Neuroimaging and Behavioral Investigation of Declarative Memory in South African Children Prenatally Exposed to Alcohol

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LIST OF ABBREVIATIONS

AA	-	absolute alcohol
ADHD	-	attention-deficit/hyperactivity disorder
ARBD	-	alcohol-related birth deficits
ARND	-	alcohol-related neurodevelopmental disorder
BA	-	Brodmann Area
BOLD	-	blood-oxygen level dependent
CDC	-	Centers for Disease Control and Prevention
CDRL	-	Child Developmental Research Laboratory
CNS	-	central nervous system
CSF	-	cerebro-spinal fluid
CVLT-C	-	California Verbal Learning Test-Children's Version
EF	-	executive functions
FAS	-	fetal alcohol syndrome
FASD	-	fetal alcohol spectrum disorders
fMRI	-	functional magnetic resonance imaging
fROI	-	functional region of interest
FSIQ	-	Full-Scale IQ
GM	-	gray matter
HE	-	Heavily exposed nonsyndromal
HRF	-	hemodynamic response function
LOC	-	lateral occipital complex
MNI	-	Montréal Neurological Institute
MTL	-	medial temporal lobe
MWM	-	Morris Water Maze
PAE	-	prenatal alcohol exposure
PFAS	-	partial FAS
PFC	-	prefrontal cortex
P-FIT	-	Parieto-Frontal Integration Theory
PIMMS	-	Predictive Interactive Multiple Memory Systems
PPA	-	parahippocampal place area
PRI	-	Perceptual Reasoning Index
PSI	-	Processing Speed Index

ROI	-	region of interest
SES	-	socioeconomic status
SM	-	subsequent memory
UCT	-	University of Cape Town
VCI	-	Verbal Comprehension Index
WC	-	Western Cape
WISC-IV	-	Wechsler Intelligence Scale for Children—Fourth Edition
WM	-	white matter
WMI	-	Working Memory Index
WSU	-	Wayne State University

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Prenatal alcohol exposure (PAE) is associated with a range of physical, growth, and neurobehavioral deficits characteristic of individuals with fetal alcohol spectrum disorders (FASD). Although declarative memory impairment is a key feature of the neurocognitive profile of FASD, the mechanisms underlying this deficit require further clarification. The aim of this cross-sectional research was to examine, both directly and indirectly (via bottom-up and top-down processes), a critical cognitive mechanism that supports successful declarative memory functioning (viz., memory encoding), in children with FASD. Data were collected from a sample (N = 88) of South African children with and without PAE. In Study I, I used a blocked design functional magnetic resonance imaging (fMRI) paradigm to investigate neural activation during visual perception, a lower-order cognitive process essential to memory encoding. The task elicited bilateral category-specific activation during the visual perception of objects and scenes in all participants. The absence of between-group differences suggests that functional recruitment of brain regions during basic visual perception is less susceptible to the effects of PAE than during higher-order processes supporting memory encoding. In Study II, I used an event-related fMRI paradigm to investigate neural activation during memory encoding itself. All participants demonstrated similar memory performance accuracy and recruited extensive bilateral networks during memory encoding. However, participants with a diagnosis of fetal alcohol syndrome (FAS) or partial FAS (PFAS) activated additional regions associated with attentional function. Within the FAS/PFAS group, higher exposure levels were associated with smaller activation increases in the parahippocampal gyri and greater activation increases in the right hippocampal formation during encoding. Data from this study therefore suggest that children with FAS/PFAS recruited more extensive neural resources to support successful memory encoding during this task. In Study III, I used a behavioral source memory paradigm to investigate higher-order executive processes essential

for memory encoding. Despite similar recognition accuracy across all diagnostic groups, participants in the FAS/PFAS group showed impaired memory for source details. This pattern of impairment was only partially mediated by working memory performance. These three studies provide novel clarification of the neural and cognitive mechanisms underlying declarative memory impairments in children with FASD.

DISSERTATION OUTLINE

This doctoral dissertation is divided into six chapters. In Chapter 1, I provide a broad, but not exhaustive, introduction to the neuropsychological domain of interest (viz., declarative memory) as well as to the neuropsychological profile of Fetal Alcohol Spectrum Disorders (FASD). Additionally, I introduce the rationale and general aims of this doctoral research. In Chapter 2, I outline the general methodological details that are (a) common to the three studies that comprise this doctoral research and (b) pertinent to investigations conducted within the Cape Town Longitudinal Cohort Study (Jacobson et al., 2008). In each of Chapters 3 - 5, I provide a brief introduction to the literature that is pertinent to the empirical study contained therein. The aim of these brief introductions is to provide the reader with sufficient information to be able to engage with the rationale of the study and to interpret the results should the chapter be read in isolation. Following this brief introduction within each chapter, I report and interpret the results of Studies I – III and comment on the limitations of each study. Finally, in Chapter 6, I provide a brief summary of the key findings of this doctoral research, synthesize the findings from Chapters 3 - 5, and comment on their clinical significance within the broader literature pertaining to FASD.

CHAPTER 1: GENERAL INTRODUCTION

The link between alcohol use during pregnancy and negative developmental consequences was first noted in the 18th century (for a review, see Calhoun & Warren, 2007). Lemoine, Harousseau, Borteyru, and Menuet (1968) gave the first systematic description of the adverse physical and behavioral outcomes associated with heavy prenatal alcohol exposure (PAE). Shortly thereafter, the term *fetal alcohol syndrome* (FAS) was introduced into medical nomenclature (Jones, Smith, Ulleland, & Streissguth, 1973; Jones & Smith, 1973). Since then, much research has been conducted to define the clinical syndromes associated with varying levels of PAE.

Globally, researchers have been working towards defining a behavioral and, more recently, a neurobiological phenotype for fetal alcohol spectrum disorders (FASD). The identification of a behavioral phenotype is particularly important in heavily exposed (HE) nonsyndromal children, who lack the classic craniofacial features seen in FAS, as it will help identify these children, thereby permitting earlier and appropriate intervention. In an attempt to define this behavioral phenotype, neuropsychological investigations have reported that children with a history of moderate to heavy PAE are impaired in a number of cognitive domains (e.g., declarative memory and executive function; for reviews, see Jacobson, Jacobson, Stanton, Meintjes, & Molteno, 2011; Mattson, Crocker, & Nguyen, 2011) and are prone to experiencing secondary disabilities (e.g., depression and anxiety; Fryer, McGee, Matt, Riley, & Mattson, 2007; Streissguth, Barr, Kogan, & Bookstein, 1996).

Research into the behavioral presentation of FASD continues, however. Specifically, it is expanding to include novel neuroimaging modalities, such as functional magnetic resonance imaging (fMRI), to allow a better understanding of the relations between alcohol-related structural and functional changes in the brain and behavioral presentation. Furthermore, neuroimaging techniques permit differentiation between behaviorally similar

phenotypes, such as FASD and attention-deficit/hyperactivity disorder (ADHD), which may have very different underlying neural substrates (Castellanos & Tannock, 2002; Jacobson et al., 2011).

Learning and memory are particularly vulnerable to the effects of PAE (Lewis et al., 2015, 2016; Manji, Pei, Loomes, & Rasmussen, 2009; Mattson & Roebuck, 2002). Of particular interest here is that contemporary research programs have placed increasing emphasis on elucidating cognitive mechanisms underlying memory deficits (e.g., impaired memory encoding vs. retrieval). Novel behavioral and neuroimaging paradigms, that assess different learning and memory components, provide an opportunity to advance understanding of the changes in brain structure and function that lead to learning and memory impairments in children with a history of PAE. The primary aim of this thesis is to systematically examine specific aspects of learning and memory functioning, at both behavioral and neural levels, in children with a history of heavy PAE, such that mechanisms underlying specific alcohol-related memory deficits may be better understood.

In the literature review below, I provide a brief overview of the topics pertinent to the rationale of this doctoral research. Specifically, I introduce (a) current neuropsychological and neuroscientific models of memory functioning, and (b) the developmental trajectory of memory functioning. In addition, I provide an overview of diagnostic criteria, prevalence rates, and neurocognitive profile of FASD. I then review the literature examining declarative memory in children with a history of PAE, thereby emphasizing the current definition of the behavioral phenotype for learning and memory impairment in this clinical population. Castellanos and Tannock (2002) propose that the definition of cognitive and/or behavioral phenotypes associated with neurodevelopmental disorders should be supported by research linking behavioral deficits with underlying lesions known to be related to those deficits. In applying this approach to FASD, Jacobson et al. (2011) argue that biobehavioural markers of

effect should be supported by a detailed understanding of the neural substrates underlying a particular cognitive function. I therefore also discuss the relevance of employing novel neuroimaging paradigms to examine the structural and functional integrity of those regions necessary for learning and memory functioning.

Declarative Memory

Neuropsychology of Learning and Memory

Memory is not a unified construct—it is both complex and multi-faceted (Nadel, Hupbach, Gomez, & Newman-Smith, 2012; Tulving, 1987). It is, however, typically conceptualized as having three main components: sensory memory, short-term memory, and long-term memory. Each of these components is defined by how it acquires, stores, and retrieves information over time (Squire, 2004). This doctoral research focuses on the declarative memory system, which falls into the broader category of long-term memory. The declarative memory system is primarily responsible for the acquisition and consolidation of verbal and non-verbal information into long-term storage, thereby facilitating conscious retrieval of semantic knowledge (i.e., semantic memory) and events (i.e., episodic memory) (Schacter & Tulving, 1994; Squire, 2004; Tulving, 2002).

Neural correlates of declarative memory. The neural correlates of declarative memory are well defined (for a review, see Eichenbaum, 2004). Of particular relevance to this thesis is research showing that the cognitive processes of encoding and consolidation are mediated by the bilateral medial temporal lobe (MTL) and supported by the prefrontal cortex (PFC; Eichenbaum, 2003, 2004). Traditional definitions of the MTL memory system propose that the hippocampus interacts with the perirhinal cortex, entorhinal cortex, and parahippocampal gyrus to form a single functional unit (Squire, Stark, & Clark, 2004; Squire & Zola-Morgan, 1991). Within this functional unit (sometimes called the hippocampal

formation; O'Keefe & Nadel, 1978), the hippocampus proper plays a critical role in the formation of associations between learned information and previously-established contextual networks, thereby facilitating the encoding and consolidation of information into long-term memory (Eichenbaum, 2004). The structure-function link between this MTL system and the encoding of memory traces is supported by human and animal lesion studies showing that damage to this region results in impaired information acquisition (Milner, Corkin, & Teuber, 1968; Squire & Zola, 1996) and spatial memory deficits (Morris, Garrud, Rawlins, & O'Keefe, 1982; Rosenbaum et al., 2000).

Although the PFC is not crucial to the encoding of new memories, it supports the formation of rich contextual details associated with episodic memories (Ofen et al., 2007; Simons & Spiers, 2003). The effective connectivity between the MTL memory system and PFC results in a functional interaction of these two regions during memory encoding, consolidation, and retrieval. More specifically, the PFC links the episodic representations of events, created by the MTL system, with rich semantic and/or phonological contexts and then organizes them into distinct memory traces (Simons & Spiers, 2003). Additionally, there are material-specific asymmetries in the functional recruitment of the MTL system and PFC during memory encoding: Encoding of verbal information is supported largely by the left MTL and PFC, whereas encoding of non-verbal information is supported largely by the right MTL and PFC (Golby et al., 2001; Milner, 1970; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994).

Structural and functional maturation of the declarative memory system. Memory researchers are placing increasing attention on tracking the developmental trajectory of the neural correlates of memory using novel functional imaging paradigms. One such study suggested that the MTL memory system is functionally mature by 8 years of age, and that its developmental trajectory is more rapid than that of the PFC (Ofen et al., 2007). This finding

is consistent with behavioral literature reporting that, although memory performance continues to improve throughout childhood, adolescence, and adulthood, the basic neural components of memory formation emerge during childhood (Brehmer, Li, Müller, von Oertzen, & Lindenberger, 2007; Ofen & Shing, 2013; Shing et al., 2010). Furthermore, the structural and functional maturation of the PFC appears to continue into early adulthood (for a review, see Romine & Reynolds, 2005). It is important, therefore, that research investigating the neural correlates of memory formation during childhood be located within a developmental context.

Perception and memory. Traditional conceptualizations of the MTL memory system propose that perception and memory are two dissociable processes (Squire & Zola-Morgan, 1991). However, recent research findings support the hypothesis that the hippocampus and associated MTL structures (e.g., perirhinal and parahippocampal cortex) are involved in the perception of complex visual scenes and in the subsequent encoding of visual information (Baxter, 2009; Buckley, 2005; Lee, Yeung, & Barense, 2012; Murray, Bussey, & Saksida, 2007; Ofen & Shing, 2013; Ofen et al., 2007). The perceptual-mnemonic hypothesis (Bussey, Saksida, & Murray, 2005) proposes that the MTL memory system is responsible for encoding contextual information pertaining to objects or scenes, which is necessary for both perception and memory processes. Further support for the association between perceptual and memory processes is provided by the Predictive Interactive Multiple Memory Systems framework (PIMMS; Henson & Gagnepain, 2010), which suggests functional interactions between perceptual, semantic, and episodic memory systems to facilitate effective information encoding and retrieval.

Extending the PIMMS framework (Henson & Gagnepain, 2010) to a developmental context, Ofen and Shing (2013) characterize the relation between perception and memory as changing with age. The developmental trajectories of perceptual and semantic systems are

such that, during concept formation, children are more reliant on perceptual information, whereas adults are more reliant on abstract semantic categories (for a review, see Ofen & Shing, 2013). As a result of this growing body of support for a perceptual-mnemonic approach to the MTL memory system, it is important to consider the relation between perception and memory when assessing the functional integrity of these regions within the developmental context. There is limited research examining perceptual-mnemonic interactions in clinical pediatric populations. Hence, future research examining the extent to which lower-order cognitive processes (e.g., perception) contribute to memory functioning is warranted in clinical pediatric samples in which declarative memory impairments have been observed (e.g., FASD; Lewis et al., 2015, 2016; Mattson, Riley, Delis, Stern, & Jones, 1996; Mattson & Roebuck, 2002; Rasmussen, Pei, Manji, Loomes, & Andrew, 2009).

Fetal Alcohol Spectrum Disorders (FASD)

Diagnosis and Classification

Since the first description of FAS (Jones & Smith, 1973) research, using both prospectively (e.g., Jacobson et al., 2008) and retrospectively (e.g., Mattson, Riley, Gramling, Delis, & Jones, 1998) recruited longitudinal cohorts, has reported a wide range of adverse growth and neurodevelopmental outcomes associated with moderate-to-heavy levels of prenatal alcohol exposure (Mattson et al., 2011). Because the timing and level of prenatal alcohol exposure (Jacobson et al., 2008), as well as a host of pre- and post-natal risk factors (e.g., genetics, maternal nutrition, post-natal infections; Carter et al., 2014; Jacobson et al., 2006; Jacobson, Jacobson, Sokol, Chiodo, & Corobana, 2004; May et al., 2011; Viljoen et al., 2001), vary considerably from one individual to the next, there is great variability in the manifestation of central nervous system (CNS), facial, and growth dysmorphology. As a result, children may not present with all of the features necessary for a diagnosis of FAS, but

may display sufficient cognitive-behavioral impairment (e.g., generally lower IQ scores, impaired attention, learning and memory, or poor eye-blink conditioning) to indicate that the teratogenic effects of alcohol have affected CNS development (Hoyme et al., 2005; Jacobson et al., 2011; Mattson et al., 1998). This variability in presentation is supported by studies documenting that children both with and without the characteristic dysmorphic features of FAS are impaired on cognitive tasks (Mattson et al., 1998). Further evidence is provided by studies documenting cognitive impairments at low-to-moderate levels of prenatal alcohol exposure (Jacobson & Jacobson, 1999; Willford, Leech, & Day, 2006).

The term fetal alcohol spectrum disorders (FASD) was, therefore, introduced as a non-diagnostic umbrella term for the wide range of effects associated with PAE (Hoyme et al., 2005). Following Hoyme et al.'s (2005) clarifications to the 1996 Institute of Medicine diagnostic categories (Stratton, Howe, & Battaglia, 1996), *FAS*, the most severe outcome along the spectrum, is diagnosed in the presence or absence of a confirmed report of PAE and when three core criteria are met: (a) deficits in CNS development (e.g., microcephaly) and cognitive functioning, (b) growth retardation (viz., height or weight measurements $\leq 10^{th}$ percentile), and (c) a specific pattern of craniofacial dysmorphology (including short palpebral fissures, thin upper lip, and smooth philtrum). *Partial FAS* (*PFAS*) is diagnosed when a history of PAE has been confirmed; two of the three characteristic facial features are present; and either the CNS, cognitive-behavioral, or physical growth symptoms are present. The category *alcohol-related birth defects* (*ARBD*) refers more specifically to diagnoses based on the confirmation of maternal drinking, the presence of two of the three characteristic facial features, as well as congenital physical abnormalities (e.g., cardiac, skeletal, and renal anomalies). These occur in the absence of physical growth symptoms and associated CNS development deficits. *Alcohol-related neurodevelopmental disorder* (*ARND*) is diagnosed when a confirmed history of PAE and deficits in CNS development or impairment in

cognitive and behavioral functioning are present, but the characteristic dysmorphic features and/or growth deficits are absent (Hoyme et al., 2005).

Despite Hoyme and colleagues' (2005) clarification of the 1996 IOM diagnostic criteria, the clinical identification of children who have a history of heavy PAE, but who lack the characteristic facial features (i.e., those children who meet the criteria for a diagnosis of ARND), remains difficult (Hoyme & Coles, 2016). Several lines of research are currently investigating novel methods for improving diagnostic specificity. For example, using a dense surface model approach to analyzing dysmorphic facial features in 3-dimensional (3D) photographs, Suttie et al. (2013) reported clusters of children with facial dysmorphology that matched the clinical diagnoses of FAS and PFAS. Of particular significance was their finding that a subset of children within the clinically defined nonsyndromal HE group had facial features indicative of PAE (i.e., dysmorphic features that matched the FAS and PFAS groups) and showed poorer performance on tests of general intelligence and verbal learning and memory. Thus, the use of 3D facial photographs in the diagnosis of FASD may help better identify children who would otherwise be classified as nonsyndromal.

Another approach has been to identify potential biobehavioural markers of effect to increase the specificity of FASD diagnoses (Jacobson et al., 2011). Here, the term biobehavioural marker refers to “a behavioral endpoint linked to FASD whose neural substrates have been identified and can be examined directly” (Jacobson et al., 2011, p. 149). For example, alcohol-related impairments in number processing (i.e., poor arithmetic skills mediated by impaired magnitude comparison) have been established using both behavioral (Jacobson, Dodge, Burden, Klorman, & Jacobson, 2011; Kopera-Frye, Dehaene, & Streissguth, 1996) and neuroimaging (Meintjes et al., 2010; Woods, Meintjes, Molteno, Jacobson, & Jacobson, 2015) paradigms. In addition, the neural correlates of number processing are well defined (for a review, see Jacobson et al., 2011). In combination, these

structural and functional findings are clinically significant and can be used to tailor the assessment of individuals with a suspected FASD.

Moreover, the introduction of the concept of biobehavioural markers into the ongoing definition of the cognitive and behavioral phenotype for FASD highlights the importance of elucidating the alcohol-related changes to neural networks supporting impaired cognitive functions. Jacobson et al. (2011) propose, therefore, that impairments in other neuropsychological domains (e.g., learning and memory) be examined using novel neuroimaging techniques to further the understanding of brain structure-function relations in FASD. It is from this broader theoretical standpoint that the studies included in this thesis were conducted.

Prevalence Rates

The Centers for Disease Control and Prevention (CDC) estimate the prevalence of FAS in the United States of America (USA) to be 0.3 cases per 1000 children aged from 7 to 9 years of age (Fox et al., 2015). However, using the active case ascertainment method, May et al. (2014) estimated the prevalence rates of FAS to be as high as 6 to 9 cases per 1000 children enrolled for the first grade in a Midwestern community in the USA. More recently, Roozen et al. (2016) estimated the prevalence rates (per 1000 cases) of the FASD diagnostic categories to be: 0.7 (FAS), 2.2 (PFAS) and 9.1 (ARND), with the prevalence of FASD estimated as 24.8 to 43.48 cases per 1000 in the USA.

Significantly higher prevalence rates have been reported in developing countries. For example, in the Western Cape (WC) province of South Africa, the prevalence of FASD is reported to be 135.1 to 207.5 cases per 1000 school-aged children (May, Blankenship, Marais, Gossage, Kalberg, Barnard, et al., 2013). May and colleagues estimated the prevalence rates (per 1000 cases) of the various FASD diagnostic categories to be: 59.3 to

91.0 (FAS); 45.3 to 69.6 (PFAS); and 30.5 to 46.8 (ARND). These rates are consistent with those reported for South Africa in a recent meta-analysis of international FASD prevalence rates (per 1000 cases): 55.42 (FAS); 28.29 (PFAS); and 20.25 (ARND; Roozen et al., 2016). These prevalence rates are among the highest reported internationally, and have been linked to both socioeconomic and maternal risk factors (see, e.g., Esper & Furtado, 2014; May et al., 2008).

FASD in the Western Cape Province of South Africa

The WC province of South Africa has a population of 6 293 200 people (i.e., 11.3% of the total population of South Africa; Statistics South Africa, 2016). Based on national census data obtained in 2011 reported by Statistics South Africa (2015), the socioeconomic strata of the WC province indicate that while this region is an economic hub (i.e., 17.3% of the households reviewed nationally fell within the upper-income category), many households reported poor economic circumstances (i.e., 10.0% and 7.1% of the households reviewed nationally fell within the no-income category and low-income categories, respectively). Additionally, it was estimated that one in four (23.2%) households within the WC province qualified as living below the food poverty line. Taken together, these data are indicative of high levels of socioeconomic inequality within South Africa that largely emerge from the legacy of apartheid legislation which divided South Africans along racial lines (e.g., national estimates indicate that 92.3% of households headed by individuals within the black African population group fell within the low-income category, whereas 50.9% of households headed by individuals within the white population group fell within the upper-income category).

Consistent with national estimates, the socioeconomic status of communities within the WC province is largely divided along the racial lines previously classified under the apartheid system. High levels of alcohol consumption have been observed in pregnant

women residing in economically disadvantaged communities in the WC province (Croxford & Viljoen, 1999; Eaton et al., 2012). Particularly severe patterns of alcohol use have been documented among farm laborers in the WC province (Gossage et al., 2014; London, 2000). These patterns have been linked to both the historical practice of the 'dop' system, in which laborers were paid with alcohol rather than receiving wages, and extremely poor living and socioeconomic conditions (McKinstry, 2005). Although the 'dop' system was outlawed in 1961, a loophole in the legislation allowed for the free provision of alcohol to farm laborers provided that it did not constitute a wage (London, 1999). Hence, this system of compensation was reported to be occurring on several farms in the Stellenbosch region some 34 years after the change in legislation (te Water Naude, London, Pitt, & Mahomed, 1998). The legacy associated with the 'dop' system is that of widespread alcohol abuse, a significant feature of which is weekend binge drinking (London, 2003; May et al., 2005).

This pattern of alcohol use and abuse is not restricted to farming communities. Indeed, it is widely reported in economically disadvantaged communities throughout the WC province (May et al., 2005; Morojele et al., 2010; Peltzer & Ramlagan, 2009). Such heavy alcohol use and abuse is associated with high disease burden (Schneider et al., 2007), high-risk sexual behavior (Morojele et al., 2006; Naimi, Lipscomb, Brewer, & Gilbert, 2003), and intimate partner violence (Eaton et al., 2012). Taking these factors, as well as high rates of alcohol addiction, into account, women residing in economically disadvantaged communities are at particularly high risk for unplanned pregnancy and for continued alcohol consumption during pregnancy (Croxford & Viljoen, 1999; Jacobson, Jacobson, Molteno, & Odendaal, 2006).

Cognitive and Behavioral Profile of FASD

Neuropsychological findings. Children with PAE present with wide-ranging deficits in cognitive functioning. Alcohol-related deficits are present in general intellectual functioning, information processing speed, attention, executive function, learning and memory, language, number processing, and visual-spatial functions (for reviews, see Kodituwakku & Kodituwakku, 2014; Mattson et al., 2011). Children with FASD diagnoses achieve lower IQ scores than those of typically developing controls (Jacobson et al., 2004; Lewis et al., 2012; Mattson, Riley, Gramling, Delis, & Jones, 1997) and show slower and less efficient processing of complex information during infancy (Jacobson, Jacobson, Sokol, Martier, & Ager, 1993; Kable & Coles, 2004), childhood, and adolescence (Aragón, Coriale, et al., 2008; Burden, Jacobson, & Jacobson, 2005; Dodge et al., 2009; Roebuck, Mattson, & Riley, 2002; Willford, Chandler, Goldschmidt, & Day, 2010). Additionally, infants and children with FASD show impaired processing of sensory (e.g., auditory or visual orienting responses) information (Carr, Agnihotri, & Keightley, 2010; Green et al., 2009; Kable & Coles, 2004; Paolozza et al., 2014a, 2014b). Parents and teachers of children with FASD often report attentional difficulties (Aragón, Coriale, et al., 2008; Nash et al., 2006). This qualitative observation is supported by alcohol-related impairments on formal tests of attention (Burden, Jacobson, Sokol, & Jacobson, 2005; Coles, Platzman, Lynch, & Freides, 2002) and by high rates of co-morbid attention-deficit/hyperactivity disorder diagnoses (ADHD; Fryer, McGee, et al., 2007).

Alcohol-related impairments in executive functioning have been documented on tests of working memory (Burden, Jacobson, Sokol, et al., 2005; Rasmussen, 2005), planning and problem-solving (Aragón, Kalberg, et al., 2008; Green, Mihic, Nikkel, et al., 2009; Mattson et al., 1999), concept formation and set-shifting (Mattson et al., 1999; McGee, Schonfeld, Roebuck-Spencer, Riley, & Mattson, 2008), verbal fluency (Kodituwakku et al., 2006), and

response inhibition (Burden et al., 2010; Kodali et al., 2017; Paolozza et al., 2014a). Children with PAE are impaired on tests of verbal learning and memory (Lewis et al., 2015; Mattson & Roebuck, 2002; Willford, Richardson, Leech, & Day, 2004), non-verbal learning and memory (Kaemingk, Mulvaney, & Halverson, 2003; Willford et al., 2004; Willoughby, Sheard, Nash, & Rovet, 2008), source monitoring (Kully-Martens, Pei, Job, & Rasmussen, 2012), and prospective memory (Lewis et al., 2016). Alcohol-related impairments in receptive and expressive language (McGee, Bjorkquist, Riley, & Mattson, 2009), number processing and arithmetic (Jacobson et al., 2011; Kopera-Frye et al., 1996; Santhanam, Li, Hu, Lynch, & Coles, 2009), and visual-spatial construction and navigation (Dodge, 2016; Hamilton, Kodituwakku, Sutherland, & Savage, 2003; Kaemingk & Halverson, 2000) have also been reported.

In addition to diffuse cognitive deficits, children with FASD show marked difficulty with social-emotional processing. These difficulties persist across development (for a review, see Kully-Martens, Denys, Treit, Tamana, & Rasmussen, 2012). In infancy, PAE is related to increased emotional withdrawal and decreased activity (Molteno, Jacobson, Carter, Dodge, & Jacobson, 2014). During childhood and early adolescence, individuals with FASD reportedly show higher rates of insecure attachment (O'Connor, Kogan, & Findlay, 2002), as well as difficulty with affect identification and theory of mind (i.e., interpreting the mental state of another individual; Greenbaum, Stevens, Nash, Koren, & Rovet, 2009; Lindinger et al., 2016). These difficulties with social-emotional processing are related to parent and teacher reports of disruptive behaviors (Greenbaum et al., 2009), and are consistent with reports of deficits in social competency (Mattson & Riley, 2000), poor social judgement (Carmichael Olson, Feldman, Streissguth, Sampson, & Bookstein, 1998), and difficulty forming social relationships (Bishop, Gahagan, & Lord, 2007). In addition to poor social skills, children with a history of PAE have an increased vulnerability for secondary psychiatric disabilities (e.g.,

depression; Fryer, McGee, et al., 2007; Streissguth et al., 1996). Although impaired social-emotional processing, and related disruptive behaviors, are considered to be a direct consequence of PAE, (Kully-Martens, Denys, et al., 2012) suggest that it is the combination of impairments in the domains of social cognition, executive function, communication skills, and sensory processing that interacts with environmental factors to hamper the development of adaptive social skills in children with FASD.

The aforementioned impairments in cognition, behavior, and social adaptive skills are present in individuals with the characteristic facial features associated with FAS, as well as in those who do not (Jacobson et al., 2011; Kully-Martens, Denys, et al., 2012; Mattson et al., 1998). It is also of clinical significance that many of the neuropsychological impairments reported in FASD cannot be attributed solely to the effects of generally lower IQ scores (e.g., Kully-Martens, Denys, et al., 2012; Lewis et al., 2015). Moreover, children with FASD show subtle differences in cognitive and behavioral functioning when compared to children with ADHD (e.g., Jacobson et al., 2011). It is, therefore, important to further investigate the neuropsychological impairments associated with each of the diagnostic categories along the FASD spectrum to further delineate the cognitive profile of children with FASD.

Neuroimaging findings. Magnetic resonance imaging (MRI) and related functional neuroimaging techniques (e.g., functional MRI [fMRI] and positron emission tomography [PET]) are used increasingly to investigate brain morphogenesis in studies investigating the neurodevelopmental outcomes associated with prenatal alcohol exposure (Coles & Li, 2011; Donald et al., 2015; Lebel, Roussotte, & Sowell, 2011; Moore, Migliorini, Infante, & Riley, 2014). MRI is a non-invasive and safe technique in which electromagnetic coils are used to generate a strong (1.5 to 7.0 Tesla) static magnetic field and to receive the MR signal (Huettel, Song, & McCarthy, 2009b). The MR signal is detected following the repeated excitation and relaxation of atomic nuclei (viz., hydrogen 1 atoms) within the brain. The MR

signal and image formation are dependent on (a) the contrast mechanism employed, and (b) biological tissue properties (e.g., relaxation time [T_1, T_2, T_2^*] and proton density). Consequently, there are multiple imaging modalities available to assess brain structure and function (for a review of structural and functional neuroimaging techniques, see Coles & Li, 2011 and Lebel et al., 2011).

Consistent with the neuropsychological findings, structural neuroimaging studies have shown diffuse abnormalities in children with prenatal alcohol exposure. Global reductions in brain size are reported for children with FASD when compared to typically-developing children. Although there is some inconsistency in the reporting of regional abnormalities when total brain volume is controlled for, the corpus callosum, cerebellum, basal ganglia, hippocampus, frontal lobes, temporal lobes, and parietal lobes are reported to be particularly susceptible to the neurotoxic effects of PAE (Archibald et al., 2001; Astley et al., 2009; O'Hare et al., 2005; Willoughby et al., 2008; for a review, see Moore et al., 2014). Hence, structural abnormalities are evident in numerous regions supporting higher-order cognitive processes in children with FASD. Consistent with this, studies using functional neuroimaging modalities (e.g., fMRI) report patterns of neural activation that are suggestive of functional impairment on tasks measuring higher-order cognitive processes (e.g., working memory, Diwadkar et al., 2013; Malisza et al., 2005; Norman et al., 2013; Spadoni et al., 2009; and response inhibition, Fryer, Tapert, et al., 2007; Kodali et al., 2017). It is noteworthy that regions (e.g., occipital lobe) supporting lower-order cognitive processes (e.g., perception) are reported to be relatively less vulnerable to the effects of PAE (Fan et al., 2015; Lebel et al., 2011). However, data from a longitudinal imaging study investigating the effects of heavy PAE on neurodevelopment suggests that the developmental trajectory of posterior (especially parietal) regions in alcohol-exposed subjects reflects less plasticity than that of typically-developing control subjects (Lebel et al., 2012).

Declarative Memory Impairments in FASD

Neuropsychological studies suggest that learning and memory performance is particularly sensitive to the effects of PAE (for reviews, see du Plooy, Malcolm-Smith, Adnams, Stein, & Donald, 2016; Manji et al., 2009). The cognitive mechanisms underlying this deficit require further clarification, however. To date, researchers investigating these cognitive mechanisms in FASD have, using behavioral measures, focused on teasing apart two component processes that are integral to effective declarative memory performance (viz., encoding and retrieval). Results of such investigations highlight memory encoding impairment as a key cognitive mechanism underlying learning and memory deficits in FASD, and suggest that retrieval is spared. Within the domain of verbal learning and memory, several studies using the California Verbal Learning Test-Children's Version (CVLT-C; Delis, Kramer, Kaplan, & Ober, 1994) have found that children with heavy PAE, both with and without a diagnosis of FAS, show a relatively consistent pattern of impaired information acquisition alongside spared retention and retrieval of information (Crocker, Vaurio, Riley, & Mattson, 2011; Lewis et al., 2015; Mattson et al., 1996; Mattson & Roebuck, 2002) This pattern of performance has also been demonstrated on several other standardized behavioral measures of verbal learning and memory (e.g., Kaemingk et al., 2003; Pei, Rinaldi, Rasmussen, Massey, & Massey, 2008).

There are, however, two important caveats to consider when characterizing the primary mechanism underlying declarative memory impairment in FASD. First, the pattern of encoding impairment is not found consistently across all studies, or across all verbal learning and memory tests (e.g., Roebuck-Spencer & Mattson, 2004). Second, the way in which encoding and retrieval are affected by PAE might vary depending on the degree of exposure. For instance, although the aforementioned pattern of impaired encoding and spared retention of verbal information was present in adolescents with low-to-moderate exposure on

the Children's Memory Scale (Cohen, 1997; Willford et al., 2004), a different pattern of impairment (suggestive of a retrieval deficit) was detected in adolescents with moderate PAE on the CVLT-C (Lewis et al., 2015). These findings suggest that retrieval deficits may occur in the absence of encoding deficits following low levels of PAE, but that encoding deficits may outweigh retrieval deficits with higher levels of exposure. In other words, different mechanisms may underlie the verbal learning and memory deficits that manifest at differing levels of PAE. In light of the uncertainty regarding these mechanisms, further characterization of the encoding deficits in children with FASD is warranted.

Potential mechanisms underlying visual-spatial learning and memory impairments in children with PAE is less clear. This lack of clarity is due partly to both the small number of studies investigating the specific effects of PAE on non-verbal learning and memory (broadly defined) in humans and the inconsistencies in the pattern of impairments observed in this domain. Specifically, of the studies reporting impaired visual-spatial learning and memory in FASD, only a few have examined encoding specifically. Two studies have demonstrated encoding-specific deficits (Coles, Lynch, Kable, Johnson, & Goldstein, 2010; Kaemingk et al., 2003), and one has demonstrated impaired retention and retrieval of visual-spatial information (Mattson & Roebuck, 2002). Additionally, studies investigating visual-spatial learning and memory suggest that lower-order cognitive processes might mediate the effects of PAE on task performance in this domain. For example, Kaemingk and Halverson (2000) tested spatial memory in 20 children with FASD (M_{age} = 11.2, *SD* = 2.5) and 20 demographically similar non-exposed controls (M_{age} = 11.1, *SD* = 2.5). Children with FASD showed impaired spatial memory relative to control children. However, when performance on tests of visual perception were controlled for statistically, the between-group difference in spatial memory was no longer significant. The authors suggested, therefore, that what appears as a material-specific visual-spatial memory impairment is actually mediated by poor visual

perception, a lower-order cognitive process that is essential to memory encoding. This interpretation is, therefore, consistent with a perceptual-mnemonic (Bussey et al., 2005) approach to MTL memory system functioning. Within this theoretical framework, impaired visual perception will impact negatively upon the encoding and retrieval of spatial information. Taken together, these findings suggest that follow-up investigations designed to clarify the specificity of the cognitive mechanisms underlying visual-spatial learning and memory impairments in FASD are warranted.

Following a different line of investigation, both animal and human studies have demonstrated hippocampal-dependent impairments in place learning and spatial navigation. Animal research has shown that PAE is associated with impaired place learning, but spared cue-based (landmark) navigation. For example, Johnson and Goodlett (2002) found that when alcohol-exposed rats were required to complete the Morris water maze (MWM), a spatial navigation task that assesses place-learning ability, they demonstrated impaired acquisition of the escape route (i.e., they showed difficulty learning the location of a constantly-located hidden target that would allow them to exit the maze), in the absence of cued-navigation deficits (i.e., they demonstrated intact navigation to a visible target, even when that target's location varied from trial to trial). Significantly, this pattern of impairment is (a) similar to that observed in animals with hippocampal damage (Morris et al., 1982) and (b) suggests a particular vulnerability of the hippocampal formation to the effects of PAE (for a review, see Berman & Hannigan, 2000).

Hamilton, Kodituwakku, Sutherland, and Savage (2003) replicated this pattern of impairment using a virtual water maze task in eight boys (M_{age} = 13.1 years; range = 9.5 – 16.5 years) with FAS and eight age- and sex-matched non-exposed controls (M_{age} = 13.2 years). Those with FAS were less efficient when navigating to the hidden target during learning trials, and demonstrated impaired recall of the location of the platform when

searching for it on a probe trial (i.e., a trial when, unbeknownst to the participant, no platform is present in the maze). However, on cued-navigation trials, boys in both the FAS and non-exposed control groups demonstrated similar performance levels, characterized by efficient navigation to a visible target. This finding suggests that impairments in place learning cannot be attributed to failures in visual-motor and/or visual-perceptual functioning, and instead may be better characterized as a hippocampal-dependent learning impairment. Taken together with the findings reported above, memory encoding (an MTL memory system process, and specifically a hippocampal-dependent process) has been highlighted as a key mechanism of learning and memory impairments in FASD. However, the specificity of this pattern of impairment in children with heavy PAE requires follow-up investigation. For instance, one question that remains is: To what extent do impairments in lower-order cognitive processes disrupt memory encoding?

As detailed above, MTL memory systems demonstrate functional interactions with the PFC to facilitate effective memory encoding. It is of clinical significance, therefore, to examine the extent to which those higher-order cognitive processes mediated by PFC substrates (e.g., executive functions; EF) facilitate effective memory encoding. Clinical populations demonstrating impairments in both EF and learning and memory provide a unique opportunity to examine such research questions. Consistent with this approach, children with FASD demonstrate less efficient use of learning strategies (e.g., semantic clustering) than typically developing non-exposed children on standardized tests of learning and memory (e.g., Lewis et al., 2015). The observation of less efficient strategy use in exposed children is consistent with the EF impairments associated with FASD (for a review, see Khoury, Milligan, & Girard, 2015). For example, Rasmussen et al. (2009) demonstrated that the development of memory strategy use was associated with the development of EF abilities (i.e., children with higher levels of EF demonstrated more complex phonological

working memory strategy use). Specifically, as EF skills (e.g., working memory and inhibition) emerge during development, children are able to hold onto and manipulate increasingly complex information. Alternatively, less efficient strategy use, and consequently less efficient memory encoding, may be accounted for by impairments in higher-order executive processes that are mediated by the PFC.

Neuroimaging Studies: Declarative Memory Impairments in FASD

A number of structural neuroimaging studies have provided support for behavioral studies suggesting that children and animals with PAE show impaired performance on hippocampally-mediated tasks of learning and memory. Specifically, PAE has been associated with volumetric reductions of the hippocampus (Coles et al., 2011), and with impaired development and functional maturation of the hippocampus (Willoughby et al., 2008). These structural and functional impairments correlate with performance impairments on tests of learning and memory in both human and animal studies of the adverse effects of PAE (Brady, Allan, & Caldwell, 2012; Coles et al., 2011). Furthermore, volumetric reductions in the basal ganglia, particularly the caudate nucleus (Archibald et al., 2001; Fryer et al., 2012), and in the frontal lobes (Astley et al., 2009; Sowell, Thompson, Mattson, et al., 2002) have been reported for children with heavy PAE. Both these structures play important roles in various aspects of performance on tasks assessing learning and memory (Squire, 2004).

Research employing functional neuroimaging techniques to investigate the effects of PAE on regional brain activation during cognitive tasks is far more limited (for a review, see Moore et al., 2014). Moreover, despite an extensive body of literature documenting learning and memory deficits in children with FASD, only one study has investigated neural activation during verbal learning and memory task performance using fMRI (Sowell et al., 2007; for a

review of this study, see Chapter 4). Because the behavioral assessment of encoding is restricted to examining recall and recognition accuracy on standardized measures of learning and memory, these paradigms are somewhat limited in their ability to discriminate between encoding and retrieval effects. A noteworthy strength of neuroimaging assessments of encoding is that they allow researchers to tease apart encoding effects on a trial-by-trial basis (e.g., by contrasting successful and unsuccessful encoding trials). Thus, given (a) the paucity of functional neuroimaging studies of learning and memory in FASD, and (b) the methodological suitability of such tasks to provide a direct examination of memory encoding, follow-up investigation using novel functional neuroimaging paradigms is warranted.

Research Rationale and Specific Aims

Neuropsychological studies have consistently demonstrated that declarative memory impairment is a key feature of the neurocognitive profile of FASD. However, the cognitive mechanisms underlying this impairment remain to be clarified. Further research is, therefore, necessary to (a) better understand the mechanisms underlying these impairments in children with a history of PAE, and (b) identify relations between changes in brain activation and performance on behavioral tasks in this cognitive domain and in this population. Hence, the overarching aim of this doctoral research was to examine, both directly and indirectly (via bottom-up and top-down processes), a critical cognitive mechanism that supports successful declarative memory functioning (viz., memory encoding) in children with FASD. To achieve this aim, I conducted three empirical studies.

In Study I (Chapter 3), I used a passively viewed, blocked design fMRI paradigm to investigate neural activation during visual perception, a lower-order cognitive process essential to memory encoding. In this study, the main research question was: Do children

with heavy PAE differ from typically developing, demographically similar non-exposed children in terms of neural activation during completion of a passive visual perception task?

In Study II (Chapter 4), I used an event-related fMRI paradigm to investigate neural activation during memory encoding. In this study, the main research question was: Do children with heavy PAE differ from typically developing, demographically similar non-exposed children in terms of neural activation during the encoding of visual scenes?

In Study III (Chapter 5), I used a behavioral source memory paradigm to investigate higher-order executive processes essential for memory encoding. In this study, the main research question was: Do children with heavy PAE differ from typically developing, demographically similar non-exposed children in terms of source memory performance?

CHAPTER 2: GENERAL METHODS

Cape Town Longitudinal Cohort

The three studies included in this doctoral thesis are nested within the ongoing Cape Town Longitudinal Cohort Study (Jacobson et al., 2008) based in the Western Cape (WC) province of South Africa. The Cape Town Longitudinal Cohort Study is a collaboration between Wayne State University (WSU; Detroit, MI) and the University of Cape Town (UCT; Cape Town, WC) and has been ongoing since 1999. Participants were assessed during infancy, at 5, 11, and 14 years of age. Data collection for each of the three studies presented in this doctoral thesis formed part of the 11-year assessment of a sub-sample ($N = 88$; hereafter referred to as the Memory Cohort) of children from the larger cohort ($N = 175$) in the ongoing prospective longitudinal study. The primary aim of this chapter is to present the general study methods that are common to each of the subsequent data chapters.

Recruitment and Assessment of Prenatal Alcohol and Drug Use

Pregnant women were recruited prospectively from a local antenatal clinic based at a maternal obstetrics unit that serves an economically disadvantaged community in which heavy drinking during pregnancy has been reported (Croxford & Viljoen, 1999; Jacobson et al., 2006; Jacobson et al., 2008). Mothers of the 88 children included in the Memory Cohort were recruited into the Cape Town Longitudinal Cohort Study between July 1999 and January 2002.

On recruitment, a research nurse conducted screening interviews to assess levels of prenatal alcohol consumption at recruitment and conception, using a timeline follow-back approach (Jacobson, Chiodo, Sokol, & Jacobson, 2002; Sokol, Martier, & Ernhart, 1983), adapted for use in South Africa (Jacobson et al., 2008). Each pregnant woman was asked about her daily drinking patterns during an average 2-week period around the time of

conception. In the event that a change in daily drinking patterns occurred following conception, alcohol use during the 2 weeks preceding the screening interview was also assessed. Alcohol use across pregnancy was ascertained in two subsequent interviews using the timeline follow-back approach: a follow-up antenatal interview assessing alcohol consumption during the 2 weeks preceding the interview, and a 1-month postpartum interview assessing a typical 2-week period during the latter part of pregnancy. For each type of alcoholic beverage consumed, the volume consumed on a daily basis was recorded and then converted to ounces of absolute alcohol (oz AA) using the following weights that reflect potency of AA in Cape Town (liquor—0.4, beer—0.05, wine—0.12, cider—0.06). Data from the three maternal alcohol interviews were averaged to provide quantitative summary measures of prenatal alcohol exposure (PAE): oz AA/day averaged across pregnancy, oz AA/occasion across pregnancy (i.e., quantity per drinking day), and number of drinking days per week across pregnancy (i.e., frequency). Questions pertaining to maternal drug and tobacco use during pregnancy were also administered. For drug use, mothers were asked how many days per week they used marijuana ("dagga"), methaqualone ("mandrax"), cocaine, or any other recreational drug during pregnancy. For tobacco use, mothers were asked how many cigarettes they smoked per day during pregnancy.

Mothers were invited to participate in the study if they reported that, during pregnancy, (a) their average consumption level of AA/day was at least 1 oz (i.e., the equivalent of about 2 standard drinks/day), which is considered heavy drinking, or (b) they engaged in binge drinking (five[1] or more standard drinks/occasion). For each drinking mother, another pregnant woman presenting for antenatal care at the same gestational age (± 2 weeks) was invited to participate if she reported drinking < 0.5 oz AA/day and did not

[1] The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has since reclassified binge drinking thresholds from 5 to 4 standard drinks/occasion for women. I used the revised binge drinking threshold of 4 drinks/occasion in the analyses in this study.

binge drink 5 drinks per occasion. All women who reported drinking during pregnancy were advised to stop or reduce their intake. Furthermore, mothers of children in both the exposed and non-exposed control groups were invited to participate in a home visitor intervention (Jacobson et al., 2008). Follow-up maternal interviews were administered at subsequent laboratory visits (viz., 5-, 11- and 14-years).

Exclusion criteria. Women younger than 18 years of age and those with diabetes, epilepsy, or cardiac problems requiring treatment were excluded. Observant Muslim women were also excluded because their religious laws prohibit alcohol consumption, and they would, therefore, have been disproportionately represented among the group of non-exposed controls. Infant exclusionary criteria were major chromosomal anomalies, neural tube defects, multiple births, and seizures.

Diagnostic Procedure

Fetal alcohol spectrum disorders (FASD) diagnosis. In September 2005, the Cape Town Longitudinal Study principal investigators (S. W. Jacobson, J. L. Jacobson, and C. D. Molteno) organized a diagnostic clinic at which each participant was examined by two U.S.-based expert FASD dysmorphologists (H. E. Hoyme and L. K. Robinson) according to standard diagnostic protocols for growth and FAS anomalies (Hoyme et al., 2005[2]; Jacobson et al., 2008). There was substantial agreement between the two dysmorphologists on the assessments of dysmorphic features, including palpebral fissure length and philtrum and vermilion ratings, based on the Astley and Clarren (2001) rating scales (*r*s = .80, .84, and .77, respectively). There was also substantial agreement with the Cape Town-based dysmorphologist (N. Khaole; median *r* =.78) who evaluated thirteen participants in the memory cohort who could not be scheduled for the 2005 clinic. FASD diagnoses were (a)

[2] Hoyme and colleagues (2016) have recently revised the clinical guidelines for the diagnosis of FASD. These updated diagnostic guidelines were not used in this doctoral research because they were published subsequent to data collection and analysis.

based on both dysmorphology assessments and PAE data (obtained from prospective maternal alcohol consumption interviews) and (b) determined by consensus at the case conferences conducted by the dysmorphologists and principal investigators. In the Memory Cohort, 50 (56.8%) participants had a history of heavy PAE. Of these participants, 13 (26%) were diagnosed with FAS, 10 (20%) with PFAS, and 27 (54%) were heavily exposed (HE) nonsyndromal. Follow-up diagnostic clinics, which adhered to the same format as the 2005 clinic, were conducted in 2009, 2013, and 2016. Diagnostic data collected at the subsequent clinics confirmed the FASD diagnoses assigned in 2005.

Attention-Deficit/Hyperactivity Disorder (ADHD) diagnosis. The research criteria used to assess ADHD symptoms were developed by the Cape Town Longitudinal Cohort Study principal investigators in collaboration with two clinical psychologists (J. Nigg and R. Klorman), both of whom are authorities in the field of ADHD research. ADHD diagnosis was based on (a) a clinical maternal/care-giver interview (viz., The Schedule for Affective Disorders and Schizophrenia for School-Aged Children; Kaufman, Birmaher, Brent, Rao, & Ryan, 1996) administered by the developmental pediatrician (C. D. Molteno), based in the Child Development Research Laboratory, and (b) a teacher report obtained using the Disruptive Behavior Disorders Scale (DBD; Pelham, Gangy, Greenslade, & Milich, 1992). Final ADHD diagnoses were assigned based on case conferences conducted by a developmental/clinical psychologist (S. W. Jacobson) and a developmental pediatrician (C. D. Molteno). A diagnosis of ADHD was made in cases where participants were reported to display (1) at least 6 of the 9 DSM-IV inattention and/or hyperactivity/impulsivity symptoms listed on the teacher DDB or maternal/caregiver K-SADS and (2) impairment (≥ 2 ADHD symptoms) in more than two settings by the age of 7 years. In the memory cohort, 25 (28.4%) participants met DSM-IV criteria for a diagnosis of ADHD. More specifically, 4 (11.8%) participants were assigned a diagnosis of ADHD hyperactive subtype, 8 (23.5%) were

assigned a diagnosis of ADHD inattentive subtype, and 13 (38.2%) were assigned a diagnosis of ADHD combined subtype; an additional 9 (26.5%) were identified as borderline ADHD (i.e., had an inattention or hyperactive symptom count of 5 or missed confirmation by second source). Pharmacological intervention for ADHD symptoms was, however, rare in the memory cohort: only one participant (girl, age = 11.0 years, nonsyndromal HE group) reported taking medication for ADHD (i.e., Ritalin).

Assessment of Maternal Sociodemographic Outcomes

Because environmental factors (e.g., socioeconomic status; SES) may confound associations between PAE and developmental outcomes, the assessment of such factors is important in studies investigating cognitive and social development in FASD (Jacobson & Jacobson, 2005). In the Cape Town Longitudinal Cohort Study all maternal interviews were conducted by a developmental pediatrician (C. D. Molteno) and were completed at multiple time points (viz., recruitment, 5- 11- and 14-year assessments) to account for socioeconomic mobility. Maternal data presented in this doctoral dissertation were obtained at the 11-year assessment.

Maternal SES was assessed using the Hollingshead (2011) Four Factor Index. Hollingshead conceptualizes SES as a multidimensional concept and, as a result, SES is evaluated using four factors: (a) education, (b) occupation, (c) sex, and (d) marital status. Maternal and, where available, paternal education and occupation are combined and stratified according to the following five levels (presented in descending order of social strata): level I, major professional; level II, minor professional or technical; level III, skilled workers; level IV, semiskilled workers; and level V, unskilled laborers.

Neuropsychological Assessment

In addition to the neuroimaging assessment described in Chapter 3 and Chapter 4, participants completed a lab-based cognitive assessment as part of the 11-year follow-up of the larger cohort.

Research setting. Neuropsychological assessment of the Cape Town Longitudinal Cohort was conducted at the Child Development Research Laboratory (CDRL) at UCT, South Africa.

Materials. There is a paucity of standardized neuropsychological assessment tools that have been developed and/or normed for research and clinical use in South Africa (Foxcroft, Paterson, le Roux, & Herbst, 2004; Shuttleworth-Edwards, 2016). Consequently, it is common practice in South African research and clinical programs to employ standardized measures of cognitive functions that have been developed and normed in Western countries. However, the socioeconomic and educational diversity, that is characteristic of the South African population, deems the blanket use of Western normative data to interpret cognitive performance of South Africans as inappropriate (Ferrett et al., 2014). Thus, rather than utilizing Western norms, the performance of children with heavy PAE was evaluated on standardized age-appropriate neuropsychological assessment tools by comparing alcohol-exposed participants to non-exposed demographically similar participants from the same community. By adopting this approach, the impact of social, environmental, and cultural differences between test and normative samples on the interpretation of test performance is reduced.

Another important factor that influences test administration, performance, and interpretation in multicultural contexts (e.g., South Africa) is language (Foxcroft, 1997; Nell, 2000). A number of members (viz., 45 [51.1%] of the 88 participants) in the memory cohort are Afrikaans-speaking. All testing materials used in the CDRL are, therefore, translated into

Afrikaans prior to the onset of test administration. The translated materials retained the original standardized structure and meaning for each test item. It is standard procedure in the CDRL for test materials to be translated by a first-language Afrikaans MA-level psychologist and back-translated by another native Afrikaans speaker.

General intellectual functioning (IQ). The Wechsler Intelligence Scales for Children-Fourth Edition (WISC-IV; Wechsler, 2003a) was administered to all participants as a part of the 11-year follow-up neuropsychological assessment battery. The WISC-IV is widely used as a standardized measure of IQ in pediatric clinical populations (Strauss, Sherman, & Spreen, 2006; Thaler, Bello, & Etcoff, 2013), and there is substantial evidence to support the validity and reliability of test outcomes (e.g., Flanagan & Kaufman, 2009). Full-Scale IQ (FSIQ) as well as scores on four domain-specific indices were derived from performance on the following WISC-IV subtests: Processing Speed Index (Coding, Symbol Search), Verbal Comprehension Index (Similarities, Vocabulary, Comprehension), Perceptual Reasoning Index (Block Design, Picture Concepts, Matrix Reasoning), and Working Memory Index (Digit Span, Letter-Number Sequencing, Arithmetic).

In the event of missing data on a subtest required to calculate the WISC-IV Index scores required to derive FSIQ scores, FSIQ was estimated using Sattler's (1992; Appendix A) formula. The validity coefficients for FSIQ scores estimated using Sattler's (1992) formula consistently exceed r =.90. Of the 88 children in the memory cohort, two failed to complete all of the required WISC-IV subtests: one boy (age = 10.5 years) with a diagnosis of FAS was missing the Comprehension subtest required for calculation of the Verbal Comprehension Index; and one boy (age = 13.6 years) with a diagnosis of PFAS was missing the Symbol Search subtest required for calculation of the Processing Speed Index.

Translation of the WISC-IV. Prior to test administration the WISC-IV test materials were translated from the original English into Afrikaans following the procedure outlined

above. The Junior South African Intelligence Scale (JSAIS; Madge, van den Berg, Robinson, & Landman, 1981) was administered during the 5-year assessment of the Cape Town longitudinal cohort. The JSAIS is a standardized measure of general intellectual functioning that has been normed for both English- and Afrikaans-speaking South African children. For the 88 children included in this research, IQ scores derived from the JSAIS were strongly positively correlated with those derived from the WISC-IV, r =.75, p < .001 (FAS/PFAS: r = .65, p = .001; HE nonsyndromal: r = .73, p < .001; Control: r = .78, p < .001). These data validate the translation and use of the WISC-IV in the Cape Town Longitudinal Cohort.

Procedure. As a part of the 11-year follow-up assessment of the larger longitudinal cohort each participant completed 2 days of neuropsychological testing. On each testing day, the research driver transported participants and their mothers/primary caregivers from their home to the CDRL in a research-dedicated van. Participants and their mothers/primary caregivers were given breakfast, a snack, and lunch over the course of the testing day. Standard WISC-IV administration and scoring instructions, as outlined in the instrument's manual (Wechsler, 2003b), were adhered to. Neuropsychological assessments were conducted in English or Afrikaans depending on the participant's primary language of school instruction.

