, M. W., Jenkinson, M., Johansen-Berg, H., Nunes, R. G., Clare, S., Matthews, P. M., Brady, J. M., & Smith, S. M. (2003). Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magnetic Resonance in Medicine, 50*(5), 1077-1088. doi:10.1002/mrm.10609

Bertrand, J., Floyd, R. L., Weber, M. K., O'Connor, M., Riley, E. P., Johnson, K. A., Cohen, D. E., & the National Task Force on FAS/FAE. (2004). Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis. Atlanta, GA: Centers for Disease Control and Prevention. Retrieved from http://www.cdc.gov/ncbddd/fasd/documents/fas_guidelines_accessible.pdf

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine, 34*(4), 537-541. doi:10.1002/mrm.1910340409

Bode, M. K., Mattila, M. L., Kiviniemi, V., Rahko, J., Moilanen, I., Ebeling, H., Tervonen, O., & Nikkinen, J. (2011). White matter in autism spectrum disorders - evidence of impaired fiber formation. *Acta Radiologica, 52*(10), 1169-1174. doi:10.1258/ar.2011.110197

Bookheimer, S. Y., & Sowell, E. R. (2005). Brain imaging in FAS: commentary on the article by Malisza et al. *Pediatric Research, 58*(6), 1148-1149. doi:10.1203/01.pdr.0000188720.59781.b3

Bressler, D., Spotswood, N., & Whitney, D. (2007). Negative BOLD fMRI response in the visual cortex carries precise stimulus-specific information. *PloS One, 2*(5), e410. doi:10.1371/journal.pone.0000410

Burden, M. J., Jacobson, S. W., & Jacobson, J. L. (2005a). Relation of prenatal alcohol exposure to cognitive processing speed and efficiency in childhood. *Alcoholism: Clinical and Experimental Research, 29*(8), 1473-1483. doi:10.1097/01.alc.0000175036.34076.a0

Burden, M. J., Jacobson, S. W., Sokol, R. J., & Jacobson, J. L. (2005b). Effects of prenatal alcohol exposure on attention and working memory at 7.5 years of age. *Alcoholism: Clinical and Experimental Research, 29*(3), 443-452.

Carmichael Olson, H., Feldman, J. J., Streissguth, A. P., Sampson, P. D., & Bookstein, F. L. (1998). Neuropsychological deficits in adolescents with fetal alcohol syndrome: clinical findings. *Alcoholism: Clinical and Experimental Research, 22*(9), 1998-2012.

Casey, B. J., Giedd, J. N., & Thomas, K. M. (2000). Structural and functional brain development and its relation to cognitive development. *Biological Psychology, 54*(1-3), 241-257. doi:10.1016/S0301-0511(00)00058-2

Centers for Disease Control and Prevention. (2015). *Alcohol Use and Binge Drinking Among Women of Childbearing Age — United States, 2011–2013*.

Cheng, Y., Chou, K. H., Chen, I. Y., Fan, Y. T., Decety, J., & Lin, C. P. (2010). Atypical development of white matter microstructure in adolescents with autism spectrum disorders. *Neuroimage, 50*(3), 873-882. doi:10.1016/j.neuroimage.2010.01.011

Cisler, J. M., Bush, K., & Steele, J. S. (2014). A comparison of statistical methods for detecting context-modulated functional connectivity in fMRI. *Neuroimage, 84*, 1042-1052. doi:10.1016/j.neuroimage.2013.09.018

Clarren, S. K., Carmichael-Olson, H., Clarren, S. G. B., & Astley, S. J. (2000). A child with fetal alcohol syndrome: The interdisciplinary team diagnostic process *M.J. Guralnick (Ed.), Interdisciplinary Clinical Assessment of Young Children with Developmental Disabilities.* Baltimore, MD: Paul H. Brookes.

Coles, C. D., & Li, Z. (2011). Functional neuroimaging in the examination of effects of prenatal alcohol exposure. *Neuropsychology Review, 21*(2), 119-132. doi:10.1007/s11065-011-9165-y

Coles, C. D., Platzman, K. A., Lynch, M. E., & Freides, D. (2002). Auditory and visual sustained attention in adolescents prenatally exposed to alcohol. *Alcoholism: Clinical and Experimental Research, 26*(2), 263-271. doi:10.1111/j.1530-0277.2002.tb02533.x

Connor, P. D., Sampson, P. D., Bookstein, F. L., Barr, H. M., & Streissguth, A. P. (2000). Direct and indirect effects of prenatal alcohol damage on executive function. *Developmental Neuropsychology, 18*(3), 331-354. doi:10.1207/S1532694204

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research, 29*(3), 162-173.

Cox, R. W., & Jesmanowicz, A. (1999). Real-time 3D image registration for functional MRI. *Magnetic Resonance in Medicine, 42*(6), 1014-1018. doi:10.1002/(SICI)1522-2594(199912)42:6<1014::AID-MRM4>3.0.CO;2-F

Curtis, C. E. (2006). Prefrontal and parietal contributions to spatial working memory. *Neuroscience, 139*(1), 173-180. doi:10.1016/j.neuroscience.2005.04.070

Darki, F., & Klingberg, T. (2015). The role of fronto-parietal and fronto-striatal networks in the development of working memory: a longitudinal study. *Cerebral Cortex, 25*(6), 1587-1595. doi:10.1093/cercor/bht352

Davenport, N. D., Karatekin, C., White, T., & Lim, K. O. (2010). Differential fractional anisotropy abnormalities in adolescents with ADHD or schizophrenia. *Psychiatry Research, 181*(3), 193-198. doi:10.1016/j.pscychresns.2009.10.012

Deco, G., Jirsa, V. K., & McIntosh, A. R. (2011). Emerging concepts for the dynamical organization of resting-state activity in the brain. *Nature Reviews: Neuroscience, 12*(1), 43-56. doi:10.1038/nrn2961

Demetriou, A., Christou, C., Spanoudis, G., & Platsidou, M. (2002). The development of mental processing: efficiency, working memory, and thinking. *Monographs of the Society for Research in Child Development, 67*(1), i-viii, 1-155; discussion 156.

Devor, A., Tian, P., Nishimura, N., Teng, I. C., Hillman, E. M., Narayanan, S. N., Ulbert, I., Boas, D. A., Kleinfeld, D., & Dale, A. M. (2007). Suppressed neuronal activity and concurrent arteriolar vasoconstriction may explain negative blood oxygenation level-dependent signal. *Journal of Neuroscience, 27*(16), 4452-4459. doi:10.1523/JNEUROSCI.0134-07.2007

Donald, K. A., Roos, A., Fouche, J. P., Koen, N., Howells, F. M., Woods, R. P., Zar, H. J., Narr, K. L., & Stein, D. J. (2015). A study of the effects of prenatal alcohol exposure on white matter microstructural integrity at birth. *Acta Neuropsychiatrica. Officieel Wetenschappelijk Orgaan van Het IGBP (Interdisciplinair Genootschap voor Biologische Psychiatrie), 27*(4), 197-205. doi:10.1017/neu.2015.35

Dosenbach, N. U., Fair, D. A., Cohen, A. L., Schlaggar, B. L., & Petersen, S. E. (2008). A dual-networks architecture of top-down control. *Trends in Cognitive Sciences, 12*(3), 99-105. doi:10.1016/j.tics.2008.01.001

Elliott, C. D. (2007). *Differential ability scales* (Second ed.). San Antonio, TX: Harcourt Assessment.

Ernst, M., Torrisi, S., Balderston, N., Grillon, C., & Hale, E. A. (2015). fMRI functional connectivity applied to adolescent neurodevelopment. *Annual Review of Clinical Psychology, 11*, 361-377. doi:10.1146/annurev-clinpsy-032814-112753

Filley, C. M. (2010). White matter: organization and functional relevance. *Neuropsychology Review, 20*(2), 158-173. doi:10.1007/s11065-010-9127-9

Flak, A. L., Su, S., Bertrand, J., Denny, C. H., Kesmodel, U. S., & Cogswell, M. E. (2014). The association of mild, moderate, and binge prenatal alcohol exposure and child neuropsychological outcomes: a meta-analysis. *Alcoholism: Clinical and Experimental Research, 38*(1), 214-226. doi:10.1111/acer.12214

Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., & Noll, D. C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magnetic Resonance in Medicine, 33*(5), 636-647. doi:10.1002/mrm.1910330508

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America, 102*(27), 9673-9678. doi:10.1073/pnas.0504136102

Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E., & Dolan, R. J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage, 6*(3), 218-229. doi:10.1006/nimg.1997.0291

Friston, K. J., Williams, S., Howard, R., Frackowiak, R. S., & Turner, R. (1996). Movement-related effects in fMRI time-series. *Magnetic Resonance in Medicine, 35*(3), 346-355. doi:10.1002/mrm.1910350312

Fryer, S. L., McGee, C. L., Matt, G. E., Riley, E. P., & Mattson, S. N. (2007). Evaluation of psychopathological conditions in children with heavy prenatal alcohol exposure. *Pediatrics, 119*(3), e733-741. doi:10.1542/peds.2006-1606

Fryer, S. L., Schweinsburg, B. C., Bjorkquist, O. A., Frank, L. R., Mattson, S. N., Spadoni, A. D., & Riley, E. P. (2009). Characterization of white matter microstructure in fetal alcohol spectrum disorders. *Alcoholism: Clinical and Experimental Research, 33*(3), 514-521. doi:10.1111/j.1530-0277.2008.00864.x

Gautam, P., Lebel, C., Narr, K. L., Mattson, S. N., May, P. A., Adnams, C. M., Riley, E. P., Jones, K. L., Kan, E. C., & Sowell, E. R. (2015). Volume changes and brain-behavior relationships in white matter and subcortical gray matter in children with prenatal alcohol exposure. *Human Brain Mapping, 36*(6), 2318-2329. doi:10.1002/hbm.22772

