The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.

University of Cape Town

Event-Based Prospective Memory in Fetal Alcohol Spectrum Disorders

Catherine O'Leary
OLRCAT001

A dissertation submitted in fulfillment of the requirements for the award of the degree of Master of Arts (Psychological Research)

Department of Psychology
Faculty of Humanities
University of Cape Town
2013

University of Cape Town

COMPULSORY DECLARATION: This work has not been previously submitted in whole, or in part, for the award of any degree. It is my own work. Each significant contribution to, and quotation in, this dissertation from the work, or works, of other people has been attributed, cited, and referenced. The financial assistance of the National Research Foundation (DAAD-NRF) towards this research is hereby acknowledged. Opinions expressed and conclusions arrived at are those of the author and are not necessarily to be attributed to the DAAD-NRF.

Signature: Date: 7 February 2013

ACKNOWLEDGEMENTS

I would like to take this opportunity to express my sincere appreciation and gratitude to my supervisor, Kevin Thomas, and my co-supervisors, Sandra Jacobson and Christopher Molteno, for their guidance and dedication to my project. In addition, I wish to thank Joseph Jacobson who gave so generously of his time and expertise to guide me through this project. I would also like to thank Matthias Kliegel for his assistance with the conceptualization of this project and for his on-going support. In addition, I would like to thank a number of people whose time and resources made this project possible: Maggie September for scheduling appointments and for her dedication to the larger project; Nadine Kilchenmann for her assistance with data collection; Neil Dodge and Renee Sun for their assistance with data management; Moira Raatz for her assistance with scheduling participants; John Minnies and Patricia Solomons for transporting participants; and Michelle Hoogenhout for assistance with statistical analysis. I also wish to thank H. Eugene Hoyme, Luther K. Robinson, and Nathaniel C.O. Khaole, who conducted the dysmorphology examinations in conjunction with the NIAAA Collaborative Initiative on Fetal Alcohol Spectrum Disorders. I further wish to express my profound appreciation to the mothers and children who participate in this research. Lastly, I wish to thank my family, partner, and friends whose unconditional love, support, and encouragement I appreciate so deeply.

This study was supported by grants from NIH National Institute on Alcohol Abuse and Alcoholism (NIAAA) R01-AA016781, two supplements to RO1-AA09524; U01-AA014790 and U24AA014815 in conjunction with CIFASD; NIH Office of Research on Minority Health; and Joseph Young, Sr., Fund, from the State of Michigan. Further support was provided by the AW Mellon Foundation and the German Academic Exchange Service (DAAD)/National Research Foundation (NRF)—a sincere note of thanks.

University of Cape Town

TABLE OF CONTENTS

University of Cape Town

University of Cape Town

University of Cape Town

University of Cape Town

LIST OF FIGURES

University of Cape Town

LIST OF TABLES

University of Cape Town

ABSTRACT

Background: Learning and memory seem to be particularly vulnerable to the effects of heavy prenatal alcohol exposure. Previous research has, however, been limited to the study of retrospective memory (i.e., episodic or declarative memory) in children with a history of prenatal alcohol exposure. Recently, memory researchers have turned their attention to the study of prospective memory (PM), or the ability to realize and act on delayed intentions, in clinical populations. There are no published studies exploring PM in FASD, however. Prospective remembering is reliant on declarative memory as well as intact executive functioning, both of which are known to be impaired in FASD. The current study aimed, therefore, to investigate event-based PM functioning in a longitudinal cohort of children with heavy prenatal alcohol exposure. It also aimed to investigate whether the relation between prenatal alcohol exposure and prospective memory was influenced by IQ, executive functioning, or retrospective memory.

Methods: Participants were 89 children (*M* age=11.1 years, *SD* = 0.4): 29 with fetal alcohol syndrome (FAS) or partial FAS (PFAS), 32 heavy exposed nonsyndromal (HE), and 28 controls born to abstainers/light drinkers. They completed two versions (Focal or Non-Focal) of the *Dresden Cruiser* (Voigt et al., 2011), a computerized car-racing game that measures event-based PM at two difficulty levels (easy or difficult). The Focal version required participants to refuel their car when encountering a yellow car on the road; the Non-Focal version required them to refuel when encountering a yellow flower on the side of the road. A mixed factorial analysis of variance sought to determine whether there was a main effect of group status, as well as whether there were any interactions between the manipulation of on-going task factors (i.e., cue focality and difficulty level) and group status. Hierarchical regression analyses assessed the relation between prenatal alcohol exposure and PM when controlling for potential confounding variables (e.g., SES, smoking during pregnancy, postnatal alcohol use), IQ, executive functioning, and declarative/retrospective memory.

Results: Results indicated that there was a main effect of FASD diagnosis on PM performance, with children in the FAS/PFAS group having more PM failures than children in either the HE or Control groups. There were no significant differences in PM performance for children in the HE and Control groups. Both cue focality and task difficulty had a significant main effect, but neither the cue focality × group nor the difficulty level × group interactions were significant. Children showed similar levels of on-going task absorption, with no

University of Cape Town

significant between-group differences in number of cars hit on all versions of the task. Furthermore, there were no significant between-group differences in self-reported computer usage or retention of on-going and PM task instructions. Regression analyses indicated that prenatal alcohol exposure has an independent effect on PM over and above the effects of potential confounding variables, executive functioning, and declarative/retrospective memory. However, WISC-IV Full Scale IQ score partially mediated the effects of prenatal alcohol exposure on PM. Follow-up investigation revealed that the WISC-IV Perceptual Reasoning and Verbal Comprehension indices, but not the Processing Speed and Working Memory indices, partially mediated the effects of prenatal alcohol exposure on PM.

Conclusion: Overall, these data suggest that impairments in event-based PM, as measured by the *Dresden Cruiser*, are only seen in children who met criteria for either FAS or PFAS. The effect of prenatal alcohol exposure on PM was independent of socio-demographic variables and persisted after control for scores on tests of executive functioning and declarative/retrospective memory, suggesting distinct PM impairment over and above any existing difficulties with either executive functioning and/or declarative/retrospective memory. The effects of prenatal alcohol exposure on PM were, however, partially mediated by general intellectual functioning. The current study is the first to document PM impairments in children with a history of heavy prenatal alcohol exposure and has important implications for the diagnosis and management of FASD. Future studies should examine whether alcohol effects on PM can be detected using a timing rather than event-related assessment in order to determine whether impaired performance might also be seen in nonsyndromal alcohol-exposed children.

University of Cape Town

Memory deficits associated with fetal alcohol spectrum disorders (FASD) have been reported widely (for review, see Manji, Pei, Loomes, & Rasmussen, 2009). Previous research has, however, been restricted to the study of retrospective memory (more specifically, declarative or episodic memory). Although memory researchers have turned their attention recently to the study of prospective memory in clinical populations, there are no published studies examining this form of memory in FASD. This study, therefore, aimed to address this gap in the FASD literature, and in so doing aimed to help expand the definition of an FASD behavioral phenotype.

Prospective Memory

Definition and Theoretical Approaches

Prospective memory (PM) is the ability to realize and execute delayed intentions (Ellis, 1996; Kliegel, McDaniel, & Einstein, 2008c). Intact PM is integral to effective everyday functioning (e.g., remembering to get a letter signed when seeing a particular person, or remembering to take medication at a specific time).

PM is classified as being either time-or event-based (Einstein & McDaniel, 1996). *Time-based PM* is the ability to realize and execute delayed intentions at a specific point in time. Einstein and McDaniel (1996, p. 129) state that time-based PM is characterized by the "appropriateness of [an] action [being] determined by a passage of time." In contrast, *event-based PM* is the ability to realize and execute delayed intentions when encountering a specific event (e.g., a person or place). This study focused on event-based PM.

Unlike retrospective memory tasks, which rely on external prompting, prospective remembering occurs as a result of an internal self-initiated response that interrupts on-going activity such that a delayed intention may be realized (Burgess & Shallice, 1997; Einstein & McDaniel, 1996). PM, whether it is cued by a period of time or by an event, is, therefore, a form of remembering that is relatively automatic and that brings an intended action to mind without a prompted memory search (McDaniel & Einstein, 2000). Although this point is held as the gold standard for identifying PM functioning in a laboratory setting, there is on-going debate into the cognitive processes underlying PM.

There are three main theoretical approaches to identifying the cognitive processes underlying PM: strategic monitoring, automatic/spontaneous retrieval, and the multiprocess framework. *Strategic monitoring theory* (Burgess & Shallice, 1997) is organized around the notion that PM functioning consists of a sequence of stages, each of which needs to be completed in order for prospective remembering to occur. These stages are intention

University of Cape Town

formation, intention retention, intention initiation (either time- or event-based), and intention execution (Ellis, 1996; Kliegel, Martin, McDaniel, & Einstein, 2002). This theory assumes that an attention switch, from the on-going task to the intended action, will take place (McDaniel & Einstein, 2000). In order for the attention switch to take place, a supervisory attention system (SAS) is needed to encode the intention, monitor for the target event during on-going activity, and interrupt the on-going activity to perform the intended action appropriately (Burgess & Shallice, 1997). McDaniel and Einstein (2000) note that the primary assumption of the strategic monitoring approach is that some attentional resources will be dedicated to monitoring the environment during on-going activity and that this monitoring will, in turn, have a cost for the on-going activity itself. This theoretical model is supported by research showing that introducing a PM component to an on-going task slows down task performance by reducing the availability of resources for performing the task (e.g., Smith, 2003; Smith et al., 2007).

The *automatic/spontaneous retrieval theory* assumes that, when a PM cue is encountered, the intended action is brought to mind automatically by a self-initiated internal response (McDaniel, Robinson-Riegler, & Einstein, 1998). This theory is supported by an involuntary automatic associative memory system (McDaniel et al., 1998). This memory system allows for external PM cues to interact with encoded intended actions such that the associated information is automatically brought to mind (McDaniel & Einstein, 2000). Due to the spontaneous nature of the memory retrieval process, there is no systematic monitoring of the environment, and therefore few cognitive resources are required (McDaniel & Einstein, 2000; Moscovitch, 1994).

The current consensus, however, holds that neither strategic monitoring nor automatic/spontaneous retrieval theories provide satisfactory explanations of PM in isolation. McDaniel and Einstein (2000), therefore, proposed a *multiprocess framework*, designed specifically for understanding event-based PM. This theoretical framework proposes that both strategic monitoring and automatic retrieval processes contribute to effective PM retrieval. Furthermore, it asserts that each underlying cognitive process contributes to a greater or lesser extent, depending on task conditions. McDaniel and Einstein (2000) argue that task conditions can be altered in several different ways: the importance of the PM task, the distinctiveness of the PM cue, the strength of association between PM cue and the intended response, the type of processing required (i.e., focal/non-focal), as well as the level of on-going task absorption.

University of Cape Town

It is beyond the scope of this review to discuss the effects of each of these task conditions on PM (see McDaniel & Einstein, 2000, for a comprehensive discussion). It is important to note, however, that altering task conditions will affect the relative contribution of strategic monitoring and automatic retrieval processes, respectively. The multiprocess framework is supported by research that evaluates the cost of PM on on-going activity under different task conditions (see, e.g., Einstein et al., 2005; Loft & Yeo, 2007; McDaniel, Guynn, Einstein, & Breneiser, 2004). PM is, therefore, best understood as being reliant on both strategic and automatic retrieval processes, with the role of each type of retrieval in prospective remembering being dependent on the exact nature of task conditions.

Retrospective versus Prospective Memory

Retrospective and prospective remembering are recognized as two distinct cognitive processes (Burgess & Shallice, 1997). Nonetheless, there are both retrospective and prospective remembering components to intact PM functioning (Burgess & Shallice, 1997; Einstein & McDaniel, 1996; Kliegel, Jäger, Altgassen, & Shum, 2008a). Einstein and McDaniel (1996) note that the retrospective component of PM is similar to cued-recall tasks, in that an individual has to remember both the intended action as well as the appropriate PM cue. Drawing on Ellis's (1996) conceptual framework for PM, Kliegel et al. (2002, 2008a) locate the retrospective component of PM as being the cognitive resource supporting the stage of intention retention.

PM failures may, therefore, occur as a direct result of retrospective memory failures at the level of intention retention. For example, Einstein, Holland, McDaniel, and Guynn (1992) found that age-related differences in PM were especially common in complex PM tasks, with older participants (aged 60 to 80 years, $M = 69.13$) having more PM failures than younger participants (aged 19 to 22 years, $M = 20.56$). The authors suggested that age differences in PM performance were the result of increasing retrospective memory failures for older participants, specifically at the level of intention retention, as the PM task became more complex. Hence, it is of clinical significance to use research designs that allow for distinguishing between retrospective and prospective failures within PM paradigms.

Prospective Memory, Executive Functioning, and the Prefrontal Lobes

PM is largely supported by intact executive functioning (EF; Kliegel, Mackinlay, & Jäger, 2008b). EF is defined as a constellation of higher-order cognitive functions that regulate and supervise goal-directed behavior (Zillmer, Spiers, & Culbertson, 2008). The

University of Cape Town

term ‘executive function’ is, therefore, an umbrella term for a variety of cognitive functions, including planning, working memory, inhibition, and self-regulation (Anderson, 2002). Neuropsychological evidence suggests that EF is mediated by the prefrontal lobes and associated neural networks (Anderson, 1998, 2002; Zillmer et al., 2008).

Anderson (2002) proposed a multiprocess model of EF. The model divides EF into four distinct domains: attentional control, information processing, cognitive flexibility, and goal setting (see Figure 1). The inter-related functioning of the four domains is conceptualized as collectively forming executive control. Specifically, attentional control has an important functional role in mediating the functioning of the other executive domains. On the other hand, cognitive flexibility, goal setting, and information processing are all functionally inter-related and inter-dependent.

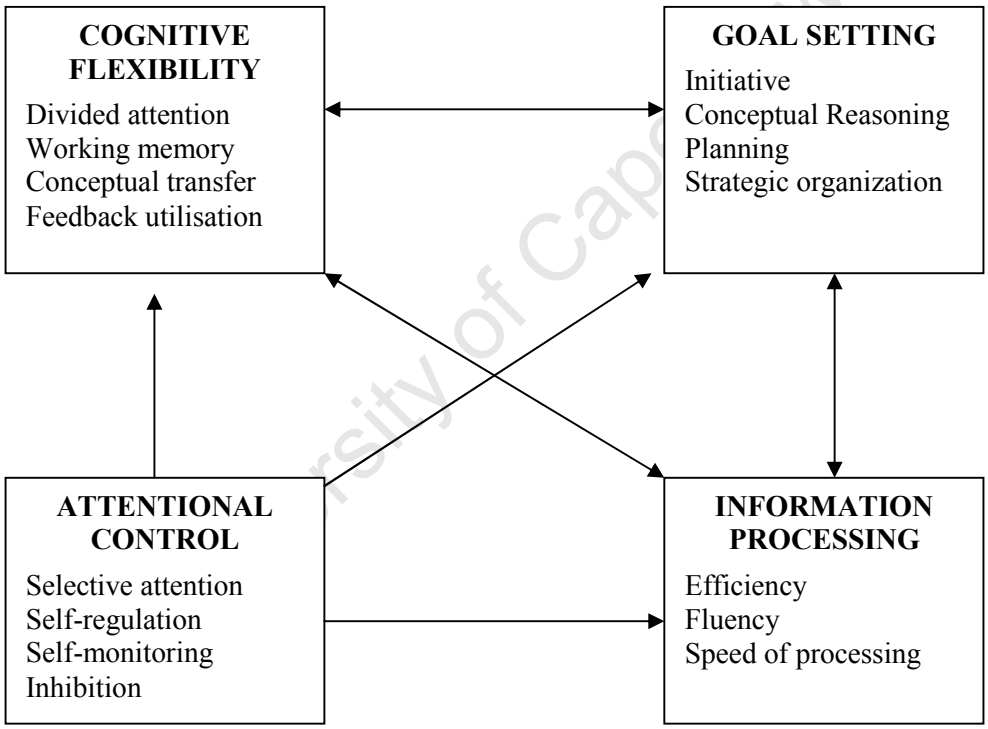

Figure 1. Anderson’s (2002) model of executive functions.

In line with Anderson’s (2002) conceptualization of EF, empirical research suggests that the various phases of PM are supported by specific aspects of EF (Kliegel et al., 2002). More specifically, intention formation is correlated with planning abilities, intention initiation is correlated with task switching (an aspect of cognitive flexibility), and intention execution is correlated with inhibition (an aspect of attentional control; Kliegel et al., 2002, 2008b; Martin, Kliegel, & McDaniel, 2003). Highlighting the significance of the functional link between EF and PM, Burgess, Quayle, and Frith (2001, p. 545) commented that “PM

functions serve to bind together complex goal-directed behavioral sequences and enable a person to carry out their plans…in a meaningful order and at the appropriate time."

The link between PM and EF is further supported by neuroimaging research, which highlights the prefrontal lobes, in particular the rostral prefrontal cortex, as functionally significant in completing PM tasks successfully (Burgess et al. 2001; Okuda et al., 2007; Reynolds, West, & Braver, 2009). For example, Simons et al. (2006) used a functional magnetic resonance imaging (fMRI) paradigm to investigate whether the phases of PM are in fact functionally discreet. Participants were required to complete both a word and a shape task. Each task was divided into three sections: on-going task, cue identification, and cue retrieval. During the word task, participants were required to distinguish between the size of words (on-going task), the semantic relation between words (cue identification), and finally, while counting the number of syllables, whether the words were in the same case (cue retrieval). During the shape task, the target shapes (triangles, circles, and squares) were presented in a grid. Participants were required to press a key in the direction of the shape that was not a triangle (on-going task), to press a key if the shapes were a chess knight's move away from each other (cue identification), and finally, while counting the number of shape sides excluding the triangle, to press a key if the shapes were presented in the same color (cue retrieval). Results indicated increased activation in the rostral prefrontal cortex (Brodmann area 10) across both cue identification and cue retrieval PM conditions. Simons and colleagues concluded, therefore, that BA 10 may be required for both biasing attention toward cue identification as well as for the internal maintenance of intended actions.

University of Cape Town

Prospective Memory versus Working Memory

Although there is a functional relation between intact PM functioning and EF, there is evidence that PM and working memory are largely functionally independent. The dissociation between these two cognitive domains has, however, caused some debate based on the aforementioned theoretical approaches to the processes underlying intact PM functioning. Briefly, those who propose that PM is reliant on the strategic monitoring of the environment, and consequently the active maintenance of a goal in mind, support a functional relation between working memory and PM (e.g., Burgess & Shallice, 1997). In contrast, those who propose that PM is a relatively automatic or spontaneous process do not support the functional relation between working memory and PM (e.g., Einstein et al., 2005). In an attempt to further explore the neurocognitive processes underlying prospective remembering,

specifically the distinction between working memory and PM, researchers have turned towards experimental designs that allow for the use of brain imaging techniques.

Reynolds, West, and Braver (2009) aimed to investigate the relation between working memory and PM using a hybrid blocked/event-related fMRI design. Participants were required to complete an on-going *n*-Back working memory task with an embedded PM cue. Use of the *n*-Back task allowed the researchers to manipulate the working memory load during the on-going task. Target detection was examined using an oddball task during which participants had to respond when they saw a word presented in a specified target color. Results indicated that, as working memory load increased, PM and working memory engaged different brain regions during sustained activity—the anterior prefrontal cortex (aPFC) and dorsolateral prefrontal cortex (DLPFC), respectively. More specifically, PM was related to "sustained top-down processes supported by the aPFC" as well as transient activations in the middle temporal gyrus that were prompted by the presentation of PM cues (Reynolds et al., 2009, p. 1219). The authors concluded, therefore, that their data supported the dissociation between working memory and PM, even though there was some overlap in functional activation.

Following a similar line of investigation, Basso, Ferrari, and Palladino (2010) examined whether PM and working memory are separate mechanisms using transcranial magnetic stimulation (TMS) during a verbal event-based PM task. Working memory demand (low, medium, or high) and PM demand (low and high) were manipulated during three studies and PM cues were embedded in the on-going working memory task. TMS was applied to the left and right dorsolateral prefrontal cortices, as these areas are regarded as largely responsible for working memory. Their results indicated that when TMS was applied bilaterally, PM errors increased, but there was only a minor effect on the on-going working memory task. Basso and colleagues interpreted these findings as evidence of the beneficial effect of the DLPFC during PM. This result, when combined with the finding that manipulating working memory and/or PM demands did not produce linear effects on on-going or PM tasks, supports the hypothesis that working memory and PM are functionally dissociable.

Interestingly, PM and working memory only seem to compete for resources at high levels of working memory demand (Reynolds et al., 2009). Consistent with this, Basso et al. (2010) concluded that working memory and PM are reliant on separate memory systems but that PM may draw on working memory resources when the on-going task is characterized by a high working memory demand. Taken together, therefore, the findings of Reynolds et al.

University of Cape Town

and Basso et al. support the hypothesis that working memory and PM are functionally independent and that they recruit different neural regions during task performance.

Prospective Memory in Children and Adolescents

Despite the functional importance[1] of the development and maintenance of intact PM during childhood and adolescence, relatively few studies have investigated PM in children and adolescents. Furthermore, most of those studies have focused on time-based PM and the role of time-monitoring. For example, Ceci and Bronfenbrenner's (1985) seminal study assessed time-based PM in typically-developing 10- and 14-year-olds (M = 10.7 years and 14.6 years respectively). The participants were required to check a clock during a cupcake-baking activity. Clock-checking was assessed both in a familiar (i.e., home) and an unfamiliar (i.e., laboratory) setting. The researchers found that older participants used more effective and strategic time-monitoring than did younger participants. For instance, in the laboratory condition, older participants checked the clock on fewer occasions than younger participants did. Ceci and Bronfenbrenner interpreted this finding as indicating that, in everyday situations, older children would be able to complete on-going tasks in conjunction with PM tasks more effectively than their younger counterparts.

The implications of this research sparked interest in the quantification of both event- and time-based PM development within a controlled environment. Subsequently, Kerns (2000) found that typically-developing children between 7 and 12 years old (M = 10.03, SD = 1.72) displayed age-related differences in time-based PM on a computerized task called the *CyberCruiser*. The on-going task required participants to drive a car while attempting to accumulate points for speed and driving skill. The PM task was that participants needed to refuel the car when the tank was ¼ full. Participants were, therefore, required to monitor the fuel level throughout the on-going task. Results indicated that older children ran out of fuel less often than younger children did. Kerns concluded, therefore, that a developmental trend exists, with older children displaying more intact PM than younger children.

Smith, Bayen, and Martin (2010) aimed to identify the cognitive components of event-based PM in children and adults by comparing the performance of typically-developing 7-year-olds, 10-year-olds, and adults (18- to 31-years-old) on a computerized task. The latter displayed better PM performance than both younger and older children, and older children displayed better PM performance than younger children. Interestingly, when the retrospective

[1] E.g., Remembering to complete homework or remembering to get a letter signed by a caregiver

University of Cape Town

component of PM was controlled for, the differences in PM performance for 7- and 10-year-olds disappeared, suggesting poorer PM performance was due to retrospective memory failures by the younger children. Smith and colleagues suggested that, for younger children, in particular, the retrospective component of a PM task may be improved by increasing the discriminability of PM cues. Nevertheless, it is noteworthy that by 10 years of age children appear to have developed a reasonably sophisticated level of PM functioning.

Consistent with the developmental trends that Kerns (2000) and Smith et al. (2010) highlighted, Ward, Shum, McKinlay, Baker-Tweney, and Wallace (2005) suggested that the developmental trajectory of PM is linked closely to the development of the prefrontal lobes and, accordingly, the development of EF. Further support for this functional link was provided by West (1996) who proposed a prefrontal lobe model for understanding PM. This model is based on two assumptions: (1) that older adults display prefrontal lobe deterioration, and (2) that they show increasing PM failures when compared to younger adults on tasks reliant on intact prefrontal lobe functioning. Ward et al. (2005) tested the developmental validity of this model, in relation to event-based PM, in a sample of children (7- to 10-year-olds, $M = 8.60$, $SD = 1.19$), adolescents (13- to 16-year-olds, $M = 14.57$, $SD = 1.30$), and adults (18- to 21-year-olds, $M = 19.07$, $SD = 1.14$). To test the functional maturity of the prefrontal lobes, the researchers manipulated on-going task conditions (e.g., by altering the cognitive demand of the on-going task) such that differing levels of prefrontal functioning were required. Overall, the results indicated that children had more PM failures than adolescents and adults, and that PM performance for adolescents and adults were on par with one another. Children also displayed poorer performances on standardized measures of EF (e.g., the Stroop test) than adolescents or adults. Consistent with previous research (e.g., Kerns, 2000), the results indicated that there was a significant relation between EF and PM performance in conditions that were highly resource-demanding. Ward and colleagues concluded, therefore, that the development of PM is supported by the functional maturation of the prefrontal lobes.

As a result of the conceptual link between EF, the prefrontal lobes, and intact PM, Kliegel et al. (2008c) suggested that researchers begin to investigate PM functioning in pediatric clinical populations, which are known to have deficits in EF. In one such example, Kerns and Price (2001) compared PM functioning in a group of children with Attention-Deficit/Hyperactivity Disorder (ADHD) and a control group of children matched for age (8- to 13-year-olds), gender, and IQ. Results indicated that on the *CyberCruiser*, a time-based measure of PM, children in the ADHD group had significantly more PM failures than those

University of Cape Town

in the control group. Kerns and Price emphasized that the between-group differences were due to inefficient time-monitoring strategies in the ADHD group, over-and-above the effect of attention. In line with this finding, children with ADHD appear to have specific EF deficits (e.g., impaired sustained attention and inhibition) that arise from abnormal structure and functioning of the prefrontal lobes, as well as impaired functioning of frontostriatal circuitry (Cherkasova & Hechtman, 2009). Kerns and Price concluded, therefore, that impaired PM in children with ADHD supports the hypothesis that frontal lobe systems play an important role in effective PM functioning.

Following this conceptual framework for understanding the role of EF in PM, it is important that research with pediatric clinical populations (e.g., children with fetal alcohol spectrum disorders) be expanded.

University of Cape Town

Fetal Alcohol Spectrum Disorders (FASD)

FASD: Diagnosis and cognitive impairments

The adverse effects of prenatal alcohol exposure have physical, social, and cognitive manifestations in the development of exposed individuals. Fetal alcohol syndrome (FAS) represents the most severe end of the spectrum of outcomes (Hoyme et al., 2005; Jones & Smith, 1973; Stratton, Howe, & Battaglia, 1996). The three main diagnostic criteria for FAS are the presence of deficits in central nervous system (CNS) development and neurocognitive functioning, deficient physical growth patterns, and craniofacial anomalies (e.g., short palpebral fissures, thin upper lip, and a broad nasal bridge).

Variability in the timing and level of prenatal alcohol exposure (Jacobson et al., 2008), genetic differences (Jacobson et al., 2006) and presence of maternal risk factors (e.g., maternal age at delivery; Jacobson, Jacobson, Sokol, & Ager, 1998; Jacobson, Jacobson, Sokol, Chiodo, & Corobana, 2004; May et al., 2005) produce a range of manifestations in the presentation of facial, CNS, and growth dysmorphology. As a result, children with a history of prenatal alcohol exposure may not present with all of the features necessary for a diagnosis of full FAS, but there may be sufficient cognitive-behavioral deficits (e.g., generally lowered IQ scores, attention and verbal learning impairments, poor eyeblink conditioning, or arithmetic ability) to indicate that the teratogenic effects of alcohol have affected CNS development (Hoyme et al., 2005; Jacobson, Jacobson, Stanton, Meintjes, & Molteno, 2011; Mattson, Riley, Gramling, Delis, & Jones, 1998).

The aforementioned variability in the timing and level of prenatal alcohol exposure has led to the inclusion of a range of diagnostic categories under the umbrella term fetal

alcohol spectrum disorders (FASD; Hoyme et al., 2005; Kodituwakku, 2007). *Partial FAS* (*PFAS*) is diagnosed when a history of prenatal alcohol exposure has been confirmed; two of the three characteristic facial features are present; and either the CNS, cognitive-behavioral, or physical growth symptoms are present (Hoyme et al., 2005). The category *alcohol-related birth defects* (*ARBD*) relates more specifically to a diagnosis based on the confirmation of maternal drinking, as well as the presence of congenital physical abnormalities (e.g., cardiac, skeletal, and renal anomalies), but not to the associated CNS development deficits (Hoyme et al., 2005). *Alcohol-related neurodevelopmental disorder* (*ARND*), on the other hand, is diagnosed when there are deficits in CNS development or impairment in cognitive and behavioral functioning, and the presence of a history of prenatal alcohol exposure without the characteristic dysmorphic features and/or growth deficits (Hoyme et al., 2005).

In line with the variability in timing and level of prenatal alcohol exposure, neuropsychological studies have shown that children with prenatal alcohol exposure present with wide-ranging deficits in cognitive functioning. Alcohol-related deficits are present in the domains of general intellectual functioning (i.e., children with FASD diagnoses achieve lower IQ scores than those of typically-developing controls), as well as with deficits in information processing speed, verbal and non-verbal learning and memory, attention, EF, and visual-spatial perception (e.g., Burden, Jacobson, Sokol, & Jacobson, 2005a; Burden, Jacobson, & Jacobson, 2005b; Coles, Lynch, Kable, Johnson, & Goldstein, 2010; Jacobson, Jacobson, Sokol, Martier, & Ager, 1993; Mattson et al., 1998; Rasmussen, 2005; Rasmussen, Horne, & Witol, 2006; see Kodituwakku, 2007 and Mattson et al., 2011, for reviews). Children with prenatal alcohol exposure also have impaired social skills (for a review, see Kully-Martens, Denys, Treit, Tamana, & Rasmussen, 2012) and an increased vulnerability to secondary disabilities (e.g., depression and anxiety; Streissguth et al., 1996; Fryer, McGee, Matt, Riley, & Mattson, 2007a). These deficits are present for individuals who display the characteristic facial features associated with heavy prenatal alcohol exposure, as well as for those who do not (Jacobson et al., 2011; Mattson et al., 1998).