Statistical Analysis

I used the Statistical Package for the Social Sciences (SPSS) version 23 to analyze the data generated by the three studies included in this doctoral research. Following convention, I set α to < .05 for decisions regarding statistical significance. Both categorical (viz., FASD diagnostic group: FAS/PFAS, nonsyndromal HE, and non-exposed control) and continuous (viz., AA/day, AA/occasion, and drinking frequency [days/week]) measures of PAE were used to examine the relation between PAE and the outcome variables detailed in Studies I –

III (Chapters 3–5). Thus, I conducted both between-group and regression-based statistical examination of these data. Whereas traditional approaches to parametric statistical analyses prioritize the reduction of Type I errors (i.e., the erroneous reporting of a relation between two variables), research conducted in the public health context is more concerned with missing a true effect (i.e., Type II error) and the consequent underestimation of a real health risk (Jacobson & Jacobson, 2005). Consistent with this approach, research investigating the effect of PAE on neurodevelopmental outcomes typically yields subtle results that are associated with small effect sizes. It is within this context that I, therefore, adopted the statistical approach that will least likely result in a Type II error occurring in the analysis of these data (e.g., analysis of variance [ANOVA] is a robust statistical test that is appropriate for use in cases where not all of the assumptions underlying the parametric test are met; Field, 2009).

Potential confounding variables. An important component of the statistical analysis of developmental outcomes is to examine sociodemographic factors (e.g., maternal SES, prenatal polysubstance exposure, and child age) that may confound the effect of PAE on cognitive development (Jacobson & Jacobson, 2005; Jacobson et al., 2004; May et al., 2005). To identify potential confounding variables eligible for inclusion in the analysis of the data generated in Studies I – III (Chapters 3 – 5), I examined relations between sociodemographic and outcome variables. As opposed to identifying potential confounding variables based exclusively on association with predictor variables (viz., in this case, PAE), this approach is advantageous because it includes additional covariates that are unrelated to PAE, and, therefore, increases precision (Kleinbaum, Kupper, & Muller, 1988). I therefore considered any sociodemographic variable that was related even weakly (at $p < .10$) to a given outcome variable a potential confounder. I then statistically controlled for the relevant potential confounding variable in the analyses detecting a significant effect of PAE on that outcome.

Ethical Considerations

The studies presented in this doctoral dissertation (See Chapters 3 – 5), adhered to the UCT's guidelines for conducting research involving human subjects as well as to those outlined in the Declaration of Helsinki (World Medical Association, 2013). Ethical approval for the Cape Town Longitudinal Cohort Study was obtained from WSU's Human Investigation Committee (IRB#: Appendix B), and from UCT's Faculty of Health Science Research Ethics Committee of the (HREC REF: 187/2008; Appendix C).

Informed consent and assent. Mothers of children in the Cape Town Longitudinal Cohort completed informed consent procedures upon recruitment and at subsequent pre- and post-natal laboratory visits. Participants between the ages of 7 and 12 years provided oral assent, whereas those over the age of 13 provided written assent. Children were informed that their participation was voluntary and that they could discontinue at any time without repercussions or penalties. Informed consent and assent were administered in either English or Afrikaans, depending on home language and primary language of school instruction. The informed consent and assent forms pertinent to this doctoral research are located in Appendix D, Appendix E, Appendix F, and Appendix G.

Confidentiality. Any information generated during interviews, neuropsychological testing, and/or neuroimaging assessment was kept strictly confidential. To ensure confidentiality and anonymity, participant data were labelled using a unique identification code rather than identifying information. All data were stored in filing cabinets housed in a secure location in both the UCT CDRL and WSU CDRL. Participant information was not released without written consent from the mother/primary caregiver. Moreover, in instances where further referral for medical, psychiatric and/or social support was warranted the developmental pediatrician (C. D. Molteno) made the referral to the appropriate service with

consent from the parent/primary caregiver and/or participant. Legally, CDRL research staff were obliged to report child abuse and/or neglect to the appropriate authorities.

Cost and compensation. Because transportation and meals were provided by the CDRL, there were no costs to the participant or their mother/primary caregiver for being involved in this research. Mothers/primary caregivers were compensated 150 South African Rand (ZAR) for each testing day and a photo of their child. Following the neuropsychological assessment, each participant was given a small age-appropriate gift (e.g., pencil crayons). Following the neuroimaging assessment, each participant was given a printed screen-shot of their high-resolution anatomical scan.

Risks and benefits. There are no risks associated with the administration of the neuropsychological tests included in the testing battery. In addition to this, MRI and associated imaging modalities are non-invasive and, therefore, have no associated direct risks. Further ethical considerations pertinent to the neuroimaging assessment are detailed in the analogous *Ethical Considerations* section in Chapter 3.

Apart from financial compensation, taking part in the studies included in this doctoral research did not yield any other direct benefits to the participants or mothers/caregivers. As with the broader aim of the larger longitudinal cohort study, this research strives to provide information pertinent to the ongoing characterization of the deleterious effects of PAE on neurodevelopment.

Memory Cohort Characteristics

Consistent with literature documenting maternal risk factors associated with FASD (Esper & Furtado, 2014; May et al., 2008), mothers of children diagnosed with FAS or PFAS were older than mothers of children in the HE and non-exposed control groups, post-hoc p's $< .05$ (Table 2.1). Although mothers of children in the FAS/PFAS group were less educated than those of children in the non-exposed control group, $p < .01$, education levels did not

differ between mothers of children in the FAS/PFAS and HE groups, $p > .10$, or between those in the HE and control groups, $p > .20$. Mothers of children in the FAS/PFAS group were more economically disadvantaged than mothers of children in either the HE or non-exposed control groups (on average Hollingshead level V—Unskilled Laborers, lowest of 5 levels), both p's $< .01$. In addition, mothers of children in the HE group were more disadvantaged than mothers of children in the non-exposed control group (on average HE mothers scored on the lower limit of level IV—Semiskilled Workers; whereas non-exposed control mothers scored on the upper limit of level IV), $p < .05$.

In the memory cohort, all but one mother of a child in the non-exposed control group abstained; the one mother reported drinking 4 drinks on one occasion around the time of conception at time of recruitment (Table 2.1). During pregnancy all of the mothers of children in the non-exposed control group reported abstaining from drinking. Mothers of children in the FAS/PFAS and HE groups met the criteria for heavy drinking (i.e., consuming, on average, approximately 2 standard drinks per day) both at the time of conception and during pregnancy. Mothers of children in the FAS/PFAS group reported drinking, on average, 8 standard drinks per occasion, and mothers of children in the HE group reported drinking 7 standard drinks per occasion during pregnancy. With regard to frequency of drinking during pregnancy (days/week), mothers of children in both exposure groups concentrated their drinking on 1 to 2 days per week. One mother whose child was diagnosed with FAS denied drinking during pregnancy. The alcohol exposure for this mother was estimated by using the median of alcohol use for mothers in the FAS group. With regard to frequency of drinking at the time of conception, mothers of children in both exposure groups concentrated their drinking on 2 days per week. Mothers of children in the FAS/PFAS group reported drinking, on average, 9 drinks per occasion, and mothers of children in the HE group 8 drinks per occasion. Mothers of children in the FAS/PFAS group reported drinking on a

Table 2.1
Sample Characteristics (N = 88)

Variable	FAS/PFAS (*n*=23[a])	HE (*n*=27)	Non-exposed control (*n*=38)	*F* or χ^2	*p*	*ESE*
Maternal variables						
Maternal age at delivery (years)	29.2 (7.3)	24.8 (4.6)	26.0 (6.1)	3.48	.04*	.08
Maternal education (years)	8.4 (2.3)	9.4 (2.4)	9.9 (2.0)	3.58	.03*	.08
Socioeconomic status	15.4 (6.4)	21.1 (7.6)	25.6 (8.0)	13.36	<.001***	.24
Alcohol consumption at conception						
AA/day (oz)[b]	1.5 (0.9)	1.7 (2.1)	0.003 (0.02)	17.79	<.001***	.30
AA/occasion (oz)	4.5 (2.3)	3.8 (3.4)	0.1 (0.3)	37.55	<.001***	.47
Frequency (days/week)	2.2 (1.4)	2.3 (2.0)	0.009 (0.05)	32.01	<.001***	.43
Prenatal alcohol exposure						
AA/day (oz)[b]	1.1 (0.8)	1.0 (1.2)	0.0 (0.0)	18.57	<.001***	.30
AA/occasion (oz)	4.2 (1.8)	3.5 (3.2)	0.0 (0.0)	40.59	<.001***	.49
Frequency (days/week)	1.6 (1.0)	1.4 (1.2)	0.0 0.0	35.65	<.001***	.46
Prenatal smoking (cigarettes/day)	6.8 (5.5)	6.9 (6.1)	2.5 (4.1)	7.82	.001**	.16
Child variables						
Child's age at testing (years)	12.3 (1.4)	10.5 (0.5)	11.0 (1.1)	18.67	<.001***	.31
Sex (% male)	56.5	40.7	42.1	1.55	.46	.13
WISC-IV IQ						
Full Scale IQ	63.9 (9.3)	75.8 (16.0)	76.8 (14.6)	6.88	.002**	.14
Processing Speed Index[c]	76.5 (8.4)	91.3 (18.3)	89.4 (17.3)	6.23	.003**	.13
Verbal Comprehension Index[d]	60.9 (8.4)	67.7 (12.1)	70.5 (14.6)	4.15	.02*	.09
Perceptual Reasoning Index	70.8 (11.1)	81.0 (16.2)	81.7 (14.3)	4.80	.01*	.10
Working Memory Index	79.3 (15.7)	90.9 (17.9)	90.6 (14.5)	4.36	.02*	.09
ADHD (% yes)	43.5	22.2	23.7	3.49	.17	.20
Inattention symptoms	4.6 (2.8)	3.3 (3.2)	2.5 (3.1)	3.44	.04*	.08
Hyperactivity symptoms	4.0 (3.1)	2.6 (2.7)	1.8 (2.8)	4.05	.02*	.09

Note. Means are presented with standard deviations in parentheses. FAS = fetal alcohol syndrome; PFAS = partial fetal alcohol syndrome; HE = heavily exposed nonsyndromal; ESE = effect size estimate; AA = absolute alcohol; WISC-IV = Wechsler Intelligence Scale for Children—Fourth Edition; IQ = general intellectual functioning; ADHD = attention deficit hyperactivity disorder. The estimate of effect size was calculated using either η^2 or φ_c depending on whether a one-way ANOVA or Chi-squared test was employed.

[a]FAS *n* = 13; PFAS *n* = 10

[b]1 oz. AA/day ≈ 2 standard drinks

[c]*n* = 87, Processing Speed Index missing for one boy (age = 13.6 years) in the FAS/PFAS group.

[d]*n* = 87, Verbal Comprehension Index missing for one boy (age = 10.5 years) in the FAS/PFAS group

*$p < .05$. **$p < .01$. ***$p < .001$.

similar number of days/week as mothers in the HE group, and their drinking levels were comparable. It is of clinical relevance that factors such as timing of exposure (Lipinski et al., 2012; Sulik, 2005), genetic vulnerability (Dodge, Jacobson, & Jacobson, 2014; Jacobson et al., 2006; Viljoen et al., 2001; Warren & Li, 2005), or nutritional status (Carter et al., 2014; May et al., 2016; May, Hamrick, et al., 2014) may contribute to differences in the diagnoses observed here.

Mothers of children with PAE (i.e., both FAS/PFAS and HE groups) smoked more than mothers of non-exposed control children, p's < .01 (Table 2.1). None of the mothers reported using cocaine during pregnancy. Ten mothers (2 FAS/PFAS; 7 HE; 1 non-exposed control) reported using marijuana during pregnancy (mean = 3.1 times/week, range = 0.8 – 7.0) and four (1 FAS/PFAS; 3 HE) reported using methaqualone ("mandrax") during pregnancy (mean = 1.6 times/week, range = 0.03 – 3.2). Because the number of prenatal drug exposure cases was too rare for statistical adjustment, I reran any analyses detecting an association between PAE and study outcome variables omitting children with prenatal marijuana or mandrax exposure in subsequent data chapters.

Children in the FAS/PFAS group were older, $p < .001$, had lower IQ scores (as indexed by WISC-IV Full-Scale IQ), $p < .01$, and performed more poorly on the WISC-IV Processing Speed Index, Perceptual Reasoning Index, and Working Memory Index scores, all p's < .05, than children in both the HE and non-exposed groups (Table 2.1). Although children in the FAS/PFAS group obtained lower Verbal Comprehension Index scores than children in non-exposed control group, this difference fell just short of significance when compared to children in the HE group, p's = .005 and .06, respectively. Children in the HE group showed a trend towards being slightly younger and had similar IQ scores when compared to children in the non-exposed control group, p's = .06 and > .20, respectively. There were no significant between-group differences in sex distribution or frequency.

Although there were no significant between-group differences in the number of children with a diagnosis of ADHD, children in the FAS/PFAS group were reported to display more inattentive and hyperactive symptoms than children in the non-exposed control group, *p*'s < .05 and .01, respectively. In addition, children in the HE group were reported to display a similar number of inattentive and hyperactive symptoms to non-exposed control children, *p*'s > .20.

CHAPTER 3: NEURAL ACTIVATION DURING VISUAL PERCEPTION IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS – STUDY I

Previous studies investigating visual-spatial learning and memory in children with fetal alcohol spectrum disorders (FASD) have suggested that documented impairments in the encoding and retrieval of information may be influenced by lower-order cognitive processes (e.g., poor visual perception; Kaemingk & Halverson, 2000). However, few studies have directly examined visual perception in children with FASD (for reviews, see Kodituwakku & Kodituwakku, 2014; Mattson et al., 2011). Moreover, there is a paucity of neuroimaging studies investigating relations between the structure and functioning of the regions recruited during visual perception in this clinical population. Further study of the effects of heavy prenatal alcohol exposure (PAE) on neural activation during basic perceptual processing is, therefore, warranted.

In this chapter, I provide a brief review of recent literature on visual perception, and then describe findings from the small number of studies investigating visual perception in FASD. Thereafter, I present the current methods employed to investigate visual perception in a sample of children with heavy PAE. Finally, I report the findings of this study and integrate them with the broader literature pertaining to relations between visual perception and memory.

Visual Perception

The visual system is one of the most thoroughly researched and clearly delineated human sensory systems. A rudimentary sketch of the system suggests that basic visual information is transmitted from the retina to the lateral geniculate nucleus, which in turn

projects to the primary visual cortex (Brodmann Area [BA] 17) in the occipital lobe (Darby & Walsh, 2005; Lynch & Corbett, 2013). Visual information is subsequently sent to visual association areas, where it is initially elaborated and synthesized (BA 18) and is then integrated with other sensory information (BA 19) as well as with information from higher-order perceptual systems (Darby & Walsh, 2005). Intact visual perception is, therefore, intrinsic to the ability to perceive and integrate basic visual percepts (e.g., light, color and shape), and to recognize higher-order visual information (e.g., objects and scenes).

Viewed from a more fine-grained perspective, visual information is processed along two primary cortical pathways: the dorsal (occipitoparietal, or "where") and ventral (occipitotemporal, or "what") visual streams (Goodale & Milner, 1992; Mishkin, Ungerleider, & Macko, 1983). The dorsal visual stream transmits information from the magnocellular layers of the lateral geniculate nucleus, to the primary visual cortex, and then to the posterior parietal lobe (Lynch & Corbett, 2013). This stream is responsible for localizing visual object information within space. Damage to regions comprising this stream, therefore, results in impaired visuospatial abilities (e.g., impaired angular judgement, construction and/or optic ataxia; Farah, 2003). The ventral visual stream transmits information from the parvocellular layers of the lateral geniculate nucleus, to the primary visual cortex, and then to the inferior temporal lobe (Lynch & Corbett, 2013). It is along this processing stream that visual information is linked to semantic knowledge such that effective object recognition can occur. Broadly speaking, damage to regions comprising the ventral visual stream can, therefore, result in impairments either at the level of integrating basic visual information into a meaningful whole (viz., apperceptive agnosia) or at the level of object recognition (viz., associative agnosia; Darby & Walsh, 2005).

Recent theoretical models of memory processing (e.g., Predictive, Interactive Multiple Memory Systems [PIMMS]; Henson & Gagnepain, 2010; see Chapter 1) include

higher-order perceptual processing, especially those aspects supported by the ventral visual stream, as an important component in the encoding of visual information. The relation between perception and memory is particularly evident within the developmental context: Children are more reliant on perceptual features during concept formation, whereas adults are more reliant on abstract semantic categories (Ofen & Shing, 2013). Because of (a) the important theoretical and anatomical distinctions between the dorsal and ventral visual stream, and (b) the developmental significance of higher-order perceptual processing in memory formation, it is of clinical and theoretical relevance to examine the integrity of the ventral visual stream in clinical populations with documented encoding impairments (e.g., FASD; Lewis et al., 2015; Mattson & Roebuck, 2002).

Ventral visual stream: Category-selective regions of interest. In recent years, novel functional magnetic resonance imaging (fMRI) study designs have been employed to investigate the functioning of the ventral visual stream in healthy populations. Results from human neuroimaging studies have identified several functionally distinct focal regions of interest that are (a) located within the anatomical constraints of the ventral visual stream, and (b) of relevance to the study of higher-order visual perception. For example, the fusiform face area (FFA; Kanwisher, McDermott, & Chun, 1997; McCarthy, Puce, Gore, & Allison, 1997; Sergent, Ohta, & Macdonald, 1992; Tong, Nakayama, Moscovitch, Weinrib, & Kanwisher, 2000), lateral occipital complex (LOC; Grill-Spector, Kourtzi, & Kanwisher, 2001; Kourtzi & Kanwisher, 2000; Malach et al., 1995), and parahippocampal place area (PPA; Aguirre, Zarahn, & D'Esposito, 1998; Epstein, Harris, Stanley, & Kanwisher, 1999; Epstein & Kanwisher, 1998) respond selectively to faces, objects, and scenes, respectively. Because these functional regions of interest (fROIs) show a high degree of category specificity during the recognition of visual objects, they are of particular relevance to the study of perceptual processes that support successful object recognition (for a review, see Grill-Spector &

Malach, 2004). Additionally, category-specific activations are relatively robust under varied conditions of stimulus presentation (e.g., line drawing vs. color image), indicating a good perceptual constancy (Grill-Spector, 2003). In this study, I focused specifically on the LOC and PPA to investigate activation associated with the processing of visual object information and scene perception, respectively.

Lateral occipital complex (LOC). The LOC is the cortical region within the occipital lobe that shows preferential bilateral activation when participants view everyday objects as opposed to visual textures (e.g., blurred images) and/or patterns (Malach et al., 1995). Although there is some across-study variation in the anatomical definition of the LOC, the consensus is that the LOC is classified as a large bilateral region located on the lateral surface of the posterior temporal cortex with both dorsal and ventral extensions within the lateral occipital cortex (for a review, see Grill-Spector et al., 2001). The LOC is functionally mature relatively early on in development (viz., by age 7), and shows functional consistency across the lifespan (Golarai et al., 2007). It is, therefore, a good candidate for the assessment of an object-selective fROI in the ventral visual stream in pediatric populations. Evidence to support both the category-selectivity of the LOC and its role in object recognition comes from (a) fMRI studies of healthy child and adult populations (Cant & Goodale, 2011; Golarai et al., 2007; Grill-Spector et al., 2001; Malach et al., 1995), and (b) lesion studies documenting the onset of impaired object recognition (i.e., visual agnosia) with damage to cortex within the LOC (e.g., occipital-temporal junction; Alexander & Albert, 1983; Moscovitch, Winocur, & Behrmann, 1997).

Parahippocampal place area (PPA). The PPA (Epstein & Kanwisher, 1998) is defined as the bilateral region of posterior parahippocampal cortex that is adjacent to the FFA and the collateral sulcus (for a review, see Epstein, 2005). The presentation of visual scenes, when contrasted to faces, objects and/or patterns, reliably results in the bilateral activation of

the PPA (Cant & Goodale, 2011; Epstein & Kanwisher, 1998; Park, Brady, Greene, & Oliva, 2011; Park & Chun, 2009). Similar to the LOC, the developmental trajectory in this case is such that the PPA displays relatively mature scene-selective activation by the age of 7 years (Golarai, Liberman, Yoon, & Grill-Spector, 2010; Ofen et al., 2007; Vuontela et al., 2013). Moreover, the functional maturation of the PPA correlates with age-related changes in recognition memory performance (Golarai et al., 2007). It is, therefore, a good candidate for the assessment of a scene-selective fROI in the ventral visual stream in pediatric populations. In addition to the PPA's role in the perception of scenes, activation in this fROI has been implicated in tasks of spatial navigation, as well as in the encoding of visual scenes (Epstein, Parker, & Feiler, 2007; Golarai et al., 2007; Ofen et al., 2007).

Visual Perception in FASD

Despite well documented alcohol-related effects on ocular functioning (Flanigan et al., 2008; Strömland & Pinazo-Durán, 2002; Strömland, 2004), visual acuity (Carter et al., 2005; Coles, Platzman, Lynch, & Freides, 2002; Landgren, Svensson, Strömland, & Grönlund, 2010), primary visual responses (Coffman et al., 2013; Scher et al., 1998), and oculomotor control (Green, Munoz, Nikkel, & Reynolds, 2007; Green, Mihic, Brien, et al., 2009; Paolozza et al., 2014a, 2014b), there is limited research investigating higher-order visual-perceptual functioning in children and adolescents with FASD. To date, neuropsychological studies have primarily focused on the assessment of visual-spatial construction in children with FASD (for a review, see Kodituwakku & Kodituwakku, 2014; Mattson et al., 2011). Results from this line of investigation consistently suggest that children with heavy PAE present with visual-constructional difficulties akin to constructional apraxia (Chiodo, Janisse, Delaney-Black, Sokol, & Hannigan, 2009; Janzen, Nanson, & Block, 1995; Jirikowic, Carmichael Olson, & Kartin, 2008; Meyer, 1998). For example, Uecker and Nadel

(1996) used the Beery Developmental Test of Visual-Motor Integration (Beery, 1989) to assess geometric figure copying in children (M_{age} = 10.0 years, *SD* = 2.3) with and without a diagnosis of FAS. Children in the FAS group reproduced significantly fewer of the test items correctly than children in the non-exposed control group. The authors identified two main qualitative characteristics as underlying the impaired performance: Children in the FAS group had more frequent errors as a result of (a) difficulty drawing corners, and (b) overall shape distortions. This interpretation is consistent with studies reporting that children with heavy PAE are impaired on tasks of angle judgement (e.g., the Judgement of Line Orientation task (Benton, Sivan, Hamsher, Varney, & Spreen, 1994; Kaemingk & Halverson, 2000; Paolozza et al., 2014b; but, cf. Janzen et al., 1995). Although the aforementioned deficits in primary visual processing and visual perception are most frequently detected in dysmorphic children (i.e., children with a diagnosis of FAS or PFAS), they have been reported in non-dysmorphic heavily exposed children (Mattson et al., 1998).

It is of relevance to note that the visual-perceptual and visual-constructive abilities examined in the neuropsychological studies reviewed above are primarily supported by the dorsal visual stream (Farah, 2003). The paucity of neuropsychological and neuroimaging research directly assessing the functioning of the ventral visual stream in children with FASD constitutes a significant gap in the literature. To date, neuropsychological investigation of ventral visual stream functioning in children with PAE has been limited to the behavioral assessment of facial recognition (Kaemingk & Halverson, 2000; Uecker & Nadel, 1996). For example, Uecker and Nadel (1996) examined facial recognition in 15 children with FAS (M_{age} = 10.0 years, *SD* = 2.3) and 15 non-exposed control children (M_{age} = 10.0 years, *SD* = 2.3) using the Face Recognition subtest of the Kaufman Achievement Battery for Children (K-ABC; Kaufman & Kaufman, 1983). Their results indicated that (a) there were no between-group differences in facial recognition performance, and (b) performance on this

task improved with age, regardless of exposure history. There remains, therefore, a novel opportunity to employ novel neuroimaging assessment paradigms that assess the visual perceptual functions that are supported by the ventral visual stream in children with a history of PAE.

Consistent with the scarcity of neuropsychological studies, the ventral visual stream has received limited attention in studies using structural and functional neuroimaging techniques to investigate the effect of PAE on brain-behavior relations. This scarcity is, at least in part, attributable to the fact that most structural neuroimaging investigations of exposure-related volumetric changes render the occipital lobes less vulnerable to the effects of PAE than structures such as the corpus callosum, cerebellum, and frontal and parietal lobes (for a reviews, see Lebel et al., 2011; Moore et al., 2014). The temporal lobes have, however, been highlighted as vulnerable to the effects of PAE. Temporal structural impairments in alcohol-exposed subjects include increased gray matter density (Sowell et al., 2001; Sowell et al., 2002), increased cortical thickness (Sowell et al., 2008; but, cf. Robertson et al., 2015; Zhou et al., 2011), decreased distance from center (Sowell, Thompson, Mattson, et al., 2002) and reduced inferior temporal asymmetry (Sowell, Thompson, Peterson, et al., 2002). In the only published study examining occipital-temporal structure and function concurrently, Li et al. (2008) reported volumetric reductions in occipital-temporal white and gray matter in a group of young adults (n = 7; M_{age} = 20.4 years, SD = 2.1) with a history of heavy PAE when compared to a group of non-exposed control participants (n = 7; M_{age} = 21.3 years, SD = 1.6). Moreover, functional activation in the occipital-temporal region (as obtained during an fMRI assessment of sustained visual attention) was located more superiorly in the alcohol-exposed group than in the non-exposed control group. Li and colleagues noted that the relative contribution of basic visual perceptual functions and visual attentional functions to higher-

order cognitive processes remains to be investigated and that, therefore, further examination of primary visual perceptual functioning in individuals with a history of PAE is warranted.

Specific Aims and Hypotheses

The main aim of this study was to investigate neural activation in children with and without heavy PAE during the visual perception of objects and scenes. I used an fMRI functional localizer task to assess neural activation in two category-specific fROIs—the LOC and PPA, both bilaterally. Additionally, I aimed to assess whether activation in either of the fROIs mediated the effect of PAE on general intellectual functioning. The use of category-specific fROIs in the ventral visual stream provides a useful opportunity not only to assess the functional integrity of the ROI itself, but its additive contribution to higher-order tasks (e.g., encoding visual information; see Chapter 4). Because this study is the first to investigate LOC and PPA activation in this clinical population, the key research questions are exploratory in nature:

1. Do children with a history of heavy PAE differ from typically-developing, demographically similar control children in the spatial extent to which they activate neurons in the LOC and PPA while passively viewing objects and scenes, respectively?
2. Do children with a history of heavy PAE differ from typically-developing, demographically similar control children in the magnitude of neural activations in the LOC and PPA while passively viewing objects and scenes, respectively?
3. Is activation in the LOC and/or PPA associated with general intellectual functioning?

Methods

Participants

This study is nested within an on-going prospective longitudinal cohort study (Cape Town Longitudinal Cohort; Jacobson et al., 2008). That longitudinal study aims to investigate the adverse effects of heavy PAE on cognitive development (for a detailed description of the study sample, see Chapter 2). The participants included in this study were drawn from a sub-sample of 88 children (the Memory Cohort) who were taking part in the 11-year assessment of the Cape Town Longitudinal Cohort. Figure 3.1 illustrates the process I followed to identify the final sample of 74 participants for inclusion in this study's analyses.

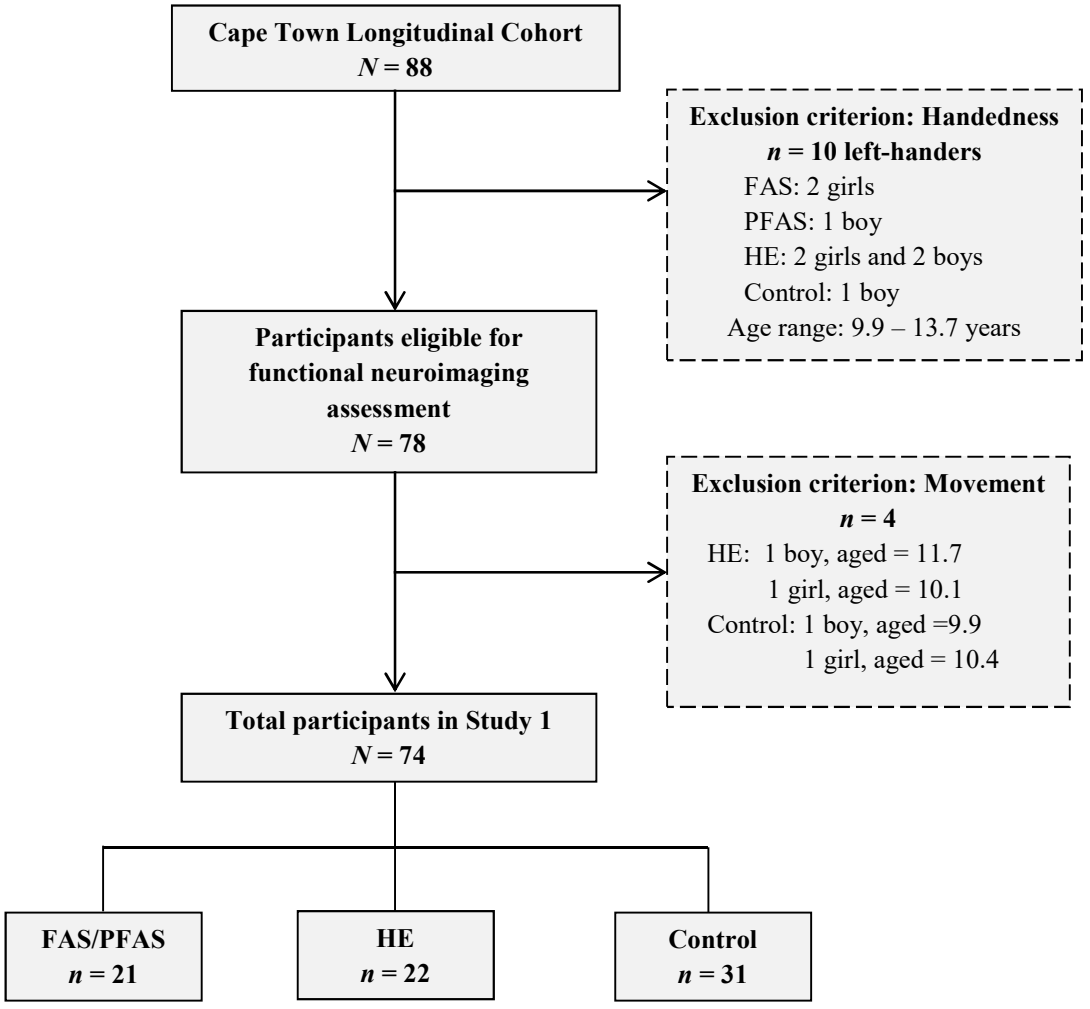

Figure 3.1. Diagram illustrating the selection of the final sub-sample of 74 participants as well as details relating to exclusion. FAS = fetal alcohol syndrome; PFAS = partial fetal alcohol syndrome; HE = heavily exposed nonsyndromal.

Exclusion criteria. This study was performed in accordance with protocols approved by the UCT and WSU Human Research Ethics Committees. The Cape Universities Brain Imaging Centre (CUBIC) MRI screening form (see Appendix H) was administered to all participants, in the presence of their parent/primary caregiver, prior to commencement of the neuroimaging assessment. Based on this screening interview, all 88 participants were deemed fit for neuroimaging assessment.

Handedness. Although rare, between-group differences in the functional lateralization of, and neural activation during, certain cognitive functions have been described when comparing left- and right-handed individuals (e.g., Singh et al., 1998; Szaflarski et al., 2002). To prevent the introduction of unwanted heterogeneity to the analysis of these data it is, therefore, common practice to exclude left-handers from functional neuroimaging assessment. Consistent with this approach, I only included right-handed children in the functional imaging procedure employed in this study.

Handedness was examined prior to the neuroimaging assessment using the Edinburgh Handedness Inventory (EHI; Oldfield, 1971), which assesses hand preference across a number of domains (e.g., writing, eating, sports). The EHI has been used extensively in pediatric neuroimaging studies (e.g., White et al., 2013) and in South African research (e.g., Ferrett, Carey, Thomas, Tapert, & Fein, 2010). Based on their EHI responses, children were assigned to one of the following categories: right-hander, mixed right-hander, mixed left-hander, or left-hander. Children qualifying as either of the latter two categories were excluded (n = 10; for details, see Figure 3.1) from the functional component of the imaging study and underwent structural scanning exclusively. Thus, 78 of the original 88 children were included in the functional neuroimaging component of the study.

In-scanner movement. A major methodological constraint within pediatric neuroimaging studies is that children move more than adults (Bookheimer, 2000; Poldrack, Paré-Blagoev, & Grant, 2002). While the application of strict thresholds for acceptable movement during image acquisition (viz., 1 mm displacement or 1° rotation in any direction [x, y, or z] and/or translation [pitch, roll, or yaw]) may be appropriate in the analysis of adult neuroimaging data, it is of limited feasibility in pediatric neuroimaging analyses. The convention in pediatric neuroimaging studies is, therefore, to exclude any subject whose movement exceeds 3 mm displacement or 3° rotation in any direction. For each subject, I examined movement data during image preprocessing (see *Preprocessing* section below). Based on these data I excluded another four children, resulting in the final analyses examining data from 74 children (for details, see Figure 3.1).

Neuroimaging Assessment

Research setting. I conducted neuroimaging data collection at the CUBIC, which is located on the University of Stellenbosch Health Sciences Campus. CUBIC is a joint initiative between Siemens, UCT, Stellenbosch University, and the University of the Western Cape. CUBIC houses a 3T Siemens Allegra MR scanner (Siemens, Erlangen Germany) with fMRI capabilities. CUBIC also has a mock scanner, which was used to help prepare children to perform cognitive tasks in the unfamiliar scanner environment, thereby reducing anxiety and facilitating completion of high-quality MRI scans (Carter, Greer, Gray, & Ware, 2010; Hallowell, Stewart, de Amorim e Silva, & Ditchfield, 2008; Malisza, Martin, Shiloff, & Yu, 2010; Rosenberg et al., 1997).

Functional localizer task. I used an fMRI functional localizer task to assess patterns of neural activation in two fROIs located in the ventral visual stream—the LOC and PPA (N. Ofen, personal communication). The functional localizer task utilizes a blocked design for

stimulus presentation (see Figure 3.2). In a standard blocked design fMRI paradigm, multiple blocks for each experimental condition are presented in alternating/random order. Within each condition, stimuli are presented sequentially throughout the block for a fixed period of time. Between the presentation of each experimental condition, a contrasting 'null' or 'rest' condition is introduced. The blood oxygen level dependent (BOLD) response reported for each experimental condition is an average of individual hemodynamic response functions for each stimulus presented within the block (Amaro & Barker, 2006; Huettel, Song, & McCarthy, 2009a; Lindquist, 2008). Blocked designs are associated with increased statistical power to detect neural activation (Amaro & Barker, 2006), and are, therefore, considered to be the gold standard for functional localizer tasks. Moreover, the use of functional localizer tasks is the recommended practice for the identification of fROIs (Saxe, Brett, & Kanwisher, 2006). Research employing this method to successfully identify and replicate neural activation within category-specific fROIs in the ventral visual stream provides further support for this recommendation (for a review, see Grill-Spector & Malach, 2004).

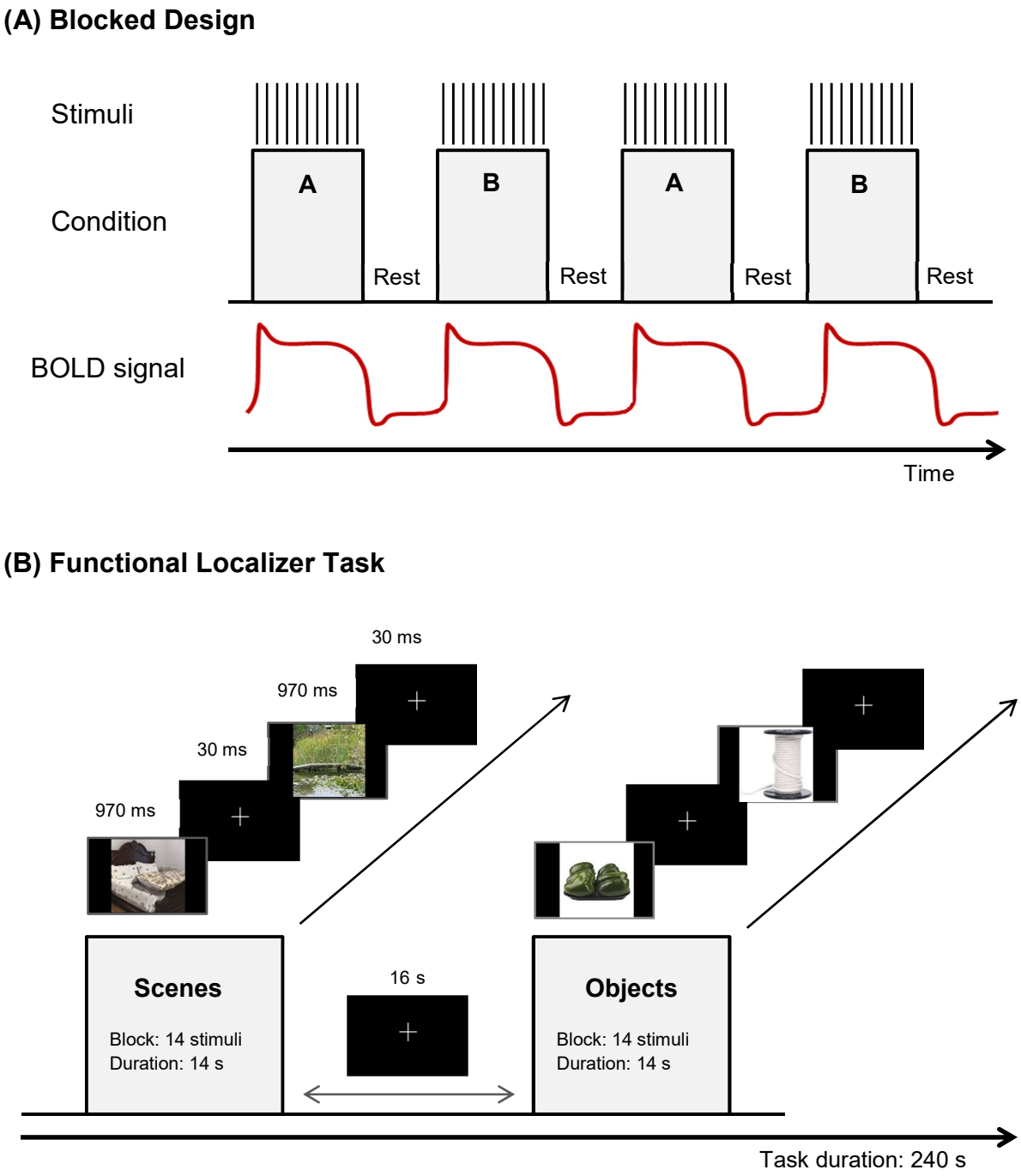

Figure 3.2. A schematic depicting the standard characteristics of an fMRI blocked design (a) adapted from Amaro & Barker (2006) and the functional localizer task design (b).

In this study, I presented alternating blocks of scenes and objects to detect activation in the two fROIs under study. The functional localizer task was programmed and run in E-Prime 2.0 (Psychology Software Tools, Inc., Pittsburgh, USA). The task consisted of 8 blocks: four blocks presenting scenes, and four presenting objects. Within each block, 14

images were shown at a rate of 1 per second, with an inter-stimulus fixation slide of 30 ms (see Figure 3.2). Between each block, a fixation slide was shown for 16 s. Task stimuli were arranged into 8 lists of 14 images, and were presented in pseudo-randomized and counterbalanced order. The order of condition presentation was determined by participant ID: Participants with an even ID number viewed a block of objects first, whereas participants with an odd ID number viewed a block of scenes first. The duration of the functional localizer task was 4 min.

Procedure. I conducted data collection with the assistance of two female MA-level psychologists. I provided detailed training on the preparation for and administration of the functional localizer task to each of these research assistants. To avoid experimenter bias, the research assistants and I (hereafter collectively referred to as the examiner) were blind to participant FASD diagnosis and/or PAE history[3], as well as to psychiatric diagnoses. Because many of the participants were Afrikaans-speaking, task instructions were delivered in English or Afrikaans based on the participant's language of school instruction and/or language proficiency (for more details, see *Neuropsychological Assessment* section in Chapter 2).

General neuroimaging study procedure. For all participants, the general study procedure was as follows: The research driver and research nurse or community worker transported mothers/primary caregivers and participants to CUBIC in a research-dedicated van. Both the research nurse and community worker have extensive experience facilitating the scanning procedure, and had performed these roles during earlier neuroimaging studies that were conducted as part of data collection for the on-going longitudinal study. Either the research nurse or one of the examiners obtained informed consent from the mother/primary caregiver and participant upon arrival at CUBIC (see *Ethical Considerations* section in Chapter 2). The CUBIC MRI screening form was also completed at this time. The participant

[3]The exception to this rule occurs in the most severe cases in which the dysmorphic features of heavy prenatal alcohol exposure resulted in the participants FASD diagnosis being apparent.

then changed out of his/her clothes and into a tunic provided by CUBIC. This was done to ensure that no metal items embedded in the child's clothing or on the child's person would inadvertently be taken into the scanner room.

The participant was then brought to the mock scanner room where s/he was (a) prepared for the scanning experience, and (b) given the opportunity to practice the neuroimaging tasks. The CUBIC mock scanner is a simplified non-functional model of an MRI scanner (Figure 3.3). During the mock scanner procedure, the examiner introduced the scanner environment, explained what the scanner does, what it sounds like, and stressed the importance of lying still during image acquisition (for the script followed by examiners, see Appendix I). The participant was given an opportunity to lie in the mock scanner, to practice looking at an image via the mirror attached to the mock coil, to listen to the sounds that would be heard during each of the imaging sequences, and to practice how to react or respond when in the scanner.

A second aim of the mock scanner procedure was to introduce participants to the neuroimaging tasks and to provide them with an opportunity to complete a practice trial for each task included in the scanner protocol (for the full imaging protocol, see Appendix J). The functional localizer task was the first task administered following the acquisition of each

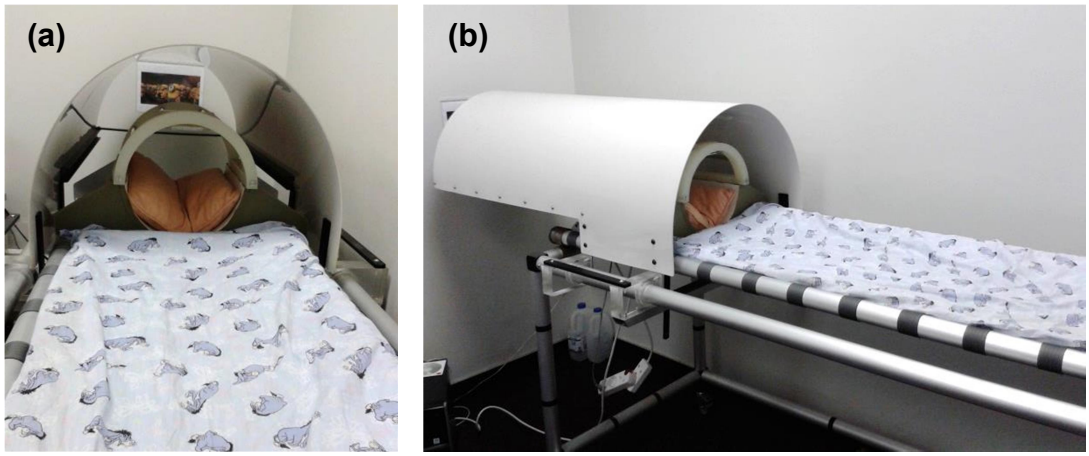

Figure 3.3. Images of the CUBIC mock scanner showing the mock scanner bore (a) and a side view of the mock scanner set up (b). The bore is slid over the participant when s/he lies on the bed.

participant's structural scan. The participant was instructed to view the stimuli passively (i.e., no button presses were required; for script read by the examiner, see Appendix K). The participant was asked to look at each picture carefully. The participant was then given an opportunity to practice looking at example images of both scenes and objects. Additionally, each participant selected an animated children's movie to watch during the acquisition of the structural scan.

After completion of the mock scanner procedure, the examiner took the participant into the scanner room where s/he was given earplugs and earphones before being positioned on the scanner bed by a radiographer. To prevent excessive head motion and to optimize each participant's head position, the radiographer placed cushions underneath and next to the head. The participant was accompanied by either the research nurse or a community worker during the entire scanner protocol. The research nurse/community worker sat next to the participant and was given a panic button to press in the event that a problem arose in the scanner (e.g., the participant became distressed). Participants were also given the option of having their mother or primary caregiver in the scanner room. Once in the scanner, the examiner communicated task instructions to the participant via an intercom. Prior to commencing each task, the examiner reminded participants of the relevant instructions and reminded them to lie still.

The same scanner protocol was followed for each participant (see Appendix J). In its entirety, the duration of the scanner protocol was 39 min and 15 s. The examiner administering the scanner protocol recorded detailed notes of the scan start and end times, the task onset times as well as of any technical issues that arose during the neuroimaging assessment. The functional localizer task stimuli were projected from the computer running the E-Prime task onto a screen positioned behind the scanner bore. Participants were able to view the screen via a mirror fixed to the head coil.

Data acquisition. Each subject was scanned, using a single-channel head coil, on a 3T Allegra MR scanner (Siemens, Erlangen Germany). High-resolution T_1-weighted magnetization-prepared rapid gradient echo (MPRAGE) anatomical scans were acquired in a sagittal orientation using a three-dimensional motion corrected multi-echo sequence (Tisdall, Hess, & van der Kouwe, 2009; van der Kouwe, Benner, Salat, & Fischl, 2008) with the following parameters: TR = 2530 ms, TE_1 = 1.53 ms, TE_2 = 3.21 ms, TE_3 = 4.89 ms, TE_4 = 6.57 ms, 128 slices, slice thickness = 1.3 mm, flip angle = 7°, field of view = 256 mm, voxel size = 1.3 × 1.0 × 1.3 mm^3, and scan time = 8:07 min. During the fMRI protocol, 124 functional T_{2*}-weighted volumes sensitive to blood-oxygen level dependent (BOLD) contrast were acquired using a gradient echo, echo planar sequence with the following parameters: TR = 2000 ms, TE = 30 ms, each volume contained 34 slices, slice thickness = 3 mm, flip angle = 90°, field of view = 200 mm, voxel size = 3.1 × 3.1 × 3.0 mm^3, and scan time = 4:12 min. The order of image acquisition was interleaved.

Neuropsychological Assessment

In addition to the neuroimaging assessment described above, participants completed a lab-based cognitive assessment as part of the 11-year follow-up of the larger cohort. General intellectual functioning was assessed using the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV; Wechsler, 2003a). For details pertaining to the standardized administration procedure for the WISC-IV in the Cape Town Longitudinal Cohort, please refer to the analogous section in Chapter 2.

Ethical Considerations

For ethical considerations pertaining to the larger Cape Town Longitudinal Cohort, please see the analogous section in Chapter 2.

Risks and benefits. Regarding the neuroimaging study, MRI and associated imaging modalities are non-invasive and, therefore, have no associated direct risks. All Child Development Research Laboratory (CDRL) staff working in the scanner environment were briefed by the CUBIC radiologists on standard MRI safety procedures. All participants and mothers/primary caregivers entering the scanner environment were screened and briefed with regard to MRI safety protocols by either the examiner or a research nurse. Participants were only scanned if they met inclusion criteria and consented to the procedure. Moreover, participants were informed that they could discontinue the neuroimaging assessment at any point in time. Participants were given earplugs and headphones to provide protection from the loud noise generated during image acquisition. The research nurse/community worker and mother/primary caregiver (if accompanying the participant) were also given earplugs to wear during image acquisition.

Data Management and Analysis

Neuroimaging data. I preprocessed and analyzed neuroimaging data from all participants using Statistical Parametric Mapping (SPM) version 8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), an extension package for MATLAB version R2008a, and Statistical Package for the Social Sciences (SPSS) version 23. To ensure that I remained blind to participant alcohol exposure history as well as to FASD diagnosis during data analysis, all data were assigned blinded identification codes by the project data manager.

Preprocessing. I used the following preprocessing steps for all fMRI data. First, I discarded the first four functional volumes from each participant's functional data to allow for T_1 equilibration. I then manually oriented each participant's functional images to the anterior commissure-posterior commissure line. Thereafter, I performed slice timing

correction to the middle slice (viz., slice 17 of 34) using SPM8's Fourier phase shift interpolation. I then corrected for head motion by realigning each participant's functional images to their mean image and by transforming them according to six movement parameters (i.e., translated in x-, y-, and z-directions as well as rotated in pitch, roll, and yaw directions). Data from all participants that exceeded movement criteria of 3 mm displacement or 3° rotation within the functional session were excluded (see *Exclusion criteria* section above). I then co-registered each participant's functional data to his/her high resolution anatomical MRI (using the mean image, created during realignment as the source image). Having done this, I spatially normalized to an age- and sex-matched pediatric template (age range: 9.9 – 14.2 years) created using the TOM8 toolbox (Wilke et al., 2008; see *Pediatric template selection* section below). Finally, I spatially smoothed all the images using a Gaussian filter of 5 mm full-width half maximum (FWHM) to reduce noise. In addition to this, I lowered SPM8's default masking threshold from 0.8 to 0.7.

Pediatric template selection. Increasingly, the convention in pediatric neuroimaging studies is to employ age-appropriate templates during the normalization of individual brain images to stereotaxic space. The use of age-appropriate normalization templates accounts for the morphological changes that occur during typical brain development, thereby reducing potential misregistration of brain structures between pediatric neuroimaging data and adult normative templates (Wilke, Schmithorst, & Holland, 2002, 2003; Yoon, Fonov, Perusse, Evans, & Group, 2009). Appropriate template choice is, therefore, of particular relevance in pediatric clinical samples with known structural brain impairments and atypical developmental trajectories (e.g., regional brain abnormalities that persist into adolescence in individuals with heavy PAE; Bookheimer & Sowell, 2005; Coles & Li, 2011).

Hence, I evaluated two pediatric normalization templates for use in this study: the standard National Institute of Health MRI Study of Normal Brain Development (NIHPD)

asymmetric brain template for children aged 10 to 14 years (Fonov et al., 2011; Fonov, Evans, McKinstry, Almli, & Collins, 2009) and an adapted NIHPD template created using the TOM8 toolbox (Wilke et al., 2008) for SPM8. The TOM8 toolbox uses reference data (N = 394) from the NIH study of normal brain development (Brain Development Research Group & Evans, 2006). I used the matched-pairs approach to construct an age- and sex-matched (age range: 9.9 – 14.2 years) template for the sample examined in this study. In this approach, a single age- and sex-matched reference map is generated for each participant. The reference maps are then averaged to create a T_1-weighted anatomic template (resolution = 1 × 1 × 1 mm^3) as well as gray matter (GM), white matter (WM) and cerebro-spinal fluid (CSF) tissue probability maps. On review, both templates provided acceptable registration to individual structural and functional brain images. Because of the added demographic specificity that the age- and sex-matched template provided, this template was selected for use in this study.

Artifact detection and quality assurance. Following preprocessing, but prior to first-level analysis, I examined each participant's functional data for spikes in global mean intensity and/or motion artefacts, over-and-above those identified during standard motion correction procedures, using the Artefact Detection Toolbox (http://gablab.mit.edu/index.php/software). For each subject, any fMRI volume containing global mean intensity and/or motion artefacts greater than 3 *SD*s or 3 mm above or below the mean, respectively, was (a) identified as an outlier scan and (b) included as a covariate in the subsequent first-level analyses of these data.

Calculation of block onset times. For each block in the functional localizer task, I extracted block onset times from each participant's raw functional localizer data. For each block, the onset time was generated and converted from ms into volumes using the following formula: $y_i = (x - z_i)/2000$, where y_i is the onset time (in volumes) of the i-th block, x is the

functional localizer start time (in ms), and z_i is the time of the first image presentation in the *i*-th block of the functional localizer task (in ms).The functional localizer task was programmed in such a way that the scanner would trigger to start after four measurements (i.e., after the first four functional volumes were obtained). Due to a mechanical scanner error, the task trigger time varied for 5 of the 74 participants included in the final sample. Specifically, the task triggered with the 6^{th} pulse for four participants (one in the FAS group, and three non-exposed controls) and with the 7^{th} pulse for one participant (non-exposed control). In the five cases where delayed task triggering occurred, the additional 'dummy volumes' were discarded from each participant's functional data (e.g., if the task triggered with the 6^{th} pulse, five functional volumes were discarded in addition to the four functional volumes originally discarded to account for T_1 equilibrium).

First-level analysis. During this stage of data analysis, I generated beta maps for each subject using a whole-brain general linear model (GLM)-based analysis (Amaro & Barker, 2006) in Montréal Neurological Institute (MNI) space. I generated the two experimental regressors of interest (viz., objects and scenes) by convolving epochs of interest with a canonical model of the hemodynamic response function (HRF). During model specification, I (a) defined two *t*-contrasts of interest: Scenes > Objects and Objects > Scenes; (b) inserted the onset time and duration for each epoch; and (c) inserted each participant's artefact detection output file as an additional regressor.

Extracting functional regions of interest (fROI). This step in the data analytic stream was aimed at extracting the outcome variables of interest for this study. Consistent with the first two research questions, I proceeded to extract both extent and magnitude of ROI activation data for each participant. For each data extraction step, I followed the procedures outlined below.

Functional ROI cluster extraction. For each participant, I extracted four fROIs (viz., left LOC, right LOC, left PPA, and right PPA) based on anatomical and functional constraints consistent with those reported in the literature. I defined the bilateral LOC (a) anatomically, by constraining activation to the occipital gyri and Brodmann area (BA) 37 (occipitotemporal cortex) using the Wake Forest University (WFU) PickAtlas tool (Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Kraft, & Burdette, 2003) and (b) functionally, as the cluster of contiguous voxels in the lateral occipital cortex that show greater activation when viewing objects than scenes (Objects > Scenes contrast; $p < .00001$, uncorrected). In cases where no activation increase was detected at this threshold, I examined clusters of contiguous voxels in the lateral occipital cortex showing increases when viewing objects compared to scenes at less stringent thresholds: $p < .0001$, $p < .001$, $p < .01$, and $p < .05$.

I defined the bilateral PPA (a) anatomically, by constraining activation to the parahippocampal and fusiform gyri using the WFU PickAtlas tool, and (b) functionally, as the cluster of contiguous voxels in the posterior parahippocampal gyrus where activation is greater when viewing scenes than objects (Scenes > Objects contrast; $p < .0001$, uncorrected). Similarly to the LOC, in cases where no activation increases were detected at this threshold, I examined clusters of contiguous voxels in the posterior parahippocampal gyrus showing increases when viewing scenes compared to objects at less stringent thresholds: $p < .001$, $p < .01$, and $p < .05$.

Taken together, fROI extraction resulted in the creation of four cluster size outcome variables for the examination of fROI spatial extent of activation: left LOC, right LOC, left PPA, and right PPA. Prior to conducting further analyses on these data, I converted each participant's LOC and PPA cluster size outcomes from number of contiguous voxels to mm^3 using the following formula: $y = x \times z$, where y = LOC/PPA volume in mm^3, x = number of

contiguous voxels, and z = voxel size (viz., $2 \times 2 \times 2mm^3$). I have presented the results for the between-group and regression-based analyses of spatial extent of fROI activation for LOC and PPA data extracted at the threshold of $p < .001$ only. This threshold was selected for two reasons: (a) Both the LOC and PPA were identified bilaterally in the majority of participants included in each exposure group (see *Results* section below), and (b) the results of between-group and regression-based analyses were consistent, regardless of fROI extraction threshold (for these data, see Appendix L).

Mean % signal change extraction. For each participant, I extracted mean % signal change data using the MarsBaR (http://marsbar.sourceforge.net/) toolbox. I obtained the Montreal Neurological Institute (MNI) coordinates for the maximally object-selective voxel in the bilateral LOC by selecting the voxel with the highest *t*-value for the Objects > Scenes contrast within the lateral occipital cortex. Similarly, I obtained the MNI coordinates for the maximally scene-selective voxel in the bilateral PPA by selecting the voxel with the highest *t*-value for the Scenes > Objects contrast within the posterior parahippocampal gyrus. Because some participants failed to activate at the most stringent fROI extraction thresholds (viz., LOC: $p < .00001$, and PPA: $p < .0001$), activation at more lenient thresholds was considered. MNI coordinates for bilateral maximally category-selective voxels were, therefore, identified at the extraction threshold at which each participant first showed LOC and PPA activation. MNI coordinates were then entered into the MarsBaR toolbox to create spherical ROIs around the maximum voxel (6mm radius) and to extract mean % signal change values for each of the fROIs. This process resulted in the creation of four mean % signal change outcome variables for the examination of fROI magnitude of activation: left LOC, right LOC, left PPA, and right PPA.