Gautam, P., Nunez, S. C., Narr, K. L., Kan, E. C., & Sowell, E. R. (2014). Effects of prenatal alcohol exposure on the development of white matter volume and change in executive function. *Neuroimage Clin, 5*, 19-27. doi:10.1016/j.nicl.2014.05.010

Gazzaley, A., Cooney, J. W., Rissman, J., & D'Esposito, M. (2005). Top-down suppression deficit underlies working memory impairment in normal aging. *Nature Neuroscience, 8*(10), 1298-1300. doi:10.1038/nn1543

Gazzaley, A., & Nobre, A. C. (2012). Top-down modulation: bridging selective attention and working memory. *Trends in Cognitive Sciences, 16*(2), 129-135. doi:10.1016/j.tics.2011.11.014

Geier, C. F., Garver, K., Terwilliger, R., & Luna, B. (2009). Development of working memory maintenance. *Journal of Neurophysiology, 101*(1), 84-99. doi:10.1152/jn.90562.2008

Glahn, D. C., Kim, J., Cohen, M. S., Poutanen, V. P., Therman, S., Bava, S., Van Erp, T. G., Manninen, M., Huttunen, M., Lonnqvist, J., Standertskjold-Nordenstam, C. G., & Cannon, T. D. (2002). Maintenance and manipulation in spatial working memory: dissociations in the prefrontal cortex. *Neuroimage, 17*(1), 201-213. doi:10.1006/nimg.2002.1161

Glass, L., Graham, D. M., Deweese, B. N., Jones, K. L., Riley, E. P., & Mattson, S. N. (2014a). Correspondence of parent report and laboratory measures of inattention and hyperactivity in children with heavy prenatal alcohol exposure. *Neurotoxicology and Teratology, 42*, 43-50. doi:10.1016/j.ntt.2014.01.007

Glass, L., Ware, A. L., & Mattson, S. N. (2014b). Neurobehavioral, neurologic, and neuroimaging characteristics of fetal alcohol spectrum disorders. *Handbook of Clinical Neurology, 125*, 435-462. doi:10.1016/B978-0-444-62619-6.00025-2

Green, C. R., Mihic, A. M., Nikkel, S. M., Stade, B. C., Rasmussen, C., Munoz, D. P., & Reynolds, J. N. (2009). Executive function deficits in children with fetal alcohol spectrum disorders (FASD) measured using the Cambridge Neuropsychological Tests Automated Battery (CANTAB). *Journal of Child Psychology and Psychiatry and Allied Disciplines, 50*(6), 688-697. doi:10.1111/j.1469-7610.2008.01990.x

Hemington, K. S., & Reynolds, J. N. (2014). Electroencephalographic correlates of working memory deficits in children with Fetal Alcohol Spectrum Disorder using a single-electrode pair recording device. *Clinical Neurophysiology*. doi:10.1016/j.clinph.2014.03.025

Hoeft, F., Barnea-Goraly, N., Haas, B. W., Golarai, G., Ng, D., Mills, D., Korenberg, J., Bellugi, U., Galaburda, A., & Reiss, A. L. (2007). More is not always better: increased fractional anisotropy of superior longitudinal fasciculus associated with poor visuospatial abilities in Williams syndrome. *Journal of Neuroscience, 27*(44), 11960-11965. doi:10.1523/JNEUROSCI.3591-07.2007

Hollingshead, A. A. (1975). *Four-factor index of social status*. Yale University. New Haven, CT.

Infante, M. A., Moore, E. M., Bischoff-Grethe, A., Migliorini, R., Mattson, S. N., & Riley, E. P. (2015a). Atypical cortical gyrification in adolescents with histories of heavy prenatal alcohol exposure. *Brain Research, 1624*, 446-454. doi:10.1016/j.brainres.2015.08.002

Infante, M. A., Moore, E. M., Nguyen, T. T., Fourligas, N., Mattson, S. N., & Riley, E. P. (2015b). Objective assessment of ADHD core symptoms in children with heavy prenatal alcohol exposure. *Physiology and Behavior, 148*, 45-50. doi:10.1016/j.physbeh.2014.10.014

Jacobson, J. L., Jacobson, S. W., Sokol, R. J., & Ager, J. W., Jr. (1998). Relation of maternal age and pattern of pregnancy drinking to functionally significant cognitive deficit in infancy. *Alcoholism: Clinical and Experimental Research, 22*(2), 345-351. doi:10.1111/j.1530-0277.1998.tb03659.x

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage, 17*(2), 825-841. doi:10.1006/nimg.2002.1132

Jenkinson, M., Beckmann, C. F., Behrens, T. E., Woolrich, M. W., & Smith, S. M. (2012). Fsl. *Neuroimage, 62*(2), 782-790. doi:10.1016/j.neuroimage.2011.09.015

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis, 5*(2), 143-156. doi:10.1016/S1361-8415(01)00036-6

Jones, K. L., Robinson, L. K., Bakhireva, L. N., Marintcheva, G., Storojev, V., Strahova, A., Sergeevskaya, S., Budantseva, S., Mattson, S. N., Riley, E. P., & Chambers, C. D. (2006). Accuracy of the diagnosis of physical features of fetal alcohol syndrome by pediatricians after specialized training. *Pediatrics, 118*(6), e1734-1738. doi:10.1542/peds.2006-1037

Jones, K. L., & Smith, D. W. (1973). Recognition of the fetal alcohol syndrome in early infancy. *Lancet, 302*(7836), 999-1001. doi:10.1016/S0140-6736(73)91092-1

Jones, K. L., Smith, D. W., Ulleland, C. N., & Streissguth, P. (1973). Pattern of malformation in offspring of chronic alcoholic mothers. *Lancet, 1*(7815), 1267-1271. doi:10.1016/S0140-6736(73)91291-9

Kerns, K. A., Don, A., Mateer, C. A., & Streissguth, A. P. (1997). Cognitive deficits in nonretarded adults with fetal alcohol syndrome. *Journal of Learning Disabilities, 30*(6), 685-693. doi:10.1177/002221949703000612

Kimura, D. (1963). Right temporal-lobe damage. Perception of unfamiliar stimuli after damage. *Archives of Neurology, 8*, 264-271. doi:10.1001/archneur.1963.00460030048004

Kindermann, S. S., Brown, G. G., Zorrilla, L. E., Olsen, R. K., & Jeste, D. V. (2004). Spatial working memory among middle-aged and older patients with schizophrenia and volunteers using fMRI. *Schizophrenia Research, 68*(2-3), 203-216. doi:10.1016/j.schres.2003.08.010

Klingberg, T. (2006). Development of a superior frontal-intraparietal network for visuo-spatial working memory. *Neuropsychologia, 44*(11), 2171-2177. doi:10.1016/j.neuropsychologia.2005.11.019

Klingberg, T., Forssberg, H., & Westerberg, H. (2002). Increased brain activity in frontal and parietal cortex underlies the development of visuospatial working memory capacity during childhood. *Journal of Cognitive Neuroscience, 14*(1), 1-10. doi:10.1162/089892902317205276

Koch, G., Oliveri, M., Torriero, S., Carlesimo, G. A., Turriziani, P., & Caltagirone, C. (2005). rTMS evidence of different delay and decision processes in a fronto-parietal neuronal network activated during spatial working memory. *Neuroimage, 24*(1), 34-39. doi:10.1016/j.neuroimage.2004.09.042

Koenigs, M., Barbey, A. K., Postle, B. R., & Grafman, J. (2009). Superior parietal cortex is critical for the manipulation of information in working memory. *Journal of Neuroscience, 29*(47), 14980-14986. doi:10.1523/JNEUROSCI.3706-09.2009

Kwon, H., Reiss, A. L., & Menon, V. (2002). Neural basis of protracted developmental changes in visuo-spatial working memory. *Proceedings of the National Academy of Sciences of the United States of America, 99*(20), 13336-13341. doi:10.1073/pnas.162486399

Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weisskoff, R. M., Poncelet, B. P., Kennedy, D. N., Hoppel, B. E., Cohen, M. S., Turner, R., Cheng, H., Brady, T. J., & Rosen, B. R. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Sciences of the United States of America, 89*(12), 5675-5679.

Le Bihan, D., Mangin, J. F., Poupon, C., Clark, C. A., Pappata, S., Molko, N., & Chabriat, H. (2001). Diffusion tensor imaging: concepts and applications. *Journal of Magnetic Resonance Imaging, 13*(4), 534-546. doi:10.1002/jmri.1076

Lebel, C., Mattson, S. N., Riley, E. P., Jones, K. L., Adnams, C. M., May, P. A., Bookheimer, S. Y., O'Connor, M. J., Narr, K. L., Kan, E., Abaryan, Z., & Sowell, E. R. (2012). A longitudinal study of the long-term consequences of drinking during pregnancy: heavy in utero alcohol exposure disrupts the normal processes of brain development. *Journal of Neuroscience, 32*(44), 15243-15251. doi:10.1523/JNEUROSCI.1161-12.2012

Lebel, C., Rasmussen, C., Wyper, K., Walker, L., Andrew, G., Yager, J., & Beaulieu, C. (2008). Brain diffusion abnormalities in children with fetal alcohol spectrum disorder. *Alcoholism: Clinical and Experimental Research, 32*(10), 1732-1740. doi:10.1111/j.1530-0277.2008.00750.x

Lebel, C., Roussotte, F., & Sowell, E. R. (2011). Imaging the impact of prenatal alcohol exposure on the structure of the developing human brain. *Neuropsychology Review, 21*(2), 102-118. doi:10.1007/s11065-011-9163-0

Lemoine, P., Harousseau, H., Borteyru, J. P., & Menuet, J. C. (1968). Les enfants de parents alcooliques: Anomalies observees: A propos de 127 Cas. *Ouest Médical, 21*, 476-482.