Consistent with the findings of such neuropsychological studies, neuroimaging studies have shown that children with prenatal alcohol exposure have structural abnormalities specific to the cerebellum, corpus callosum, basal ganglia, frontal lobes, and hippocampus (for review, see Coles & Li, 2011, and Spandoni, McGee, Fryer, & Riley, 2007). These findings and similar data from other studies (e.g., Jacobson & Jacobson, 2002; Mattson, Schoenfeld, & Riley, 2001) suggest that neuropsychological impairments need to be investigated in each of the categories along the FASD diagnostic spectrum.

University of Cape Town

FASD, Executive Functioning, and the Prefrontal Lobes

EF deficits are widely reported in individuals with FASD (for review, see Rasmussen, 2005). These deficits are present in cases with and without the characteristic FAS facial dysmorphology (Connor, Sampson, Bookstein, Barr, & Streissguth, 2000; Mattson, Goodman, Caine, Delis, & Riley, 1999; Rasmussen & Bisanz, 2009). Furthermore, the negative effects of prenatal alcohol exposure on EF are present even when IQ scores are controlled for (Noland, Singer, Arendt, Minnes, Short, & Bearer, 2003). In other words, EF deficits associated with FASD cannot be attributed solely to generally lowered IQ scores.

Individuals with FASD have impairments in all four of Anderson's (2002) EF domains. Within FASD, there are specific EF deficits on tests of set-shifting, sequencing, and working memory (domain of cognitive flexibility), planning, problem solving, and conceptual reasoning (domain of goal setting), fluency and processing speed (domain of information processing), and inhibition, self-regulation, and self-monitoring (domain of attentional control; Burden et al., 2005a; Connor et al., 2000; Kodituwakku et al., 2006; Kodituwakku, Kalberg, & May, 2001; Rasmussen & Bisanz, 2009).

Mattson et al. (1999) used the Delis-Kaplan Executive Functioning Scale (DKEFS; Delis, Kaplan, & Kramer, 2001) to compare EF across three diagnostic groups of children (8-15 years): fetal alcohol syndrome (FAS, M_{age} = 11.0, SD = 1.90), prenatal alcohol exposure (PAE, M_{age} = 11.9, SD = 2.38), and non-exposed controls (NC, M_{age} = 12.1, SD = 1.95). Participants were assessed on tasks of cognitive flexibility, response inhibition, planning, and concept formation and reasoning. Their results indicated that alcohol-exposed participants (FAS and PAE) performed more poorly than NC participants on all tests. Significantly, participants in the FAS and PAE groups performed at a similar level. It is important to note that all of the children in the PAE group were heavily exposed but nonsyndromal. Following a similar line of investigation, Green et al. (2009) compared EF across two diagnostic groups: FASD (including FAS, PFAS, and ARND) and a non-exposed control group (NC), with participants aged from 8 to 15 years (M = 10.70, SD = 2.0). Participants were assessed on four aspects of EF: planning, strategy use, attention, and spatial working memory. Participants in the FASD group performed more poorly on all four measures of EF than those in the NC group, with participants diagnosed with FAS, PFAS, and ARND all performing at a similar level. Taken together, the findings of Mattson et al. and Green et al. indicate that EF appears to be particularly vulnerable to the effects of prenatal alcohol exposure.

Consistent with the aforementioned results from neuropsychological studies, neuroimaging research implicates the frontal lobes and associated networks as being

University of Cape Town

vulnerable to the effects of prenatal alcohol exposure. Sowell et al. (2002) used high-resolution 3-D structural magnetic resonance imaging (sMRI) to determine regional brain shape abnormalities in adolescents with a history of heavy prenatal alcohol exposure. Their results indicated reduced surface area in the left orbital frontal cortex, as well as shape abnormalities in the dorsolateral prefrontal cortex. These findings are consistent with neuropsychological data suggesting that individuals with FASD are impaired on tasks of inhibition and planning, respectively (Mattson et al., 1999). Consistent with the findings of Sowell et al. (2002), Fryer et al. (2007b) compared blood oxygen level-dependent (BOLD) responses, using functional magnetic resonance imaging (fMRI), across two groups: alcohol-exposed (ALC) and non-exposed controls (NC), with participants aged from 8 to 18 years. Participants performed a response inhibition task while in the scanner. Although behavioral data suggested that participants in the ALC and NC groups performed the task at a similar level, the ALC group showed, relative to the NC group, increased and decreased BOLD responses in the prefrontal cortex and caudate nucleus, respectively. Fryer and colleagues concluded that this pattern indicates alcohol-related alterations in the activation of frontostriatal circuits during response inhibition.

Following a similar line of enquiry, O'Hare et al. (2009) used fMRI to investigate the neural basis of working memory in two groups: FASD and non-exposed controls (NC), with participants aged from 7 to 15 years (M = 10.70, SD = 2.40). Participants in the FASD and NC groups performed similarly on the verbal Sternberg working memory task, and participants in both groups drew on cerebrocerebellar networks during task performance. However, participants in the FASD group recruited a wider range of brain regions. Of particular interest is the suggestion that frontoparietal processing was less efficient for FASD participants, with increased activation in the left dorsal frontal lobe relative to NC participants. O'Hare and colleagues concluded that prenatal alcohol exposure alters activation in frontoparietal circuits, leading to less effective processing during working memory performance.

In another fMRI study, Diwadkar et al. (in press) investigated neural activation during working memory performance on an *n*-Back task in children, aged from 8.9 to 10.6 years, who were grouped according to FASD diagnosis (viz., FAS/PFAS, heavily exposed nonsyndromal (HE), or non-exposed controls). Behavioral data suggested there were no between-group differences on the 1-Back task performed in the scanner, but imaging data suggested that there were such differences: Across the three diagnostic groups, children recruited different aspects of the cortico-striatal-cerebellar network that supports working

University of Cape Town

memory when comparing regional activations during the 1-Back task relative to those during the 0-back task. Specifically, children in the FAS/PFAS group showed increased activation in parietal and cerebellar regions, children in the HE group showed increased activation in a more extensive fronto-striatal network, and children in the control group showed increased activation in Broca's area.

Taken together, the findings of O'Hare et al. (2009) and Diwadkar et al. (in press) are consistent with other fMRI studies of FASD in reporting that exposed children do not activate the neural network that is most efficient for performing a given cognitive task, but instead activate an alternative, often more extensive, network, presumably to compensate for a functional deficit in the network normally used to perform that task (Meintjes et al., 2010).

In summary, neuropsychological and neuroimaging research suggests that structural and functional abnormalities in the frontal lobes and associated networks underlie the widespread EF impairments associated with a diagnosis of FASD.

University of Cape Town

Rationale, Specific Aims and Hypotheses

In light of the aforementioned alcohol-related deficits in EF and the associated structural and functional abnormalities in prefrontal lobes, it is of clinical relevance to investigate whether PM functioning is impaired in children with a history of prenatal alcohol exposure. Furthermore, if prenatal alcohol exposure is associated with impaired PM, it would be useful to identify the processes underlying the breakdown in functioning, and to determine whether these PM effects are the result of a specific effect of prenatal alcohol exposure and, therefore, whether PM impairments persist after controlling for potential confounding variables, IQ, EF, and retrospective memory.

The current study was nested within an on-going prospective longitudinal cohort study investigating the neurobehavioral effects of heavy prenatal alcohol exposure on development (see Jacobson et al., 2008). The purpose of this study was two-fold: (1) I aimed to ascertain whether children with a history of heavy prenatal alcohol exposure had impaired event-based PM performance on the *Dresden Cruiser* (Voigt, Aberle, Schönfeld, & Kliegel, 2011) and (2) if PM performance was impaired, then I aimed to investigate whether the relation between prenatal alcohol exposure and PM was influenced by potential confounding variables and/or other potential predictor variables (viz., IQ, EF, or retrospective memory).

The design of this study allowed testing of these specific hypotheses:

1. Children with a history of heavy prenatal alcohol exposure will show impaired PM performance when compared to typically-developing, demographically similar controls born to mothers who either abstained from or drank minimally during pregnancy.
2. Deficits in PM performance are related to the effects of prenatal alcohol exposure and not to the effects of potential confounding socio-demographic variables such as prenatal drug exposure and maternal IQ.
3. Deficits in PM performance will be related to prenatal alcohol exposure after controlling for IQ.
4. Deficits in PM performance will be related to prenatal alcohol exposure after controlling for EF.
5. Deficits in PM performance will be related to prenatal alcohol exposure after controlling for retrospective memory.

University of Cape Town

METHODS

Design and Setting

This study used a prospective longitudinal cohort design and is nested within an on-going prospective longitudinal cohort study (Jacobson et al., 2008) that was initiated in 1999, when pregnant women from a Cape Town community were recruited into the study. Data were obtained from participants during their 9-year follow-up assessments. This study featured a 2 × 2 × 3 mixed-factorial design. The *Dresden Cruiser* allowed for two within-subjects factors, each with two levels, to be varied: (1) cue focality (focal vs. non-focal) and (2) task difficulty (low vs. high difficulty). FASD diagnosis was the between-subjects factor and had three levels: (1) FAS/PFAS, (2) heavily exposed nonsyndromal (HE), and (3) non-exposed controls.

Aside from the effects of prenatal alcohol exposure, environmental factors, such as prenatal health, socioeconomic status (SES), maternal age at birth, and education can all affect cognitive and social development (Jacobson, Jacobson, Sokol, Chiodo, & Corobana, 2004; Jacobson & Jacobson, 2005; May et al., 2005). This study, therefore, included potentially influential socio-demographic factors in the statistical analysis of the data.

All testing took place in the Child Development Research Laboratory on the University of Cape Town's Health Sciences Campus. In order to avoid experimenter bias, all

test administrators were blind to the participant's FASD diagnosis and prenatal alcohol exposure history.

Participants

The sample consisted of 89 children who participated in the 9-year follow-up assessment of the large longitudinal cohort study. These assessments formed part of the on-going research program, which required neuropsychological assessments during infancy and at 5 and 9 years of age.

Recruitment

Mothers of the 89 children included in this study were recruited between July 1999 and January 2002 for the prospective longitudinal study, investigating effects of prenatal alcohol exposure on neurobehavioral development, referred to above. Children were born to women residing in a low SES, predominantly Cape Colored (mixed ancestry) area of the Cape Town. The incidence of FAS and PFAS in this segment of the Western Cape population is among the highest in the world, with 68.0 to 89.2 cases per 1000 (May et al., 2007).

Screening and recruitment interviews assessing levels of prenatal alcohol consumption were conducted at a local antenatal clinic. Mothers were invited to participate in the research if they reported that, during pregnancy, (a) their average consumption level of absolute alcohol (AA)/day was equal to or above 1.0 oz (i.e., the equivalent of about 2 standard drinks/day), which is classified as heavy exposure, or (b) they engaged in binge drinking (4 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 binge drink. Alcohol use across pregnancy was ascertained in two subsequent interviews using the timeline follow-back approach (Sokol, Martier, & Ernhart, 1983; Jacobson, Chiodo, Sokol, & Jacobson, 2002; Jacobson et al., 2008). Data from these three interviews were then averaged to provide a quantitative summary measure of prenatal alcohol exposure. Questions pertaining to maternal drug use (i.e., marijuana, cocaine, methaqualone (mandrax), and tobacco) during pregnancy were also asked using a similar procedure. From this, quantitative summary measures of drug (days/week) and cigarette (cigarettes/day) use across pregnancy were generated.

University of Cape Town

Women younger than 18 years 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 controls. Infant exclusionary criteria were major chromosomal anomalies, neural tube defects, multiple births, and seizures.

Dysmorphology Assessment

In September 2005 the children were examined by two expert FASD dysmorphologists (H. E. Hoyme and L. K. Robinson) according to standard diagnostic protocols for growth and FAS anomalies (Hoyme et al., 2005; see Jacobson et al, 2008). There was substantial agreement between the two dysmorphologists on the assessments of dysmorphic features, including palpebral fissure length, 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* = 0.78) who evaluated eight children who could not be scheduled for the clinic. FASD diagnosis was determined by consensus at a case conference conducted by the dysmorphologists HEH and LKR with S. W. Jacobson, C. D. Molteno, and J. L. Jacobson. Based on the outcome of these assessments, children were assigned to the diagnostic groups used as the between-subjects factor in this study (i.e., FAS/PFAS, HE, or Control).

Materials

Although the tests outlined below have no published South African norms, the standardized measures included in this study are widely used within clinical research in this country. This study, therefore, compared test scores for participants with a history of heavy prenatal alcohol exposure to those of the control participants and not to the published normative data, thereby removing from consideration the fact that socio-environmental and cultural differences between test samples and normative samples may influence interpretation of performance.

Many of the participants included in this study were Afrikaans-speaking. Test instructions for the PM, EF, and retrospective memory tests were, therefore, translated from the original English by an Afrikaans-speaking MA-level child psychologist with extensive experience working with the children in this cohort and communicating with them in their dialect. Prior to the onset of testing for the current study, the WISC-IV was translated into Afrikaans and then back translated by Clinical Psychologists. At the 5-year follow-up of this

University of Cape Town

cohort, the Junior South African Intelligence Scale (JSAIS; Madge, van den Berg, Robinson, & Landman, 1981), which is available in Afrikaans and English and has been normed for South African children, was administered. IQ scores obtained using the JSAIS at 5 years were strongly correlated with the 9-year WISC-IV scores, $r = .79$, thus providing validation for this translation. Testing was conducted in Afrikaans or English, depending on the primary language used in the child's home and school.

Prospective Memory Test

The *Dresden Cruiser* (Voigt et al., 2011) is a computerized driving task, based on Kerns' (2000) *CyberCruiser*. The *CyberCruiser* and *Dresden Cruiser* are engaging for children (see, e.g., Voigt et al., 2011; Kerns, 2000) and appear to be suited for use with clinical populations (see, e.g., Kerns & Price, 2001). The *Dresden Cruiser* PM allows for easy manipulation of task conditions (e.g., cue focality and task difficulty). Table 1 presents a list of outcome variables that can be derived from this task.

During the on-going task, participants are required to drive a car using the arrow keys on a keyboard (see Figure 2 for a screen shot of both versions of the task). Points are awarded if the participant successfully steers his/her car around the other cars on the road. Points are lost for each car crash that occurs. The PM task is embedded within the on-going task and takes the form of the participant needing to refuel the car when a specific event occurs. In the *focal condition*, participants need to refuel when they encounter a yellow car driving on the road. In the *non-focal condition*, participants need to refuel when they encounter yellow flowers on the roadside. Participants are awarded bonus points for every successful refuel. They are given five opportunities to refuel during both the focal and non-focal versions of the on-going task. If successful refueling takes place each time the PM cue is presented, the participant is considered to have intact PM functioning.

Executive Functioning Tests

Due to the reported deficits in EF in children with a history of prenatal alcohol exposure, as well as the proposed functional link between EF and PM, we included executive function tests in the assessment. Specifically, each participant's EF was assessed using seven neuropsychological tests, each designed to measure performance within one of the four domains of Anderson's (2002) model (attentional control, information processing, cognitive flexibility, and goal setting). Table 1 presents the EF outcome variables that were included in statistical analyses.

University of Cape Town

Table 1. ***Outcome Variables***

Variable	Definition
	Dresden Cruiser
Focal Task	
Refuel Count[a]	Number of correct refuels (max = 5) for each difficulty version
Hit Count[b]	Total number of cars hit during each difficulty version
Non-Focal Task	
Refuel Count	Number of correct refuels (max = 5) for each difficulty version
Hit Count	Total number of cars hit during each difficulty version
	Executive Functioning
Attentional Control	
Rubia Stop Signal Reaction Time	SSRT is measured as the time taken by an individual to inhibit a response after being presented with the stop signal (i.e., when an explosion follows the presentation of an airplane).
DKEFS Color-Word Interference Test (Inhibition)	Total completion time on the inhibition trial.
Information Processing	
DKEFS Verbal Fluency, Phonemic	Sum of total number of words generated across three letter trials.
DKEFS Verbal Fluency, Category	Sum of total number of words generated across the three category trials.
DKEFS Verbal Fluency, Category Switch	Total number of words generated on the category switch trial.
Cognitive Flexibility	
CCTT 2 Total Time	Total completion time on CCTT2.
DKEFS Color-Word Interference Test (Inhibition/Switching)	Total completion time on the inhibition/switching trial.
WISC-IV Digit Span Backwards	Maximum number of digits recalled backwards.
Goal Setting	
TOL, Total Move Score	Sum of moves taken to complete the 10 test items.
	General Intellectual Functioning
WISC-IV FSIQ	Full Scale IQ derived from performance on 15 subtests.
Verbal Comprehension Index	Index score derived from the similarities, vocabulary, and comprehension subtests of the WISC-IV.
Perceptual Reasoning Index	Index score derived from the block design, picture concepts, and matrix reasoning subtests of the WISC-IV.
Working Memory Index	Index score derived from the digit span and letter-number sequencing subtests of the WISC-IV.
Processing Speed Index	Index score derived from the coding and symbol search subtests of the WISC-IV.
	Retrospective Memory
CVLT-C Long Delay Free Recall	Number of words correctly recalled on the long delay free recall trial.

Note. SSRT = stop signal reaction time; DKEFS = Delis-Kaplan Executive Functioning System; CCTT = Children's Color Trails Test; WISC-IV = Wechsler Intelligence Scale for Children—Fourth Edition; TOL = Tower of London; FSIQ = full scale IQ; CVLT-C = California Verbal Learning Test—Children's Version.

[a]Measures prospective memory performance.

[b]Measures on-going task absorption.

University of Cape Town

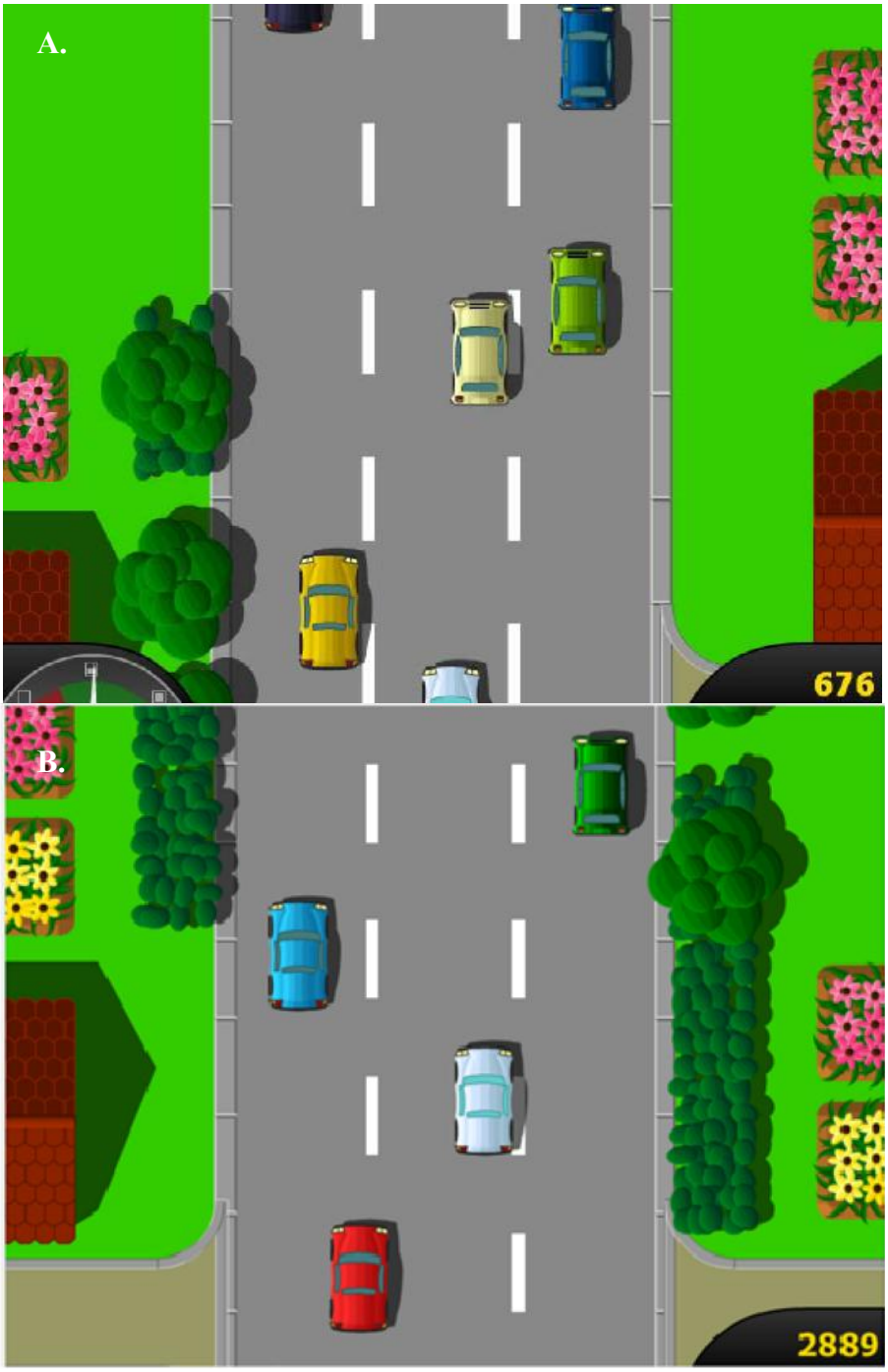

Figure 2. (A) Dresden Cruiser screen shot including focal PM cue (yellow car); (B) Dresden Cruiser screen shot including non-focal PM cue (yellow flowers).

Attentional Control

The *Rubia Stop Task* (Rubia, Oosterlaan, Sergeant, Brandeis, & van Leeuwen, 1998) assessed performance in the domain of attentional control. Although this task is not a standardized measure of response inhibition, the Stop Task paradigm is considered the gold standard measure of response inhibition in studies of children with ADHD, and has proven to be a reliable measure within pediatric clinical samples (see Nigg, 2005). During the task, airplanes fly horizontally, heading either left or right, across a computer screen. Participants are required to press either the right or left arrow key to indicate the airplane's flight path. If, however, the appearance of an airplane is followed by an explosion, participants must refrain from pressing the buttons. Participants are therefore required to inhibit a learned motor response and to self-monitor their behavior.

The inhibition condition of the *Color-Word Interference Test* from the *Delis-Kaplan Executive Functioning System* (D-KEFS; Delis et al., 2001) also assessed attentional control. Previously published studies in this field (Mattson et al., 1999; Rasmussen & Bisanz, 2009) have used the Color-Word Interference test, which has good reliability and validity (Delis et al. 2001), to assess response inhibition in children with FASD. The inhibition condition of this task is based on the traditional Stroop task and requires the participant to inhibit the learned response of word-reading and to identify the ink color instead.

University of Cape Town

Information Processing

The DKEFS *Verbal Fluency Test* assessed performance in the domain of information processing. According to Delis et al. (2001), the Verbal Fluency Test has good reliability and validity. It has also been used to assess verbal generativity in children with FASD (Mattson et al., 1999; Rasmussen & Bisanz, 2009).

The test has three conditions: letter fluency, category fluency, and category switching. During letter fluency, participants are given three separate sub-tasks, each with a time limit of 1 minute. The task is to generate as many words as possible beginning with a particular letter (in this study, the letters were B, R, and S[2]). During category fluency, participants are given two separate sub-tasks, each again with a time limit of 1 minute. The task here was to generate as many words as possible that belong to a particular category (animals and

[2] The target letters in the English version of the test are F, A, and S. Because these letters are not linguistically equivalent in terms of frequency of use across English and Afrikaans, both English- and Afrikaans-speaking participants were asked to respond to the more commonly used, and linguistically equivalent, letters B, R, and S.

boy's/girl's names). During category switching, participants are given 1 minute to generate as many words as possible while alternating between the categories of fruit and vegetables and clothing.

Cognitive Flexibility

The *Children's Color Trails Test* (CCTT; Llorente, Williams, Satz, & D'Elia, 2003) assessed performance in the domain of cognitive flexibility. The CCTT is sensitive to subtle neurological dysfunction, has good reliability and construct validity, and is cross-culturally valid (Llorente et al., 2003). The CCTT is divided into two subtests: CCTT-1 and CCTT-2. During CCTT-1, the participant is presented with a stimulus sheet that contains a series of numbers from 1 to 15. S/he was asked to draw lines, in the correct numerical order, from the numbers 1 to 15. During CCTT-2, the participant is presented with a stimulus sheet that contains a series of numbers from 1 to 15. Each number is presented twice on the page: once in a yellow circle, and once in a pink circle. The participant is asked to connect the circles, in the correct numerical order, but this time alternating between colors (e.g., yellow 1, pink 2, yellow 3, etc.).

The inhibition/switching condition of the *Color-Word Interference Test* from the D-KEFS also assessed cognitive flexibility. The Color-Word Interference test has been used to assess cognitive flexibility in children with FASD (Mattson et al., 1999; Rasmussen & Bisanz, 2009). The inhibition/switching condition of this task, although based on the traditional Stroop task, adds the additional requirement of asking the participant to switch, in the course of reading a single page, between reading the color word and inhibiting that response by identifying the ink in which that word is printed.

The *Digit Span Backwards* subtest of the *Wechsler Intelligence Scale for Children—Fourth Edition* (WISC-IV; Wechsler, 2003) also assessed cognitive flexibility. This task is designed to assess working memory specifically. The WISC-IV digit span test has been widely used within clinical populations (Strauss, Sherman, & Spreen, 2006) and has good validity and reliability (Wechsler, 2003). Furthermore, the WISC Digit Span test is sensitive to the effects of prenatal alcohol exposure and has been widely used to document exposure-related impairments in working memory (see Rasmussen, 2005). Digit Span Backwards requires participants to repeat a series of digits in the opposite order from that in which they were presented by the examiner.

University of Cape Town

Goal Setting

The *Tower of London 2nd Edition* (TOL; Culbertson & Zillmer, 2001) assessed performance in the domain of goal setting. According to its developers, the TOL is a reliable and valid measure of planning and problem-solving skills in children and adults. Test stimuli include two pegboards and six beads (two each in red, blue, and green). The examiner arranges his/her three beads (one red, one blue, one green) into a particular configuration on his/her pegboard; the participant is then required to solve the problem on his/her pegboard, using his/her beads, in as few moves as possible. There are 10 such test items, with each allocated a time limit of 2 minutes for problem solving. Participants are required to follow specific rules during their attempts at problem solving (e.g., they are allowed to move only one bead at a time).

General Intellectual Functioning Test

In studies of cognitive functioning in children with prenatal alcohol exposure, it is of major interest to control for the effects of low IQ scores on test performance in order to determine whether observed cognitive deficits are due primarily to fetal alcohol exposure rather than being secondary to, or simply reflecting, impaired general intellectual function (Coles et al., 2010; Jacobson et al., 2011; Kodituwakku, 2007; Vaurio, Riley, & Mattson, 2011). In the current study, the *Wechsler Intelligence Scale for Children—Fourth Edition* (WISC-IV; Wechsler, 2003) assessed general intellectual functioning. The WISC-IV has been widely used with clinical populations (Strauss, Sherman, & Spreen, 2006), and has good validity and reliability (Wechsler, 2003). Table 1 presents the WISC-IV variables that were included in statistical analyses.

University of Cape Town

Retrospective Memory Test

The *California Verbal Learning Test—Children's Version* (CVLT-C; Delis, Kramer, Kaplan, & Ober, 1994) assessed declarative memory. This list-learning task involves the administration of 5 learning trials, a distractor list, free and cued recall trials after both a short and long delay, and a recognition trial. The CVLT-C has good reliability and validity (Delis et al., 1994), and has been used extensively to document verbal learning and memory impairments in children with moderate to heavy prenatal alcohol exposure (Crocker et al., 2011; Mattson et al., 1998; Mattson & Roebuck, 2002; O'Leary et al., 2011; Willoughby, Sheard, Nash, & Rovet, 2008). Table 1 presents the CVLT-C variables that were included in statistical analyses.

Procedure

Ethical Considerations

This study adhered to the guidelines outlined in the University of Cape Town's code for research involving human subjects and in the Declaration of Helsinki of 2008 (World Medical Association, 2008). Ethical approval for the larger study was obtained from the Research Ethics Committee of the University of Cape Town's Faculty of Health Science (HREC REF: 187/2008; see Appendix E) and from Wayne State University's Human Investigation Committee (IRB#: 026708B3F, see Appendix F). Informed consent and assent were obtained, as part of the larger research projects, from all of the mothers and children at time of recruitment into the study and prior to the administration of neuropsychological measures (see Appendices G and H).

All test results and information gathered during interviewing or assessment are kept strictly confidential. Data collected for each participant were recorded with a code number ensuring confidentiality and anonymity. All participant files are kept in locked cabinets in the Child Development Research Laboratory at the University of Cape Town. Personal information is not given out for medical or remedial reasons unless the parent provides written consent. If it became evident that further psychiatric, medical, or social support was needed, the principal investigators of the larger study made the relevant referral to an organization that could provide the necessary support.

The mothers or children who took part in this research incurred no costs related to their participation. Mothers were given ZAR150 as compensation for each completed 2-day testing session, and were given a photo of the child at the conclusion of their participation. Children were given a small gift of educational relevance (e.g., pencil crayons and drawing materials) at the end of each testing day. Mothers and children were given breakfast, a snack, and lunch on each testing day. There are no risks associated with administration of any of the tests described above. Participants are informed that they may discontinue testing or leave the study at any point in time. Furthermore, if the participants have any questions or concerns they are provided with the contact details for the principal investigators.

Testing Procedure

The larger project's research nurse scheduled testing appointments. The project driver transported participants to and from the research site in a research-dedicated van. The main test of interest for this study, the *Dresden Cruiser*, formed part of a larger neuropsychological battery that was administered, in the same order for each participant, over two days. Each

University of Cape Town

participant was, therefore, required to come into the laboratory for two consecutive days of testing. The *Dresden Cruiser* was administered at the same point in the battery for each participant on both testing days. The neuropsychological battery was administered by N. Kilchenmann, an MA level neuropsychology student, and myself. Ms. Kilchenmann is a full-time research assistant on the FASD project; I trained her to administer the *Dresden Cruiser*. I administered both the focal and non-focal versions of the *Dresden Cruiser* to 18 children; Ms. Kilchenmann administered both the focal and non-focal versions to 58 children. For the remaining 13 children, either I administered the focal task and Ms. Kilchenmann administered the non-focal task, or vice-versa. There were no differences in performance related to examiner, $F(2, 86) = 1.96$, $p > .10$.