Statistical analyses. Prior to conducting further between-group and regression-based analyses, I used comprehensive descriptive statistics to examine the distributions of predictor

and outcome variables, to identify outliers in the aforementioned distributions and to test the assumptions underlying parametric statistical tests (for these data, see Appendix M).

Potential confounding variables. Following the procedure detailed in the analogous section in Chapter 2, I considered six potential confounding variables for inclusion in statistical analyses: child sex and age at testing, maternal age at delivery, education, socioeconomic status (SES), and smoking during pregnancy. I considered any sociodemographic variable that was related even weakly (at $p < .10$) to a given outcome variable a potential confounder of performance measured by that outcome. To control for confounders, I reran any analyses detecting an association between PAE and the outcome with the relevant sociodemographic variable entered as a covariate in the ANCOVAs or as a predictor at the second step in a hierarchical regression analysis.

No mother reported using cocaine, and prenatal exposure to marijuana ($n = 8$) and methaqualone ("mandrax"; $n = 3$) were too rare for statistical adjustment. I, therefore, reran any analyses detecting an association between PAE and the outcome omitting children with either prenatal marijuana or mandrax exposure.

Between-group analysis. I used a series of one-way analyses of variance (ANOVAs) to examine potential between-group differences in the spatial extent and magnitude of activation in LOC and PPA fROIs. In all analyses, the between-subjects factor was FASD diagnostic status (viz., FAS/PFAS, nonsyndromal HE, and non-exposed control). Group membership was determined based on FASD diagnostic status as identified by expert dysmorphologists (see *Dysmorphology Clinic* section in Chapter 2).

Regression-based analysis. I used hierarchical regression analysis to examine relations between prospectively obtained continuous measures of PAE (viz., AA/day, AA/occasion, and frequency of drinking [days/week]) and the extent and magnitude of activation in the LOC and PPA fROIs. First, I used Pearson correlation to determine whether

any of the three continuous predictor variables were significantly associated to spatial extent or magnitude of activation outcome variables in the bilateral LOC and PPA. In the event that such an association was identified, I progressed to conduct a hierarchical regression analysis entering the predictor variable at the first step and, where eligible, potential confounding variables at the second step. The aim of these analyses was, therefore, twofold: (a) Assess relations between continuous measures of PAE and the outcome, and (b) assess the degree to which potential confounding variables contribute to predicting the outcome.

Relations between category-selective activation and IQ. Here, the main aim was to assess whether either extent or magnitude of activation in any of the four fROIs was associated with general intellectual functioning. Thus, I used a correlation-based analysis to determine whether there was a significant association between the spatial extent and magnitude of activation in the bilateral LOC and PPA and WISC-IV Full-Scale IQ (FSIQ) scores.

Results

Sample Characteristics

Mothers of children in the FAS/PFAS group were significantly older at delivery than mothers of children in the HE group, $p = .02$ (Table 3.1). The other two pairwise comparisons of this variable did not detect statistically significant results, $p = .053$ for FAS/PFAS versus non-exposed control and $p = .50$ for HE versus non-exposed control. Although the analysis examining the relationship between group membership and maternal education did not detect a statistically significant association, a post hoc pairwise comparison suggested that mothers of children in the FAS/PFAS group completed significantly fewer years of formal education than mothers of children in the non-exposed control group, $p = .03$. Consistent with this finding, mothers of children in the FAS/PFAS group were significantly more economically

disadvantaged (on average Hollingshead Level V—Unskilled Laborers, lowest of 5 levels) than mothers of children in both the HE and non-exposed control groups (on average, Hollingshead Level IV—Semiskilled workers), both *p*'s < .01. Although, on average, mothers of children in the HE and control groups fell into the same Hollingshead level, the pairwise comparison between those two groups fell just short of conventional levels of significance, $p = .06$, with means suggesting that mothers of children in the non-exposed control group were somewhat less economically disadvantaged than mothers of children in the HE group. Although the overall group difference in the proportion of mothers who were married was not significant, more of the non-exposed control mothers were married when compared with the two exposure groups combined, $\chi^2 = 3.67$, $p = .06$.

Table 3.1
Sample Characteristics (N = 74)

Variable	FAS/PFAS (*n* = 21[a])	HE (*n* = 22)	Non-exposed Control (*n* = 31)	*F* or χ^2	*p*	*ESE*
Maternal variables						
Age at delivery (years)	30.1 (7.0)	25.6 (4.7)	26.7 (6.2)	3.28	.04*	.09
Level of education (years)	8.4 (2.5)	9.3 (2.5)	9.8 (2.0)	2.53	.09†	.07
Marital status (% married)	33.3	31.8	54.8	3.68	.16	.22
Socioeconomic status	15.1 (6.5)	21.4 (7.9)	25.4 (7.7)	11.85	<.001***	.25
Prenatal alcohol exposure[b]						
AA/day (oz)	1.5 (0.8)	0.9 (0.9)	0.0 (0.0)	22.12	<.001***	.38
AA/occasion (oz)	4.4 (1.8)	3.6 (3.4)	0.0 (0.0)	33.78	<.001***	.49
Frequency (days/week)	1.7 (0.9)	1.4 (1.1)	0.0 (0.0)	36.82	<.001***	.51
Prenatal smoking (cig/day)	7.3 (5.5)	6.0 (5.2)	2.4 (4.3)	7.00	.002**	.17
Child variables						
Age at testing (years)	12.4 (1.4)	10.5 (0.5)	11.1 (1.2)	17.84	<.001***	.33
Sex (% male)	57.1	40.9	41.9	1.49	.48	.14
WISC-IV IQ						
Full-Scale IQ	63.6 (9.5)	77.2 (16.9)	76.4 (14.1)	6.69	.002**	.16

Note. Means are presented with standard deviations in parentheses. FAS = fetal alcohol syndrome; PFAS = partial fetal alcohol syndrome; HE = heavily exposed nonsyndromal; ESE = effect size estimate; AA = absolute alcohol; cig = cigarettes; WISC-IV = Wechsler Intelligence Scale for Children—Fourth Edition. Test statistics were either *F* or χ^2 depending on whether the variable under consideration was continuous or categorical. The estimates of effect sizes were calculated using partial eta squared (η^2) and Phi (φ) for one-way ANOVAs and χ^2 tests, respectively.

[a]FAS: *n* = 12; PFAS *n* = 9

[b]1 oz AA/day ≈ 2 standard drinks

$^{\dagger}p < .10$. $^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$.

Mothers of children in both the FAS/PFAS and HE groups consumed more alcohol (on average, 3 and 2 standard drinks, respectively) than mothers of children in the non-exposed control group, *p*'s < .001 (Table 3.1). None of the mothers of children in the non-exposed control group reported drinking during pregnancy. Frequency and dose/occasion of alcohol consumption did not differ between the FAS/PFAS and HE groups, $p = .19$.

Mothers of children in the FAS/PFAS and HE groups smoked more cigarettes during pregnancy than mothers of children in the non-exposed control group, *p*'s < .05, whereas mothers of children in the FAS/PFAS and HE groups smoked a similar number of cigarettes during pregnancy, $p > .20$ (Table 3.1). None of the mothers reported using cocaine during pregnancy. Three (1 FAS/PFAS, 2 HE) mothers reported using methaqualone ("mandrax"; mean = 1.3 times/week; range = 0.03 – 3.2). Eight (2 FAS/PFAS, 5 HE, 1 control) mothers reported using marijuana during pregnancy (mean = 2.9 times/week; range = 0.8 – 7.0).

Children in the FAS/PFAS group were significantly older than those in both the HE and non-exposed control groups, *p*'s < .001, whereas children in the HE group were significantly younger than those in the non-exposed control group, $p = .04$ (Table 3.1). There were no sex differences with regard to the proportion of boys versus girls in each diagnostic group. Children in the FAS/PFAS group had lower WISC-IV FSIQ scores than children in both the HE and non-exposed control groups, all *p*'s < .05, with the latter two groups performing similarly, all *p*'s > .20.

Identification of Potential Confounding Variables

I evaluated six potential confounding variables. Four of these variables were significantly correlated with spatial extent of activation outcome variables: Maternal SES was positively correlated with both left and right LOC cluster size, maternal age at delivery was negatively correlated with left PPA cluster size, and child age and maternal smoking during pregnancy were both negatively correlated with right PPA cluster size (Table 3.2). Similarly, three of the potential confounding variables were significantly correlated with magnitude of activation outcome variables: Maternal smoking during pregnancy was negatively correlated with right LOC mean % signal change, and both maternal education and SES were positively correlated with right PPA mean % signal change. Thus, where a significant alcohol-effect is reported, I included the aforementioned four potential confounding variables as covariates/additional predictor variables in the relevant ANCOVAs and/or regression analyses of these data.

Table 3.2
Identification of Potential Confounding Variables (N = 74)

	Child		Maternal			
Variable	Sex	Age	Age at delivery	Level of education	Socioeconomic status	Smoking during pregnancy (cigarettes/day)
Cluster size ($p < .001$)						
Lateral occipital complex						
Left[a]	.14	-.08	-.04	.14	.24*	.00
Right[b]	.18	-.10	-.11	.19	.29*	-.02
Parahippocampal place area						
Left[c]	.07	-.10	-.24†	.12	.06	-.01
Right[d]	.18	-.24†	-.20	.21	.21	-.26*
Mean % signal change						
Lateral occipital complex						
Left	-.01	.01	-.06	.01	-.06	-.12
Right[e]	.11	-.007	-.02	-.02	.04	-.29*
Parahippocampal place area						
Left[f]	.05	-.04	-.10	.09	.05	-.12
Right[g]	.02	-.05	-.08	.31**	.32**	-.10

Note. Statistics presented are Pearson correlation coefficients (*r*). All tests are two-tailed.
[a]*n* = 69. Cluster size data are only presented for participants who activated at the designated extraction threshold. Data from non-responders were excluded.
[b]*n* = 66. Cluster size data are only presented for participants who activated at the designated extraction threshold. Data from non-responders were excluded.
[c]*n* = 54. Cluster size data are only presented for participants who activated at the designated extraction threshold. Data from non-responders were excluded.
[d]*n* = 59. Cluster size data are only presented for participants who activated at the designated extraction threshold. Data from non-responders were excluded.
[e]*n* = 73. One boy (age: 11.0 years) in the FAS/PFAS group did not activate at the most lenient threshold ($p < .05$).
[f]*n* = 73. One boy (age: 10.2 years) in the FAS/PFAS group did not activate at the most lenient threshold ($p < .05$).
[g]*n* = 72. Two boys (aged: 10.2 and 13.6 years, respectively) in the FAS/PFAS group did not activate at the most lenient threshold ($p < .05$).
†$p < .10$. *$p < .05$. **$p < .01$.

Spatial Extent of Activation

Lateral occipital complex. At a threshold of $p < .001$ (uncorrected), the analysis detected the left LOC (average MNI coordinates derived for the sample as a whole[4]: $x = -49$, $y = -74$, $z = -6$; Figure 3.4) in 69 children (i.e., 93.2% of the sample): 20 children (95.2%) in the FAS/PFAS group, 21 children (95.5%) in the HE group, and 28 children (90.3%) in the non-exposed control group. The analysis detected the right LOC (average MNI coordinates derived for the sample as a whole: $x = 48$, $y = -71$, $z = -8$) in 66 children (i.e., 89.2% of the sample): 20 children (95.2%) in the FAS/PFAS group, 18 children (81.8%) in the HE group, and 28 children (90.3%) in the non-exposed control group.

[4] The MNI coordinates presented here are for all participants who showed significant activation increases for the Objects > Scenes (LOC) and Scenes > Objects (PPA) contrasts across all extraction thresholds, and not just for those participants who activated at a threshold of $p < .001$.

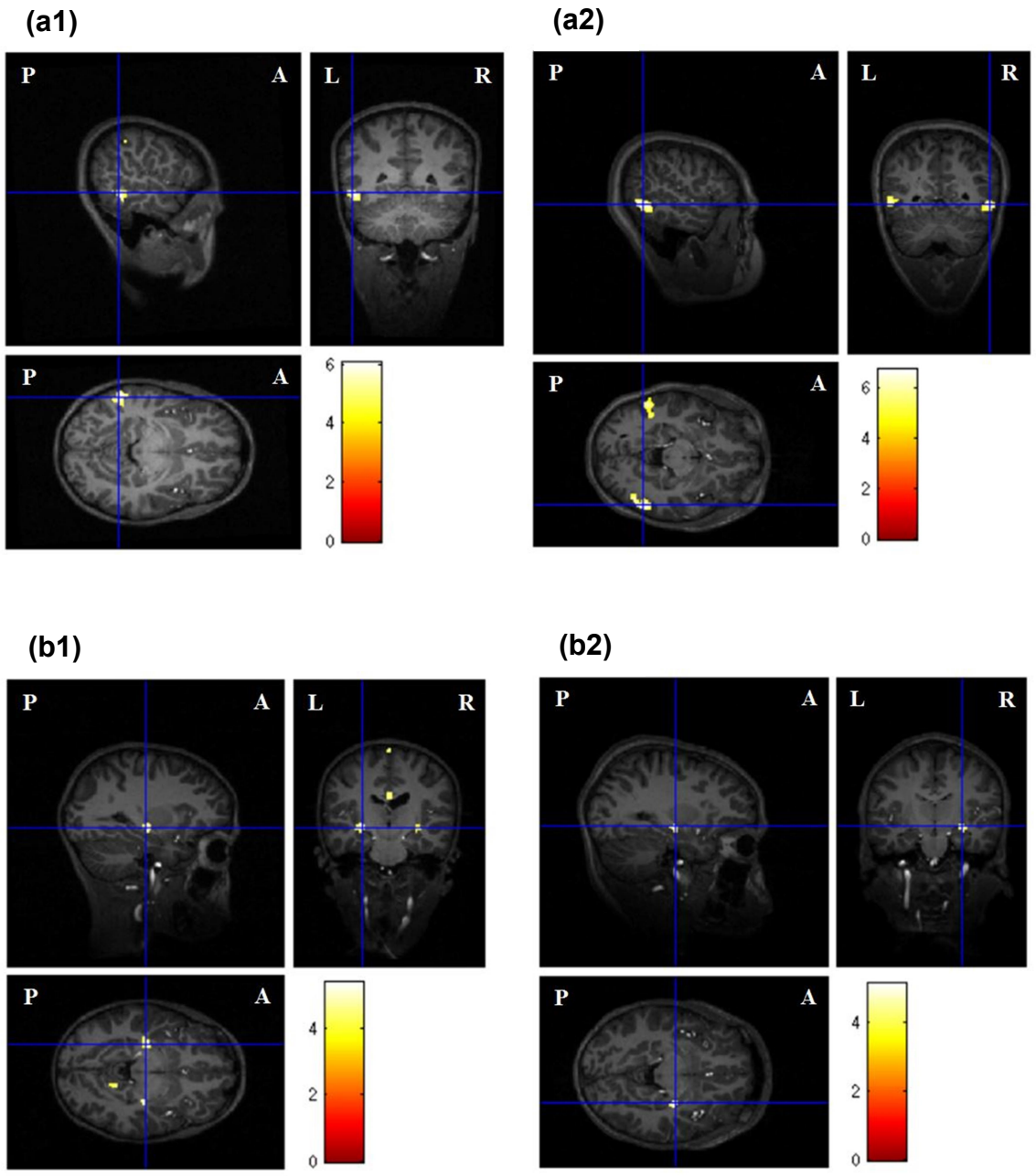

Figure 3.4. Images displaying bilateral lateral occipital complex (LOC) and parahippocampal place area (PPA) for four representative participants. Each participant's functional data is overlaid on their high-resolution T1-weighted structural scan. The crosshairs are placed at the point of peak activation in each figure. The individual images show left LOC (MNI coordinates: -50, -74, -6) extracted from the Object > Scene contrast (p = .00001) in a male participant from the Control group (age: 10.6 years) (a1); right LOC (MNI coordinates: 48, -78, -10) extracted from the Object > Scene contrast (p = .00001) in a female participant from the Control group (age: 10.8 years) (a2); left PPA (MNI coordinates: -26, -44-6) extracted from the Scene > Object contrast (p = .0001) in a male participant from the FAS/PFAS group (age: 12.6 years) (b1); and right PPA (MNI coordinates: 28, -44, -8) extracted from the Scene > Object contrast (p = .0001) in a male participant from the Control group (age: 11.0 years) (b2). P = posterior; A = anterior; L = left; R = right.

When examining data from the diagnostic groups, analyses detected no significant between-group differences in spatial extent of activation for the contrast Objects > Scenes for both left and right LOC (Table 3.3). Although cluster size was larger in the left LOC (M = 2464.3; SD = 2857.8) than in the right LOC (M = 2033.1; SD = 2332.0) across all children, this difference fell just short of statistical significance, $t(64) = 1.89$, $p = .06$. Consistent with the results of between-group analyses, neither left nor right LOC cluster size correlated significantly with the continuous measures of alcohol exposure, all p's > .20 (Table 3.4).

Table 3.3
Between-Group Differences in Spatial Extent of Activation (N = 74)

Cluster size ($p < .001$)	FAS/PFAS ($n = 21$[a])	HE ($n = 22$)	Non-exposed Control ($n = 31$)	F	df	p	η^2
Lateral occipital complex							
Left[b]	2444.0 (3171.9)	2197.8 (2767.4)	2372.6 (2689.1)	0.04	2, 66	.96	.001
Right[c]	2043.6 (2512.8)	2055.2 (2517.5)	1939.1 (2144.5)	0.02	2, 63	.98	.001
Parahippocampal place area							
Left[d]	680.0 (648.0)	588.0 (603.7)	459.9 (626.3)	0.55	2, 51	.58	.02
Right[e]	600.5 (499.9)	639.6 (675.5)	580.4 (630.1)	0.05	2, 56	.95	.002

Note. Values are means (standard deviations) in mm^3. FAS = fetal alcohol syndrome; PFAS = partial fetal alcohol syndrome; HE = heavily exposed nonsyndromal.
[a]FAS: $n = 12$; PFAS: $n = 9$
[b]$n = 69$. Cluster size data are only presented for participants who activated at the designated extraction threshold. Data from non-responders were excluded.
[c]$n = 66$. Cluster size data are only presented for participants who activated at the designated extraction threshold. Data from non-responders were excluded.
[d]$n = 54$. Cluster size data are only presented for participants who activated at the designated extraction threshold. Data from non-responders were excluded.
[e]$n = 59$. Cluster size data are only presented for participants who activated at the designated extraction threshold. Data from non-responders were excluded.

Table 3.4
Relation Between Continuous Measures of Prenatal Alcohol Exposure and Spatial Extent of Activation (N = 74)

Cluster size ($p < .001$)	AA/day	AA/occasion	Frequency (days/week)
Lateral occipital complex			
Left[a]	-.13	-.16	.03
Right[b]	-.06	-.11	.06
Parahippocampal place area			
Left[c]	.13	.23	.11
Right[d]	.12	.23[†]	.05

Note. Statistics presented are Pearson correlation coefficients (r). All tests are two-tailed. AA = absolute alcohol.
[a]$n = 69$. Cluster size data are only presented for participants who activated at the designated extraction threshold. Data from non-responders were excluded.
[b]$n = 66$. Cluster size data are only presented for participants who activated at the designated extraction threshold. Data from non-responders were excluded.
[c]$n = 54$. Cluster size data are only presented for participants who activated at the designated extraction threshold. Data from non-responders were excluded.
[d]$n = 59$. Cluster size data are only presented for participants who activated at the designated extraction threshold. Data from non-responders were excluded.
[†]$p < .10$.

Parahippocampal place area. At a threshold of $p < .001$ (uncorrected), the analysis detected the left PPA (average MNI coordinates derived for the sample as a whole [see Footnote 4]: $x = -25$, $y = -44$, $z = -8$; Figure 3.4) in 54 children (i.e., 73.0% of the sample): 13 children (61.9%) in the FAS/PFAS group, 18 children (81.8%) in the HE group, and 23 children (74.2%) in the non-exposed control group. The analysis detected the right PPA (average MNI coordinates: $x = 27$, $y = -42$, $z = -9$) in 59 children (i.e., 79.7 % of the sample): 15 children (71.4%) in the FAS/PFAS group, 20 children (90.9%) in the HE group, and 24 children (77.4%) in the non-exposed control group.

When examining data from the diagnostic groups, analyses detected no significant between-group differences were detected in spatial extent of activation for the contrast Scenes > Objects for both left and right PPA (Table 3.3). Cluster size was similar in the left ($M = 575.9$; $SD = 621.8$) and right ($M = 667.7$; $SD = 616.6$) PPA, $t(51) = -1.35$, $p = .18$ across all children. Neither left nor right PPA cluster size correlated significantly with AA/day or drinking frequency (days/week; Table 3.4). Correlations between left and right PPA cluster size and AA/occasion were of similar strength, but only the correlation between right PPA cluster size and AA/occasion approached conventional levels of statistical significance, $p = .08$.

Magnitude of Activation

Lateral occipital complex. When examining data from the diagnostic groups, analyses detected no significant between-group differences in mean % signal change for the contrast Objects > Scenes for both left and right LOC (Table 3.5). Although mean % signal change values across all children were larger in the right LOC ($M = 1.8$, $SD = 0.8$) than in the left LOC ($M = 1.6$, $SD = 0.7$), this difference fell short of statistical significance, $t(72) = -1.81$, $p = .08$. Left LOC mean % signal change was significantly negatively correlated to

AA/day, whereas the relation between left LOC and both AA/occasion and drinking frequency (days/week) fell just short of statistical significance, *p*'s = .06 (Table 3.6). Right LOC mean % signal change was significantly negatively correlated with AA/occasion, *p* = .03.

Table 3.5
Between-Group Differences in Magnitude of Activation (N = 74)

Mean % signal change	FAS/PFAS (*n* = 21[a])	HE (*n* = 22)	Non-exposed Control (*n* = 31)	*F*	*df*	*p*	η^2
Lateral occipital complex							
Left	1.6 (0.7)	1.4 (0.6)	1.6 (0.7)	0.92	2, 71	.40	.03
Right[b]	1.6 (0.9)	1.6 (0.8)	1.9 (0.8)	0.99	2, 70	.38	.03
Parahippocampal place area							
Left[c]	0.7 (0.4)	0.8 (0.4)	0.7 (0.4)	0.95	2, 70	.39	.03
Right[d]	0.8 (0.4)	1.0 (0.4)	1.0 (0.4)	0.63	2, 69	.54	.02

Note. Means are presented with standard deviations in parentheses. FAS = fetal alcohol syndrome; PFAS = partial fetal alcohol syndrome; HE = heavily exposed nonsyndromal.
[a]FAS: *n* = 12; PFAS: *n* = 9
[b]*n* = 73. One boy (age: 11.0 years) in the FAS/PFAS group did not activate at the most lenient threshold ($p < .05$).
[c]*n* = 73. One boy (age: 10.2 years) in the FAS/PFAS group did not activate at the most lenient threshold ($p < .05$).
[d]*n* = 72. Two boys (aged: 10.2 and 13.6 years, respectively) in the FAS/PFAS group did not activate at the most lenient threshold ($p < .05$).

Table 3.6
Relation Between Prenatal Alcohol Exposure and Magnitude of Activation (N = 74)

Mean % signal change	AA/day	AA/occasion	Frequency (days/week)
Lateral occipital complex			
Left	-.24[*]	-.22[†]	-.22[†]
Right[a]	-.17	-.25[*]	-.14
Parahippocampal place area			
Left[b]	.09	.12	.02
Right[c]	.13	.12	.01

Note. Statistics presented are Pearson correlation coefficients (*r*). All tests are two-tailed. AA = absolute alcohol.
[a]*n* = 73. One boy (age: 11.0 years) in the FAS/PFAS group did not activate at the most lenient threshold ($p < .05$).
[b]*n* = 73. One boy (age: 10.2 years) in the FAS/PFAS group did not activate at the most lenient threshold ($p < .05$).
[c]*n* = 72. Two boys (aged: 10.2 and 13.6 years, respectively) in the FAS/PFAS group did not activate at the most lenient threshold ($p < .05$).
[†]$p < .10$. [*]$p < .05$.

Control for potential confounding variables. Right LOC mean % signal change was significantly associated with one potential confounding variable: maternal smoking during pregnancy (cigarettes/day; Table 3.2). Therefore, I conducted a hierarchical regression analysis in which AA/occasion was entered at Step 1 and maternal smoking during pregnancy was entered at Step 2, so as to further examine the relation between continuous measures of PAE and right LOC mean % signal change. The magnitude of this effect decreased when maternal smoking during pregnancy was entered into the model at Step 2; the association between PAE and right LOC mean % signal change became non-significant, β = -.16, p = .18. Maternal cigarette use during pregnancy fell just short of significance as a predictor of the outcome, β = -.24, p = .06.

Additionally, the magnitude of the effect of oz AA/day on left LOC mean % signal change remained essentially unchanged when the three children prenatally exposed to mandrax and the eight children prenatally exposed to marijuana were excluded from the analysis, βs = -.22 and -.19, respectively. Similarly, the magnitude of the effect of oz AA/occasion on right LOC mean % signal change remained essentially unchanged when the three children prenatally exposed to mandrax and the eight children prenatally exposed to marijuana were excluded from the analysis, βs = -.26 and -.23, respectively.

Parahippocampal place area. When examining data from the diagnostic groups, analyses detected no significant between-group differences in mean % signal change for both left and right PPA (Table 3.5). Across all children, mean % signal change values were significantly larger for the right PPA (M = 0.9, SD = 0.4) than for the left PPA (M = 0.7, SD = 0.4), $t(71)$ = -4.07, $p < .001$. Consistent with the results of between-group analyses, neither left nor right PPA mean % signal change correlated significantly with the continuous measures of alcohol exposure, all p's > .20 (Table 3.6).

Relation Between Category-selective Activation and General Intellectual Functioning

I computed Pearson correlation coefficients to examine the association between category-selective activation and general intellectual functioning (Table 3.7). Mean % signal change in the right PPA was significantly positively correlated with WISC-IV FSIQ scores. All other associations were non-significant, all *p*'s > .20.

Table 3.7
Relation Between Category Selective Activation and General Intellectual Functioning (N = 74)

Variable	WISC-IV Full-Scale IQ
Cluster size ($p < .001$)	
Lateral occipital complex	
Left[a]	-.02
Right[b]	-.02
Parahippocampal place area	
Left[c]	.15
Right[d]	.16
Mean % signal change	
Lateral occipital complex	
Left	-.06
Right[e]	.05
Parahippocampal place area	
Left[f]	.06
Right[g]	.41***

Note. Statistics presented are Pearson correlation coefficients (*r*). All tests are two-tailed. WISC-IV = Wechsler Intelligence Scale for Children—Fourth Edition.
[a]*n* = 69. Cluster size data are only presented for participants who activated at the designated extraction threshold. Data from non-responders were excluded.
[b]*n* = 66. Cluster size data are only presented for participants who activated at the designated extraction threshold. Data from non-responders were excluded.
[c]*n* = 54. Cluster size data are only presented for participants who activated at the designated extraction threshold. Data from non-responders were excluded.
[d]*n* = 59. Cluster size data are only presented for participants who activated at the designated extraction threshold. Data from non-responders were excluded.
[e]*n* = 73. One boy (age: 11.0 years) in the FAS/PFAS group did not activate at the most lenient threshold ($p < .05$)
[f]*n* = 73. One boy (age: 10.2 years) in the FAS/PFAS group did not activate at the most lenient threshold ($p < .05$)
[g]*n* = 72. Two boys (aged: 10.2 and 13.6 years, respectively) in the FAS/PFAS group did not activate at the most lenient threshold ($p < .05$)
***$p < .001$.

Discussion

The primary aim of this study was to investigate visual perceptual functioning in children with heavy PAE. I assessed visual perception using a functional neuroimaging paradigm designed to elicit neural activation in two category-specific functional regions of interest. Focusing on these two fROIs (the lateral occipital cortex and the parahippocampal place area) allowed me to examine object and scene perception, respectively. To my knowledge, this is the first study to examine category-specific activation in children with a history of heavy PAE. The results of this study are, therefore, both novel and exploratory and require replication in future research.

In this study, I investigated whether children with heavy PAE differ in the spatial extent and/or magnitude of activation within the fROIs when compared to typically developing, non-exposed control children. Additionally, I examined whether spatial extent and/or magnitude of activation within the fROIs was associated with higher-order cognitive processes (as indexed by general intellectual functioning). In this section, I first discuss the findings pertaining to each research question and locate them within the broader literature pertaining to visual perception. Subsequently, I address the limitations of this study and suggest future research directions.

Category-Selective Activation

The functional localizer task successfully elicited object- and scene-selective activations in the bilateral LOC and PPA, respectively. Although a small proportion of participants did not respond even at the most lenient extraction threshold ($p < .05$, uncorrected), the number of responders for, and the average location of, each of the fROIs were consistent with those reported in the developmental literature (e.g., Vuontela et al., 2013 reported bilateral PPA activation in 14 of 16 [87.5%] of children). Hence, these data not only

validate the use of functional localizer tasks to elicit category-specific activation within the ventral visual stream in typically-developing children and adolescents, but are the first to extend their assessment suitability to FASD.

Neither spatial extent nor magnitude of bilateral LOC activation differed across FASD diagnostic groups (viz., FAS/PFAS, nonsyndromal HE, and non-exposed controls). Although cluster size and magnitude of activation were somewhat greater in the left and right LOC, respectively, these differences fell short of conventional levels of significance. Similarly, neither spatial extent nor magnitude of bilateral PPA activation differed across diagnostic groups. Overall, however, scene-selective activation was greater in the right PPA than in the left PPA, with no significant differences in cluster size. Thus, regardless of diagnosis, participants recruited the bilateral LOC and PPA similarly during object and scene perception, respectively. Interpretation of these data may, however, be limited by between-group differences in the number of responders within each FASD diagnostic group.

The absence of between-group differences in neural activation during category-specific activation is consistent with the suggestion that neural regions supporting perceptual functioning are less vulnerable to the effects of PAE than those recruited during higher-order cognitive functioning (Fan et al., 2015; Lebel et al., 2011). Moreover, the fROIs examined in this study do not act in isolation, but rather appear to have extensive functional connectivity to regions that form a part of the neural networks supporting higher-order cognitive functioning (Baldassano, Beck, & Fei-Fei, 2013; Hutchison, Culham, Everling, Flanagan, & Gallivan, 2014). Thus, similar perceptual activation in the fROIs examined in this study does not preclude between-group differences in more complex cognitive tasks that recruit a more extensive neural network to facilitate successful task completion.

This finding is also consistent with the developmental trajectory of category-specific fROIs in the ventral visual stream. Specifically, the LOC and PPA are reported to be largely

functionally mature early in development, whereas functional maturation of the fusiform face area, for example, continues throughout adolescence (Gogtay et al., 2004; Golarai et al., 2007, 2010; Grill-spector, Golarai, & Gabrieli, 2008; Scherf, Behrmann, Humphreys, & Luna, 2007). Although dorsal visual stream impairments have been the predominant focus of research programs examining atypical development of visual-perceptual functioning (for a review, see Grinter, Maybery, & Badcock, 2010), the functional topography of the ventral visual stream is increasingly being investigated in clinical populations (e.g., Williams's syndrome: O'Hearn et al., 2011; Sarpal et al., 2008; and Autism Spectrum Disorders [ASD]: Humphreys, Hasson, Avidan, Minshew, & Behrmann, 2008; Simmons et al., 2009). For example, Scherf and colleagues (2010) examined ventral visual stream activation in 10 high-functioning boys (M_{age} = 12.2 years; range: 10 – 14 years) with a diagnosis of ASD and 10 typically-developing age-, sex-, and IQ-matched control participants. Their primary aim was to assess the functional integrity of face-, object- and scene-selective regions using a blocked design fMRI task. Participants passively viewed short film clips displaying faces, buildings, natural scene navigation, and common objects during fMRI data acquisition. Findings indicated developmentally atypical activation of the FFA in the absence of between-group differences in activation of object- and scene-selective areas in ASD participants. These data are consistent with the between-group findings reported in this study in suggesting typical development of object- and scene-selective functional topography.

The absence of between-group differences in this study stands in contrast to Li and colleagues' (2008) finding of exposure-related occipital-temporal (i.e., ventral visual stream) hypoactivation during a sustained visual attention task. It is important to note, however, that the cognitive load of the sustained visual attention task used by Li and colleagues was markedly greater than that of the functional localizer task administered in this study. In the current study, participants were instructed to passively view blocks of object and scene

stimuli (i.e., there was no objective measurement of task-oriented attention). In contrast, participants in the Li et al. study were required to monitor the task stimuli and to press a response button when the target stimulus was detected, thereby recruiting higher-order sustained attentional resources. It is plausible, therefore, that the absence of between-group differences in magnitude of activation in this study may be attributed to the fact that participants recruited only low-order perceptual resources in the ventral visual stream during object and scene perception in this study. Taken together, these data suggest that exposure-related impairment in ventral visual stream functioning may become more apparent as the cognitive demand of the task increases.

Further support for this suggestion is provided by recent fMRI studies reporting significant associations between a positive history of PAE and differences in regional activation during tasks measuring spatial working memory (e.g., Malisza et al., 2005; Norman et al., 2013). Although the use of a passive functional localizer task may be considered a methodological limitation of the current study, Epstein and Kanwisher (1998) argue that it is in fact a strength of any design including functional localizers because they are able to elicit category-selective activation both with and without embedded attention tasks. This assertion is supported by data from several studies examining the efficacy of ventral visual stream functional localizer designs (see e.g., Berman et al., 2010).

Somewhat more consistent with Li and colleagues' (2008) data is the current finding that continuous measures of PAE were associated with object-selective activation patterns. Specifically, AA/day was negatively associated with left LOC activation, whereas AA/occasion was associated with right LOC activation. Such associations were not observed for magnitude of activation of the bilateral PPA, but there was a (non-significant) trend towards decreased right PPA cluster size with increased AA/occasion. These data support the observation that measures of exposure that are (a) prospectively-obtained and (b)

continuously-scaled variables may be more sensitive indicators of associations between exposure and outcome than are between-group comparisons (De Guio et al., 2014; Lindinger et al., 2016; Robertson et al., 2015). It is important to note, however, that PAE only accounted for a small proportion of the variance associated with object-selective activation. Moreover, further examination of this association using hierarchical regression analyses indicated that maternal smoking during pregnancy confounded the relation between AA/occasion and right LOC activation. However, the growing body of evidence of associations between PAE and structural and functional alterations within occipital-temporal regions suggests, at least, that these findings warrant further investigation.

Relation of Category-selective Activation to General Intellectual Functioning

It is noteworthy that higher levels of general intellectual functioning, as measured by WISC-IV Full-Scale IQ, were associated with increased magnitude of activation in the right PPA. This finding suggests that during the passive viewing of task stimuli children with higher levels of general intellectual functioning might engage in an encoding-type process without explicit instruction to do so. Consistent with this interpretation is the body of research demonstrating that the PPA is recruited to support both the basic perceptual processing and maintenance of visual scene information during the performance of working memory tasks (Ranganath, De Gutis, & D'Esposito, 2004; Wendelken, Baym, Gazzaley, & Bunge, 2011). Top-down regulation of scene-selective activation by the prefrontal cortex (PFC) is such that the magnitude of activation in the PPA is either suppressed or enhanced when visual scenes are ignored or attended to, respectively (Gazzaley, Cooney, McEvoy, Knight, & D'Esposito, 2005). In an fMRI-based study examining the typical development of this top-down regulation of category-specific activation during the performance of a visual working memory task, Wendelken et al. (2011) reported that children (M_{age} = 11.5; range = 8

– 13 years) showed less efficient regulation of PPA activity during such tasks than young adults (M_{age} = 21.9; range = 19 – 26 years). The effectiveness of the top-down regulation of PPA activation (a) matures along a developmental trajectory that is consistent with that of executive components of working memory (Anderson, 2002), and (b) is proposed to be supported by functional connectivity between this region and the PFC in both typically developing (Vuontela et al., 2013) and healthy adult populations (Hutchison et al., 2014). Data from this study suggests, therefore, that children with higher levels of intellectual functioning demonstrate neural activation in the right PPA that may be suggestive of spontaneous visual scene encoding.

The association between general intellectual functioning and magnitude of activation in the right PPA stands in contrast to the absence of such an association in studies investigating category-selective activation in William's Syndrome (O'Hearn et al., 2011) and ASD (Scherf et al., 2010). This association is, however, consistent with Jung and Haier's (2007) Parieto-Frontal Integration Theory (P-FIT) of general intellectual functioning. P-FIT proposes that posterior visual association cortex (in addition to auditory association cortex) plays an integral role in a feed-forward network of posterior, parietal, and frontal regions to support general intellectual functioning. Jung and Haier (2007) suggest that activation of this distributed network is primarily bilateral, with some evidence to support lateralization to the left hemisphere.

In this study, however, the association between general intellectual functioning and magnitude of activation was only significant in the right PPA. Additionally, despite bilateral scene-selective activation in the PPA, degree of PPA activation was greater, for all participants, in the right than in the left hemisphere. Although the lateralization of these findings to the right hemisphere makes them somewhat more difficult to interpret, several lines of converging evidence support the relation between right PPA activation and higher-

order cognitive processes. For example, Prince et al., (2009) used an event-related fMRI paradigm to demonstrate that right PPA activation is preferentially associated with scene encoding, whereas left PPA activation is associated with both scene encoding and retrieval. Prince and colleagues interpreted these data within the framework of lateralization effects during episodic memory processing: Visual form processing is lateralized to the right, whereas abstract and/or autobiographical processing (e.g., semantic labelling) is lateralized to the left. Thus, the lateralization of the association between general intellectual functioning and magnitude of PPA activation to the right may be (a) indicative of the fact that participants were viewing visual information and (b) suggestive of recruitment of this fROI by children with higher general intellectual functioning, similar to that observed in studies investigating PPA recruitment during higher-order cognitive processes. Following a different line of investigation, a recent study examining cortical thickness in a sample of 78 children (M_{age} = 10.7, *SD* = 0.6 years) with and without a diagnosis of FASD (FAS/PFAS *n* = 28; nonsyndromal HE *n* = 28; non-exposed control *n* = 22; Robertson et al., 2015). Robertson and colleagues (2015) reported that exposure-related cortical thinning in an occipital-temporal ROI mediated the effect of PAE on general intellectual functioning – a finding that is in turn supported by the association between cortical thickness and IQ in typically developing samples (e.g., Schnack et al., 2015).

Limitations and Future Directions

Several key methodological constraints hinder neuroimaging research in populations of individuals with a history of PAEs (Coles & Li, 2011). A limitation of particular relevance to this study is that between-group comparisons in fMRI activation can be confounded by underlying exposure-related differences in brain morphology (e.g., microcephaly). Coles and Li (2011) advocate for the importance of integrating structural and functional neuroimaging

results within the context of PAE research. There is some evidence to support exposure-related structural impairments in the occipital-temporal region (see e.g., Li et al., 2008; Robertson et al., 2015). It was, however, beyond the scope of this study to examine possible between-group or exposure-related differences in occipital-temporal structure. Although there were no between-group differences in neural activation in either of the fROIs examined in this study, these findings do not exclude the possibility of underlying structural impairments in this sample. Every effort was, however, taken to prepare neuroimaging data appropriately for between-group comparison (e.g., use of a pediatric age- and sex-matched template during spatial normalization; for further details, see *Preprocessing* section above).

A second noteworthy limitation of neuroimaging research investigating the effects of PAE on cognitive functioning is the difficulty obtaining accurate information pertaining to the timing and amount of PAE during pregnancy (Lebel et al., 2011). However, alcohol data obtained prospectively from mothers is a more sensitive indicator of exposure effects than data obtained retrospectively (Jacobson et al., 2002). As described in Chapter 2, detailed information pertaining to alcohol exposure during pregnancy was obtained from mothers of children in the Cape Town Longitudinal Cohort Study prospectively across three time-points during pregnancy (Jacobson et al., 2008). Additionally, prospective interviews obtained during pregnancy have been validated in relation to meconium (Bearer et al., 2003), infant behavior (Jacobson et al., 2002; Molteno et al., 2014), and a broad range of behavioral and neuroimaging outcomes (Lewis et al., 2015, 2016; Lindinger et al., 2016; Robertson et al., 2015; Woods et al., 2015). Hence, the inclusion of prospectively-obtained continuous PAE predictor variables, in addition to FASD diagnosis, is a methodological strength of this study. Consistent with this, the continuous measures of PAE were a more sensitive predictor of neuroimaging results in this study.

This study did not include behavioral tasks designed to assess visual perceptual functioning as supported by the ventral visual stream. As noted previously, an extensive literature confirms that children with heavy PAE experience impaired basic visual functioning (e.g., poor oculomotor control and/or visual acuity), and that exposure-related impairments in higher-order visual perceptual functioning are mediated by the dorsal visual stream (e.g., visual-construction and angular judgment; for a review, see Mattson et al., 2011). There is, however, a paucity of neuropsychological research investigating ventral visual stream functioning. Although this study contributes towards filling this gap, future research should aim to develop this literature further by conducting follow-up neuroimaging investigations of (a) the recruitment of ventral visual stream resources during higher-order cognitive processes (e.g., scene-selective activation in the PPA during visual scene encoding) and (b) the top-down regulation of ventral visual stream resources in children with FASD.

Conclusions

In summary, the findings reported in this study suggest that object- and scene-selective activation in bilateral LOC and PPA is (a) consistent with the typical development of category-selective visual perception in the ventral visual stream, and (b) less susceptible to the effects of heavy PAE than tasks assessing higher-order cognition. Additionally, greater magnitude of activation in the right PPA was associated with higher levels of general intellectual functioning—a noteworthy finding that is suggestive of more spontaneous encoding of visual stimuli in children with higher WISC-IV Full-Scale IQ scores. To my knowledge, this is the first study to assess object- and scene-selective activation in children with a history of PAE. Because of this novelty, these findings warrant replication within other samples of individuals with a history of PAE before they may be generalized. Nevertheless,

they provide an important and novel contribution to the literature working towards defining a neurobehavioral profile of FASD.

Research questions addressing perceptual functioning as a possible mediator of higher-order deficits observed in clinical populations add a significant theoretical contribution not only to the literature pertinent to the developmental disorder under study, but to theoretical models proposing functional integration of perceptual and memory functions (e.g., PIMMS; Henson & Gagnepain, 2010). This approach is particularly relevant to the field of FASD, in which the relation between perception and higher-order cognitive functioning (e.g., memory) has been highlighted as a significant gap in the literature. The finding that PPA activation was related to performance on tasks measuring higher-order cognition in this sample validates the PPA as an ideal candidate for investigation in studies addressing such research questions. More specifically, examining PPA activation during the encoding of visual scenes allows for direct assessment of Kaemingk and Halverson's (2000) suggestion that impaired visual perceptual functioning may underlie the learning and memory deficits frequently documented in FASD. Thus, it is of clinical significance to extend the findings of this study with follow-up research addressing relations between perception and memory in FASD.

CHAPTER 4: NEURAL ACTIVATION DURING MEMORY ENCODING IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS – STUDY II

Neuropsychological investigations of verbal and visual-spatial memory functioning in children with a history of prenatal alcohol exposure (PAE) suggest impaired memory encoding (i.e., information acquisition) might be a primary mechanism underlying exposure-related memory deficits (Crocker et al., 2011; Lewis et al., 2015; Mattson et al., 1996, 1998; Mattson & Roebuck, 2002; Willford et al., 2004). Behavioral measures of learning and memory performance are somewhat limited in their ability to discriminate between deficits in encoding and those in retrieval when investigating PAE-related memory deficits (see Chapter 1). Neuroimaging studies, however, provide a novel opportunity to examine the possibility of encoding-specific deficits through the direct examination of activation patterns during successful and unsuccessful encoding trials. Such direct examination of neural activation during memory encoding remains to be conducted in children with a history of PAE. This constitutes a significant gap in the literature, and warrants further investigation using novel neuroimaging methods.

In this chapter, I provide a brief review of functional neuroimaging investigations designed to directly assess neural activation patterns during memory encoding. The review places special emphasis on studies that examine (a) memory encoding directly, using event-related functional magnetic resonance imaging (fMRI) paradigms and (b) neural activation during memory encoding in both typically developing children and clinical samples. I then present a review of the small number of studies associating memory task performance with functional neuroimaging data in children with heavy PAE. Finally, I report the results of this

study and integrate them with the broader literature on learning and memory functioning in children with heavy PAE.

Neural Activation During Memory Encoding

The neural correlates of declarative memory have been well defined by studies using lesion- and neuroimaging-based methods (for a brief review, see Chapter 1). Of particular relevance to the current study is that medial temporal lobe (MTL) and prefrontal cortex (PFC) structures are both implicated in successful encoding (that is, the acquisition and movement of new information into long-term memory stores; for a review, see Simons & Spiers, 2003). One method of investigation that has reliably demonstrated this association is that of the event-related fMRI *subsequent memory (SM)* paradigm (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Wagner, Schacter, et al., 1998). The primary objective of this paradigm is to assess patterns of neural activation that are associated with successful memory encoding. Participants are presented a large number of novel stimuli (either visual or verbal) during fMRI image acquisition. During the scanner protocol, participants may complete an unrelated task (e.g., judging whether each presented stimulus is an image of an indoor or an outdoor scene). At the conclusion of the scanner protocol, participants are given a recognition memory test comprised of target stimuli (i.e., those viewed during image acquisition) and foil stimuli (i.e., novel stimuli not viewed previously). Based on the participant's behavioral responses during recognition testing, images are sorted into two conditions: hits (i.e., images remembered) and misses (i.e., images forgotten). By subtracting regions activated for misses from those activated for hits, researchers are able to directly examine patterns of activation associated with successful memory encoding. Neural activation associated with successful item encoding is thereby operationally defined as activation that is greater for items remembered than for items forgotten, and is labelled a 'subsequent memory (SM) effect'.

In a meta-analysis of 74 studies using the SM paradigm to investigate neural activation associated with successful memory encoding in healthy young adults, Kim (2011) detected five neural regions that consistently demonstrate SM effects regardless of the modality of stimulus presentation: left inferior frontal cortex, bilateral fusiform cortex, bilateral hippocampal formation, bilateral premotor cortex, and bilateral posterior parietal cortex. Kim also noted that there was modulation in activation based on the modality (either visual or verbal) of stimuli being studied. Interestingly, SM effects in the bilateral hippocampal formation were stronger in studies using visual stimuli than in studies using verbal stimuli. Thus, the use of visual stimuli in the SM paradigm is particularly advantageous for research programs aiming to examine the functional integrity of bilateral MTL activation during successful memory formation.

Few studies have used the SM paradigm to investigate neural activation during memory encoding in pediatric samples. In the first study to investigate the developmental trajectory of SM effects, Ofen et al. (2007) examined neural activation associated with successful memory encoding in a sample of 49 right-handed, typically-developing participants (age range: 8 – 24 years). The SM paradigm employed by Ofen and colleagues detected encoding-associated neural activation in several MTL and PFC regions that were consistent with those reported in adult samples (for a review, see Kim, 2011). When examining age-related differences in neural activation, Ofen and colleagues reported developmental increases in PFC activation, whereas MTL activation remained consistent as age increased.

This pattern of prolonged PFC functional maturation is consistently reported in studies using the SM paradigm (Maril et al., 2010, 2011; Shing, Brehmer, Heekeren, Bäckman, & Lindenberger, 2016), as well as in studies using alternative fMRI study designs (e.g., blocked design, Chiu, Schmithorst, Brown, Holland, & Dunn, 2006; Menon, Boyett-

Anderson, & Reiss, 2005; for a review, see Ofen, 2012) to investigate typical development of memory encoding capabilities. In contrast, MTL structures have been reported to show developmental increases in neural activation only under certain task conditions (e.g., simple vs. complex scenes, Chai, Ofen, Jacobs, & Gabrieli, 2010; recollection of item detail, Ghetti, DeMaster, Yonelinas, & Bunge, 2010). Taken together, these functional activation patterns are consistent with (a) the prolonged structural and functional maturation of the PFC (Anderson, 2002; Tsujimoto, 2008) and (b) the prolonged functional specialization of the MTL (Ghetti et al., 2010).

Research using the SM paradigm to investigate neural activation during memory encoding in clinical pediatric samples is even scarcer. The clinical relevance of such investigations is that it allows for the cognitive and/or behavioral phenotypes associated with particular neurodevelopmental disorders to be defined in terms of behavior *and* related brain structure and functioning (Castellanos & Tannock, 2002; Jacobson et al., 2011). In the case of Attention-Deficit/Hyperactivity Disorder (ADHD), for example, neuropsychological investigations have demonstrated less efficient learning and memory performance that is thought to be mediated by less efficient top-down regulation of memory processing due to structural and functional impairments in the PFC (Crocker et al., 2011; Egeland, Johansen, & Ueland, 2010; Storm & White, 2010; Zang et al., 2005). Consistent with this interpretation, Krauel et al., (2007) used a visual variant of the SM paradigm to demonstrate between-group differences in neural activation associated with successful memory formation in adolescents with a diagnosis of ADHD (M_{age} = 14.5, SD = 0.7) and typically-developing control adolescents (M_{age} = 15.2, SD = 1.3). Both groups demonstrated SM effects in the PFC and inferior temporal cortex, but the ADHD group showed increased activation in the superior parietal lobe and precuneus, whereas control participants showed increased activation in the anterior cingulate cortex. This between-group difference was, to a certain extent, mitigated by

increasing the salience of the visual material presented during the task. Krauel and colleagues, therefore, made effective use of the SM paradigm to demonstrate clinically significant between-group differences in the functional recruitment of regions associated with successful memory encoding in adolescents with a diagnosis of ADHD. Thus, there exists a novel opportunity to apply this method to a pediatric clinical sample with documented structural and behavioral impairment in key memory encoding regions (e.g., fetal alcohol spectrum disorders [FASD]; Lewis et al., 2015; Mattson & Roebuck, 2002).

Neural Activation During Memory Encoding in FASD

Previous neuropsychological and structural neuroimaging studies have demonstrated an association between heavy PAE, impaired learning and memory performance, and hippocampal structural anomalies (for a brief review, see Chapter 1). Although fMRI paradigms have been used to investigate neural activation associated with arithmetic and numerical processing (Meintjes et al., 2010; Santhanam et al., 2009; Woods et al., 2015), response inhibition (Fryer, Tapert, et al., 2007; Kodali et al., 2017; O'Brien et al., 2013; Ware et al., 2015), and verbal and visual-spatial attention and working memory (Diwadkar et al., 2013; Li et al., 2008; Malisza et al., 2005; Norman et al., 2013; O'Hare et al., 2009; Spadoni et al., 2009) in individuals with a history of PAE, only one published study has used an fMRI task to assess neural activation associated with verbal learning in this clinical population (Sowell et al., 2007). In that study, Sowell and colleagues used a paired-associates learning task to assess verbal learning and memory in a sample of 11 children with heavy PAE (M_{age} = 10.7 years, *SD* = 2.0; FAS *n* = 2, PFAS *n* = 4, and ARND *n* = 5) and 16 non-exposed typically developing children (M_{age} = 10.8 years, SD = 2.7). To control for differences in general intellectual functioning, an IQ-matched sub-set (M_{age} = 11.7, *SD* = 2.6; *n* = 11) of the non-exposed control children was used for additional between-group comparisons. fMRI data

were acquired for both learning and recall trials of the task, and these data were combined for further analysis of neural activation associated with verbal learning and memory. Although performance accuracy was not acquired during completion of the in-scanner task, Sowell and colleagues obtained an estimate of task performance using a post-scanner recognition test. They reported that the full group of non-exposed control participants performed significantly better than heavily exposed participants, but that this difference fell short of conventional levels of significance when comparing heavily exposed and IQ-matched participants.

Sowell and colleagues (2007) compared neural activation during verbal learning and recall trials and rest trials to examine memory-associated activation. Overall, non-exposed control participants showed hippocampal and parahippocampal gyri activation that was restricted to the left hemisphere. Bilateral activation was reported in several regions including the posterior perisylvian regions, inferior parietal cortices, and inferior frontal gyri. Alcohol-exposed participants showed a different pattern of activation during verbal learning and recall to non-exposed control participants, with increased unilateral activation noted in the left dorsolateral PFC and decreased activation in the left medial and posterior temporal regions. Additionally, exposure-related decreases in activation in the left medial and posterior temporal regions remained significant when performance accuracy was controlled for.

Thus, taken together, the results of this study indicate functional activation abnormalities (independent of estimated performance differences) associated with verbal learning and memory recall in children with a history of heavy PAE. These findings are consistent with other fMRI studies of FASD in suggesting that exposed children do not activate neural networks that are most efficient for performing a given cognitive task, but instead activate alternative, often more extensive, networks, presumably to compensate for a functional deficit in the network normally used to perform that task (e.g., Diwadkar et al., 2013; Fryer, Tapert, et al., 2007; Meintjes et al., 2010).

An important limitation of Sowell and colleagues' (2007) study design was that learning and recall trials were combined for the analysis of associated neural activation. This approach limits the degree to which the authors could make precise interpretation of the ways in which functional activation abnormalities were related to deficient learning and memory, and of the notion of such deficits as a unified construct with a discrete underlying mechanism. It is well established by other strands of the literature, however, that memory encoding and retrieval involve distinct neural processes (for a brief review, see Chapter 1). Moreover, these constructs are best teased apart through the use of neuroimaging paradigms designed to assess memory encoding *or* retrieval directly (e.g., the SM paradigm). Thus, the behavioral evidence suggesting that impaired memory encoding is the primary mechanism underlying exposure-associated deficits in learning and memory performance warrants follow-up neuroimaging investigation (for a review, see Chapter 1). Because the SM paradigm allows for the direct examination of neural activation at the time of successful memory encoding, it provides an appropriate method to underpin a novel investigation of encoding-specific neural activation in children with a history of heavy PAE. Moreover, increasing the specificity of investigations that examine functional neural activation patterns associated with behavioral performance provides a novel contribution to the literature working towards defining biobehavioral markers of effect associated with PAE—especially within the domain of learning and memory. In addition, these findings could potentially contribute to development of interventions specifically tailored to FASD deficits in this domain.

Specific Aims and Objectives

The main aim of this study was to investigate neural activation in children with and without a history of heavy PAE during the encoding of visual scenes. I used an fMRI memory encoding task (designed in accordance with the SM paradigm) to achieve this aim. Another aim was to assess neural activation patterns within the *a priori* derived bilateral scene-selective functional region of interest (fROI; viz., parahippocampal place area) identified in Chapter 3. To accomplish this aim, I examined whether impaired visual scene perception may contribute to impairments in non-verbal memory performance associated with heavy PAE. Because this is the first study to directly examine neural activation during memory encoding in this clinical population, the key research questions are exploratory in nature:

1. Does the pattern of whole-brain activation associated with memory encoding in children with and without heavy PAE replicate SM effects reported in previous studies?
2. Are there differences in magnitude of activation within memory encoding fROI across the FASD diagnostic groups (viz., FAS/PFAS, nonsyndromal HE, and non-exposed control)?
3. Do children with a diagnosis of FASD recruit a more extensive neural network during memory encoding than non-exposed individuals?
4. Are continuous measures of PAE associated with differences in magnitude of activation within the memory encoding fROIs?
5. Are between-group differences in behavioral memory performance associated with between-group differences in magnitude activation within the memory encoding fROIs?

Methods

Participants

This study is nested within the Cape Town Longitudinal Cohort study (Jacobson et al., 2008) and drew participants from the Memory Cohort (N = 88) described in Chapter 2. Apart from one child (a boy, 10.2 years old, in the FAS/PFAS group) who became behaviorally non-compliant partway through the memory encoding task and, therefore, failed to complete the scanner protocol, all right-handed participants in the study sample (n = 77 of N = 88) completed the memory encoding task. Figure 4.1 illustrates the process I followed to construct the final sample for this study. Some details of that process are provided below.