Li, L., Coles, C. D., Lynch, M. E., & Hu, X. (2009). Voxelwise and skeleton-based region of interest analysis of fetal alcohol syndrome and fetal alcohol spectrum disorders in young adults. *Human Brain Mapping, 30*(10), 3265-3274. doi:10.1002/hbm.20747

Logothetis, N. K. (2008). What we can do and what we cannot do with fMRI. *Nature, 453*(7197), 869-878. doi:10.1038/nature06976

Lowe, M. J., Dzemidzic, M., Lurito, J. T., Mathews, V. P., & Phillips, M. D. (2000). Correlations in low-frequency BOLD fluctuations reflect cortico-cortical connections. *Neuroimage, 12*(5), 582-587. doi:10.1006/nimg.2000.0654

Lowe, M. J., Mock, B. J., & Sorenson, J. A. (1998). Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. *Neuroimage, 7*(2), 119-132. doi:10.1006/nimg.1997.0315

Luna, B., Garver, K. E., Urban, T. A., Lazar, N. A., & Sweeney, J. A. (2004). Maturation of cognitive processes from late childhood to adulthood. *Child Development, 75*(5), 1357-1372. doi:10.1111/j.1467-8624.2004.00745.x

Ma, X., Coles, C. D., Lynch, M. E., Laconte, S. M., Zurkiya, O., Wang, D., & Hu, X. (2005). Evaluation of corpus callosum anisotropy in young adults with fetal alcohol syndrome according to diffusion tensor imaging. *Alcoholism: Clinical and Experimental Research, 29*(7), 1214-1222. doi:10.1097/01.ALC.0000171934.22755.6D

Ma, Z., Cao, P., Sun, P., Zhao, L., Li, L., Tong, S., Lu, Y., Yan, Y., Chen, Y., & Chai, X. (2016). Inverted optical intrinsic response accompanied by decreased cerebral blood flow are related to both neuronal inhibition and excitation. *Scientific Reports, 6*, 21627. doi:10.1038/srep21627

Maier, S. E., & West, J. R. (2001). Drinking patterns and alcohol-related birth defects. *Alcohol Res Health, 25*(3), 168-174.

Malisza, K. L., Allman, A. A., Shiloff, D., Jakobson, L., Longstaffe, S., & Chudley, A. E. (2005). Evaluation of spatial working memory function in children and adults with fetal alcohol spectrum disorders: a functional magnetic resonance imaging study. *Pediatric Research, 58*(6), 1150-1157. doi:10.1203/01.pdr.0000185479.92484.a1

Malisza, K. L., Buss, J. L., Bolster, R. B., de Gervai, P. D., Woods-Frohlich, L., Summers, R., Clancy, C. A., Chudley, A. E., & Longstaffe, S. (2012). Comparison of spatial working memory in children with prenatal alcohol exposure and those diagnosed with ADHD; A functional magnetic resonance imaging study. *Journal of Neurodevelopmental Disorders, 4*(1), 12. doi:10.1186/1866-1955-4-12

Mattson, S. N., Crocker, N., & Nguyen, T. T. (2011). Fetal alcohol spectrum disorders: neuropsychological and behavioral features. *Neuropsychology Review, 21*(2), 81-101. doi:10.1007/s11065-011-9167-9

Mattson, S. N., Foroud, T., Sowell, E. R., Jones, K. L., Coles, C. D., Fagerlund, A., Autti-Ramo, I., May, P. A., Adnams, C. M., Konovalova, V., Wetherill, L., Arenson, A. D., Barnett, W. K., Riley, E. P., & Collaborative Initiative on Fetal Alcohol Spectrum Disorders. (2010a). Collaborative initiative on fetal alcohol spectrum disorders: methodology of clinical projects. *Alcohol, 44*(7-8), 635-641. doi:10.1016/j.alcohol.2009.08.005

Mattson, S. N., Riley, E. P., Gramling, L., Delis, D. C., & Jones, K. L. (1998). Neuropsychological comparison of alcohol-exposed children with or without physical features of fetal alcohol syndrome. *Neuropsychology, 12*(1), 146-153. doi:10.1037/0894-4105.12.1.146

Mattson, S. N., Roesch, S. C., Fagerlund, A., Autti-Ramo, I., Jones, K. L., May, P. A., Adnams, C. M., Konovalova, V., Riley, E. P., & Collaborative Initiative on Fetal Alcohol Spectrum, Disorders. (2010b). Toward a neurobehavioral profile of fetal alcohol spectrum disorders. *Alcoholism: Clinical and Experimental Research, 34*(9), 1640-1650. doi:10.1111/j.1530-0277.2010.01250.x

Mattson, S. N., Roesch, S. C., Glass, L., Deweese, B. N., Coles, C. D., Kable, J. A., May, P. A., Kalberg, W. O., Sowell, E. R., Adnams, C. M., Jones, K. L., Riley, E. P., & Collaborative Initiative on Fetal Alcohol Spectrum Disorders. (2013). Further development of a neurobehavioral profile of fetal alcohol spectrum disorders. *Alcoholism: Clinical and Experimental Research, 37*(3), 517-528. doi:10.1111/j.1530-0277.2012.01952.x

May, P. A., Baete, A., Russo, J., Elliott, A. J., Blankenship, J., Kalberg, W. O., Buckley, D., Brooks, M., Hasken, J., Abdul-Rahman, O., Adam, M. P., Robinson, L. K., Manning, M., & Hoyme, H. E. (2014). Prevalence and characteristics of fetal alcohol spectrum disorders. *Pediatrics, 134*(5), 855-866. doi:10.1542/peds.2013-3319

May, P. A., & Gossage, J. P. (2011). Maternal risk factors for fetal alcohol spectrum disorders: not as simple as it might seem. *Alcohol Res Health, 34*(1), 15-26.

May, P. A., Gossage, J. P., Brooke, L. E., Snell, C. L., Marais, A. S., Hendricks, L. S., Croxford, J. A., & Viljoen, D. L. (2005). Maternal risk factors for fetal alcohol syndrome in the Western cape province of South Africa: a population-based study. *American Journal of Public Health, 95*(7), 1190-1199. doi:10.2105/AJPH.2003.037093

May, P. A., Gossage, J. P., Kalberg, W. O., Robinson, L. K., Buckley, D., Manning, M., & Hoyme, H. E. (2009). Prevalence and epidemiologic characteristics of FASD from various research methods with an emphasis on recent in-school studies. *Dev Disabil Res Rev, 15*(3), 176-192. doi:10.1002/ddrr.68

McCarthy, G., Blamire, A. M., Puce, A., Nobre, A. C., Bloch, G., Hyder, F., Goldman-Rakic, P., & Shulman, R. G. (1994). Functional magnetic resonance imaging of human prefrontal cortex activation during a spatial working memory task. *Proceedings of the National Academy of Sciences of the United States of America, 91*(18), 8690-8694.

McIntosh, A. R. (2000). Towards a network theory of cognition. *Neural Networks, 13*(8-9), 861-870. doi:10.1016/S0893-6080(00)00059-9

McLaren, D. G., Ries, M. L., Xu, G., & Johnson, S. C. (2012). A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. *Neuroimage, 61*(4), 1277-1286. doi:10.1016/j.neuroimage.2012.03.068

McNamara, T. K., Orav, E. J., Wilkins-Haug, L., & Chang, G. (2005). Risk during pregnancy--self-report versus medical record. *American Journal of Obstetrics and Gynecology, 193*(6), 1981-1985. doi:10.1016/j.ajog.2005.04.053

Moore, E. M., Migliorini, R., Infante, M. A., & Riley, E. P. (2014). Fetal Alcohol Spectrum Disorders: Recent Neuroimaging Findings. *Current Developmental Disorders Reports, 1*(3), 161-172. doi:10.1007/s40474-014-0020-8

Mori, S., Oishi, K., Jiang, H., Jiang, L., Li, X., Akhter, K., Hua, K., Faria, A. V., Mahmood, A., Woods, R., Toga, A. W., Pike, G. B., Neto, P. R., Evans, A., Zhang, J., Huang, H., Miller, M. I., van Zijl, P., & Mazziotta, J. (2008). Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *Neuroimage, 40*(2), 570-582. doi:10.1016/j.neuroimage.2007.12.035

Nagel, B. J., Herting, M. M., Maxwell, E. C., Bruno, R., & Fair, D. (2013). Hemispheric lateralization of verbal and spatial working memory during adolescence. *Brain and Cognition, 82*(1), 58-68. doi:10.1016/j.bandc.2013.02.007

Nagy, Z., Westerberg, H., & Klingberg, T. (2004). Maturation of white matter is associated with the development of cognitive functions during childhood. *Journal of Cognitive Neuroscience, 16*(7), 1227-1233. doi:10.1162/0898929041920441

Nee, D. E., & D'Esposito, M. (2015). Working Memory. In A. W. Toga (Ed.), *Brain Mapping: An Encyclopedic Reference* (Vol. 2, pp. 589-595): Elsevier.

Nelson, C. A., Monk, C. S., Lin, J., Carver, L. J., Thomas, K. M., & Truwit, C. L. (2000). Functional neuroanatomy of spatial working memory in children. *Developmental Psychology, 36*(1), 109-116. doi:10.1037/0012-1649.36.1.109

Norman, A. L., O'Brien, J. W., Spadoni, A. D., Tapert, S. F., Jones, K. L., Riley, E. P., & Mattson, S. N. (2013). A functional magnetic resonance imaging study of spatial working memory in children with prenatal alcohol exposure: contribution of familial history of alcohol use disorders. *Alcoholism: Clinical and Experimental Research, 37*(1), 132-140. doi:10.1111/j.1530-0277.2012.01880.x

O'Conaill, C. R., Malisza, K. L., Buss, J. L., Bolster, R. B., Clancy, C., de Gervai, P. D., Chudley, A. E., & Longstaffe, S. (2015). Visual search for feature conjunctions: an fMRI study comparing alcohol-related neurodevelopmental disorder (ARND) to ADHD. *Journal of Neurodevelopmental Disorders, 7*(1), 10. doi:10.1186/s11689-015-9106-9

O'Reilly, J. X., Woolrich, M. W., Behrens, T. E., Smith, S. M., & Johansen-Berg, H. (2012). Tools of the trade: psychophysiological interactions and functional connectivity. *Social Cognitive and Affective Neuroscience, 7*(5), 604-609. doi:10.1093/scan/nss055

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences of the United States of America, 87*(24), 9868-9872.