We administered the *Dresden Cruiser* in a controlled testing environment following the protocol outlined by M. Kliegel (personal communication, August 18, 2010). The *Dresden Cruiser's* experimental procedure is based on recommendations by Kvavilashvili, Kyle, and Messer (2008) for laboratory-based PM research with children (see Figure 3). Kvavilashvili et al.'s experimental procedure requires that the PM task be broken up into several sub-components so that children remain engaged with the task. In line with this requirement, each participant was first given on-going task instructions (see Appendices A to D for focal and non-focal task instructions in both English and Afrikaans). To make sure that s/he understood and remembered the task instructions, s/he was asked to repeat them. Once it was clear that the child understood on-going task instructions, s/he played a 1-minute practice trial to familiarize him/herself with the on-going task. The child was then provided with the PM task instructions and, once again, asked to recall the PM and on-going task instructions. Following this, the child completed filler tasks during a 15-minute filled delay (e.g., EF tasks). After completing the filler tasks, the child played the first experimental trial. This trial lasted 4 minutes, during which there were either five or four opportunities, on the focal and non-focal versions of the task respectively, for refueling when the PM cue was encountered. No further mention of the task instructions was allowed. Thereafter, another 15-minute delay occurred. At the end of that delay, the child played the second and final experimental trial. At the end of this trial, the child's retrospective memory for the on-going and PM task instructions was assessed, thus allowing for any failures due to poor recall of the instructions to be examined. The *Dresden Cruiser* software automatically recorded all responses generated during the experimental trials into an electronic database. I imported data from the electronic database into an SPSS file.

University of Cape Town

After completing the *Dresden Cruiser*, the child was asked about previous experience playing computer and/or video games as well as about their everyday access to computers and/or video games. The responses to this question provided a measure of the novelty of engaging with a computer-based task.

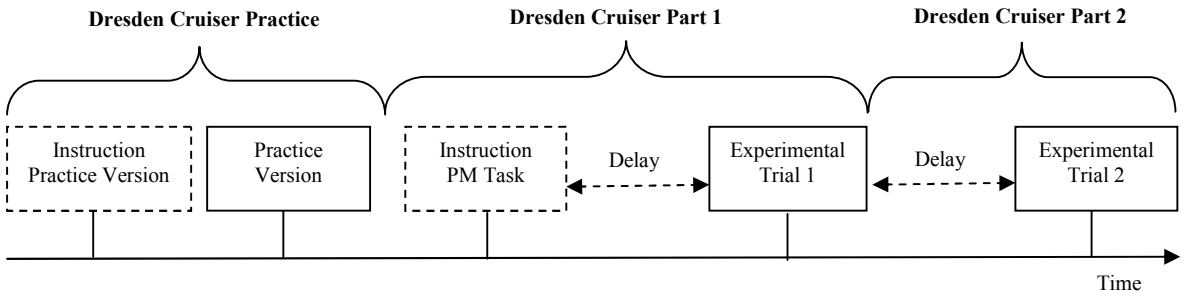

Figure 3. General procedure for the Dresden Cruiser (following Kvavilashvili et al., 2008).

The *Dresden Cruise*r was administered to each participant twice, once at the same point in the battery on each testing day, using the same administration procedure in each instance. In line with McDaniel and Einstein's (2000) multiprocess framework, manipulating task conditions on the *Dresden Cruiser* aimed to alter whether strategic or automatic processes were mediating PM functioning. The two factors that were manipulated in this study were cue focality and task difficulty. Cue focality refers to the extent to which the PM cue was related to the on-going task. On the first day of testing, the participant was administered the focal version of the task. The focal PM cue was that of a yellow car driving on the road and was, therefore, highly related to the on-going task. Focal PM cues are understood to activate automatic retrieval processes (McDaniel & Einstein, 2000). On the second day of testing, the participant was administered the non-focal version of the task. The non-focal PM cue was that of yellow flowers on the side of the road and was, therefore, not related directly to the on-going task of driving a car. Non-focal PM cues are understood to activate strategic retrieval processes (McDaniel & Einstein, 2000).

Task difficulty was manipulated in order to rule out any ceiling effects on both the focal and non-focal versions of the task. The first experimental trial was set at the low-difficulty level, whereas the second experimental trial was set at the high-difficulty level. The difference between these levels was related solely to the number of cars present on the road during the on-going task: The low-difficulty level had fewer cars on the road than the high-difficulty level. Hence, the latter required a greater degree of on-going task absorption if the participant was to avoid crashing into the cars.

University of Cape Town

For the tests of EF, general intellectual functioning, and declarative memory, standardized administration, data recording, and scoring procedures were followed. These tasks were also administered, in the same order for each participant, over the 2 testing days.

Statistical Analysis

I used the Statistical Package for the Social Sciences (SPSS) version 20.0 to analyze the data. Following convention, I set α to < .05 for decisions pertaining to statistical significance. Traditional guidelines for hypothesis testing place great emphasis on avoiding Type I errors (i.e., erroneously reporting a relation between two variables). Stringent methods for the control of Type I errors often result in an increased likelihood of making a Type II error (i.e., erroneously dismissing a relation between two variables). Within the context of public health research, however, the greater concern is missing real effects and consequently underestimating a real health risk (Jacobson & Jacobson, 2005). Consistent with the increased risk of making a Type II error, the effects of prenatal alcohol exposure on neurocognitive functioning is often subtle and, on statistical examination, associated with small effect sizes (Jacobson & Jacobson, 2005). These subtle effects are, however, of clinical importance. In this study, therefore, the approach towards the analysis and interpretation of the data was informed by the context of public health research, and the concern over making a Type II error, than it was by stringent concerns over Type I errors.

Stage 1: Descriptive Statistics

Comprehensive descriptive statistics were used to (a) investigate sample characteristics, (b) examine the distributions of predictor and outcome variables, (c) identify any outliers in the distributions of predictor and outcome variables, (d) test the assumptions underlying parametric statistical tests, and (e) identify potential confounding variables.

With regards to (e), a control variable cannot be the true cause of an observed deficit unless it is related to both the independent or predictor variable (in this case, prenatal alcohol exposure) and the dependent or outcome variable (Schlesselman, 1982). Association with either exposure or outcome can, therefore, be used as a criterion for identification of potential confounders. Selection in relation to outcome has the additional advantage of including covariates unrelated to exposure, which can increase precision (Kleinbaum, Kupper, & Muller, 1988). Hence, in this study any control variable that was related even weakly (at $p <$ .10) to a given developmental outcome was identified as a potential confounder and then controlled statistically in all analyses of effects on that outcome. Five potential confounding

University of Cape Town

variables were, therefore, evaluated for inclusion in regression-based statistical analyses: child's gender and age at testing, mother's SES (Hollingshead, 1975), maternal IQ composite scores (calculated based on non-verbal reasoning ability, Raven et al., 1992; and Peabody Picture Vocabulary Test-Revised IQ scores, PPVT-R, Dunn & Dunn, 1981), and smoking during pregnancy. No mother reported using methaqualone ("mandrax"); and prenatal exposure to marijuana (n = 6) and cocaine (n = 1) were too rare for statistical adjustment. Any association between prenatal alcohol use and the outcome was, therefore, rerun omitting children with either prenatal marijuana or cocaine exposure.

Stage 2: Between-group Analyses

A mixed-design factorial analysis of variance (ANOVA) and a series of one-way ANOVAs tested between-group differences in PM performance and on-going task absorption, respectively. With regards to the latter analyses, one-way ANOVAs were run for each version of the *Dresden Cruiser* (i.e., both focal and non-focal tasks at both easy and difficult levels). I examined the potential differences in the retention of task instructions and self-reported computer usage data using Chi-Squared tests.

Prospective memory performance

The aim of these analyses was to determine whether there were between-group differences in PM performance. Following the assumption that manipulating different aspects of the task will engage different processes underlying PM function (i.e., different aspects of executive function; Kliegel et al., 2002; McDaniel & Einstein, 2000), these analyses considered cue focality and task difficulty as within-subjects factors and group status as the between-subjects factor in a mixed-design factorial ANOVA.

Focal task data were missing for one participant in the FAS/PFAS group (a 10-year-old girl diagnosed with FAS) and one participant in the Control group (an 11-year-old girl) on the easy version of the game. Focal task data were also missing for one participant in the Control group (a 10-year-old boy) on the difficult version of the game. These missing data resulted from software error during data collection.

It is important to note that ANOVA is a robust method of statistical analysis (Field, 2009), and that in cases where the assumptions underlying parametric tests were not all met, use of more conservative, nonparametric tests would have run the risk of Type II error; that is, an underestimation of the effects of prenatal alcohol exposure on PM functioning

University of Cape Town

(Jacobson & Jacobson, 2005). Where post-hoc examination of statistically significant results was warranted, I performed Least-Significant Difference (LSD) tests.

On-going task factors: Task absorption, retention of task instructions, and computer usage

The aim of these analyses was to determine whether performance on other aspects of the *Dresden Cruiser,* retrospective recall of task instructions, or prior computer usage were responsible for any potential between-group differences in PM performance. Between-group differences in the level of on-going task absorption (i.e., hit count; number of cars hit during the on-going task) were investigated using a series of one-way ANOVAs for each version of the *Dresden Cruiser*. Additionally, self-report data on (a) questions addressing the retention of task instructions (see Appendices A-D) and (b) frequency of computer usage, collected prior to and after test administration, were examined using frequency distributions and chi-squared tests.

Following the same logic as the previous set of analyses, parametric ANOVAs were employed as the statistical method of choice despite the assumptions of parametric testing not being met in all cases. Where post-hoc examination of statistically significant results was warranted, I performed Least-Significant Difference (LSD) tests.

Stage 3: Factor Analysis

The purpose of this exploratory factor analysis was to reduce the number of variables selected for inclusion in subsequent regression analyses. To investigate the factor structure underlying PM and EF outcome variables, a principal components analysis (PCA) with varimax rotation was run. Based on the results of this analysis, performance scores for the variables entered into the PCA were then converted into *z*-scores. The latter were then averaged to create composite scores. These composite scores were then entered into the hierarchical regression analyses described below.

Stage 4: Regression Analyses

These analyses used a continuous measure of prenatal alcohol exposure (oz AA/day) as the primary predictor of PM performance. Hence, they differed from the between-group analyses in that they investigated whether there is a relation between *level* of prenatal alcohol exposure and PM performance, rather than investigating whether there were *categorical* differences in performance. These regression analyses also served to indicate to what extent the relation between level of prenatal alcohol exposure and PM performance was influenced

University of Cape Town

by potentially confounding socio-demographic variables and other cognitive and EF variables (i.e., WISC-IV IQ and composite scores, verbal fluency composite scores, cognitive flexibility composite scores, planning composite scores, and CVLT-C long-delay free recall scores).

Before beginning regression analyses, I transformed the skewed distribution of oz AA/day scores. The continuous measure of prenatal alcohol exposure was significantly positively skewed and was, therefore, normalized using a natural log transformation ($ln[x + 1]$). I then created nine separate regression models each with PM composite scores as the outcome variable. In each model, prenatal alcohol exposure was entered at the first step and other potential confounding variables or potential predictors were entered at the second step. Comprehensive model diagnostics and investigations of the assumptions underlying each regression model are presented in the relevant section of the Results. Following the procedure recommended by Baron and Kenny (1986), regression analyses investigating the relation between prenatal alcohol exposure, WISC-IV IQ variables, and PM were extended to consider both FSIQ and composite scores as mediators of the effect of prenatal alcohol exposure. The Sobel Test (Preacher & Leonardelli, 2010; Sobel, 1982) tested the significance of the mediation models.

University of Cape Town

RESULTS

Sample Characteristics

Child Sample Characteristics

Table 2 presents socio-demographic and cognitive characteristics for the three groups of children. There was a significant between-group difference in age at testing which was associated with a small estimate of effect size. Post hoc tests indicated that children in the HE group were slightly older than children in both the FAS/PFAS and Control groups, but that there were no differences in age for children in the FAS/PFAS group and children in the Control group. Regarding sex, 55.10% of the sample was male ($N = 49$), but there were no significant between-group differences in terms of sex distribution.

Regarding WISC-IV performance, there was, as expected, a significant between-group difference for FSIQ scores which was associated with a small effect size estimate. Post-hoc tests indicated that children in the FAS/PFAS group performed more poorly than those in both the HE and Control groups, although the latter two groups did not differ

Table 2. ***Child Sample Characteristics (N = 89)***

Variable	FAS/PFAS (*N* = 29)	HE (*N* = 32)	Control (*N* = 28)	Test Statistic	*p*	ESE
Child's age at testing (years)	11.00 (0.48)	11.21 (0.39)	10.90 (0.30)	4.77**	.01	.10
Gender (% male)	55.20	59.40	50.00	0.53	.78	.08
WISC-IV						
FSIQ	64.53 (10.84)	74.90 (11.78)	75.57 (11.95)	8.40***	<.001	.16
WMI[a]	78.00 (15.87)	87.71 (13.82)	88.39 (13.96)	4.63*	.01	.10
PRI	70.76 (11.34)	84.19 (13.44)	82.00 (13.92)	9.18***	<.001	.18
PSI[b]	75.92 (11.13)	81.65 (13.65)	82.93 (14.34)	2.15	.12	.05
VCI[c]	64.28 (9.68)	70.00 (11.06)	72.86 (11.56)	4.58*	.01	.10
CVLT-C long delay free recall	7.70 (2.93)	9.93 (2.81)	9.46 (2.72)	4.23*	.02	.10
Executive Functioning						
Attentional Control						
Rubia Stop Signal Reaction Time[d]	383.31 (112.15)	258.08 (117.14)	291.28 (100.72)	9.07***	<.001	.19
DKEFS Color-Word Interference Test (Inhibition)[e]	98.86 (17.05)	100.15 (21.26)	105.24 (16.22)	0.82	.45	.02
Information Processing						
Verbal Fluency, Phonemic[f]	12.96 (5.99)	17.30 (8.37)	16.43 (7.42)	2.55†	.08	.06
Verbal Fluency, Category[g]	17.08 (4.92)	23.26 (6.49)	20.93 (6.28)	7.55**	.001	.16
Verbal Fluency, Switch[h]	8.35 (2.23)	9.70 (2.71)	9.61 (2.28)	2.62†	.08	.06
Cognitive Flexibility						
CCTT 2	84.86 (31.29)	62.53 (16.43)	66.46 (20.62)	7.68**	.001	.15
DKEFS Color-Word Interference Test (Inhibition/ Switching)[i]	121.57 (35.29)	103.05 (24.43)	109.25 (20.96)	3.03†	.06	.08
Digit Span, Backwards	4.28 (2.14)	5.69 (1.51)	5.50 (1.48)	5.81**	.004	.12
Goal Setting						
TOL, Total Move Score	45.14 (15.66)	39.44 (14.79)	40.71 (15.15)	1.16	.32	.03

Note. Means are presented with standard deviations in parentheses. FAS = fetal alcohol syndrome; PFAS = partial FAS; HE = heavily exposed nonsyndromal; ESE = estimate of effect size; WISC-IV = Wechsler Intelligence Scale for Children – Fourth Edition; FSIQ = full scale IQ; WMI = working memory index; PRI = perceptual reasoning index; PSI = processing speed index; VCI = verbal comprehension index; CCTT2 = Children's Color Trails Test 2; TOL = Tower of London. Test statistics were either *F* or χ^2 depending on whether the variable under consideration was continuous or categorical. The estimate of effect size was calculated using either η^2 or ϕ depending on whether a one-way ANOVA or chi-square test was employed. [a]Data missing for one child in the HE group. [b]Data missing for three children in the FAS/PFAS group and one child in the HE group. [c]Data missing for one child in the FAS/PFAS group. [d]Data missing for four children in the FAS/PFAS group, three children in the HE group, and two children in the Control group. [e]Data missing for six children in the FAS/PFAS group, two in the HE group, and three in the Control group. [f]Data missing for four children in the FAS/PFAS group and two in the HE group. [g]Data missing for three children in the FAS/PFAS group and two in the HE group. [h]Data missing for three children in the FAS/PFAS group and two in the HE group. [i]Data missing for six children in the FAS/PFAS group, three in the HE group, and three in the Control group.

†$p < .10$. *$p < .05$. **$p < .01$. ***$p < .001$.

University of Cape Town

detectably from one another. This pattern of data was repeated for the Working Memory Index, Perceptual Reasoning Index, and Verbal Comprehension Index scores. There were no significant between-group differences for the Processing Speed Index scores.

Executive functioning profile

In order to assess the assumption that children with heavy prenatal alcohol exposure are impaired on tasks of EF when compared to typically developing non-exposed controls, descriptive statistics for EF tasks were examined and between-group differences were assessed using one-way ANOVAs (see Table 2). Prior to computing between-group comparisons the distributions for EF variables were examined. One outlier > 3*SD*s above the mean was identified in the distributions of Phonemic Verbal Fluency and Category Verbal Fluency. Two outliers > 3*SD*s above the mean were identified in the distributions of CCTT2 total time and TOL total move count. In order to prevent these outliers from exerting undue influence on the statistical analyses, outliers in each of the distributions discussed above were, therefore, recoded to 1 point below the next lowest observed value (Winer, 1971).

The assumption of independence was met for all EF variables. Shapiro-Wilk tests (Shapiro & Wilk, 1965) were run in order to assess whether the EF variables were normally distributed. Table 3 presents the results of these analyses. The assumption of normality was met for the distributions of Verbal Fluency, Switch; Verbal Fluency, Phonemic; Verbal Fluency, Semantic. The assumption of normality was not, however, upheld for the distributions of Stroop interference, Stroop set shift, Digit Span Backwards, Rubia Stop, CCTT2 Time, and TOL total move score. Levene's statistic was examined in order to assess whether the assumption of homogeneity of variance was upheld for EF variables. Homogeneity of variance was upheld for all of the EF variables except CCTT2 Total Time and Stroop Set Shift. As stated previously, ANOVA is a robust method of statistical analysis (Field, 2009); hence, I used that technique to investigate the potentially subtle effects of prenatal alcohol exposure on EF despite the aforementioned violations of the assumptions underlying the parametric test.

I grouped EF tasks according to Anderson's (2002) model of EF. Table 2 presents data and results related to these tasks. In terms of attentional control, there were between-group differences in stop signal reaction times (SSRT) on the Rubia Stop task which were associated with a small estimate of effect size. Post-hoc tests indicated that children in the FAS/PFAS group had significantly longer SSRTs (i.e., they were less successful at inhibiting responses) than children in both the HE and Control groups. There were no significant

University of Cape Town

differences in SSRT between children in the HE and Control groups. There were no significant between-group differences in time taken to complete the Stroop interference trial.

Table 3. ***Tests of Normality and Homogeneity of Variance for Executive Functioning Variables***

	Shapiro-Wilk Test			Levene's Test		
Executive Functioning Variable	*W*	*df*	*p*	*Levene's Statistic*	*df*	*p*
Attentional Control						
Rubia Stop Signal Reaction Time	0.96*	80	.02	0.04	77	.96
DKEFS Color-Word Interference Test (Inhibition)	0.97*	78	.04	1.01	75	.37
Information Processing						
Verbal Fluency, Phonemic	0.98	83	.30	1.66	80	.20
Verbal Fluency, Category	0.97	84	.06	2.23	81	.11
Verbal Fluency, Switch	0.98	84	.10	0.46	81	.63
Cognitive Flexibility						
CCTT 2	0.78**	89	<.001	6.66**	86	.002
DKEFS Color-Word Interference Test (Inhibition/Switching)	0.90**	77	<.001	4.99**	74	<.001
Digit Span, Backwards	0.93**	89	<.001	1.15	86	.32
Goal Setting						
TOL, Total Move Score	0.97*	89	.02	0.09	86	.91

Note. DKEFS = Delis-Kaplan Executive Function System; CCTT2 = Children's Color Trails Test 2; TOL = Tower of London. Unless otherwise noted, degrees of freedom on which the statistics were evaluated were 89. [a]Degrees of freedom on which the statistics were evaluated was 87.
*$p < .05$. **$p < .01$.

University of Cape Town

In terms of information processing, between-group differences fell just short of conventional levels of significance for the phonemic and switching versions of the DKEFS Verbal Fluency task, *p*s = .08 with a very small estimate of effect size. There were, however, significant between-group differences for the category version of the task which were also associated with a small estimate of effect size. Post-hoc tests indicated that children in the FAS/PFAS group generated fewer words than children in both the HE and Control groups and that there were no significant differences in number of words generated by children in the HE and Control groups.

In terms of cognitive flexibility, there were significant between-group differences in the total time taken to complete the CCTT2 which were associated with a small estimate of effect size. Post-hoc tests indicated that children in the FAS/PFAS group took longer to complete this task than children in both the HE and Control group. There were no significant differences in time taken to complete the CCTT2 by children in the HE and Control group. Between-group differences in time taken to complete the Stroop set shift task fell just short of conventional levels of significance, $p = .06$, with a small effect size. There were, however,

significant between-group differences for Digit Span Backwards, which were associated with a small estimate of effect size. Post-hoc tests indicated that children in the FAS/PFAS group had a shorter backwards Digit Span than children in both the HE and Control groups. There were no significant differences in Digit Span Backwards performance by children in the HE and Control groups.

In terms of goal setting, there were no significant between-group differences in ToL total number of moves.

Maternal Sample Characteristics

Table 4 presents socio-demographic, cognitive, and substance-use characteristics for mothers of the children in the three diagnostic groups. There were between-group differences for maternal age at delivery which were associated with a small estimate of effect size. Post-hoc tests indicated that mothers of children in the FAS/PFAS group were older than mothers of children in either the HE or Control groups. By contrast, there were no differences in age at delivery between the HE and Control groups. There were also between-group differences for maternal parity (i.e., live births) and these too were associated with a small estimate of effect size. Post-hoc tests indicated that mothers of children in the FAS/PFAS group had had more live births than mothers of children in the HE and in the Control groups. There were no significant differences in parity between mothers of children in the HE and Control groups. There were between-group differences for marital status, which were associated with a medium effect size, with more mothers of children in the control group being married than mothers of children in the FAS/PFAS group of whom, in turn, a larger proportion were married than mothers of children in the HE group.

Regarding mothers/primary caregiver's level of education, there were also significant between-group differences which were associated with a small estimate of effect size. Post-hoc tests indicated that mothers/primary caregivers of children in both the HE and Control groups reached a higher level of education than those of children in the FAS/PFAS group. There was also a significant between-group difference for SES, associated with a small estimate of effect size, with post-hoc tests indicating that Control group families were of a higher SES than HE and FAS/PFAS group families. There were no differences in SES between the HE and FAS/PFAS groups.

Regarding maternal IQ, there were significant between-group differences for PPVT-R scores which were associated with a small estimate of effect size. Post-hoc tests indicated that mothers of children in the FAS/PFAS group had lower IQ scores than mothers of children in

University of Cape Town

Table 4. ***Maternal Sample Characteristics***

Variable	FAS/PFAS (N = 29)	HE (N = 32)	Control (N = 28)	Test Statistic	p	ESE
Age at delivery (years)	29.09 (7.36)	25.23 (4.84)	25.72 (3.86)	4.26*	.02	.09
Parity	2.76 (1.77)	1.66 (0.97)	1.86 (1.11)	5.88**	.004	.12
Marital Status (% Married)	41.40	34.40	67.90	7.30*	.03	.29
HLOE[a]	7.35 (2.53)	9.16 (2.40)	10.11 (1.65)	11.13**	<.001	.21
Socioeconomic status (SES)[b]	17.64 (8.00)	21.74 (10.32)	27.41 (10.84)	7.01**	.002	.14
PPVT-R[c]	50.21 (13.36)	62.87 (15.63)	71.36 (19.50)	11.50***	<.001	.22
RPM[d]	24.24 (9.48)	32.60 (11.28)	32.44 (8.75)	6.41**	.003	.14
Prenatal Alcohol Exposure[e]						
AA/day (oz)[f]	1.18 (1.41; 0.00-7.36)	0.49 (0.45; 0.00-1.86)	0.0009[g] (0.003; 0.00-0.01)	13.92***	<.001	.42
AA/occasion (oz)	3.73 (2.18; 0.00-8.97)	3.11 (2.28; 0.00-12.60)	0.06[g] (0.24; 0.00-1.16)	32.13***	<.001	.65
Frequency (days/week)	2.1 (1.4; 0.00-0.95)	1.4 (0.7; 0.00-0.43)	0.007[g] (0.03; 0.00-0.02)	26.99***	<.001	.39
Cigarette use during pregnancy (cigarettes/day)	7.83 (5.72)	5.91 (5.79)	3.64 (6.17)	3.47*	.04	.08

Note. Means are presented with standard deviations in parentheses. FAS = fetal alcohol syndrome; PFAS = partial FAS; HE = heavily exposed nonsyndromal; ESE = estimate of effect size; HLOE = Highest level of education; SES = Socioeconomic status; PPVT-R = Peabody Picture Vocabulary Test-Revised; RPM = Raven's Progressive Matrices; AA = absolute alcohol. Test statistics were either F or χ^2 depending on whether the variable under consideration was continuous or categorical. The estimate of effect size was calculated using either η^2 or ϕ depending on whether a one-way ANOVA or Chi-square test was employed.

[a]Data missing for one mother in the HE group and one mother in the Control group

[b]Based on Hollingshead Four Factor Index. Data missing for one mother in the HE group and one mother in the Control group.

[c]Data missing for one mother in the FAS/PFAS group, two mothers in the HE group, and three mothers in the Control group.

[d]Data missing for two mothers in the HE group and three mothers in the Control group.

[e]Means are presented with standard deviations and range statistics in parentheses.

[f]1 oz AA/day ≈ about 2 standard drinks

[g]Two mothers in the Control group reported alcohol use: one drank about 1 drink on 5 occasions; the other drank about 2 drinks on 2-3 occasions.

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

the HE group and in the Control group. The difference in maternal PPVT IQ scores fell just short of conventional levels of significance for mothers of children in the HE and Control groups, $p = .06$. Regarding maternal non-verbal reasoning, there were significant between-group differences on the Raven's Progressive Matrices (Raven, 1992) which were associated with a small estimate of effect size. Post-hoc tests indicated that mothers of children in the FAS/PFAS group had lower scores than mothers of children in the HE and Control groups. On this measure, there were no significant differences between mothers of children in the HE and Control groups.

University of Cape Town

Regarding level of prenatal alcohol exposure there were, as expected, significant between-group differences for the average amount of alcohol consumed per day across pregnancy, for the average amount of alcohol consumed per occasion, and for the frequency of drinking days per week. These differences were associated with moderate to large estimates of effect sizes. In terms of the average amount of alcohol consumed per day across pregnancy and the frequency of drinking days per week, post-hoc tests indicated that there was a dose-dependent effect of alcohol exposure: Children in the FAS/PFAS group were exposed to more alcohol prenatally than children in both the HE and Control groups and children in the HE group were exposed to more alcohol prenatally than children in the Control group. Regarding average amount of alcohol consumed per occasion, post-hoc tests indicated that children in the FAS/PFAS and HE groups were both exposed to more alcohol than children in the Control group, with no difference in level of exposure between children in the FAS/PFAS and HE groups. Hence, although mothers of children in the FAS/PFAS and HE groups drank similar amounts of alcohol per occasion, mothers of the FAS/PFAS children drank, on average, 1.5 times as often as mothers of the HE children.

Regarding maternal cigarette and drug use, there were between-group differences, associated with a small estimate of effect size, with mothers of children in the FAS/PFAS group having smoked more cigarettes per day than mothers of children in the Control group. There were no differences in number of cigarettes smoked per day between the FAS/PFAS and HE group or between the HE and Control Group. Only one mother (of a child in the FAS/PFAS group) reported using cocaine during pregnancy, with a mean frequency of 2.6 occasions per week. Six mothers (three of children in the FAS/PFAS group, two of children in the HE group, and one of a child in the Control group) reported using marijuana during pregnancy, with a mean frequency of 1.3 occasions per week and a range of 0.03-3.1 occasions per week. There were, therefore, too few cases to include prenatal cocaine or marijuana exposure as potential confounding variables. To rule out the potential influence of these cases, we reran the analyses detailed below excluding these cases. The magnitude of the effects, assessed using η^2 or β, remained virtually unchanged.

University of Cape Town

Between-Group Analyses

Prospective Memory Performance

A mixed-factorial ANOVA tested the hypothesis that children with a history of heavy prenatal alcohol exposure would show poorer PM performance on the *Dresden Cruiser*

relative to typically developing, demographically similar controls (i.e., they would have fewer correct refuels). It also tested whether the PM performance of the FASD groups was altered by the manipulation of the task factors (i.e., cue focality and difficulty level).

Prior to conducting between-group analyses, the distributions of refuel count scores were examined for all versions of the *Dresden Cruiser*. There were no outliers in the distributions of refuel count scores for any version. The distributions of *Dresden Cruiser* outcome variables were further investigated to determine whether the assumptions underlying parametric testing were upheld. The assumption of independence was upheld for refuel count on all versions of the *Dresden Cruiser*. The distributions of refuel count scores deviated significantly from normality across all versions of the *Dresden Cruiser* (see Table 5). The assumption of homogeneity of variance was violated for the distribution of refuel count scores for all versions of focal and non-focal task, except the difficult version of the non-focal task (see Table 6).

Table 5. ***Shapiro-Wilk Tests of Normality for Dresden Cruiser Outcome Variables***

	Refuel Count		Hit Count	
Task Version	*W*	*p*	*W*	*p*
Focal Task				
Easy[a]	0.78**	<.001	0.93**	<.001
Difficult	0.67**	<.001	0.97†	.06
Non-Focal Task				
Easy	0.68**	<.001	0.92**	<.001
Difficulty	0.70**	<.001	0.97*	.04

Note. Unless otherwise noted, degrees of freedom on which the statistics were evaluated were 89.
[a]Degrees of freedom on which the statistics were evaluated was 87.
†$p < .10$. *$p < .05$. **$p < .01$.