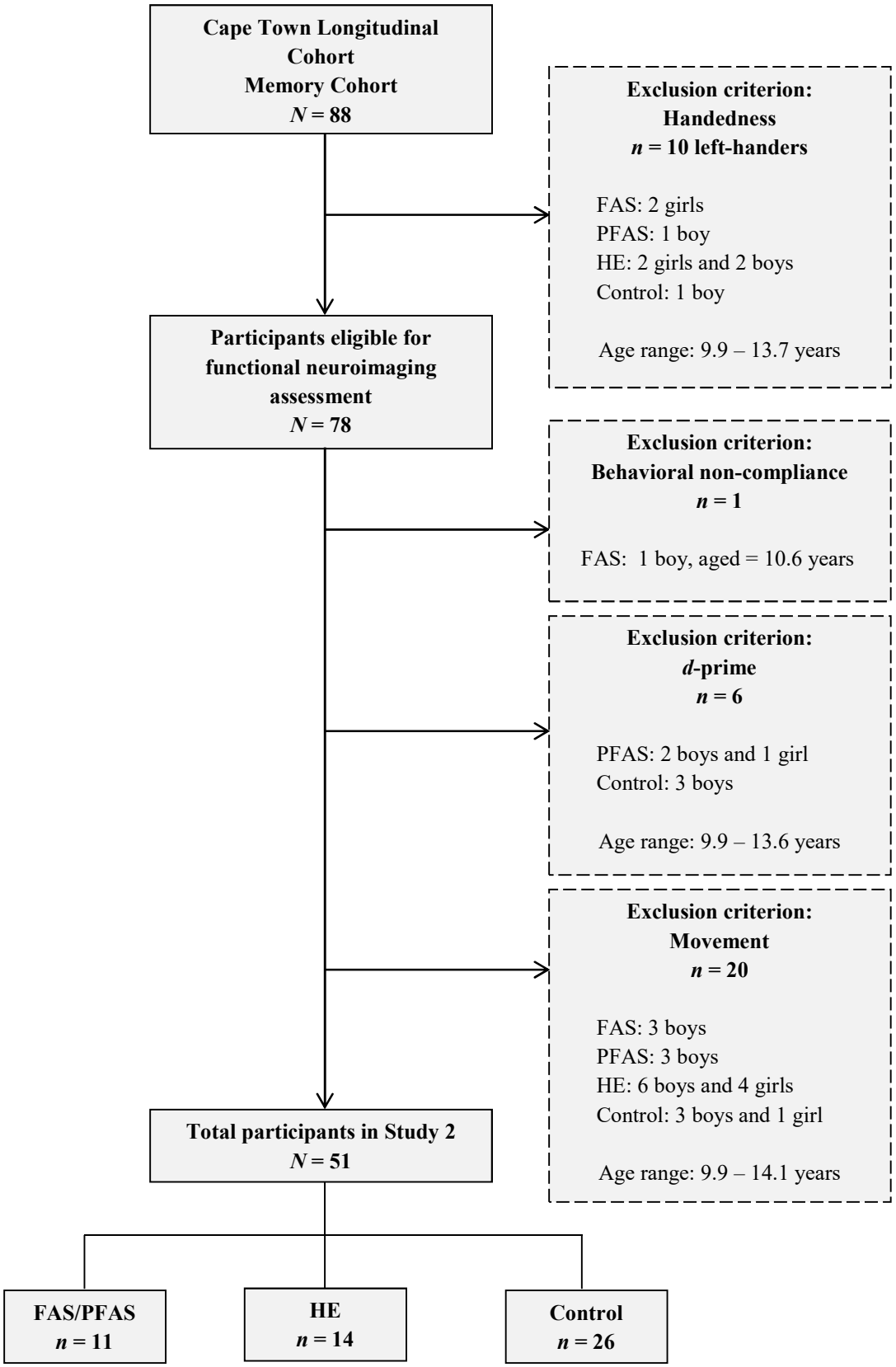

Figure 4.1. Diagram illustrating the selection of the final sub-sample of 51 participants as well as details relating to exclusion. FAS = fetal alcohol syndrome; PFAS = partial fetal alcohol syndrome; HE = heavily exposed nonsyndromal.

Exclusion criteria for neuroimaging study. The analogous section in Chapter 3 provides specific details on the standard MRI safety screening interview and handedness.

In-scanner movement. For each participant, I examined movement data during image preprocessing (see *Preprocessing* section below). Following the convention outlined in Chapter 3, any participant whose movement exceeded 3 mm displacement or 3° rotation in any direction during the memory encoding fMRI sessions was excluded from further analyses. Based on these criteria, I excluded a total of 20 participants (8 participants with movement during one of the three fMRI sessions, 7 participants with movement during two of the three fMRI sessions, and 5 participants with movement during all three fMRI sessions; see Figure 4.1 for details of the demographic characteristics of each of these excluded individuals).

Memory encoding task performance. I examined each participant's behavioral performance accuracy on the memory encoding task using a *d*-prime analysis. Based on the distribution of *d*-prime scores in this sample, a score of < 0.3 was suggestive of a chance performance (i.e., guessing). Based on this criterion, I excluded a further 6 participants from subsequent analyses. This resulted in a final sample size of $N = 51$ (see for details of the demographic characteristics of each of these individuals).

Neuroimaging Assessment

Research setting. I conducted neuroimaging data collection at CUBIC (see analogous section in Chapter 3).

Memory encoding task. I used an fMRI task to assess patterns of neural activation during the encoding of visual scenes (Ofen et al., 2007). The memory encoding task utilized an event-related fMRI design for stimulus presentation (see Figure 4.2). A fundamental assumption of event-related designs is that the temporal resolution of fMRI allows for the

sampling of the hemodynamic response function (HRF) in response to individual events of interest (Amaro & Barker, 2006; Josephs & Henson, 1999). In a standard event-related fMRI design, therefore, events of interest are presented as short-duration discrete trials, and images are acquired using an acquisition time (TR) of 1 to 2 s. A significant advantage of this experimental design is that both condition order and interstimulus intervals may be randomized. The interstimulus interval separates events of interest and typically ranges from 2 to 20 s in duration (Huettel et al., 2009a). This randomization procedure is referred to as jittering, and serves to both optimize event-related BOLD signal detection and control for individual variation in attentional control (D'Esposito, Zarahn, & Aguirre, 1999). Although blocked designs (see Chapter 3) yield more power to detect activation than event-related designs, event-related designs provide more flexibility, allow for accurate estimation of the shape and timing of the HRF, and are well-suited to the study of psychological processes (e.g., episodic memory, Spaniol et al., 2009).

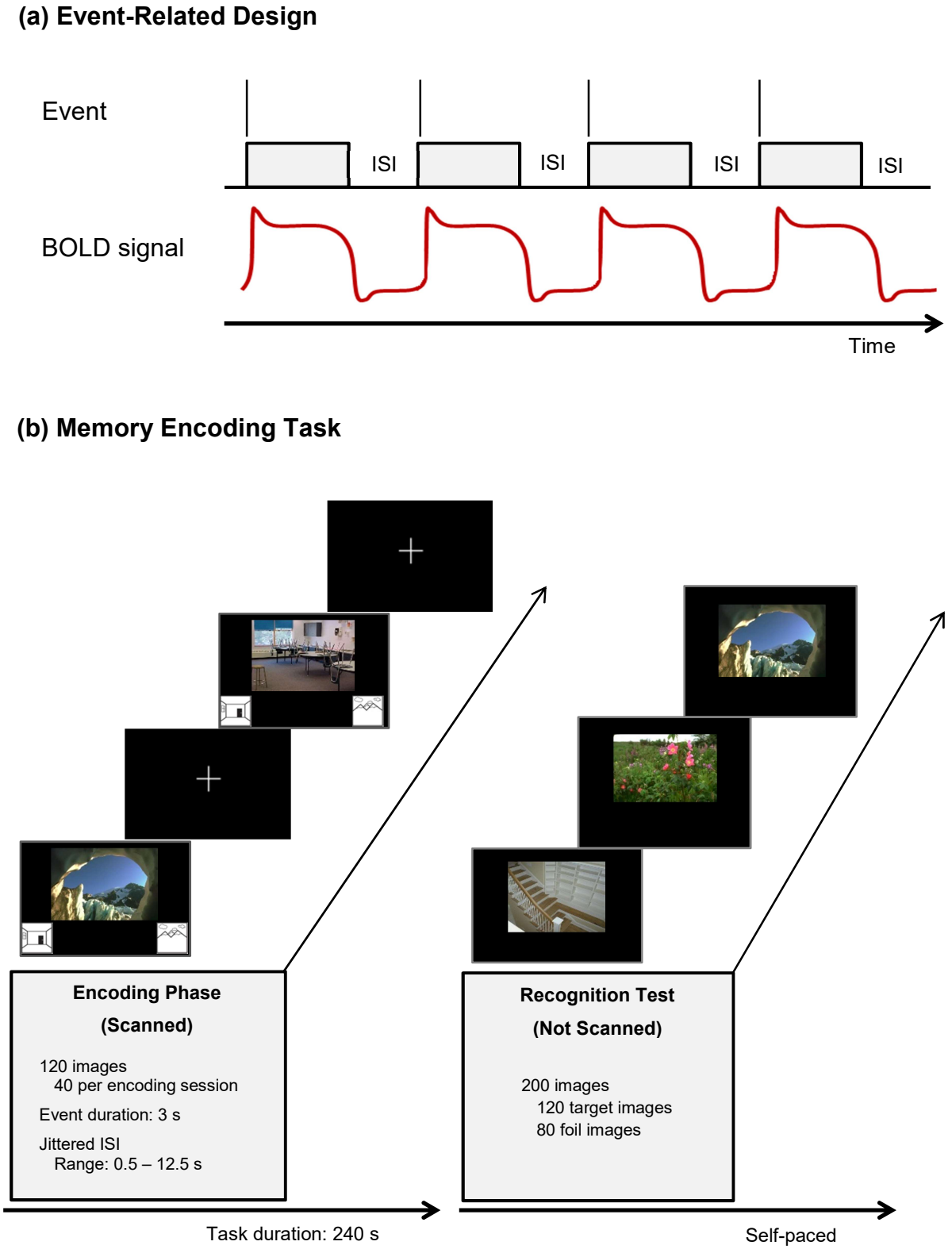

Figure 4.2. A schematic depicting the standard characteristics of an fMRI event-related design (a) adapted from Amaro & Barker (2006) and the memory encoding task design (b). ISI = interstimulus interval.

The memory encoding task (Ofen et al., 2007) used in this study was based on the SM paradigm (Brewer et al., 1998; Wagner, Schacter, et al., 1998) and was, therefore, divided into two parts: (a) the in-scanner encoding phase, and (b) the post-scan recognition memory test. Both parts of the memory encoding task were programmed and run in E-Prime 2.0 (Psychology Software Tools, Inc., Pittsburgh, USA). During the scanner phase of the task, 120 novel images of indoor and outdoor scenes were presented across three sessions (40 images per session). Task stimuli were arranged into six lists of 40 images (20 indoor and 20 outdoor scenes). The order of list presentation was pseudo-randomized using participant ID. Within each session, stimuli were displayed for 3 seconds with a jittered interstimulus interval ranging between 0.5 and 12.5 s (see Figure 4.2). A fixation cross was displayed for the duration of the interstimulus interval. The task was programmed to run an embedded attention task: For each stimulus presented during the scanner phase, participants were instructed to make a judgment about whether the image was of an indoor or an outdoor scene. In the event of an incorrect indoor/outdoor judgment, the image was excluded from subsequent neuroimaging analyses to prevent possible variations in attention from exerting undue influence on the analysis of SM effects. The duration of each encoding session was 4 minutes.

The post-scan recognition memory test consisted of 200 images of indoor and outdoor scenes: 120 target images (i.e., those presented earlier, during the encoding sessions) and 80 never-before-seen foil images. The task was self-paced, but the examiner completed the input of behavioral responses for each stimulus. This administration procedure was used to facilitate optimal task engagement throughout the post-scan recognition test. Images were drawn from six lists of 200 images (120 target and 80 foil). Images were presented across three blocks, with a self-paced inter-block break. Based on behavioral responses during the recognition memory test, the 120 target images were classified as either a hit (i.e., image

remembered correctly) or a miss (i.e., image forgotten) and the 80 foil images were classified as either a false-alarm or a correct rejection (see Table 4.1 for definitions of these outcome variables).

Table 4.1
Behavioral Memory Encoding Outcome Variables

Variable	Definition
d-prime	Recognition accuracy calculated using the formula: *d*-prime = *Z*(hit total) – *Z*(false alarm total)
Hit total	Number of target images correctly remembered on recognition testing.
Miss total	Number of target images not remembered on recognition testing.
False alarm	Number of foil images falsely identified as target images on recognition testing
Correct rejection	Number of foil images correctly identified as such on recognition testing

Procedure. I conducted the data collection with the assistance of two female MA-level psychologists, who are both research assistants in the UCT Child Development Research Laboratory (CDRL). I provided detailed training on the administration of both the in-scanner encoding and post-scan recognition memory parts of the memory encoding task.

General neuroimaging study procedure. The general neuroimaging procedure for this study followed the same procedure as outlined in the analogous section in Chapter 3. Participants completed a practice trial for both the in-scanner and post-scan portions of the memory encoding task. For the in-scanner part of the task, participants were instructed to make an indoor/outdoor judgment for each picture presented (for the task instructions, see Appendix N). To make their response, participants were required to press a response button with their index finger for an indoor scene and their middle finger for an outdoor scene. They were further informed that the task was a memory task and that their recognition memory for the task stimuli would be assessed following the scan.

For the post-scan part of the task, participants were instructed to look at each image presented and to state whether or not they recognized the picture as a target image. They were

further informed that the task was self-paced, that the examiner would enter their response, and that they should try to be as accurate in their responses as possible.

During each of the in-scanner encoding sessions, task stimuli were projected from the computer running the E-Prime task onto a screen positioned behind the scanner bore. Participants were able to view the screen via a mirror fixed to the head coil. Participants' indoor/outdoor responses were recorded using a Lumitouch response box system (Photon Control Inc., Burnaby, Canada). Behavioral responses were logged in E-Prime.

Data acquisition. Each subject was scanned, using a single-channel head coil, on a 3T Allegra MR scanner (Siemens, Erlangen Germany). High-resolution T_1-weighted magnetization-prepared rapid gradient echo (MPRAGE) anatomical scans were acquired in a sagittal orientation using a three-dimensional motion corrected multi-echo sequence (Tisdall et al., 2009; van der Kouwe et al., 2008) with the following parameters: TR = 2530 ms, TE_1 = 1.53 ms, TE_2 = 3.21 ms, TE_3 = 4.89 ms, TE_4 = 6.57 ms, 128 slices, slice thickness = 1.3 mm, flip angle = 7°, field of view = 256 mm, voxel size = 1.3 × 1.0 × 1.3 mm^3, and scan time = 8:07 min. Each of the three encoding sessions followed the same fMRI acquisition protocol. Specifically, within each session, 124 functional T_{2*}-weighted volumes sensitive to blood-oxygen level dependent (BOLD) contrast were acquired using a gradient echo, echo planar sequence with the following parameters: TR = 2000 ms, TE = 30 ms, each volume contained 34 slices, slice thickness = 3 mm, flip angle = 90°, field of view = 200 mm, voxel size = 3.1 × 3.1 × 3.0 mm, and scan time = 4:12 min. The order of image acquisition was interleaved.

Ethical Considerations

The ethical considerations pertaining to the larger Cape Town Longitudinal Cohort Study are detailed in the analogous section in Chapter 2. The ethical considerations pertaining specifically to neuroimaging procedures are detailed in the analogous section in Chapter 3.

Data Management and Analysis

Neuroimaging data. I preprocessed and analyzed neuroimaging data from all participants using Statistical Parametric Mapping (SPM) version 8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), an extension package for MATLAB version R2008a, and Statistical Package for the Social Sciences (SPSS) version 23. To ensure that I remained blind to participant alcohol exposure history as well as to FASD diagnosis during data analysis, all data were assigned blinded identification codes by the project data manager.

Preprocessing. Data from all three functional sessions were preprocessed following the protocol detailed in the analogous section of Chapter 3. There is one notable difference between this study and Study I: During realignment, data from each of the three functional sessions was realigned to the first volume of the first session to ensure good image registration across the three sessions, whereas in Study I functional data was realigned to each participant's mean image.

Calculation of event onset times. Based on participant responses during the post-scan recognition test, target images were classified as either a hit or a miss. For each memory encoding session, I extracted hit and miss event onset times from each participant's raw memory encoding session data. For each event, the onset time was generated and converted from ms to volumes using the following formula: $y_i = (x - z_i)/2000$, where y_i is the event onset time (in volumes) of the i-th event, x is the encoding session start time (in ms), and z_i is

the image presentation time (in ms). The in-scanner part of the memory encoding task was programmed to be triggered to start by the scanner after four measurements had been acquired (i.e., after the first four functional volumes had been obtained). However, due to a mechanical error, the task trigger time varied for one or more of the encoding sessions for 13 of the 51 participants included in the final study sample. In the event that delayed task triggering occurred, the additional 'dummy volumes' were discarded from each participant's functional data in addition to the four functional volumes originally discarded to account for T_1 equilibrium (e.g., if the task triggered with the 6th pulse, five functional volumes were discarded). In one case (a boy aged, 10.0 years, in the non-exposed control group), the second encoding session began with the 1st pulse and, therefore, no 'dummy volumes' were excluded.

First-level analysis. During this stage of data analysis, I generated beta maps for each participant using a general linear model analysis (GLM; Amaro & Barker, 2006) in Montréal Neurological Institute (MNI) space. I generated two experimental regressors of interest (viz., hits and misses) by convolving events of interest with a canonical model of the HRF as implemented in SPM 8. During model specification, I defined the *t*-contrast of interest (viz., Hit > Miss) and inserted the onset time for each event of interest. Additionally, I inserted each participant's movement parameters (obtained during the realignment step of data preprocessing) as a nuisance covariate in their first-level model. Including motion parameters as a nuisance covariate in this manner ensures that individual variance in head movement is modeled for each participant and, therefore, reduces the likelihood of reporting false-positive results.

Second-level analysis. To examine within- and between-group patterns of neural activation during successful scene encoding, I conducted two whole-brain voxelwise analyses. To do so, I inserted each participant's Hit > Miss contrast data, defined at the first-

level, into a fixed-effects model. The primary aim of the within-group analysis was to identify fROIs (see analogous section below) for the sample as a whole (N = 51). Thus, within-group contrasts were created using a one-sample t-test with the threshold set at p (familywise error [FWE] corrected) < .05. The primary aim of the between-group analysis was to examine patterns of differential activation across FASD diagnostic groups. Between-group contrasts were created using independent-sample t-tests; however, the threshold was set at a less stringent level of p (uncorrected) < .001.

Review of automated anatomical labels. For each significant cluster identified during within- and between-group analyses, I looked up the anatomical label for each MNI coordinate using the Wake Forest University (WFU) PickAtlas tool (Maldjian et al., 2004, 2003). Because several of the automatically generated anatomical labels were non-descript (e.g., sub-lobar, extra-nuclear), I reviewed all cluster labels with a highly-experienced neuroanatomist (C. Warton, M.D.) For each cluster, I displayed the MNI coordinates for the within-cluster peak on the SPM single-subject T_1 template. Both original and revised anatomical labels are presented in Appendix O. Because the anatomical labels reviewed by CW provide far greater descriptive precision, revised labels were used in this study.

Functional region of interest (fROI) analysis. This step in the data analytic stream aimed to identify SM-related fROIs. I identified the fROIs for this study using two approaches: (1) functional cluster extraction for the Hit > Miss contrast at the second-level (i.e., SM effects), and (2) individual bilateral parahippocampal place area (PPA) as defined in Study I (see analogous section in Chapter 3).

Regarding approach (1), 22 clusters showed significant activation increases for events that were hits when evaluated against events that were misses at a threshold of p (FWE) < .05 (see *Results* section below). To assess magnitude of activation within each of these clusters, mean % signal change values for both hit and miss events were extracted using the MarsBaR

toolbox (http://marsbar.sourceforge.net/). To assess increases in magnitude of activation associated with successful memory encoding within these fROIs, I created a mean % signal change difference scores for each cluster by subtracting mean % signal change extracted for miss events from mean % signal change extracted for hit events. Here the aim was to assess activation increases that were unique to hit events.

Regarding approach (2), all but 1 individual (girl, 10.4 years old, non-exposed control) displayed scene-selective activation in the functionally and anatomically defined bilateral PPA (Chapter 3). To assess magnitude of activation during visual encoding within bilateral PPA, mean % signal change was extracted from a spherical ROI around the maximally scene-selective voxel (6mm radius) identified in Study I. I then calculated bilateral PPA mean % signal change difference scores using the same procedure as detailed above.

I will hereafter refer to the fROIs defined in (1) and (2) as the memory encoding ROIs.

Between-group analysis. I used a series of one-way analyses of variance (ANOVAs) to examine whether there were between-group differences in magnitude of activation in the memory encoding ROIs. The categorical predictor variable was FASD diagnostic status—participants were assigned to the FAS/PFAS, nonsyndromal HE or non-exposed control group based on their exposure history and dysmorphology examination (for more details, see Chapter 2). In the instance of a significant *F*-test result, post-hoc examination of these data was conducted using Least-Significant Difference (LSD) tests.

Correlation-based analysis. I used a correlation-based analysis (viz., Pearson correlation) to examine the association between three continuous measures of PAE (viz., oz AA/day, oz AA/occasion, and frequency of drinking [days/week]) and magnitude of activation in the memory encoding ROIs. The primary aim of these analyses was to assess

whether there is a dose-response association between PAE and memory encoding-related activation.

Behavioral data. I analyzed behavioral memory performance data using SPSS version 23. The key behavioral outcome variables are detailed in Table 4.1. Prior to conducting parametric analyses of these data, I used comprehensive descriptive statistics to examine the distributions of predictor and outcome variables to identify possible influential cases/outliers and to test other assumptions underlying parametric statistical tests (for these data, see Appendix P).

Potential confounding variables. Following the same procedure outlined in Chapter 3, I examined relations between sociodemographic variables and outcome variables to identify potential confounding variables eligible for inclusion in the analysis of memory encoding activation. In this study, I considered six potential confounding variables for inclusion in the statistical analyses: child sex and age at testing, and maternal age at delivery, education, socioeconomic status (SES; Hollingshead, 2011), and smoking during pregnancy. I considered any sociodemographic variable that was related even weakly (at $p < .10$) to a given outcome variable a potential confounder. To control for confounders, I reran any analyses detecting an association between PAE and the outcome with the relevant sociodemographic variable entered as a covariate in the ANCOVAs or as a predictor at the second step in a hierarchical regression analysis.

No mother reported using cocaine, and prenatal exposure to marijuana ($n = 5$) and methaqualone ("mandrax"; $n = 3$) were too rare for statistical adjustment. I, therefore, reran any analyses detecting an association between PAE and the outcome omitting children with either prenatal marijuana or mandrax exposure. All effects remained essentially unchanged (for these data, see Appendix Q).

Between-group analysis. I used a series of one-way ANOVAs to examine potential between-group differences in behavioral memory performance. As with the previous between-group comparisons, the between-subjects factor was FASD diagnostic status (viz., FAS/PFAS, nonsyndromal HE or non-exposed control group). In the instance of a significant *F*-test result, post-hoc examination of these data was conducted using Least-Significant Difference (LSD) tests.

Correlation-based analysis. I conducted two sets of bivariate correlational analyses, both using Pearson correlation coefficients (*r*). The first set of analyses examined, within each of the exposed groups, the association between three continuous measures of PAE (viz., oz AA/day, oz AA/occasion, and frequency of drinking [days/week]) and magnitude of activation in the memory-encoding ROIs described above. The second set of analyses examined whether behavioral memory performance was associated with differential magnitude of activation in the memory-encoding ROIs. Previous neuroimaging research within the Cape Town Longitudinal Cohort suggests that there may be differential patterns of structural and functional impairment when comparing activation and performance data for children in the FAS/PFAS and HE nonsyndromal groups (e.g., Diwadkar et al., 2013). I, therefore, conducted correlational analysis within each of the FASD diagnostic groups.

Results

Sample Characteristics

Mothers of children in the FAS/PFAS group were older at delivery than mothers of children in both the HE and non-exposed control groups, both post-hoc *p*'s < .05 (Table 4.2). Although mothers of children in the FAS/PFAS group were had completed significantly fewer years of formal education than had mothers of children in the non-exposed control group, $p < .01$, education levels did not differ between mothers of children in the FAS/PFAS

and HE groups, $p > .20$, or between those in the HE and control groups, $p > .10$. A smaller proportion of mothers of children in the FAS/PFAS group were married, compared to mothers of those in the HE group and to mothers of those in the non-exposed control group. This result was driven primarily by the high proportion of mothers of children in the non-exposed control group who were married. Mothers of children in the FAS/PFAS group were more economically disadvantaged than mothers of children in both of the other groups (on average Hollingshead level V—Unskilled Laborers, lowest of 5 levels), both post-hoc *p*'s < .05. Additionally, mothers of children in the HE group were more disadvantaged than mothers of children in the non-exposed control group (on average HE mothers scored on the lower limit of level IV—Semiskilled Workers; whereas non-exposed control mothers scored on the upper limit of level IV), $p < .05$.

Table 4.2
Sample Characteristics (N = 51)

Variables	FAS/PFAS ($n = 11$[a])	HE ($n = 14$)	Non-exposed control ($n = 26$)	Test statistic	*p*	ESE
Maternal variables						
Age at delivery (years)	30.8 (4.0)	26.0 (5.2)	26.4 (6.1)	2.97	.06†	.11
Level of education (years)	7.8 (1.7)	8.9 (2.9)	10.1 (1.7)	4.72	.01*	.16
Marital status (% married)	9.1	28.6	61.5	10.04	.01*	.44
Socioeconomic status	11.5 (2.3)	21.3 (8.2)	26.6 (6.9)	19.98	< .001***	.45
Prenatal alcohol exposure[b]						
AA/day (oz)	1.3 (0.8)	0.9 (1.0)	0.0 (0.0)	20.10	<.001***	.46
AA/occasion (oz)	4.8 (2.1)	3.7 (3.0)	0.0 (0.0)	34.87	<.001***	.59
Frequency (days/week)	2.1 (0.7)	1.4 (0.7)	0.0 (0.0)	31.59	<.001***	.57
Prenatal smoking (cigarettes/day)	8.0 (6.8)	4.5 (4.3)	2.9 (4.7)	3.88	.03*	.14
Child variables						
Age at testing (years)	12.4 (1.5)	10.6 (0.5)	11.2 (1.3)	7.60	.001**	.24
Sex (% male)	27.3	28.6	30.8	0.05	.97	.03
WISC-IV FSIQ	65.5 (10.7)	76.1 (17.7)	77.6 (12.9)	3.01	.06†	.11

Note. Unless otherwise stated, values presented are means with standard deviations in parentheses. FAS = fetal alcohol syndrome; PFAS = partial fetal alcohol syndrome; HE = heavily exposed nonsyndromal; ESE = estimate of effect size; AA = absolute alcohol; WISC-IV = Wechsler Intelligence Scale for Children—Fourth Edition; FSIQ = full scale IQ. Test statistics are either *F* or χ^2 depending on whether the variable under consideration was continuous or categorical. The estimates of effect sizes were calculated using partial eta squared (η^2) and Phi (φ) for one-way ANOVAs and Pearson's Chi-squared tests respectively.
[a]FAS $n = 7$; PFAS $n = 4$.
[b]1 oz AA/day ≈ 2 standard drinks.
$^{\dagger}p < .10$. $^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$.

During pregnancy, all mothers of children in the non-exposed control group reported abstaining from drinking (Table 4.2). On average, mothers of children in the FAS/PFAS and HE groups consumed a similar amount of alcohol across pregnancy, with both groups meeting the criteria for heavy drinking (i.e., on average, approximately 2 standard drinks per day). Although mothers of children in the FAS/PFAS group drank the same quantity per occasion as mothers of children in the HE group, they drank more often (viz., 2 days a week). Mothers of children in the HE group concentrated their drinking on 1 day a week.

Although mothers of children in the FAS/PFAS group reported smoking more cigarettes/day than mothers of children in the non-exposed control group, $p < .01$, smoking during pregnancy did not differ between mothers of children in the FAS/PFAS and HE groups, $p = .10$, or between those in the HE and non-exposed control groups, $p > .20$ (Table 4.2). Regarding maternal drug use, none of the mothers of children reported using cocaine during pregnancy. Five mothers (1 FAS/PFAS, 3 HE, and 1 non-exposed control) used marijuana (mean = 2.1 times/week, range = 0.8 – 3.7). Three mothers (1 FAS/PFAS and 2 HE) reported using methaqualone ("mandrax") during pregnancy (mean = 1.3 times/week, range = 0.03 – 3.2).

Children in the FAS/PFAS group were older than those in both the HE and non-exposed control groups, both post-hoc p's $< .01$ (Table 4.2). There were no significant differences in the proportion of boys to girls within any of the FASD diagnostic groups. Although, on average, general intellectual functioning (as indexed by WISC-IV Full-Scale IQ) was poorer in the FAS/PFAS group than in the non-exposed control group, post-hoc $p < .05$, this difference fell short of conventional levels of significance when comparing children in the FAS/PFAS and HE groups, post-hoc $p = .07$, and in the HE and non-exposed control group, post-hoc $p > .20$.

Identification of Potential Confounding Variables

Maternal age at delivery was significantly positively correlated to recognition accuracy (as indexed by *d*-prime; Table 4.3). Child sex was significantly positively correlated with activation increases in the left intraparietal sulcus and right parahippocampal gyrus (Table 4.4). Child age at testing was positively correlated with activation increases in the right intraparietal sulcus and the posterior-superior inferior temporal gyrus. Maternal education was positively correlated with activation increases in the right intraparietal sulcus, and was negatively correlated with activation increases in the left posterior superior occipital gyrus. Maternal SES was negatively correlated with activation increases in the left intraparietal sulcus. Thus, where a significant alcohol effect is reported, I included the aforementioned potential confounding variables as covariates/additional predictor variables in the relevant ANCOVAs and/or regression analyses of these data.

Table 4.3
Identification of Potential Confounders of Behavioral Memory Performance (N = 51)

	Child		Maternal			
Variable	Sex	Age	Cigarette smoking	Age at delivery	Education	SES
d-prime	.20	.06	.07	.25*	-.04	.05
Hit total	.11	-.03	.10	-.01	.06	-.10
Miss total	-.12	.03	-.10	.01	-.07	.11
False alarm	-.03	-.11	.08	-.11	.06	-.10
Correct rejection	.03	.11	-.08	.12	-.07	.09

Note. Statistics presented are Pearson correlation coefficients (*r*). All tests are two-tailed. SES = socioeconomic status.
*$p < .10$. **$p < .05$.

Table 4.4
Identification of Potential Confounders of Encoding-Associated Activation Increases (N = 51)

	Child		Maternal			
Region	Sex	Age	Cigarette smoking	Age at delivery	Education	SES
Frontal						
R Anterior inferior frontal sulcus	.17	-.07	-.01	.19	.16	.09
R Anterior insula	.03	.09	.03	.20	-.10	-.05
R Inferior frontal sulcus (premotor)	-.14	.12	-.07	.15	-.14	-.12
Parietal						
L Intraparietal sulcus	.26*	.14	-.02	.09	-.10	-.03
R Intraparietal sulcus (medial branch)	.18	.24*	-.03	.06	.26*	.07
L Intraparietal sulcus	.03	.04	.11	.02	-.21	-.26*
Occipital						
R Middle occipital gyrus (lateral surface, occipital)	.03	.07	-.10	.17	-.15	-.03
R Posterior inferior temporal gyrus	-.07	-.03	-.19	.02	-.03	-.15
L Posterior superior occipital gyrus	.04	-.02	.02	.11	-.24*	-.16
L Inferior occipital gyrus	.06	.11	-.02	.03	-.16	-.05
R posterior-superior inferior temporal gyrus (occipital)	.15	.25*	.14	.18	-.18	-.02
L Superior occipital gyrus (lateral surface)	.12	.03	-.06	-.03	-.20	-.06
R Fusiform gyrus	-.18	.06	-.17	.08	.01	.09
Limbic						
L Posterior parahippocampal gyrus	.21	.18	-.02	.15	-.13	-.01
R Parahippocampal gyrus	.27*	-.01	-.11	.06	-.06	.08
R Parahippocampal gyrus	-.01	.07	-.04	-.05	-.21	-.01
Hippocampus						
L Hippocampus, body	.07	.01	.20	-.08	-.13	-.05
R Hippocampus, tail	.09	.07	-.12	.01	-.02	-.06
R Hippocampus, body	-.08	-.06	.04	.09	.05	.07
R Hippocampus, head	.11	.15	.01	.10	.05	.02
R Hippocampus, body	.02	-.01	<.001	.04	-.13	.06
R Hippocampus, tail	.18	.15	-.03	.23	-.09	-.07
Additional ROIs						
L Parahippocampal place area[a]	-.08	.09	-.03	-.04	-.12	-.05
R Parahippocampal place area[a]	-.06	-.04	-.10	.08	-.002	.13

Note. Statistics presented are Pearson correlation coefficients (*r*). All tests are two-tailed. SES = socioeconomic status; R = right; L = left; ROIs = regions of interest.
[a]*n* = 50; one girl (10.4 years old) in the non-exposed control group did not demonstrate scene-selective activation at the least stringent threshold ($p < .05$; see Chapter 3)
*$p < .10$. **$p < .05$.

Behavioral Results

I examined data from the post-scanner recognition test to assess whether there were between-group differences in behavioral memory performance (Table 4.5). Recognition accuracy (*d*-prime) was equivalent across all FASD diagnostic groups. On average, all children in this sample had a hit rate of 49.8%. However, there were small but significant between-group differences in total number of hits, misses, and false alarms, and a difference just short of conventional levels of significance for total number of correct rejections. None of these were related to potential confounding variables, however (see Table 4.3). Results from the post-hoc tests suggested that children in the HE group had more correct hits and more false alarms and fewer misses and correct rejections than non-exposed controls. Although not significantly different from the other groups, the response pattern in the FAS/PFAS group was more similar to that of the controls than that of HE participants.

Table 4.5
Between-Group Differences in Behavioral Memory Performance (N = 51)

	FAS/PFAS (n = 11[a])	HE (n = 14)	Non-exposed control (n = 26)	F	p	η^2
d-prime	0.7 (0.2)	0.7 (0.3)	0.7 (0.3)	0.21	.812	.01
Hit total (%)	48.0 (19.2)	60.2 (22.7)	44.9 (16.3)	4.39[b]	.018[*]	.16
Miss total (%)	51.8 (19.2)	39.8 (22.7)	55.0 (16.4)	4.34[c]	.019[*]	.15
False alarm (%)	25.8 (12.3)	34.8 (13.2)	22.3 (11.1)	3.21[d]	.049[*]	.12
Correct rejection (%)	74.4 (12.3)	65.3 (13.2)	77.6 (11.2)	3.12[e]	.053[†]	.12

Note. Unless otherwise stated, values presented are means with standard deviations in parentheses. FAS = fetal alcohol syndrome; PFAS = partial fetal alcohol syndrome; HE = heavily exposed nonsyndromal.
[a]FAS n = 7; PFAS n = 4.
[b]FAS/PFAS = Non-exposed (p > .20) < HE (p's = .06 and .005, respectively)
[c]FAS/PFAS = Non-exposed (p > .20) > HE (p's = .06 and .005, respectively)
[d]FAS/PFAS = HE (p = .14) and Non-exposed (p > .20); HE > CON (p < .05)
[e]FAS/PFAS = HE (p = .14) and Non-exposed (p > .20); HE < CON (p < .05)
[†]p < .10. [*]p < .05.

Memory Encoding Activation

Whole-brain analysis. For the sample as a whole, and at a corrected threshold of p(FWE) < .05, the Hit > Miss contrast detected significant neural activation increases in 22 regions (sub-maxima clusters excluded; Table 4.6). This pattern of activation included bilateral recruitment of several posterior occipital, parietal and temporal regions, as well as a few PFC regions during successful memory encoding. More specifically, activation included a large band of bilateral occipital activation that extended (a) dorsally to the bilateral intraparietal sulcus and (b) ventrally to the right fusiform gyrus, bilateral parahippocampal gyrus, and bilateral hippocampal formation. PFC activation was restricted to the inferior frontal sulcus in the right hemisphere.

Table 4.6
Whole-Brain Voxelwise Analysis Showing Regions With Greater Neural Activation During Successful Scene Encoding (N = 51)

Hit > Miss p(FWE) < .05

Region	BA	MNI Coordinates x	y	z	Peak T value	Volume (mm^3)
Frontal						
R Anterior inferior frontal sulcus	46	48	32	18	6.18	24
R Anterior insula	-	28	30	-8	5.80	24
R Inferior frontal sulcus (premotor)	9	42	2	28	5.63	8
Parietal						
L Intraparietal sulcus	-	-22	-66	54	6.97	288
L Intraparietal sulcus	-	-22	-60	46	5.76	
R Intraparietal sulcus (medial branch)	-	20	-64	52	6.45	88
L Intraparietal sulcus	19	-28	-74	40	5.71	24
Occipital						
R Middle occipital gyrus (lateral surface, occipital)	39	44	-78	26	7.95	2240
R Superior occipital gyrus (occipital)	-	32	-82	26	7.64	
R Middle occipital gyrus (occipital)	-	32	-86	10	7.02	
R Posterior inferior temporal gyrus	-	52	-62	-12	7.93	408
R Posterior-superior inferior temporal gyrus	-	42	-62	-8	6.08	
L Posterior superior occipital gyrus	-	-42	-84	24	7.91	456
L Inferior occipital gyrus	-	-48	-60	-8	7.47	1136
L Posterior-superior inferior temporal gyrus	-	-48	-52	-14	6.67	
L Inferior occipital gyrus	-	-48	-72	-4	6.00	
R Posterior-superior inferior temporal gyrus (occipital)	-	52	-52	-10	6.44	312
L Superior occipital gyrus (lateral surface)	19	-30	-84	28	6.37	360
R Fusiform gyrus	-	30	-58	-12	5.80	24
Limbic						
L Posterior parahippocampal gyrus	-	-20	-36	-12	8.43	3024
L Parahippocampal gyrus	36	-26	-30	-20	8.27	
L Parahippocampal gyrus	37	-30	-40	-14	7.77	
R Parahippocampal gyrus	37	32	-38	-12	7.78	1696
R Parahippocampal gyrus	-	24	-36	-14	7.76	
R Fusiform gyrus (occipital-temporal junction)	37	34	-48	-18	7.45	
R Parahippocampal gyrus	-	22	-24	-18	5.89	8
Hippocampus						
L Hippocampus, body	-	-36	-16	-18	6.30	40
R Hippocampus, tail	-	18	-34	-2	6.12	88
R Hippocampus, body	-	32	-28	-2	6.05	8
R Hippocampus, head	-	24	-6	-12	5.87	8
R Hippocampus, body	-	34	-18	-14	5.81	16
R Hippocampus, tail	-	26	-32	2	5.63	8

Note. In cases where significant submaxima clusters were identified, details are provided in italics under maxima.
FWE = family-wise error corrected; MNI = Montréal Neurological Institute; BA = Brodmann Area; L = left; R = right.

Between-group analysis of degree of activation within the fROIs. I extracted mean % signal change data from each of the 22 discrete memory encoding fROIs identified by the whole-brain voxelwise analysis. Participants showed similar encoding-associated activation increases in all but three of the memory encoding fROIs, regardless of FASD group membership. Two of those three differences fell short of statistical significance ($p < .10$; Table 4.7). Regarding the left intraparietal sulcus, participants in the FAS/PFAS group showed significantly greater activation increases than those in both the HE and non-exposed control groups, with the latter two groups showing similar activation increases in this region. Regarding the right intraparietal sulcus, between-group differences fell short of conventional levels of significance. Although these findings are of interest (see Discussion below), the number of regions in which significant differences were seen did not exceed chance. Thus, no reliable between-group differences were seen across the regions activated by the sample as a whole. In addition to the memory-encoding ROIs, I examined activation increases in the bilateral parahippocampal place area (PPA). Analyses of both left and right PPA yielded no significant between-group differences.

Table 4.7
Between-Group Differences in Magnitude of Activation During Successful Scene Encoding (Hit > Miss; N = 51)

Region	FAS/PFAS (n = 11[a])	HE (n = 14)	Non-exposed control (n = 26)	F	p	η^2
Frontal						
R Anterior inferior frontal sulcus	0.2 (0.2)	0.2 (0.2)	0.1 (0.2)	0.59	.56	.02
R Anterior insula	0.2 (0.2)	0.1 (0.2)	0.2 (0.2)	0.85	.43	.03
R Inferior frontal sulcus (premotor)	0.2 (0.2)	0.1 (0.2)	0.1 (0.2)	0.66	.52	.03
Parietal						
L Intraparietal sulcus	0.3 (0.1)	0.1 (0.2)	0.2 (0.2)	1.29	.28	.05
R Intraparietal sulcus (medial branch)	0.3 (0.2)	0.1 (0.2)	0.2 (0.2)	2.49[b]	.09[†]	.09
L Intraparietal sulcus	0.3 (0.1)	0.1 (0.2)	0.1 (0.2)	3.35[c]	.04[*]	.12
Occipital						
R Middle occipital gyrus (lateral surface, occipital)	0.2 (0.2)	0.2 (0.2)	0.2 (0.1)	0.55	.58	.02
R Posterior inferior temporal gyrus	0.2 (0.2)	0.2 (0.2)	0.2 (0.1)	0.14	.86	.006
L Posterior superior occipital gyrus	0.2 (0.1)	0.1 (0.1)	0.1 (0.1)	1.64	.21	.06
L Inferior occipital gyrus	0.2 (0.2)	0.1 (0.1)	0.2 (0.1)	0.53	.59	.02
R posterior-superior inferior temporal gyrus (occipital)	0.2 (0.1)	0.1 (0.2)	0.2 (0.1)	0.64	.53	.03
L Superior occipital gyrus (lateral surface)	0.2 (0.1)	0.2 (0.3)	0.2 (0.2)	0.33	.72	.01
R Fusiform gyrus	0.2 (0.2)	0.2 (0.3)	0.2 (0.2)	0.09	.91	.004
Limbic						
L Posterior parahippocampal gyrus	0.2 (0.1)	0.1 (0.1)	0.2 (0.1)	0.86	.43	.03
R Parahippocampal gyrus	0.2 (0.1)	0.2 (0.2)	0.2 (0.1)	0.26	.77	.01
R Parahippocampal gyrus	0.2 (0.1)	0.1 (0.2)	0.1 (0.2)	0.49	.62	.02
Hippocampus						
L Hippocampus, body	0.1 (0.2)	0.1 (0.2)	0.1 (0.1)	0.31	.73	.01
R Hippocampus, tail	0.2 (0.1)	0.2 (0.2)	0.1 (0.1)	2.89[d]	.07[†]	.11
R Hippocampus, body	0.1 (0.1)	0.1 (0.2)	0.1 (0.1)	0.71	.50	.03
R Hippocampus, head	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.84	.44	.03
R Hippocampus, body	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.36	.70	.02
R Hippocampus, tail	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	2.07	.14	.08
Additional ROIs						
L Parahippocampal place area[e]	0.2 (0.1)	0.1 (0.1)	0.1 (0.2)	0.76	.48	.03
R Parahippocampal place area[e]	0.1 (0.2)	0.1 (0.2)	0.1 (0.1)	0.59	.56	.03

Note. Values presented are means with standard deviations in parentheses. FAS = fetal alcohol syndrome; PFAS = partial fetal alcohol syndrome; HE = heavily exposed nonsyndromal; R = right; L = left; ROIs = regions of interest.
[a]FAS n = 7; PFAS n = 4.
[b]FAS/PFAS > HE (p < .05); FAS/PFAS = non-exposed control (p = .14); HE = non-exposed control (p > .20)
[c]FAS/PFAS > HE (p < .05) = non-exposed control (p = .05)

[d]FAS/PFAS = HE ($p > .20$); FAS/PFAS = non-exposed control ($p > .20$); HE > non-exposed control ($p < .05$)
[e]$n = 50$; one girl (10.4 years old) in the non-exposed control group did not demonstrate scene-selective activation at the least stringent threshold ($p < .05$; see Chapter 3)
[†]$p < .10$. [*]$p < .05$.

Group comparisons in a whole-brain analysis. Although the groups did not differ in encoding-associated activation increases within the fROIs identified in the initial whole-brain analysis, a second set of whole-brain analyses was conducted to determine whether between-group differences might be seen outside the brain network identified for the sample as a whole. The Hit > Miss contrast was examined at an uncorrected threshold of *p*(uncorrected) < .001 (Table 4.8). At this threshold, significant between-group differences in differential neural activation were evident for the following contrasts: FAS/PFAS > non-exposed control and HE groups. Specifically, participants in the FAS/PFAS group showed significantly more activation in several regions, including the left postcentral sulcus, right postcentral gyrus, and right cerebellar lobule VIII, when compared to non-exposed controls. When compared to participants in the HE group, participants in the FAS/PFAS group showed significantly more activation in several regions, including the left precentral gyrus, left paracentral lobule, left intraparietal sulcus, and right posterior-superior temporal sulcus.

Table 4.8
Between-Group Whole-Brain Voxelwise Comparison Showing Differential Neural Activation During Successful Scene Encoding (N = 51)

Hit > Miss *p*(unc) < .001						
		MNI Coordinates				
Region	BA	x	y	z	Peak *T* value	Volume (mm^3)
Non-exposed control > FAS/PFAS		No significant differences				
Non-exposed control > HE		No significant differences				
HE > Non-exposed control		No significant differences				
HE > FAS/PFAS		No significant differences				
FAS/PFAS > Non-exposed control						
Frontal						
L Postcentral sulcus (extending into paracentral white matter)	-	-14	-34	66	5.19	1848
R Paracentral lobule	-	0	-40	62	4.09	
R Paracentral lobule	-	2	-40	52	3.82	
Parietal						
R Postcentral gyrus	43	64	-10	22	4.23	264
R Precentral gyrus (frontal)	-	56	-10	24	3.50	
Cerebellum posterior						
R Cerebellar lobule VIII	-	24	-54	-46	5.00	288
FAS/PFAS > HE						
Frontal						
L Precentral gyrus	-	-14	-32	68	4.51	440
L Precentral gyrus	4	-22	-28	64	3.86	
L Paracentral lobule	5	-10	-40	52	4.46	432
Parietal						
L Intraparietal sulcus (posterior medial branch)	-	-14	-56	60	4.87	272
Temporal						
R Posterior superior temporal sulcus (close proximity to occipital-temporal junction)	-	40	-64	20	4.38	544
R Posterior superior temporal sulcus	-	36	-54	24	3.86	

Note. In cases where significant submaxima clusters were identified, details are provided in italics under maxima. unc = uncorrected; MNI = Montréal Neurological Institute; BA = Brodmann Area; FAS = fetal alcohol syndrome; PFAS = partial fetal alcohol syndrome; HE = heavily exposed nonsyndromal; L = left; R = right.

Association of continuous measures of PAE with degree of activation in the memory encoding network. Although the groups did not differ in encoding-associated activation increases within the memory-encoding fROIs identified in the initial whole brain analysis, one continuous measure of PAE—average dose (oz AA)/occasion—was related to degree of activation in five fROIs in the Hit > Miss contrast in the FAS/PFAS group. Greater AA/occasion was associated with smaller activation increases in the left and right parahippocampal gyri and right anterior insula, and with greater activation increases in the tail and body of the right hippocampus (Table 4.9). Smaller activation increases were also seen in the right PPA. Activation increases in the right parahippocampal gyrus were

associated with child sex as a potential confounder of AA/occasion. This association persisted when child sex was entered into a hierarchical regression analysis. In contrast to the pattern of data present in the FAS/PFAS group, there were no significant associations between continuous measures of PAE and levels of activation within the nonsyndromal HE group.

Table 4.9

Relation of Continuous Measures of Prenatal Alcohol Exposure to Magnitude of Activation During Successful Scene Encoding (Hit > Miss; N = 25)

	FAS/PFAS (n = 11[a])			HE (n = 14)		
Region	AA/day	AA/occasion	Frequency	AA/day	AA/occasion	Frequency
Frontal						
R Anterior inferior frontal sulcus	-.30	-.31	-.12	.09	.02	-.01
R Anterior insula	-.32	-.64*	-.35	-.05	-.11	-.20
R Inferior frontal sulcus (premotor)	.14	-.13	-.09	.07	-.03	.13
Parietal						
L Intraparietal sulcus	.39	.24	.14	-.15	-.25	-.20
R Intraparietal sulcus (medial branch)	.51	-.03	.42	-.05	-.10	-.35
L Intraparietal sulcus	-.19	-.20	.41	.12	.23	.21
Occipital						
R Middle occipital gyrus (lateral surface, occipital)	-.34	-.30	-.44	-.15	-.11	-.09
R Posterior inferior temporal gyrus	-.29	-.42	-.29	-.19	-.17	-.21
L Posterior superior occipital gyrus	-.27	-.17	-.39	.07	-.02	.26
L Inferior occipital gyrus	-.32	-.48	-.34	-.16	-.13	-.21
R posterior-superior inferior temporal gyrus (occipital)	-.06	-.27	.09	.16	.18	.07
L Superior occipital gyrus (lateral surface)	-.15	-.45	-.21	.08	.13	.12
R Fusiform gyrus	-.20	-.11	-.31	-.08	-.10	-.14
Limbic						
L Posterior parahippocampal gyrus	-.15	-.67*	.03	-.13	-.13	-.10
R Parahippocampal gyrus	-.04	-.62*[b]	.11	-.13	-.22	-.16
R Parahippocampal gyrus	.07	-.40	.28	-.28	-.19	-.21
Hippocampus						
L Hippocampus, body	.28	-.06	.37	-.18	-.10	-.43
R Hippocampus, tail	.22	.66*	-.10	-.08	-.07	-.37
R Hippocampus, body	.07	.60*	-.18	-.29	-.23	-.25
R Hippocampus, head	.62*	.31	.54†	.31	.34	-.10
R Hippocampus, body	-.32	-.31	-.17	.19	.25	-.02
R Hippocampus, tail	.46	.33	.18	-.30	-.36	-.42
Additional ROIs						
L Parahippocampal place area[c]	-.52	-.41	-.44	-.002	.05	-.07
R Parahippocampal place area[c]	-.19	-.72*	-.02	-.02	-.16	.10

Note. Values presented are Pearson correlation coefficients (r). All significance tests are two-tailed. oz AA = ounces absolute alcohol; FAS = fetal alcohol syndrome;

PFAS = partial FAS; HE = heavily exposed nonsyndromal; AA = absolute alcohol; R = right; L = left; ROIs = regions of interest.
[a]FAS $n = 7$; PFAS $n = 4$.
[b]Standardized beta value for AA/occasion when controlling for child sex: $\beta = -.62$, $p < .05$
[c]$n = 50$; one girl (10.4 years old) in the non-exposed control group did not demonstrate scene-selective activation at the least stringent threshold ($p < .05$; see Chapter 3)
$^{\dagger}p < .10$. $^{*}p < .05$.

Association between memory encoding differential degree of activation and behavioral memory performance. I assessed relations between encoding-associated activation increases and recognition accuracy (i.e., *d*-prime; Table 4.10) within each FASD group separately, using Pearson correlation coefficients. In the non-exposed control group, greater activation increases in the left posterior-superior occipital gyrus, right posterior-superior inferior temporal gyrus, and right parahippocampal gyrus were positively associated with *d*-prime scores. Activation increases in these three regions were also associated with three potential confounding variables: primary caregiver's level of education, child age, and child sex. The effects were essentially unchanged after control for confounders, although in two cases they fell just below conventional levels of significance. Consistent with this pattern of findings, neither child age nor child sex significantly predicted activation increases in the right posterior-superior inferior temporal gyrus or right parahippocampal gyrus, respectively, both p's < .20.

In both the FAS/PFAS and HE groups, the number of regions in which significant associations were seen did not exceed chance. It is noteworthy nonetheless that memory encoding activation was not related to recognition accuracy in the two heavily exposed groups.

Table 4.10
Relation Between Recognition Accuracy (d-Prime) and Magnitude of Activation in Memory and Parahippocampal Regions of Interest (Hit > Miss; N = 51)

	d-prime		
Region	FAS/PFAS (n = 11[a])	HE (n = 14)	Non-exposed control (n = 26)
Frontal			
R Anterior inferior frontal sulcus	.53	.15	-.05
R Anterior insula	.15	.49†	.22
R Inferior frontal sulcus (premotor)	-.43	-.45	-.12
Parietal			
L Intraparietal sulcus	-.48	.02	.14
R Intraparietal sulcus (medial branch)	-.40	.11	-.14
L Intraparietal sulcus	-.24	-.31	.09
Occipital			
R Middle occipital gyrus (lateral surface, occipital)	.14	-.10	.29
R Posterior inferior temporal gyrus	.24	-.06	.26
L Posterior superior occipital gyrus	-.52	-.10	.40^{*b}
L Inferior occipital gyrus	.29	-.15	.39†
R posterior-superior inferior temporal gyrus (occipital)	.27	-.24	.39^{*c}
L Superior occipital gyrus (lateral surface)	-.07	-.22	.10
R Fusiform gyrus	.20	-.18	.08
Limbic			
L Posterior parahippocampal gyrus	.15	-.09	.22
R Parahippocampal gyrus	-.07	-.06	.43^{*d}
R Parahippocampal gyrus	.24	-.05	.01
Hippocampus			
L Hippocampus, body	.34	.25	-.02
R Hippocampus, tail	-.43	.41	.13
R Hippocampus, body	-.41	-.14	.17
R Hippocampus, head	-.18	.03	.06
R Hippocampus, body	.01	.26	.23
R Hippocampus, tail	-.84**	.43	-.13
Additional ROIs			
L Parahippocampal place area[e]	-.01	-.17	-.04
R Parahippocampal place area[e]	-.06	-.32	-.02

Note. Values presented are Pearson correlation coefficients (r). All significance tests are two-tailed. FAS = fetal alcohol syndrome; PFAS = partial FAS; HE = heavily exposed nonsyndromal; R = right; L = left; ROIs = regions of interest.
[a]FAS n = 7; PFAS n = 4.
[b]Standardized beta value for *d*-prime when controlling for primary caregiver's education: $\beta = .39$, $p < .05$
[c]Standardized beta value for *d*-prime when controlling for child age: $\beta = .37$, $p = .07$
[d]Standardized beta value for *d*-prime when controlling for child sex: $\beta = .38$, $p = .07$
[e]n = 50; one girl (10.4 years old) in the non-exposed control group did not demonstrate scene-selective activation at the least stringent threshold ($p < .05$; see Chapter 3)
$^{\dagger}p < .10$. $^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$.

I also assessed relations between encoding-associated activation increases and behavioral response style (as indexed by hit and false alarm responses; Table 4.11) within each FASD group separately, again using Pearson correlation coefficients. In all three groups, smaller activation increases were associated with increased hits and false alarms. However, the pattern of significant regions differed for each of these groups. Most noteworthy is the

finding that smaller activation increases in several of the bilateral hippocampal formation fROIs were predominantly associated with increased hit responses in the non-exposed control group, whereas children in both alcohol-exposed groups showed significant associations between smaller activation increases and increased hit and/or false alarm responses predominantly in the occipital lobe fROIs. Children in the FAS/PFAS group also demonstrated associations of a similar pattern in frontal and parietal fROIs. The effects remained unchanged in all but one fROI (left posterior superior occipital gyrus) when controlling for potential confounding variables. In addition to significant associations between magnitude of activation and behavioral memory performance, trends towards significant associations were noted in several regions for all FASD groups.