Ostby, Y., Tamnes, C. K., Fjell, A. M., & Walhovd, K. B. (2011). Morphometry and connectivity of the fronto-parietal verbal working memory network in development. *Neuropsychologia, 49*(14), 3854-3862. doi:10.1016/j.neuropsychologia.2011.10.001

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Human Brain Mapping, 25*(1), 46-59. doi:10.1002/hbm.20131

Paolozza, A., Rasmussen, C., Pei, J., Hanlon-Dearman, A., Nikkel, S. M., Andrew, G., McFarlane, A., Samdup, D., & Reynolds, J. N. (2014). Working memory and visuospatial deficits correlate with oculomotor control in children with fetal alcohol spectrum disorder. *Behavioural Brain Research, 263*, 70-79. doi:10.1016/j.bbr.2014.01.024

Peters, B. D., Szeszko, P. R., Radua, J., Ikuta, T., Gruner, P., DeRosse, P., Zhang, J. P., Giorgio, A., Qiu, D., Tapert, S. F., Brauer, J., Asato, M. R., Khong, P. L., James, A. C., Gallego, J. A., & Malhotra, A. K. (2012). White matter development in adolescence: diffusion tensor imaging and meta-analytic results. *Schizophrenia Bulletin, 38*(6), 1308-1317. doi:10.1093/schbul/sbs054

Pierce, D. R., & West, J. R. (1986). Blood alcohol concentration: a critical factor for producing fetal alcohol effects. *Alcohol, 3*(4), 269-272. doi:10.1016/0741-8329(86)90036-4

Pierpaoli, C., & Basser, P. J. (1996). Toward a quantitative assessment of diffusion anisotropy. *Magnetic Resonance in Medicine, 36*(6), 893-906. doi:10.1002/mrm.1910360612

Pulsifer, M. B. (1996). The neuropsychology of mental retardation. *Journal of the International Neuropsychological Society, 2*(2), 159-176. doi:10.1017/S1355617700001016

Quattlebaum, J. L., & O'Connor, M. J. (2013). Higher functioning children with prenatal alcohol exposure: is there a specific neurocognitive profile? *Child Neuropsychology, 19*(6), 561-578. doi:10.1080/09297049.2012.713466

Rasmussen, C., Soleimani, M., & Pei, J. (2011). Executive functioning and working memory deficits on the CANTAB among children with prenatal alcohol exposure. *Journal of Population Therapeutics and Clinical Pharmacology, 18*(1), e44-53.

Rottschy, C., Langner, R., Dogan, I., Reetz, K., Laird, A. R., Schulz, J. B., Fox, P. T., & Eickhoff, S. B. (2012). Modelling neural correlates of working memory: a coordinate-based meta-analysis. *Neuroimage, 60*(1), 830-846. doi:10.1016/j.neuroimage.2011.11.050

Roussotte, F. F., Rudie, J. D., Smith, L., O'Connor, M. J., Bookheimer, S. Y., Narr, K. L., & Sowell, E. R. (2012). Frontostriatal connectivity in children during working memory and the effects of prenatal methamphetamine, alcohol, and polydrug exposure. *Developmental Neuroscience, 34*(1), 43-57. doi:10.1159/000336242

Rychwalska, A. (2013). Understanding Cognition Through Functional Connectivity. In A. Nowak, K. Winkowska-Nowak, & D. Brée (Eds.), *Complex Human Dynamics* (pp. 21-34). Berlin: Springer

Rykhlevskaia, E., Gratton, G., & Fabiani, M. (2008). Combining structural and functional neuroimaging data for studying brain connectivity: a review. *Psychophysiology, 45*(2), 173-187. doi:10.1111/j.1469-8986.2007.00621.x

Santhanam, P., Coles, C. D., Li, Z., Li, L., Lynch, M. E., & Hu, X. (2011). Default mode network dysfunction in adults with prenatal alcohol exposure. *Psychiatry Research, 194*(3), 354-362. doi:10.1016/j.pscychresns.2011.05.004

Scherf, K. S., Sweeney, J. A., & Luna, B. (2006). Brain basis of developmental change in visuospatial working memory. *Journal of Cognitive Neuroscience, 18*(7), 1045-1058. doi:10.1162/jocn.2006.18.7.1045

Schmahmann, J. D., Pandya, D. N., Wang, R., Dai, G., D'Arceuil, H. E., de Crespigny, A. J., & Wedeen, V. J. (2007). Association fibre pathways of the brain: parallel observations from diffusion spectrum imaging and autoradiography. *Brain, 130*(Pt 3), 630-653. doi:10.1093/brain/awl359

Schweinsburg, A. D., Nagel, B. J., & Tapert, S. F. (2005). fMRI reveals alteration of spatial working memory networks across adolescence. *Journal of the International Neuropsychological Society, 11*(5), 631-644. doi:10.1017/S1355617705050757

Sen, P. N., & Basser, P. J. (2005). A model for diffusion in white matter in the brain. *Biophysical Journal, 89*(5), 2927-2938. doi:10.1529/biophysj.105.063016

Shaffer, D., Fisher, P., Lucas, C. P., Dulcan, M. K., & Schwab-Stone, M. E. (2000). NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. *Journal of the American Academy of Child and Adolescent Psychiatry, 39*(1), 28-38. doi:10.1097/00004583-200001000-00014

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping, 17*(3), 143-155. doi:10.1002/hbm.10062

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., Watkins, K. E., Ciccarelli, O., Cader, M. Z., Matthews, P. M., & Behrens, T. E. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage, 31*(4), 1487-1505. doi:10.1016/j.neuroimage.2006.02.024

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage, 23 Suppl 1*, S208-219. doi:10.1016/j.neuroimage.2004.07.051

Sowell, E. R., Johnson, A., Kan, E., Lu, L. H., Van Horn, J. D., Toga, A. W., O'Connor, M. J., & Bookheimer, S. Y. (2008a). Mapping white matter integrity and neurobehavioral correlates in children with fetal alcohol spectrum disorders. *Journal of Neuroscience, 28*(6), 1313-1319. doi:10.1523/JNEUROSCI.5067-07.2008

Sowell, E. R., Mattson, S. N., Kan, E., Thompson, P. M., Riley, E. P., & Toga, A. W. (2008b). Abnormal cortical thickness and brain-behavior correlation patterns in individuals with heavy prenatal alcohol exposure. *Cerebral Cortex, 18*(1), 136-144. doi:10.1093/cercor/bhm039

Sowell, E. R., Thompson, P. M., Mattson, S. N., Tessner, K. D., Jernigan, T. L., Riley, E. P., & Toga, A. W. (2002). Regional brain shape abnormalities persist into adolescence after heavy prenatal alcohol exposure. *Cerebral Cortex, 12*(8), 856-865. doi:10.1093/cercor/12.8.856

Spadoni, A. D., Bazinet, A. D., Fryer, S. L., Tapert, S. F., Mattson, S. N., & Riley, E. P. (2009). BOLD response during spatial working memory in youth with heavy prenatal alcohol exposure. *Alcoholism: Clinical and Experimental Research, 33*(12), 2067-2076. doi:10.1111/j.1530-0277.2009.01046.x

Spear, L. P. (2000). The adolescent brain and age-related behavioral manifestations. *Neuroscience and Biobehavioral Reviews, 24*(4), 417-463. doi:10.1016/S0149-7634(00)00014-2

Spencer-Smith, M., Ritter, B. C., Murner-Lavanchy, I., El-Koussy, M., Steinlin, M., & Everts, R. (2013). Age, sex, and performance influence the visuospatial working memory network in childhood. *Developmental Neuropsychology, 38*(4), 236-255. doi:10.1080/87565641.2013.784321

Spohr, H. L., Willms, J., & Steinhausen, H. C. (2007). Fetal alcohol spectrum disorders in young adulthood. *Journal of Pediatrics, 150*(2), 175-179, 179 e171. doi:10.1016/j.jpeds.2006.11.044

Streissguth, A. P., Bookstein, F. L., Barr, H. M., Sampson, P. D., O'Malley, K., & Young, J. K. (2004). Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. *Journal of Developmental and Behavioral Pediatrics, 25*(4), 228-238.