Table 6. ***Levene's Test of Homogeneity of Variance for Dresden Cruiser Outcome Variables***

	Refuel Count		Hit Count	
Task Version	Levene's statistic	*p*	Levene's statistic	*p*
Focal Task				
Easy[a]	5.42*	.006	2.26	.11
Difficult	6.55*	.002	0.85	.43
Non-Focal Task				
Easy	5.19*	.007	2.24	.11
Difficulty	1.55	.22	1.00	.34

Note. Unless otherwise noted, degrees of freedom on which the statistics were evaluated were (2, 86).
[a]Degrees of freedom on which the statistics were evaluated were (2, 84).
*$p < .01$

Table 7 presents results from this analysis. There was a significant main effect of cue focality in the absence of a cue focality × group interaction effect. These results suggest, regardless of group status, children performed more poorly on the Non-Focal version of the task ($M = 3.21$, $SE = .12$) than on the Focal version of the task ($M = 3.78$, $SE = .13$). There

University of Cape Town

was also a significant main effect of difficulty level in the absence of a difficulty level × group interaction effect. These results suggest that, regardless of group status, children performed more poorly on the difficult version of the task ($M = 3.61$, $SE = .11$) than on the easy version ($M = 3.38$, $SE = .12$). Furthermore, the cue focality × difficulty level interaction was significant, suggesting that, regardless of group status, children performed more poorly on the Non-Focal than the Focal version of the task at both difficulty levels (see Figures 4 and 5). These results were all associated with small estimates of effect size.

Table 7. ***Tests of Within-Subjects Effects on Prospective Memory Performance***

Factors	*SS*	*df*	*MS*	*F*	*p*	η^2
Cue Focality	28.54	1	28.54	18.45**	<.001	.18
Cue Focality × Group	2.82	2	1.41	0.91	.41	.02
Error (Cue Focality)	128.43	83	1.55			
Difficulty Level	4.74	1	4.74	7.18*	.009	.08
Difficulty Level × Group	1.08	2	.54	0.82	.44	.02
Error (Difficulty Level)	54.77	83	.66			
Cue Focality × Difficulty Level	4.53	1	4.53	8.30*	.005	.09
Cue Focality × Difficulty Level × Group	1.06	2	.53	0.97	.38	.02
Error (Cue Focality × Difficulty Level)	45.24	83	.55			
Group	11.92	2	5.96	6.55*	.002	.14
Error (Group)	75.46	83	.91			

Note. SS = sum of squares; df = degrees of freedom; MS = mean square. All values presented are sphericity assumed.
*$p < .01$. **$p < .001$.

Regarding between-group factors, there was a significant main effect of group on PM performance (see Table 7). Means for the refuel count for each version of the *Dresden Cruiser* are shown in Table 8. Post-hoc tests indicated that children in the FAS/PFAS group refueled fewer times than children in both the HE and Control groups. There were no significant differences in refuel count for children in the HE and Control groups.

Table 8. ***Refuel Count for Each Group on Each Version of the Dresden Cruiser (N = 89)***

Task Version	FAS/PFAS ($n = 29$)	HE ($n = 32$)	Control ($n = 28$)
Focal Task			
Easy[a]	2.86 (1.69)	4.06 (1.11)	3.74 (1.23)
Difficult[b]	3.41 (1.88)	4.28 (1.02)	4.11 (1.18)
Non-Focal Task			
Easy	2.69 (1.44)	3.31 (1.23)	3.61 (0.79)
Difficult	2.83 (1.28)	3.38 (1.07)	3.46 (1.04)

Note. Means are presented with *SD*s in parentheses. FAS = fetal alcohol syndrome; PFAS = partial FAS; HE = heavily exposed nonsyndromal.
[a]Data missing for one child in the FAS/PFAS group and for one child in the Control group.
[b]Data missing for one child in the Control group.

University of Cape Town

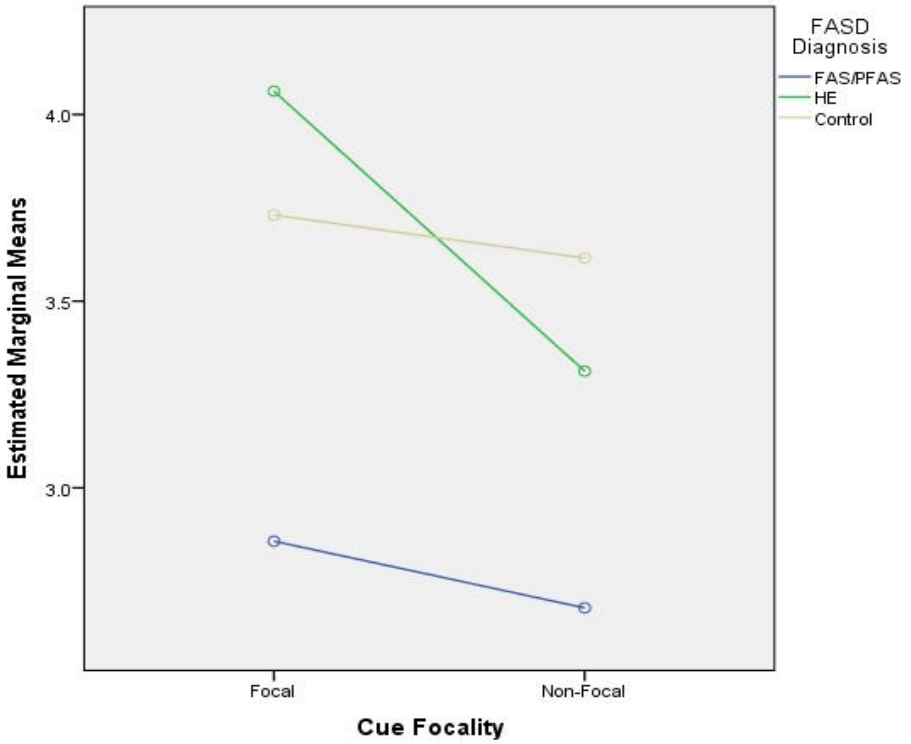

Figure 4. Profile plot of prospective memory performance for the focal and non-focal cues at difficulty level 1.

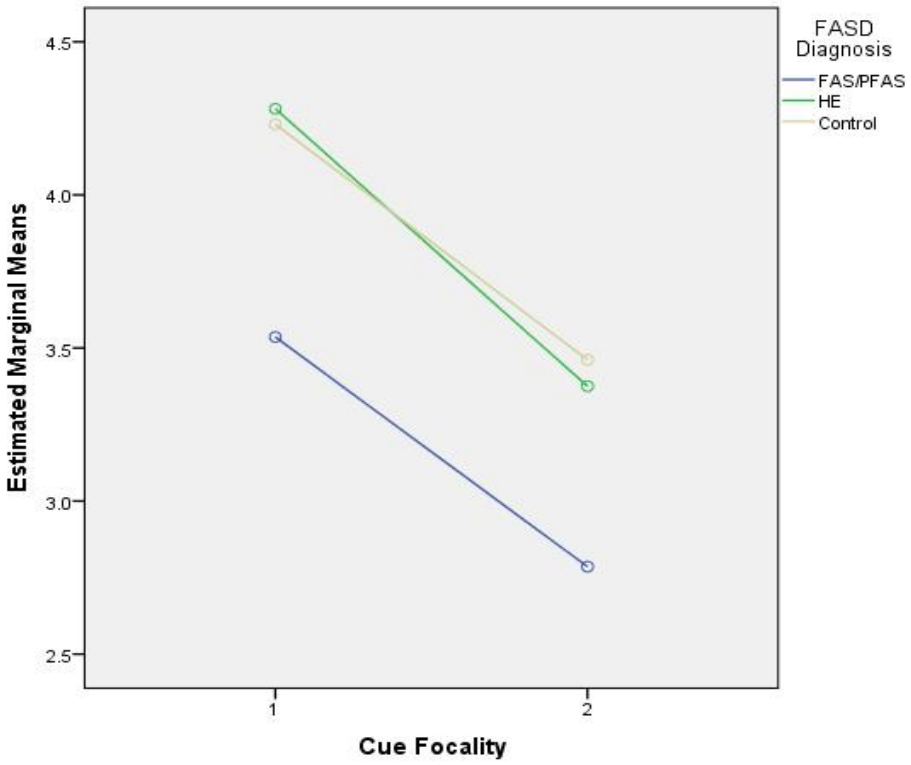

Figure 5. Profile plot of prospective memory performance for the focal and non-focal cues at difficulty level 2.

On-going Task Absorption, Retention of Task Instructions, and Computer Usage

A series of one-way ANOVAs and chi-squared tests examined whether on-going task absorption, retention of task instructions, or previous experience using computers influenced on-going task performance. Before conducting between-group analyses, the distributions of hit count scores were examined for all of the tasks. One outlier (> 3*SD*s above the sample mean) was identified in the distribution of hit count scores on the focal task (easy and difficult versions) and on the non-focal task (easy version). To prevent these outliers from exerting undue influence on the statistical analyses, they were recoded to 1 point below the next lowest observed value (Winer, 1971).

The distributions of hit count outcome variable for each version of the *Dresden Cruiser* were further investigated to determine whether the assumptions underlying parametric testing were upheld. The assumption of independence was met for hit count on all versions of the *Dresden Cruiser*. The assumption of normality was upheld for the distribution of hit count scores on the focal task, difficult version, but was not upheld for the other versions (see Table 5). The assumption of homogeneity of variance was upheld for hit count scores on all versions of the *Dresden Cruiser* (see Table 6).

There were no significant between-group differences in on-going task absorption (as measured by number of car crashes) for the focal and the non-focal task (see Table 9). Although the between-group differences for the focal and non-focal task, fell just short of conventional levels of significance, in each case the magnitude of effect was very small. These results suggest that, across groups, children displayed similar levels of on-going task involvement across the difficulty levels of the focal and non-focal tasks.

University of Cape Town

Table 9. ***Between-group Comparisons of Hit Count for Each Version of the Dresden Cruiser***

Task Version	FAS/PFAS (N = 29)	HE (N = 32)	Control (N = 28)	F	P	η^2
Focal Task,						
Easy[a]	20.50 (10.36)	15.63 (9.26)	16.63 (6.34)	2.45†	.09	.06
Difficult[b]	29.14 (11.73)	22.34 (10.49)	26.48 (9.76)	3.14†	.05	.07
Non-Focal Task,						
Easy	16.38 (8.95)	11.81 (7.61)	12.04 (7.09)	3.11†	.05	.07
Difficult	27.28 (14.14)	19.91 (11.45)	23.54 (10.75)	2.78†	.07	.06

Note. Means presented with SDs in parenthesis. FAS = fetal alcohol syndrome; PFAS = partial FAS; HE = heavily exposed nonsyndromal.
[a]Data missing for one child in the FAS/PFAS group and one child in the Control group
[b]Data missing for one child in the Control group
$^{\dagger}p < .10$.

These results were consistent with data assessing the retention of *Dresden Cruiser* instructions. Table 10 presents the results of these analyses. With regards to the focal task, there were no between-group differences in terms of the immediate recall of on-going task or PM task instructions. More specifically, 96.50% ($N = 82$) of the sample correctly recalled the on-going task instructions, and 95.40% ($N = 83$) of the sample correctly recalled the PM task instructions. Furthermore, there were no between-group differences in the delayed recall of the on-going task or PM task instructions. More specifically, 98.80% ($N = 82$) of the sample correctly recalled the on-going task instructions and 97.10% ($N = 68$) of the sample correctly recalled the PM task instructions upon post-test questioning. With regards to the non-focal task, there were no between-group differences in terms of the immediate recall of on-going task or PM task instructions. More specifically, 100% ($N = 86$) of the sample correctly recalled on-going task instructions, and 98.80% ($N = 85$) correctly recalled PM task instructions. Furthermore, there were no between-group differences in the delayed recall of the on-going task or PM task instructions, with 100% ($N = 82$) of the sample correctly recalling on-going task instructions, and 98.5% ($N = 64$) of the sample correctly recalling PM task instructions upon post-test questioning.

Table 10. ***Between-Group Comparisons of Retention of Dresden Cruiser Instructions***

	Focal Task			Non-Focal Task		
Recall of Instructions	χ^2	*p*	ϕ	χ^2	*p*	ϕ
Immediate						
On-going task	0.02	.99	.01	--[a]	--[a]	--[a]
PM task	3.85	.15	.21	2.34	.31	.17
Delayed						
On-going task	2.10	.35	.16	--[a]	--[a]	--[a]
PM task	0.94	.62	.12	2.89	.32	.19

[a] Chi-squared test not applicable as 100% of the sample recalled task instructions correctly.

The aforementioned results were also consistent with those derived from the self-report data collected to assess previous computer and/or video game usage in this sample. Table 11 presents the results from these analyses. There were no between-group differences in number of children who reported playing computer and/or video games, of the children who reported playing computer and/or video games, there were no between-group differences for the number of days in a week that computer and/ or video games were played. Furthermore, 46.40% ($N = 39$) of the sample reported having a computer/video game player at home. Of the 53.60% ($N = 45$) of children who reported not having access to a

University of Cape Town

computer/video game player at home, 69.2% ($N = 36$) reported having somewhere else (e.g., school or relative/friend's house) to access a computer/video game player.

Table 11. ***Between-Group Comparisons of Computer/Video Game Usage***

Response	FAS/PFAS ($N = 28$)	HE ($N = 32$)	Control ($N = 29$)	χ^2	p	ϕ
Play Games (%)[a]	65.50	87.10	74.10	3.21	.20	.19
Days/Week[b]	3.00 (2.30)	3.30 (2.40)	2.6 (2.20)	16.17	.30	.47

[a]Data missing for 1 child in each of the FAS/PFAS, HE, and Control groups.
[b]Only children who reported playing computer/video games ($N = 74$)

Factor Analysis: Creating Prospective Memory and Executive Functioning Composites

An exploratory principal components analysis with varimax rotation examined the degree to which PM and EF measures were related. The analysis generated four factors with eigenvalues > 1. Together, these factors accounted for 61.8% of the variance. Table 12 shows these factors and the variables that load onto them.

As expected, the tasks of verbal fluency all loaded onto the same factor, which was named accordingly (Factor 1 in Table 12). Similarly, the four *Dresden Cruiser* PM outcome variables loaded onto Factor 2, which was also named accordingly. Consistent with Anderson's (2002) model of EF, the D-KEFS tasks of inhibition and set-shifting, as well as the CCTT2, loaded onto Factor 3, which was named cognitive flexibility. The final factor was dominated by planning performance on the TOL, but also incorporated working memory and inhibition. Factor 4 was, therefore, named self-monitoring and planning as this best captured the skills necessary to complete the associated tasks. Importantly, the analysis showed that PM represents a factor that is separate and independent from the other EF components.

Because the results of the principal components factor analysis indicated that the data featured four separate and independent factors, I created four composite measures (viz. Verbal Fluency, PM, Cognitive Flexibility, and Self-Monitoring and Planning) based on those factors. To create these composite scores, I first standardized the raw scores for the relevant outcome variables within each factor. Composite scores were then calculated as the average *z*-score of the tests that loaded onto each of the four factors. These composite scores were then used as continuous predictors in the regression models.

University of Cape Town

Table 12. ***Varimax Rotated Factors (N = 70)***

Outcome Variables	Verbal Fluency (1)	Prospective Memory (2)	Cognitive Flexibility (3)	Self-Monitoring and Planning (4)
D-KEFS Verbal Fluency				
Phonemic	**.74**	-.06	-.09	-.37
Category	**.66**	.07	-.31	.03
Switch	**.90**	.06	-.09	.02
Dresden Cruiser (Refuel Count)				
Focal, Easy	.09	**.68**	.24	-.15
Focal, Difficult	.25	**.64**	.40	-.01
Non-Focal, Easy	-.07	**.72**	-.41	-.17
Non-Focal, Difficult	-.08	**.81**	-.32	.11
D-KEFS Color-Word Interference Test				
Interference	-.15	.03	**.63**	.01
Set-Shift	-.33	-.05	**.55**	.33
Children's Color Trails Test 2 (Time)	-.18	-.10	**.67**	.34
Tower of London (Total Moves)	.20	.16	.15	**.80**
Digit Span, Backwards	.38	.18	-.15	**-.57**
Rubia Stop (SSRT)	-.21	-.30	.08	**.60**
Eigenvalue	3.47	2.00	1.50	1.08
Variance explained (%)	26.72	15.21	11.50	8.32

Note. D-KEFS = Delis-Kaplan Executive Functions System; SSRT = stop signal reaction time.

University of Cape Town

Hierarchical Regression Analyses

Prior to conducting hierarchical regression analyses, I examined the frequency distributions of possible predictor and outcome variables in order to identify whether there were any outliers. Outliers were defined as any score > 3*SD*s above or below the mean (Winer, 1971). There was one outlier (> 3*SD*s above the mean) for the distributions of prenatal alcohol exposure, verbal fluency composite scores, and maternal smoking during pregnancy. There were two outliers (> 3*SD*s above the mean) for the distribution of cognitive flexibility composite scores. There was one outlier (> 3*SD*s below the mean) for the distributions of PM composite scores and CVLT-C long-delay free recall scores. Following the recommendations of Winer (1971), outliers in all of the distributions except prenatal alcohol exposure were recoded to 1 point above or below the next lowest or highest observed value. The outlier in the distribution of prenatal alcohol exposure was not recoded because the distribution of prenatal alcohol exposure scores had already been normalized.

To assess whether the variables identified for inclusion in the regression analyses were normally distributed, Shapiro-Wilk tests (Shapiro & Wilk, 1965) were run (see Table 13). WISC-IV FSIQ, Perceptual Reasoning Index, and Verbal Comprehension Index, self-monitoring and planning composite scores, CVLT-C long-delay free recall, and child's age at testing were normally distributed. The distributions of prenatal alcohol exposure, PM

composite scores, WISC-IV Working Memory Index and Processing Speed Index, verbal fluency composite scores, cognitive flexibility composite scores, maternal age at delivery, maternal IQ, SES, and smoking during pregnancy deviated significantly from normal.

Table 13. ***Shapiro-Wilk Tests of Normality for Variables included in Regression Analyses***

Predictor Variables	*W*	*df*	*p*
Prenatal Alcohol Exposure (oz AA/day)	.82**	89	<.001
Prospective Memory Composite Score	.81**	89	<.001
WISC-IV			
FSIQ	.98	89	.12
WMI	.95*	88	.003
PRI	.99	89	.72
PSI	.93**	85	<.001
VCI	.98	88	.15
Verbal Fluency Composite Score	.95*	84	.001
Cognitive Flexibility Composite Score	.93**	88	<.001
Self-Monitoring and Planning Composite Score	.98	89	.17
CVLT-C Long Delay Free Recall	.98	82	.17
Potential Confounding Variables			
Child's Age at Testing	.99	89	.39
Maternal IQ[a]	.96*	89	.005
SES	.95*	87	.002
Smoking During Pregnancy	.83**	89	<.001

Note. AA = absolute alcohol; WISC-IV = Wechsler Intelligence Scale for Children – Fourth Edition; FSIQ = full scale IQ; WMI = working memory index; PRI = perceptual reasoning index; PSI = processing speed index; VCI = verbal comprehension index; CVLT-C = California Verbal Learning Test—Children's Version; SES = socioeconomic status

[a]Maternal IQ composite score calculated based on maternal non-verbal reasoning ability (Raven et al., 1992) and Peabody Picture Vocabulary Test-Revised IQ (PPVT-R; Dunn & Dunn, 1981)

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

University of Cape Town

Correlation Matrix

In order to assess the relation between prenatal alcohol exposure, PM, potential confounding variables, and potential predictor variables, I ran two correlation matrices. The first correlation matrix aimed to assess associations between PM and the following five potential confounding variables: child's age at testing, child's sex, maternal IQ, maternal SES, and maternal cigarette smoking during pregnancy. Based on the results of tests of normality, the Pearson *r* correlation coefficient was used for correlations of child's age at testing and child's sex, whereas the Spearman rho correlation coefficient (ρ) was used for correlations of PM composite scores with maternal IQ, SES, and maternal cigarette smoking during pregnancy.

Table 14 presents the results of this first set of correlations. As the table shows, only maternal IQ and SES were significantly positively correlated to PM composite scores. Hence,

the other three potential confounder variables (child's age at testing, child's sex, and maternal cigarette smoking during pregnancy) were not included in regression models controlling for such variables.

The second correlation matrix aimed to assess associations between PM and prenatal alcohol exposure, the five WISC-IV outcome variables (FSIQ, Working Memory, Perceptual Reasoning, Processing Speed, and Verbal Comprehension Index scores), the three EF composite scores (verbal fluency, cognitive flexibility, and self-monitoring and planning), and CVLT-C long-delay free recall scores. Based on the results of tests of normality, the Pearson *r* correlation coefficient was used for correlations of PM composite scores with prenatal alcohol exposure, the five WISC-IV outcome variables, one EF composite score (self-monitoring and planning), and CVLT-C long-delay free recall scores, whereas the Spearman ρ correlation coefficient was used for correlations of PM composite scores with the other two EF composite scores (verbal fluency and cognitive flexibility).

Table 15 presents the results of this second set of correlations. As the table shows, PM composite scores, WISC-IV FSIQ, Working Memory, Perceptual Reasoning, and Verbal Comprehension Index scores, and verbal fluency composite scores were significantly negatively correlated to prenatal alcohol exposure, whereas cognitive flexibility composite scores were significantly positively correlated to prenatal alcohol exposure. WISC-IV FSIQ, the four WISC-IV composite scores, and verbal fluency composite scores were significantly positively correlated to PM composite scores, whereas cognitive flexibility composite scores and CVLT-C long delay free recall scores were significantly negatively correlated to PM composite scores. PM was, however, not significantly related to the self-monitoring and planning composite score from the factor analysis.

University of Cape Town

Model 1: Relation between Prenatal Alcohol Exposure and Prospective Memory, Controlling for Potential Confounding Variables

To examine the degree to which potential socio-demographic confounding variables influenced the association between prenatal alcohol exposure and PM performance, I conducted a hierarchical regression analysis, in which prenatal alcohol exposure was entered as the predictor variable at the first step and maternal IQ and SES were entered at the second step. Table 16 shows that prenatal alcohol exposure significantly predicted PM performance.

Table 14. ***Correlation Matrix for Prospective Memory and Potential Confounding Variables***

Variable	1	2[a]	3[a]	4[b]	5	6
1. Prospective Memory	1.00					
2. Child's Age at Testing[a]	-.04	1.00				
3. Child Sex[a]	-.08	-.21**	1.00			
4. Maternal IQ[b]	.21*	.03	.03	1.00		
5. SES	.31***	-.31***	-.06	.53****	1.00	
6. Maternal Cigarette Smoking	-.17	.18*	-.07	-.27**	-.39****	1.00

Note. PAE = Prenatal Alcohol Exposure; Statistics presented are Spearman correlation coefficients (ρ) unless otherwise stated. All tests are 2-tailed. [a]Statistics presented are Pearson correlation coefficients (r). [b]Maternal IQ composite score calculated based on maternal non-verbal reasoning ability (Raven et al., 1992) and Peabody Picture Vocabulary Test-Revised IQ (PPVT-R; Dunn & Dunn, 1981)
$^{*}p < .10$. $^{**}p \leq .05$. $^{***}p < .01$. $^{****}p \leq .001$.

Table 15. ***Correlation Matrix for Prenatal Alcohol Exposure, Prospective Memory, and Predictor Variables***

Variable	1	2[a]	3	4	5	6	7	8[a]	9[a]	10	11
1. AA/day	1.00										
2. Prospective memory[a]	-.34****	1.00									
WISC-IV											
3. FSIQ	-.40****	.35***	1.00								
4. WMI	-.28***	.23*	.81***	1.00							
5. PRI	-.37****	.45***	.88***	.68***	1.00						
6. PSI	-.27**	.26*	.74***	.50***	.55***	1.00					
7. VCI	-.33***	.27*	.88***	.63***	.66***	.57***	1.00				
Executive Functioning											
8. Verbal Fluency[a]	-.28***	.27*	.58***	.54***	.60***	.41***	.54***	1.00			
9. Cognitive Flexibility[a]	.24**	-.26*	-.54***	-.39***	-.48***	-.50***	-.43***	-.37***	1.00		
10. Self-Monitoring and Planning	-.04	-.03	-.02	.08	-.03	-.12	.003	-.01	.14	1.00	
11. CVLT-C Long Delay	-.21*	.20†	.54***	.53***	.35***	.40***	.47***	.26*	-.43***	-.08	1.00

Note. AA = ounces of absolute alcohol; WISC-IV = Wechsler Intelligence Scale for Children-Fourth Edition; FSIQ = Full Scale IQ; WMI = Working Memory Index, PRI = Perceptual Reasoning Index; PSI = Processing Speed Index; VRI = Verbal Reasoning Index; CVLT-C = California Verbal Learning Test-Children's Version; Statistics presented are Pearson correlation coefficients (r) unless otherwise stated. All tests are 2-tailed. [a]Statistics presented are Spearman correlation coefficients (ρ)
$^{*}p < .10$. $^{**}p < .05$. $^{***}p < .01$. $^{****}p \leq .001$.

University of Cape Town

This effect remained significant when maternal IQ and SES were entered into the model, indicating an independent effect of prenatal alcohol exposure on PM performance. Neither maternal IQ nor SES were significant predictors of PM performance when prenatal alcohol exposure was included in the regression analysis. Together, these three variables accounted for 15.40% of the variance in PM composite scores, $F(3, 86) = 5.02$, $p = .003$.

Regarding the assumptions underlying the regression model, the average VIF score was not substantially greater than one ($M_{VIF} = 1.5$) indicating that there was no multicollinearity between predictors. The Durbin-Watson statistic was 2.23, indicating that the assumption of independence of model residuals was upheld. The plot of standardized residuals against standardized predicted residuals indicated that the assumption of homoscedasticity was not upheld (see Appendix A, Figure A1). The assumption of normality of standardized residuals was not met, $W(87) = 0.91$, $p < .001$. Hence, one should exercise caution when attempting to generalize the model beyond this sample (Field, 2009).

Regarding regression model diagnostics, Cook's distance was within the acceptable limits (i.e., < 1) given the sample size. Mahalanobi's distance had a maximum value of 20.38, which is raised relative to the conventional cut-off of 15 (Fields, 2009) and indicates a possible influential case in the distribution of residual scores. This possible influential case is in keeping with the outlier previously identified in the distribution of prenatal alcohol exposure scores. Hence, one should again exercise caution when generalizing the model beyond this sample (Field, 2009).

University of Cape Town

Table 16. ***Hierarchical Regression Analysis Controlling for Potential Confounding Variables (N = 87)***

Variable Entered	*B*	*SE B*	*β*
Step 1			
Constant	.20	.10	
AA/day	-.63	.19	-.34**
Step 2			
Constant	-.16	.25	
AA/day	-.42	.22	-.23*
Maternal IQ[a]	.06	.10	.07
SES	.01	.01	.18

Note. AA = Absolute Alcohol; SES = socioeconomic status. $R^2 = .11$ for Step 1, $\Delta R^2 = .04$ for Step 2 ($p > .05$).

[a]Maternal IQ composite score calculated based on maternal non-verbal reasoning ability (Raven et al., 1992) and Peabody Picture Vocabulary Test-Revised IQ (PPVT-R; Dunn & Dunn, 1981)

*$p = .05$. **$p = .001$.

Models 2 to 6: Relation between Prenatal Alcohol Exposure, WISC-IV Performance, and Prospective Memory

Model 2: Relation between prenatal alcohol exposure, FSIQ, and prospective memory

Prenatal alcohol exposure and WISC-IV FSIQ were entered as separate predictors of PM, and at separate steps, into this hierarchical regression model. Table 17 shows that both variables significantly predicted PM performance. However, the effects of prenatal alcohol exposure fell just short of conventional levels of significance when FSIQ was entered into the model, $p = .06$. The magnitude of this effect dropped from a moderate effect to a small effect when FSIQ was entered into the model. Together, these two variables accounted for 22.60% of the variance in PM performance, $F(2, 86) = 12.53$, $p < .001$.

Regarding the assumptions underlying the regression model, the average VIF score was not substantially greater than 1 ($M_{VIF} = 1.2$), indicating that there was no multicollinearity between predictors. The Durbin-Watson statistic was 2.35, indicating that the assumption of independence of model residuals was upheld. The plot of standardized residuals against standardized predicted residuals indicated that the assumption of homoscedasticity was not upheld (see Appendix A, Figure A2). Furthermore, the assumption of normality of standardized residuals was not met, $W(89) = 0.89$, $p < .001$. One should, therefore, exercise caution when attempting to generalize the model beyond this sample (Field, 2009).

Regarding regression model diagnostics, Cook's distance was within the acceptable limits (i.e., < 1) given the sample size. Mahalanobi's distance had a maximum value of 19.33, which is raised, relative to the conventional cut-off of 15 (Fields, 2009), and indicates a possible influential case in the distribution of residual scores. This possible influential case is in keeping with the outlier previously identified in the distribution of prenatal alcohol exposure scores. One should, therefore, exercise caution when attempting to generalize the model beyond this sample (Field, 2009).

Because the effects of prenatal alcohol exposure fell short of statistical significance after WISC-IV FSIQ was entered into the model, the data suggest that FSIQ partially mediated the effects of prenatal alcohol exposure on PM performance (see Figure 6). This finding of partial mediation was substantiated by a significant result on the Sobel Test, $z = -2.58$ (0.10), $p = .01$.