Table 4.11

Relation Between Behavioral Memory Performance and Magnitude of Activation in Memory and Parahippocampal Regions of Interest (Hit > Miss; N = 51)

	Hit			False Alarms		
Region	FAS/PFAS (n = 11[a])	HE (n = 14)	Non-exposed control (n = 26)	FAS/PFAS (n = 11[a])	HE (n = 14)	Non-exposed control (n = 26)
Frontal						
R Anterior inferior frontal sulcus	-.42	.48†	-.32	-.68*	.40	-.16
R Anterior insula	-.60†	.07	-.32	-.54†	-.20	-.36†
R Inferior frontal sulcus (premotor)	-.74**	-.40	-.37†	-.50	-.35	-.12
Parietal						
L Intraparietal sulcus	-.33	-.24	.08	-.17	-.30	-.02
R Intraparietal sulcus (medial branch)	-.06	-.17	.23	.15	-.31	.27
L Intraparietal sulcus	-.74**[b]	-.37	-.24	-.59†	-.19	-.19
Occipital						
R Middle occipital gyrus (lateral surface, occipital)	-.69*	-.59*	-.23	-.68*	-.58*	-.25
R Posterior inferior temporal gyrus	-.58†	-.59*	.13	-.64*	-.62*	-.04
L Posterior superior occipital gyrus	-.61*[c]	-.27	.05	-.37	-.27	-.16
L Inferior occipital gyrus	-.78**	-.49†	-.27	-.84**	-.49†	-.38†
R posterior-superior inferior temporal gyrus (occipital)	-.06	-.69**[d]	-.46*[e]	-.17	-.62*[f]	-.51**[g]
L Superior occipital gyrus (lateral surface)	-.64*	-.67**	-.08	-.54†	-.61*	-.06
R Fusiform gyrus	-.51	-.47†	-.45*	-.56†	-.47†	-.33†
Limbic						
L Posterior parahippocampal gyrus	-.43	-.40	-.20	-.46	-.41	-.25
R Parahippocampal gyrus	-.15	-.43	-.31	-.09	-.50†	-.45*[h]
R Parahippocampal gyrus	.20	-.37	-.20	.17	-.25	-.14
Hippocampus						
L Hippocampus, body	.56†	-.55*	-.39*	.42	-.64*	-.23
R Hippocampus, tail	-.13	-.24	-.04	-.01	-.45	-.13
R Hippocampus, body	.32	.20	-.29	.45	.32	-.28
R Hippocampus, head	.12	-.20	-.49*	.13	-.22	-.38†
R Hippocampus, body	.15	-.51†	-.40*	.17	-.60*	-.35†
R Hippocampus, tail	-.35	.44	-.47*	.001	.21	-.17
Additional ROIs						
L Parahippocampal place area[i]	-.09	-.50†	-.30	-.09	-.45	-.21
R Parahippocampal place area[i]	-.34	-.51†	-.18	-.23	-.49†	-.07

Note. Values presented are Pearson correlation coefficients (r). All significance tests are two-tailed. FAS = fetal alcohol syndrome; PFAS = partial FAS; HE = heavily exposed nonsyndromal; R = right; L = left; ROIs = regions of interest.

[a]FAS n = 7; PFAS n = 4.

[b]Standardized beta value for hit when controlling for socioeconomic status: $\beta = -.83$, $p < .05$
[c]Standardized beta value for hit when controlling for primary caregiver's education: $\beta = -.54$, $p = .11$
[d]Standardized beta value for hit when controlling for child age: $\beta = -.69$, $p < .01$
[e]Standardized beta value for hit when controlling for child age: $\beta = -.49$, $p < .05$
[f]Standardized beta value for false alarm when controlling for child age: $\beta = -.62$, $p < .05$
[g]Standardized beta value for false alarm when controlling for child age: $\beta = -.50$, $p < .05$
[h]Standardized beta value for false alarm when controlling for child age: $\beta = -.41$, $p < .05$
[i]$n = 50$; one girl (10.4 years old) in the non-exposed control group did not demonstrate scene-selective activation at the least stringent threshold ($p < .05$; see Chapter 3)
$^{\dagger}p < .10$. $^{*}p < .05$. $^{**}p \leq .01$. $^{***}p < .001$.

Discussion

The primary aim of this study was to examine neural activation during memory encoding in children with heavy PAE. Neural activation was assessed using an event-related fMRI task based on the SM paradigm (Ofen et al., 2007). All children, regardless of exposure history, demonstrated similar memory performance accuracy and recruited extensive bilateral networks including the hippocampal formation, posterior parietal cortex, and prefrontal cortex during memory encoding—a pattern consistent with previous fMRI studies of typically developing children. However, during encoding children with a diagnosis of FAS or PFAS shower greater activation increases in the left intraparietal sulcus, and activated additional regions associated with attentional function. Within the FAS/PFAS group, higher levels of exposure were associated with smaller activation increases in the parahippocampal gyri accompanied by greater activation increases in the right hippocampal formation during encoding. Given the absence of between-group differences in recognition accuracy, these data suggest that children with FAS/PFAS recruited more extensive neural resources to perform successfully on this visual-spatial memory encoding task.

Each FASD group demonstrated different patterns of association between behavioral memory performance and encoding-associated activation increases. This array of differential patterns of association is consistent with between-groups variation in behavioral response styles, a variability that exists despite similarly accurate performance on the recognition task. The effects of PAE described above could not be attributed to potentially confounding sociodemographic variables, or to other prenatal smoking and/or drug exposure.

To the best of my knowledge, this is the first study to demonstrate functional impairment during memory encoding in an FASD sample. The results of this study are, therefore, both novel and exploratory and require replication in future research. In this section, I address the findings relating to each research question and relate them to the

broader literature pertaining to neural activation during memory encoding and declarative memory functioning in FASD. Additionally, I address the limitations of this study and suggest future research directions.

Behavioral Memory Performance

Overall, the behavioral performance of this sample on the memory encoding task was consistent with performance patterns reported in studies of typically developing samples. For example, on an fMRI visual scene encoding task similar to the one used in this study, Ofen et al. (2007) reported a hit rate of 51% and a correct rejection rate of 79% for their sample (N = 49, age range: 8 – 24 years). Because the age range of the current sample is narrower, it is impressive that these overall response patterns were replicated in the current study (viz., hit rate of 49.8% and correct rejection rate of 73.5%). Moreover, the absence of between-group differences in recognition accuracy performance suggests that the behavioral component of the memory encoding task was sufficiently simple to enable all participants to be able to complete the task successfully. This finding is relevant because it allowed me to investigate the basic functional integrity of regions associated with successful memory encoding in the absence of exposure-related differences in performance accuracy.

Despite this absence of between-group differences in performance accuracy, children in the nonsyndromal HE group demonstrated a different pattern of responses to those present in the other two groups. Specifically, children in this group had higher hit and false alarm rates, and lower correct rejection and miss rates, than children in the non-exposed control group. Children in the FAS/PFAS group appeared to follow a similar response pattern to those in the non-exposed control group. One way to explain this difference in response style relies on examination of the way in which responses are formulated. The pattern of high numbers of correct hits and false alarms seen in the nonsyndromal HE group is consistent

with a more impulsive response style, whereas a pattern of more misses and correct rejections seen in the non-exposed control group (and, to a lesser extent, in the FAS/PFAS group) is consistent with a more deliberative and exhaustive memory search.

The differences in response patterns between FASD groups are intriguing for several reasons. First, it is somewhat surprising that the more impulsive response pattern exhibited by the nonsyndromal HE group was not observed in the FAS/PFAS group. However, this pattern does fit with clinical observations of the Cape Town Longitudinal Cohort: Many of the children with FAS/PFAS seem to have a more careful, deliberate cognitive style, even though they perform less well than children in the nonsyndromal HE group. Additionally, the nonsyndromal HE group tends to have a more variation in performance, with some children performing at levels on par with non-exposed controls while others demonstrate extreme versions of the impulsive response pattern. In the absence of statistical outliers, this variation in cognitive ability gives credence to the suggestion that this heterogeneity of exposure-related outcomes within the HE nonsyndromal diagnostic category may reflect interactions between the timing of exposure during prenatal development (Lipinski et al., 2012; Sulik, 2005), genetic differences (Dodge et al., 2014; Viljoen et al., 2001; Warren & Li, 2005), and/or nutritional status (Carter et al., 2014; May, Hamrick, et al., 2014). In the absence of dysmorphic features, this variability in presentation represents a significant diagnostic challenge and warrants follow-up investigation using novel experimental methods to facilitate further clarification of this diagnostic category (e.g., Suttie et al., 2013). Nevertheless, the differences in cognitive processing styles observed in this study suggest that very different approaches to intervention are warranted for children with FAS and PFAS than for children with nonsyndromal HE.

Memory Encoding Activation

Regions recruited during memory encoding. All participants, regardless of exposure-history, demonstrated a SM effect on the event-related fMRI task used in this study. This is the first study to report SM-like effects in children with FASD. Hence, it provides a novel contribution to the literature working toward clarifying mechanisms underlying PAE-related learning and memory impairments, and validates the task for use in this pediatric clinical sample.

Of particular note here is that the regions that showed greater activation for images remembered than images forgotten (i.e., successful memory encoding) are consistent with those reported in adult samples (for a review, see Kim, 2011) and in typically-developing pediatric samples (Chai et al., 2010; Maril et al., 2011; Shing et al., 2016). In addition, these regions are largely consistent with the three broad functional categories considered to be integral to effective memory encoding. Kim (2011) suggests organization of SM-related regions into those that primarily support (1) content processing (e.g., posterior parahippocampal gyrus activation during visual scene processing; Epstein & Kanwisher, 1998), (2) information storage (e.g., MTL and hippocampal formation during the binding of content and memory representation; Henke, Buck, Weber, & Wieser, 1997), and (3) attention (e.g., a frontoparietal network that recruits primary motor cortex and posterior parietal cortex during tasks assessing visual attention; (Corbetta, Kincade, & Shulman, 2002; Corbetta, Patel, & Shulman, 2008). Moreover, preferential activation of the right inferior frontal cortex and bilateral MTL structures (e.g., hippocampal formation and parahippocampal gyri) is consistent with literature documenting modality specific activation patterns when processing visual-spatial information (Golby et al., 2001).

Relation of prenatal alcohol exposure to activation patterns within the fROIs identified for the sample as a whole. Overall, all participants, both with and without heavy

PAE, demonstrated encoding-associated activation increases within the memory encoding fROIs. Although the number of regions showing between-group differences did not exceed chance, the finding of greater activation increases in the left intraparietal sulcus, as well as the trend towards greater activation increases in the right intraparietal sulcus, in dysmorphic participants compared to non-exposed controls is noteworthy for several reasons. First, previous fMRI studies have found PAE-related differences in activation of this region during completion of visual-spatial attention and working memory (Astley et al., 2009; Malisza et al., 2012; Norman et al., 2013), verbal working memory (Diwadkar et al., 2013; O'Hare et al., 2009), and number processing (Meintjes et al., 2010; Santhanam et al., 2009) tasks. Moreover, the between-group differences in this region appear to be bilateral, which suggests that it is less likely to be a chance finding. Additionally, previous studies using MRI to investigate the structural integrity of posterior parietal regions have reported exposure-related differences in the intraparietal sulci specifically (e.g., decreased sulcal depth in the left intraparietal sulcus and increased sulcal fold opening in bilateral intraparietal sulci (De Guio et al., 2014), as well as atypical developmental trajectories in bilateral inferior parietal regions (Lebel et al., 2012). The findings suggesting greater activation increases in the intraparietal sulci in the FAS/PFAS group, therefore, warrant further investigation.

The relation between bilateral intraparietal sulci activation and successful memory encoding is well established in the SM literature. In a meta-analytic review of SM effects, Kim (2011) described the bilateral intraparietal sulci as the locus of posterior parietal activation during memory encoding. This is important because the intraparietal sulci form an integral part of the frontoparietal attentional system (Corbetta et al., 2002, 2008). Thus, the finding that dysmorphic participants show greater activation increases in the intraparietal sulci for items that were successfully encoded suggests a need to recruit additional attentional resources to successfully encode the stimuli in this relatively simple task.

Regarding scene-selective activation in the bilateral PPA, the absence of between-group differences in encoding-associated activation increases in this region suggests that participants in all three groups recruit the bilateral PPA to the same degree for both images remembered and images forgotten. Previous research has demonstrated that (a) the bilateral PPA shows functional specialization for the perception of visual scenes (Cant & Goodale, 2011; Epstein & Kanwisher, 1998; Epstein, 2005), and (b) activation in this region is associated with successful visual-spatial memory formation (Epstein et al., 2007; Golarai et al., 2007). In this study, the absence of between-group effects in PPA recruitment is consistent with the finding that participants in all three diagnostic groups demonstrated equivalent scene-selective recruitment of the bilateral PPA during visual scene perception (see, Chapter 3). These data thus suggest that basic scene-perceptual processing is not altered by PAE.

The a priori decision to examine associations between continuous measures of PAE and activation levels within the FAS/PFAS and HE groups separately was validated by the differing patterns of behavioural response style between these two groups (see, Table 4.5). Although no reliable exposure-group differences were seen in activation levels within the fROIs identified for the sample as a whole, average alcohol dose/occasion was associated with smaller activation increases in the right PPA and greater activation increases in two hippocampal regions in the FAS/PFAS group. The hippocampal formation plays an integral role in the acquisition and consolidation of novel information into long-term memory (Eichenbaum, 2003; Squire & Zola-Morgan, 1991). This finding suggests that, for the dysmorphic children, increased exposure is associated with smaller activation increases in this region for images remembered, compared with images forgotten. The data in Table 4.10 show that for controls greater activation increases in the right hippocampal gyrus were associated with better encoding, measured by *d*-prime. The data in Table 4.9 point to smaller

activation increases in this region and in left posterior parahippocampal gyrus and right anterior insula in the FAS/PFAS group and greater activation increases in two hippocampal regions, which may compensate, in part, for the lower level of activation in the right PPA. Taken together with between-group differences in intraparietal sulci activation, these data suggest there may be functional impairment in regions that mediate attentional control and the integration of perceptual information during memory encoding in participants with a diagnosis of FAS or PFAS.

The absence of any associations between continuous measures of PAE and activation levels in the nonsyndromal HE group is also noteworthy. Although there were no differences in the amount of exposure (viz. AA/day and AA/occasion), mothers of participants in the FAS/PFAS group reported more frequent binge drinking during pregnancy than mothers of participants in the nonsyndromal HE group (viz., > 4 drinks on 2 vs. 1 occasion per week, respectively). Previous studies investigating dose-response associations between PAE and developmental outcomes suggest that binge drinking is particularly detrimental to the structural and functional maturation of the brain (e.g., Flak et al., 2014). Furthermore, evidence from animal models has shown that high dose/occasion is often more deleterious than high total alcohol exposure provided in lower doses (Bonthius & West, 1990; Goodlett, Kelly, & West, 1987). Although no finite threshold for exposure has been established, what is evident is that the timing and amount of exposure impacts the severity of associated outcomes (e.g., heavy PAE during first trimester is associated with dysmorphic features of FAS and PFAS; May, Blankenship, Marais, Gossage, Kalberg, Joubert, et al., 2013; Sulik, 2005). The failure of degree of exposure to predict activation increases in specific brain regions in the nonsyndromal HE group may, therefore, be attributable to heterogeneity in timing and frequency of PAE reported by mothers of children in this diagnostic category.

Group differences in activation of brain regions outside those activated by sample as a whole. Although patterns of activation in the memory encoding fROIs identified for the sample as a whole was generally similar across the exposure groups, examination of a whole-brain analysis comparing the three groups detected that children in the FAS/PFAS group showed a more diffuse pattern of activation during successful memory encoding than those in both the nonsyndromal HE and non-exposed control groups. For instance, when compared to non-exposed control participants, children with FAS/PFAS showed greater activation increases in bilateral postcentral cortex and right cerebellar lobule VIII. These findings suggest that participants with a diagnosis of FAS or PFAS showed, relative to typically-developing non-exposed participants, more extensive recruitment of regions implicated in the executive control of attentional resources during successful memory formation. These data are consisted with those of Sowell et al. (2007), who reported increased reliance on frontal memory systems in participants with heavy PAE. Moreover, recruitment of the right cerebellar lobule VIII is consistent with findings reported by Diwadkar et al. (2013), who demonstrated that, relative to non-exposed controls, participants with a diagnosis of FAS/PFAS are more reliant on left cerebellar lobule VIII sub-region during a verbal working memory fMRI task.

Interestingly, children in the FAS/PFAS group also showed a more diffuse pattern of differential activation when compared to participants in the nonsyndromal HE group. Children with FAS/PFAS were showed greater activation increases in the left precentral gyrus, left paracentral lobule, left intraparietal sulcus, and right posterior-superior temporal sulcus than nonsyndromal participants. In this instance, the pattern may be best described as increased reliance on posterior parietal attentional and perceptual networks. This is consistent with the between-group differences in intraparietal sulci activation seen in the FAS/PFAS group, as well as in other fMRI studies showing greater recruitment of parietal visual

attention networks (e.g., spatial working memory, Malisza et al., 2012); number processing, Woods et al., 2015). Moreover, these data are consist with the general pattern of more diffuse fMRI activation in children with FAS and PFAS that is suggestive of compensatory activation that is thought to mediate effective behavioral task completion in severely affected participants (Diwadkar et al., 2013; Fryer, Tapert, et al., 2007; Meintjes et al., 2010).

Relation between behavioral memory performance and memory encoding activation. Despite the absence of between-group differences in behavioral recognition accuracy (i.e., *d*-prime scores), only children in the non-exposed group showed associations between encoding-associated activation increases and accuracy. Within the non-exposed control group, greater activation increases in several bilateral (although predominantly right) posterior occipital-temporal regions were associated with better accuracy. Together, these regions (viz., left posterior-superior occipital gyrus, right posterior-superior inferior temporal gyrus, and right parahippocampal gyrus) form a part of the ventral visual processing stream that is implicated in the initial processing and integration of visual-spatial information into long-term memory stores (Henson & Gagnepain, 2010). The finding that virtually no significant associations were seen for the FAS/PFAS and nonsyndromal HE groups may be suggestive of a functional impairment in children with PAE. Alternately, the absence of significant associations may be due to the small sample sizes in the two exposure groups. Within the FAS/PFAS group, the finding of a strong association with smaller activation increases in the right hippocampal tail and non-significant moderate associations in several other hippocampal regions lends support to the latter explanation.

The associations between encoding-associated activation increases and response patterns (indexed by number of hit and false alarm responses) are best interpreted within the framework of two types of encoding style: faster, more impulsive encoders vs. slower more comprehensive encoders. These data appear to suggest that faster encoders (viz., children in

the nonsyndromal HE group) exhibit encoding-associated activation increases in fewer regions within the encoding network, whereas more comprehensive encoders (viz., children in the non-exposed control group) show encoding-associated activation increases in several regions that are particularly relevant to the encoding of visual-spatial information. For example, smaller activation increases in several regions within the bilateral (although predominantly right) hippocampal formation, the right posterior-superior inferior temporal gyrus, and right fusiform gyrus were associated with increased hit responses for children in the non-exposed control group. The finding that all but one of these regions was lateralized to the right hemisphere is consistent with the literature reporting increased reliance on right hemisphere neural resources during the perception and encoding of visual-spatial material (Golby et al., 2001; Milner, 1970; Wagner, Poldrack, et al., 1998).

The finding that the two alcohol-exposed groups appear not to differ in the relation of their response style to activation increases within the encoding network is noteworthy. The response style adopted by children in the FAS/PFAS group was closer to that of children in the non-exposed control group (i.e., slower, more comprehensive encoders) than that of children in the nonsyndromal HE group (i.e., faster, more impulsive encoders). A possible explanation for this apparent discrepancy is that, when compared to children in both the nonsyndromal HE and non-exposed control groups, children in the FAS/PFAS group (a) have generally slower processing speed (as demonstrated by between-group performance differences in WISC-IV Processing Speed Index scores, F (2, 48) = 4.39, p = .02, η^2 = .16), and (b) recruited additional regions, suggestive of compensatory activation.

Limitations and Future Directions

As detailed in the Limitations section in Chapter 3, several problems arise when conducting fMRI investigations to examine relations between heavy PAE and cognitive

outcomes. A limitation of particular relevance to this study is the potential confounding effect of exposure-related differences in brain morphology on between-group comparisons in fMRI activation (Coles & Li, 2011). Although it was beyond the scope of this study to examine structural differences in the regions demonstrating SM-related activation, this is a pertinent limitation to these data. For example, Li et al. (2008) demonstrated that the location of functional impairment associated with heavy PAE in the occipital-temporal cortex was consistent with volumetric reductions in white and gray matter in this region. Thus, underlying structural abnormalities may mediate the effect of PAE on functional activation in a given region. This fact is particularly relevant because exposure-related structural impairments have been documented in several of the regions recruited during successful memory formation in this study (for a review, see Moore et al., 2014). A future direction for this line of investigation is, therefore, to examine structural and functional data simultaneously in regions demonstrating SM effects.

In this study, the sample size for both the FAS/PFAS and HE groups was small, but consistent with, if not slightly larger than, previous neuroimaging studies in children with heavy PAE (e.g., heavy PAE n = 11, Sowell et al., 2007; FAS/PFAS n = 17, nonsyndromal HE n = 13, Diwadkar et al., 2013). In this study, movement during neuroimaging data acquisition was the primary constraining factor on sample size related to neuroimaging data analysis. Specifically, datasets with movement exceeding acceptable thresholds were excluded. However, it is a relative strength of the current study that the participants included in this study represent the cleanest sample possible with regard to movement artifact. One possible option to increase sample size in the heavy PAE groups is to include participants whose movement exceeding acceptable thresholds was restricted to one encoding fMRI session (n = 8). In cases where the participant's movement spiked near the beginning (n = 1) or end (n = 3) of the fMRI session, the problematic volumes could be dropped and data from

the rest of the session retained. In cases where the participant's movement was intermittent throughout the fMRI session (n = 4), the session would, however, have to be excluded entirely.

With regard to future directions for the investigation of learning and memory impairment in FASD, this study has demonstrated that the SM paradigm is appropriate for use in samples of children with a history of heavy PAE. In addition to adding to the current FASD literature documenting exposure-related deficits in learning and memory performance, the use of such a task is particularly relevant to longitudinal study designs aiming to track the neurodevelopmental trajectory of such cognitive domains. Currently, the literature documenting age-related changes in SM effects is restricted to correlation-based assessment of activation across different age groups (e.g., Ofen et al., 2007). Thus, access to longitudinal studies, such as the one within which this doctoral research is nested, provides a unique opportunity to use the SM paradigm to assess changes in the recruitment of the MTL and PFC during memory encoding across development.

It was beyond the scope of the current study to examine the results of other experimental manipulations embedded within the event-related fMRI task. Thus, a follow-up cross-sectional study of SM effects in the memory encoding subset of the Cape Town Longitudinal Cohort aims to assess whether scene complexity (low- vs. high-complexity) and/or recognition response confidence (viz., remember vs. familiar) elicit differential patterns of neural activation than the Hit > Miss contrast employed in this study. Additionally, investigation of these experimental manipulations may help to clarify both the behavioral and activation patterns observed in the heterogeneous HE nonsyndromal group.

Another pertinent line of investigation is to examine mediators of the alcohol effects observed primarily in the FAS/PFAS group in this study. A methodological constraint when investigating neurodevelopmental outcomes associated with PAE in human samples is that

study designs are, by definition, correlational. While potential confounding variables may provide an alternate explanation for an observed alcohol-effect, mediator variables serve to clarify the relation between exposure and outcome. For example, PAE is associated with impaired general intellectual functioning (Jacobson et al., 2004; Mattson et al., 1997), which is, in turn, associated with impaired verbal learning and memory performance (Mattson et al., 1998). When evaluated statistically, general intellectual functioning mediates the effect of PAE (at moderate levels of exposure) on behavioral memory encoding performance (Lewis et al., 2015; but cf. Vaurio, Riley, & Mattson, 2011). It was beyond the scope of this study to investigate mediator variables, but such investigation is an important future direction.

It is of clinical relevance that both behavioral symptoms akin to those observed in ADHD and co-morbid diagnoses of ADHD are frequently reported in children with PAE (Aronson, Hagberg, & Gillberg, 1997; Coles, 2001; Fryer, McGee, et al., 2007; Mick, Biederman, Faraone, Sayer, & Kleinman, 2002). However, the etiology and neuropsychological presentation of children with both PAE and ADHD differs from those with idiopathic ADHD (Crocker et al., 2011; Jacobson et al., 2011; Kingdon, Cardoso, & McGrath, 2016). Krauel et al. (2007) demonstrated that adolescents with ADHD activate regions in the superior parietal lobe and precuneus that are suggestive of compensatory activation of attentional resources during encoding. Although the exposure-related activation patterns occurred within different regions for children with FAS/PFAS in this study, it is striking that both clinical pediatric populations recruit compensatory networks to facilitate successful encoding. Although it was beyond the scope of this research to examine associations between PAE, ADHD, and encoding activation, such examination is an important future direction.

Conclusions

This study is the first to examine patterns of neural activation during memory encoding directly in children and adolescents with FASD, and in so doing became the first to report SM effects in this pediatric sample. Within the FAS/PFAS group, the findings of this study demonstrate a striking functional impairment during memory encoding that is compensated for by (a) the recruitment of additional neural regions outside of the encoding network identified for the sample as a whole, and (b) different activation patterns within key regions of the encoding network. Taken together with the behavioral observation of differing encoding styles between FASD groups, these data suggest that the same learning and memory intervention strategy may not be appropriate for all children with PAE. Thus, further research is warranted to clarify the pattern of exposure-related impairment within this cognitive domain. Given that children in the FAS/PFAS group recruited additional neural resources to facilitate the executive control of attentional resources during encoding, it is of clinical significance to extend the findings of this study with follow-up research questions investigating memory performance on tasks designed to recruit higher-order executive processes (e.g., working memory) to facilitate encoding.

CHAPTER 5: SOURCE MEMORY PERFORMANCE IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS – STUDY III

Neuropsychological investigations suggest that impaired executive function (EF), and in particular working memory (WM) deficits, are a core feature of the cognitive and behavioral profile of children with fetal alcohol spectrum disorders (FASD; Burden, Jacobson, Sokol, et al., 2005; Green, Mihic, Nikkel, et al., 2009; Kodituwakku, Kalberg, & May, 2001; Mattson et al., 1999; Rasmussen, 2005). WM facilitates the manipulation and organization of complex information during information acquisition (Baddeley, 1992, 2003). In this way, WM supports the formation of long-term memories rich in contextual detail – a key feature of an episodic memory.

WM is, therefore, (a) essential to effective long-term memory encoding, and (b) important to evaluate as a possible mediator of the effect of prenatal alcohol exposure (PAE) on learning and memory performance. Thus, a pertinent line of investigation for the indirect examination of this relation is that of behavioral paradigms assessing the acquisition of memories rich in contextual detail (viz., source memory). To date, there is limited research assessing source memory performance in children with a history of PAE. Investigations using source memory paradigms, therefore, provide a novel opportunity to elucidate the role of EF (in particular, the WM component of EF) as a mediator of exposure-related impairments in learning and memory.

In this chapter, I provide a brief review of source memory literature and on the limited related findings in the FASD literature. I then present the methods used to examine source memory and WM performance. Finally, I report the results of this study and integrate them with the broader literature pertaining to relations between source memory, EF, and PAE.

Source Memory

Source memory is perhaps best defined as "the ability to specify contextual information surrounding a memory" (Drummey & Newcombe, 2002, p.503). As a psychological concept, it is analogous to 'source monitoring', and indeed was first introduced to the literature as a part of the source monitoring theoretical framework (Johnson, Hashtroudi, & Lindsay, 1993). Within this framework, the term *source* refers specifically to the characteristics (e.g., spatial, emotional, and temporal) associated with an event or with novel information at the time of memory encoding. Johnson and colleagues specified three different conditions for the empirical identification of source details: (i) reality source monitoring (i.e., distinguishing between externally and internally generated sources of information; e.g., "Did person A close the door or did I imagine closing the door?"); (ii) external source monitoring (i.e., distinguishing between two externally generated sources of information; e.g., "Did person A or person B close the door?"); and (iii) internal source monitoring (i.e., distinguishing between two internally generated sources of information; e.g., "Did I close the door or did I think that I closed the door?"). Under all conditions, successful source memory is dependent on the initial acquisition and subsequent judgement of perceptual, contextual, semantic, and affective information. Any cognitive factors (e.g., impaired EF; de Chastelaine, Friedman, & Cycowicz, 2007; Janowsky, Shimamura, & Squire, 1989; Ruffman, Rustin, Garnham, & Parkin, 2001), that impede the "contextualizing of information" during memory encoding will impair source memory performance (Johnson et al., 1993; p. 5). Therefore, empirical investigations of source memory performance provide an opportunity to assess higher-order cognitive processes (e.g., EF) that might influence memory encoding.

Experimental investigations of the source monitoring framework typically assess both item recognition and memory for source details. Although primarily non-standardized, such

investigations are predominantly characterized by (a) an initial study phase during which there is exposure to both item (e.g., word list) and source details (e.g., person who read the word list), and (b) a subsequent old-new recognition memory test for both item (e.g., "did you hear this word?") and source details (e.g., "who read the word list?"). Researchers agree that memory for item and source are not entirely dissociable (Glisky, Polster, & Routhieaux, 1995; Johnson et al., 1993), but that each is supported by different cognitive processes. Whereas item recognition is primarily reliant on retrieval-based processes, source memory is primarily reliant on higher-order executive processes (Mammarella & Fairfield, 2008; Wheeler, Stuss, & Tulving, 1997).

Regarding these executive processes, the umbrella term EF refers to those complex cognitive processes mediated by the prefrontal lobes and associated neural networks (Anderson, 2002). In Anderson's (2002) multiprocess model, EF is conceptualized as consisting of four functionally interrelated domains (viz., attentional control, information processing, cognitive flexibility, and goal setting). WM, a cognitive process within the domain of cognitive flexibility, has been highlighted as crucial to the cognitive process of source memory encoding (Mammarella & Fairfield, 2008). By definition, WM facilitates the manipulation and maintenance of complex information (Baddeley, 1992, 2003). Additionally, as a component process of cognitive flexibility, WM supports executive processes within other EF domains (e.g., information processing; Anderson, 2002). Within the source monitoring framework, therefore, WM plays an important role in facilitating the acquisition and recognition of source details.

Support for the theoretical link between source memory and EF is provided by several noteworthy lines of investigation. First, research using functional neuroimaging techniques to assess the neural correlates of source memory indicate a network of medial temporal lobe (MTL), prefrontal cortex (PFC), parietal cortex, and posterior perceptual regions (e.g., lateral

occipital complex) that activates to facilitate effective task performance (for a review, see Mitchell & Johnson, 2009). Of particular relevance here is that similar fronto-parietal regions are recruited during executive control of attentional processes (Corbetta et al., 2002, 2008) Additionally, evidence from clinical investigations suggests that frontal dysfunction is associated with less efficient source detail acquisition in individuals with structural and/or functional impairments in the PFC (e.g., Ciaramelli & Spaniol, 2009; Janowsky et al., 1989), as well as in older adults with less efficient higher-order executive processing as a result of normal aging (e.g., Meusel, Grady, Ebert, & Anderson, 2017; Swick, Senkfor, & Petten, 2006).

The relatively small field of research investigating the typical developmental of source memory suggests that it matures throughout childhood and follows a similar trajectory to the development of EF (for a review, see Raj & Bell, 2011). In typically developing children, developmental gains in source memory performance are observed between the ages of 4 and 6 years (Drummey & Newcombe, 2002), and are partially predicted by EF ability (Rajan, Cuevas, & Bell, 2014). There is, however, a paucity of research examining source memory performance in pediatric samples with developmental or acquired deficits in higher-order executive processes. For example, Hala et al. (2005) examined source memory performance across the three conditions defined within the source monitoring framework (viz., reality, external, and internal source monitoring) in 13 children with Autism Spectrum Disorders (ASD; M_{age} = 8 years 5 months, *SD* = 2 years 10 months) and 13 typically developing controls (M_{age} = 6 years 2 months, *SD* = 0 years 10 months). Although children with ASD demonstrated similar recognition memory performance to controls, they performed more poorly on the source memory component of the task. Hala and colleagues suggested these source memory deficits may be accounted for by impaired EF in children with ASD. Although the aforementioned research programs have established a clear theoretical

association between source memory and EF in both adult and pediatric samples, few studies have examined this relation via direct statistical adjustment (for a review, see Haj & Allain, 2012). Thus, there is a significant gap in the literature working towards systematically defining the relation between source memory and EF, particularly within pediatric populations demonstrating impaired EF (e.g., FASD; Kingdon et al., 2016; Mattson et al., 1999).

Source Memory in FASD

Previous neuropsychological investigations have demonstrated impairments in EF in children with heavy PAE, both with and without syndromal features (Green, Mihic, Nikkel, et al., 2009; Kingdon et al., 2016; Mattson et al., 1999; for a review, see Kodituwakku & Kodituwakku, 2014). WM has been highlighted as a core deficit in FASD (Burden, Jacobson, Sokol, et al., 2005; Rasmussen, 2005) and is thought to mediate impairments in other cognitive domains (e.g., arithmetic, Rasmussen & Bisanz, 2011). EF deficits persist following control for general intellectual functioning and sociodemographic variables, suggesting a specific effect of PAE on this higher-order cognitive process (Connor, Sampson, Bookstein, Barr, & Streissguth, 2000; Noland et al., 2003).

Following a different line of investigation, Diwadkar et al. (2013) demonstrated that children with a diagnosis of FAS/PFAS (n = 17; M_{age} = 9.3, SD = 0.2) or heavily exposed nonsyndromal (HE; n = 13; M_{age} = 9.7, SD = 0.6) recruit different neural regions to support effective completion of a simple WM task than typically-developing children (n = 17; M_{age} = 9.3, SD = 0.4). Because all participants showed equivalent behavioral performance on the WM task, these differences in functional activation could not be attributed to performance differences. It is of clinical significance that children in the FAS/PFAS and nonsyndromal HE groups demonstrated different patterns of neural activation: Syndromal children showed

increased reliance on cerebellar and parietal regions, whereas nonsyndromal children showed increased reliance on fronto-striatal regions. Taken together with the suggestion that children with FASD make less efficient use of executive learning strategies during the completion of learning and memory tasks (Lewis et al., 2015; Rasmussen et al., 2009), and that children with heavy PAE demonstrate structural and functional impairment in the neural regions proposed to support source memory (for a brief review, see Chapter 1), the aforementioned exposure-related WM deficits indicate that the investigation of source memory in this pediatric clinical population provides an opportunity to indirectly assess the encoding of rich contextual details as well as to examine the contribution of higher-order executive processes to such encoding.

In a preliminary assessment of source memory in FASD, Kully-Martens et al. (2012) examined reality, external, and internal source monitoring in a sample of 19 children with PAE (M_{age} = 9.05, range: 6 – 12 years) and 38 typically developing age- and sex-matched controls (M_{age} = 8.97, range: 6 – 12 years). The authors investigated the prediction that children with FASD would show impaired recognition and source monitoring performance on an audio-verbal source monitoring task. The task had three conditions (viz., reality, external, and internal source monitoring) and was comprised of two phases (viz., stimuli presentation and a memory test). For each condition, the participant was required to repeat and/or listen to the examiner/s repeating a 10-word list. Thereafter, the participant was presented with a list of 20 words (10 ‘old’ and 10 ‘new’ foil words) and was required to make an old/new judgement, as well as to identify the source of words recognized as ‘old’.

Kully-Martens and colleagues (2012) reported that participants in the FASD group demonstrated poorer memory for both item and source details than controls. However, that the pattern of task performance across conditions was similar regardless of exposure-history: all children demonstrated poorest performance on the internal condition (i.e., “did I say this

or think this"), with slightly better performance on the external condition (i.e., "did examiner A or examiner B say this?"), and the best performance on the reality condition (i.e., "did I say this or did examiner A say this?"). This overall pattern of performance gains based on task conditions is consistent with developmental literature, in which the internal condition is the most challenging of the three conditions within the source monitoring framework (e.g., (Foley, Johnson, & Raye, 1983). Although the authors made a clear theoretical link between exposure-related deficits in WM and source memory, they did not examine this association statistically. Moreover, the children recruited into the FASD group in this study were clinic-referred. Although this is indicative of sound diagnostic procedures, exposure data are obtained retrospectively—a methodological approach that may result in less reliable estimation of PAE (Jacobson et al., 2002). There exists, therefore, a novel opportunity to further clarify the association between WM and source memory performance in FASD.

A second pertinent extension of the investigation of source memory performance in children with heavy PAE is to examine whether there are performance differences between children diagnosed with FASD and those diagnosed with attention-deficit/hyperactivity disorder (ADHD). ADHD is clinically defined according to the presence of inattentive and/or hyperactive-impulsive symptoms, and has three diagnostic subtypes: Predominantly inattentive presentation, predominantly hyperactive/impulsive presentation, and combined presentation (Diagnostic and Statistical Manual for Mental Disorders [DSM]-IV; American Psychiatric Association, 2013). Although both behavioral symptoms, similar to those observed in ADHD, and co-morbid diagnoses of ADHD are frequently reported in children with FASD, the etiology of ADHD in children with and without heavy PAE differs (Coles, 2001; Fryer, McGee, et al., 2007; Jacobson et al., 2011; Mick et al., 2002). Consequently, children with heavy PAE do not respond as well as children with idiopathic ADHD to pharmacological interventions meant to target their attentional deficits (O'Malley, Koplin, &

Dohner, 2000; Oesterheld et al., 1998; Peadon & Elliott, 2010). Moreover, there is evidence to support distinguishable profiles of neuropsychological and neurophysiological impairment in children with FASD and co-morbid ADHD when compared to children with idiopathic ADHD (Burden et al., 2010; Jacobson et al., 2011; Kingdon et al., 2016; Vaurio, Riley, & Mattson, 2008). For example, within the domain of learning and memory, children with heavy PAE and a co-morbid diagnosis of ADHD demonstrate impaired information acquisition (a pattern similar to children with heavy PAE and without a diagnosis of ADHD), whereas children with idiopathic ADHD demonstrate impaired information retrieval on a standardized test of verbal learning and memory (Crocker et al., 2011; but, cf. Krauel et al., 2007). This latter pattern of impairment is consistent with the marked executive dysfunction that is central to the cognitive profile of ADHD (for a reviews, see Castellanos & Tannock, 2002; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005).

Interestingly, children with FASD and ADHD have different profiles of executive dysfunction. Those with FASD are more impaired within Anderson's (2002) domains of cognitive flexibility, goal setting, and information processing, whereas those with ADHD are primarily impaired within the domain of attentional control (for a review, see Mattson et al., 2011). It is, therefore, of clinical relevance to examine whether source memory performance differs in children with heavy PAE and co-morbid ADHD versus those with heavy PAE and no ADHD. Given the theoretical link between WM and memory for source details, experimental examination of source memory may be a sensitive indicator of the contributions of higher-order executive processes to the acquisition of memories rich in contextual detail. Additionally, these findings may contribute to the development of intervention strategies that are tailored to the differential patterns of performance deficits observed in FASD and ADHD.

Specific Aims and Hypotheses

The main aim of this study was to investigate source memory performance in a sample of children with and without a history of PAE whose mothers were recruited and interviewed prospectively during pregnancy. In addition, if source memory impairments were found in this sample, I aimed to assess the extent to which the relation between PAE and source memory persisted after adjustment for potential confounding variables and the higher-order executive processes of WM. I further aimed to investigate source memory performance in exposed children with and without ADHD, as well as in non-exposed children with and without ADHD. The design of this study allowed the following hypotheses to be tested:

1. Children and adolescents with a history of heavy PAE will, relative to non-exposed control children, show impaired performance in memory for both item and source details.
2. Deficits in source memory performance will be related to PAE over and above the effects of potentially confounding sociodemographic variables (e.g., maternal age at delivery and/or socioeconomic status).
3. Deficits in source memory performance will be mediated by WM performance.
4. Deficits in source memory performance will not be attributable to the presence of a comorbid diagnosis of ADHD.

Methods

Research Design and Setting

I used a cross-sectional design to examine source memory performance at an 11-year follow-up assessment of the Memory Cohort (see Chapter 2). Participants were assigned to one of three groups based on their FASD diagnosis (viz., FAS/PFAS, nonsyndromal HE, and non-exposed controls; see Chapter 2). Additionally, I used prospectively-obtained continuous

measures of exposure (viz., oz. AA/day, AA/occasion, and drinking frequency [days/week] during pregnancy) to examine the relation between exposure and source memory task performance.

I assessed source memory performance using a computerized task (Ofen et al., 2007). As detailed above, WM has been highlighted as integral to effective source memory performance. I therefore assessed WM performance as a potential cognitive mediator of source memory performance in participants with a history of heavy PAE. For the further details of these tasks, please refer to the *Materials* section below.

All neuropsychological testing was completed in the Child Development Research Laboratory (CDRL) based at the University of Cape Town (UCT). I completed data collection with the assistance of three female MA-level psychologists. I provided detailed training on the administration of the source memory task. Except in the most severe cases, examiners were blind to participant's FASD diagnosis and exposure history.

Participants

This study is nested within the Cape Town Longitudinal Cohort Study (Jacobson et al., 2008) and drew participants from the Memory Cohort ($N = 88$) described in Chapter 2. I examined each participant's behavioral performance on a source memory task using a *d*-prime analysis. Based on the distribution of *d*-prime scores, there were two cases suggestive of chance performance (i.e., guessing) with scores falling between -0.3 and 0. I, therefore, excluded these participants' data from subsequent analyses. This resulted in a final sample size of $N = 86$ (see Figure 5.1 for details).

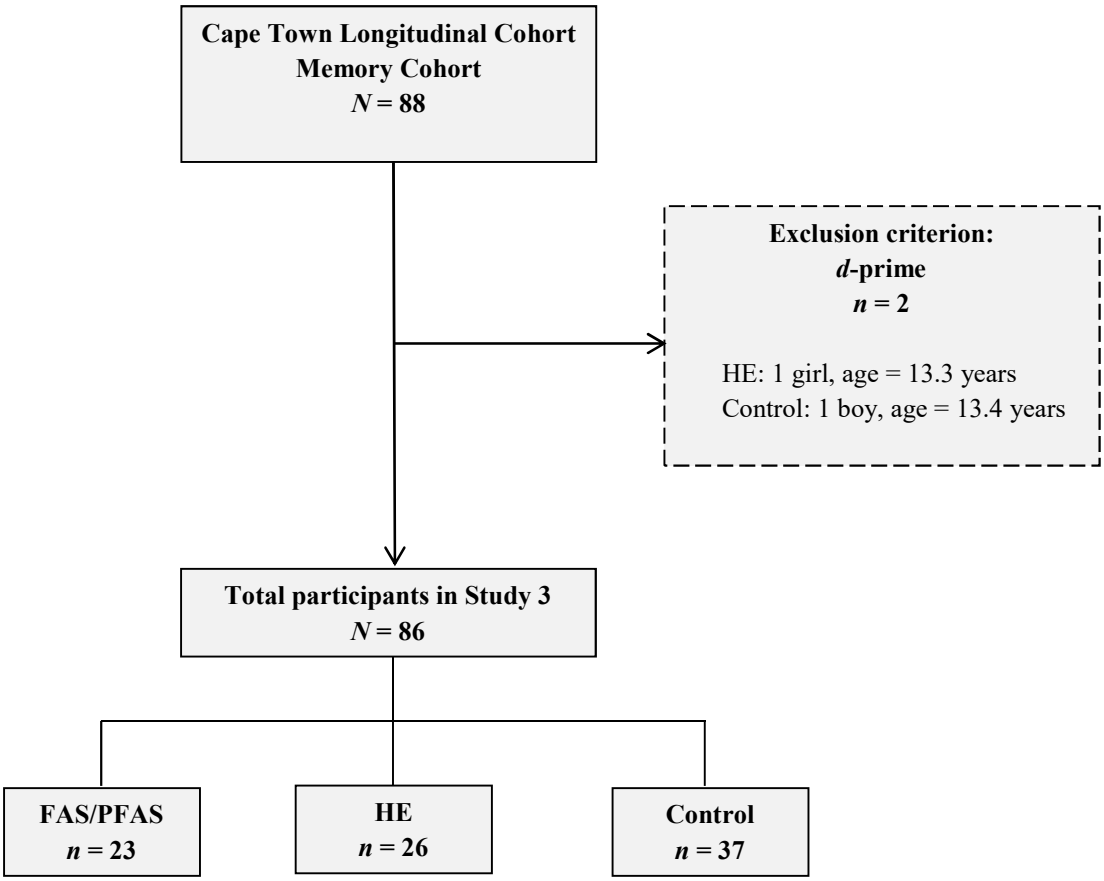

Figure 5.1. Diagram illustrating the selection of the final sub-sample of 86 participants as well as details relating to exclusion. FAS = fetal alcohol syndrome, PFAS = partial fetal alcohol syndrome, HE = heavily exposed nonsyndromal.

Materials

Source memory test. I assessed memory for item and source using a task programmed in E-Prime 2.0 (Psychology Software Tools, Inc., Pittsburgh, USA). This task has been used previously to assess source memory in a sample of children and adults (age range: 8 – 24 years; Ofen et al., 2007). The task had two phases: (a) study and (b) test. To ensure that sufficient trials were acquired for subsequent statistical analysis, the task was administered twice, with novel stimuli displayed during each administration.

During each of the study phases, participants viewed two sets of 16 unique line drawings, drawn from a pool of four sets. Each study drawing was displayed for 3 seconds and was presented on either the left or right side of the screen, in red or in green, and was

associated with a specific question pertaining either to animacy (*is this a living thing?*) or size (*is this bigger than a shoe box?*). The latter three details (viz., location, color, and question) were objectively defined as the source details for each item.

During each of the test phases, recognition memory for both item and source were tested. Hence, participants completed a self-paced recognition test comprised of the 16 studied drawings and 16 novel foil drawings. For each drawing presented, participants were required to make a recognition judgement (old/new). For each item identified as 'old' (i.e., seen previously, during study phase), participants were required to answer questions pertaining to each of the source details. All line drawings presented during study and test phases were selected from Snodgrass and Vanderwart's (1980) standardized images.

I combined data from both administrations of the source memory task so that recognition memory for a combined total of 32 study drawings and 32 foils could be examined. I extracted five outcome variables from this dataset: hits, misses, false alarms, correct rejections, and source memory score (Table 5.1). I calculated the source memory score based on the approach employed by Ofen et al. (2007). I also examined overall behavioral performance accuracy by calculating a *d*-prime score.

Table 5.1
Source Memory Task Outcome Variables

Variable	Definition
d-prime	Recognition accuracy, calculated using the formula: $d\text{-prime} = Z(\text{hit total}) - Z(\text{false alarm total})$
Hit total	Number of target images correctly remembered on recognition testing.
Miss total	Number of target images not remembered on recognition testing.
False alarm	Number of foil images falsely identified as target images on recognition testing.
Correct rejection	Number of foil images correctly identified as such on recognition testing.
Source memory score	Percentage of correct source judgements (viz., side, color, and question) for all images correctly identified as 'old' (i.e., hit responses).

Working memory test. I assessed WM performance using the *Digit Span Backwards* subtest from the *Wechsler Intelligence Scale for Children—Fourth Edition* (WISC-IV;

Wechsler, 2003a). In this test, participants are required to verbally repeat a series of numbers in the inverse order of their presentation. It is widely used to assess WM performance in clinical populations, and is a sensitive indicator of WM impairment in children with FASD (for a review, see Rasmussen, 2005). Additionally, this WISC-IV subtest has good reliability and validity (Wechsler, 2003b). For details pertaining to the standardized administration procedure of the WISC-IV in the Memory Cohort, please refer to Chapter 2.

Procedure

The source memory task was administered in a controlled testing environment over two sessions on 1 testing day, as part of the larger 11-year follow-up assessment battery (see Chapter 2). Prior to beginning the first session of the source memory task, the examiner explained the rules of the task and administered a study and test practice session to each participant (for the script read by the examiner, see Appendix R). As a part of the introduction to the task rules, the examiner assessed each participant's ability to identify left from right, and to distinguish between red and green. In the event of left/right confusion, the examiner asked the participant to point to the side of the screen that s/he wished to indicate for both practice and test items. All participants were able to distinguish between red and green. Additionally, the examiner gave explicit instructions with regard to assessing memory for the items viewed during the study phase of the source memory task. These instructions further informed participants that the examiner would enter their response and that they should try to be as accurate as possible when responding.

The participant then completed the first session of the source memory task (i.e., a study phase, followed immediately by a test phase). After completion of that session, the participant completed four tasks from the larger 11-year follow-up neuropsychological battery during a filled delay. After the filled delay, the participant was reminded of the source

memory task rules and was informed that s/he was going to study a new set of pictures. Thereafter, the participant completed the second source memory session.

Each source memory session, including instruction administration, took approximately 10 minutes to complete. All task responses were entered by the examiner and logged by E-Prime. In the event of an error during data capturing (e.g., if the examiner pressed the incorrect response button following a participant's verbal response), the examiner recorded detailed notes of the error and the output file was corrected. Finally, I exported participant data to SPSS for subsequent analyses.

Ethical Considerations

The ethical considerations pertaining to this study and the larger Cape Town Longitudinal Cohort study are detailed in the analogous section in Chapter 2.

Statistical Analysis

I analyzed source memory task performance data in SPSS version 23. To ensure that I remained blind to participant alcohol exposure history as well as FASD diagnosis during data analysis, all data were assigned blinded identification codes by the project data manager. Prior to conducting parametric analysis of these data, I used comprehensive descriptive statistics to examine distributions of predictor and outcome variables to identify possible influential cases/outliers and to test the assumptions underlying parametric statistical tests (for these data, see Appendix S).

Potential confounding variables. Following the same procedure outlined in Chapter 2, I examined relations between sociodemographic variables and outcome variables to identify potential confounding variables eligible for inclusion in the analysis of source memory task performance. In this study, I considered six potential confounding variables for

inclusion in the statistical analyses: child sex and age at testing; maternal age at delivery, education, socioeconomic status (SES; Hollingshead, 2011), and smoking during pregnancy. I considered any sociodemographic variable that was related even weakly (at $p < .10$) to a given outcome variable a potential confounder of performance measured by that outcome. To control for confounders, I reran any analyses detecting an association between PAE and the outcome with the relevant sociodemographic variable entered as a covariate in the ANCOVAs or as a predictor at the second step in a hierarchical regression analysis.

No mother reported using cocaine, and prenatal exposure to marijuana ($n = 9$) and methaqualone ("mandrax"; $n = 3$) were too rare for statistical adjustment. I therefore reran any analyses detecting an association between PAE and the outcome omitting children with either prenatal marijuana or mandrax exposure.

Between-group analysis. I used a series of one-way ANOVAs to examine potential between-group differences in source memory task performance. In all analyses, the between-subjects factor was FASD diagnostic status (viz., FAS/PFAS, HE, or non-exposed control). In the instance of a significant *F*-test result, post-hoc examination of these data was conducted using Least-Significant Difference (LSD) tests. I re-ran any analysis detecting a significant relation between FASD diagnostic status and source memory task performance using ANCOVA to examine whether between-group differences persist after control for potential confounding and/or mediator variables.

Correlation-bases analysis. I used Pearson correlation coefficients to examine the association between continuous measures of PAE (viz., AA/day, AA/occasion, and drinking frequency [days/week]) and source memory task performance within each of the exposed groups. The aim of these analyses was to assess whether there is a differential pattern of association between PAE and source memory task performance within the FAS/PFAS and HE groups. This approach is consistent with that taken in Study II. In addition, I used Pearson

correlation coefficients to examine the association between WM performance (as indexed by WISC-IV digit span backwards) and source memory task performance.

Mediation analysis. I used a series of hierarchical regression analyses to examine the predictive relation of (a) FASD diagnostic status and memory for source details when controlling for WM performance, and (b) WM and memory for source details when controlling for FASD diagnostic status. Here, the main aim was to assess whether WM performance mediates the effect of FASD diagnostic status on source memory.

Relation between prenatal alcohol exposure, ADHD, and source memory task performance. I conducted two sets of independent sample *t*-tests to compare source memory task performance in participants with and without a diagnosis of ADHD. First, I compared source memory task performance in participants with and without a diagnosis of ADHD, regardless of FASD diagnostic status. The aim of these analyses was to examine similarities and differences in patterns of source memory impairment in participants with and without a diagnosis of ADHD. Second, I compared source memory task performance in (a) non-exposed participants (i.e., AA/day = 0) with and without a diagnosis of idiopathic ADHD, and (b) exposed participants (i.e., AA/day > 0) with and without a co-morbid diagnosis of ADHD. The aim of these analyses was to assess whether distinguishable patterns of source memory impairment were present for children with a diagnosis of idiopathic ADHD and children with a comorbid diagnosis of ADHD. I used a Bonferroni correction to control for the inflated Type 1 error rate associated with conducting multiple pairwise comparisons.

Results

Sample Characteristics

Here, I describe only the statistically significant results presented in Table 5.2. Mothers of children in the FAS/PFAS group were older than mothers of children in both the HE and non-exposed control groups, post-hoc *p*'s < .05 (Table 5.2). Mothers of children in the FAS/PFAS group had also completed fewer years of education than mothers of children in the non-exposed control group, $p < .01$. A smaller proportion of mothers in the HE group were married than mothers of those in either the FAS/PFAS or non-exposed control group. Mothers of children in the FAS/PFAS group were more economically disadvantaged than mothers of children in either the HE or non-exposed control groups (on average Hollingshead level V—Unskilled Laborers, lowest of 5 levels), both *p*'s < .01. Additionally, mothers of children in the HE group were more disadvantaged than mothers of children in the non-exposed control group (on average HE mothers scored at the lower limit of level IV—Semiskilled Workers, whereas non-exposed control mothers scored closer to the upper limit of level IV), $p < .05$. The effect sizes associated with all between-group differences in maternal sample characteristics were in the small-to-moderate range.

Table 5.2
Sample Characteristics (N = 86)

Variables	FAS/PFAS (n = 23[a])	HE (n = 26)	Non-exposed controls (n = 37)	F or χ^2	p	ESE
Maternal variables						
Age at delivery (years)	29.2 (7.27)	24.9 (4.7)	26.0 (6.1)	3.26	.04*	.07
Level of education (years)	8.4 (2.3)	9.5 (2.4)	10.0 (2.0)	3.99	.02*	.09
Marital status (% married)	34.8	11.5	40.5	6.40	.04*	.27
Socioeconomic status[b]	15.4 (6.4)	21.6 (7.3)	25.8 (8.2)	13.46	<.001***	.25
Prenatal alcohol exposure[c]						
AA/day (oz)	1.0 (0.8)	1.0 (1.2)	0.0 (0.0)	17.40	<.001***	.30
AA/occasion (oz)	4.2 (1.8)	3.5 (3.3)	0.0 (0.0)	38.35	<.001***	.48
Frequency (days/week)	1.6 (1.0)	1.4 (1.2)	0.0 (0.0)	33.66	< .001***	.45
Prenatal smoking (cig./day)	6.8 (5.5)	6.8 (6.1)	2.5 (4.1)	7.14	.001**	.15
Child variables						
Age at testing (years)	13.8 (0.7)	13.0 (0.4)	13.2 (0.8)	9.69	< .001***	.19
Sex (% male)	56.5	42.3	40.5	1.60	.45	.14
WISC-IV						
FSIQ	63.9 (9.3)	76.0 (16.3)	77.3 (14.4)	7.28	.001**	.15
Digit span backwards	4.7 (1.8)	6.1 (2.3)	6.1 (1.5)	4.63	.01**	.10
ADHD (% yes)	43.5	19.2	21.6	4.53	.10	.23

Note. Unless otherwise stated, values presented are means with standard deviations in parentheses. FAS = fetal alcohol syndrome; PFAS = partial fetal alcohol syndrome; HE = heavily exposed nonsyndromal; ESE = estimate of effect size; AA = absolute alcohol; cig. = cigarettes; WISC-IV = Wechsler Intelligence Scale for Children—Fourth Edition; FSIQ = Full Scale IQ; ADHD = attention-deficit/hyperactivity disorder. The estimates of effect sizes were calculated using partial eta squared (η^2) and Phi (φ) for one-way ANOVAs and χ^2 tests, respectively.
[a]FAS n = 13; PFAS n = 10.
[b]Data missing for one mother of a girl (age = 12.6 years) in the non-exposed control group.
[c]1 oz AA/day ≈ 2 standard drinks.
*p < .05. **p < .01. ***p < .001.

All mothers of children in the non-exposed control group reported abstaining from drinking during pregnancy (Table 5.2). Mothers of children in the FAS/PFAS and HE groups consumed a similar amount of alcohol on average across pregnancy, with both groups meeting the criteria for heavy drinking (i.e., on average, approximately 2 standard drinks per day). On average, mothers of children in the FAS/PFAS group drank a similar quantity per occasion and at a similar frequency per week (viz., 4 drinks on 1 to 2 occasions per week) as mothers of children in the HE group, p's > .20.