Streissguth, A. P., Sampson, P. D., & Barr, H. M. (1989). Neurobehavioral dose-response effects of prenatal alcohol exposure in humans from infancy to adulthood. *Annals of the New York Academy of Sciences, 562*, 145-158. doi:10.1111/j.1749-6632.1989.tb21013.x

Sui, J., Huster, R., Yu, Q., Segall, J. M., & Calhoun, V. D. (2014). Function-structure associations of the brain: evidence from multimodal connectivity and covariance studies. *Neuroimage, 102 Pt 1*, 11-23. doi:10.1016/j.neuroimage.2013.09.044

Tapert, S. F., Brown, G. G., Kindermann, S. S., Cheung, E. H., Frank, L. R., & Brown, S. A. (2001). fMRI measurement of brain dysfunction in alcohol-dependent young women. *Alcoholism: Clinical and Experimental Research, 25*(2), 236-245. doi:10.1111/j.1530-0277.2001.tb02204.x

Taylor, P. A., Jacobson, S. W., van der Kouwe, A., Molteno, C. D., Chen, G., Wintermark, P., Alhamud, A., Jacobson, J. L., & Meintjes, E. M. (2015). A DTI-based tractography study of effects on brain structure associated with prenatal alcohol exposure in newborns. *Human Brain Mapping, 36*(1), 170-186. doi:10.1002/hbm.22620

Thirion, B., Pinel, P., Meriaux, S., Roche, A., Dehaene, S., & Poline, J. B. (2007). Analysis of a large fMRI cohort: Statistical and methodological issues for group analyses. *Neuroimage, 35*(1), 105-120. doi:10.1016/j.neuroimage.2006.11.054

Thomas, J. D., Wasserman, E. A., West, J. R., & Goodlett, C. R. (1996). Behavioral deficits induced by bingelike exposure to alcohol in neonatal rats: importance of developmental timing and number of episodes. *Developmental Psychobiology, 29*(5), 433-452. doi:10.1002/(SICI)1098-2302(199607)29:5<433::AID-DEV3>3.0.CO;2-P

Thomas, K. M., King, S. W., Franzen, P. L., Welsh, T. F., Berkowitz, A. L., Noll, D. C., Birmaher, V., & Casey, B. J. (1999). A developmental functional MRI study of spatial working memory. *Neuroimage, 10*(3 Pt 1), 327-338. doi:10.1006/nimg.1999.0466

Treit, S., Lebel, C., Baugh, L., Rasmussen, C., Andrew, G., & Beaulieu, C. (2013). Longitudinal MRI reveals altered trajectory of brain development during childhood and adolescence in fetal alcohol spectrum disorders. *Journal of Neuroscience, 33*(24), 10098-10109. doi:10.1523/JNEUROSCI.5004-12.2013

US Department of Health and Human Services. (2005). *Surgeon General's Advisory on Alcohol Use in Pregnancy*. Washington, DC Retrieved from http://www.health.gov/dietaryguidelines/dga2005/document/default.htm.

van Asselen, M., Kessels, R. P., Neggers, S. F., Kappelle, L. J., Frijns, C. J., & Postma, A. (2006). Brain areas involved in spatial working memory. *Neuropsychologia, 44*(7), 1185-1194. doi:10.1016/j.neuropsychologia.2005.10.005

Vandenberghe, R., Gitelman, D. R., Parrish, T. B., & Mesulam, M. M. (2001). Functional specificity of superior parietal mediation of spatial shifting. *Neuroimage, 14*(3), 661-673. doi:10.1006/nimg.2001.0860

Vestergaard, M., Madsen, K. S., Baare, W. F., Skimminge, A., Ejersbo, L. R., Ramsoy, T. Z., Gerlach, C., Akeson, P., Paulson, O. B., & Jernigan, T. L. (2011). White matter microstructure in superior longitudinal fasciculus associated with spatial working memory performance in children. *Journal of Cognitive Neuroscience, 23*(9), 2135-2146. doi:10.1162/jocn.2010.21592

Wager, T. D., & Smith, E. E. (2003). Neuroimaging studies of working memory: a meta-analysis. *Cognitive, Affective & Behavioral Neuroscience, 3*(4), 255-274.

Ware, A. L., O'Brien, J. W., Crocker, N., Deweese, B. N., Roesch, S. C., Coles, C. D., Kable, J. A., May, P. A., Kalberg, W. O., Sowell, E. R., Jones, K. L., Riley, E. P., Mattson, S. N., & Collaborative Initiative on Fetal Alcohol Spectrum Disorders. (2013). The effects of prenatal alcohol exposure and attention-deficit/hyperactivity disorder on psychopathology and behavior. *Alcoholism: Clinical and Experimental Research, 37*(3), 507-516. doi:10.1111/j.1530-0277.2012.01953.x

White, N., Roddey, C., Shankaranarayanan, A., Han, E., Rettmann, D., Santos, J., Kuperman, J., & Dale, A. (2010). PROMO: Real-time prospective motion correction in MRI using image-based tracking. *Magnetic Resonance in Medicine, 63*(1), 91-105. doi:10.1002/mrm.22176

Wozniak, J. R., Mueller, B. A., Bell, C. J., Muetzel, R. L., Hoecker, H. L., Boys, C. J., & Lim, K. O. (2013). Global functional connectivity abnormalities in children with fetal alcohol spectrum disorders. *Alcoholism: Clinical and Experimental Research, 37*(5), 748-756. doi:10.1111/acer.12024

Wozniak, J. R., Mueller, B. A., Chang, P. N., Muetzel, R. L., Caros, L., & Lim, K. O. (2006). Diffusion tensor imaging in children with fetal alcohol spectrum disorders. *Alcoholism: Clinical and Experimental Research, 30*(10), 1799-1806. doi:10.1111/j.1530-0277.2006.00213.x

Wozniak, J. R., Mueller, B. A., Muetzel, R. L., Bell, C. J., Hoecker, H. L., Nelson, M. L., Chang, P. N., & Lim, K. O. (2011). Inter-hemispheric functional connectivity disruption in children with prenatal alcohol exposure. *Alcoholism: Clinical and Experimental Research, 35*(5), 849-861. doi:10.1111/j.1530-0277.2010.01415.x

Wozniak, J. R., & Muetzel, R. L. (2011). What does diffusion tensor imaging reveal about the brain and cognition in fetal alcohol spectrum disorders? *Neuropsychology Review, 21*(2), 133-147. doi:10.1007/s11065-011-9162-1

Wozniak, J. R., Muetzel, R. L., Mueller, B. A., McGee, C. L., Freerks, M. A., Ward, E. E., Nelson, M. L., Chang, P. N., & Lim, K. O. (2009). Microstructural corpus callosum anomalies in children with prenatal alcohol exposure: an extension of previous diffusion tensor imaging findings. *Alcoholism: Clinical and Experimental Research, 33*(10), 1825-1835. doi:10.1111/j.1530-0277.2009.01021.x

Yang, Y., Roussotte, F., Kan, E., Sulik, K. K., Mattson, S. N., Riley, E. P., Jones, K. L., Adnams, C. M., May, P. A., O'Connor, M. J., Narr, K. L., & Sowell, E. R. (2012). Abnormal cortical thickness alterations in fetal alcohol spectrum disorders and their relationships with facial dysmorphology. *Cerebral Cortex, 22*(5), 1170-1179. doi:10.1093/cercor/bhr193