University of Cape Town

Table 17. ***Hierarchical Regression Analyses Controlling for WISC-IV Performance***

Variables Entered	*B*	*SE B*	*β*	*p*
Model 2: Controlling for WISC-IV Full Scale IQ ($N = 89$)[a]				
Step 1				
Constant	.21	.10		
AA/day	-.63	.19	-.34**	.001
Step 2				
Constant	-1.44	.48		
AA/Day	-.36	.19	-.20†	.06
Full Scale IQ	.02	.006	.36**	.001
Model 3: Controlling for WISC-IV Working Memory Index ($N = 88$)[b]				
Step 1				
Constant	.20	.10		
AA/day	-.62	.19	-.34**	.001
Step 2				
Constant	-.77	.46		
AA/day	-.51	.19	-.28*	.007
Working Memory Index	.01	.005	.22*	.06
Model 4: Controlling for WISC-IV Perceptual Reasoning Index ($N = 89$)[c]				
Step 1				
Constant	.21	.10		
AA/day	-.63	.19	-.34**	.001
Step 2				
Constant	-1.37	.46		
AA/day	-.40	.19	-.21*	.03
Perceptual Reasoning Index	.02	.005	.36**	.001
Model 5: Controlling for WISC-IV Processing Speed Index ($N = 85$)[d]				
Step 1				
Constant	.18	.10		
AA/day	-.51	.20	-.28*	.008
Step 2				
Constant	-.89	.49		
AA/day	-.39	.20	-.21*	.03
Processing Speed Index	.01	.006	.24†	.08
Model 6: Controlling for WISC-IV Verbal Comprehension Index ($N = 88$)[e]				
Step 1				
Constant	.23	.10		
AA/day	-.72	.21	-.35**	.001
Step 2				
Constant	-1.09	.51		
AA/day	-.53	.22	-.27*	.01
Verbal Comprehension Index	.02	.007	.24*	.002

Note. WISC-IV = Wechsler Intelligence Scale for Children—Fourth Edition; AA = Absolute Alcohol

[a] $R^2 = .12$ for Step 1, $\Delta R^2 = .09$ for Step 2 ($p = .001$).

[b] $R^2 = .11$ for Step 1, $\Delta R^2 = .05$ for Step 2 ($p = .03$).

[c] $R^2 = .12$ for Step 1, $\Delta R^2 = .11$ for Step 2 ($p = .001$).

[d] $R^2 = .08$ for Step 1, $\Delta R^2 = .05$ for Step 2 ($p = .03$).

[e] $R^2 = .12$ for Step 1, $\Delta R^2 = .07$ for Step 2 ($p = .01$).

† $p = .06$; * $p \leq .05$; ** $p \leq .001$.

University of Cape Town

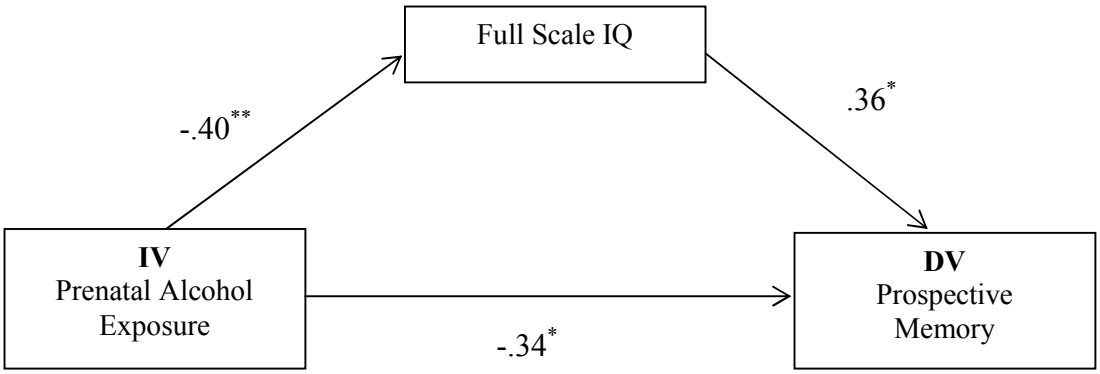

Figure 6. Partial mediating relation between the predictor variables (a) prenatal alcohol exposure and (b) Full Scale IQ and the outcome variable of prospective memory composite scores. Values presented are standardized beta values. IV = independent variable; DV = dependent variable; * p <.01. ** p < .001.

To better understand which aspects of IQ mediate the effects of prenatal alcohol exposure on PM performance, I created four separate regression models, each examining one of the four WISC-IV composite scores as a potential mediating variable.

Model 3: Relation between prenatal alcohol exposure, Working Memory Index, and prospective memory

Prenatal alcohol exposure and WISC-IV Working Memory Index were entered as separate predictors of PM, and at separate steps, in this hierarchical regression model. Table 17 shows that both variables significantly predicted PM performance. Furthermore, the effects of prenatal alcohol exposure remained significant when Working Memory Index scores were entered into the model, indicating an independent effect of prenatal alcohol exposure on PM performance. Together, these two variables accounted for 15.90% of the variance in PM scores, $F(2, 85) = 8.01$, $p = .001$.

Regarding the assumptions underlying the regression model, the average VIF score was not substantially greater than 1 ($M_{VIF} = 1.1$), indicating that there was no multicollinearity between predictors. The Durbin-Watson statistic was 2.27, indicating that the assumption of independence of model residuals was upheld. The plot of standardized residuals against standardized predicted residuals indicated that the assumption of homoscedasticity was not upheld (see Appendix A, Figure A3). Furthermore, the assumption of normality of standardized residuals was not met, $W(88) = 0.89$, $p < .001$. One should, therefore, exercise caution when attempting to generalize the model beyond this sample (Field, 2009).

University of Cape Town

Regarding regression model diagnostics, Cook's distance was within the acceptable limits (i.e., < 1) given the sample size. Mahalanobi's distance had a maximum value of 19.08, which is raised, relative to the conventional cut-off of 15 (Fields, 2009), and indicates a possible influential case in the distribution of residual scores. This possible influential case is in keeping with the outlier previously identified in the distribution of prenatal alcohol exposure scores. One should, therefore, exercise caution when attempting to generalize the model beyond this sample (Field, 2009).

Even though the effects of prenatal alcohol exposure maintained an independent effect on PM performance when WISC-IV Working Memory Index scores were entered into the model, I considered the possibility that Working Memory Index scores were mediating the effects of prenatal alcohol exposure. Figure 7 shows that Working Memory Index scores did not mediate the effects of prenatal alcohol exposure on PM performance. This finding was substantiated by a non-significant result on the Sobel Test, $z = -1.60$ (0.06), $p = .11$.

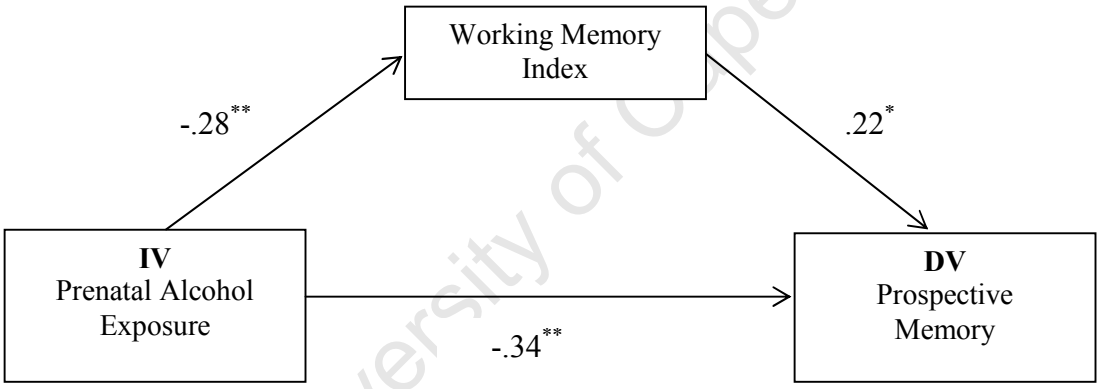

Figure 7. Absence of a mediating relation between the predictor variables (a) prenatal alcohol exposure and (b) Working Memory Index, and the outcome variable of prospective memory composite scores. Values presented are standardized beta values. IV = independent variable; DV = dependent variable. * $p < .05$. ** $p < .01$.

Model 4: Relation between prenatal alcohol exposure, Perceptual Reasoning Index, and prospective memory

Prenatal alcohol exposure and WISC-IV Perceptual Reasoning Index scores were entered as separate steps the hierarchical regression analysis, as predictors of PM. Table 17 shows that both prenatal alcohol exposure and Perceptual Reasoning Index scores were significant predictors of PM performance. Furthermore, the effects of prenatal alcohol exposure remained significant when Perceptual Reasoning Index scores were entered into the model, indicating an independent effect of prenatal alcohol exposure on PM performance.

University of Cape Town

Together, these two variables accounted for 22.5% of the variance in PM scores, $F(2, 86) = 12.52$, $p < .001$.

With regards to the assumptions underlying the regression model, the average VIF score was not substantially greater than 1 ($M_{VIF} = 1.2$) indicating that there was no multicollinearity between predictors. The Durbin-Watson statistic was 2.23 indicating that the assumption of independence of model residuals was upheld. The plot of standardized residuals against standardized predicted residuals indicated that the assumption of homoscedasticity was not upheld (see Appendix A, Figure A4). Furthermore, the assumption of normality of standardized residuals was not met, $W(89) = 0.91$, $p < .001$. Caution should, therefore, be exercised when generalizing the model beyond this sample (Field, 2009).

With regards to regression model diagnostics, Cook's distance was within the acceptable limits (i.e., < 1) given the sample size. Mahalanobi's distance had a maximum value of 19.24, which is raised, relative to the conventional cut-off of 15 (Fields, 2009), and indicates a possible influential case in the distribution of residual scores. This possible influential case is in keeping with the outlier previously identified in the distribution of prenatal alcohol exposure scores. Caution should, therefore, be exercised when generalizing the model beyond this sample (Field, 2009).

Even though the effects of prenatal alcohol exposure maintained an independent effect on PM performance when WISC-IV Perceptual Reasoning Index scores were entered into the model, I considered the possibility that Perceptual Reasoning Index scores were mediating the effects of prenatal alcohol exposure. Figure 8 shows that Perceptual Reasoning Index scores partially mediated the effects of prenatal alcohol exposure on PM performance. This finding was substantiated by a significant result on the Sobel Test, $z = -2.70$ (0.09), $p = .007$.

University of Cape Town

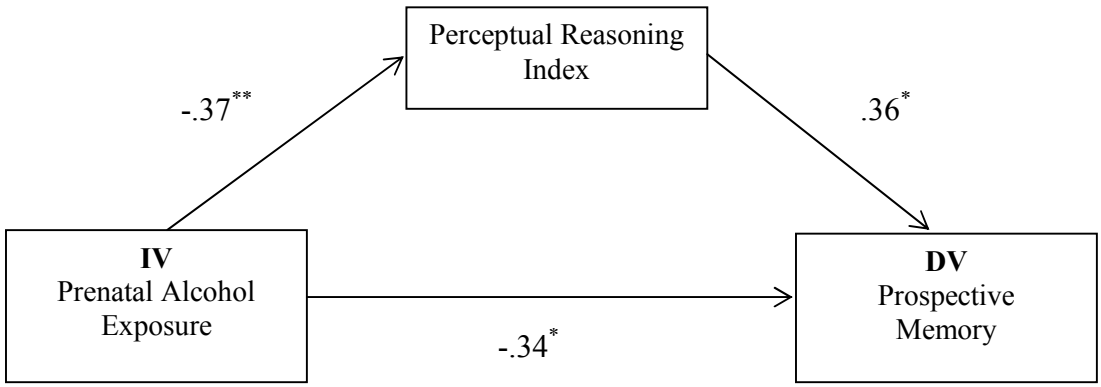

Figure 8. Partial mediation relation between the predictor variables (a) prenatal alcohol exposure and (b) Perceptual Reasoning Index, and the outcome variable of prospective memory composite scores. Values presented are standardized beta values. IV = independent variable; DV = dependent variable. * $p < .01$; ** $p < .001$.

Model 5: Relation between prenatal alcohol exposure, Processing Speed Index, and prospective memory

Prenatal alcohol exposure and WISC-IV Processing Speed Index scores were entered as separate steps the hierarchical regression analysis, as predictors of PM. Table 17 shows that both prenatal alcohol exposure and Processing Speed Index scores were significant predictors of PM performance. The effects of prenatal alcohol exposure, however, fell just short of conventional levels of significance when Processing Speed Index scores were entered into the model, $p = .05$. The magnitude of this effect dropped from being large to medium when Processing Speed Index scores were entered into the model. Together, these two variables accounted for 12.80% of the variance in PM scores, $F(2, 82) = 6.03$, $p = .004$.

With regards to the assumptions underlying the regression model, the average VIF score was not substantially greater than 1 ($M_{VIF} = 1.1$) indicating that there was no multicollinearity between predictors. The Durbin-Watson statistic was 2.02 indicating that the assumption of independence of model residuals was upheld. The plot of standardized residuals against standardized predicted residuals indicated that the assumption of homoscedasticity was not upheld (see Appendix A, Figure A5). Furthermore, the assumption of normality of standardized residuals was not met, $W(85) = 0.88$, $p < .001$. Caution should, therefore, be exercised when generalizing the model beyond this sample (Field, 2009).

With regards to regression model diagnostics, Cook's distance was within the acceptable limits (i.e., < 1) given the sample size. Mahalanobi's distance had a maximum value of 20.98, which is raised, relative to the conventional cut-off of 15 (Fields, 2009), and indicates a possible influential case in the distribution of residual scores. This possible influential case is in keeping with the outlier previously identified in the distribution of prenatal alcohol exposure scores. Caution should, therefore, be exercised when generalizing the model beyond this sample (Field, 2009).

Because the effects of prenatal alcohol exposure were no longer significant when WISC-IV Processing Speed Index scores were entered into the model, I examined whether Processing Speed Index scores mediated the effects of prenatal alcohol exposure on PM performance. Figure 9 shows that Processing Speed Index scores did not mediate the effects of prenatal alcohol exposure on PM performance. This finding was substantiated by a non-significant result on the Sobel Test, $z = -1.40$ (0.07), $p = .16$.

University of Cape Town

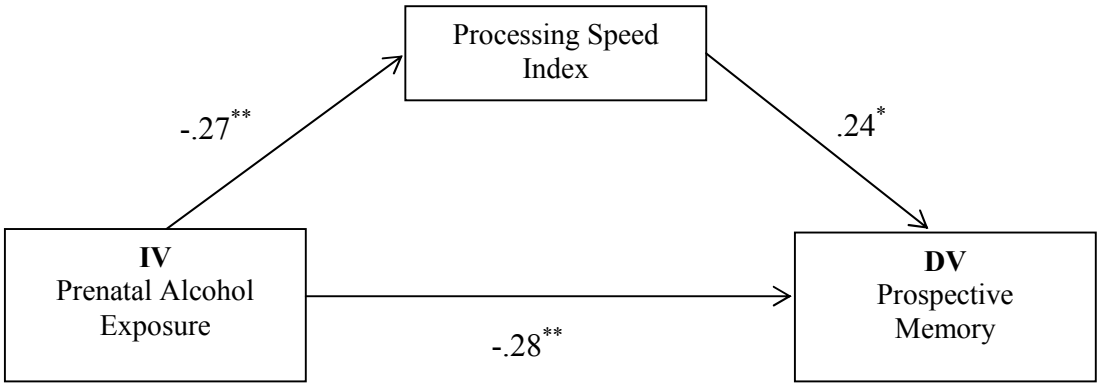

Figure 9. Absence of a mediating relation between the predictor variables (a) prenatal alcohol exposure and (b) Processing Speed Index, and the outcome variable of prospective memory composite scores. Values presented are standardized beta values. IV = independent variable; DV = dependent variable. $^{*}p < .05$. $^{**}p \leq .01$.

Model 6: Relation between prenatal alcohol exposure, Verbal Comprehension Index, and prospective memory

Prenatal alcohol exposure and WISC-IV Verbal Comprehension Index scores were entered as separate steps the hierarchical regression analysis, as predictors of PM. Table 17 shows that both prenatal alcohol exposure and Verbal Comprehension Index scores were significant predictors of PM performance. Furthermore, the effects of prenatal alcohol exposure remained significant when Verbal Comprehension Index scores were entered into the model, indicating an independent effect of prenatal alcohol exposure on PM performance. Together, these two variables accounted for 18.40% of the variance in PM scores, $F(2, 85) = 9.61$, $p < .001$.

With regards to the assumptions underlying the regression model, the average VIF score was not substantially greater than 1 ($M_{VIF} = 1.1$) indicating that there was no multicollinearity between predictors. The Durbin-Watson statistic was 2.24 indicating that the assumption of independence of model residuals was upheld. The plot of standardized residuals against standardized predicted residuals indicated that the assumption of homoscedasticity was not upheld (see Appendix A, Figure A6). Furthermore, the assumption of normality of standardized residuals was not met, $W(88) = 0.91$, $p < .001$. Caution should, therefore, be exercised when generalizing the model beyond this sample (Field, 2009).

With regards to regression model diagnostics, Cook's and Mahalanobi's distances were within the acceptable limits (i.e., < 1 and 15 respectively) given the sample size. This model is, therefore, a good fit to the data.

University of Cape Town

Even though the effects of prenatal alcohol exposure maintained an independent effect on PM performance when WISC-IV Verbal Comprehension Index scores were entered into the model, I considered the possibility of Verbal Comprehension Index scores mediating the effects of prenatal alcohol exposure. Figure 10 shows that Verbal Comprehension Index scores partially mediated the effects of prenatal alcohol exposure on PM performance. This finding was substantiated by a significant result on the Sobel Test, z = -2.15 (0.10), p = .03.

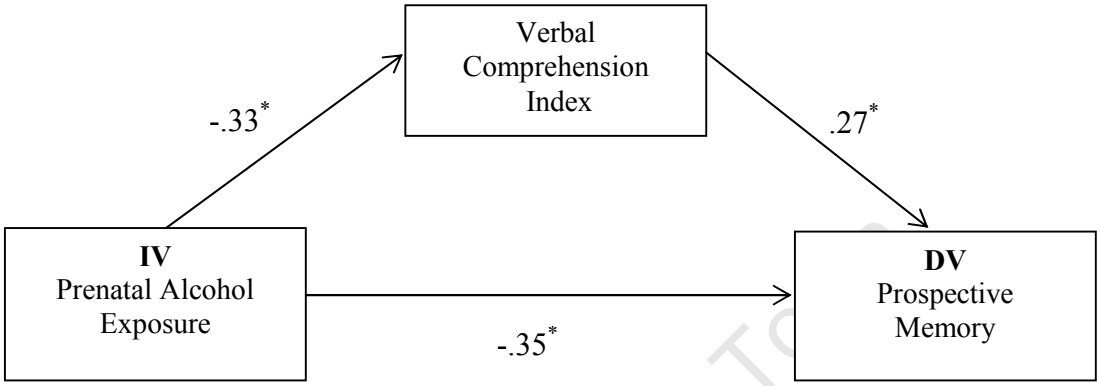

Figure 10. Partial mediation relation between the predictor variables (a) prenatal alcohol exposure and (b) Verbal Comprehension Index, and the outcome variable of prospective memory composite scores. Values presented are standardized beta values. IV = independent variable; DV = dependent variable. * $p \leq .01$.

Models 7 and 8: Relation between Prenatal Alcohol Exposure, Executive Functioning, and Prospective Memory

In the models described below I examined the degree to which alcohol-related EF deficits were responsible for the effects of prenatal alcohol exposure on PM. Verbal Fluency and Cognitive Flexibility composite scores were included based on their significant relation to PM performance (Table 15).

Model 7: Relation between prenatal alcohol exposure, verbal fluency composite scores, and prospective memory

To examine whether the effects of prenatal alcohol exposure on PM were present over-and-above those of verbal fluency, prenatal alcohol exposure and verbal fluency composite scores were entered as predictors of PM, at separate steps, into a regression analysis. Table 18 shows that prenatal alcohol exposure was significantly related to PM performance. Furthermore, the effects of prenatal alcohol exposure remained significant when verbal fluency was entered into the model, indicating an independent effect of prenatal alcohol exposure on PM performance Verbal fluency was, however, not a significant predictor of PM performance when prenatal alcohol exposure was included in the regression

analysis. Together, these two variables accounted for 10.90% of the variance in PM scores, $F(2, 81) = 4.94$, $p = .01$.

With regards to the assumptions underlying the regression model, the average VIF score was not substantially greater than 1 ($M_{VIF} = 1.1$) indicating that there was no multicollinearity between predictors. The Durbin-Watson statistic was 2.31 indicating that the assumption of independence of model residuals was upheld. The plot of standardized residuals against standardized predicted residuals indicated that the assumption of homoscedasticity was not upheld (see Appendix A, Figure A7). Furthermore, the assumption of normality of standardized residuals was not met, $W(84) = 0.86$, $p < .001$. Caution should, therefore, be exercised when generalizing the model beyond this sample (Field, 2009).

With regards to regression model diagnostics, Cook's distance was within the acceptable limits (i.e., < 1) given the sample size. Mahalanobi's distance had a maximum value of 21.18, which is raised, relative to the conventional cut-off of 15 (Fields, 2009), and indicates a possible influential case in the distribution of residual scores. This possible influential case is in keeping with the outlier previously identified in the distribution of prenatal alcohol exposure scores. Caution should, therefore, be exercised when generalizing the model beyond this sample (Field, 2009).

Model 8: Relation between prenatal alcohol exposure, cognitive flexibility composite scores, and prospective memory

Prenatal alcohol exposure and cognitive flexibility composite scores were entered as separate predictors of PM, at separate steps, into a regression model. Table 18 shows that prenatal alcohol exposure and cognitive flexibility were both predictors of PM performance. Furthermore, the effects of prenatal alcohol exposure remained significant when cognitive flexibility was entered into the model, indicating an independent effect of prenatal alcohol exposure on PM functioning. Together, these two variables accounted for 13.70% of the variance in PM scores, $F(2, 85) = 6.73$, $p < .01$.

With regards to the assumptions underlying the regression model, the average VIF score was not substantially greater than 1 ($M_{VIF} = 1.1$) indicating that there was no multicollinearity between predictors. The Durbin-Watson statistic was 2.06 indicating that the assumption of independence of model residuals was upheld. The plot of standardized residuals against standardized predicted residuals indicated that the assumption of homoscedasticity was not upheld (see Appendix A, Figure A8). Furthermore, the assumption

University of Cape Town

of normality of standardized residuals was not met, $W(88) = 0.87$, $p < .001$. Caution should, therefore, be exercised when generalizing the model beyond this sample (Field, 2009).

Table 18. ***Hierarchical Regression Analysis Controlling for EF Composite Scores and Retrospective Memory***

Variables Entered	*B*	*SE B*	*β*	*p*
Model 7: Controlling for Verbal Fluency Composite Scores ($N = 84$)[a]				
Step 1				
Constant	.20	.10		
AA/day	-.51	.20	-.29**	.008
Step 2				
Constant	.17	.10		
AA/day	-.43	.20	-.24*	.03
Verbal Fluency	.15	.10	.17	.12
Model 8: Controlling for Cognitive Flexibility Composite Scores ($N = 88$)				
Step 1				
Constant	.20	.10		
AA/day	-.56	.19	-.31**	.003
Step 2				
Constant	.18	.10		
AA/day	-.47	.19	-.26*	.02
Cognitive Flexibility	-.18	.09	-.21*	.047
Model 9: Controlling for Retrospective Memory ($N = 82$)				
Step 1				
Constant	.18	.11		
AA/day	-.56	.23	-.27*	.02
Step 2				
Constant	-.37	.29		
AA/day	-.46	.23	-.22*	.047
CVLT-C Long Delay	.06	.03	.22*	.04

Note. AA = Absolute Alcohol; CVLT-C = California Verbal Learning Test—Children's Version.
[a] $R^2 = .08$ for Step 1, $\Delta R^2 = .03$ for Step 2 ($p > .05$).
[b] $R^2 = .10$ for Step 1, $\Delta R^2 = .04$ for Step 2 ($p = .05$)
[c] $R^2 = .07$ for Step 1, $\Delta R^2 = .05$ for Step 2 ($p < .05$)
* $p < .05$; ** $p < .01$

University of Cape Town

With regards to regression model diagnostics, Cook's distance was within the acceptable limits (i.e., < 1) given the sample size. Mahalanobi's distance had a maximum value of 20.03, which is raised, relative to the conventional cut-off of 15 (Fields, 2009), and indicates a possible influential case in the distribution of residual scores. This possible influential case is in keeping with the outlier previously identified in the distribution of prenatal alcohol exposure scores. Caution should, therefore, be exercised when generalizing the model beyond this sample (Field, 2009).

Model 9: Relation between prenatal alcohol exposure, retrospective memory, and prospective memory

The regression model described below examined the degree to which retrospective memory impairments are responsible for the effects of prenatal alcohol exposure on PM performance. Levels of prenatal alcohol exposure and scores on the CVLT-C long-delay free recall trial were entered as separate predictors of PM, and at separate steps, into the model. Table 18 shows that prenatal alcohol exposure and declarative memory both significantly predicted PM performance. Furthermore, the effects of prenatal alcohol exposure remained significant when CVLT-C long-delay free recall scores were entered into the model, indicating that prenatal alcohol exposure has an independent effect on PM performance. Together, these two variables accounted for 11.80% of the variance in PM scores, $F(2, 79) = 5.29$, $p = .007$.

With regards to the assumptions underlying the regression model, the average VIF score was not substantially greater than 1 ($M_{VIF} = 1.1$) indicating that there was no multicollinearity between predictors. The Durbin-Watson statistic was 2.32 indicating that the assumption of independence of model residuals was upheld. The plot of standardized residuals against standardized predicted residuals indicated that the assumption of homoscedasticity was not upheld (see Appendix A, Figure A9). Furthermore, the assumption of normality of standardized residuals was not met, $W(82) = 0.90$, $p < .001$. Caution should, therefore, be exercised when generalizing the model beyond this sample (Field, 2009).

With regards to regression model diagnostics, Cook's and Mahalanobi's distances were all within the acceptable limits (i.e., < 1 and 15 respectively) given the sample size indicating that the model was a good fit for the data.

University of Cape Town

DISCUSSION

This study is the first to examine PM performance in children with FASD. I aimed to investigate two broad aims: (a) whether children with a history of heavy prenatal alcohol exposure had impaired event-based PM performance on the *Dresden Cruiser* (Voigt et al., 2011) and (b) if PM performance was impaired, whether the relation between prenatal alcohol exposure and PM was influenced by potential confounding socio-demographic variables and/or other potential predictor variables (viz., IQ, EF, or retrospective memory).

I accomplished these broad aims by testing five specific hypotheses: (1) children with a history of heavy prenatal alcohol exposure show impaired PM performance when compared to typically-developing, demographically similar controls born to mothers who either

abstained from alcohol or who drank minimally during pregnancy; (2) alcohol-related deficits in PM performance are not attributable to confounding variables (e.g., prenatal smoking or other drug exposure, maternal age at delivery); (3) deficits in PM performance are related to prenatal alcohol exposure after controlling for IQ; (4) deficits in PM performance are related to prenatal alcohol exposure after controlling for EF; and (5) deficits in PM performance are related to prenatal alcohol exposure after controlling for retrospective memory functioning.

In this section, I discuss the findings relating to each of my hypotheses systematically and within the context of relevant and recently-published literature. I begin with a discussion of the results of between-group analyses (i.e., those relating to Hypothesis 1). I then discuss results from the regression-based analyses that examined the association between prenatal alcohol exposure and PM performance when potentially confounding socio-demographic variables (e.g., SES) and potential predictor variables (viz., IQ, EF, and retrospective memory) were controlled for (i.e., analyses relating to Hypotheses 2–5). Finally, I address the limitations of the study, directions for future research based on the current findings, and the clinical significance of the results reported here.

University of Cape Town

Prospective Memory Functioning across Groups

Hypothesis 1 stated that children with a history of heavy prenatal alcohol exposure would show impaired PM functioning when compared to typically-developing, demographically similar control children who were born to mothers who either abstained from alcohol or who drank minimally during pregnancy. A mixed-factorial ANOVA examined this hypothesis; hence, the effects of manipulating within-subjects factors (i.e., cue focality and task difficulty) could be considered alongside the between-group effects of prenatal alcohol exposure.

Prospective Memory Impairments in FASD

The analyses showed that children in the FAS/PFAS group performed significantly more poorly than children in the HE and Control groups on both the focal and non-focal versions of the *Dresden Cruiser*. There were, however, no significant differences in PM performance between the HE and Control groups. To my knowledge, this is the first study to examine and document such impairments in syndromal children with heavy prenatal alcohol exposure.

This novel finding is particularly relevant to the on-going process of defining a cognitive-behavioral phenotype for FASD (for a review, see Jacobson et al., 2011 and

Mattson et al., 2011). In some cognitive domains (e.g., IQ and verbal learning and memory), alcohol-related deficits are present in children both with and without the characteristic facial features of FAS (Chasnoff et al., 2010; Mattson et al., 1998; Jacobson et al., 2011; Willoughby et al., 2008). In contrast to the findings of Mattson et al. (1998) and Willoughby et al. (2008) regarding retrospective memory, the findings of the current study suggest that impairments in PM are specific to children with dysmorphic features. This finding suggests, therefore, that PM deficits are a specific result of very heavy levels of prenatal alcohol exposure (here, the mean level of exposure in FAS/PFAS group was 1.18 oz AA/day, *SD* = 1.41), and that these deficits are not seen in children who have a history of heavy prenatal alcohol exposure but who lack the dysmorphic features necessary for a diagnosis of FAS or PFAS (here, the mean level of exposure in the HE group was 0.49 oz AA/day, *SD* = 0.45).

One possible reason for the absence of PM impairments in children in the HE group is that, at this age (i.e., prepuberty), these children's functioning, in terms of executive control, is similar to that of control children despite a history of heavy prenatal alcohol exposure in the former group. More specifically, children in the FAS/PFAS group performed more poorly than children in the HE and control groups on tasks involving response inhibition, verbal generativity, cognitive flexibility, and working memory. There were no significant differences between children in the HE and Control groups. This EF profile is not consistent with previous research (e.g., Kodituwakku, Kalberg, & May, 2001; Rasmussen, 2005) reporting EF impairments in children both with and without the characteristic dysmorphic features necessary for a diagnosis of FAS. Nevertheless, in the current study EF impairments, observed in children with FAS/PFAS, provide partial support for the assertion that the developmental trajectory of EF in children with heavy prenatal alcohol exposure is slower than in typically developing children (Rasmussen & Bisanz, 2009).The pattern of impairment observed in the current study is, therefore, consistent with the notion that impairments in EF result in poorer PM performance (Kliegel et al., 2008c; Ward et al., 2005). Hence, children in the HE and Control groups were performing at similar levels on both tasks of EF and PM, whereas children in the FAS/PFAS group showed significant impairments on tasks of EF and, consequently, on tasks of PM.