Mothers of children in both the FAS/PFAS and HE groups smoked more cigarettes/day than mothers of children in the non-exposed control group, p's < .01, but the effect size was small (Table 5.2). None of the mothers reported using cocaine during pregnancy. Nine mothers (2 FAS/PFAS, 6 HE, 1 non-exposed control) used marijuana during

pregnancy (mean = 2.9 times/week, range = 0.8 – 7.0). Three mothers (1 FAS/PFAS and 2 HE) used methaqualone ("mandrax") during pregnancy (mean = 1.3, range = 0.03 – 3.2).

Children in the FAS/PFAS group were older than children in both the HE and non-exposed control groups, *p*'s < .01. There were no differences in the proportion of males to females in any of the FASD diagnostic groups. Although general intellectual functioning (as indexed by WISC-IV Full Scale IQ) was poorer for children in the FAS/PFAS group than for children in either the HE or non-exposed control groups, *p*'s < .01, it did not differ between children in the HE and non-exposed control groups, *p* > .20. There was a significant between-group difference in WM performance with children in the FAS/PFAS group performing more poorly on the WISC-IV Digit Span Backwards subtest than children in both the HE and non-exposed control groups, *p*'s ≤ .01. Consistent with FSIQ scores, WM performance did not differ between children in the HE and non-exposed control groups, *p* > .20.

Identification of Potential Confounding Variables

I evaluated six potential confounding variables of source memory task performance.. Only one variable was identified as a potential confounder of source memory performance: Child age at testing was relatively strongly, and negatively, correlated to source memory scores (Table 5.3). Thus, where a significant alcohol effect on source memory scores is reported, I included this potential confounder variable as a covariate/additional predictor variable in the relevant ANCOVA and/or regression analysis of these data.

Table 5.3
Identification of Potential Confounding Variables of Source Memory Task Performance (N = 86)

	Child		Maternal			
Variable	Age	Sex	Age at delivery	Education level	SES	Smoking during pregnancy
d-prime	-.07	-.04	-.07	.16	.07	-.03
Hit	.12	-.10	-.02	.09	-.03	.09
Miss	-.12	.10	.02	-.09	.03	-.09
False alarm	.16	-.07	.06	-.09	-.09	.14
Correct rejection	-.16	.07	-.06	.09	.09	-.14
Source memory score	-.20†	-.07	-.06	.16	.16	-.001

Note. Values presented are Pearson correlation coefficients. All statistics reported are two-tailed. SES = socioeconomic status.
$^{\dagger}p < .10$.

Source Memory Task Performance

There were no between-group differences in recognition memory accuracy (as indexed by *d*-prime; Table 5.4). Regarding response style, participants, regardless of diagnostic group membership, demonstrated similar hit, miss, false alarm, and correct rejection rates. There was, however, a significant between-group difference in source memory scores, with children in the FAS/PFAS group recalling fewer source details than children in both the HE and non-exposed control group, post-hoc *p*'s < .01. The pairwise comparison of the HE group and the non-exposed control group did not detect statistically significant differences, however, $p > .20$[5]. This significant between-group difference in source memory scores persisted after controlling for age at testing, $F(2, 82) = 3.20$, $p = .046$, $\eta^2 = .01$. Age at testing was not a significant between-group factor, $F(1, 82) = 0.46$, $p = .50$, $\eta^2 = .07$. Additionally, significant between-group differences in source memory scores remained essentially unchanged when data from the 9 children with prenatal marijuana exposure were excluded, $F(2, 74) = 3.36$, $p = .03$, $\eta^2 = .08$, as well as when data from the 3 children with prenatal methaqualone exposure were excluded, $F(2, 80) = 4.26$, $p = .02$, $\eta^2 = .10$.

[5] It is noteworthy that adjustment for spontaneous self-corrections did not change the pattern of between-group differences reported here (see, Appendix T).

Table 5.4
Between-Group Differences in Source Memory Task Performance (N = 86)

Variable	FAS/PFAS (n = 23[a])	HE (n = 26)	Non-exposed Control (n = 37)	F	p	η^2
d-prime	2.7 (0.5)	2.7 (0.5)	2.8 (0.5)	1.23	.30	.03
Hit (%)	85.6 (3.4)	79.4 (3.8)	83.4 (3.0)	2.13	.13	.05
Miss (%)	14.7 (3.4)	20.6 (3.8)	16.6 (3.0)	2.13	.13	.05
False alarm (%)	4.4 (1.5)	3.4 (1.4)	2.2 (0.8)	2.09	.13	.05
Correct rejection (%)	95.6 (1.5)	96.6 (1.4)	97.8 (0.8)	2.09	.13	.05
Source memory score	62.9 (9.5)	70.1 (8.4)	69.1 (8.5)	4.90	.01*	.11

Note. Unless otherwise stated, values presented are means with standard deviations in parenthesis. FAS = fetal alcohol syndrome; PFAS = partial fetal alcohol syndrome; HE = heavily exposed nonsyndromal.
[a]FAS n = 13; PFAS n = 10.
*$p < .05$.

Relations Between Continuous Measures of Prenatal Alcohol Exposure and Source Memory Task Performance

I used Pearson correlation coefficients to examine associations between continuous measures of PAE (viz., AA/day, AA/occasion, and frequency of drinking [days/week]) and source memory task performance, for children in the FAS/PFAS and HE groups separately (Table 5.5). Within the FAS/PFAS group, none of the continuous measures of PAE were associated with source memory task performance. Within the HE group, there was an unexpected significant positive correlation between AA/day and recognition accuracy (as indexed by *d*-prime). However, an examination of a scatter plot of AA/day with WISC-IV FSIQ showed what appeared to be three bivariate outliers (i.e., children with both high exposure levels and FSIQ scores), and the test for Mahalanobi's distance indicated that two were significant bivariate outliers. When these two children were removed from the analysis reported in Table 5.5, the unexpected positive association between AA/day and recognition accuracy was no longer of statistically significant magnitude, $r = .20$, $p > .20$.

Table 5.5
Association Between Continuous Measures of Prenatal Alcohol Exposure and Source Memory Performance (N = 49)

	FAS/PFAS (n = 23[a])			HE (n = 26)		
Variable	AA/day	AA/occasion	Frequency	AA/day	AA/occasion	Frequency
d-prime	.06	-.08	.15	.46*	.35†	.18
Hit	-.06	-.03	-.03	.34†	.21	.25
Miss	.06	.03	.03	-.34†	-.21	-.25
False alarm	-.21	-.01	-.26	-.16	-.20	.12
Correct rejection	.21	.01	.26	.16	.20	-.12
Source memory score	-.29	-.40†	-.29	.33†	.26	.31

Note. FAS = fetal alcohol syndrome; PFAS = partial FAS; HE = heavily exposed nonsyndromal; AA = absolute alcohol. All statistics reported are two-tailed.
[a]FAS n = 13; PFAS n = 10.
$^{\dagger}p < .10$. $^{*}p < .05$. $^{**}p < .01$.

Relations Between FASD diagnosis, Source Memory, and Working Memory

I used Pearson correlation coefficients to examine associations between WM performance (as indexed by scores on the WISC-IV Digit Span Backwards subtest) and source memory task performance (Table 5.6). Source memory scores were significantly positively correlated with WM performance, $p = .003$. The between-group difference in source memory scores fell short of significance when controlling for WM performance, $F(2, 82) = 2.76$, $p = .07$, $\eta^2 = .06$. Additionally, there was a significant main effect of WM on source memory performance, $F(1, 82) = 4.86$, $p = .03$, $\eta^2 = .06$.

Table 5.6
Relation Between Source Memory Task Performance and Working Memory (N = 86)

Variable	WISC-IV digit span backwards
d-prime	-.15
Hit	-.20†
Miss	.20†
False alarm	-.06
Correct rejection	.06
Source memory score	.31**

Note. Values presented are Pearson correlation coefficients. All statistics reported are two-tailed. WISC-IV = Wechsler Intelligence Scale for Children—Fourth Edition.
$^{\dagger}p < .10$. $^{**}p < .01$.

Because the between-group FASD difference in source memory scores fell short of statistical significance after WISC-IV Digit Span Backwards score was entered as a covariate, the analysis suggests that WM performance partially mediates the effects of FASD diagnosis on source memory performance. To allow for further investigation of mediation by WM, I generated a dichotomous predictor variable based on FASD diagnosis (viz., FAS/PFAS vs. HE and non-exposed controls). The HE and non-exposed control participants were grouped together as a result of their similar source and WM performance, post-hoc *p*'s > .20. Hierarchical regression analyses examining possible mediation of the relation between FASD diagnosis and source memory performance by WM performance indicated that both FASD diagnosis and WM are unique predictors of source memory performance differences (Table 5.7). However, the drop in the strength of the predictive association between FASD diagnosis and source memory performance when WM is entered into the model supports partial mediation by the latter variable.

Table 5.7
Mediation of Association Between FASD Diagnosis and Source Memory Performance by Working Memory (N = 86)

		Predictor variable[a]		Mediator variable[b]	
Mediator	*N*	r_1	β_1	r_2	β_2
WISC-IV digit span backwards	86	.32**	.25*	.31**	.24*

Note. Each row summarizes results from a multiple regression analysis examining the effect of fetal alcohol spectrum disorder (FASD) diagnosis and the indicated mediator variable on source memory performance. r_1 indicates the unadjusted correlation between FASD diagnosis and source memory performance, and β_1 indicates the standardized beta value for FASD diagnosis when the mediator variable is entered into the regression model, whereas r_2 indicates the unadjusted correlation between the mediator variable and source memory performance, and β_2 indicates the standardized beta value for the mediator variable when FASD diagnosis is entered into the regression model. WISC-IV = Wechsler Intelligence Scale for Children—Fourth Edition.

[a] $R^2 = .10$ for Step 1, $\Delta R^2 = .05$ for Step 2 ($p < .05$)

[b] $R^2 = .10$ for Step 1, $\Delta R^2 = .06$ for Step 2 ($p < .05$)

* $p < .05$. ** $p < .01$.

Relations Between Continuous Measures of Prenatal Alcohol Exposure, Source Memory, and ADHD

To examine whether performance on the source memory task differed in children with and without ADHD, regardless of FASD diagnostic status, I ran several independent sample *t*-tests (Table 5.8). On average, there were no significant between-group differences for recognition accuracy, response style, or source memory outcome variables.

Table 5.8
Between-Group Comparison: Source Memory Performance in Children With and Without ADHD (N = 86)

Variable	ADHD – yes (*n* = 23)	ADHD – no (*n* = 63)	*t*	*p*
d-prime	2.7 (0.5)	2.8 (0.5)	-1.22	.23
Hit (%)	82.5 (3.2)	82.8 (3.5)	-0.14	.89
Miss (%)	17.5 (3.2)	17.2 (3.5)	0.14	.89
False alarm (%)	4.4 (1.6)	2.8 (1.1)	1.52	.13
Correct rejection (%)	95.9 (1.6)	97.2 (1.1)	-1.52	.13
Source memory score	65.9 (8.7)	68.4 (9.3)	-1.13	.26

Note. Unless otherwise stated, values presented are means with standard deviation in parenthesis. All statistics reported are equal variances assumed and two-tailed. ADHD = attention-deficit/hyperactivity disorder.

I also examined whether there performance on the source memory task differed in non-exposed participants (i.e., AA/day = 0) with and without a diagnosis of idiopathic ADHD, and in exposed children (i.e., AA/day > 0) with and without a co-morbid diagnosis of ADHD (Table 5.9). In the former set of between-group comparisons, there was a trend towards poorer recognition accuracy (as indexed by *d*-prime) by children with ADHD. However, this trend did not survive Bonferroni correction (corrected $p = .008$) and is, therefore, suggestive of a finding that might have occurred by chance.

Table 5.9
Between-Group Comparison: Source Memory Performance in Children With and Without ADHD, Both With and Without Prenatal Alcohol Exposure (N = 86)

Variable	ADHD – yes	ADHD – no		
Non-exposed: AA/day = 0	(*n* = 9)	(*n* = 33)	*t*	*p*
d-prime	2.6 (0.3)	2.9 (0.5)	-1.84[a]	.08[†]
Hit (%)	81.3 (3.0)	84.1 (3.1)	-0.74	.47
Miss (%)	18.8 (3.0)	16.3 (3.1)	0.74	.47
False alarm (%)	3.4 (1.3)	2.2 (0.8)	1.16	.25
Correct rejection (%)	96.6 (1.3)	97.8 (0.8)	-1.16	.25
Source memory score	67.2 (8.2)	68.9 (8.5)	-0.55	.58
Exposed: AA/day > 0	(*n* = 14)	(*n* = 30)	*t*	*p*
d-prime	2.7 (0.7)	2.7 (0.5)	-0.28	.78
Hit (%)	83.1 (3.5)	81.6 (3.9)	0.42	.68
Miss (%)	16.9 (3.5)	18.4 (3.9)	-0.42	.68
False alarm (%)	4.7 (1.8)	3.4 (1.3)	0.84	.40
Correct rejection (%)	95.3 (1.8)	96.6 (1.3)	-0.84	.40
Source memory score	65.0 (9.2)	67.8 (10.2)	-0.86	.40

Note. Unless otherwise stated, values presented are means with standard deviations in parenthesis and all statistics reported are equal variances assumed and two-tailed. ADHD = attention-deficit/hyperactivity disorder; AA = absolute alcohol.
[a]Equal variances not assumed, Levene's statistic = 4.28, $p < .05$.
[†]$p < .10$.

Discussion

The primary aim of this study was to examine source memory performance in children with heavy prenatal alcohol exposure. Memory for item and source was assessed using a behavioral source memory paradigm. Despite demonstrating similar recognition accuracy and behavioral response style to children in the nonsyndromal HE and non-exposed control groups, children in the FAS/PFAS group showed impaired memory for source details. This significant finding survived the addition of potential confounding variables and prenatal marijuana/methaqualone exposure to the statistical modeling. Furthermore, although both PAE and WM performance independently predicted memory for source details, the association between PAE and memory for source details was partially mediated by WM performance. Finally, source memory task performance did not differ when comparing (a) children with ADHD to those without, (b) heavily exposed children with co-morbid ADHD to those without, and (c) non-exposed children with idiopathic ADHD to those without.

To my knowledge, this is the first study to demonstrate impaired memory for source details in a prospectively recruited sample of children with heavy PAE. Moreover, the direct statistical examination of the relation between PAE, WM performance, and source memory performance is a novel contribution to the broader source memory literature that is working towards delineating the higher-order cognitive processes that support effective source memory performance.

In the rest of this section, I first discuss the findings pertaining to each hypothesis and relate them within the broader literature relating to source memory and FASD. Subsequently, I address the limitations of this study and suggest future research directions.

Source Memory Performance

The main hypothesis tested was that children with heavy PAE would demonstrate impairments in both item and source memory. Between-group analyses did not detect significant differences in recognition accuracy (as indexed by *d*-prime scores) or behavioral response styles (as indexed by hit, miss, false alarm, and correct rejection rates) on the source memory task. The absence of such between-group differences does not confirm the hypothesized pattern of impairment, and is inconsistent with Kully-Martens et al.'s (2012) report of exposure-related impairments in the item recognition component of source memory tasks. Additionally, this finding stands in contrast to previous reports of impaired recognition memory in children with heavy PAE on tasks of verbal learning and memory (Crocker et al., 2011; Lewis et al., 2015; Mattson et al., 1996). Partial confirmation of this hypothesis was, however, provided by the finding that memory for source details was impaired for children in the FAS/PFAS group when compared to children in both the nonsyndromal HE and non-exposed control children. Between-group analyses did not, however, detect performance

differences between the children in the nonsyndromal HE group and the non-exposed control group.

There are several possible explanations for these findings. First, on average, all participants were highly accurate in their responses on the recognition memory test (mean percentage of correct responses for all participants = 82.8%, range = 53.1 – 96.9%), and they made very few false alarm errors (mean percentage of false alarms for all participants = 3.2%, range = 0 – 18.8%). Although not quite indicative of a ceiling performance, these findings suggest that the task was simple enough to elicit superior recognition accuracy for all participants, regardless of exposure history. It is particularly striking, therefore, that children with FAS/PFAS recalled fewer source details than nonsyndromal HE and non-exposed control children. Additionally, between-group differences in memory for source details persisted after control for child's age at testing. It is interesting that the older age of participants in the FAS/PFAS group did not benefit memory for source details—a pattern that is markedly different to that reported in the literature investigating the typical development of source memory (e.g., Cycowicz, Friedman, Snodgrass, & Duff, 2001; de Chastelaine et al., 2007; Drummey & Newcombe, 2002; Rajan et al., 2014). This pattern may, however, be best explained by the fact that the age differences observed between children in the FAS/PFAS group and children in both the nonsyndromal HE and non-exposed control group were large enough to be statistically significant, but not so large as to have clinical significance.

The source memory deficit demonstrated by children in the FAS/PFAS group is clinically significant for several reasons. First, this finding is consistent with Kully-Martens and colleague's (2012) suggestion that source memory impairments may occur as a result of less efficient feature-binding during the encoding of source details. Feature-binding is the process through which contextual details are integrated and encoded as part of a cohesive memory trace, and is primarily mediated by the hippocampal formation (Henke et al., 1997).

Mammarella and Fairfield (2008) propose that feature-binding is a key component of WM that facilitates the acquisition of source details and, consequently, the subsequent retrieval thereof. This finding is, therefore, consistent with (a) structural and functional impairment of the hippocampal formation in children with FASD (Brady et al., 2012; Coles et al., 2011; Willoughby et al., 2008), and (b) the partial mediation of source memory performance by WM (see discussion below).

In the current study, children in the nonsyndromal HE group performed, on average, as well as children in the non-exposed control group on measures of general intellectual functioning (as indexed by WISC-IV Full-Scale IQ) and of WM (as indexed by WISC-IV Digit Span Backwards). The absence of source memory impairments for children in the nonsyndromal HE group may, therefore, be an artifact of the complexity level of the source memory task. Specifically, the task may not have been complex enough to engage higher-order executive processes in those children, and so the likelihood of impaired performance might have decreased. This interpretation is supported by previous research demonstrating that (a) there is a pattern of impaired EF in children both with and without the syndromal characteristics associated with a diagnosis of FAS/PFAS (Green, Mihic, Nikkel, et al., 2009; Mattson et al., 1999; Noland et al., 2003), and (b) children with heavy PAE are more impaired on tasks engaging strategic processing than those engaging relatively automatic/spontaneous processes (Aragón, Kalberg, et al., 2008; Burden, Jacobson, & Jacobson, 2005).

Alternatively, the absence of apparent source memory impairments within the nonsyndromal HE group might be due to the variation in cognitive ability demonstrated within this FASD diagnostic group. As noted previously, three children in this group demonstrate general intellectual functioning at levels similar to non-exposed control children, despite high levels of PAE. This discrepancy, which seems counterintuitive, may be due to

differences in the timing and amount of PAE (Lipinski et al., 2012; Sulik, 2005), genetic differences (Dodge et al., 2014; Jacobson et al., 2006; Viljoen et al., 2001; Warren & Li, 2005), and nutritional status (Carter et al., 2014; May, Hamrick, et al., 2014). Thus, follow-up investigation using techniques to further clarify diagnostic status within the nonsyndromal HE group is warranted.

In addition to facilitating the acquisition of episodic memories that are rich in contextual detail, intact source memory serves several real-world purposes. Empirical investigations suggest that intact source memory is associated with effective reality monitoring (e.g. Garrison, Bond, Gibbard, Johnson, & Simons, 2017), and theory of mind (e.g., Bright-Paul, Jarrold, & Wright, 2008; Lind & Bowler, 2009), whereas less efficient and/or impaired source memory is associated with a tendency toward false memory formation (e.g., Fandakova, Shing, & Lindenberger, 2013; Johnson, 1997). Moreover, impaired source memory is associated with the clinical presentation of delusions (e.g., schizophrenia; Nelson, Whitford, Lavoie, & Sass, 2014; Thoresen, Endestad, Petter, Sigvartsen, & Server, 2014), source amnesia (e.g., acquired PFC damage; Ciaramelli & Spaniol, 2009; Janowsky et al., 1989; Swick et al., 2006), and confabulation (e.g., Barba, Nedjam, & Dubois, 1999; Johnson, O'Connor, & Cantor, 1997). These empirical and clinical observations bear a noteworthy resemblance to qualitative clinical observations and parent reports of limited understanding of consequences, perceived lying, and poor social interactions in children diagnosed with FASD (Jacobson & Jacobson, 2002). Previous research has suggested that these behavioral deficits may be explained by impairments in the domains of executive functioning and/or social cognition (for a review, see Kully-Martens, Denys, et al., 2012). Taken together with data presented by Kully-Martens et al. (2012), the source memory deficits observed in the current study suggest the possibility of additional (or alternative) cognitive mechanism underlying behavioral symptoms observed frequently in FASD. Thus, these data emphasize

the importance of incorporating of cognitive rehabilitation methods into the management of behavioral symptoms associated with FASD.

Association Between FASD, Source Memory, and Working Memory

The second major hypothesis tested was that exposure-related source memory impairments would be mediated by a higher-order executive process (viz., WM). The association of increased memory for source details with higher levels of WM performance, as measured by the WISC-IV Digit Span Backwards subtest, supports this hypothesis. Further, but only partial, confirmation of this hypothesis is provided, in part, by the finding that the source memory performance deficits observed in the FAS/PFAS group were only partially mediated by WM performance. In other words, the source memory impairments documented in the current study cannot be explained solely by exposure-related WM impairment, and hence the hypothesis is neither fully confirmed nor disconfirmed.

It is, however, of relevance that both FASD diagnostic status (i.e., FAS/PFAS vs. nonsyndromal HE and non-exposed control) and WM retained independent effects on source memory performance. This finding suggests that there is a specific effect of heavy PAE on source memory performance in children with a diagnosis of FAS/PFAS, over and above exposure-related impairments in WM. As indicated previously, a possible explanation for the specificity of this effect may be that PAE affects the process of hippocampally mediated feature-binding during the encoding of rich contextual memories. Additionally, direct statistical adjustment for WM performance provides empirical evidence for (a) the association between source memory and WM as well as for (b) the discriminant validity of source memory and WM tasks. These data therefore make a novel contribution to the literatures working toward defining a specific pattern of learning and memory impairment in

children with FASD, and toward validating a theoretical association between source memory and EF.

Source Memory Performance in Children with FASD and ADHD

The final research question addressed here was whether source memory deficits were attributable to a co-morbid diagnosis of ADHD. To investigate this question, I first compared source memory task performance in children with and without a diagnosis of ADHD (across the entire sample, regardless of FASD diagnosis). I then compared source memory performance in non-exposed participants (i.e., AA/day = 0) with and without a diagnosis of idiopathic ADHD, and finally compared source memory performance in exposed children (i.e., AA/day > 0) with and without a co-morbid diagnosis of ADHD.

None of the three comparisons detected significant between-group differences. In other words, in this sample children with and without a diagnosis ADHD, regardless of exposure history, demonstrated similar source memory performance on all task outcome variables. The absence of source memory deficits in children with a diagnosis of ADHD is not consistent with previous research demonstrating impaired memory for source details in this clinical population (e.g., Kerns & Macoun, 2014).

This disparity between the current results and those reported in previously published studies may be best explained by examining overall task performance: In this study, all children, regardless of exposure history and/or ADHD diagnostic status, performed well on the source memory task. Thus, a possible explanation for the absence of performance differences associated with ADHD diagnosis may be that the task used in this study was not sufficiently complex to engage the higher-order executive processes that are typically impaired in children with a diagnosis of ADHD. Additionally, the absence of source memory deficits may also speak to differential patterns of impairment observed in children with heavy

PAE and children with ADHD: Children with FASD demonstrate more marked impairment in WM and information encoding than children with ADHD (Burden, Jacobson, Sokol, et al., 2005; Crocker et al., 2011), who demonstrate more marked impairment in sustained attention and information retrieval than children with FASD (Coles et al., 1997; Crocker et al., 2011). Indeed, in this study only children with a diagnosis of FAS/PFAS *and* WM impairment demonstrated impaired memory for source details. Nevertheless, these findings make a novel contribution to the clinical differentiation of the neuropsychological profile of children with heavy PAE and children with ADHD, and warrant follow-up investigation.

Limitations and Future Directions

One possible limitation of this study was that the source memory task was (a) a relatively simple way to assess memory for item and source details, and (b) restricted to the assessment of the reality monitoring condition within Johnson et al.'s (1993) source monitoring framework. Regarding (a), the finding that the task was simple enough for all participants to perform at relatively high levels suggests that it may not have been sensitive enough to detect source memory performance deficits in the nonsyndromal HE participants and/or in participants with an ADHD diagnosis. The use of a more complex source memory task may, therefore, be beneficial in this context. For instance, a pertinent line of investigation might be to examine source memory performance on a task that manipulates the condition under which source judgements are made (e.g., Hala et al., 2005; Kully-Martens, Pei, et al., 2012). Regarding (b), it was beyond the scope of the current investigation to assess the external and internal conditions of the source monitoring framework. Given the clinical significance of source memory impairments outlined above, it is of relevance to further delineate the deficits displayed in prospectively recruited heavily exposed children. Such

investigations may inform both behavioral and cognitive interventions for children with FASD.

It is noteworthy that the predominant study design used to examine source memory performance within pediatric samples is cross-sectional. It is important to locate the findings from cross-sectional research (including the current study) within the context of typical and/or atypical neurodevelopmental trajectories. To do so, researchers need to employ a longitudinal research design in which children are assessed at multiple time points across development. Such a design would be especially relevant and useful given the theoretical association between source memory and EF, both of which have been demonstrated to undergo functional maturation during childhood and adolescence (Anderson, 2002). Longitudinal study design has proved to be particularly effective for assessing neurodevelopmental effects in children with FASD using both behavioral and neuroimaging methods (e.g. Jacobson et al., 2008; Jacobson, Stanton, et al., 2011; Lebel et al., 2012). Thus, longitudinal cohort studies investigating the neurodevelopmental trajectory of children with FASD provide a unique opportunity to further examine the pattern of source memory impairment observed in the current study.

Conclusion

This study is the first to report impaired memory for source details in children with a diagnosis of FAS/PFAS whose mothers were recruited and interviewed prospectively during pregnancy. Additionally, this is the first study to demonstrate (a) partial mediation of source memory impairments by WM, and (b) the absence of performance differences in children with and without a diagnosis of ADHD, regardless of FASD diagnosis, as well as in non-exposed participants (i.e., AA/day = 0; with and without a diagnosis of idiopathic ADHD) and in exposed participants (i.e., AA/day > 0; with and without a co-morbid diagnosis of

ADHD). Taken together, these data suggest that PAE has a specific effect on the acquisition of contextually rich episodic memories in syndromal children. Taking this suggestion one speculative step further, the current data might fit with the proposition that the component processes of encoding itself (e.g., feature-binding) warrant further investigation. Additionally, the current data suggest that the effect of PAE on source memory is only partially explained by exposure-related deficits in a higher-order executive process (viz., WM), and thereby emphasize the importance of statistical adjustment for potential cognitive mediators of the effects of PAE. The findings of this study, therefore, make significant contributions to both the ongoing process of defining the cognitive and behavioral profile of children with FASD and the literature working towards further elucidation of the association between source memory and EF.

CHAPTER 6: SYNTHESIS

Prenatal alcohol exposure (PAE) is associated with a range of physical, growth, and neurobehavioral deficits. These deficits are, therefore, characteristic of individuals with fetal alcohol spectrum disorders (FASD; for reviews, see (Kodituwakku & Kodituwakku, 2014; Mattson et al., 2011). Globally, some of the highest FASD prevalence rates are found in the Western Cape (WC) province of South Africa, where heavy alcohol consumption by pregnant women is frequently observed in economically disadvantaged communities (Croxford & Viljoen, 1999; Eaton et al., 2012; Jacobson et al., 2006; May, Blankenship, Marais, Gossage, Kalberg, Barnard, et al., 2013; Roozen et al., 2016). There exists, therefore, a unique opportunity to examine, using novel assessment techniques, the relations between heavy PAE and neurodevelopmental outcomes in this context.

Although declarative memory impairment is a key feature of the neurocognitive profile of FASD (Kaemingk et al., 2003; Lewis et al., 2015; Manji et al., 2009; Mattson & Roebuck, 2002; Willford et al., 2004), the cognitive mechanisms underlying this deficit are not well understood. Neuropsychological investigations suggest that impaired memory encoding may be the primary mechanism underlying general learning and memory deficits. The overarching aim of this doctoral research was, therefore, to examine, both directly and indirectly (via bottom-up and top-down processes), a critical cognitive mechanism that supports successful declarative memory functioning (viz., memory encoding) in children with FASD. The key research questions I asked in this dissertation were:

Study I: Do children with heavy PAE differ from typically developing, demographically similar non-exposed children in terms of neural activation during completion of a passive visual perception task?

Study II: Do children with heavy PAE differ from typically developing, demographically similar non-exposed children in terms of neural activation during the encoding of visual scenes?

Study III: Do children with heavy PAE differ from typically developing demographically similar non-exposed children in terms of source memory performance?

In this final chapter, I summarize and interpret the major findings from each study and comment on their significance within the context of the broader literature regarding declarative memory. I conclude with a brief discussion of the clinical significance of these findings, particularly with respect to intervention strategies.

Major Findings Related to Memory Encoding

Neural Activation during Visual Perception

In Study I (Chapter 3), I used a passively viewed, blocked design functional magnetic resonance imaging (fMRI) paradigm, designed by N. Ofen (personal communication), to investigate neural activation during visual perception, a lower-order cognitive process essential to memory encoding. The absence of between-group differences in object- and scene-selective activation in the bilateral lateral occipital complex (LOC; Malach et al., 1995) and parahippocampal place area (PPA; Epstein & Kanwisher, 1998), respectively, is clinically significant for several reasons. First, the pattern of neural activation reported here is consistent with the typical development of category-selective activation within the ventral visual stream (Golarai et al., 2007; Vuontela et al., 2013) This finding suggests, therefore, that neural activation within the LOC and PPA is less susceptible to the effects of heavy PAE during passive viewing than it might be in regions activated during tasks measuring higher-order cognitive processes.

This finding is consistent with neuroimaging investigations demonstrating relative sparing of neural regions supporting perceptual functioning in children with heavy PAE (Fan et al., 2015; Lebel et al., 2011). However, the category-selective perceptual regions examined in Study I show extensive functional connectivity to the neural networks supporting higher-order cognitive processes (Baldassano et al., 2013; Hutchison et al., 2014), and are recruited during the maintenance of visual information in working memory during encoding processes (Cansino, Maquet, Dolan, & Rugg, 2002; Gazzaley et al., 2007; Ranganath et al., 2004; Wendelken et al., 2011). Thus, the failure to detect between-group differences in neural activation during basic visual processing of objects and scenes does not preclude exposure-related impairment in these ventral visual stream regions during higher-order cognitive tasks.

This interpretation is consistent with my finding that higher general intellectual functioning, as measured by Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV; Wechsler, 2003a) Full Scale IQ, was associated with a greater degree of activation in the right PPA during the passive viewing task. This finding suggests that higher intellectual functioning may be associated with spontaneous encoding of visual information. Moreover, these data are consistent with contemporary models of general intellectual functioning that emphasize the recruitment of perceptual resources to facilitate higher-order cognitive processes (e.g., Parieto-Frontal Integration Theory; Jung & Haier, 2007). To address the question of whether the lower-order cognitive processing assessed in this task plays a role in impaired memory encoding in this FASD, follow-up investigation was required.

Neural Activation During Memory Encoding

In Study II (Chapter 4), I used an event-related fMRI paradigm (Ofen et al., 2007, using the subsequent memory paradigm; Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Wagner et al., 1998) to investigate neural activation during memory encoding. The alcohol-

exposed and control groups demonstrated equivalent behavioral memory performance accuracy, and both groups recruited an extensive bilateral network of regions (including the hippocampal formation, posterior parietal cortex, and prefrontal cortex) during the encoding of visual scenes. This pattern of activation is consistent with encoding-associated activation reported in typically-developing children and adults (Kim, 2011; Ofen et al., 2007).

However, children with a diagnosis of fetal alcohol syndrome (FAS) or partial FAS (PFAS) also recruited additional neural regions outside of the encoding network identified for the sample as a whole. Given their similar memory performance accuracy, this pattern of more extensive recruitment of neural resources may be indicative of compensatory activation to facilitate effective task completion—a pattern that has been demonstrated in children with FAS/PFAS during task completion within other cognitive domains (Diwadkar et al., 2013; Fryer, Tapert, et al., 2007; Kodali et al., 2017; Meintjes et al., 2010).

Additionally, children in the FAS/PFAS group differed from children in the nonsyndromal heavily exposed (HE) and non-exposed control groups in showing smaller increases in the magnitude of activation in several key memory encoding functional regions of interest (fROIs), including the intraparietal sulci, parahippocampal gyri, and right hippocampal formation, during encoding. Interestingly, the bilateral PPA, as identified in Study I, demonstrated encoding-associated activation increases that were similar for all children, regardless of PAE.

Therefore, the findings from Study II are consistent with those from Study I in suggesting that the basic perceptual processing of scenes is relatively spared during memory encoding in children with FASD. This suggestion is consistent with data from a resting state fMRI study on this cohort, which indicated that perceptual processing is relatively spared in FASD (Fan et al., 2015). The current data are also consistent with contemporary models of declarative memory proposing that both perceptual and mnemonic resources are recruited to

facilitate effective memory encoding (e.g., the Predictive Interactive Multiple Memory System framework; Henson & Gagnepain, 2010).

Source Memory Performance

In Study III (Chapter 5), I used a behavioral source memory paradigm (Ofen et al., 2007) to investigate higher-order executive processes essential for memory encoding. All children demonstrated similar and highly accurate recognition memory accuracy for items. The finding of intact recognition memory in children with heavy PAE is not consistent with a preliminary assessment of source memory in children with FASD (Kully-Martens, Pei, et al., 2012), nor is it consistent with previous reports of impaired recognition memory on a standardized assessment of verbal learning and memory (Crocker et al., 2011; Lewis et al., 2015; Mattson et al., 1996). However, the absence of between-group differences in recognition memory on this task strengthens the inference that the lower source memory scores in the FAS/PFAS group were attributable to a specific deficit in their ability to recall source details. Moreover, the pattern of impairment observed in the FAS/PFAS group was not attributable to sociodemographic confounding variables and/or prenatal smoking and/or drug exposure.

Interestingly, memory for source details was partially mediated by working memory ability. Thus, the poorer source memory performance observed in children with FAS/PFAS is suggestive of an encoding deficit that may result from less efficient feature-binding during the encoding of source details. Although feature-binding is defined as a component process of working memory that facilitates information acquisition, it is primarily mediated by the hippocampal formation (Henke et al., 1997; Mammarella & Fairfield, 2008). These data, therefore, provide support for the hypothesis that learning and memory deficits in children

with FAS/PFAS may be mediated by hippocampal- and prefrontal-dependent encoding and working memory processes.

Clinical Significance and Future Directions

Specificity of Encoding Deficits in FASD

The findings described in this dissertation make novel contributions to the literature working toward elucidating cognitive mechanisms underlying learning and memory impairments associated with heavy PAE. Taken together, the findings of Studies II and III provide evidence for a specific encoding deficit in children with FAS/PFAS that is at least partially mediated by higher-order cognitive processes. Although lower-order cognitive processes appear relatively intact during both basic perceptual processing (Study I) and higher-order encoding (Study II), both the pattern of differential neural activation in children in the FAS/PFAS group (Study II) and their less efficient memory for source details (Study III) suggest difficulty integrating perceptual information into contextually-rich memory traces during the encoding of visual information. When interpreted together, the findings from Studies II and III implicate both medial temporal lobe (MTL) and prefrontal cortex (PFC) mediated processes in the specific encoding deficit observed in children with FAS/PFAS. This interpretation is consistent with previous behavioral investigations showing (a) impairing effects of PAE on encoding in both verbal and visual-spatial measures of learning and memory (for a review, see du Plooy et al., 2016), and (b) less efficient use of executive learning strategies during information acquisition in FASD (Lewis et al., 2015; Rasmussen et al., 2009).

These data expand on prior behavioral investigations of learning and memory in this clinical population in several important respects. First, neuroimaging studies provide a novel opportunity to tease apart encoding effects first documented on behavioral measures of

learning and memory performance. They do so by directly contrasting patterns of neural activation during successful and unsuccessful encoding trials. In Study II, the direct examination of encoding, on a trial-by-trial basis, revealed particular patterns of encoding-associated activation in the FAS/PFAS group. These patterns were suggestive of compensatory recruitment of neural resources, with such recruitment necessary to attain performance levels similar to those of typically developing non-exposed control children. Further evidence of this functional impairment in children with FAS/PFAS is provided by the finding that behavioral memory performance accuracy was equivalent among the three FASD groups (viz., FAS/PFAS, nonsyndromal HE, and non-exposed control).

By contrast, the finding of impaired memory for source details in Study III suggests that whereas compensation can mask performance deficits on the recognition memory component of the relatively simple source memory task, when the cognitive load of the task is increased, children with FAS/PFAS can no longer compensate effectively for their underlying functional encoding impairments. However, follow-up neuroimaging investigations of encoding and source memory performance are necessary to directly test this inference, and to assess the generalizability of these findings.

This latter point speaks to the broader clinical significance of these data with regard to defining the cognitive and behavioral profile of FASD more generally. Although children with FASD present with a neuropsychological profile that may be best characterized by (a) generalized impairment across several cognitive domains and (b) diffuse structural and functional impairment of several cortical and subcortical brain regions (for reviews, see Donald et al., 2015; Moore et al., 2014) increasing evidence supports the notion that impaired declarative memory is a central deficit associated with heavy PAE. Study II provides convincing evidence of a specific encoding deficit in children with FAS/PFAS, thereby extending prior behavioral investigations of the mechanisms of learning and memory

impairment in FASD (e.g., Lewis et al., 2015; Mattson & Roebuck, 2002). However, previous studies have demonstrated a specific deficit in information retrieval at moderate levels of PAE (Lewis et al., 2015), suggesting a different pattern of declarative memory impairment to that observed at heavy levels of PAE. Thus, a pertinent line of follow-up investigation would be to administer an alternative version of the memory encoding task used in Study II to assess neural activation during information retrieval at varying levels of PAE. To achieve this, participants would be required to complete the encoding phase of the task outside of the scanner and to complete the recognition memory test while undergoing fMRI data acquisition (e.g., Ofen, Chai, Schuil, Whitfield-Gabrieli, & Gabrieli, 2012). Neuroimaging data obtained from such an investigation would further elucidate the specificity of learning and memory impairments as a central deficit within the cognitive profile of FASD.

Relation Between Cognitive Load and Declarative Memory Impairment

The findings of Studies II and III demonstrate the importance of cognitive load in eliciting (a) behavioral performance differences in children with FASD, and (b) compensatory neural activation to facilitate effective task completion. Specifically, as cognitive load increases, performance-based impairments are likely to become evident because adaptation efforts have been focused on coping with the core deficit (e.g., memory encoding) and compensatory efforts are no longer sufficient to produce performance equivalent to that of typically developing children (a pattern that is indicated by, for example, less efficient recall of source details in Study III). This suggestion is consistent with the finding that children with FAS/PFAS are less efficient at processing complex information (i.e., that dependent on the recruitment of strategic processes) than simple information (i.e., that dependent on more spontaneous or automatic processes; Aragón, Kalberg, et al., 2008;

Burden, Jacobson, & Jacobson, 2005; Kodituwakku, 2009). As an experimental construct, cognitive load has been proven to be important in studies of impairment in both normal aging (Cappell, Gmeindl, & Reuter-Lorenz, 2010; Gazzaley, Cooney, Rissman, & D'Esposito, 2005; Mitchell, Johnson, Raye, Mather, & D'Esposito, 2000) and neuropsychological disorders (e.g., HIV; Fellows, Byrd, & Morgello, 2014). Thus, follow-up fMRI investigations that are designed to include an experimental manipulation of cognitive load during memory encoding are of particular relevance to the future study of declarative memory impairment in FASD.

Just as we can manipulate both behavioral and neuroimaging experimental task design to elicit deficits under conditions of high cognitive load (e.g., manipulating task difficulty, Aragón, Kalberg, et al., 2008; Lewis et al., 2016; Sowell et al., 2007), manipulation of cognitive load can be useful in designing intervention strategies. For example, within the field of educational psychology, Cognitive Load Theory (Sweller, 1994) has proven very useful in (a) assessing cognitive ability of each individual and (b) optimizing learning conditions such that the extraneous cognitive load is reduced and learning is enhanced (for reviews, see (Kalyuga & Singh, 2016; van Merriënboer & Sweller, 2005). Although future research is required to assess the suitability of integrating such an approach into interventions tailored to the specific encoding deficits observed in children with FAS/PFAS, this approach should be particularly well suited to adapting interventions to the performance capacity of the individual child, which is important given the variability in cognitive proficiency in children with FASD.

Performance Variability in the Nonsyndromal HE Group

An important component of the overall design of this doctoral research was to examine the extent to which differences in patterns of neural activation (Studies I and II) and

behavioral performance (Studies II and III) differed among the three groups (viz., FAS/PFAS, nonsyndromal HE, and non-exposed control). Comparisons of this nature are of clinical significance because they contribute to further delineating the cognitive and behavioral profile associated with the full spectrum of exposure-related diagnostic categories. Improved definition of this profile is particularly necessary for children within the nonsyndromal HE group.

Although children in the nonsyndromal HE group demonstrated considerable performance overlap with children in the non-exposed control group across the three studies presented here, they employed a distinctive behavioral response style during completion of Study II's memory encoding task. Additionally, children in the nonsyndromal HE group demonstrated noteworthy variation in cognitive ability (e.g., a few children with heavy PAE had unexpectedly high WISC-IV Full-Scale IQ scores relative to other children in the study; Study III). The heterogeneity of alcohol-related outcomes within the nonsyndromal HE group occurs within the context of maternal reports of similar quantities of dose/occasion and frequency of drinking (days/week) during pregnancy to mothers of children in the FAS/PFAS group (Chapter 2). Differences in the timing of exposure (Lipinski et al., 2012; Sulik, 2005), genetic vulnerability (Dodge et al., 2014; Jacobson et al., 2006; Viljoen et al., 2001; Warren & Li, 2005), and nutritional status (Carter et al., 2014; May et al., 2016; May, Hamrick, et al., 2014) may account for both (a) the fetal alcohol-related effects observed here and (b) the variation in cognitive impairment observed within the nonsyndromal HE group.

The heterogeneity in exposure-related outcomes results in added complexity in the characterization of the between-group differences reported in this doctoral research. Because mothers in the Cape Town Longitudinal Cohort Study were recruited and interviewed prospectively during pregnancy, it was possible to calculate three continuous measures of prenatal alcohol (viz., AA/day, AA/occasion, and drinking frequency [days/week]), which

were subsequently validated against levels of fatty acid ethyl esters (FAEEs) in meconium samples (Bearer et al., 2003), infant behavior (Jacobson et al., 2002; Molteno et al., 2014), and a broad range of behavioral and neuroimaging outcomes (De Guio et al., 2014; du Plessis et al., 2014; Lewis et al., 2015, 2016; Lindinger et al., 2016; Woods et al., 2015). It is noteworthy that prospectively-obtained continuous measures of PAE are often more sensitive indicators of exposure-related deficits than both retrospective indicators of PAE (e.g., Meintjes et al., 2014; Robertson et al., 2015) and FASD diagnostic categories (e.g., Lindinger et al., 2016), as was the case in Studies I and II. The heterogeneity of exposure-related outcomes observed in the nonsyndromal HE group warrants investigation into both (a) improved approaches for determining which nonsyndromal children with confirmed heavy PAE meet criteria for alcohol-related neurodevelopmental disorder and alcohol-related birth deficits (Hoyme & Coles, 2016), and (b) new approaches for identifying affected children in this group through the use of novel research methods (e.g., 3D facial mapping; Suttie et al., 2013) and revised diagnostic protocols (e.g., Goh et al., 2016; Hoyme et al., 2016). The impulsive response style seen in Study II and the distinctive compensatory neural activation patterns observed in a recent neuroimaging study (Diwadkar et al., 2013) suggest that specific intervention strategies may be warranted for children in the nonsyndromal HE group.

Conclusion

This is the first study to examine, both directly and indirectly (via bottom-up and top-down processes), a critical cognitive mechanism that supports successful declarative memory functioning (viz., memory encoding) in children with FASD. The data presented in the three studies that comprise this dissertation provide strong support for the hypothesis that learning and memory impairments are mediated, in part, by a specific functional impairment in memory encoding for children with a diagnosis of FAS or PFAS. This conclusion is

supported by evidence of (a) the unique recruitment, by children in the FAS/PFAS group, of compensatory neural resources during successful memory encoding in Study II, and (b) less efficient formation of contextually rich memories by the same group of children in Study III. Interestingly, the results of Studies I – III suggest that while lower-order perceptual processing was less vulnerable to the effects of heavy PAE, higher-order cognitive processes mediated encoding efficiency for children in the FAS/PFAS group.

In contrast to the specificity of the encoding deficit observed in the FAS/PFAS group, children in the nonsyndromal HE group demonstrated a distinctive behavioral encoding style, but did not differ from non-exposed control participants in either their pattern of neural activation during encoding (Study II) or recognition memory accuracy (Studies II and III). Although children in both the FAS/PFAS and nonsyndromal HE groups met the criteria for heavy PAE (viz., $\geq$ 2 oz AA/day), the latter group was comprised of both affected and unaffected children. Indeed, children in the nonsyndromal HE group demonstrated considerable variation in cognitive performance in the current study. Follow-up investigation is, therefore, necessary for the further clarification of the learning and memory profile within this clinical subgroup. Additionally, these data highlight the need to develop robust and reliable criteria for diagnosing alcohol-related neurodevelopmental disorder. Nevertheless, the data presented here speak to the importance of designing intervention strategies based on evidence from both neuropsychological and neuroimaging studies. Such studies can contribute to the design of strategies tailored to the specific presentation of each of the fetal alcohol-related neurodevelopmental disorders.

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APPENDIX A

Sattler's (1992) Formula to Estimate WISC-IV Full-Scale IQ

For participants with missing Wechsler Intelligence Scale for Children—Fourth Edition (WISC-IV) subtest data, Full-Scale IQ was estimated using Sattler's (1992) formula:

$$DQ = (15 \div S_c)(X_c - M_c) + 100$$

where

X_c = Sum of (available) subtest scaled scores,

M_c = Normative Mean; $M_c = 10 * n$, where n = (available) number of subtests

$S_c = S_s \sqrt{n + (2 * \sum rjk)}$;

S_s = subtest standard deviation = 3

n = (available) number of subtests

$\sum rjk$ = Sum of intercorrelations between all (available) subtests

APPENDIX B

Wayne State University Ethics Approval Certificates

WAYNE STATE UNIVERSITY

IRB Administration Office
87 East Canfield, Second Floor
Detroit, Michigan 48201
Phone: (313) 577-1628
FAX: (313) 993-7122
http://irb.wayne.edu

NOTICE OF EXPEDITED AMENDMENT APPROVAL

To: Sandra Jacobson
Psychiatry
University Square Office Plaza

From: Dr. Scott Millis _____
Chairperson, Behavioral Institutional Review Board (B3)

Date: May 25, 2012

RE: IRB #: 026708B3F
Protocol Title: Neural Bases of Eyeblink Conditioning in FASD
Funding Source: Sponsor: NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM
Sponsor: NATIONAL INSTITUTES OF HEALTH
Protocol #: 0802005726

Expiration Date: March 14, 2013

Risk Level / Category: 45 CFR 46.404 - Research not involving greater than minimal risk

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The above-referenced protocol amendment, as itemized below, was reviewed by the Chairperson/designee of the Wayne
State University Institutional Review Board (B3) and is APPROVED effective immediately.

- Protocol – Change in treatment which includes collecting the blood draw at 1-3 weeks instead of 6 weeks. The earlier blood draw provides a more accurate reflection of iron transport across the placenta during pregnancy. This change does not affect risks to participants.
- Consent Form (dated 05/21/2012) – Parental Permission/Research Informed Consent (English and Afrikaans Versions) updated to reflect protocol changes.

WAYNE STATE UNIVERSITY

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NOTICE OF FULL BOARD AMENDMENT APPROVAL

To: Sandra Jacobson
Psychiatry
Department of Psychiatry and B

From: Dr. Scott Millis or designee
Chairperson, Behavioral Institutional Review Board (B3)

Date: July 18, 2013

RE:

IRB #:	026708B3F
Protocol Title:	Neural Bases of Eyeblink Conditioning in FASD
Funding Source:	Sponsor: NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM Sponsor: NATIONAL INSTITUTES OF HEALTH
Protocol #:	0802005726
Expiration Date:	February 20, 2014
Risk Level / Category:	45 CFR 46.404 - Research not involving greater than minimal riskResearch not involving greater than minimal risk

The above-referenced protocol amendment, as itemized below, was reviewed by the Wayne State University Institutional Review Board (B3) and is **APPROVED** effective immediately.

- Protocol – Change in enrollment criteria includes the addition of children ages 13-14 to complete the 2r phase of the longitudinal study. This change does not affect risks to participants.
- Oral Assent Script – Resubmission of Oral Assent Script for Ages 7-12 (English Version and Afrikaans Version).
- Assent Form (dated 6/4/2013) – Addition of Documentation of Adolescent Assent Form for Ages 13-14 (English Version and Afrikaans Version).
- Consent Form (dated 4/18/2013, Protocol Version #2r) - Parental Permission/Research Informed Consent (English Version and Afrikaans Version) updated to reflect change in age range and telephone number.
- Consent Form (dated 4/18/2013, Protocol Version #2rr Alternate) - Parental Permission/Research Informed Consent (English Version and Afrikaans Version) updated to reflect change in telephone number.

WAYNE STATE UNIVERSITY

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NOTICE OF EXPEDITED AMENDMENT APPROVAL

To: Sandra Jacobson
Psychiatry
Department of Psychiatry and B

From: Dr. Deborah Ellis or designee
Chairperson, Behavioral Institutional Review Board (B3)

Date: June 11, 2014

RE:

IRB #:	026708B3F
Protocol Title:	Neural Bases of Eyeblink Conditioning in FASD
Funding Source:	Sponsor: NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM Sponsor: NATIONAL INSTITUTES OF HEALTH
Protocol #:	0802005726
Expiration Date:	February 19, 2015
Risk Level / Category:	45 CFR 46.404 - Research not involving greater than minimal riskResearch not involving greater than minimal risk

The above-referenced protocol amendment, as itemized below, was reviewed by the Chairperson/designee of the Wayne State University Institutional Review Board (B3) and is APPROVED effective immediately.

- Protocol - Enrollment criteria modified to reflect change in participants to be seen between ages of 8 to 13 years to ages of 8 to 17 years.
- Protocol - Other - Compensation modified to reflect change to Rand/Dollar conversion update. The compensation remains R150 regardless of USD.
- Consent Form - Parental Permission/Research Informed Consent - English and Afrikaans versions (revision dated 5/27/2014) - Consent Form modified to reflect change in enrollment criteria (increased age range to 8-17 years of age) and compensation amount of R150 due to conversion update between Rand and USD.

WAYNE STATE UNIVERSITY

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NOTICE OF FULL BOARD CONTINUATION APPROVAL

To: Sandra Jacobson
Psychiatry
Department of Psychiatry and B

From: Dr. Deborah Ellis or designee D Ellis, PhD
Chairperson, Behavioral Institutional Review Board (B3)

Date: December 21, 2015

RE: IRB #: 026708B3F

Protocol Title: Neural Bases of Eyeblink Conditioning in FASD

Funding Source: Sponsor: NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM
Sponsor: NATIONAL INSTITUTES OF HEALTH
Institute Proposal: 15111866

Protocol #: 0802005726

Expiration Date: December 16, 2016

Risk Level / Category: 45 CFR 46.404 - Research not involving greater than minimal riskResearch not involving greater than minimal risk

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Continuation for the above-referenced protocol and items listed below (if applicable) were **APPROVED** following Full Board review by the Wayne State University Institutional Review Board (B3) for the period of 12/21/2015 through 12/16/2016. This approval does not replace any departmental or other approvals that may be required.

- Actively accruing participants.
- Infant Pilot Study Prescreening consent (#4r), dated 8/4/10, in English and Afrikaan
- Infant Study Consent (#4.1r), dated 11/14/14, in English and Afrikaan
- Infant MRI Pilot Study Consent (#4.2), dated 1/6/12, in English and Afrikaan

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- Federal regulations require that all research be reviewed at least annually. You *may* receive a *"Continuation Renewal Reminder"* approximately two months prior to the expiration date; however, it is the Principal Investigator's responsibility to obtain review and continued approval ***before*** the expiration date. Data collected during a period of lapsed approval is unapproved research and can *never* be reported or published as research data.
- All changes or amendments to the above-referenced protocol require review and approval by the IRB **BEFORE** implementation.
- Adverse Reactions/Unexpected Events (AR/UE) must be submitted on the appropriate form within the timeframe specified in the IRB Administration Office Policy (http://www.irb.wayne.edu/policies-human-research.php).

NOTE:

1. Upon notification of an impending regulatory site visit, hold notification, and/or external audit the IRB Administration Office must be contacted immediately.
2. Forms should be downloaded from the IRB website at **each** use.

APPENDIX C

University of Cape Town Ethics Approval Certificates

HUMAN RESEARCH ETHICS COMMITTEE
05 OCT 2012
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30/5/2013
☐ Not approved	See attached comments		
Signature Chairperson of the HREC	Signed	Date Signed	9/10/12

Principal Investigator to complete the following:

1. Protocol information

Date form submitted	October 3, 2012		
HREC REF Number	187/2008	Current Ethics Approval was granted until	30/05/2012
Protocol title	Neural Bases of Eyeblink Conditioning in FASD		
Protocol number (if applicable)			
Principal Investigator	A/Prof EM Meintjes		
Department / Office Internal Mail Address	Department of Human Biology, Room 5.14 Anatomy Building, Faculty of Health Sciences, Anzio Road, Observatory		

1.1 Does this protocol receive US Federal funding?	X☐ Yes	☐ No
1.2 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.	☐ Yes	☐X No

2. List of documentation

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

UNIVERSITY OF CAPE TOWN

HUMAN RESEARCH ETHICS COMMITTEE
24 JUL 2013
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA0001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.5.2014
☐ Not approved	See attached comments		
Signature Chairperson of the HREC	Signed	Date Signed	26/07/2013

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date form submitted	18 July 2013		
HREC REF Number	187/2008	Current Ethics Approval was granted until	30/5/2013
Protocol title	Neural Bases of Eyeblink Conditioning in FASD		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes X No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	A/Prof EM Meintjes		
Department / Office Internal Mail Address	Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Observatory, 7925		

1.1 Does this protocol receive US Federal funding?	X Yes	☐ No
1.2 Does this study require full committee approval?	☐ Yes	X No

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES

Form FHS006: Protocol Amendment

HREC office use only (FWA00001637; IRB00001938)			
☑ Approved	☐ Type of review: Expedited	☐ Full committee	
This serves as notification that all changes and documentation described below are approved.			
Signature Chairperson of the HREC	Signed	Date	19/6/2014

Note: All amendments should include a Synopsis justifying the changes for the amendment (please see notice dated 23 April 2012)

Principal Investigator to complete the following:

1. Protocol Information

Date form submitted	19 June 2014		
HREC REF Number	187/2008		
Protocol title	Neural Bases of Eyeblink Conditioning in FASD		
Protocol number (if applicable)			
Principal Investigator	A/Prof EM Meintjes		
Department / Office Internal Mail Address	Human Biology		
1.1 Is this a major or a minor amendment? (see FHS006hlp)		☐ Major	X Minor
1.2 Does this protocol receive US Federal funding?		X Yes	☐ No
1.3 If the amendment is a major amendment and receives US Federal Funding, does the amendment require full committee approval?		☐ Yes	X No

2. List of Proposed Amendments with Revised Version Numbers and Dates

Please itemise on the page below, all amendments with revised version numbers and dates, which need approval.
This page will be detached, signed and returned to the PI as notification of approval. Please add extra pages if necessary

FHS006 – Protocol Amendment – Neural Bases of Eyeblink Conditioning in FASD – **Addendum to perform an ERP Study of Number Processing and Error Detection in FAS and ADHD**

New English and Afrikaans maternal consent forms attached
English and Afrikaans Assent forms attached
Amended Synopsis Attached

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: nosi.tsama@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

24 August 2015

HREC REF: 471/2015

Prof E Meintjes
Biomedical Engineering
Human Biology
Anatomy Building

Dear Prof Meintjes

PROJECT TITLE: NEURAL BASES OF COGNITIVE AND BEHAVIOURAL EFFECTS OF FASD

Thank you for your response to the Faculty of Health Sciences Human Research Ethics Committee dated 21 August 2015.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th August 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

Signed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki guidelines.