FIGURES

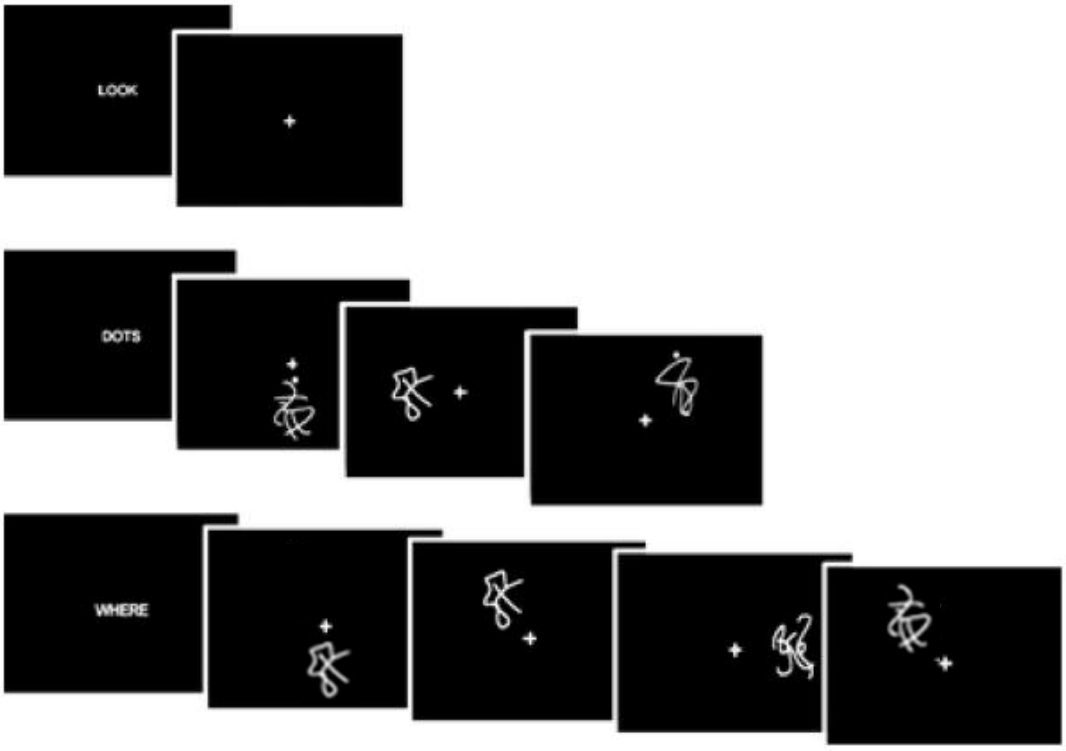

Figure 1. Schematic of the Spatial Working Memory task

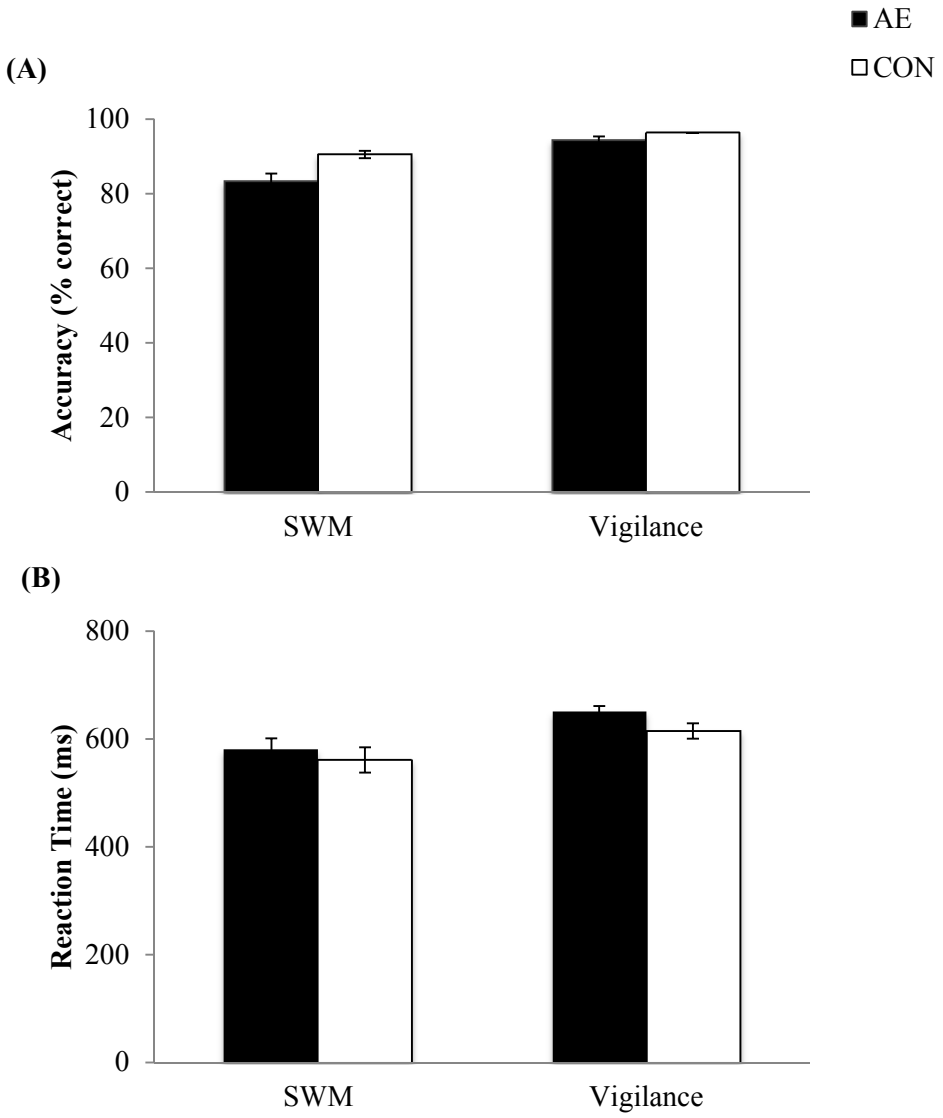

Figure 2. Behavioral performance in AE and CON participants on the SWM task. (A) Mean percent accuracy and (B) mean reaction time for SWM and vigilance trials. Error bars indicate SE.

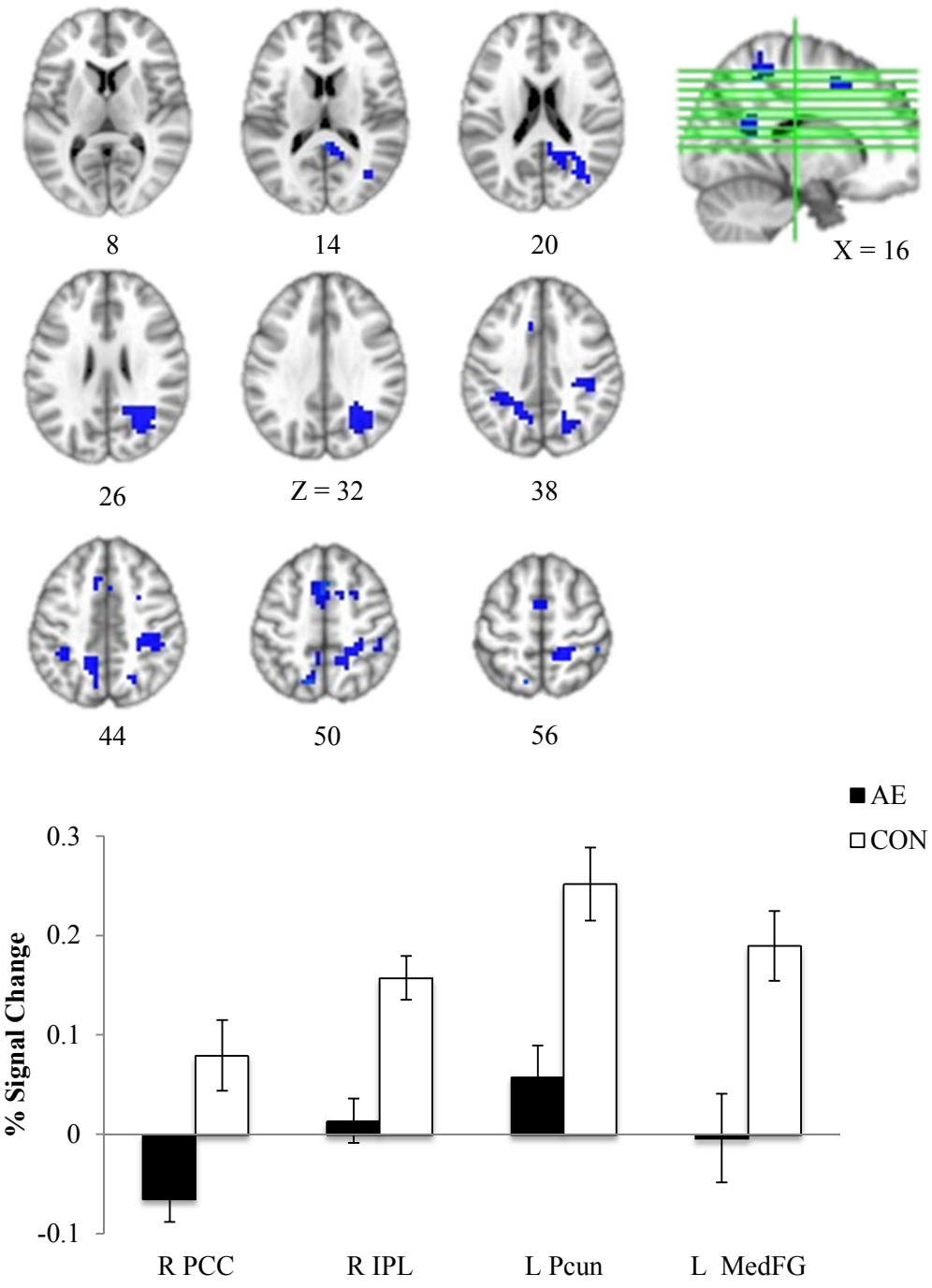

Figure 3**.** Regions showing group differences in brain activation to the SWM – vigilance contrast. In all regions the CON group showed greater BOLD response compared to the AE group. Images are displayed in the neurological convention (i.e., left side of brain corresponds to left side of image). Bar graphs represent the average percent signal change for the SWM –vigilance contrast in each group. Error bars indicate SE. R = Right; L = Left; PCC = Posterior Parietal Cortex; IPL = Inferior Parietal Lobule; Pcun = Precuneus; MedFG = Medial Frontal Gyrus.

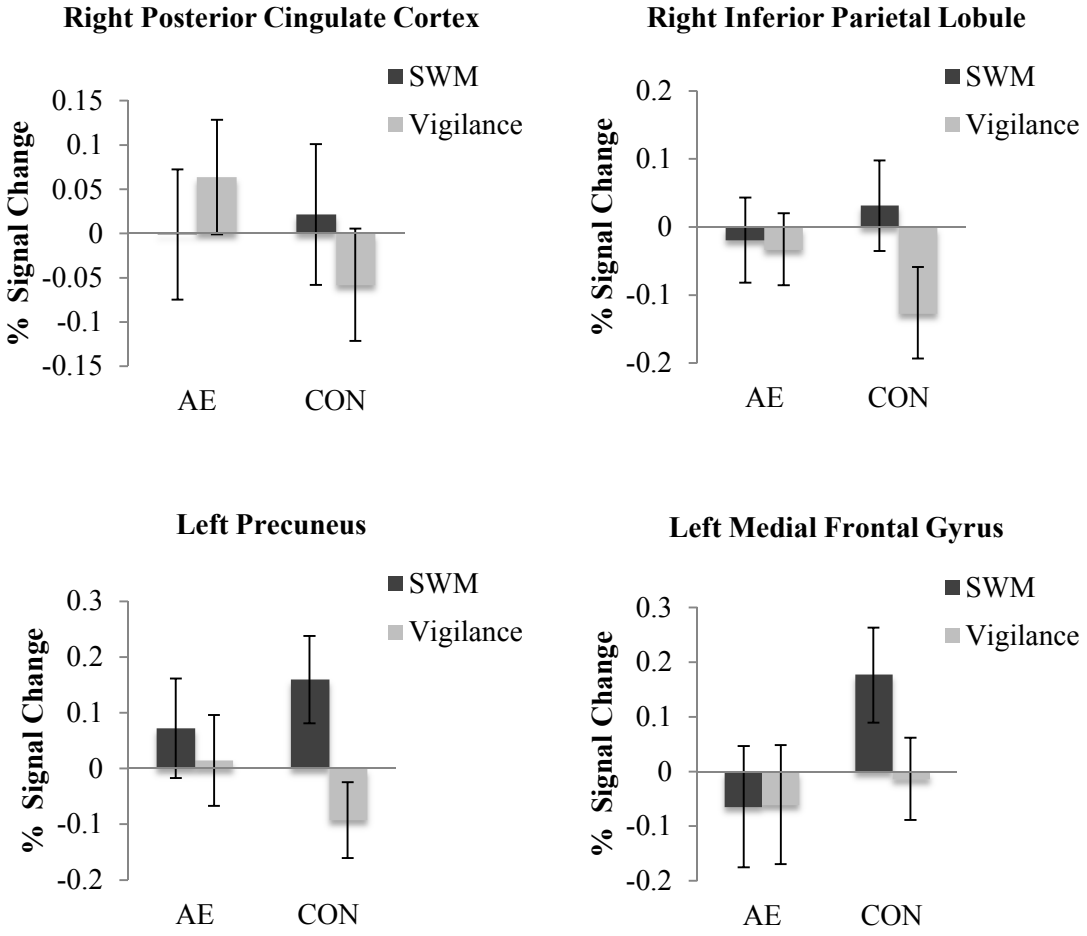

Figure 4. Bar graphs show the average percent signal change during the SWM and vigilance trials (each relative to fixation) for the AE and CON groups. Error bars indicate SE.