This interpretation is supported by Ward et al.'s (2005) finding that the developmental trajectory of event-based PM is closely linked to the functional maturation of the prefrontal lobes. Consistent with this developmental model, Wang et al. (2011) investigated the development of event-based PM across adolescence in a sample of 119 Chinese individuals. Participants were grouped according to age: 60 adolescents aged 11 to 14 years (mean age =

University of Cape Town

13.26, *SD* = 0.50) and 59 young adults aged 17 to 21 years (mean age = 19.70, *SD* = 0.87). The authors hypothesized that PM develops during adolescence and that the cognitive functions supported by the development of the prefrontal lobes (e.g., working memory and controlled attention) are associated with age-related differences in PM performance. To investigate these hypotheses, they manipulated two between-subjects factors: age (adolescents versus young adults) and cue focality (focal versus non-focal). There was a significant age × cue focality interaction, with young adults performing much better than adolescents on the non-focal version of the PM task. There were no age differences in performance on the focal version of the PM task, however. There were also no age differences in terms of on-going task performance, indicating that the differences in performance on the non-focal version of the task are representative of PM performance and not the result of task difficulty. In line with Ward et al.'s (2005) developmental model, Wang and colleagues suggested, therefore, that the development of controlled attention and working memory support the emergence of effective and strategic processing on non-focal cues in prospective remembering.

Given the developmental and functional links between the prefrontal lobes, EF, and PM, the PM impairments documented in the current study are, therefore, consistent with neuroimaging studies that have documented structural and functional abnormalities in the prefrontal lobes for children with a history of prenatal alcohol exposure (Diwadkar et al., in press; O'Hare et al., 2009; Sowell et al., 2002; Spandoni et al., 2007). Hence, these studies have provided further support for the relation between heavy prenatal alcohol exposure and impaired EF. When compared to typically developing control children, children with heavy prenatal alcohol exposure show decreased overall brain volume (Archibald et al., 2001), as well as regional growth abnormalities in the prefrontal lobes (for a review see, Spandoni et al., 2007). For example, Sowell et al. (2002) found a decreased distance from the center of the brain to the left orbitofrontal cortex in children with heavy prenatal alcohol exposure (aged 8 to 22 years, *M* = 12.60) compared to typically developing control children (aged 8 to 25 years, *M* = 13.50). Structural abnormalities have been further noted in the basal ganglia in children with heavy prenatal alcohol exposure (Archibald et al., 2001). Because of the association between the basal ganglia (i.e., fronto-striatal circuits) and EF (Cummings, 1993), structural abnormalities in the basal ganglia in children with heavy prenatal alcohol exposure might be functionally related to impairments in EF (Mattson et al., 1999).

Of particular relevance to the current study is the finding that children with a history of heavy prenatal alcohol exposure recruit more widespread neural networks during task

University of Cape Town

completion (i.e., their processing of task stimuli is less efficient; Diwadkar et al., in press; Meintjes et al., 2010; O'Hare et al., 2009). Diwadkar et al. (in press) compared working memory performance, as measured by a 1-Back task, in children (aged 8.9 to 10.6 years) who were grouped by FASD diagnosis. When comparing neural activations during 1-Back and 0-Back tasks, children in the FAS/PFAS and HE groups showed increased activation, across a more diffuse network, than children in the control group. Furthermore, the increased activation shown by the HE group recruited areas that would typically be activated during the more difficult 2-Back task. In future neuroimaging studies, it would be of interest to know whether HE children rely on less efficient neural networks for processing PM stimuli. Taken together, therefore, the aforementioned alcohol-related abnormalities in the structural and functional maturation of the brain support the idea that children with a history of prenatal alcohol exposure show an atypical developmental trajectory of EF and are, consequently, impaired on cognitive tasks mediated by EF (e.g., PM).

The between-group differences in PM functioning reported here are also consistent with those reported in the literature for other pediatric clinical populations with EF impairments. Kerns and Price (2001) reported impaired time-based PM functioning for 8-13-year-old children diagnosed with ADHD compared to age-, sex, and IQ-matched typically-developing controls. The authors considered these impairments to be as a result of inefficient time-monitoring and they were present over-and-above the effects of impaired attention. Their results suggested, therefore, that deficits in frontal lobe functioning, such as those seen in ADHD, have a negative impact on PM performance.

Studies investigating the sequelae of pediatric traumatic brain injuries (pTBI) have reported similar findings. Deficits in executive function have been documented for children with mild, moderate, and severe pTBIs (for a meta-analysis, see Babikian & Asarnow, 2009). Building on this finding, McCauley et al. (2010) used sMRI and an event-based PM task in a sample of 40 children (7 to 17 years old) with moderate-to-severe TBIs who were 3 months post-injury. They compared those children's brain structure and PM performance to that of 41 children who had sustained orthopedic injuries (not including head injuries). Children in the pTBI group were less effective at completing the PM task than children in the control group, and they showed marked cortical thinning in the frontal and temporal regions. This pattern of cortical thinning was correlated to event-based PM performance and was consistent with findings (e.g., Burgess et al., 2001) that these brain regions are involved in PM functioning.

Taken together, the findings of the current study, Kerns and Price (2001), and Babikian and Asarnow (2009) all support the functional link between EF and PM (Kliegel et

University of Cape Town

al., 2008). Furthermore, these studies all demonstrate that pediatric clinical populations that display EF impairments also tend to display PM impairments.

Manipulation of On-going Task Factors: Cue Focality and Task Difficulty

The analyses detected significant main effects of both cue focality and difficulty level, but no significant interactions between each of these factors and group status. This pattern of data suggests that the manipulation of on-going task factors resulted, on average, in children across all groups performing more poorly on the non-focal version of the task than the focal version. The pattern of data also suggests that participants, regardless of group, found the difficult version of the task more challenging than the easier version of the task.

These results are consistent with previous research demonstrating that the manipulation of on-going task factors (e.g., cue focality) produces different levels of successful prospective remembering. For example, as part of a larger study investigating the relative contribution of strategic monitoring and automatic/spontaneous processes to PM performance, Einstein et al. (2005) found that, in group of 24 university students, participants performed better on the focal than on the non-focal version of a PM task. The authors interpreted this finding as being consistent with the Multiprocess Framework (McDaniel & Einstein, 2000), which suggests that, depending on on-going task conditions, the type of strategy (i.e., either strategic monitoring or automatic/spontaneous) employed during prospective remembering will differ. With specific regard to the Dresden Cruiser, or similar tasks, the Multiprocess Framework predicts that focal cues should be processed in a relatively automatic/spontaneous manner, whereas non-focal cues should be processed in a strategic manner (McDaniel & Einstein, 2000).

Clearly, then, the current study's results provide at least partial support for the Multiprocess Framework theory of event-based PM. Specifically, children in the FAS/PFAS group performed more poorly on the non-focal than focal version of the task, suggesting that they did not engage in a strategic manner to complete the former task successfully. This result is completely consistent with a Multiprocess Framework account of event-based PM. Regarding performance of the HE group and whether it is consistent with predictions from the Multiprocess Framework, previous studies suggest that children with heavy prenatal alcohol exposure tend to struggle with the types of EF that support the processing of non-focal cues (e.g., sustained attention and cognitive switching; Rasmussen, 2005). Hence, the prediction for children in this group was that they too would perform more poorly on the non-focal than focal version of the task. This prediction was confirmed.

University of Cape Town

Of note here, however, is that the cue focality × group interaction effect was not significant; more specifically, the analysis did not detect any differences between the performance of HE and Control groups on both the focal and non-focal versions of the *Dresden Cruiser*. There are at least two possible ways to account for this pattern of data. First, the EF data suggest that children in the HE group performed, on average, as well as Control children on tasks that required engagement of strategic monitoring. Hence, one might expect that these groups would perform equivalently on the non-focal version of the task, if that task required engagement of such processes. Second, it is possible that the non-focal version of the *Dresden Cruiser*, a relatively simple and child-friendly event-based PM task, was not complex enough to engage complex executive processes and, therefore, engaged the more automatic/spontaneous processes. Given that previous studies (e.g., Aragón et al., 2008; Burden et al., 2005b) suggest that children with heavy prenatal alcohol exposure are not impaired on tasks requiring engagement of such processes, one might expect that these groups would perform equivalently on both the focal and non-focal versions of the task, if those tasks both required engagement of such processes.

Support for the second account listed above emerges from the fact that there appeared to be a ceiling effect in the performance of both groups on the non-focal version of the *Dresden Cruiser*. Although both the focal and non-focal versions of the task were set to have a maximum of five refuel opportunities during the on-going task, 22 children in the HE group (68.80%) and 21 children in the Control group (75.0%) refueled four times during the easy version of the non-focal task, and 20 children in the HE group (62.50%) and 20 children in the Control group (71.40%) refueled four times during the difficult version of the non-focal task. The distribution of refuel scores were also positively skewed for the FAS/PFAS group, with 9 (31.0%) and 11 (37.90%) children having refueled either three or four times, respectively, on the easy version of the non-focal task, and 7 (24.10%) and 12 (41.40%) children having refueled either three or four times, respectively, on the difficult version of the non-focal task.

A consequence of this observed ceiling effect is that, whereas there were five refuel opportunities during the focal task, there were, in practice, only four during the non-focal task. Hence, although one might accept the explanation that the relatively low cognitive demand of the on-going *Dresden Cruiser* task resulted in non-focal cues being processed automatically, in a similar manner to focal cues, the significant main effect of cue focality (non-focal task performed more poorly than focal task) might be accounted for, simply, by a discrepancy in refuel opportunities across the two versions of the task.

University of Cape Town

Another point to make here is that all of the speculation above is based on the assumption that the cue focality difference is a real effect, and that it was not simply an artifact of the method, which did not involve counter-balancing. The focal task was always administered before the non-focal task, and so better-than-expected performance, particularly by children in the HE group, might be attributed (at least partially) to practice effects. The design of the current study does not, unfortunately, allow one to disentangle all of these possible effects on PM task performance. As noted later in the Discussion, future studies might attempt to do so.

Finally, the current data with regard to the main effect of cue focality are not consistent with McDaniel et al.'s (2004) proposal of a 'discrepancy-plus-search' approach to prospective remembering. This approach draws on the discrepancy-attribution hypothesis (Whittlesea & Williams, 2001a, 2001b), which states that discrepancies in event familiarity will influence the recognition of a target event. That is to say, individuals may rely on the familiarity of an event to prompt the allocation of attentional resources. Consequently, this familiarity aids in the recognition and execution of the target event. McDaniel et al.'s (2004) results support the idea that both discrepancy-attribution and more automatic reflexive-associative processes underlie intact PM functioning. Furthermore, their results are relevant to the processing of non-focal cues in tasks such as the *Dresden Cruiser*, where the PM cue is unrelated to the on-going task and/or the intended PM action (McDaniel & Einstein, 2000). Hence, the discrepancy-plus-search theory would predict that performance on the non-focal task might be better than that on focal task because it was easier to identify the non-focal than the focal cue correctly, given that the former was unfamiliar in the on-going task environment. This prediction was disconfirmed by the current data: Across groups, and regardless of task difficulty, performance on the non-focal version of the *Dresden Cruiser* was worse than that on the focal version.

University of Cape Town

On-going Task Absorption and Computer Usage

In order to ascertain whether the aforementioned impairments in PM functioning could be accounted for substantially by differences in on-going task performance, I used between-group analyses to compare the number of cars hit (i.e., on-going task absorption) on each version of the *Dresden Cruiser*. Consistent with previous research (e.g., Voigt et al., 2011), the current data analyses detected no significant between-group differences in on-going task absorption. This pattern of data suggests that, regardless of group, children were

engaged equally in the on-going task across both difficulty levels of both versions of the *Dresden Cruiser*.

Consistent with this finding, there were also no significant between-group differences in terms of previous computer usage (i.e., the number of children in each group who reported playing computer games previously, or in the number of days per week that they play computer games). The absence of a task difficulty × group interaction provides further support for similar levels of task absorption in that children, regardless of group, showed poorer performance on the difficult version of the than on the easy version.

Taken together, these findings suggest that impairments in PM functioning for children in the FAS/PFAS group cannot be attributed to these children finding the tasks less engaging, or more novel, or disproportionately more difficult than children in either the HE or Control groups.

Summary of Prospective Memory Functioning Across Groups

Overall, results from the mixed-factorial ANOVA provide partial support for the prediction that children with heavy prenatal alcohol exposure would show PM impairments when compared to typically-developing demographically similar control children. Interestingly, these impairments were only seen in children in the FAS/PFAS group, suggesting that this effect is only detectable in dysmorphic children who have a history of very heavy levels of prenatal alcohol exposure. There are two possible interpretations of this finding: Firstly, children in the HE group may have been functioning at a similar level of executive control to children in the Control group, with children in the FAS/PFAS group functioning worse than both. Secondly, the event-based version of the *Dresden Cruiser* may not have been sensitive enough to reveal any potential PM impairments in children in the HE group. Consistent with this interpretation, it should also be noted that the magnitude of effect for the PM impairments in the FAS/PFAS group was small and PM impairments may, therefore, only have been revealed in the most severe cases. Small effect sizes are, however, a common finding in research into the neurocognitive effects of prenatal alcohol exposure (Jacobson & Jacobson, 2005). The clinical relevance of the observation of impaired PM performance in children with a diagnosis of FAS/PFAS should not, therefore, be discounted on the basis of a small effect size.

University of Cape Town

Relation between Prenatal Alcohol Exposure and Prospective Memory when Controlling for Potential Confounding Variables.

To ascertain the mechanism underlying cognitive and behavioral impairments in FASD samples, it is important that developmental teratology researchers consider socio-demographic variables as potential confounding variables (Jacobson & Jacobson, 2005). Hence, Hypothesis 2 stated that deficits in PM functioning would be due primarily to the effects of prenatal alcohol exposure, and would not be accounted for primarily by the effects of potential confounding variables (e.g., prenatal drug exposure, maternal age at delivery). I tested this prediction using a hierarchical regression model. This model examined the association between prenatal alcohol exposure and PM, when controlling for maternal IQ and SES (i.e., the socio-demographic variables that preliminary analyses suggested were significantly associated with PM performance outcome). Results indicated that, even after these two potential confounding variables were entered into the model, prenatal alcohol exposure remained a significant predictor of PM performance. Neither maternal IQ nor SES were significant predictors of PM performance. These results suggest, therefore, that prenatal alcohol exposure has a specific effect on PM performance over-and-above the effects of potentially confounding socio-demographic factors.

Previous studies investigating PM performance in pediatric clinical samples have tended to control for participant variables only (e.g., age, sex, and IQ). For example, Kerns and Price (2001) found that PM performance was not related to general intellectual functioning or participant's sex. Similarly, McCauley et al. (2010) found that when SES was entered as a covariate, it did not have an effect on PM performance when comparing children with moderate to severe TBIs and typically developing control children. Thus, these results are consistent with the prediction that aforementioned impairments in PM performance are due to the effects of prenatal alcohol exposure and not to the effects of potential confounding variables.

Relation between Prenatal Alcohol Exposure, Prospective Memory, and IQ

Prenatal alcohol exposure is one of the leading causes of deficits in general intellectual functioning (Abel & Sokol, 1987), and has a specific effect on IQ test performance (for a review, see Mattson et al., 2011). These deficits have been documented in children with a history of heavy prenatal alcohol exposure, both with and without the physical features of FAS (Dalen, Bruaroy, Wentzel-Larsen, & Laegried, 2009; Mattson et al.,

University of Cape Town

1997), and in children with a history of moderate levels of exposure (Willford, Leech, & Day, 2006; Jacobson et al., 2004).

Because prenatal alcohol exposure affects IQ, alcohol effects on FSIQ may mediate or account for effects on other cognitive tests. Researchers have, therefore, used various statistical techniques in their attempts to control for the effects of IQ. For example, Coles et al. (2010) included FSIQ scores as a covariate in the statistical analysis of verbal and nonverbal memory data. Their results indicated that, despite the presumed overlap between learning and memory and IQ, there were specific effects of prenatal alcohol exposure on recall and recognition memory. In some cases of moderate prenatal alcohol exposure, however, IQ scores fall within the normal range, even though performance on tasks measuring the cognitive functions underlying FSIQ scores is impaired (e.g., arithmetic; for a review see, Jacobson & Jacobson, 1999). Hence, instead of focusing solely on control for FSIQ, it may be useful to examine the relative contribution of separate components of FSIQ (e.g., the four WISC-IV index scores) as a means to understand which specific domain of IQ is affected by prenatal alcohol exposure. Therefore, I examined the effects of FSIQ and each of the four WISC-IV index scores on the association between prenatal alcohol exposure and PM. Hypothesis 3 stated that deficits in PM functioning would be predicted by level of prenatal alcohol exposure even after controlling for WISC-IV FSIQ and various components thereof. Five separate hierarchical regression models (one for each of the WISC-IV outcome variables) tested this hypothesis.

The first of these models examined the association between prenatal alcohol exposure and PM performance when WISC-IV FSIQ scores were controlled for. When FSIQ was entered at the second step of the model, the effects of prenatal alcohol exposure on PM fell just short of conventional levels of significance, while WISC-IV FSIQ was a significant predictor. Further investigation revealed that FSIQ partially mediated the effects of prenatal alcohol exposure on PM performance. This result, then, disconfirms Hypothesis 3 partially.

This result is, however, consistent with that reported by Narberhaus et al. (2007), who investigated PM performance, on the Rivermead Behavioral Memory Test (RBMT), in a sample of 44 adolescents who were born at a gestational age ≤ 32 weeks and with a birthweight of ≤ 1, 500g (i.e., very low birthweight) and 44 typically developing socio-demographically matched controls. Increased vulnerability for impaired general intellectual functioning has been documented in children with very low birth weights (Weisglas-Kuperus et al., 2009).Narberhaus and colleagues found that gestational age predicted both FSIQ (as measured by either the Wechsler Intelligence Scale for Children-Revised or the Wechsler

University of Cape Town

Adult Intelligence Scale-Third Edition) and PM. Their results further indicated that when FSIQ was entered as a covariate in an ANCOVA, between-group differences in PM were no longer significant. Consistent with the results of the current study, Narberhaus and colleagues concluded that the effects of prematurity on general intellectual functioning accounted for the between-group differences in PM.

These findings do, however, stand in contrast to those of Kerns and Price (2001), who reported that the PM impairments in children with ADHD could not be attributed to the effects of general intellectual functioning. Deficits in general intellectual functioning have been documented in children and adolescents with ADHD in comparison to typically developing children and adolescents (for a review, see Frazier, Demaree, & Youngstrom , 2004). Kerns and Price (2001) found that IQ, as measured by the Kaufman Brief Intelligence Test (K-BIT; Kaufman & Kaufman, 1990), was not related to PM failures. The absence of a relation between IQ and PM may, however, be due to the fact that the children included in this study had IQ scores that fell within the average to high-average range (Experiment 1: Mean IQ for ADHD group = 106.50, *SD* = 15.50; mean IQ for control group = 109.70, *SD* = 9.70; Experiment 2: Mean IQ for ADHD group = 104.40, *SD* = 14.20; and mean IQ for control group = 111.20, *SD* = 10.90) and children in the ADHD group may, therefore, have been better able to compensate for any subtle differences in general intellectual functioning. This interpretation is consistent with the theory of Cognitive Reserve, which suggests that individuals with brain dysfunction or damage who have higher levels of education and/or IQ are more effective at employing compensatory networks during task performance (Stern, 2003).

The second WISC-IV regression model examined the association between prenatal alcohol exposure and PM performance when scores on the WISC-IV Working Memory Index were controlled for. When Working Memory Index scores were entered at the second step of the model, prenatal alcohol exposure remained a significant predictor of PM performance. Although Working Memory Index scores were also a significant predictor of PM performance, they did not mediate the effects of prenatal alcohol exposure on PM performance. Within Anderson's (2002) model of EF, working memory is located in the domain of cognitive flexibility. The finding that Working Memory Index scores predict PM performance is, therefore, consistent with the notion that cognitive flexibility supports the intention initiation stage of prospective remembering (Kliegel et al., 2002, 2008a).

Consistent with the current finding regarding working memory, previous studies suggest that, relative to matched controls, children with a history of prenatal alcohol exposure

University of Cape Town

display impairments on behavioral working memory tasks (Rasmussen , 2005), recruit different brain regions (O'Hare et al., 2009), and exhibit relatively inefficient activations of neural networks associated with working memory (Diwadkar et al., in press). Diwadkar et al. (in press) found that children with heavy prenatal alcohol exposure recruited a more extensive network of brain regions in order to meet the cognitive demands of a simple working memory task. Diwadkar and colleague's findings are consistent with the suggestion that alcohol-related impairments in working memory become more evident as the complexity and demand of the task increases (Kodituwakku, 2001).

The absence of a mediating effect of Working Memory Index scores may, therefore, reflect the finding that both focal and non-focal cues on the *Dresden Cruiser* were processed in an automatic/spontaneous manner, and apparently did not require the engagement of complex task switching and/or working memory processes. This interpretation is further consistent with the findings of Basso et al. (2010), who suggested that working memory and PM only compete for resources as working memory demand increases. It also provides further support for the functional dissociation between working memory and PM (Basso et al., 2010; Reynolds et al., 2009) under task conditions that require relatively automatic/spontaneous processing of PM cues (Einstein et al., 2005).

The third WISC-IV regression examined the association between prenatal alcohol exposure and PM performance when scores on the WISC-IV Perceptual Reasoning Index were controlled for. When Perceptual Reasoning Index scores were entered at the second step of the model, prenatal alcohol exposure remained a significant predictor of PM performance. Perceptual Reasoning Index scores were also a significant predictor of PM performance, and it partially mediated the effects of prenatal alcohol exposure on PM performance.

This finding, along with the fact that Perceptual Reasoning Index scores were the WISC-IV index most strongly correlated with prenatal alcohol exposure, $r = -.37$, $p < .001$, and with PM functioning, $\rho = .45$, $p < .001$, suggests that children were relying heavily on the perceptual aspects of the *Dresden Cruiser* to complete the PM task successfully. Consistent with this interpretation, children in the FAS/PFAS group had lower Perceptual Reasoning Index scores than children in either the HE or Control group, with children in the latter two groups performing at a similar level. Taken together, therefore, these results suggest that alcohol-related impairments in visual-spatial perception are likely to impair performance on cognitive tasks, such as the Dresden Cruiser, containing perceptual elements.

This suggestion is consistent with data presented by Kaemingk and Halverson (2000), who documented impairments on a task of visual-spatial perception in children, aged 6 to 16

University of Cape Town

years, with FAS or fetal alcohol effects (FAE; M_{age} = 11.15, *SD* = 2.50) when compared to non-exposed control children (M_{age} = 11.13, *SD* = 2.48). They aimed to investigate whether spatial memory deficits in children with prenatal alcohol exposure are a consequence of specific impairments in memory functioning, or of impaired visual-spatial perception. Their results suggested that impairments in visual-spatial perception accounted for some of the spatial memory deficits seen in children with heavy prenatal alcohol exposure. Taken together, the current results and those from Kaemingk and Halverson (2000) suggest that deficits in perceptual reasoning mediate the effects of prenatal alcohol exposure on PM task performance.

The fourth WISC-IV regression model examined the association between prenatal alcohol exposure and PM performance when scores on the WISC-IV Processing Speed Index (PSI) were controlled for. When Processing Speed Index scores were entered at the second step of the model, prenatal alcohol exposure remained a significant predictor of PM performance. Although Processing Speed Index scores were also a significant predictor of PM performance, it did not mediate the effects of prenatal alcohol exposure on PM performance.

Impairments in processing speed are seen early in development for children with prenatal alcohol exposure (e.g., Jacobson et al., 1993) and persist throughout childhood (Burden et al., 2005a, b). The absence of a mediating relation between WISC-IV Processing Speed Index scores and prenatal alcohol exposure is, however, consistent with the suggestion that processing speed is only impaired for children with heavy prenatal alcohol exposure on more complex tasks, and is not impaired in instances where automatic processing is required (Burden et al., 2005b). Supporting that suggestion, Aragon et al. (2008) reported that, when compared to children with PFAS and typically-developing demographically similar children, children with FAS showed consistently poorer performance on tasks requiring complex information processing. They further suggested that these impairments follow a dose-response pattern, with children at the most severe end of the FASD diagnostic spectrum performing worse than those who were diagnosed with PFAS. The findings of Burden et al. and Aragon et al. are consistent with the suggestion that more automatic/spontaneous retrieval processes were engaged during both the focal and non-focal versions of the task because the *Dresden Cruiser* is a relatively simple event-based PM task. They are further consistent with results of the current between-group analyses. More specifically, the *Dresden Cruiser* may have been complex enough to elicit PM impairments in severely affected children (i.e., children in the FAS/PFAS group), but not for children in the HE group. Future

University of Cape Town

studies should, therefore, administer more sensitive PM tasks in order to further elucidate the pattern of impairment for children with FASD.

The fifth, and final, WISC-IV regression model examined the association between prenatal alcohol exposure and PM performance when scores on the WISC-IV Verbal Comprehension Index (VCI) were controlled for. When Verbal Comprehension Index scores were entered at the second step of the model, prenatal alcohol exposure remained a significant predictor of PM performance. Verbal Comprehension Index scores were also a significant predictor of PM performance, and partially mediated the effects of prenatal alcohol exposure on PM performance.

The finding that Verbal Comprehension Index scores predict PM performance is consistent with the suggestion that retrospective memory (i.e., the ability to comprehend and maintain task instructions) can influence PM performance at the level of intention retention (Kliegel, 2008a). However, earlier data analyses in the current study detected no between-group differences in retention of the on-going and PM task instructions. It is particularly interesting, then, that Verbal Comprehension Index scores nonetheless partially mediated the effect of prenatal alcohol exposure on PM performance. Taken together, these data suggest that (a) PM impairments observed in children with very heavy levels of exposure are not due to a failure in declarative/retrospective memory, but that (b) the ability to comprehend and then apply the task instructions may interfere with successful prospective remembering.

The latter part of this suggestion is consistent with the findings of McGee, Schonfeld, Roebuck-Spencer, Riley, and Mattson (2008). In their study, performance on measures of concept formation was compared in children both with and without a diagnosis of FAS (ALC group, M_{age} = 11.24, SD = 2.21) and typically-developing control children (CON group, M_{age} = 11.31, SD = 2.03) aged 8 to 18 years. Children in the ALC group displayed greater difficulty in concept formation for both verbal and non-verbal information. McGee and colleagues suggested that impairment in the formation and execution of concepts contributes towards less effective problem solving. Within the context of PM performance, planning and problem-solving skills support the stage of intention formation (Kliegel et al., 2002). The absence of between-group differences in the retention of on-going task instructions and presence of a mediating relation between prenatal alcohol exposure and verbal comprehension may, therefore, be indicative of alcohol-related impairments in concept formation and, consequently, difficulty with fulfilling PM task requirements.

University of Cape Town

Summary of the relation between prenatal alcohol exposure, WISC-IV performance, and prospective memory performance

Results from the five regression models described above do not support the prediction that the effects of prenatal alcohol exposure on PM would be independent of the effects of general intellectual functioning on PM. However, the statistical control for WISC-IV IQ yields an interesting interpretation of the effect of prenatal alcohol exposure on PM performance. More specifically, children with heavy prenatal alcohol exposure and, consequently, lower FSIQ scores appear to be more susceptible to PM failures. Furthermore, the mediating effects of WISC-IV IQ are specific to the Perceptual Reasoning and Verbal Comprehension Index scores. These findings are of particular importance to the delineation of cognitive-behavioral profiles associated with FASD.

The current results are also consistent with the finding that IQ and facial dysmorphology reflect, to a certain extent, the developmental trajectory of the brain and related cognitive functions (Lebel et al., 2012). In their longitudinal study, Lebel et al. (2012) compared changes in regional brain volumes in children with heavy prenatal alcohol exposure and typically-developing demographically similar control children. Their results suggested that the structural maturation of the brain in children with heavy prenatal alcohol exposure is marked by less plasticity and premature synaptic pruning. Furthermore, more severe facial dysmorphology and lower IQ scores were related to maturational trajectories in more diffuse brain regions in children with prenatal alcohol exposure. These findings support the suggestion that atypical structural and functional brain maturation in children with prenatal alcohol exposure impedes the developmental trajectory of the prefrontal lobes and, consequently, of EF—a cognitive domain that is essential to successful PM. The current study's findings regarding cognitive function in FASD are consistent with that neuroanatomical account.

Relation between Prenatal Alcohol Exposure, Prospective Memory, and Executive Functioning

Hypothesis 4 stated that deficits in PM performance would be present over-and-above any deficits in EF. Two separate hierarchical regression models tested this prediction. The first of these models examined the association between prenatal alcohol exposure and PM performance when the verbal fluency composite score, derived from the factor analysis, was controlled for. When verbal fluency was entered at the second step of the model, prenatal

University of Cape Town

alcohol exposure remained a significant predictor of PM performance. On its own, verbal fluency was not a significant predictor of PM performance.

Given the nature of the verbal fluency tests and that they are mediated by extensive frontal-subcortical circuits (Cummings, 1993; Henry & Crawford, 2004), it is not surprising that performance on the current verbal fluency tests would be uncorrelated to PM. Nevertheless, the zero-order correlation (ρ = .27) between verbal fluency composite scores and PM performance was the reason for including that composite in the regression models. The strength of that correlation may, however, reflect the influence of information processing (viz., processing speed) on task performance, rather than reflecting a specific relation between verbal generativity and PM performance. As mentioned previously, children with a history of prenatal alcohol exposure display impairments on tests of processing speed (Burden et al., 2005a, b; Jacobson et al., 1993; Kable & Coles, 2004). The finding that this verbal fluency composite, which was heavily influenced by processing speed, was not a significant predictor of PM performance, and that prenatal alcohol exposure remained a significant predictor of PM performance even after inclusion of that composite in the model is, therefore, consistent with the aforementioned findings that (a) prenatal alcohol exposure remained a significant predictor of PM performance even after WISC-IV Processing Speed Index score was entered into the regression model, and (b) WISC-IV Processing Speed Index score did not mediate the effects of prenatal alcohol exposure on PM performance.