HREC 471/2015

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

APPENDIX D

Informed Consent: English

Parental Permission/Research Informed Consent
Title of Study: Neural Bases of Eyeblink Conditioning in FASD

We are pleased to invite you and your child _____ to continue to take part in the study that you have been in since you were pregnant and your baby was born. Please read this form and ask us any questions you have before agreeing to be in the study. The people conducting this study are doctors and scientists from the Faculty of Health Sciences of the University of Cape Town School in South Africa and Wayne State University School of Medicine in the United States: Ernesta Meintjes, Ph.D., and Christopher Molteno, M.D., from University of Cape Town, and Sandra W. Jacobson, Ph.D., and Joseph L. Jacobson, Ph.D., from Wayne State University in the United States. It is being paid for by the National Institute on Alcohol Abuse and Alcoholism in the United States and the Department of Science and Technology and the National Research Foundation of South Africa.

Study Purpose: In this study we want to learn whether some aspects of a child's thinking and behavior are different when a mother drinks or and smokes during pregnancy, and whether genes (characteristics that you inherit from your parents) make it more or less likely that the child will show these differences. Other purposes of the study are to see whether your child's abilities when s/he was a baby and 5 years old predict how he or she is doing at 8-17 years of age. To help decide whether or not to agree to take part with your child in this study, a project staff member has talked with you about the risks and benefits of the study. This consent form summarizes the information given to you by the project staff member during this informed consent process.

The study will use new methods for studying the brain called MRI neuroimaging to better understand how drinking alcohol and smoking during pregnancy can affect a child's development. In neuroimaging, the child lies in a scanner that uses magnets to take pictures of the brain. In this part of the study, we will take pictures on the new scanner at Tygerberg Hospital while your child lies still and watches a video and does some simple finger tapping, attention, and memory tasks.

Study Procedures: If you agree to have your child take part in this study, we will bring you and your child to the our laboratory at the University of Cape Town (UCT) for 2-3 visits that will each take about 4 hours and to Tygerberg Hospital for 1-2 visits that should take about 3-4 hours in total.

- During the visits to University of Cape Town, your child will do simple tasks involving finger tapping, attention, learning and memory, arithmetic, word meanings, puzzles, circle drawing, and mazes (Wechsler Intelligence Scale for Children; paced/unpaced finger tapping; Circle Drawing task; timing and pitch perception tasks; California Verbal Learning Test).
- We will test your child's vision.
- In one task, your child will put on a special helmet. While your child is watching a video, a puff of air from the helmet will cause him/her to blink while hearing a tone. We will ask your child questions about the video afterwards.
- We will weigh and measure your child and take a photograph to look for facial features that often relate to alcohol exposure during pregnancy.

- During this visit, we will ask you some questions about your child's behavior and attention (Disruptive Behavior Disorders assessment), daily activities (Child Behavior Checklist), school and health history, and any medications that s/he is taking.
- We will ask you to update us about stressful experiences in your daily life during the past year (Life Events Scale), your current drinking, smoking, and drug use, attention problems you may have had as a child (Barkley-Murphy ADHD Scale), and stressful feelings that you experience, including sadness, anxiety, and distress (Beck Depression Inventory; Structured Clinical Interview for DSM-IV).
- At the end of the first visit, our research driver and nurse will take you and your child to a nearby clinic, where a technician/nurse will take a 5 cc blood sample (approximately 1 teaspoon) from your child's vein to test for lead and iron deficiency anemia. About 10 cc of blood (about 2 teaspoons) will be obtained from your child and yourself to study genetic differences that you and your child inherited from your family and have been found to be related to differences in alcohol use, depression, attachment, or child attention/behavior and development. These samples will be stored and used for future genetic analyses.
- During the first visit to Tygerberg, your child will first practice the finger tapping, and attention and memory tasks s/he will be doing on a computer while lying in the scanner. During the neuroimaging, your child will lie on a padded plastic bed that slides into the scanner. We will ask him/her to lie as still as possible while the pictures are being taken. Taking these pictures of the brain does not hurt and is used every day by many people in the hospital. During the second visit to Tygerberg, our assistant will again practice the finger tapping and attention/memory tasks with your child and review with him/her the airpuff learning task that s/he has done in our laboratory at UCT. Your child will be shown special goggles that s/he will wear in the scanner and told that s/he will feel the airpuff and hear some tones while watching a video and that we will be asking him/her some questions about the video at the end of the scan. During some of the time in the scanner, your child will watch videos and during some of the time s/he will do the finger tapping and other tasks that were practiced before entering the scanner. There will be two sessions in the scanner at each visit to Tygerberg—both on the same day—one in the morning and one after lunch, which we will give you and your child while you are at Tygerberg. Each session in the scanner will last no longer than 45-60 minutes. Children with the following may not have an MRI but will take part in the rest of the visits: implanted medical devices, such as aneurysm clips in the brain, heart pacemakers, and cochlear (inner ear) implants; lead-based tattoos; or pieces of metal close to or in an important organ (such as, the eye); claustrophobia or fear of being in a small space.

Benefits: There may be no direct benefits for you; however, information from this study may help other people now or in the future. We will give you information about your child's development at this age. We will use the findings from this study for research purposes only. However, if a serious problem is found, we will tell you and refer your child to a doctor and/or someone who can help, if you would like us to do so. If your child is suffering from any major illness, we will send you Red Cross Children's Hospital. No information about your child will be given to any doctors, hospitals, or schools unless you ask us and allow us to do so in writing.

Risks: None of the procedures we use at UCT or Tygerberg are dangerous for you or your child. The risks of drawing blood include some temporary discomfort or swelling, and rarely, infection. These risks that will be minimized because the procedure will be done by a trained phlebotomist (nurse/technician who has been specially trained to draw blood). We will begin by introducing you and your child to the research staff and will give you both breakfast each day before the assessment begins. You will be present in a room nearby during all of your child's assessments and will be present with your child during the physical examination and

blood draw. During the MRI neuroimaging assessments, certain metal objects, such as, watches, credit cards, hairpins, and writing pens, may be damaged by the MRI scanner or pulled away from the body by the magnet. For these reasons, we will ask your child to remove these before going into the scanner. When the scanner makes the pictures, the bed may shake, and your child will hear loud banging noises. S/he will be given earplugs or headphones to protect the ears. Also, some people feel nervous in a small closed space, such as when they are in the scanner. Your child will be able to see out of the scanner at all times, and we will not start until s/he tells us that s/he is comfortable. S/he will be able to stop the scanning at any time by squeezing a ball that s/he will hold in one hand and can talk to us using an intercom that is built into the scanner. There are no known harmful long-term effects of the magnetic fields used in this study. There is little risk that anything you tell us will be told to people outside the study and we will do everything we can to keep this information secret, as described below, except that evidence of child abuse or neglect will be reported to the appropriate authorities, as required by law, and may report other illegal activities that are reported to us during the visit.

Research Related Injuries: If you or your child is injured during the study, you will get treatment including first aid, emergency treatment and follow-up care, as needed. No reimbursement, compensation, or free medical care is offered by Wayne State University or the University of Cape Town. If you think that your child has suffered a research related injury, let the investigator know right away.

Study Costs: There will be no cost to you or your child for taking part in this research study, and you and your child will be transported to the laboratory at University of Cape Town and Tygerberg Hospital by our driver.

Compensation: For taking part in this research study, we will give you R180 for each visit and a photo of your child, and we will give your child a small gift. You and your child will also be given breakfast and lunch each time you and your child come to University of Cape Town or Tygerberg Hospital.

Confidentiality: We will keep all information collected about you and your child during the study secret to the extent permitted by law. This information will not be used in any way that can allow anyone else to know what you or your child has told us, except that evidence of child abuse or neglect will be reported to the appropriate authorities, as required by law. You and your child's names will not be in the research records, only your code number. We will not give out any information that names you or your child unless you give us written permission, but your records may be reviewed by the study sponsor, the Human Investigation Committee at Wayne State University, the University of Cape Town Research Ethics Committee, or governmental agencies with appropriate regulatory oversight. The list linking names and code numbers will be stored in locked file cabinets in the research laboratory. Only project staff members who need to contact you by telephone or in person will be allowed to look in these files. Information from this study, including photos may be presented in scientific meetings or journals or for teaching purposes, but your and your child's names will be kept secret.

Voluntary Participation/Withdrawal: Taking part in this study is voluntary. You may decide to have your child take part and later change your mind and quit the study. You and your child are also free not to answer any questions or to stop any task before it is finished. Withdrawal from the study would not lead to any problems for you or your child. The researcher or the sponsor may also stop your child's taking part in this study without your agreeing to it.

Questions: If you have any questions now or in the future, you may contact Drs. Ernesta Meintjes or Christopher Molteno at 021-406-6291 or Dr. Sandra W. Jacobson at 001-313-

993-5454. If you have questions or concerns about you or your child's rights as a research participant, you can contact the Chairs of either the University of Cape Town Research Ethics Committee (021 406-6338) or the Wayne State University Human Investigation Committee (001-313-577-1628).

Consent to Participate in a Research Study: To voluntarily agree to have your child take part in this study, you must sign on the line below. If you decide to take part with your child, you or your child may quit at any time. You are not giving up any of your or your child's legal rights by signing this form. Your signature shows that you have read, or had read to you, this whole consent form, including the risks and benefits, and that we have answered all your questions. We will give you a copy of this consent form to take home.

Signature of Parent or Legally Authorized Guardian	Date
Printed Name of Parent or Authorized Guardian	Time
Oral Assent (children age 7-12 years)	Date
**Signature of Witness (When applicable)	Date
Printed Name of Witness	Time
Signature of Person Obtaining Consent	Date
Printed Name of Person Obtaining Consent	Time

** Use when parent has had consent form read to them (i.e. illiterate, legally blind, translated into foreign language).

APPENDIX E

Informed Assent: English

Documentation of Adolescent Assent Form (ages 13-17)
Title: Neural Bases of Eyeblink Conditioning in FASD
Study Investigator: Sandra W. Jacobson, Joseph L. Jacobson, Christopher D. Molteno, Ernesta M. Meintjes

Why am I here?

This is a research study. Only people who choose to take part are included in research studies. You are being asked to take part in this study because you are one of a large group of children who have been taking part in this study since you were born and have taken part in visits as an infant and at 5 years of age. We are inviting you to take part in the next phase of this study. Please take time to make your decision. Talk to your family about it and be sure to ask questions about anything you don't understand.

Why are they doing this study?

This study is being done to find out how children learn and remember things and solve simple problems. We are trying to understand whether and how diet, alcohol, smoking, and drug exposure during pregnancy may affect development. We study children at different ages using different tasks to see how they grow and develop.

What will happen to me?

Here at University of Cape Town, we will be studying what happens when you feel a puff of air in your eye. You will sit in a chair wearing a special helmet and will watch a video. From time to time, you will feel a puff of air from the helmet and sometimes you will hear a tone. You will also do simple tasks involving tapping your finger, naming pictures, learning lists of words, reading and arithmetic, puzzles, mazes, memory and computer tasks, and tasks about how other people feel and understand another person's point of view. We will also weigh you, measure how tall you are, take a photo, and check how well you can see. You will spend this morning here and will come back to University of Cape Town another day to do the air puff task and the other tasks that I mentioned.

The second part of the study involves neuroimaging, which is a new way to learn about the brain by taking pictures of the brain. These pictures can help us better understand how the brain works. For this part of the study we will drive you and your mother to Tygerberg Hospital. During the neuroimaging, you will lie on a plastic bed that slides into a large machine called a scanner. We will ask you to lie as still as possible while the pictures are being taken. Taking these pictures of the brain does not hurt and is used everyday by many people in the hospital. During some of the time in the scanner, you will watch videos and during some of the time you will do simple tasks involving tapping your finger or doing simple puzzles, or reading and arithmetic, or learning and memory, or looking at pictures and figuring out if two people seem to have the same feeling. There will be one session in the scanner.

We will also ask you to give us a sample of your spit (saliva) and have a nurse take a small amount of blood from your arm to study how your genes (family characteristics that you get from your parents) affect how you do these tasks and how you act.

How long will I be in the study?

You will be in the study for this phase two days for about 3-4 hours at our laboratory at University of Cape Town (including breakfast, a snack, and lunch) and one visit involving about 45-50 minutes in the scanner and 1 hour of training and assessment outside the scanner at Tygerberg Hospital.

Will the study help me?

You will not benefit from being in this study; however information from this study may help other people in the future better understand how the brain performs different tasks and whether diet, alcohol, smoking, or drug exposure during pregnancy affects how the brain performs.

While taking part in this phase of the research study, we will give you a small gift and a photo taken of your brain at the end of the scanning. We will provide breakfast, a snack, and lunch each time you come to our laboratory at University of Cape Town or Tygerberg Hospital.

Will anything bad happen to me?

There are no risks from being in the scanner at Tygerberg Hospital or from any of the tasks we do with you in our laboratory at University of Cape Town. The risk of drawing blood include some temporary discomfort swelling and rarely infection. These risks will be small because the blood will be taken by a trained person (nurse/technician). Some people feel nervous in a small closed space, such as when they are in the scanner. You will practice what it is like in a pretend scanner beforehand. We will give you earplugs or headphones so that the loud banging of the scanner will not bother you. There is a button you can press to ask questions or stop the scan at anytime. You can see out of the scanner at all times, and we will not start until you are comfortable with the set-up.

Do my parents or guardians know about this? (If applicable)

This study information has been given to your parents/guardian and they said that you could take part in the study. You can talk this over with them before you decide.

Research Related Injuries

In the event that this research related activity results in an injury, treatment will be made available including first aid, emergency treatment, and follow-up care as needed. Care for such will be billed in the ordinary manner to you or your insurance company/South African public assistance. No reimbursement, compensation, or free medical care is offered by Wayne State University or the University of Cape Town. If you think that you have suffered a research related injury, please contact the Cape Town PI (Dr. Christopher Molteno) right away at 021-406-6291.

What about confidentiality?

Every reasonable effort will be made to keep your records (medical or other) and/or your information confidential, however we do have to let some people look at your study records.

We will keep your records private unless we are required by law to share any information. The law says we have to tell someone if you might hurt yourself or someone else. The study doctor can use the study results as long as you cannot be identified. The following information must be released/reported to the appropriate authorities if at any time during the study there is concern that:

- child abuse or elder abuse has possibly occurred,
- you disclose illegal criminal activities, illegal substance abuse or violence

What if I have any questions?

For questions about the study please call Dr. Christopher Molteno at 021-406-6291. If you have questions or concerns about your rights as a research participant, the Chair of the Institutional Review Board can be contacted at 001-313-577-1628 or you can contact the Chair of the University of Cape Town Research Ethics Committee at 021-406-6338.

Do I have to be in the study?

You don't have to be in this study if you don't want to or you can stop being in the study at any time. Please discuss your decision with your parents and researcher. No one will be angry if you decide to stop being in the study.

AGREEMENT TO BE IN THE STUDY
Your signature below means that you have read the above information about the study and have had a chance to ask questions to help you understand what you will do in this study. Your signature also means that you have been told that you can change your mind later and withdraw if you want to. By signing this assent form you are not giving up any of your legal rights. You will be given a copy of this form.

_____ _____
Signature of Participant (13 yrs & older) Date

_____
Printed name of Participant (13 yrs & older)

_____ _____
**Signature of Witness (When applicable) Date

_____
Printed Name of Witness

_____ _____ _____
Signature of Person who explained this form Date

_____
Printed Name of Person who explained form

** Use when participant has had consent form read to them (i.e., illiterate, legally blind, translated into foreign language).

APPENDIX F

Informed Consent: Afrikaans

Toestemming deur Ouer/Ingeligte Toestemming tot Navorsing
Titel van Studie: Neurale Basis van Oogknip Kondisionering in FASD

Jy en u kind _____ word uitgenooi om deel te neem aan ons navorsingstudie. Lees asseblief hierdie vorm deur en vra vir ons enige vrae wat u het voordat u instem om in die studie te wees. Die mense wat hierdie studie doen is dokters en wetenskaplikes aan die Universiteit van Kaapstad se Fakulteit Gesondheidswetenskappe in Suid-Afrika en Wayne State Universiteit Mediese Skool in die Verenigde State: Ernesta Meintjes, Ph.D., en Christopher Molteno, M.D., van die Universiteit van Kaapstad, en Sandra W. Jacobson, PhD., en Joseph L. Jacobson, Ph.D., van Wayne State Universiteit in die Verenigde State. Die studie word geborg deur die Nasionale Instituut oor Alkohol Misbruik en Alkoholisme in die Verenigde State en die Departement van Wetenskap en Tegnologie en die Nasionale Navorsingsraad van Suid-Afrika.

Doel van die Studie: In hierdie studie wil ons leer hoe sommige aspekte van hoe ‘n kind dink en optree verskillend is wanneer ‘n ma drink en/of rook tydens swangerskap, en of gene (eienskappe wat jy van u ouers erf) dit meer of minder waarskynlik maak dat die kind hierdie verskille sal wys. Bykomende doelwitte van die studie is om te ondersoek die mate waartoe toetse wat gedoen is tydens die babajare en tydens 5-jarige ouderdom die kind se prestasie op 8-14-jarige ouderdom voorspel. Om u te help met u besluit om aan die studie deel te neem of nie, het ‘n projek personeellid die risiko’s en voordele met u bespreek. Hierdie toestemmingsvorm is ‘n opsomming van die inligting wat aan u gegee is deur die projek personeellid tydens hierdie ingligte toestemmingsproses.

Hierdie studie sal nuwe metodes wat MRI neurobeelding genoem word, gebruik om beter te verstaan hoe die drink van alkohol en rook tydens swangerskap ‘n kind se ontwikkeling kan affekteer. In neurobeelding lê die kind in ‘n skandeerder wat magnete gebruik om prentjies van die brein te neem. In hierdie deel van die studie sal ons prentjies neem met die nuwe skandeerder by Tygerberg Hospitaal terwyl u kind stil lê en na ‘n video kyk, en sekere eenvoudige take doen waartydens hy/sy sy/haar vingers moet tik, moet aandag gee, en sekere goed moet onthou.

Studie Prosedures: Indien jy instem om u kind aan hierdie studie te laat deelneem, sal ons u en u kind na ons laboratorium bring by die Universiteit van Kaapstad (UK) vir 2-3 besoeke wat elk ongeveer 4 ure sal duur, en na Tygerberg Hospitaal vir 1 - 2 besoeke wat elk omtrent 3-4 ure in totaal behoort te duur.

- Tydens die besoeke aan die Universiteit van Kaapstad sal u kind eenvoudige take doen waartydens hy/sy sy/haar vingers moet tik, moet aandag gee, dinge probeer onthou, somme doen, betekenis van woorde moet gee, legkaarte doen, doolhowe doen, en sirkels teken (Wechsler Intelligensie Skaal vir Kinders; vingertik taak; Sirkel Teken Taak, tyd en frekwensie persepsie take; Californieë Verbale Leer Toets).
- Ons sal u kind se visie toets / toets hoe goed u kind kan sien.
- In een taak sal u kind ‘n spesiale helm opsit. Terwyl u kind na ‘n video kyk, sal ‘n blasie lug uit die helm kom wat sal maak dat u kind sy/haar oog knip terwyl hy/sy ‘n geluid hoor.
- Ons sal u kind weeg en meet en ‘n foto neem om te kyk vir gesigskenmerke wat dikwels verbandhou met alkohol blootstelling tydens swangerskap.

- Tydens hierdie besoek sal ons u ook 'n paar vrae vra oor u kind se gedrag, vermoë om aandag te gee (Steurende Gedragsteuring Toets), daaglikse aktiwiteite (Kindergedrag Vraelys), skool en gesondheidsgeskiedenis, sowel as enige medikasie wat hy/sy neem.
- Ons sal u vra om ons op hoogte te bring oor stresvolle ervarings in u daaglikse lewe gedurende die afgelope jaar (Lewensgebeurtenis Skaal), u huidige drank- en dwelmgebruik en rookpatrone, probleme wat jy as ‘n kind mag gehad het om aandag te gee (Barkley-Murphy AAHV Skaal), en stresvolle gevoelens wat jy ervaar, insluitend hartseer, angs, en bekommernis (Beck Depressie Vraelys, Gestruktureerde Kliniese Onderhoud vir DSM-IV).
- Aan die einde van die eerste besoek sal ons navorsingsbestuurder en verpleegster u en u kind neem na 'n nabye kliniek, waar 'n tegnikus/verpleegster ‘n 5cc bloedmonster (ongeveer 1 teelepel) van u kind se aar sal neem om te toets vir lood en ystertekort anemie. Omtrent 10 cc bloed (ongeveer 2 teelepels) sal geneem word van u en u kind om genetiese verskille te bestudeer wat verband hou met verskille in alkohol metabolisme, depressie, gehegtheid, of die kind se aandag en ontwikkeling. Hierdie monsters sal gestoor word en gebruik word vir toekomstige genetiese analises.
- Tydens die eerste besoek aan Tygerberg, sal u kind eers die vingertik- en aandag en geheuetake oefen wat hy/sy op ‘n rekenaar sal doen terwyl hy/sy in die skandeerder lê. Gedurende die neurobeelding sal u kind op ‘n sagte plastiek bed lê wat in die skandeerder inskuif. Ons sal hom/haar vra om so stil as moontlik te lê terwyl die prentjies geneem word. Die afneem van hierdie prentjies (foto’s) van die brein maak nie seer nie en word elke dag deur baie mense in die hospitaal gebruik. Tydens die tweede besoek aan Tygerberg sal ons assistent weer die vingertik- en aandag/geheuetake met u kind oefen en met hom/haar hersien die lugblasie leertaak wat hy/sy in ons laboratorium by UK gedoen het. Tydens die skandeerbesoeke sal ons vir u kind spesiale brille wys wat hy/sy sal dra in die skandeerder. Ons sal vir u kind sê dat hy/sy die lugblasie sal voel en ‘n soort geluid sal hoor terwyl hy/sy na ‘n video kyk en dat ons vir hom/haar ‘n paar vrae oor die video sal vra aan die einde van die skandering. Vir 'n gedeelte van die tyd in die skandeerder sal u kind na videos kyk, en vir 'n gedeelte van die tyd sal hy of sy die vingertik en ander take doen wat ons geoefen het voordat hy/sy die skandeerder binnegegaan het. Daar sal gedurende elk van die besoeke aan Tygerberg twee sessies in die skandeerder wees – albei op dieselfde dag - een in die oggend en een na middagete. Ons sal vir u en u kind middagete gee terwyl julle by Tygerberg is. Elke sessie in die skandeerder sal niks langer as 45-60 minute duur nie. Kinders met enige van die volgende toestande mag nie 'n MRI onderneem nie: ingeplante mediese toestelle soos aneurisme knippies in die brein, hart pasaangeërs, en binne-oor inplantings; loodgebasseerde tattoeërmerke, of stukkies metaal naby aan of binne-in 'n belangrike orgaan (soos die oog); engtevrees of die vrees om binne 'n klein ruimte beperk te wees.

Voordele: Daar mag dalk geen direkte voordele vir u wees nie, maar inligting van hierdie studie mag ander mense help, nou of in die toekoms. Jy sal inligting ontvang oor u kind se huidige ontwikkeling op hierdie ouderdom. Ons sal die bevindings van hierdie studie slegs gebruik vir navorsingsdoeleindes. Indien 'n ernstige probleem egter gevind word, sal ons vir u sê en u kind verwys na 'n dokter en/of iemand wat kan help, indien jy dit wil hê. Indien u kind aan enige ernstige siekte ly, sal ons u na die Rooikruis Kinderhospitaal stuur. Geen inligting oor u kind sal uitgegee word aan enige dokters, hospitale, of skole tensy jy dit skriftelik versoek en toelaat nie.

Risiko’s: Geen prosedures wat ons by UK of Tygerberg sal gebruik is gevaarlik vir u of u kind nie. Die risiko’s van bloedtrek sluit soms ‘n bietjie tydelike ongemak of swelling in, en

by uitsondering, infeksie. Hierdie risiko's sal verminder word omdat die prosedure deur 'n opgeleide flebotomis (verpleegster/tegnikus wat spesiaal opgelei is om bloed te trek) gedoen sal word. Ons sal begin deur u en u kind aan die projekpersoneel bekend te stel en sal vir julle albei ontbyt gee elke dag voordat die toetse begin. Terwyl al u kind se toetse gedoen word sal jy in 'n vertrek naby u kind wees en jy sal saam met u kind wees tydens die fisiese ondersoek en wanneer die bloed getrek word. Tydens die MRI neurobeelding mag sekere voorwerpe soos horlosies, kredietkaarte, haarknippies en skryfpenne beskadig word deur die MRI skandeerder of deur die magnet weggetrek word van die liggaam. Om hierdie redes sal ons u kind vra om hierdie voorwerpe af te haal voordat hy/sy die skandeerder binnegaan. Wanneer die skandeerder die prentjies neem, mag die bed skud, en u kind sal harde kapgeluide hoor. Hy/sy sal oorpluisies en oorfone gegee word om sy/haar ore te beskerm. Sommige mense voel ook senuweeagtig in 'n klein beperkte spasie soos wanneer hulle in die skandeerder is. U kind sal te alle tye by die skandeerder kan uitsien, en ons sal nie begin voordat hy/sy nie vir ons sê dat hy/sy gemaklik is nie. Hy/sy sal ook enige tyd kan stop deur 'n bal te druk wat hy/sy in een hand sal vashou en hy/sy sal met ons kan praat deur 'n interkom wat in die skandeerder ingebou is. Sover almal weet is daar geen skadelike langtermyn effekte as gevolg van die magnetise velde wat in hierdie studie gebruik word nie. Daar is baie min kans dat enigiets wat jy vir ons vertel vir ander mense buite die studie gesê sal word en ons sal alles doen wat ons kan om hierdie inligting geheim te hou behalwe, soos hieronder beskryf, indien daar tekens is van kindermishandeling of –verwaarlosing sal dit egter aan die toepaslike owerhede gerapporteer word, soos deur die wet vereis. Ons mag ook ander onwettige aktiwiteite rapporteer wat aan ons tydens die besoek bekend gemaak word.

Navorsingsverwante Beserings: Indien jy of u kind tydens die studie beseer word sal jy behandeling ontvang wat insluit eerstehulp, noodbehandeling en opvolg-sorg soos benodig. Geen vergoeding, terugbetaling, of gratis mediese sorg word verskaf deur Wayne State Universiteit of die Universiteit van Kaapstad nie. Laat die navorser onmiddelik weet as jy dink dat u kind 'n navorsingsverwante besering opgedoen het.

Studiekostes: Daar sal geen koste wees vir u of u kind om aan hierdie navorsing deel te neem nie, en jy en u kind sal deur ons bestuurder vervoer word na die laboratorium by UK en Tygerberg Hospitaal.

Vergoeding: Vir u deelname aan hierdie navorsingstudie sal ons u R150 ($25) gee vir elke besoek en 'n foto van u kind, en vir u kind sal ons 'n klein geskenkie gee. Ons sal ook vir u en u kind ontbyt en middagete gee elke keer as julle na UK of Tygerberg Hospitaal toe kom.

Vertroulikheid: Ons sal alle inligting wat ons tydens die studie versamel oor u en u kind geheim hou tot die mate waartoe die wet dit toelaat. Hierdie inligting sal nie gebruik word op enige manier wat enigiemand anders sal toelaat om te weet wat jy of u kind vir ons vertel het nie, behalwe dat tekens van kindermishandeling of –verwaarlosing aan die toepaslike owerhede gerapporteer sal word, soos deur die wet vereis. Jy en u kind sal in ons navorsingsrekords slegs deur 'n kodenommer geïdentifiseer word en julle name sal nie op die rekords verskyn nie. Ons sal nie inligting uitgee wat u of u kind by name noem nie tensy jy ons skriftelik toestemming gee, maar u rekords mag hersien word deur die studie borg, die Menslike Navorsings Komitee by Wayne State Universiteit, of regeringsliggame met toepaslike regulatoriese oorsig. Die lys wat deelnemers se identifikasienommers met hul name verbind sal gestoor word in geslote kabinette in die navorsingslaboratorium. Slegs personeellede wat nodig het om u telefonies of persoonlik te kontak sal toegelaat word om na hierdie leêrs te kyk. Inligting vanaf hierdie studie, insluitend foto's en videos mag aangebied word by wetenskaplike vergaderings of joernale of vir opleidingsdoeleindes gebruik word, maar u en u kind se name sal geheim gehou word.

Vrywillige Deelname/Onttrekking: Deelname aan hierdie studie is vrywillig. Jy mag besluit om u kind aan die studie te laat deelneem en later van besluit verander en die studie los. Jy en u kind is ook vry om enige vrae nie te beantwoord nie, of om enige taak te stop voordat dit klaar is. Onttrekking aan die studie sal geen probleme vir u of u kind veroorsaak nie. Die navorser of die borg mag u kind se deelname aan hierdie studie stop sonder dat jy daartoe instem.

Vrae: Indien jy enige vrae het nou of in die toekoms, kan jy Drs. Ernesta Meintjes of Christopher Molteno kontak by 021-406-6291 of Dr. Sandra W. Jacobson by 091-313-993-5454. Indien jy enige vrae of bekommernisse het oor u of u kind se regte as 'n deelnemer aan die navorsing, kan jy die voorsitters kontak van die Universiteit van Kaapstad Navorsings-Etiek Komitee (021 406-6338) of die Wayne State Universiteit se Menslike Navorsings Komitees (001-313-577-1628).

Toestemming om aan 'n Navorsingstudie deel te neem: Om vrywilliglik in te stem om u kind te laat deelneem aan hierdie studie, moet jy op die lyn hieronder teken. Indien jy besluit om met u kind deel te neem, mag jy of u kind enige tyd stop. Jy gee nie enige van u of u kind se regte op deur hierdie vorm te teken nie. U handtekening wys dat jy hierdie hele toestemmingsvorm gelees het of dat dit aan u voorgelees is, insluitend die risiko's en voordele, en dat ons al u vrae beantwoord het. Ons sal vir u 'n kopie van hierdie toestemmingsvorm gee om huis toe te neem.

_____	_____
Handtekening van Ouer of Wetlik Gemagtigde Voog	Datum
_____	_____
Naam in drukskrif van Ouer of Wetlik Gemagtigde Voog	Tyd
_____	_____
Mondelinge Instemming (kinders van ouderdom 7-12)	Datum
_____	_____
**Handtekening van Getuie (wanneer van toepassing)	Datum
_____	_____
Naam van Getuie in drukskrif	Tyd
_____	_____
Handtekening van Persoon wat Toestemming neem	Datum
_____	_____
Naam in drukskrif van Persoon wat Toestemming neem	Tyd

**Gebruik wanneer toestemmingsvorm aan ouer voorgelees is (bv. wanneer ongeletterd, wetlik blind, vertaal in 'n vreemde taal).

APPENDIX G

Informed Assent: Afrikaans

Dokumentasie van Adolessente Instemming Form (Ouderdomme 13-17)
Titel: Neurale Basis van Oogknip Kondisionering in FASD
Studie Navorsers: Sandra W. Jacobson, Joseph L. Jacobson, Christopher D. Molteno, Ernesta M. Meintjes

Hoekom is ek hier?

Hierdie is ‘n navorsingstudie. Slegs mense wat kies om deel te neem word ingesluit by navorsingstudies. Jy word gevra om deel te neem aan hierdie studie omdat jy een van ‘n groot groep kinders is wat al aan hierdie studie deelneem vandat jy gebore is en het deel geneem aan besoeke toe jy ‘n baba was en toe jy 5 jaar oud was. Ons nooi jou uit om deel te neem aan die volgende fase van hierdie studie. Vat asseblief jou tyd om ‘n besluit te neem. Gesels met jou familie daaroor en maak seker om vrae te vra oor enige iets wat jy nie verstaan nie.

Hoekom doen hulle hierdie studie?

Hierdie studie word gedoen om uit te vind hoe kinders dinge leer en onthou en hoe hulle eenvoudige probleme oplos. Ons probeer om te verstaan hoe en of dieet, alkohol, rook, en blootstelling aan dwelms gedurende swangerskap ontwikkeling kan beïnvloed. Ons bestudeer kinders op verskillende ouderdomme met verskillende take om te sien hoe hulle groei en ontwikkel.

Wat sal met my gebeur?

Hier by die Universiteit van Kaapstad, sal ons bestudeer wat gebeur wanneer jy 'n blasie lug in jou oog voel. Jy sal in 'n stoel sit met 'n spesiale helm op jou kop en jy sal 'n video kyk. Elke nou en dan, sal jy 'n lugblasie uit die helm voel kom en soms sal jy 'n geluid hoor. Jy sal ook eenvoudige take doen waartydens jy jou vinger moet tik, prentjies benoem, lyste met woorde leer, lees en somme doen, legkaarte doen, doolhowe doen, geheue en rekenaar take doen en take oor hoe ander mense voel en 'n ander persoon se oogpunt insien. Ons sal jou ook weeg, meet hoe lank jy is, 'n foto neem en kyk hoe goed jy kan sien. Jy sal vanoggend hier spandeer en sal terug kom na die Universiteit van Kaapstad toe op 'n ander dag om die lugblasie taak en die ander take wat ek genoem het te doen.

Die tweede deel van die studie behels neurobeelding, wat ‘n nuwe manier is om van die brein te leer deur prentjies te neem van die brein. Hierdie prentjies kan ons help om beter te verstaan hoe die brein werk. Vir hierdie deel van die studie sal ons jou en jou ma na Tygerberg Hospitaal toe vervoer. Gedurende die neurobeelding, sal jy op ‘n plastiek bed lê wat in ‘n groot masjien inskuif wat ‘n skandeerder genoem word. Ons sal jou vra om so stil as moontlik te lê terwyl die prentjies geneem word. Die afneem van hierdie prentjies (foto’s) van die brein maak nie seer nie en word elke dag deur baie mense in die hospitaal gebruik. Vir 'n gedeelte van die tyd in die skandeerder sal jy na videos kyk, en vir 'n gedeelte van die tyd sal jy eenvoudige take doen waartydens jy jou vinger moet tik of eenvoudige legkaarte doen, of lees en somme doen, of dinge probeer onthou, of na prentjies kyk en probeer uitwerk of twee mense dieselfde gevoelens voel. Daar sal een sessie in die skandeerder wees.

Ons sal jou ook vra om vir ons ‘n bietjie van jou spoeg (speeksel) te gee en 'n verpleegster sal 'n klein hoeveelheid bloed van jou arm neem om te bestudeer hoe jou gene (familie eienskappe wat jy van jou ouers af kry) beïnvloed hoe jy hierdie take doen en hoe jy optree.

Hoe lank sal ek in die studie wees?

Jy sal twee dae in die studie wees vir hierdie fase, vir ongeveer 3-4 ure by ons laboratorium by die Universiteit van Kaapstad (insluitend ontbyt, 'n peuselhappie, en middagete) en een besoek van

sowat 45-50 minute in die skandeerder en 1 uur van opleiding en assessering buite die skandeerder by Tygerberg Hospitaal.

Sal die studie my help?

Jy sal nie daarby baat om in hierdie studie te wees nie, maar inligting uit hierdie studie kan ander mense in die toekoms help om beter te verstaan hoe die brein verskillende take verrig en of dieet, alkohol, rook, of blootstelling aan dwelms gedurende swangerskap beïnvloed hoe die brein werk.

Terwyl jy in hierdie fase van die navorsing deel neem, sal ons vir jou 'n klein geskenkie gee en 'n foto wat van jou brein geneem is aan die einde van die skandering. Ons sal ontbyt, 'n peuselhappie, en middagete voorsien elke keer as jy na ons laboratorium toe kom by die Universiteit van Kaapstad of Tygerberg Hospitaal.

Sal enige iets sleg met my gebeur?

Daar is geen risiko's verbonde aan om in die skandeerder by Tygerberg Hospitaal te wees nie, of enige van die take wat ons met jou doen in ons laboratorium aan die Universiteit van Kaapstad nie. Die risiko van bloed trek sluit in 'n bietjie tydelike ongemak, swelling en selde infeksie. Hierdie risiko's sal klein wees, want die bloed sal geneem word deur 'n opgeleide persoon (verpleegster/tegnikus).

Sommige mense voel senuweeagtig in ‘n klein beperkte spasie, soos wanneer hulle in die skandeerder is. Jy sal voor die tyd oefen hoe dit gaan voel in 'n oefen skandeerder. Ons sal vir jou oorpluisies of oorfone gee sodat die harde geraas van die skandeerder jou nie pla nie. Daar is 'n knoppie wat jy kan druk om vrae te vra of die skandering te stop op enige tyd. Jy kan te alle tye by die skandeerder uitsien, en ons sal nie begin voordat jy gemaklik is nie.

Weet my ouers of voogde hiervan? (Indien van toepassing)

Hierdie studie inligting is aan jou ouers/voogde gegee en hulle het gesê dat jy kan deel neem aan die studie. Jy kan met hulle hieroor praat voordat jy besluit.

Navorsingsverwante Beserings

Indien hierdie navorsingsverwante aktiwiteite lei tot 'n besering, sal behandeling beskikbaar gemaak word, insluitend eerstehulp, noodbehandeling, en opvolg-sorg soos benodig. Sulke sorg sal betaalbaar wees in die gewone manier deur jou of jou versekerings maatskappy/Suid-Afrikaanse openbare hulp. Geen terugbetaling, vergoeding, of gratis mediese sorg word verskaf deur Wayne State Universiteit of die Universiteit van Kaapstad nie. As jy dink dat jy 'n navorsingsverwante besering opgedoen het, kontak asseblief dadelik die Kaapstad hoofnavorser (Dr Christopher Molteno) by 021-406-6291.

Wat van vertroulikheid?

Elke redelike poging sal aangewend word om jou rekords (mediese of ander) en/of jou inligting konfidensieel te hou, maar ons moet sommige mense na jou studie rekords laat kyk. Ons sal jou rekords geheim hou tensy ons deur die wet vereis word om enige inligting te deel. Die wet sê dat ons iemand moet vertel as jy dalk jouself of iemand anders mag seer maak. Die studie dokter kan die studie resultate gebruik so lank as wat jy nie geïdentifiseer kan word nie.

Die volgende inligting moet vrygelaat word/gerapporteer word aan die toepaslike owerhede indien daar te eniger tyd gedurende die studie kommer is dat:

- kindermisbruik of mishandeling van bejaardes moontlik plaasgevind het,
- jy onwettige kriminele aktiwiteite openbaar, onwettige drank-en dwelmmisbruik, of geweld

Wat as ek enige vrae het?

Vir vrae oor die studie kontak asseblief vir Dr Christopher Molteno by 021-406-6291. Indien jy enige vrae of bekommernisse het oor jou regte as 'n deelnemer aan die navorsing, kan die voorsitter van die Wayne State Universiteit se Menslike Navorsings Komitee gekontak word by 001-313-577-1628 of jy kan die voorsitter van die Universiteit van Kaapstad Navorsings-Etiek Komitee kontak by 021-406-6338.

Moet ek in die studie wees?

Jy hoef nie in hierdie studie te wees as jy nie wil nie of jy kan ophou om in die studie te wees op enige stadium. Bespreek asseblief jou besluit met jou ouers en navorser. Niemand sal kwaad wees as jy besluit om op te hou om in die studie te wees nie.

INSTEMMING OM IN DIE STUDIE TE WEES

Jou handtekening hieronder beteken dat jy die bogenoemde inligting oor die studie gelees het, en dat jy kans gekry het om vrae te vra om jou te help verstaan wat jy in hierdie studie gaan doen. Jou handtekening beteken ook dat daar aan jou verduidelik is dat jy later van besluit mag verander en onttrek as jy wil. Jy gee nie enige van jou regte op deur hierdie vorm te teken nie. Ons sal vir jou 'n kopie van hierdie toestemmingsvorm gee.

_____ _____

Handtekening van Deelnemer (13 j. & ouer) Datum

_____

Naam van Deelnemer in drukskrif (13 j. & ouer)

_____ _____

**Handtekening van Getuie (Wanneer van toepassing) Datum

_____

Naam van Getuie in drukskrif

_____ _____

Handtekening van Persoon wat vorm verduidelik het Datum

_____

Naam van Persoon wat vorm verduidelik het

**Gebruik wanneer toestemmingsvorm aan deelnemer voorgelees is (bv. wanneer ongeletterd, wetlik blind, vertaal in 'n vreemde taal).

APPENDIX H

Cape Universities Brain Imaging Centre (CUBIC) MRI Screening Form

Cape Universities Brain Imaging Centre (CUBIC)

MRI SCREENING FORM

Patient /Participant Information:

Name	Radiographer
Date of Birth	Ward/Clinic (*if applicable*)
Weight	Folder number/Project name

The following information is very important to ensure your safety and to prevent any interference during the MR procedure.

Please answer the following questions (mark with an X):

	Yes	No	Don't know
Pacemaker			
Aneurysm Clip(s)			
Artificial Heart valve			
Vena Cava Filter			
Prosthesis (e.g. eye, breast, hip etc.)			
Shrapnel in eye or body			
Neurostimulator			
Cochlear implant (ear) or Hearing Aid			
? Any other implants (e.g. Screws, plates, joint replacements)			
? Pregnant			
? Previous MRI Investigation with Intravenous Contrast			
Is there any other device implanted or are there any other ailments that you think that we should be aware of?			
In case of Intravenous Injections:			
? Diabetic			
? Renal Impairment			
? Asthma/Respiratory disease			
? Allergies			

I hereby acknowledge that the potential risks of the examination have been explained to me and that during the course of the investigation it may be necessary for the intravenous injection of a contrast agent.

Attention: It is the policy of this institution not to discuss results of the MR investigation with the patients for ethical reasons. All enquiries in this regard should be directed to the referring physician.

Signature: **Date:**

Cape Universities Brain Imaging Centre
Fisan Building, Faculty of Health Sciences, University of Stellenbosch, Tygerberg, 7505
Tel: 27-21-938-9646 Fax: 27-21-938-9728 www.sun.ac.za/cubic

APPENDIX I

Mock Scanner Protocol

English Script

Introduction to mock scanner. The examiner read the following script to introduce the mock scanner.

"Today you are going to go into a machine that looks like this, it's just a bit bigger. You are going to lie in the tunnel, but only your head is going to go inside. The big machine takes pictures of the inside of your body. If you lie with your stomach in the big machine, it will take a picture of the inside of your stomach (show picture). If you lie with your foot in the big machine, it will take a picture of the inside of your foot (show picture). If you lie with your head in the big machine, it will take a picture of your brain (show picture). Because you are going to be lying with your head inside the big machine, we are going to take pictures of your brain today. It doesn't hurt you at all, it is just like a camera that takes photos. Have you ever had a photo taken before? It did not hurt you hey? Just like a camera, if you move during a picture it is going to be blurry. So you need to lie very still when the machine is busy taking pictures. You will know that the machine is busy taking pictures when it is very noisy. Just now we will give you a chance to lie in a practice machine and listen to what the sounds are like. When you are in the big machine and you hear the noises you will need to lie very still, because it is taking pictures. When we are all finished today, you will get a picture of your brain!

When you are in the big machine you will get to wear earphones so that you can hear the movie. We will also be talking to you the whole time--We will remind you to lie still. You will lie on your back and watch the movie and then you will play some games. You will have something like this (show computer mouse) on your stomach to help you play the games. We will practice the games here before you go into the big machine. The games that we practice here will be shorter than the games you play when you are in the big machine. After we practice the games, we will practice staying still in a pretend machine."

Practice mock scan. After completing the procedure for practicing the behavioural component of the tasks, the examiner then took each participant through a practice session in the mock scanner:

"Would you like to feel what it is like to lie inside the machine? First they will give you ear plugs and then you will put some earphones on. You are going to lie on your back and have a thing like this (use computer mouse) that will be on your tummy and you are

going to have to press the buttons like we practiced just now. You will also have a thing like this above your head. We put this thing on because it has a small mirror inside it. The mirror will show you what is behind you and will let you see the movie. Can you see the picture on the wall now?

While you are in the big machine we will talk to you. We will ask you questions and then you must answer 'yes' or 'no' but without moving your head. Let's practice. Is your name___? Are you ____ years old? Are you lying still? Remember, you must try not to talk in the big machine. If you talk your head moves and then the picture is blurry.

(Examiner to encourage the child to respond without moving their head)

You are going to lie in the big machine and you will hear different noises. Remember, when you hear the loud noises it means that the machine is taking pictures and that you will need to lie very still. Let's listen to some of the noises."

(Examiner to play scanner noises from Laptop. While the noises are playing reassure the child that the noises don't hurt them and remind them to lie still in the big machine.)

Afrikaans Script

Introduction to mock scanner. The examiner read the following script to introduce the mock scanner.

"Vandag gaan jy in 'n groot masjien in wat lyk soos hierdie, maar wat net 'n bietjie groter is. Jy gaan in 'n tonnel lê, maar net jou kop gaan binne in. Die groot masjien neem foto's van die binnekant van jou lyf. As jy met jou maag binne die groot masjien lê, sal dit 'n foto van die binnekant van jou maag neem (show picture). As jy met jou voet in die groot masjien lê, sal dit 'n foto van die binnekant van jou voet neem (show picture). As jy met jou kop in die groot masjien lê, sal dit 'n foto van jou brein neem (show picture). Omdat jy vandag met jou kop in die groot masjien gaan lê, gaan ons foto's van jou brein neem. Dit maak glad nie seer nie, dis net soos 'n kamera wat foto's neem. Het iemand al ooit 'n foto van jou geneem? Dit was nie seer nie, nê? Net soos 'n kamera, as jy beweeg trewyl die foto geneem word, gaan dit onduidelik uitkom. So jy moet baie stil lê terwyl die masjien foto's neem. Jy sal weet dat die masjien foto's neem wanneer dit 'n groot geraas maak. Ons sal jou nou nou kans gee om in die oefen masjien te lê en te hoor hoe die geluide klink. Wanneer jy in die groot masjien is, en jy hoor die geluide, gaan jy baie stil moet lê want dan is dit besig om foto's te neem. Wanneer ons heeltemal klaar maak vandag, sal jy 'n foto van jou brein kry!

Wanneer jy in die groot masjien is, sal jy oorfone dra sodat jy die fliek kan hoor. Ons sal ook die heeltyd met jou gesels – Ons sal jou herinner om stil te lê. Jy gaan op jou rug lê en fliek kyk en dan gaan jy ‘n paar speletjies speel. Jy sal iets soos hierdie hê (show computer mouse) wat op jou maag gaan lê om jou te help om die speletjies te speel. Ons sal die speletjies hier oefen voordat jy in die groot masjien ingaan. Die speletjies wat ons hier gaan oefen sal korter wees as die speletjies wat jy gaan speel as jy in die groot masjien is. Nadat ons die speletjies geoefen het, sal ons oefen hoe om stil te lê in die groot masjien.”

Practice mock scan. After completing the procedure for practicing the behavioural component of the tasks, the examiner then took each participant through a practice session in the mock scanner:

“Wil jy voel hoe dit voel om in die masjien te lê? Eerste sal hulle vir jou oorpluisies gee en dan sal jy oorfone op jou ore sit. Jy gaan op jou rug lê en iets soos hierdie hê (use computer mouse) wat op jou maag lê en dan gaan jy die knoppies moet druk net soos wat ons nou geoefen het. Jy sal ook iets soos hierdie bo jou kop hê. Ons sit hierdie ding op, want hy het ‘n klein spïeeltjie aan die binnekant. Die spïeeltjie sal jou help om te sien wat agter jou is en sal jou ook die fliek kan laat sien. Kan jy nou die prentjie op die muur sien?

Terwyl jy in die groot masjien is sal ons met jou gesels. Ons sal vir jou vrae vra en dan sal jy ‘ja’ of ‘nee’ moet antwoord, maar sonder om jou kop te beweeg. Kom ons oefen. Is jou naam___? Is jy ____ jaar oud? Lê jy stil? Onthou, jy moet probeer om andersins nie te praat in die groot masjien nie. As jy praat, dan beweeg jou kop en die foto kom onduidelik uit.

(Examiner to encourage the child to respond without moving their head)

Jy gaan in die groot masjien lê en dan sal jy verskillende geluide hoor. Onthou, wanneer jy die harde geluide hoor beteken dit dat die masjien besig is om foto’s te neem en dat jy baie stil moet lê. Luister na van die geluide wat jy gaan hoor.”

(Examiner to play scanner noises from Laptop. While the noises are playing reassure the child that the noises don’t hurt them and remind them to lie still in the big machine.)

APPENDIX J

Cape Town Longitudinal Cohort 11-Year Neuroimaging Protocol

The neuroimaging tasks included in Chapters 3 and 4 were administered as part of a larger imaging protocol administered during the 11-year assessment of the Cape Town Longitudinal Cohort. Figure J.1 illustrates the protocol followed for each of the 78 children who participated in the functional neuroimaging assessment. Data acquired during 1 and 2 were included in Chapter 3, whereas data acquired during 1, 4, 5 and 6 were included in Chapter 4. Data acquired during 3 and 7 were not included in this doctoral dissertation.

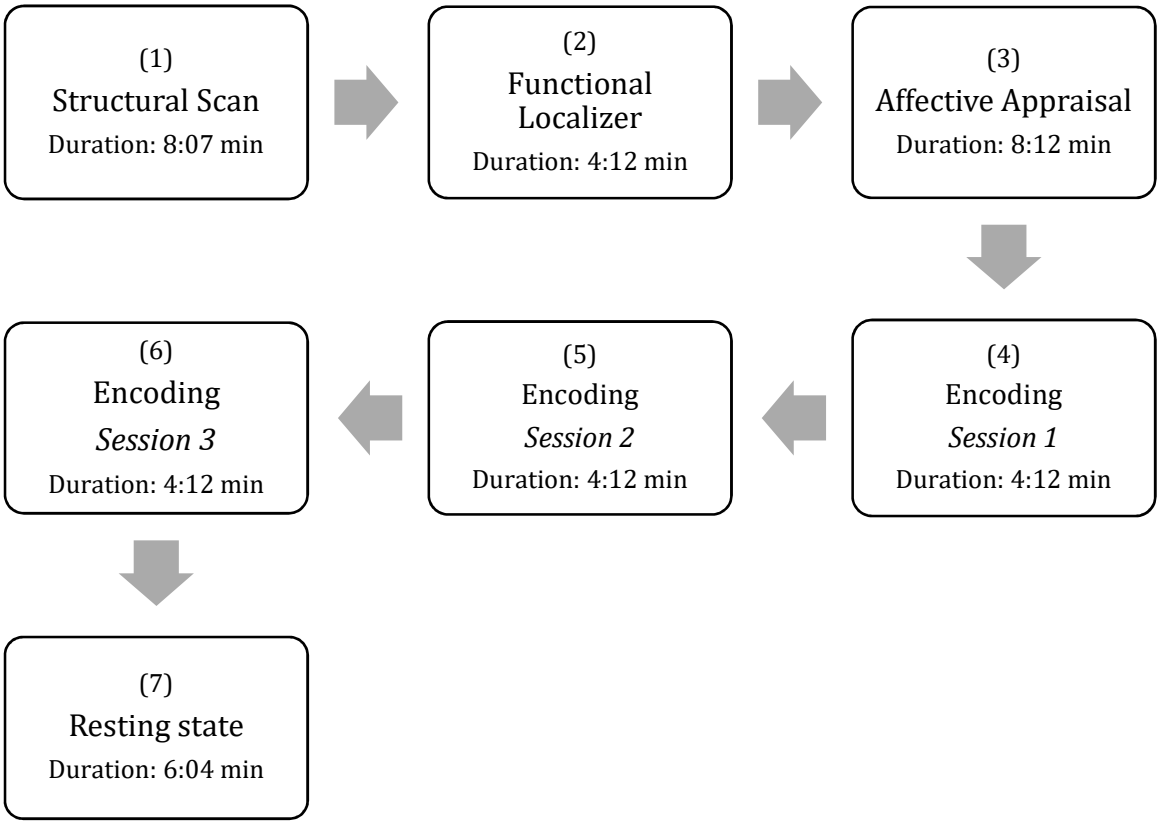

Figure J.1. Schematic showing the full neuroimaging procedure used in the Cape Town Longitudinal Cohort.

APPENDIX K

Functional Localizer Task Protocol

English Script

Practice functional localizer task. The examiner reads the following script to introduce the functional localizer task.

"After you have finished watching the movie in the big machine, we are going to show you some pictures. I want you to lie very still and look at the pictures carefully. This is going to be the first game you will play in the big machine. Do you have any questions?

Let's practice."

Functional localizer task. The examiner reads the following script via the intercom system before administering the functional localizer task.

"Hi (name). Great job! Remember, it is important that you stay still. We are going to play the picture game now. I want you to lie very still and look at the pictures carefully. Remember, you don't have to press any buttons during this game. Are you comfortable and ready to start?"

Afrikaans Script

Practice functional localizer task. The examiner reads the following script to introduce the functional localizer task.

"Nadat jy die fliek gekyk het in die groot masjien, gaan ons vir jou 'n paar prentjies wys. Ek wil hê jy moet baie stil lê en mooi na die prentjies kyk. Dit sal die eerste speletjie wee swat jy in die groot masjien gaan speel. Het jy enige vrae?

Kom ons oefen."

Functional localizer task. The examiner reads the following script via the intercom system before administering the functional localizer task.

"Haai (name). Goeie werk! Onthou, dit is belangrik dat jy stil hou. Ons gaan nou die prentjie speletjie speel. Ek wil hê jy moet baie stil lê en mooi na die prentjies kyk. Onthou, jy druk geen knoppies gedeurende hierdie speletjie nie. Is jy gemaklik en reg om te begin?"

APPENDIX L

Chapter 3: Supplementary Results

Lateral Occipital Complex

Extracted at $p < .00001$. At this threshold, the analyses detected the left LOC in 48 children (i.e., 64.9% of the sample): 12 (57.1%) in the FAS/PFAS group, 15 (68.2%) in the HE group, and 21 (67.7%) in the control group. I detected the right LOC in 51 children (i.e., 68.9% of the sample): 15 (71.4%) in the FAS/PFAS group, 13 (59.1%) in the HE group, and 23 (74.2%) in the control group. Results of between group, regression- and correlation-based analyses are presented in Table L.1, Table L.2, Table L.3 and Table L.4.

Extracted at $p < .0001$. At this threshold, the analyses detected the left LOC in 62 children (i.e., 83.8% of the sample): 18 (85.7%) in the FAS/PFAS group, 19 (86.4%) in the HE group, and 25 (80.6%) in the control group. I detected the right LOC in 59 children (i.e., 79.7% of the sample): 17 (81.0%) in the FAS/PFAS group, 16 (72.7%) in the HE group, and 26 (83.9%) in the control group. Results of between group, regression- and correlation-based analyses are presented in Table L.1, Table L.2, Table L.3 and Table L.4.

Parahippocampal Place Area

Extracted at $p < .0001$. At this threshold, the analyses detected the left PPA in 39 children (i.e., 52.7% of the sample): 11 (52.4%) in the FAS/PFAS group, 14 (63.6%) in the HE group, and 14 (45.2%) in the control group. I detected the right PPA in 47 children (i.e., 63.5% of the sample): 12 (57.1%) in the FAS/PFAS group, 14 (63.6%) in the HE group, and 21 (67.7%) in the control group. Results of between group, regression- and correlation-based analyses are presented in Table L.1, Table L.2, Table L.3 and Table L.4.

Table L.1
Identification of Potential Confounding Variables for Spatial Extent of Activation Outcome Variables (N = 74)

	Child		Maternal				
Cluster size[a]	Sex	Age	Cigarette smoking	Age at delivery	Education	Marital status	SES
Left lateral occipital complex							
$p < .00001$ ($n = 48$)	.08	.19	.09	-.27*	.19	.17	.38***
$p < .0001$ ($n = 62$)	.14	.02	.02	-.16	.23*	.12	.35***
Right lateral occipital complex							
$p < .00001$ ($n = 51$)	.07	-.14	.02	-.24*	.20	.08	.20
$p < .0001$ ($n = 59$)	.13	-.10	.06	-.16	.19	.06	.25*
Left parahippocampal place area							
$p < .0001$ ($n = 39$)	.11	-.23	-.21	-.21	.19	.09	.19
Right parahippocampal place area							
$p < .0001$ ($n = 47$)	.15	-.39***	-.23	-.21	.32**	-.07	.33**

Note. Statistics presented are Pearson correlation coefficients (r). All tests are two-tailed. SES = socioeconomic status.
[a]Cluster size data is only presented for participants who activated at the designated extraction threshold. Non-responders were excluded.
*$p < .10$. **$p < .05$. ***$p < .01$.