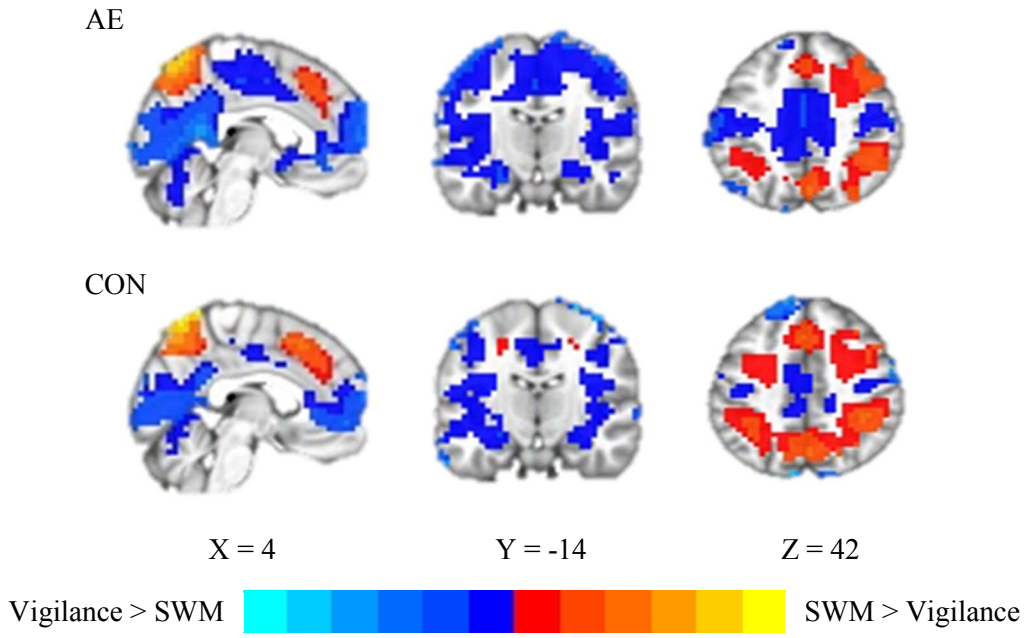

Figure 5. Regions showing significant BOLD response to the SWM – vigilance contrast in the AE (top row) and CON (bottom row) groups. Images are displayed in the neurological convention (i.e., left side of brain corresponds to left side of image).

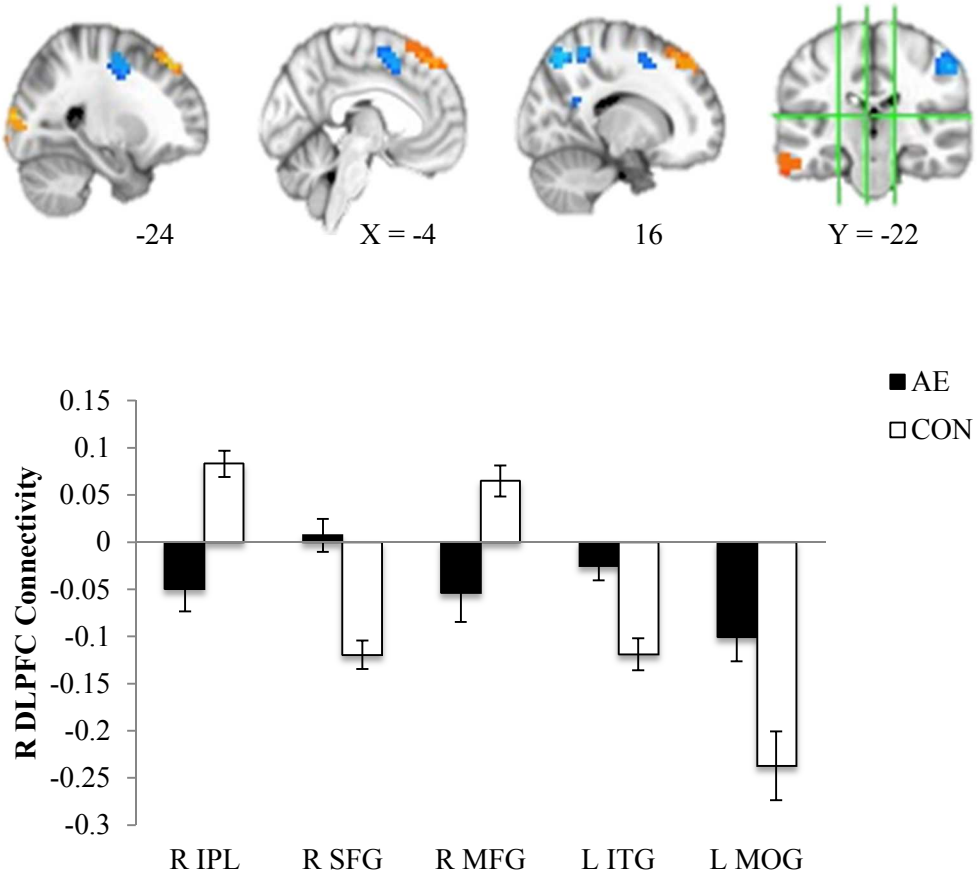

Figure 6. Regions showing group differences in functional connectivity with the right dorsolateral prefrontal cortex seed during the SWM – vigilance contrast. Images are displayed in the neurological convention (i.e., left side of brain corresponds to left side of image). Bar graphs depict extracted measures of connectivity (PPI parameter estimates) within each group. Error bars indicate SE. R = right; L = left; DLPFC = dorsolateral prefrontal cortex; IPL = inferior parietal lobule; SFG = superior frontal gyrus; MFG = middle frontal gyrus; ITG = inferior temporal gyrus; MOG = middle occipital gyrus.

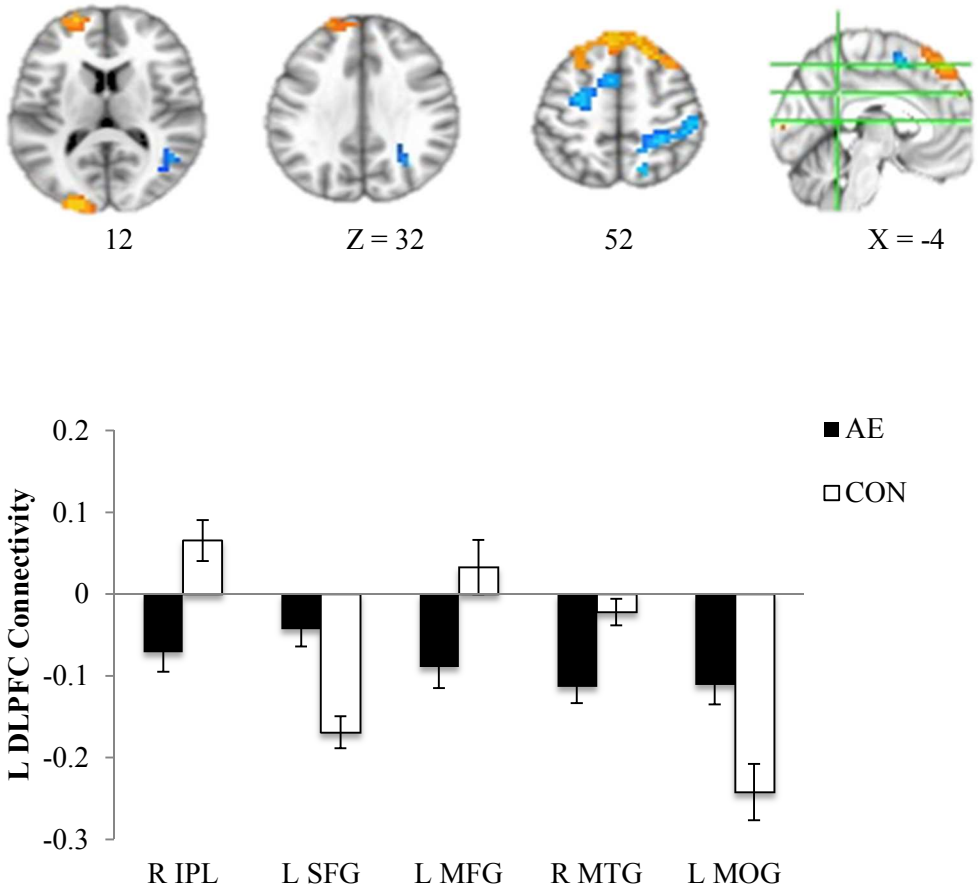

Figure 7. Regions showing group differences in functional connectivity with the left dorsolateral prefrontal cortex seed during the SWM – vigilance contrast. Images are displayed in the neurological convention (i.e., left side of brain corresponds to left side of image). Bar graphs depict extracted measures of connectivity (PPI parameter estimates) within each group. Error bars indicate SE. R = right; L = left; DLPFC = dorsolateral prefrontal cortex; IPL = inferior parietal lobule; SFG = superior frontal gyrus; MFG = middle frontal gyrus; MTG = middle temporal gyrus; MOG = middle occipital gyrus.