The second of the EF models examined the association between prenatal alcohol exposure and PM performance when the cognitive flexibility composite score, derived from the factor analysis, was controlled for. When cognitive flexibility was entered at the second step of the model, prenatal alcohol exposure remained a significant predictor of PM performance. Cognitive flexibility was also, on its own, a significant predictor of PM performance.

These data are consistent with the suggestion that cognitive flexibility is supports the stage of intention initiation during successful prospective remembering (Kliegel et al., 2002, 2008a). Impairments in cognitive flexibility have been well documented for children with prenatal alcohol exposure (e.g., Mattson et al., 1999; Rasmussen & Bisanz, 2009). Performance on tests of cognitive flexibility is supported by optimal functioning in prefrontal cortical regions. Findings from neuroimaging research indicate that children with heavy prenatal alcohol exposure display structural and functional abnormalities in such regions (e.g., rostral prefrontal cortex; this region also supports intact PM functioning; Burgess et al., 2001; Spandoni et al., 2007; Simons et al., 2006; Sowell et al., 2007). O'Hare et al. (2009)

University of Cape Town

reported that children with FASD showed increased activation in the rostral prefrontal cortex during a task of working memory when compared to typically developing controls. Thus, these results indicate that even though prenatal alcohol exposure has a specific adverse effect on PM performance, impaired cognitive flexibility might also influence PM performance.

Taken together, the results from these two models confirm the prediction that alcohol-related impairments in PM performance would be present over-and-above any deficits in EF. This finding is of clinical significance in that prenatal alcohol exposure remained an independent predictor of PM performance when EF variables were controlled for in both models. When interpreted in conjunction with the findings from between-group analyses (i.e., that it is children with very heavy levels of prenatal alcohol exposure who display impairments in PM performance), these data provide a novel contribution to the process of defining the neuropsychological profile of FASD.

Relation between Prenatal Alcohol Exposure, Prospective Memory, and Retrospective Memory

Hypothesis 5 stated that deficits in PM performance would be present over-and-above any deficits in retrospective memory functioning (i.e., declarative or episodic memory). I tested this prediction using a hierarchical regression model that examined the association between prenatal alcohol exposure and PM performance when CVLT-C long-delay free recall score was controlled for. When the latter variable was entered at the second step of the model, prenatal alcohol exposure remained a significant predictor of PM performance. CVLT-C long delay free recall score, on its own, also predicted PM performance.

These results address the theoretical distinction between retrospective memory and PM (Burgess & Shallice, 1997). More specifically, the finding that retrospective memory predicts PM performance is consistent with the suggestion that retrospective memory supports the stage of intention retention (Kliegel et al., 2002, 2008a). Even though PM and retrospective memory are two distinct cognitive processes (Burgess & Shallice, 1997), there is a retrospective component (viz., accurately retaining and recalling task instructions) to PM (Ellis & Kvavilashvili, 2000). In studies of age-related changes in memory functioning (e.g., Einstein, Holland, McDaniel, & Guyunn, 1992; Kvavilashvili, Kornbrot, Mash, Cockburn, & Milne, 2009), impaired retrospective memory, has been shown to negatively impact upon PM performance specifically at the level of intention retention.

The fact that retrospective memory, on its own, predicted PM performance is most likely due to the performance differences seen on the CVLT-C: Children in the FAS/PFAS

University of Cape Town

group recalled significantly fewer words than children in either the HE or Control groups, who performed at a similar level. These alcohol-related impairments in delayed recall are consistent with previous research documenting verbal learning and memory impairments in FASD (for a review, see Manji, Pei, Loomes, & Rasmussen, 2009). The finding that retrospective memory predicted PM performance should, however, be interpreted in light of the fact that most children in this sample recalled on-going and PM task instructions accurately. In other words, PM failures cannot be attributed to failures at the level of intention retention.

Taken together, therefore, these findings indicate that even though retrospective memory predicted PM performance, impairments in PM are not explained by failures at the level of intention retention. Furthermore, these results support the prediction that impairments in PM are due to specific effects of prenatal alcohol exposure and cannot be attributed solely to retrospective memory failures.

Limitations and Future Directions

Several limitations of this study should be addressed in future by researchers who aim to delineate further the relation between prenatal alcohol exposure and PM. Furthermore, given the increased concern with Type II errors in developmental teratology research (Jacobson & Jacobson, 2005) and the small estimates of effect size in the current study, it is important that the results from the current study be replicated.

One possible limitation of this study was that the primary task used was not sensitive enough to detect the effects under consideration. Specifically, the statistical analyses detected no significant differences in PM performance between children in the HE and Control groups. One possible reason for the absence of this between-group difference is that the event-based *Dresden Cruiser* task was not complex enough to elicit PM deficits in children in the HE group. It is possible, therefore, that the use of more complex measures of PM (e.g., Kliegel, Ropeter, & MacKinlay, 2006) might detect PM dysfunction in children who have a history of heavy prenatal alcohol exposure but who are nonsyndromal. The use of a more complex PM task will also allow for the identification of the stage(s) (i.e., intention formation, intention retention, intention initiation, or intention execution) of PM that might be particularly vulnerable to the effects of prenatal alcohol exposure. The use of more complex measures of PM will also allow for the manipulation of other on-going task factors (e.g., cognitive demand or on-going task absorption) and will, therefore, allow for further testing of the Multiprocess Framework (McDaniel & Einstein, 2000).

University of Cape Town

It would also be of clinical relevance to investigate time-based PM in children with prenatal alcohol exposure. Time-based PM tasks appear to be more reliant on strategic monitoring and related EF (e.g., Mäntylä, Carelli, & Forman, 2007). Furthermore, Khan, Sharma, and Dixit (2008) found that in a sample of 80 adults (mean age = 26.41, *SD* = 3.01), more successful prospective remembering occurred on an event-based task than on a time-based task. Time-based PM tasks may, therefore, be more challenging, and may therefore be more sensitive to subtle differences in EF. Future researchers should, therefore, aim to replicate these findings and to extend them to include time-based PM tasks as well as more complex and sensitive measures of PM.

Regarding the current study's methodology, one possible improvement to the study design would be to counter-balance the presentation of the different versions of the *Dresden Cruiser*. The choice not to counter-balance here was a consequence of attempting to remain consistent with the procedures of the on-going longitudinal cohort study within which the current research was nested. Counter-balancing has, however, been the gold standard in previous studies investigating the effect of manipulating task factors on PM performance (e.g., Einstein et al., 2005; Voigt et al., 2011). If it is feasible, therefore, future researchers should aim to use counter-balancing in their study design. This design element will, for instance, strengthen the causal inferences one might draw about the influence of manipulating task factors on PM performance, and will control for any practice or order effects.

Much of the focus in recent literature has been on documenting the developmental trajectory of PM through childhood and adolescence and into young- and older-adulthood (e.g., Kliegel, Mackinlay, & Jäger, 2008b). It is important, therefore, to view findings of cross-sectional studies (such as the current study) within the context of the developmental trajectory of the functions necessary to complete the task in question. Future studies investigating the relation between prenatal alcohol exposure and PM should, therefore, aim to extend the findings of the current study by documenting PM performance during childhood and adolescence, as the structural and functional maturation of the frontal lobes and related EF continues. Relatedly, future studies should also incorporate the use of PM tasks that are suitable for use in neuroimaging paradigms (e.g., McCauley et al., 2010). The use of neuroimaging techniques will allow for further elaboration of the alcohol-related developmental differences, both structural and functional, in the prefrontal lobes; the relation between EF, PM, and the prefrontal lobes; and the neural correlates of PM.

University of Cape Town

Clinical Significance

The current study identified impairments in PM performance in a sample of South African children with very heavy levels of prenatal alcohol exposure. This finding is important because it provides a novel contribution to the definition of the neuropsychological profiles of children on the FASD diagnostic spectrum (see, e.g., Jacobson et al., 2011; Kodituwakku, 2009; Mattson et al., 2011). Furthermore, the current data speak to the functional link between PM and EF: Children in the FAS/PFAS group showed performance deficits on both PM and EF tasks, whereas children in the HE and Control groups performed similarly on those tasks. Additionally, the findings that the PM impairments are specific to children in the FAS/PFAS group (i.e., children with dysmorphic features), and that the effects of prenatal alcohol exposure are mediated by IQ, are consistent with the suggestion that severity of dysmorphic features and IQ impairments may be indicative of underlying structural brain abnormalities (Lebel et al., 2012).

It is of clinical relevance to compare the cognitive/behavioral performance of children with prenatal alcohol exposure to that of children who have been diagnosed with other developmental disorders (e.g., ADHD). For example, impairments in PM have already been documented in children with ADHD (Kerns & Price, 2001; Kliegel et al., 2006). Significantly, there is a high co-morbidity between prenatal alcohol exposure and ADHD (for a review, see O'Malley & Nansen, 2002). Future research should, therefore, aim to compare PM performance in children with prenatal alcohol exposure, co-morbid diagnoses of prenatal alcohol exposure and ADHD, and children with a diagnosis of ADHD in the absence of prenatal alcohol exposure in order to further disentangle the effects of prenatal alcohol exposure and possible co-morbid attentional impairments on PM performance.

Furthermore, the results of the current study support the inclusion of PM-targeted interventions into programs designed for children with a history of heavy prenatal alcohol exposure. Intact PM is necessary for optimal functioning in the educational environment (e.g., remembering to complete homework or remembering to have an important letter signed by caregivers), and it is important, therefore, that appropriate compensatory strategies be developed in children who display PM impairments. Several specific PM rehabilitation/compensatory techniques (e.g., diary or memory aid use) have been used in pediatric populations (for a review, see Shum, Fleming, & Neulinger, 2002). Future research is necessary, however, to ascertain which of these techniques would be most useful for children with a history of prenatal alcohol exposure.

University of Cape Town

Conclusion

This is the first study to document PM impairments in children with a history of heavy prenatal alcohol exposure. These findings contribute, therefore, to the growing body of work attempting to define a cognitive-behavioral phenotype for FASD. In addition, this study highlighted the importance of considering the effects of other potential confounding variables and potential predictor variables on cognitive-behavioral functioning. The PM impairments observed here seem, however, to be restricted to syndromal children with very heavy levels of exposure. Given the implications of impaired structural and functional brain maturation in children with FASD, the absence of differences in PM performance between children who are nonsyndromal but who have a confirmed history of prenatal alcohol exposure and typically-developing demographically similar children warrants further investigation.

University of Cape Town

REFERENCES

Abel, E. L., & Sokol, R. J. (1987). Incidence of fetal alcohol syndrome and economic impact of FAS-related anomalies. *Drug and Alcohol Dependence, 19*, 51–70.

Anderson, P. (2002). Assessment and development of executive function (EF) during childhood. *Child Neuropsychology, 8,* 71-82.

Anderson, V. (1998). Assessing executive functions in children: Biological, psychological, and developmental considerations. *Neuropsychological Rehabilitation, 8,* 319-349.

Aragón, A. S., Kalberg, W. O., Buckley, D., Barela-Scott, L., Tabachnick, B. G., & May, P. A. (2008). Neuropsychological study of FASD in a sample of American Indian children: Processing simple versus complex information. *Alcoholism: Clinical and Experimental Research, 32,* 2136-2148.

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

Astley, S. J., & Clarren, S. K. (2001). Measuring the facial phenotype of individuals with prenatal alcohol exposure: Correlations with brain dysfunction. *Alcohol and Alcoholism, 36,* 147-159.

Babikian, T., & Asarnow, R. (2009). Neurocognitive outcomes and recovery after pediatric TBI: Meta-analytic review of the literature. *Neuropsychology, 23,* 283-296.

Baron, R. M., & Kenny, D. A. (1986). The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology, 51,* 1173-1182.

Basso, D., Ferrari, M., & Palladino, P. (2010). Prospective memory and working memory: Asymmetrical effects during frontal lobe TMS stimulation. *Neuropsychologia, 48,* 3283-3290.

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

Burden, M.J., Jacobson, S.W., & Jacobson, J.L. (2005b). The relation of prenatal alcohol exposure to cognitive processing speed and efficiency in childhood. *Alcoholism: Clinical and Experimental Research, 29*, 1473–1483.

Burgess, P. W., Quayle, A., & Frith, C. D. (2001). Brain regions involved in prospective memory as determined by positron emission tomography. *Neuropsychologica, 39,* 545-555.

Burgess, P. W., & Shallice, T. (1997). The relationship between prospective and retrospective memory: Neuropsychological evidence. In M. A. Conway (Ed.), *Cognitive models of memory* (pp. 247-272). Hove East Sussex, UK: Psychology Press.

University of Cape Town

Ceci, S. J., & Bronfenbrenner, U. (1985). "Don't forget to take the cupcakes out of the oven": Prospective memory, strategic time-monitoring, and context. *Child Development, 56,* 152-164.

Chasnoff, I. J., Wells, A. M., Telford, E., Schmidt, C., & Messer, G. (2010). Neurodevelopmental functioning in children with FAS, pFAS, and ARND. *Journal of Developmental and Behavioral Pediatrics, 31*, 192–201.

Cherkasova, M. V., & Hechtman, L. (2009). Neuroimaging in Attention-Deficit Hyperactivity Disorder: Beyond the frontostriatal circuitry. *The Canadian Journal of Psychiatry, 54,* 651 – 664.

Coles, C. D., & Li, Z. (2011). Functional neuroimaging in the examination of effects of prenatal alcohol exposure. *Neuropsychology Review, 21,* 119-132.

Coles, C. D., Lynch, M. E., Kable, J. A., Johnson, K. C., Goldstein, F. C. (2010). Verbal and nonverbal memory in adults prenatally exposed to alcohol. *Alcoholism: Clinical and Experimental Research, 34,* 897-906.

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

Crocker, N., Vaurio, L., Riley, E. P., Mattson, S. N. (2011). Comparison of verbal learning and memory in children with heavy prenatal alcohol exposure or attention-deficit/hyperactivity disorder. *Alcoholism: Clinical and Experimental Research, 35,* 1-8.

Culbertson, W. C., & Zillmer, E. A. (2001). *Tower of London – Drexel University (TOL^{DX}): Technical Manual.* North Tonawanda, NY: Multi-Health Systems.

Cummings, J. L. (1993). Frontal-subcortical circuits and human behavior. *Archives of neurology*, *50*, 873.

Dalen, K., Bruaroy, S., Wentzel-Larsen, T., & Laegreid, L. M. (2009). Cognitive functioning in children prenatally exposed to alcohol and psychotropic drugs. Neuropediatrics, 40(4), 162–167.

Delis, D.C., Kaplan, E., & Kramer, J.H. (2001). *The Delis-Kaplan Executive Function System: Examiner's Manual*. San Antonio, TX: The Psychological Corporation.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (1994). *California Verbal Learning Test–Children's Version: Manual*. San Antonio, TX: The Psychological Corporation.

Diwardkar, V., Meintjes, E.M., Goradia, D., Dodge, N.C., Molteno, C.D., Jacobson, J.L., & Jacobson, S.W. (in press). Differences in cortico-striatal-cerebellar activations during working memory in syndromal and non-syndromal children with prenatal alcohol exposure. *Human Brain Mapping*.

Dunn, L. M., & Dunn, L. M. (1981). *PPVT Manual for Forms L and M*. Circle Pines, MN: American Guidance Service.

University of Cape Town

Einstein, G. O., Holland, L. J., McDaniel, M. A., & Guynn, M. J. (1992). Age-related deficits in prospective memory: The influence of task complexity. *Psychology and Aging, 7,* 471-478.

Einstein, G. O., & McDaniel, M. A. (1996). Retrieval processes in prospective memory: Theoretical approaches and some new empirical findings. In M. Brandimonte, G. O. Einstein, & M. A. McDaniel (Eds.), *Prospective memory: Theory and applications* (pp. 115-142). Mahwah, NJ: Lawrence Erlbaum Associates.

Einstein, G. O., McDaniel, M. A., Thomas, R., Mayfield, S., Shank, H., Morrisette, N., & Breneiser, J. (2005). Multiple processes in prospective memory retrieval: Factors determining monitoring versus spontaneous retrieval. *Journal of Experimental Psychology: General, 134,* 327-342.

Ellis, J. (1996). Prospective memory or the realization of delayed intentions: A conceptual framework for research. In M. Brandimonte, G. O. Einstein, & M. A. McDaniel (Eds.), *Prospective memory: Theory and applications* (pp. 1-22). Mahwah, NJ: Lawrence Erlbaum Associates.

Ellis, J., & Kvavilashvili, L. (2000). Prospective memory in 2000: Past, present, and furture directions. *Applied Cognitive Psychology, 14,* S1-S9.

Field, A. (2009). *Discovering Statistics Using SPSS* (3rd ed.). Thousand Oaks, California: SAGE Publications Ltd.

Frazier, T. W., Demaree, H. A., & Youngstrom, E. A. (2004). Meta-analysis of intellectual and neuropsychological test performance in attention-deficit/hyperactivity disorder. *Neuropsychology, 18,* 543-555.

Fryer, S. L., McGee, C. L., Matt, G. E., Riley, E. P., & Mattson, S. N. (2007a). Evaluation of psychopathological conditions in children with heavy prenatal alcohol exposure. *Pediatrics, 119,* e733-e741.

Fryer, S. L., Tapert, S. F., Mattson, S. N., Paulus, M. P., Spandoni, A. D., & Riley, E. P. (2007b). Prenatal alcohol exposure affects fronto-striatal BOLD response during inhibitory control. *Alcoholism: Clinical and Experimental Research, 31,* 1415-1424.

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

Henry, J. D., & Crawford, J. R. (2004). A meta-analytic review of verbal fluency performance following focal cortical lesions. *Neuropsychology, 18,* 284-295.

Hollingshead, A. B. (1975). *Four Factor Index of Social Status*. Unpublished manuscript. Yale University, New Haven, CT.

Hoyme, H. E., May, P. A., Kalberg, W. O., Kodituwakku, P., Gossage, J. P., Trujillo, P. M., … Robinson, L. K. (2005). A practical clinical approach to diagnosis of fetal alcohol

University of Cape Town

spectrum disorders: Clarification of the 1996 Institute of Medicine criteria. *Paediatrics, 115,* 39-48.

Jacobson, J. L., Jacobson, S. W., Sokol, R. J., & Ager, J. W. (1998). Relation of maternal age and pattern of pregnancy drinking to functionally significant cognitive deficit in infancy. *Alcoholism: Clinical and Experimental Research, 22*, 345-351.

Jacobson, J. L., & Jacobson, S. W. (1999). Drinking moderately and pregnancy: Effects on child development. *Alcohol Research and Health, 23,* 25-30.

Jacobson, J. L., & Jacobson, S. W. (2002). Effects of prenatal alcohol exposure on child development. *Alcohol Research & Health, 26,* 282-286.

Jacobson, J. L., & Jacobson, S. W. (2005). Methodological issues in research on developmental exposure to neurotoxic agents. *Neurotoxicology and Teratology, 27,* 395-406.

Jacobson, J. L., Jacobson, S. W., Molteno, C. D., & Odendaal, H. (2006). A prospective examination of the incidence of heavy drinking during pregnancy among Cape Coloured South African women. *Alcoholism: Clinical and Experimental Research, 30,* 233A.

Jacobson, S. W., Carr, L. G., Croxford, J., Sokol, R. J., Li, T.-K., & Jacobson, J. L. (2006). Protective effects of the alcohol dehydrogenase-*ADH1B* allele in African American children exposed to alcohol during pregnancy. *Journal of Pediatrics, 148*, 30-37.

Jacobson, J. L., Jacobson, S. W., Sokol, R. J., Martier, S. S., & Ager, J. W. (1993). Prenatal alcohol exposure and infant information processing ability. *Child Development, 64,* 1706-1721.

Jacobson, S.W., Jacobson, J. L., Sokol, R. J., Chiodo, L. M., & Corobana, R. (2004). Maternal age, alcohol abuse history, and quality of parenting as moderators of the effects of prenatal alcohol exposure on 7.5-year intellectual function. *Alcoholism: Clinical and Experimental Research, 28,* 1732-1745.

Jacobson, S. W., Chiodo, L. M., Sokol, R. J., & Jacobson, J. L. (2002). Validity of maternal report of prenatal alcohol, cocaine, and smoking in relation to neurobehavioural outcome. *Paediatrics, 109,* 815-825.

Jacobson, S. W., Jacobson, J. L., Stanton, M. E., Meintjes, E. M., & Molteno, C. D. (2011). Biobehavioral markers of adverse effect in fetal alcohol spectrum disorder. *Neuropsychology Review, 21,* 148-166.

Jacobson, S. W., Stanton, M. E., Molteno, C. D., Burden, M. J., Fuller, D. S., Hoyme, H. E., … Jacobson, J. L. (2008). Impaired eyeblink conditioning in children with fetal alcohol syndrome. *Alcoholism: Clinical and Experimental Research, 32,* 365-372.

Jones, K. L. & Smith, D. W. (1973). Recognition of the fetal alcohol syndrome in early infancy. *Lancet, 2,* 999-1001.

University of Cape Town

Kable, J. A., & Coles, C. D. (2004). The impact of prenatal alcohol exposure on neurophysiological encoding of environmental events at six months. *Alcoholism: Clinical and Experimental Research, 28,* 489-496.

Kaemink, K. L., & Halverson, P. T. (2000). Spatial memory following prenatal alcohol exposure: More than a material specific memory deficit. *Child Neuropsychology, 6,* 115-128.

Kleinbaum, D. G., Kupper, L. L., & Muller, K. E. (1988). *Applied Regression Analysis and Other Mutivariable Methods* (2nd ed.). Boston: PWS-Kent.

Kerns, K. (2000). The CyberCruiser: An investigation of development of prospective memory in children. *Journal of the International Neuropsychological Society, 6,* 62-70.

Kerns, K., & Price, K. J. (2001). An investigation of prospective memory in children with ADHD. *Child Neuropsychology, 7,* 162-171.

Khan, A., Sharma, N. K., & Dixit, S. (2008). Cognitive load and task condition in event- and time-based prospective memory: An experimental investigation. *The Journal of Psychology, 142,* 517-531.

Kliegel, M. A., Jäger, T., Altgassen, M., & Shum, D. (2008a). Clinical neuropsychology of prospective memory. In M. Kliegel, M. A. McDaniel, & G. O. Einstein (Eds.), *Prospective memory: Cognitive, neuroscience, developmental, and applied perspectives* (pp. 283-308). New York, NY: Lawrence Erlbaum Associates.

Kliegel, M., Mackinlay, R., & Jäger, T. (2008b). A life span approach to the development of complex prospective memory. In M. Kliegel, M. A. McDaniel, & G. O. Einstein (Eds.), *Prospective memory: Cognitive, neuroscience, developmental, and applied perspectives* (pp. 187-216). New York, NY: Lawrence Erlbaum Associates.

Kliegel, M., Martin, M., McDaniel, M. A., & Einstein, G. O. (2002). Complex prospective memory and executive control of working memory: A process model. *Psychologische Beitrage, 44,* 303-318.

Kliegel, M., McDaniel, M. A., & Einstein, G. O. (2008c). *Prospective memory: Cognitive, neuroscience, developmental, and applied perspectives.* New York, NY: Lawrence Erlbaum Associates.

Kliegel, M., Ropeter, A., & Mackinlay, R. (2006). Complex prospective memory in children with ADHD. *Child Neuropsychology, 12,* 407-419.

Kodituwakku, P. W. (2007). Defining the behavioral phenotype in children with fetal alcohol spectrum disorders: A review. *Neuroscience and Behavioral Reviews, 31,* 192-201.

Kodituwakku, P. W., Adnams, C. M., Hay, A., Kitching, A. E., Burger, E., Kalberg, W. O., ... May, P. A. (2006). Letter and category fluency in children with fetal alcohol syndrome from a community in South Africa. *Journal of Studies on Alcohol, 67,* 502-509.

University of Cape Town

Kodituwakku, P. W., Kalberg, W., & May, P. A. (2001). The effects of prenatal alcohol exposure on executive functioning. *Alcohol Research and Health, 25,* 192-198.

Kvavilashvili, L., Kornbrot, D. E., Mash, V., Cockburn, J., & Milne, A. (2009). Differential effects of age on prospective and retrospective memory tasks in young, young-old, and old-old adults. *Memory, 17,* 180-196.

Kvavilashvili, L., Kyle, F. E., & Messer, D. J. (2008). The development of prospective memory in children: methodological issues, empirical findings, and future directions. In M. Kliegel, M. A. McDaniel, & G. O. Einstein (Eds.), *Prospective memory: Cognitive, neuroscience, developmental, and applied perspectives* (pp. 115-140). New York, NY: Lawrence Erlbaum Associates.

Kully-Martins, K., Denys, K., Treit, S., Tamana, S., & Rasmussen, C. (2012). A review of social skills deficits in individuals with fetal alcohol spectrum disorders and prenatal alcohol exposure: Profiles, mechanisms, and interventions. *Alcoholism: Clinical and Experimental Research, 36,* 568-576.

Llorente, A. M., Williams, J., Satz, P., & D'Elia, L. F. (2003). *Children's Color Trails Test: Professional manual.* Odessa, FL: Psychological Assessment Resources.

Loft, S., & Yeo, G. (2007). An investigation into the resource requirements of event-based prospective memory. *Memory & Cognition, 35,* 263-274.

Madge, E. M., van den Berg, A. R., Robinson, M., & Landman, J. (1981). *Junior South African Individual Scales*. Human Sciences Research Council, Pretoria.

Manji, S., Pei, J., Loomes, C., & Rasmussen, C. (2009). A review of the verbal and visual memory impairments in children with foetal alcohol spectrum disorders. *Developmental Neurorehabilitation, 12,* 239-247.

Mäntylä, T., Carelli, M. G., & Forman, H. (2007). Time monitoring and executive functioning in children and adults. *Journal of Experimental Child Psychology, 96,* 1-19.

Martin, M., Kliegel, M., & McDaniel, M. A. (2003). The involvement of executive functions in prospective memory performance of adults. *International Journal of Psychology, 38,* 195-206.

Mattson, S. N., Goodman, A. M., Caine, C., Delis, D. C., & Riley, E. P. (1999). Executive functioning in children with heavy prenatal alcohol exposure. *Alcoholism: Clinical and Experimental Research, 23,* 1808-1815.

Mattson, S. N., Riley, E. P., Gramling, L. J., Delis, D. C., & Jones, K. L. (1997). Heavy prenatal alcohol exposure with or without physical features of fetal alcohol syndrome leads to IQ deficits. *Journal of Pediatrics, 131*, 718–721.

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

University of Cape Town

Mattson, S. N., Riley, E. P., Sowell, E. R., Jernigan, T. L., Sobel, D. F., & Jones, K. L. (1996). A decrease in the size of the basal ganglia in children with fetal alcohol syndrome. *Alcoholism: Clinical and Experimental Research, 20*, 1088–1093.

Mattson, S. N., & Roebuck, T. M. (2002). Acquisition and retention of verbal and nonverbal information in children with heavy prenatal alcohol exposure. *Alcoholism: Clinical and Experimental Research, 26,* 875-882.

Mattson, S. N., Schoenfeld, A. M., & Riley, E. P. (2001). Teratogenic effects of alcohol on brain and behavior. *Alcohol Research and Health, 25,* 185-191.

May, P. A., Gossage, J. P., Brooke, L. E., Snell, C. L., Marais, A-S., Hendricks, L. S., . . . Viljoen, D. L. (2005). Maternal risk factors for fetal alcohol syndrome in the Western Cape Province of South Africa: A population-based study. *American Journal of Public Health, 95,* 1190-1199.

May, P. A., Gossage, J. P., Marais, A-S., Adnams, C., Hoyme, H. E., Jones, K. L., . . ., Viljoen, D. L. (2007). The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. *Drug and Alcohol Dependence, 88,* 259-271.

McCauley, S. R., Wilde, E. A., Merkley, T. L., Schnelle, K. P., Bigler, E. D., Hunter, J. V., . . ., Levin, H. S. (2010). Patterns of cortical thinning in relation to event-based prospective memory performance three months after moderate to severe traumatic brain injury in children. *Developmental Neuropsychology, 35,* 318-332.

McDaniel, M. A., & Einstein, G. O. (2000). Strategic and automatic processes in prospective memory retrieval: A multiprocess framework. *Applied Cognitive Psychology, 14,* 127-144.

McDaniel, M. A., Guynn, M. J., Einstein, G. O., & Breneiser, J. (2004). Cue-focused and reflexive-associative processes in prospective memory retrieval. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 30,* 605-614.

McDaniel, M. A., Robinson-Riegler, B., & Einstein, G. O. (1998). Prospective remembering: Perceptually driven or conceptually driven processes? *Memory & Cognition, 26,* 121-134.

McGee, C. L., Schonfeld, A. M., Roebuck‐Spencer, T. M., Riley, E. P., & Mattson, S. N. (2008). Children with heavy prenatal alcohol exposure demonstrate deficits on multiple measures of concept formation. *Alcoholism: Clinical and Experimental Research*, *32*, 1388-1397.

Meintjes, E. M., Jacobson, J. L., Molteno, C. D., Gatenby, C., Warton, C., Cannistraci, J., Hoyme, H. E., Robinson, L. K., Khaole, N., Gore, J. C., & Jacobson, S. W. (2010). An fMRI study of number processing in children with fetal alcohol syndrome. *Alcoholism: Clinical and Experimental Research, 34,* 1450-1464.

Moscovitch, M. (1994). Memory and working with memory: Evaluation of a component process model and comparisons with other models. In D. L. Schacter & E. Tulving (Eds.), *Memory systems* (pp. 269–310). Cambridge, MA: MIT Press.

University of Cape Town

Narberhaus, A., Segarra, D., Giménez, M., Junqué, C., Pueyo, R., & Botet, F. (2007). Memory performance in a sample of very low birth weight adolescents. *Developmental neuropsychology*, *31*, 129-135.

Nigg, J. T. (2005). Neuropsychologic theory and findings in Attention-Deficit/Hyperactivity Disorder: The state of the field and salient challenges for the coming decade. *Biological Psychiatry, 57,* 1424-1435.

Noland, J. S., Singer, L. T., Arendt, R. E., Minnes, S., Short, E. J., & Bearer, C. F. (2003). Executive functioning in preschool-age children prenatally exposed to alcohol, cocaine, and marijuana. *Alcoholism: Clinical and Experimental Research, 27,* 647-656.