Table L.2
Between-Group Differences in Spatial Extent of Activation (N = 74)

Cluster size	FAS/PFAS	HE	Control	*F*	*df*	*p*	η^2
Left lateral occipital complex							
$p < .00001$[a]	631.4 (839.7)	429.3 (601.8)	495.7 (575.2)	0.32	2,45	.73	.01
$p < .0001$[b]	831.2 (1199.8)	766.8 (1005.7)	925.8 (1022.3)	0.12	2,59	.89	.004
Right lateral occipital complex							
$p < .00001$[c]	438.5 (487.0)	357.6 (439.7)	313.7 (433.4)	0.35	2,48	.71	.01
$p < .0001$[d]	928.9 (1088.0)	870.1 (1130.3)	708.3 (812.0)	0.29	2,56	.75	.01
Left parahippocampal place area							
$p < .0001$[e]	369.5 (444.4)	344.0 (350.3)	367.4 (439.8)	0.02	2,36	.98	.001
Right parahippocampal place area							
$p < .0001$[f]	320.0 (221.0)	400.6 (435.7)	321.2 (401.1)	0.22	2,44	.80	.01

Note. Means are presented with standard deviations in parentheses. FAS = fetal alcohol syndrome; PFAS = partial fetal alcohol syndrome; HE = heavily exposed nonsyndromal.
[a]FAS/PFAS: $n = 12$; HE: $n = 15$; control: $n = 21$
[b]FAS/PFAS: $n = 18$; HE: $n = 19$; control: $n = 25$
[c]FAS/PFAS: $n = 15$; HE: $n = 13$; control: $n = 23$
[d]FAS/PFAS: $n = 17$; HE: $n = 16$; control: $n = 26$
[e]FAS/PFAS: $n = 11$; HE: $n = 14$; control: $n = 14$
[f]FAS/PFAS: $n = 12$; HE: $n = 14$; control: $n = 21$

Table L.3

Relation Between Continuous Measures of Prenatal Alcohol Exposure and Spatial Extent of Activation (N = 74)

Cluster size[a]	AA/day (oz)	AA/occasion (oz)	Frequency (days/week)
Left lateral occipital complex			
$p < .00001$ ($n = 48$)	-.09	-.12	.07
$p < .0001$ ($n = 62$)	-.13	-.17	.004
Right lateral occipital complex			
$p < .00001$ ($n = 51$)	.001	-.05	.12
$p < .0001$ ($n = 59$)	-.04	-.07	.08
Left parahippocampal place area			
$p < .0001$ ($n = 39$)	-.02	.14	-.09
Right parahippocampal place area			
$p < .0001$ ($n = 47$)	.08	.11	.07

Note. Statistics presented are Pearson correlation coefficients (r). All tests are two-tailed. AA = absolute alcohol.

[a]Cluster size data is only presented for participants who activated at the designated extraction threshold. Non-responders were excluded.

Table L.4
Relation Between Spatial Extent of Activation and General Intellectual Functioning (N = 74)

Cluster size[a]	WISC-IV Full-Scale IQ
Left lateral occipital complex	
$p < .00001$ ($n = 48$)	.05
$p < .0001$ ($n = 62$)	.15
Right lateral occipital complex	
$p < .00001$ ($n = 51$)	-.07
$p < .0001$ ($n = 59$)	-.02
Left parahippocampal place area	
$p < .0001$ ($n = 39$)	.21
Right parahippocampal place area	
$p < .0001$ ($n = 47$)	.21

Note. Statistics presented are Pearson correlation coefficients (r). All tests are two-tailed. WISC-IV = Wechsler Intelligence Scale for Children—Fourth Edition.
[a]Cluster size data is only presented for participants who activated at the designated extraction threshold. Non-responders were excluded.

APPENDIX M

Chapter 3: Statistical Assumptions

Outliers

The distribution of maternal education scores contained one outlier > 3*SD*s below the mean. The distributions of SES, left and right LOC cluster size, left and right PPA cluster size, and right LOC mean % signal change all contained one outlier value > 3*SD*s above the mean. In order to prevent outliers exerting undue influence on further statistical analysis of these data, I recoded the aforementioned outliers to 1 point above the next highest observed value (Winer, 1971). Although the distributions of oz. AA/day, oz. AA/occasion, and drinking frequency (days/week) all contained one outlier value > 3*SD*s above the mean, these values reflect true scores and were, therefore, not recoded.

Statistical Assumptions

The assumption of independence was upheld for all sample characteristic, neuroimaging, and behavioral variables. The distribution of maternal education and smoking during pregnancy; child's age; as well as all extent of activation outcome variables and right LOC mean % signal change, deviated significantly from normality (Table M.1). Additionally, the distribution of child's age, and WISC-IV Full-Scale IQ violated the assumption of homogeneity of variance.

Table M.1
Tests of Normality and Homogeneity of Variance (N = 74)

	Kolmogorov-Smirnov			Levene's Test		
	Statistic	*df*	*p*	*Statistic*	*df*	*p*
Maternal variables						
Age at delivery	0.08	74	.20	0.66	2, 71	.52
Highest level of education	0.11	74	.03*	0.20	2, 71	.82
Socioeconomic status	0.07	74	.20	0.23	2, 71	.80
Smoking during pregnancy (cig/day)	0.18	74	< .001***	1.35	2, 71	.27
Child variables						
Age at testing	0.28	74	< .001***	8.49	2, 71	<.001***
WISC-IV Full-Scale IQ	0.09	74	.18	3.03	2, 71	.05
Outcome variables						
Cluster size ($p < .001$)						
Left lateral occipital complex[a]	0.21	69	< .001***	0.59	2, 66	.56
Right lateral occipital complex[b]	0.20	66	< .001***	0.03	2, 63	.98
Left parahippocampal place area[c]	0.22	54	< .001***	0.09	2, 51	.91
Right parahippocampal place area[d]	0.16	59	.001**	0.76	2, 56	.47
Mean % signal change						
Left lateral occipital complex	0.07	74	.20	0.34	2, 71	.71
Right lateral occipital complex[e]	0.15	73	.001**	0.13	2, 70	.88
Left parahippocampal place area[f]	0.08	73	.20	0.15	2, 70	.86
Right parahippocampal place area[g]	0.05	72	.20	0.04	2, 69	.96

Note. Cig = cigarettes; WISC-IV = Wechsler Intelligence Scale for Children—Fourth Edition.
[a]$n = 69$. Cluster size data are only presented for participants who activated at the designated extraction threshold. Data from non-responders were excluded.
[b]$n = 66$. Cluster size data are only presented for participants who activated at the designated extraction threshold. Data from non-responders were excluded.
[c]$n = 54$. Cluster size data are only presented for participants who activated at the designated extraction threshold. Data from non-responders were excluded.
[d]$n = 59$. Cluster size data are only presented for participants who activated at the designated extraction threshold. Data from non-responders were excluded.
[e]$n = 73$. One boy (age: 11.0 years) in the FAS/PFAS group did not activate at the most lenient threshold ($p < .05$).
[f]$n = 73$. One boy (age: 10.2 years)in the FAS/PFAS group did not activate at the most lenient threshold ($p < .05$)
[g]$n = 72$. Two boys (aged: 10.2 and 13.6 years, respectively) in the FAS/PFAS group did not activate at the most lenient threshold ($p < .05$)
*$p < .05$. **$p < .01$. ***$p < .001$.

APPENDIX N

Memory Encoding Task Instructions

English Script

Practice memory encoding task. The examiner read the following script to introduce the memory encoding task.

"This next part is going to be the last game you play in the big machine. It is a memory game where we will ask you questions to see how well you remember pictures. You will see many pictures and for each picture you will have to decide if the pictures show indoor or outdoor spaces. Examples of inside pictures are pictures like these (show them the inside pictures) showing the inside of a kitchen, restaurant, or bathroom. When you see an inside picture, I want you to press this button (5) with your pointer finger. Examples of outside pictures are pictures like these (show them the outside pictures) showing rocks, farms, or mountains. When you see an outside picture, I want you to press this button (6) with your middle finger. On top of deciding whether a picture is inside or outside, I want you to try to remember all of the pictures as best you can. Remember, this is a memory game, and we will ask you questions about the pictures after you get out of the big machine. You will see many pictures, and you might not remember all of them, but I want you to try your best to remember as many of the pictures as you can.

I want you to try your best to remember the pictures you see because we will ask you about them after you get out of the big machine. This memory game is difficult, but I want you to try your best to remember as many of the pictures as you can. When the pictures come up on the screen you will also see pictures like this (point to inside/outside icons). These pictures are here for reminders. The picture in the bottom corner on this side (point to left bottom corner) is a picture of the inside of a room so use your pointer finger for inside pictures. This picture in the bottom corner on this side (point to right bottom corner) is a picture of mountains outside, so use your middle finger for outside pictures.

Administer paper practice with button presses.

Now we will practice with only a few pictures that you need to remember and we will ask you questions about them immediately afterwards.

Do you have any questions?

Ready? Here we go.

As they are practicing, stress the importance of trying as best they can to remember the pictures: It is important that you try as best as you can to remember all of the pictures you

will see in the big machine, because we will ask you questions about ALL of those pictures when you are done. It will hard work, but try as best you can."

Practice recognition testing. The examiner reads the following script to introduce the post-scanner recognition test.

"Well done! Now we are going to ask you questions about all of the practice pictures you just saw. This part of the memory game will be done after you are finished with the big machine. In the big machine you will see many pictures. I want you to do your best at remembering the pictures.

Now I am going to show you a few pictures again. Some of them are the same as the ones you have just seen, but others are new and you have never seen them before. I want you to carefully decide whether you saw each picture or not. If you think that you saw the picture before (or in the big machine) I want you to say 'yes'. If you did not see the picture before (or in the big machine) I want you to say 'no'.

This part of the game is not timed. Please take as much time as you need to make the best decision. Don't rush to answer. You also don't have to worry about pressing buttons this time, because I will be pressing the buttons for you.

Once you have decided if you have seen the picture before, we will ask you how sure you are. If you have seen it before and you are sure that you have seen it, say you are 'sure'. If you are not sure if you have seen it, tell me that you are 'not sure'. Even if you said you haven't seen the picture before, tell me if you are sure or not sure.

Try to gauge whether or not they understand the instructions: So what will you say if you have seen the picture before? And what will you say if you haven't seen the picture before?

Do you have any questions? Are you ready?"

Afrikaans Script

Practice memory encoding task. The examiner read the following script to introduce the memory encoding task.

"Hierdie volgende deel sal die laaste speletjie wees wat jy in die groot magneet gaan speel. Dit is 'n geheue speletjie waarin ons jou gaan vrae vra om te sien hoe goed jy prentjies onthou. Jy gaan baie prentjies sien en vir elke prentjie sal jy moet besluit of die prentjie 'n plek wys wat binne of buite is. Voorbeelde van plekke wat binne is, is prentjies soos hierdie (show them the inside pictures) wat die binnekant van 'n kombuis, eetplek, of badkamer wys. Wanneer jy 'n prentjie van 'n plek sien wat binne is, wil ek hê jy moet hierdie knoppie druk

(5) met jou wysvinger. Voorbeelde van plekke wat buite is, is prentjies soos hierdie (show them the outside pictures) wat klippe, plase, of berge wys. Wanneer jy ‘n prentjie van ‘n plek sien wat buite is, wil ek hê jy moet hierdie knoppie druk (6) met jou middelvinger. Behalwe om te besluit of die prentjies plekke wys wat binne of buite is, wil ek hê jy moet ook probeer om al die prentjies so goed as moontlik te onthou. Onthou, hierdie is ‘n geheue speletjie en ons gaan jou vrae vra oor al daai prentjies nadat jy uit die groot masjien uitkom. Jy gaan baie prentjies sien, en jy mag dalk nie almal van hulle onthou nie, maar ek wil hê jy moet jou beste probeer om so baie van die prentjies te onthou as wat jy kan.

Ek wil hê jy moet jou beste probeer om die prentjies te onthou, want ons gaan jou vrae vra oor hulle nadat jy uit die groot masjien uitkom. Die geheue speletjie is moeilik, maar ek wil hê jy moet jou beste probeer om so baie van die prentjies te onthou as wat jy kan. Wanneer die prentjies op die skerm kom, sal jy ook prentjies soos hierdie sien (point to inside/outside icons). Hierdie prentjies is hier as herinneringe. Die prentjie in die onderste hoek aan diekant (point to left bottom corner) is ‘n prentjie van die binnekant van ‘n kamer, so gebruik jou wysvinger vir plekke wat binne is. Die prentjie in die onderste hoek aan diekant (point to right bottom corner) is ‘n prentjie van berge wat buite is, so gebruik jou middelvinger vir plekke wat buite is.

Administer paper practice with button presses.

Nou gaan ons oefen met net ‘n paar prentjies wat jy gaan moet onthou en ons sal jou vrae oor hulle vra direk na die tyd.

Het jy enige vrae?

Is jy reg? Hier gaan ons.

As they are practicing, stress the importance of trying as best they can to remember the pictures: Dit is belangrik dat jy jou beste probeer om all die prentjies te onthou, want ons gaan jou vrae vra oor hulle ALMAL nadat jy klaar is. Dit gaan harde werk wees, maar probeer net jou beste.”

Practice recognition testing. The examiner reads the following script to introduce the post-scanner recognition test.

“Goeie werk! Nou gaan ons vir jou vrae vra oor al die oefen prentjies wat jy nou net gesien het. Die deel van die geheue speletjie sal gedoen word nadat jy klaar is in die groot masjien. In die groot masjien sal jy baie prentjies sien. Ek wil hê jy moet jou beste probeer om die prentjies te onthou.

Nou gaan ek weer vir jou ‘n paar prentjies wys. Van die prentjies sal dieselfde wees as die wat jy nou net gesien het, maar ander sal nuwes wees wat jy nog nooit gesien het nie.

Ek wil hê jy moet versigitg besluit of jy elke prentjie al gesien het of nie. As jy dink dat jy die prentjie al voorheen gesien het (in die groot masjien) wil ek hê jy moet ‘ja’ sê. As jy nog nie die prentjie voorheen (in die groot masjien) gesien het nie wil ek hê jy moet ‘nee’ sê.

In die deel van die speletjie moet jy asseblief soveel tyd vat as wat jy nodig het om die beste besluit te maak. Moenie haastig wees om te antwoord nie. Jy hoef ook nie te bekommer oor knoppies druk die keer nie, want ek sal die knoppies vir jou druk.

Sodra jy besluit het of jy al die prentjie voorheen gesien het, sal ons vir jou vra hoe seker jy is oor jou antwoord. As jy die prentjie al voorheen gesien het en jy is seker dat jy dit al gesien het, dan sê jy jy is ‘seker’. As jy nie seker is of jy dit al voorheen gesien het nie, dan sê jy ‘nie seker nie’. Al sê jy dat jy nog nie voorheen die prentjie gesien het nie, moet jy vir my sê of jy seker is of nie.

Try to gauge whether or not they understand the instructions: So wat sal jy vir my sê as jy al voorheen die prentjie gesien het? En wat sal jy vir my sê as jy nog nie voorheen die prentjie gesien het nie?

Het jy enige vrae? Is jy reg?”

APPENDIX O

Review of Anatomical Labels

Table O.1

Within-Group Whole-Brain Voxelwise Analysis Showing Regions With Greater Neural Activation During Successful Scene Encoding (N = 51)

Hit > Miss p(FWE) < .05; all subjects

WFU PickAtlas Anatomical Label	Anatomical Label based on CW Review	BA	MNI Coordinates			Peak T value	Volume (mm^3)
			x	y	z		
Frontal							
R Middle frontal gyrus	R Anterior inferior frontal sulcus	46	48	32	18	6.18	24
R Inferior frontal gyrus	R Anterior insula	-	28	30	-8	5.80	24
R Inferior frontal gyrus	R Inferior frontal sulcus (premotor)	9	42	2	28	5.63	8
Parietal							
L Superior parietal lobule	L Intraparietal sulcus	-	-22	-66	54	6.97	288
L Precuneus	*L Intraparietal sulcus*	-	-22	-60	46	5.76	
R Precuneus	R Intraparietal sulcus (medial branch)	-	20	-64	52	6.45	88
L Precuneus	L Intraparietal sulcus	19	-28	-74	40	5.71	24
Occipital							
R Inferior temporal gyrus	R Posterior inferior temporal gyrus	-	52	-62	-12	7.93	408
R Sub-gyral	*R posterior-superior inferior temporal gyrus*	-	42	-62	-8	6.08	
L Superior occipital gyrus	L Posterior superior occipital gyrus	-	-42	-84	24	7.91	456
L Middle occipital gyrus	L Inferior occipital gyrus	-	-48	-60	-8	7.47	1136
L Sub-gyral (temporal)	*L posterior-superior inferior temporal gyrus*	-	-48	-52	-14	6.67	
L Inferior temporal gyrus	*L inferior occipital gyrus*	-	-48	-72	-4	6.00	
L Cuneus	L Superior occipital gyrus (lateral surface)	19	-30	-84	28	6.37	360
R Fusiform gyrus	R Fusiform gyrus	-	30	-58	-12	5.80	24
Limbic							
L Parahippocampal gyrus	L Posterior parahippocampal gyrus	-	-20	-36	-12	8.43	3024
L Parahippocampal gyrus	*L Parahippocampal gyrus*	36	-26	-30	-20	8.27	
L Parahippocampal gyrus	*L Parahippocampal gyrus*	37	-30	-40	-14	7.77	
R Parahippocampal gyrus	R Parahippocampal gyrus	37	32	-38	-12	7.78	1696
R Parahippocampal gyrus	*R Parahippocampal gyrus*	-	24	-36	-14	7.76	

R Fusiform gyrus (temporal)	*R Fusiform gyrus (occipital-temporal junction)*	37	34	-48	-18	7.45	
R Parahippocampal gyrus	R Parahippocampal gyrus	-	22	-24	-18	5.89	8
R Parahippocampal gyrus	R Hippocampus, body	-	34	-18	-14	5.81	16
Temporal							
R Middle temporal gyrus	R Middle occipital gyrus (lateral surface, occipital)	39	44	-78	26	7.95	2240
R Superior occipital gyrus (occipital)	*R Superior occipital gyrus (occipital)*	-	32	-82	26	7.64	
R Middle occipital gyrus (occipital)	*R Middle occipital gyrus (occipital)*	-	32	-86	10	7.02	
R Sub-gyral	R posterior-superior inferior temporal gyrus (occipital)	-	52	-52	-10	6.44	312
Sub-lobar							
L Lateral Ventricle	L Hippocampus, body	-	-36	-16	-18	6.30	40
R Extra-nuclear	R Hippocampus, tail	-	18	-34	-2	6.12	88
R Extra-nuclear	R Hippocampus, body	-	32	-28	-2	6.05	8
R Extra-nuclear	R Hippocampus, head	-	24	-6	-12	5.87	8
R Extra-nuclear	R Hippocampus, tail	-	26	-32	2	5.63	8

Note. In cases where significant submaxima clusters were identified, details are provided in italics under maxima. FWE = family-wise error corrected; WFU = Wake Forest University; CW = Dr Christopher Warton; MNI = Montréal Neurological Institute; BA = Brodmann Area; L = left; R = right.

Table O.2

Between-Group Whole-Brain Voxelwise Comparison Showing Differential Neural Activation During Successful Scene Encoding (N = 51)

Hit > Miss *p*(unc) < .001							
			MNI Coordinates				
WFU PickAtlas Anatomical Label	Anatomical Label based on CW Review	BA	x	y	z	Peak *T* value	Volume (mm^3)
Control > FAS/PFAS				No significant differences			
Control > HE				No significant differences			
HE > Control				No significant differences			
HE > FAS/PFAS				No significant differences			
FAS/PFAS > Control							
Frontal							
L Sub-gyral	L Postcentral sulcus (extending into paracentral white matter)	-	-14	-34	66	5.19	1848
R Paracentral lobule	*R Paracentral lobule*	-	0	-40	62	4.09	
R Paracentral lobule	*R Paracentral lobule*	-	2	-40	52	3.82	
Parietal							
R Postcentral gyrus	R Postcentral gyrus	43	64	-10	22	4.23	264
R Precentral gyrus (frontal)	*R Precentral gyrus (frontal)*	-	56	-10	24	3.50	
Cerebellum posterior							
R Cerebellar tonsil	R Cerebellar lobule 8	-	24	-54	-46	5.00	288
FAS/PFAS > HE							
Frontal							
L Precentral gyrus	L Precentral gyrus	-	-14	-32	68	4.51	440
L Precentral gyrus	*L Precentral gyrus*	4	-22	-28	64	3.86	
L Paracentral lobule	L Paracentral lobule	5	-10	-40	52	4.46	432
Parietal							
L sub-gyral	L Intraparietal sulcus (posterior medial branch)	-	-14	-56	60	4.87	272
Temporal							
R middle temporal gyrus	R Posterior superior temporal sulcus (close proximity to occipital-temporal junction)	-	40	-64	20	4.38	544
R sub-gyral	*R Posterior superior temporal sulcus*	-	36	-54	24	3.86	

Note. In cases where significant submaxima clusters were identified, details are provided in italics under maxima. unc = uncorrected; WFU = Wake Forest University; CW = Dr Chris Warton; MNI = Montréal Neurological Institute; BA = Brodmann Area; FAS = fetal alcohol syndrome; PFAS = partial FAS; HE = heavily exposed nonsyndromal; L = left; R = right.

APPENDIX P

Chapter 4: Statistical Assumptions

Outliers

The distributions of maternal socioeconomic status, AA/day, and AA/occasion as well as child *d*-prime scores all contained one outlier > 3*SD*s above the mean. The distributions of magnitude of activation in the following regions contained 1 outlier < 3*SD*s below the mean: left posterior parahippocampal gyrus, left superior occipital gyrus, right fusiform gyrus, right parahippocampal gyrus, right hippocampus body; whereas the distributions of magnitude activation in the following regions contained 1 outlier > 3*SD*s above the mean: left posterior-superior occipital gyrus, right hippocampus head, right fusiform gyrus, right hippocampus tail, left parahippocampal place area. In order to prevent outliers exerting undue influence on further statistical analysis of these data, I recoded the aforementioned outliers to 1 point above or below the next highest observed value (Winer, 1971).

Statistical Assumptions

The assumption of independence was met for all sample, predictor and outcome variables examined in this study. The distributions of maternal education, AA/day, AA/occasion, frequency drinking (days/week), and smoking during pregnancy; child age at testing; magnitude of activation in the right parahippocampal place area all deviated significantly from normal (Table P.1). Magnitude of activation in the left posterior parahippocampal place area showed a trend towards deviating from being normally distributed. In addition to this, the distributions of maternal AA/day, AA/occasion and frequency drinking (days/week); child age at testing; magnitude of activation in left intraparietal sulcus, right posterior-superior inferior temporal gyrus, left superior occipital gyrus, and right fusiform gyrus all violated the assumption of homogeneity of variance. The

distribution of right posterior-inferior temporal gyrus magnitude activation showed a trend toward violating the assumption of homogeneity of variance.

Table P.1
Tests of Normality and Homogeneity of Variance (N = 51)

	Kolmogorov-Smirnov			Levene's Test		
	Statistic	*df*	*p*	*Statistic*	*dfs*	*p*
Maternal variables						
Age at delivery	0.08	51	.20	1.81	2, 48	.18
Highest level of education	0.14	51	.02*	0.94	2, 48	.40
Socioeconomic status	0.09	51	.20	2.35	2, 48	.11
AA/day	0.31	51	<.001***	17.54	2, 48	<.001***
AA/occasion	0.32	51	<.001***	16.83	2, 48	<.001***
Frequency (days/week)	0.33	51	<.001***	21.01	2, 48	<.001***
Smoking during pregnancy (cig./day)	0.21	51	<.001***	1.59	2, 48	.21
Child variables						
Age at testing	0.28	51	<.001***	5.07	2, 48	.01*
WISC-IV full scale IQ	0.09	51	.20	1.81	2, 48	.18
Outcome variables						
Behavioral variables						
d-prime	0.09	51	.20	0.56	2, 48	.57
Hit	0.08	51	.20	0.48	2, 48	.62
Miss	0.09	51	.20	0.47	2, 48	.63
False alarm	0.09	51	.20	0.003	2,48	1.00
Correct rejection	0.09	51	.20	0.01	2, 48	1.00
Mean % signal change						
Frontal						
R Anterior inferior frontal sulcus	0.09	51	.20	0.07	2, 48	.93
R Anterior insula	0.11	51	.20	0.51	2, 48	.60
R Inferior frontal sulcus (premotor)	0.08	51	.20	0.43	2, 48	.65
Parietal						
L Intraparietal sulcus	0.07	51	.20	3.30	2, 48	.05*
R Intraparietal sulcus (medial branch)	0.09	51	.20	1.59	2, 48	.21
L Intraparietal sulcus	0.06	51	.20	1.26	2, 48	.29
Occipital						

R Middle occipital gyrus (lateral surface, occipital)	0.09	51	.20	1.23	2, 48	.30
R Posterior inferior temporal gyrus	0.09	51	.20	2.50	2, 48	.09†
L Posterior superior occipital gyrus	0.08	51	.20	1.30	2, 48	.28
L Inferior occipital gyrus	0.07	51	.20	0.20	2, 48	.82
R posterior-superior inferior temporal gyrus (occipital)	0.07	51	.20	7.54	2, 48	.001**
L Superior occipital gyrus (lateral surface)	0.09	51	.20	3.69	2, 48	.03*
R Fusiform gyrus	0.07	51	.20	3.46	2, 48	.04*
Limbic						
L Posterior parahippocampal gyrus	0.12	51	.08†	0.44	2, 48	.65
R Parahippocampal gyrus	0.07	51	.20	0.88	2, 48	.42
R Parahippocampal gyrus	0.07	51	.20	0.37	2, 48	.69
Hippocampus						
L Hippocampus, body	0.08	51	.20	1.58	2, 48	.22
R Hippocampus, tail	0.08	51	.20	1.00	2, 48	.37
R Hippocampus, body	0.09	51	.20	1.67	2, 48	.20
R Hippocampus, head	0.09	51	.20	0.48	2, 48	.62
R Hippocampus, body	0.06	51	.20	0.93	2, 48	.40
R Hippocampus, tail	0.07	51	.20	0.26	2, 48	.77
Additional ROIs						
L Parahippocampal place area[a]	0.09	50	.20	0.71	2, 47	.50
R Parahippocampal place area[a]	0.13	50	.04*	1.50	2, 47	.23

Note. Cig. = cigarettes; WISC-IV = Wechsler Intelligence Scale for Children—Fourth Edition; L = Left; R = Right.

[a] $n = 50$; one participant in the control group failed to demonstrate scene-selective activation at the least stringent threshold ($p < .05$; see Chapter 3)

$^{\dagger}p < .10$; $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$.

APPENDIX Q

Chapter 4: Control for Prenatal Drug Exposure

Analyses Excluding Children Prenatally Exposed to Marijuana (*n* = 46)

Table Q.1
Between-Group Differences in Behavioral Memory Performance (N = 46)

	FAS/PFAS (*n* = 10)	HE (*n* = 11)	Non-exposed control (*n* = 25)	*F*	*p*	η^2
d-prime	0.7 (0.2)	0.7 (0.3)	0.7 (0.3)	0.13	.876	.01
Hit total (%)	47.0 (19.8)	62.6 (22.7)	44.6 (16.6)	5.16[a]	.010*	.19
Miss total (%)	52.8 (19.8)	37.4 (22.7)	55.4 (16.6)	5.15[b]	.010*	.19
False alarm (%)	25.0 (12.8)	37.5 (13.4)	22.0 (11.3)	4.05[c]	.024*	.16
Correct rejection (%)	75.0 (12.8)	62.5 (13.4)	78.0 (11.3)	4.05[d]	.024*	.16

Note. Unless otherwise stated, values presented are means with standard deviations in parentheses. FAS = fetal alcohol syndrome; PFAS = partial FAS; HE = heavily exposed nonsyndromal.
[a]FAS/PFAS = Non-exposed control ($p > .20$) < HE (ps = .03 and .003, respectively)
[b]FAS/PFAS = Non-exposed control ($p > .20$) > HE (ps = .03 and .003, respectively)
[c]FAS/PFAS = Non-exposed control ($p > .20$) < HE (p = .07 and .007, respectively)
[d] FAS/PFAS = Non-exposed control ($p > .20$) < HE (p = .07 and .007, respectively)
*$p < .05$.

Table Q.2

Relation of Continuous Measures of Prenatal Alcohol Exposure to Magnitude of Activation During Successful Scene Encoding (Hit > Miss; N = 46)

	FAS/PFAS (n = 10[a])			HE (n = 11)		
Region	AA/ day	AA/ occasion	Frequency	AA/ day	AA/ occasion	Frequency
Frontal						
R Anterior inferior frontal sulcus	-.30	-.31	-.12	.13	.05	-.01
R Anterior insula	-.32	-.64*	-.35	-.22	-.13	-.42
R Inferior frontal sulcus (premotor)	.14	-.14	-.08	-.09	-.15	.006
Parietal						
L Intraparietal sulcus	.43	.29	.12	-.29	-.30	-.34
R Intraparietal sulcus (medial branch)	.52	-.05	.46	-.09	-.10	-.47
L Intraparietal sulcus	-.19	-.21	-.40	.28	.37	.39
Occipital						
R Middle occipital gyrus (lateral surface, occipital)	-.35	-.32	-.44	-.14	-.09	-.05
R Posterior inferior temporal gyrus	-.29	-.44	-.28	-.10	-.10	-.13
L Posterior superior occipital gyrus	-.27	-.17	-.39	-.25	-.19	.05
L Inferior occipital gyrus	-.32	-.48	-.34	-.11	-.06	-.17
R posterior-superior inferior temporal gyrus (occipital)	-.06	-.27	.08	.18	.19	.05
L Superior occipital gyrus (lateral surface)	-.15	-.46	-.21	.13	.14	.19
R Fusiform gyrus	-.21	-.13	-.30	-.03	-.04	-.12
Limbic						
L Posterior parahippocampal gyrus	-.16	-.69*	.09	-.08	-.06	-.05
R Parahippocampal gyrus	-.05	-.64*	.09	-.29	-.28	-.32
R Parahippocampal gyrus	.08	-.40	.26	-.10	.02	-.01
Hippocampus						
L Hippocampus, body	.30	-.04	.37	-.12	-.03	-.44
R Hippocampus, tail	.23	.66*	-.09	<.001	.01	-.37
R Hippocampus, body	.07	.60†	-.09	-.21	-.06	-.15
R Hippocampus, head	.66*	.31	.60†	.34	.45	-.21
R Hippocampus, body	-.32	-.33	-.16	.13	.21	-.18
R Hippocampus, tail	.47	.33	.21	-.60†	-.48	-.73*
Additional ROIs						
L Parahippocampal place area[b]	-.73*	-.52	-.71*	.02	.10	-.08
R Parahippocampal place area[b]	-.19	-.72*	-.02	-.31	-.38	-.12

Note. Values presented are Pearson correlation coefficients (r). All significance tests are two-tailed. oz AA = ounces absolute alcohol; FAS = fetal alcohol syndrome; PFAS = partial FAS; HE = heavily exposed nonsyndromal; AA = absolute alcohol; R = right; L = left; ROIs = regions of interest.

[a]FAS $n = 6$; PFAS $n = 4$
[b]$n = 50$; one girl (10.4 years old) in the non-exposed control group did not demonstrate scene-selective activation at the least stringent threshold ($p < .05$; see Chapter 3)
[†]$p < .10$. [*]$p < .05$.

Table Q.3
Relation Between Recognition Accuracy and Magnitude Activation in Memory and Parahippocampal Regions of Interest (Hit > Miss; N = 46)

	d-prime		
Region	FAS/PFAS (n = 10)	HE (n = 11)	Non-exposed control (n = 25)
Frontal			
R Anterior inferior frontal sulcus	.53	.14	-.05
R Anterior insula	.15	.51	.21
R Inferior frontal sulcus (premotor)	-.45	-.50	-.13
Parietal			
L Intraparietal sulcus	-.52	-.01	.12
R Intraparietal sulcus (medial branch)	-.42	.12	-.14
L Intraparietal sulcus	-.25	-.41	.09
Occipital			
R Middle occipital gyrus (lateral surface, occipital)	.14	-.12	.28
R Posterior inferior temporal gyrus	.24	-.05	.25
L Posterior superior occipital gyrus	-.52	-.19	.43*
L Inferior occipital gyrus	.29	-.16	.38†
R posterior-superior inferior temporal gyrus (occipital)	.28	-.35	.38†
L Superior occipital gyrus (lateral surface)	-.07	-.25	.10
R Fusiform gyrus	.21	-.17	.07
Limbic			
L Posterior parahippocampal gyrus	.16	-.09	.21
R Parahippocampal gyrus	-.07	-.11	.42*
R Parahippocampal gyrus	.25	-.03	.01
Hippocampus			
L Hippocampus, body	.35	.27	-.04
R Hippocampus, tail	-.43	.44	.17
R Hippocampus, body	-.41	-.14	.20
R Hippocampus, head	-.19	<.001	.10
R Hippocampus, body	.01	.23	.20
R Hippocampus, tail	-.86**	.40	-.16
Additional ROIs			
L Parahippocampal place area	-.003	-.18	-.06
R Parahippocampal place area	-.06	-.40	-.06

Note. Values presented are Pearson correlation coefficients (r). All significance tests are two-tailed. R = right; L = left; ROIs = regions of interest.
†$p < .10$. *$p < .05$. **$p < .01$. ***$p < .001$.

Table Q.4

Relation Between Behavioral Memory Performance and Magnitude of Activation in Memory and Parahippocampal Regions of Interest (Hit > Miss; N = 46)

	Hit			False Alarms		
Region	FAS/PFAS (n = 10)	HE (n = 11)	Non-exposed control (n = 25)	FAS/PFAS (n = 10)	HE (n = 11)	Non-exposed control (n = 25)
Frontal						
R Anterior inferior frontal sulcus	-.44	.57†	-.33	-.70*	.47	-.16
R Anterior insula	-.61†	-.17	-.31	-.55†	-.44	-.35†
R Inferior frontal sulcus (premotor)	-.73*	-.49	-.36†	-.49	-.39	-.11
Parietal						
L Intraparietal sulcus	-.47	-.35	.10	-.26	-.39	< .001
R Intraparietal sulcus (medial branch)	.004	-.32	.23	.21	-.47	.27
L Intraparietal sulcus	-.73*	-.30	-.24	-.58†	-.08	-.19
Occipital						
R Middle occipital gyrus (lateral surface, occipital)	-.67*	-.59†	-.21	-.67*	-.59†	-.23
R Posterior inferior temporal gyrus	-.56†	-.62*	.16	-.63†	-.69*	-.02
L Posterior superior occipital gyrus	-.64*	-.51	.03	-.39	-.42	-.18
L Inferior occipital gyrus	-.79**	-.58†	-.26	-.84**	-.59†	-.37†
R posterior-superior inferior temporal gyrus (occipital)	-.11	-.72*	-.45*	-.20	-.62*	-.50*
L Superior occipital gyrus (lateral surface)	-.65*	-.67*	-.07	-.54	-.60†	-.06
R Fusiform gyrus	-.48	-.60†	-.44*	-.55	-.60*	-.32
Limbic						
L Posterior parahippocampal gyrus	-.54	-.49	-.19	-.55	-.51	-.25
R Parahippocampal gyrus	-.24	-.55†	-.30	-.15	-.59†	-.44*
R Parahippocampal gyrus	.16	-.45	-.20	.14	-.37	-.14
Hippocampus						
L Hippocampus, body	.54	-.57†	-.38†	.40	-.69*	-.22
R Hippocampus, tail	-.10	-.30	-.08	.01	-.56†	-.17
R Hippocampus, body	.33	.12	-.33	.45	.23	-.31
R Hippocampus, head	.21	-.42	-.57**	.19	-.40	-.44*
R Hippocampus, body	.19	-.48	-.38†	.20	-.57†	-.34†
R Hippocampus, tail	-.32	.44	-.46*	.03	.20	-.15
Additional ROIs						
L Parahippocampal place area	-.35	-.64*	-.29	-.28	-.57†	-.20
R Parahippocampal place area	-.35	-.64*	-.14	-.24	-.55†	-.04

Note. Values presented are Pearson correlation coefficients (r). All significance tests are two-tailed. R = right; L = left; ROIs = regions of interest.

$^{\dagger}p < .10$. $^{*}p < .05$. $^{**}p \leq .01$. $^{***}p < .001$.

Analyses Excluding Children Prenatally Exposed to Methaqualone (*n* = 48)

Table Q.5
Between-Group Differences in Behavioral Memory Performance (N = 48)

	FAS/PFAS (*n* = 10)	HE (*n* = 12)	Non-exposed control (*n* = 26)	*F*	*p*	η^2
d-prime	0.7 (0.2)	0.7 (0.3)	0.7 (0.3)	0.08	.91	.004
Hit total (%)	48.8 (20.1)	59.8 (24.5)	44.9 (16.3)	3.50[a]	.04[*]	.14
Miss total (%)	51.1 (20.0)	40.3 (24.5)	55.0 (16.4)	3.46[b]	.04[*]	.13
False alarm (%)	26.1 (12.9)	35.3 (14.3)	22.3 (11.1)	2.92[c]	.06[†]	.12
Correct rejection (%)	73.9 (12.9)	64.8 (14.3)	77.6 (11.2)	2.84[d]	.07[†]	.11

Note. Unless otherwise stated, values presented are means with standard deviations in parentheses. FAS = fetal alcohol syndrome; PFAS = partial FAS; HE = heavily exposed non-syndromal.
[a]FAS/PFAS = Non-exposed ($p > .20$) and HE ($p > .10$); HE > Non-exposed ($p = .01$)
[b]FAS/PFAS = Non-exposed ($p > .20$) and HE ($p > .10$); HE < Non-exposed ($p = .01$)
[c]FAS/PFAS = Non-exposed ($p > .20$) and HE ($p > .10$); HE > Non-exposed ($p = .02$)
[d]FAS/PFAS = Non-exposed ($p > .20$) and HE ($p > .10$); HE < Non-exposed ($p = .02$)
[*]$p < .05$.

Table Q.6

Relation of Continuous Measures of Prenatal Alcohol Exposure to Magnitude Activation During Successful Scene Encoding (Hit > Miss; N = 48)

	FAS/PFAS (n = 10[a])			HE (n = 12)		
Region	AA/ day	AA/ occasion	Frequency	AA/ day	AA/ occasion	Frequency
Frontal						
R Anterior inferior frontal sulcus	-.27	-.28	-.11	.13	.05	-.01
R Anterior insula	-.35	-.68*	-.36	-.19	-.19	-.37
R Inferior frontal sulcus (premotor)	.16	-.11	-.09	-.09	-.15	.01
Parietal						
L Intraparietal sulcus	.37	.21	.14	-.29	-.32	-.33
R Intraparietal sulcus (medial branch)	.52	-.02	.42	-.07	-.13	-.45
L Intraparietal sulcus	-.18	-.19	-.41	.24	.40	.34
Occipital						
R Middle occipital gyrus (lateral surface, occipital)	-.33	-.30	-.44	-.14	-.05	-.06
R Posterior inferior temporal gyrus	-.27	-.40	-.29	-.11	-.07	-.14
L Posterior superior occipital gyrus	-.23	-.09	-.45	-.23	-.22	-.06
L Inferior occipital gyrus	-.34	-.50	-.34	-.11	-.06	-.17
R posterior-superior inferior temporal gyrus (occipital)	-.12	-.36	.09	.15	.24	.03
L Superior occipital gyrus (lateral surface)	-.14	-.44	-.21	.12	.18	.17
R Fusiform gyrus	-.24	-.15	-.33	-.03	-.06	-.11
Limbic						
L Posterior parahippocampal gyrus	-.13	-.66*	.04	-.08	-.07	-.05
R Parahippocampal gyrus	-.001	-.60†	.13	-.28	-.29	-.31
R Parahippocampal gyrus	.02	-.50	.28	-.10	.02	-.01
Hippocampus						
L Hippocampus, body	.24	-.16	.41	-.13	-.01	-.45
R Hippocampus, tail	.21	.65*	-.11	.003	-.004	-.37
R Hippocampus, body	.12	.68*	-.18	-.19	-.10	-.14
R Hippocampus, head	.63†	.31	.54	.33	.37	-.19
R Hippocampus, body	-.30	-.29	-.17	.10	.26	-.18
R Hippocampus, tail	.48	.35	.19	-.59*	-.49	-.72**
Additional ROIs						
L Parahippocampal place area[b]	-.50	-.39	-.44	.02	.08	-.07
R Parahippocampal place area[b]	-.15	-.72*	-.01	-.31	-.38	-.12

Note. Values presented are Pearson correlation coefficients (r). All significance tests are two-tailed. oz AA = ounces absolute alcohol; FAS = fetal alcohol syndrome; PFAS = partial FAS; HE = heavily exposed non-syndromal; AA = absolute alcohol; R = right; L = left; ROIs = regions of interest.

[a]FAS $n = 6$; PFAS $n = 4$
[b]$n = 50$; one participant in the control group failed to demonstrate scene-selective activation at the least stringent threshold ($p < .05$; see Chapter 3)
$^{\dagger}p < .10$. $^{*}p < .05$. $^{**}p < .01$.

Table Q.7
Relation Between Recognition Accuracy and Magnitude Activation in Memory and Parahippocampal Regions of Interest (Hit > Miss; N = 48)

	d-prime		
Region	FAS/PFAS (*n* = 10)	HE (*n* = 12)	Non-exposed control (*n* = 26)
Frontal			
R Anterior inferior frontal sulcus	.60†	.14	-.05
R Anterior insula	.14	.47	.22
R Inferior frontal sulcus (premotor)	-.42	-.50†	-.12
Parietal			
L Intraparietal sulcus	-.53	-.01	.14
R Intraparietal sulcus (medial branch)	-.40	.12	-.14
L Intraparietal sulcus	-.24	-.38	.09
Occipital			
R Middle occipital gyrus (lateral surface, occipital)	.15	-.11	.29
R Posterior inferior temporal gyrus	.27	-.05	.26
L Posterior superior occipital gyrus	-.53	-.18	.40*
L Inferior occipital gyrus	.28	-.16	.39†
R posterior-superior inferior temporal gyrus (occipital)	.23	-.32	.39*
L Superior occipital gyrus (lateral surface)	-.06	-.24	.10
R Fusiform gyrus	.17	-.17	.08
Limbic			
L Posterior parahippocampal gyrus	.19	-.09	.22
R Parahippocampal gyrus	-.02	-.11	.43*
R Parahippocampal gyrus	.20	-.03	.01
Hippocampus			
L Hippocampus, body	.30	.27	-.02
R Hippocampus, tail	-.46	.44	.13
R Hippocampus, body	-.39	-.14	.17
R Hippocampus, head	-.19	<.001	.06
R Hippocampus, body	.04	.21	.23
R Hippocampus, tail	-.84**	.39	-.13
Additional ROIs			
L Parahippocampal place area	.02	-.18	-.04
R Parahippocampal place area	-.003	-.40	-.02

Note. Values presented are Pearson correlation coefficients (*r*). All significance tests are two-tailed. R = right; L = left; ROIs = regions of interest.
$^{\dagger}p < .10$. $^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$.

Table Q.8
Relation Between Behavioral Memory Performance and Magnitude Activation in Memory and Parahippocampal Regions of Interest (Hit > Miss; N = 48)

	Hit			False Alarms		
Region	FAS/PFAS (n = 10)	HE (n = 12)	Non-exposed control (n = 26)	FAS/PFAS (n = 10)	HE (n = 12)	Non-exposed control (n = 26)
Frontal						
R Anterior inferior frontal sulcus	-.40	.49	-.32	-.68*	.40	-.16
R Anterior insula	-.63†	.05	-.32	-.56	-.19	-.36†
R Inferior frontal sulcus (premotor)	-.74*	-.43	-.37†	-.50	-.35	-.12
Parietal						
L Intraparietal sulcus	-.37	-.26	.08	-.19	-.30	-.02
R Intraparietal sulcus (medial branch)	-.05	-.17	.23	.16	-.31	.27
L Intraparietal sulcus	-.74*	-.42	-.24	-.59†	-.23	-.19
Occipital						
R Middle occipital gyrus (lateral surface, occipital)	-.69*	-.61*	-.23	-.68*	-.61*	-.25
R Posterior inferior temporal gyrus	-.57†	-.61*	.13	-.63*	-.67*	-.04
L Posterior superior occipital gyrus	-.65*	-.33	.05	-.39	-.27	-.16
L Inferior occipital gyrus	-.80**	-.50†	-.27	-.85**	-.52†	-.38†
R posterior-superior inferior temporal gyrus (occipital)	-.13	-.77**	-.46*	-.22	-.69*	-.51**
L Superior occipital gyrus (lateral surface)	-.64*	-.68*	-.08	-.54	-.62*	-.06
R Fusiform gyrus	-.56†	-.46	-.45*	-.60†	-.48	-.33†
Limbic						
L Posterior parahippocampal gyrus	-.41	-.41	-.20	-.45	-.43	-.25
R Parahippocampal gyrus	-.11	-.46	-.31	-.07	-.51†	-.45*
R Parahippocampal gyrus	.16	-.40	-.20	.15	-.33	-.14
Hippocampus						
L Hippocampus, body	.57†	-.57†	-.39*	.43	-.68*	-.23
R Hippocampus, tail	-.15	-.24	-.04	-.02	-.47	-.13
R Hippocampus, body	.38	.23	-.29	.49	.32	-.28
R Hippocampus, head	.11	-.22	-.49*	.13	-.22	-.38†
R Hippocampus, body	.18	-.57†	-.40*	.19	-.64*	-.35†
R Hippocampus, tail	-.35	.44	-.47*	.01	.23	-.17
Additional ROIs						
L Parahippocampal place area	-.07	-.51†	-.30	-.08	-.46	-.21
R Parahippocampal place area	-.31	-.57†	-.18	-.22	-.50	-.07

Note. Values presented are Pearson correlation coefficients (r). All significance tests are two-tailed. R = right; L = left; ROIs = regions of interest.
$^{\dagger}p < .10$. $^{*}p < .05$. $^{**}p \leq .01$. $^{***}p < .001$.

APPENDIX R

Source Memory Task Instructions

English Script

Study. The examiner read the following script to introduce the study phase of the source memory task in English.

"We are going to play a memory game. In this game, I am going to show you some pictures. I want you to try your best to remember as many of the pictures as possible. You will see many pictures, and you might not remember all of them, but I want you to try your best to remember as many of them as possible. When you have finished looking at the pictures, I am going to ask you which ones you remember.

The pictures will be shown on the left or the right side of the screen (*check that the participant can identify left and right—have them point to the screen*) in either red or green (*ask them to identify red and green color patches*). After each picture you will be asked one question about it. There are only two questions that I will ask. The first question is: Is this a living thing? For example, a dog is a living thing, but a ball is not. Can you give me an example of a living thing (*alternate phrasing: a thing that is alive*)? The second question is: Is it bigger than a shoe box? This is a shoe box (*show participant shoe box*). Is a dog bigger than a shoe box (*alternate phrasing: does a dog fit into this shoe box*)? After looking at each picture I will ask you one of those questions.

I want you to try your best to remember what the picture is. I also want you to try and remember the color of the picture, where the picture was on the screen, and which question you were asked about the picture. There are lots of things to try and remember – I want you to try your best to remember as much as you can.

Do you have any questions? Let's practice." *Administer study practice.*

Test. The examiner read the following script to introduce the test phase of the source memory task in English.

"Now I am going to ask you about which pictures you remember. I am going to show you more pictures. Some of them will be the pictures you just saw and some of them will be new pictures that you have never seen before. I want you to look at each picture carefully and decide whether you remember the picture or not. If you do remember the picture, I am going to ask you some questions. First, I will ask you how certain you are about your choice. In other words, if there is something specific you remember about the picture then you would be sure that you saw the picture before – you remember it. If there is something about the picture

that you remember, but you are not certain of your choice, you will say that you saw the picture, but it is just familiar. Then, I will ask you where the picture was on the screen. Then I will ask you what color the picture was presented in. Finally, I will ask you which questions you were asked about the picture. I want you to try and be as accurate as possible when you are answering these questions. Try your best to remember as many of the pictures, that you just saw, as you can.

Do you have any questions? Let's practice." *Administer test practice*.

Afrikaans Script

Study. The examiner read the following script to introduce the study phase of the source memory task in Afrikaans.

"Ons gaan 'n geheue speletjie speel. In hierdie speletjie gaan ek vir jou 'n paar prentjies wys. Ek will hê jy moet jou beste probeer om soveel van die prentjies as moontlik to onthou. Jy sal baie prentjies sien en jy mag dalk nie almal van hulle onthou nie, maar ek wil hê jy moet jou beste probeer om soveel van hulle te onthou as wat jy kan. Wanneer jy klaar na prentjies gekyk het, gaan ek jou vra watter van hulle jy onthou.

Die prentjies sal op die linker-of die regterkant van die skerm gewys word (*check that the participant can identify left and right—have them point to the screen*) in rooi of in groen (*ask them to identify red and green color patches*). Na elke prentjie gaan ek jou een vraag daaroor vra. Daar is net twee vrae wat ek sal vra. Die eerste vraag is: Is dit 'n leewendige ding? Byvoorbeeld, 'n hond is 'n lewendige ding, maar 'n bal is nie. Kan jy vir my 'n voorbeeld van 'n lewendige ding gee (*alternate phrasing:'n ding wat lewendig is*)? Die tweede vraag is: Is dit groter as 'n skoenboks? Hierdie is 'n skoenboks (*show participant shoe box*). Is 'n hond groter as 'n skoenboks (*alternate phrasing: pas 'n hond in hierdie boks in*)? Na elke prentjie sale k jou een van hierdie vrae vra.

Ek wil hê jy moet jou beste probeer om te onthou wat die prentjie is. Ek wil ook hê jy moet probeer onthou wat die kleur van die prentjie is, waar die prentjie op die skerm wys, en watter vraag ek jou vra oor die prentjie. Daar is baie goed om te probeer onthou – ek wil hê jy moet jou beste probeer om soveel te onthou as wat jy kan.

Het jy enige vrae? Kom ons oefen." *Administer study practice.*

Test. The examiner read the following script to introduce the test phase of the source memory task in Afrikaans.

"Nou gaan ek jou vra oor watter prentjies jy onthou. Ek gaan vir jou nog prentjies wys. Sommige van hulle sal die prentjies wees wat jy nou net gesien het en sommige van

hulle sal nuwe prentjies wees wat jy nog nooit gesien het nie. Ek wil hê jy moet versigtig na elke prentjie kyk en besluit of jy die prentjie onthou of nie. As jy die prentjie onthou, gaan ek vir jou ‘n paar vrae vra. Eerstens, sal ek jou vra hoe seker jy is oor jou keuse. Met ander woorder, as daar iets spesefiek is wat jy onthou van die prentjie dan sal jy seker wees dat jy die prentjie voorheen gesien het – jy onthou dit. As daar iets is was jy onthou van die prentjie, maar jy is nie seker oor jou keuse nie, sal jy sê dat jy daardie prentjie gesien het, maar hy lyk net bekend. Ek sal jou dan vra waar die prentjie op die skerm gewys het. Dan sale k jou vra watter kleur die prentjie was. Laastens, sale k jou vra watter vraag jy gevra was oor die prentjie. Ek wil hê jy moet probeer om so akkuraat as moontlik to wees wanner jy hierdie vrae antwoord. Probeer jou beste om soveel van die prentjies te onthou wat jy nou net gesien het as wat jy kan.

Het jy enige vrae? Kom ons oefen.” *Administer test practice*.

APPENDIX S

Chapter 5: Statistical Assumptions

Outliers

The distributions of maternal socioeconomic status, child, Miss, and False Alarm scores all contained one outlier > 3*SD*s above the mean. The distributions of maternal education level, Hit, and Correct Rejection scores all contained one outlier < 3*SD*s below the mean. In order to prevent outliers exerting undue influence on further statistical analysis of these data, I recoded the aforementioned outliers to 1 point above or below the next highest observed value (Winer, 1971). Although the distributions of continuous prenatal alcohol exposure outcomes all contained one (AA/occasion) or two (AA/day and drinking frequency [days/week]) outlier value > 3*SD*s above the mean, these values reflect true scores and were, therefore, not recoded.

Statistical Assumptions

The assumption of independence was met for all sample, predictor, and outcome variables examined in this study. The distributions of maternal age at delivery, education level, drinking during pregnancy (AA/day, AA/occasion and drinking frequency [days/week]), and smoking during pregnancy; child age at testing; hit, Miss, False Alarm, Correct Rejection, and WISC-IV digit span backwards scores deviated from the normal (Table S.1). The distributions of maternal drinking during pregnancy (AA/day, AA/occasion, and frequency drinking [days/week]); child age at testing, violated the assumption of homogeneity of variance. Additionally, Levene's statistic fell just short of significant for the distributions of maternal smoking during pregnancy and child WISC-IV Full Scale IQ indicating a trend toward violating the assumption of homogeneity of variance.

Table S.1
Tests of Normality and Homogeneity of Variance (N = 86)

	Kolmogorov-Smirnov			Levene's Test		
	Statistic	*df*	*p*	*Statistic*	*dfs*	*p*
Maternal variables						
Age at delivery	0.11	86	.01*	1.38	2, 83	.27
Highest level of education	0.12	86	.003**	0.18	2, 83	.84
Socioeconomic status[a]	0.07	85	.20	0.79	2, 82	.46
AA/day	0.27	86	< .001***	18.63	2, 83	< .001***
AA/occasion	0.27	86	< .001***	22.00	2, 83	< .001***
Frequency (days/week)	0.27	86	< .001***	27.52	2, 83	< .001***
Smoking during pregnancy (cig./day)	0.19	86	< .001***	2.57	2, 83	.08†
Child variables						
Age at testing	0.10	86	.03*	3.57	2, 83	.03*
WISC-IV full scale IQ	0.08	86	.20	3.06	2, 83	.05†
Outcome variables						
d-prime	0.07	86	.20	0.77	2, 83	.47
Hit	0.15	86	< .001***	0.55	2, 83	.58
Miss	0.15	86	< .001***	0.55	2, 83	.58
False alarm	0.32	86	< .001***	2.30	2, 83	.11
Correct rejection	0.32	86	< .001***	2.30	2, 83	.11
Source memory score	0.08	86	.20	0.01	2, 83	.99
Mediator variable						
WISC-IV digit span backwards	0.23	86	< .001***	0.63	2, 83	.54

Note. AA = absolute alcohol; Cig. = cigarettes; WISC-IV = Wechsler Intelligence Scale for Children—Fourth Edition.
[a]Data missing for one mother of a participant (female, age = 12.6 years) in the non-exposed control group.
†$p < .10$. *$p < .05$. **$p < .01$. ***$p < .001$.

APPENDIX T

Corrected Source Memory Task Performance

Table T.1
Between-Group Differences in Source Memory Performance, Adjusted for Self-Corrections (N = 86)

Variable	FAS/PFAS (n = 23)	HE (n = 26)	Non-exposed Control (n = 37)	F	p	η^2
d-prime	2.8 (0.5)	2.7 (0.5)	2.8 (0.5)	1.06	.35	.03
Hit (%)	85.3 (3.5)	79.7 (3.8)	83.4 (2.9)	1.96	.15	.05
Miss (%)	14.7 (3.5)	20.3 (3.8)	16.6 (2.9)	1.96	.15	.05
False alarm (%)	4.1 (1.5)	3.1 (1.4)	2.2 (0.8)	1.82	.17	.04
Correct rejection (%)	95.9 (1.5)	96.9 (1.4)	97.8 (0.8)	1.82	.17	.04
Source memory score	63.3 (9.4)	70.3 (8.4)	69.1 (8.6)	4.46[a]	.02[*]	.10

Note. Unless otherwise stated, values presented are means with standard deviations in parenthesis. FAS = fetal alcohol syndrome, PFAS = partial FAS, HE = heavily-exposed nonsyndromal.
[a]FAS/PFAS < HE = non-exposed control
[*]$p < .05$.