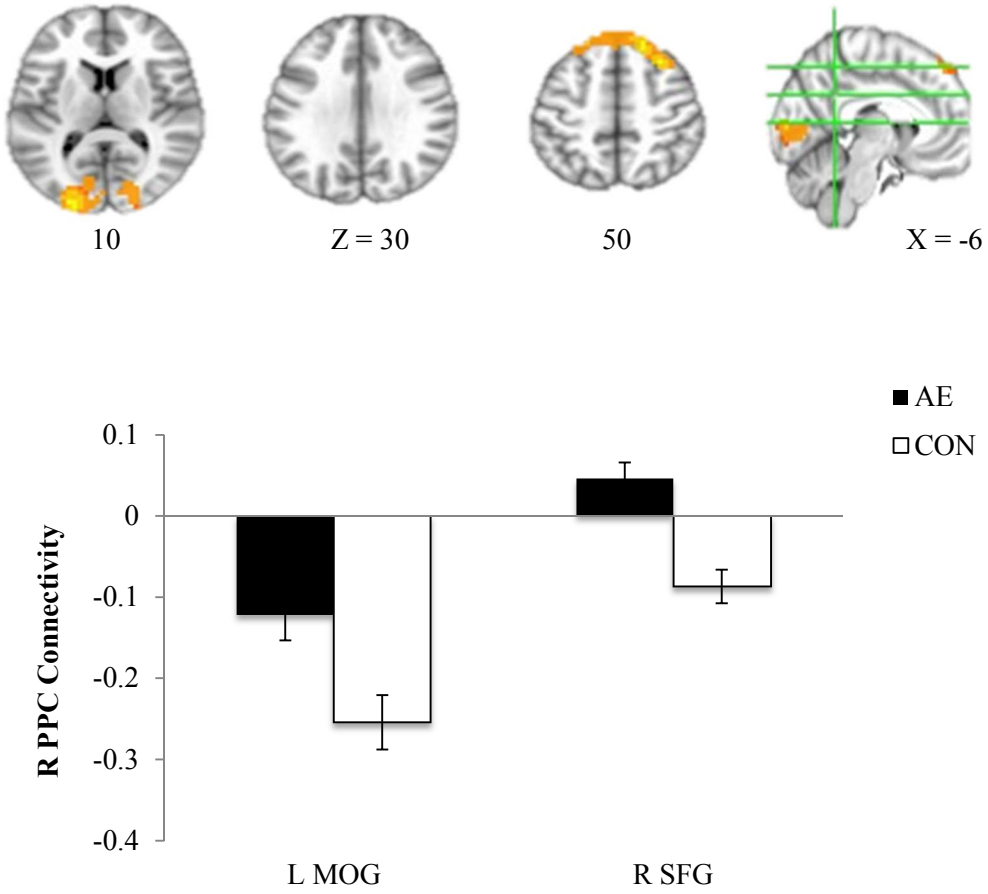

Figure 8. Regions showing group differences in functional connectivity with the right posterior parietal cortex seed during the SWM – vigilance contrast. Images are displayed in the neurological convention (i.e., left side of brain corresponds to left side of image). Bar graphs depict extracted measures of connectivity (PPI parameter estimates) within each group. Error bars indicate SE. R = right; L = left; PPC = posterior parietal cortex; MOG = middle occipital gyrus; SFG = superior frontal gyrus.

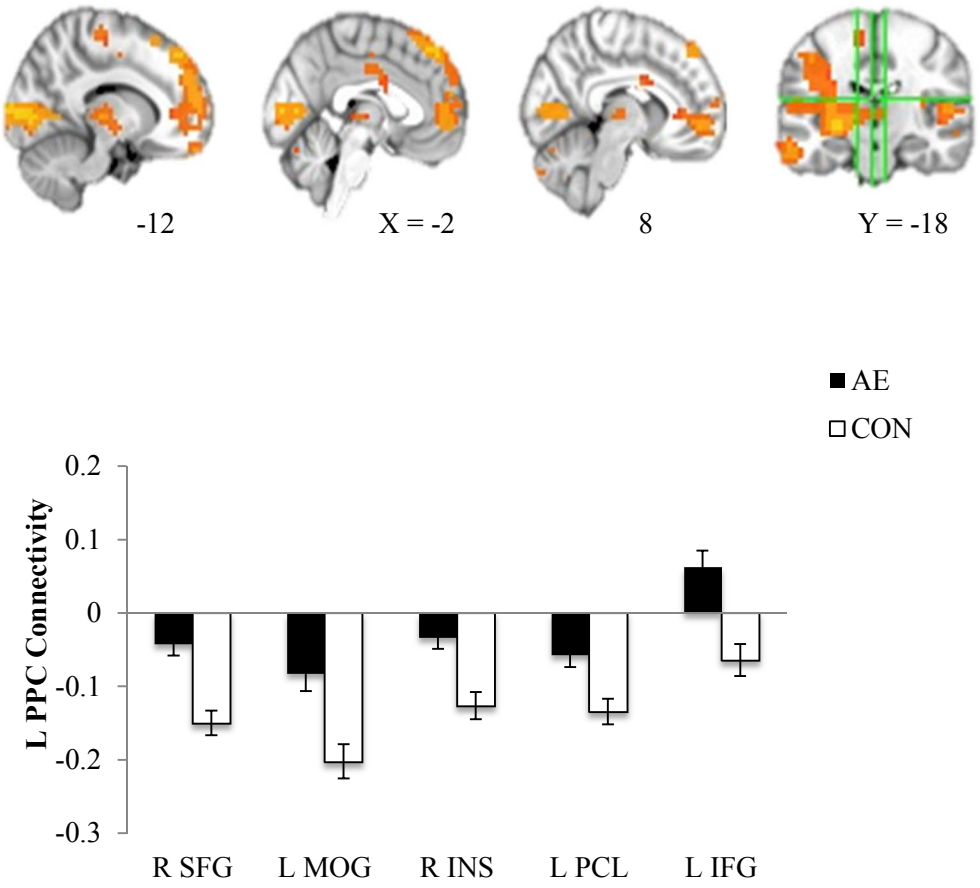

Figure 9. Regions showing group differences in functional connectivity with the left posterior parietal cortex seed during the SWM – vigilance contrast. Images are displayed in the neurological convention (i.e., left side of brain corresponds to left side of image). Bar graphs depict extracted measures of connectivity (PPI parameter estimates) within each group. Error bars indicate SE. R = right; L = left; PPC = posterior parietal cortex; SFG = superior frontal gyrus; MOG = middle occipital gyrus; INS = insula; PCL = paracentral lobule; IFG = inferior frontal gyrus.

TABLES

Table 1. Demographic characteristics of study participants by group

Variable	Group	
	AE (*n* = 18)	CON (*n* = 19)
Sex [*n* (%) Female]	8 (44.4)	8 (42.11)
Race [*n* (%) White]	10 (55.56)	7 (36.84)
Ethnicity [*n* (%) Hispanic]	7 (38.89)	3 (15.79)
Handedness [*n* (%) Right]	14 (77.78)	18 (94.74)
Age in years [*M* (*SD*)]	13.89 (2.09)	13.52 (2.52)
SES [*M* (*SD*)	43.78 (12.88)	47.87 (11.41)
GCA [*M* (*SD*)]*	85.83 (8.75)	110.58 (15.55)

Note. SES = socioeconomic status; GCA = general conceptual ability score. *Significant at the $p < .001$ level.

Table 2. Regions showing significant group differences in BOLD response to the SWM – vigilance contrast

Anatomic location	Voxels	MNI coordinates			*t*(35)	Cohen's *d*
		x	*y*	*z*		
R posterior cingulate	165	4	-48	14	-2.08	-0.70
R inferior parietal lobule	89	48	-40	54	-2.63	-0.89
L precuneus	87	-12	-68	50	-2.76	-0.93
L medial frontal gyrus	85	-0	-0	58	-2.27	-0.77

Note. Coordinates refer to location of the peak voxel within the cluster. Peak coordinates are reported in MNI152 space. MNI = Montreal Neurological Institute; R = right; L = left.

Table 3. Regions showing significant group differences in functional connectivity

Seed / Anatomic location	Voxels	MNI coordinates *x*	*y*	*z*	*t*(35)	Cohen's *d*
R DLPFC						
R inferior parietal lobule	378	40	-40	42	-3.40	-1.15
R superior frontal gyrus	254	32	24	54	3.80	1.28
R middle frontal gyrus	189	24	-8	58	-2.39	-0.81
L inferior temporal gyrus	94	-60	-20	-22	3.10	1.05
L middle occipital gyrus	77	-20	-100	10	3.61	1.22
L DLPFC						
R inferior parietal lobule	298	36	-40	42	-3.52	-1.19
L superior frontal gyrus	242	-24	20	54	2.70	0.91
L middle frontal gyrus	102	-24	-8	50	-2.80	-0.95
R middle temporal gyrus	101	32	-64	26	-2.69	-0.91
L middle occipital gyrus	84	-20	-100	10	3.47	1.17
R PPC						
L middle occipital gyrus	291	-20	-96	10	3.49	1.18
R superior frontal gyrus	149	20	36	50	3.07	1.04
L PPC						
R superior frontal gyrus	1738	20	36	50	3.58	1.21
L middle occipital gyrus	655	-20	-96	10	3.37	1.14
R insula	210	40	8	22	3.08	1.04

Table 3: Continued

Seed	Voxels	MNI coordinates			*t*(35)	Cohen's *d*
Anatomic location		*x*	*y*	*z*		
L paracentral lobule	88	-4	-12	46	2.40	0.81
L inferior frontal gyrus	79	-48	16	26	3.85	1.30

Note. Coordinates refer to location of the peak voxel within the cluster. Peak coordinates are reported in MNI152 space. MNI = Montreal Neurological Institute; R = right; L = left; DLPFC = dorsolateral prefrontal cortex; PPC = posterior parietal cortex.