O'Hare, E. D., Lu, L. H., Houston, S. M., Bookheimer, S. Y., Mattson, S. N., O'Connor, M. J., & Sowell, E. R. (2009). Altered fronto-parietal functioning during verbal working memory in children and adolescents with heavy prenatal alcohol exposure. *Human Brain Mapping, 30,* 3200-3208.

Okuda, J., Fujii, T., Ohtake, H., Tsukiura, T., Yamadori, A., Frith, C. D., & Burgess, P. W. (2007). Differential involvement of regions of rostral prefrontal cortex (Brodmann Area 10) in time- and event-based prospective memory. *International Journal of Psychophysiology, 64,* 233-246.

O'Leary, C. E., Thomas, K. G. F., Molteno, C. D., Jacobson, J. L., & Jacobson, S. W. (2011). Verbal learning and memory in fetal alcohol spectrum disorders: Findings from Cape Town and Detroit. *Alcoholism: Clinical and Experimental Research, 35(s1),* 1A-339A.

O'Malley, K. D., & Nanson, J. (2002). Clinical implications of a link between fetal alcohol spectrum disorder and attention-deficit hyperactivity disorder. *Canadian Journal of Psychiatry, 47*, 349-354.

Preacher, K. J., & Leonardelli, G. J. (2010). *Calculation for the Sobel Test: An interactive calculation tool for mediation tests*. Retrieved: May 17, 2011 from http://people.ku.edu/~preacher/sobel/sobel.htm.

Rasmussen, C. (2005). Executive functioning and working memory in fetal alcohol spectrum disorder. *Alcoholism: Clinical and Experimental Research, 29,* 1359-1367.

Rasmussen, C., Horne, K., & Witol, A. (2006). Neurobehavioural functioning in children with fetal alcohol spectrum disorder. *Child Neuropsychology, 12,* 453-468.

Rasmussen, C., & Bisanz, J. (2009). Executive functioning in children with fetal alcohol spectrum disorders: Profiles and age-related differences. *Child Neuropsychology, 15,* 201-215.

Raven, J. C. (1992). *Raven's Progressive Matrices (RPM)*. Los Angeles, CA.

Reynolds, J. R., West, R., & Braver, T. (2009). Distinct neural circuits support transient and sustained processes in prospective memory and working memory. *Cerebral Cortex, 19,* 1208-1221.

University of Cape Town

Rubia, K., Oosterlaan, J., Sergeant, J. A., Brandeis, D., & van Leeuwen, T. (1998). Inhibitory dysfunction in hyperactive boys. *Behavioral Brain Research, 94,* 25-32.

Schlesselman, J. (1982). *Case-Control Studies: Design, Conduct, Analysis*. New York: Oxford University Press.

Shapiro, S. S., & Wilk, M. B. (1965). An analysis of variance test for normality (compete samples). *Biometrika, 52,* 591-611.

Shum, D., Fleming, J., & Neulinger, K. (2002). Prospective memory and traumatic brain injury: A review. *Brain Impairment*, *3*, 1-16.

Simons, J. S., Schölvinck, M. L., Gilbert, S. J., Frith, C. D., & Burgess, P. W. (2006). Differential components to prospective memory? Evidence from fMRI. *Neuropsychologica, 44,* 1388-1397.

Smith, R. E. (2003). The cost of remembering to remember in event-based prospective memory: Investigating the capacity demands of delayed intention performance. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 29,* 347-361.

Smith, R. E., Bayen, U. J., & Martin, C. (2010). The cognitive processes underlying event-based prospective memory in school-age children and young adults: A formal model-based study. *Developmental Psychology, 46,* 230-244.

Smith, R. E., Hunt, R. R., McVay, J. C., & McConnell, M. D. (2007). The cost of event-based prospective memory: Salient target events. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 33,* 734-746.

Sobel, M. E. (1982). Asymptotic intervals for indirect effects in structural equations models. In S. Leinhart (Ed.). *Sociological Methodology 1982* (pp.290-312). San Francisco: Jossey-Bass.

Sokol, R. J., Martier, S., & Ernhart, C. (1983). Identification of alcohol abuse in the prenatal clinic. In: N. C., Chang & M., Chao (Eds.), *Early Identification of Alcohol Abuse*. Rockville, MD: Alcohol, Drug Abuse, and Mental Health Administration Research. Monograph No. 17.

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

Spandoni, A. D., McGee, C. L., Fryer, S. L., & Riley, E. P. (2007). Neuroimaging and fetal alcohol spectrum disorders. *Neuroscience and Behavioral Reviews, 31,* 239-245.

Stern, Y. (2003). The concept of cognitive reserve: A catalyst for research. *Journal of Clinical and Experimental Neuropsychology, 25,* 589-593.

Stratton, K. R., Howe, C. J., Battaglia, F. C., (Eds.). (1996). *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment*. Washington, DC: National Academy Press.

University of Cape Town

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). General cognitive functioning, neuropsychological batteries, and assessment of premorbid intelligence. In *A Compendium of Neuropsychological Tests: Administration, Norms and Commentary* (pp. 310-337). New York, NY: Oxford University Press.

Streissguth, A. P., Barr, H. M., Kogan, J., & Bookstein, F. L. (1996). Understanding the occurrence of secondary disabilities in clients with fetal alcohol syndrome (FAS) and fetal alcohol effects (FAE): Final report to the Centres for Disease Control and Prevention. University of Washington Fetal Alcohol and Drug Unit, Seattle, WA.

Vaurio, L., Riley, E. P., & Mattson, S. N. (2011). Neuropsychological comparison of children with heavy prenatal alcohol exposure and an IQ-matched comparison group. *Journal of the International Neuropsychological Society, 17,* 463-473.

Voigt, B., Aberle, I., Schönfeld, J., & Kliegel, M. (2011). Time-based prospective memory in school children: The role of self-initiation and strategic time monitoring. *Journal of Psychology, 219,* 92-99.

Ward, H., Shum, D., Mckinlay, L., Baker-Tweney, S., & Wallace, G. (2005). Development of prospective memory: Tasks based on the prefrontal-lobe model. *Child Neuropsychology, 11,* 527-549.

Wang, L., Altgassen, M., Liu, W., Xiong, W., Akgün, C., & Kliegel, M. (2011). Prospective memory across adolescence: The effects of age and cue focality. *Developmental Psychology, 47,* 226-232.

Wechsler, D. (2003). *WISC-IV Administration Manual*. San Antonio, TX: The Psychological Corporation.

Weisglas-Kuperus, N., Hille, E. T. M., Duivenvoorden, H. J., Finken, M. J. J., Wit, J. M., van Buuren, S., . . ., Dutch POPS-19 Collaborative Study Group. (2009). Intelligence of very preterm or very low birthweight infants in young adulthood. *Archives of Disease in Childhood-Fetal and Neonatal Edition*, *94,* F196-F200.

West, R. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychological Bulletin, 120,* 272-292.

Whittlesea, B. W. A., & Williams, L. D., (2001a). The discrepancy-attribution hypothesis: I. The heuristic basis of feelings of familiarity. *Journal of Experimental Psychology: Learning, memory, and cognition, 27,* 3-13.

Whittlesea, B. W. A., & Williams, L. D., (2001b). The discrepancy-attribution hypothesis: II. Expectation, uncertainty, surprise, and feelings of familiarity. *Journal of Experimental Psychology: Learning, memory, and cognition, 27,* 14-33.

Willford, J. A., Leech, S. L., & Day, N. L. (2006). Moderate prenatal alcohol exposure and cognitive status of children at age 10. Alcoholism: Clinical and Experimental Research, 30(6), 1051–1059.

University of Cape Town

Willoughby, K. A., Sheard, E. D., Nash, K., & Rovet, J. (2008). Effects of prenatal alcohol exposure on hippocampal volume, verbal learning, and verbal and spatial recall in late childhood. *Journal of the International Neuropsychological Society, 14,* 1022-1033.

Winer, B. J. (1971). *Statistical Principles in Experimental Design* (2nd ed.). New York, NY: McGraw-Hill.

World Medical Association. (2008). *Declaration of Helsinki*. Retrieved May 10, 2011, from http://www.wma.net/en/30publications/10policies/b3/index.html

Zillmer, E. A., Spiers, M. V., & Culbertson, W. C. (2008). Memory, attention, emotion and executive functioning. In *Principles of Neuropsychology, 2nd Ed,* (pp. 224 – 265). Belmont, CA: Thomson Wadsworth.

University of Cape Town

APPENDIX A
Dresden Cruiser English Instructions: Focal Version

Pre-Practice Instructions:

We are going to play a computer game in which you are going to be driving a car. You gain lots of points if you don't hit the other cars on the road. You can go around the other cars by moving the arrow keys like this (Demonstrate). If you press this arrow key the car goes this way (point to the left section of the screen). If you press this arrow key the car will move this way (point to the right section of the screen). It will be a bit easier if you press the keys like this, rather than like this (hold arrow key in). You can't go faster or slower, you can only go from side to side. Sometimes it will be difficult not to hit the cars, but you must just try your best. Remember, try not to hit any cars so that you can earn lots of points!

Pre-Practice Questions:

1. So can you tell me what you have to do to earn lots of points?
2. Well done, and can you remember how to make the car move from side to side?

Now let's begin.

Pre-Experimental Trial Instructions:

Now we are going to play the same game, but this time you have to remember to fill up with petrol. Every time you see a yellow car driving on the road you need to fill up with petrol. To do this you press the space bar. The yellow car will look just like this one (show the participant the screen shot). So remember, only press that space bar to fill your car with petrol when you see a yellow car and don't hit any cars so that you can earn lots of points!

Pre-Experimental Trial Questions:

1. What do you have to do to fill up your car with petrol?
2. How do you know when you have to fill up with petrol?
3. What do you have to do so that you can earn lots of points?

Now remember what you have to do in the game because before we play on the computer again we are going to play a different game.

Participants complete distracter task.

Now let's play that computer game again.

NB: No further mention of the need to refuel.

Before we play that game again we are going to play another game.

Participants complete distracter task.

Let's play that computer game again.

Post-Experiment Questions:

You have worked hard today. I just have a few more questions and then we are done.

1. Do you remember when you just played that driving game, what did you have to do to earn lots of points?
2. Was there something else you had to do along the way?

If 2 incorrect:

3. Do you remember what you had to do when you saw a yellow car driving on the road?
4. Did you think this game was very easy, sort of easy, sort of hard, or very hard?

Thank you very much.

University of

APPENDIX B

Dresden Cruiser Afrikaans Instructions: Focal Version

Pre-Practice Instructions:

Ons gaan ‘n rekenaarspeletjie speel waarin jy ‘n motor gaan bestuur. Jy kry baie punte as jy nie teen die ander karre in die pad bots nie. Jy kan rondom die ander karre gaan deur die pyltjieknoppies te beweeg soos dit. As jy hierdie pyltjie druk, gaan die kar daardie kant toe (wys na die links). Hierdie pyltjie beweeg die kar daai kant toe (wys na die regte kant van die skerm). Dit sal ‘n bietjie makliker wees as jy die pylkieknoppie soos dit druk (demonstrate), leiwers as dit (hold arrow key in). Jy kan noe vinniger of stadiger gaan nie, jy kan net ven die een kant na die ander kant toe gaan. Partykeer is dit nie so maklik om nie met die ander karre te bots nie, maar probeer net jou bes. Onthou om nie in enige ander karre vas te ry nie sodat jy baie punte kan kry!

Pre-Practice Questions:

3. Sê vir my, wat moet jy doen ombaie punte te kry?
4. Kan jy onthou hoe jy die kar kan laat beweeg van die een kant na die ander kant?

Kom ons oefen.

Pre-Experimental Trial Instructions:

Before instructions make sure that the child can discriminate between different car colors (name all of the colors on the color cue cards)

Nou gaan ons weer dieselfde speletjie doen, maar hierdie keer moet jy onthou om petrol in te gooi. Elke keer wat jy ‘n geel kar in die pad sien moet jy jou kar volmaak met petrol. Om dit te doen, moet jy die spasieknop druk. Die geel motor sal net soos hierdie een lyk (Wys die skerm prentjie vir die kind). So onthou – druk die spasieknop net wanneer jy ‘n geel kar in die pad sien ry en onthou om nie in enige karre vas te ry nie om baie punte te kry!

Pre-Experimental Trial Questions:

4. Wat moet jy doen om jou kar vol petrol te maak?
5. Hoe gaan jy weet wanneer jy jou kar vol petrol moet maak?
6. Wat moet jy doen om baie punte te kry?

Nou onthou wat jy moet doen in die speletjie want voordat ons weer op die rekenaar gaan speel gaan ons eers ‘n ander speletjie speel.

Participants complete distracter task.

rsity of Cape Town

Nou gaan ons weer daai rekenaar speletjie speel.

NB: No further mention of the need to refuel.

Nou gaan ons weer ‘n ander speletjie doen voordat ons weer die rekenaar speletjie gaan speel.

Participants complete distracter task.

Kom ons speel weer vir daai rekenaarspeletjie.

Post-Experiment Questions:

Jy het vandag so mooi gewerk. Ek het nog ‘n paar vrae en dan is ons klaar.

5. Onthou jy toe jy nou net daai bestuurspeletjie gespeel het, wat moes jy doen om baie punte te kry?
6. Mooi. En was daar iets anders wat jy ook moes doen langs die pad?

If 2 incorrect:

7. Kan jy onthou wat jy moes doen as jy ‘n geelkar in die pad sien ry het?
8. Het jy gedink dat hierdie speletjie was baie maklik, soort van maklik, soort van mooilik, of baie mooilik?

Baie dankie.

Universi

APPENDIX C

Dresden Cruiser English Instructions: Non-Focal Version

Pre-Practice Instructions:

We are going to play a computer game in which you are going to be driving a car. You gain lots of points if you don't hit the other cars on the road. You can go around the other cars by moving the arrow keys like this (Demonstrate). If you press this arrow key the car goes this way (point to the left section of the screen). If you press this arrow key the car will move this way (point to the right section of the screen). It will be a bit easier if you press the keys like this, rather than like this (hold arrow key in). You can't go faster or slower, you can only go from side to side. Sometimes it will be difficult not to hit the cars, but you must just try your best. Remember, try not to hit any cars so that you can earn lots of points!

Pre-Practice Questions:

5. So can you tell me what you have to do to earn lots of points?
6. Can you remember how to make the car move from side to side?

Pre-Experimental Trial Instructions:

Now let's begin.

Now we are going to play the same game, but this time you have to remember to fill up with petrol. Every time you see yellow flowers next to the road you need to fill up with petrol. To do this you press the space bar. So remember, only press that space bar to fill your car with petrol when you see yellow flowers next to the road and don't hit any cars so that you can earn lots of points!

Pre-Experimental Trial Questions:

7. What do you have to do to fill up your car with petrol?
8. How do you know when you have to fill up with petrol?
9. What do you have to do so that you can earn lots of points?

Now remember what you have to do in the game because before we play on the computer again we are going to play a different game.

Participants complete distracter task.

Now let's play that computer game again.

NB: No further mention of the need to refuel.

University of Cape Town

Before we play that game again we are going to play another game.

Participants complete distracter task.

Let's play that computer game again.

Post-Experiment Questions:

You have worked hard today. I just have a few more questions and then we are done.

9. Do you remember when you just played that driving game, what did you have to do to earn lots of points?
10. Good, and was there something else you had to do along the way?

If 2 incorrect:

11. Do you remember what you had to do when you saw yellow flowers next to the road?
12. Did you think this game was very easy, sort of easy, sort of hard, or very hard?

Thank you very much.

University of

APPENDIX D

Dresden Cruiser Afrikaans Instructions: Non-Focal Version

Pre-Practice Instructions:

Ons gaan ‘n rekenaarspeletjie speel waarin jy ‘n motor gaan bestuur. Jy kry baie punte as jy nie teen die ander karre in die pad bots nie. Jy kan rondom die ander karre gaan deur die pyltjieknoppies te beweeg soos dit. As jy hierdie pyltjie druk, gaan die kar daardie kant toe (wys na die links). Hierdie pyltjie beweeg die kar daai kant toe (wys na die regte kant van die skerm). Dit sal ‘n bietjie makliker wees as jy die pylkieknoppie soos dit druk (demonstrate), leiwers as dit (hold arrow key in).Jy kan noe vinniger of stadiger gaan nie, jy kan net ven die een kant na die ander kant toe gaan. Partykeer is dit nie so maklik om nie met die ander karre te bots nie, maar probeer net jou bes. Onthou om nie in enige ander karre vas te ry nie sodat jy baie punte kan kry!

Pre-Practice Questions:

7. Sê vir my, wat moet jy doen ombaie punte te kry?
8. Kan jy onthou hoe jy die kar kan laat beweeg van die een kant na die ander kant?

Kom ons oefen.

Pre-Experimental Trial Instructions:

Goed. Dit was baie mooi. Nou gaan ons weer dieselfde speletjie doen, maar hierdie keer moet jy onthou om petrol in te gooi. Elke keer wat jy geel blomme lanks die pad sien moet jy jou kar volmaak met petrol. Om dit te doen, moet jy die spasieknop druk. Die geel blomme sal net soos hierdie een lyk (Wys die skerm prentjie vir die kind). So onthou – druk die spasieknop net wanneer jy geel blomme lanks die pad pad sien en onthou om nie in enige karre vas te ry nie om baie punte te kry!

Pre-Experimental Trial Questions:

10. Wat moet jy doen om jou kar vol petrol te maak?
11. Hoe gaan jy weet wanneer jy jou kar vol petrol moet maak?
12. Wat moet jy doen om baie punte te kry?

Nou onthou wat jy moet doen in die speletjie want voordat ons weer op die rekenaar gaan speel gaan ons eers ‘n ander speletjie speel.

Participant completes distracter task.

Nou gaan ons weer daai rekenaarspeletjie speel.

University of Cape Town

NB: No further mention of the need to refuel.

Nou gaan ons weer ‘n ander speletjie doen voordat ons weer die rekenaar speletjie gaan speel.

Participant completes distracter task.

Kom ons speel weer vir daai rekenaarspeletjie.

Post-Experiment Questions:

Jy het vandag so mooi gewerk. Ek het nog ‘n paar vrae en dan is ons klaar.

13. Onthou jy toe jy nou net daai bestuurspeletjie gespeel het, wat moes jy doen om baie punte te kry?
14. Mooi. En was daar iets anders wat jy ook moes doen langs die pad?

If 2 incorrect:

15. Kan jy onthou wat jy moes doen as jy geel blomme lanks die pad gesien het?
16. Het jy gedink dat hierdie speletjie was baie maklik, soort van maklik, soort van mooilik, of baie mooilik?

Baie dankie.

University

APPENDIX E

Ethics Renewal Certificate: University of Cape Town, Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

05 OCT 2012

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	5/10/2013
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		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	30/08/2012
Protocol title	Neural Bases of Eyeblink Conditioning in FASD		
Protocol number (if applicable)			
Principal Investigator	A/Prof EM Mcintjes		
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 (FHS013) if the study is completed within the approval period)

APPENDIX F

Ethics Renewal Certificate: Wayne State University

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 FULL BOARD CONTINUATION APPROVAL

To: Sandra Jacobson
Psychiatry
University Square Office Plaza

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

Date: March 15, 2012

RE: IRB #: 026708B3F
Protocol Title: Neural Bases of Eyeblink Conditioning in FASD
Sponsor: ° NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM
° 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

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 03/15/2012 through 03/14/2013. This approval does not replace any departmental or other approvals that may be required.

- Actively accruing participants
- Research Informed Consent: Detroit Adult Study (Pilot version #1r, dated 07/07/2011)
- Parental Permission/Research Informed Consent: Detroit Child Pilot (Protocol version #2, dated 08/04/2010)
- Parental Permission/Research Informed Consent - English and Afrikaans Versions (Protocol version #2r, dated 11/30/2009)
- Parental Permission/Research Informed Consent - English and Afrikaans Versions (Protocol version #2rr Alternate, dated 07/27/2010)
- Parental Permission/Research Informed Consent: Blood Draw and Diagnostic Clinic Consent - English and Afrikaans Versions (Protocol version #3r, dated 08/27/2009)
- Research Informed Prescreening Consent: Infant Pilot Study - English and Afrikaans Versions (Protocol version #4r, dated 08/03/2010)
- Parental Permission/Research Informed Consent: Cape Town Infant Study - English and Afrikaans Versions (Protocol version #4.1r, dated 01/04/2012)
- Parental Permission/Research Informed Consent: Cape Town Infant MRI Study - English and Afrikaans Versions (Protocol version #4.2, dated 01/06/2012)
- Parental Permission/Research Informed Consent: ERP Infant Study - English and Afrikaans Versions (Protocol version #4.3r, dated 05/18/2011)
- Adult Permission/Research Informed Consent: Adult Comparison Group - English and Afrikaans Versions (Protocol version #5, dated 11/30/2009)

° 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.

APPENDIX G
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 8-10 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 one visit 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 to see if s/he learns to use the tone as a signal to blink before the air puff arrives.
- 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).

University of Cape Town

- 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 anaemia. 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. We will also ask you and your child to give a small sample of saliva (about 1 teaspoon) to study genetic differences that have been found to be related to differences in alcohol metabolism, depression, attachment, or child attention/behavior, and development. These samples will be stored and used for future genetic analyses.
- During the 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 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—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 to 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 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 assessment, 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 we tell you 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

University of Cape Town

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 R150 ($25) 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.

University of Cape Town

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 021-406-6212 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).

University of Cape Town

APPENDIX H

Parental Permission/Research Informed Consent (Afrikaans)

Titel van Studie: Neurale Basis van Oogknip Kondisionering in FASD

Jy en jou kind _____ word uitgenooi om deel te neem aan die navorsingstudie waarin jy betrokke was sedert jy swanger was en jou baba gebore is. Lees asseblief hierdie vorm deur en vra enige vrae wat jy mag hê voordat jy 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 jou 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 8-10-jarige ouderdom voorspel. Om jou te help met jou besluit om aan die studie deel te neem of nie, het ‘n projek personeellid die risiko’s en voordele met jou bespreek. Hierdie toestemmingsvorm is ‘n opsomming van die inligting wat aan jou 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 jou 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.

University of Cape Town

Studie Prosedures: Indien jy instem om jou kind aan hierdie studie te laat deelneem, sal ons jou en jou 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 een besoek wat omtrent 3-4 ure in totaal behoort te duur.

- Tydens die besoeke aan die Universiteit van Kaapstad sal jou 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 jou kind se visie toets / toets hoe goed jou kind kan sien.
- In een taak sal jou kind ‘n spesiale helm opsit. Terwyl jou kind na ‘n video kyk, sal ‘n blasie lug uit die helm kom wat sal maak dat jou kind sy/haar oog knip terwyl

hy/sy ‘n geluid hoor om te sien of hy/sy leer om die geluid te gebruik as ‘n teken om sy/haar oog te knip voordat die lugblasie kom.

- Ons sal jou 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 jou ook 'n paar vrae vra oor jou 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 jou vra om ons op hoogte te bring oor stresvolle ervarings in jou daaglikse lewe gedurende die afgelope jaar (Lewensgebeurtenis Skaal), jou 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 jou en jou kind neem na 'n nabye kliniek, waar 'n tegnikus/verpleegster ‘n 5cc bloedmonster (ongeveer 1 teelepel) van jou kind se aar sal neem om te toets vir lood en ystertekort anemie. Omtrent 10 cc bloed (ongeveer 2 teelepels) sal geneem word van jou en jou kind om genetiese verskille te bestudeer wat verband hou met verskille in alkohol metabolisme, depressie, gehegtheid, of die kind se aandag en ontwikkeling. Ons sal ook vra dat jy en jou kind 'n klein monster spoeg (omtrent 1 teelepel) gee om genetiese verskille te bestudeer wat verbandhou 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 besoek aan Tygerberg sal jou kind eers oefen om eenvoudige take te doen waartydens hy/sy sy/haar vingers moet tik, ruimtes probeer onthou, moet aandag gee, en somme doen op 'n rekenaar terwyl hy/sy in die skandeerder lê. Hy of sy sal gevra word om so stil as moontlik te lê terwyl prentjies geneem word. Dit maak nie seer wanneer hierdie prentjies geneem word nie en dit word elke dag deur baie mense in die hospitaal gebruik. Vir 'n gedeelte van die tyd in die skandeerder sal jou 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 twee sessies in die skandeerder wees – albei op dieselfde dag - een in die oggend en een na middagete. Ons sal vir jou en jou 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 jou wees nie, maar inligting van hierdie studie mag ander mense help, nou of in die toekoms. Jy sal inligting ontvang oor jou 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 jou sê en jou kind verwys na 'n dokter en/of iemand wat kan help, indien jy dit wil hê. Indien jou kind aan enige ernstige siekte ly, sal ons jou na die Rooikruis Kinderhospitaal stuur. Geen inligting oor jou kind sal uitgegee word aan enige dokters, hospitale, of skole tensy jy dit skriftelik versoek en toelaat nie.

Universiteit van Pretoria

Risiko's: Geen prosedures wat ons by UK of Tygerberg sal gebruik is gevaarlik vir jou of jou 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 jou en jou kind aan die projekpersoneel bekend te stel en sal vir julle albei ontbyt gee elke dag voordat die toetse begin. Terwyl al jou kind se toetse gedoen word sal jy in 'n vertrek naby jou kind wees en jy sal saam met jou 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 jou 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 jou 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. Jou 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 jou 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 jou kind 'n navorsingsverwante besering opgedoen het.

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

Vergoeding: Vir jou deelname aan hierdie navorsingstudie sal ons jou R150 ($25) gee vir elke besoek en 'n foto van jou kind, en vir jou kind sal ons 'n klein geskenkie gee. Ons sal ook vir jou en jou 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 jou en jou 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 jou 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 jou 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 jou of jou kind by name noem nie tensy jy ons skriftelik toestemming gee, maar jou 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

University of Cape Town

name verbind sal gestoor word in geslote kabinette in die navorsingslaboratorium. Slegs personeellede wat nodig het om jou 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 jou en jou kind se name sal geheim gehou word.

Vrywillige Deelname/Onttrekking: Deelname aan hierdie studie is vrywillig. Jy mag besluit om jou kind aan die studie te laat deelneem en later van besluit verander en die studie los. Jy en jou 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 jou of jou kind veroorsaak nie. Die navorser of die borg mag jou 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 021-406-6212 of Dr. Sandra W. Jacobson by 091-313-993-5454. Indien jy enige vrae of bekommernisse het oor jou of jou 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 jou kind te laat deelneem aan hierdie studie, moet jy op die lyn hieronder teken. Indien jy besluit om met jou kind deel te neem, mag jy of jou kind enige tyd stop. Jy gee nie enige van jou of jou kind se regte op deur hierdie vorm te teken nie. Jou handtekening wys dat jy hierdie hele toestemmingsvorm gelees het of dat dit aan jou voorgelees is, insluitend die risiko's en voordele, en dat ons al jou vrae beantwoord het. Ons sal vir jou 'n kopie van hierdie toestemmingsvorm gee om huis toe te neem.

University of Cape Town

_____ _____
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).

University of Cape Town

APPENDIX I

Hierarchical Regression Analyses: Scatterplots of standardised residuals and standardised predicted residuals

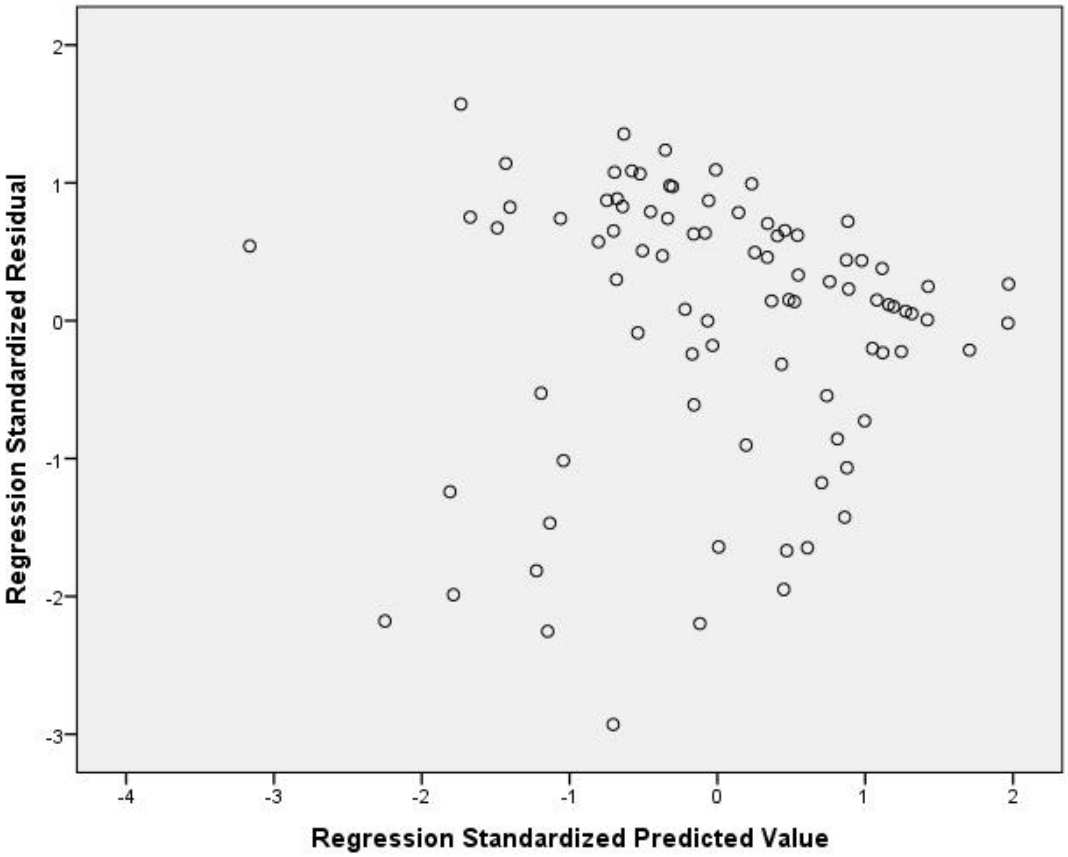

Figure I1. Scatterplot showing heteroscedasticity within Prospective Memory residual values in regression model 1.

Univer

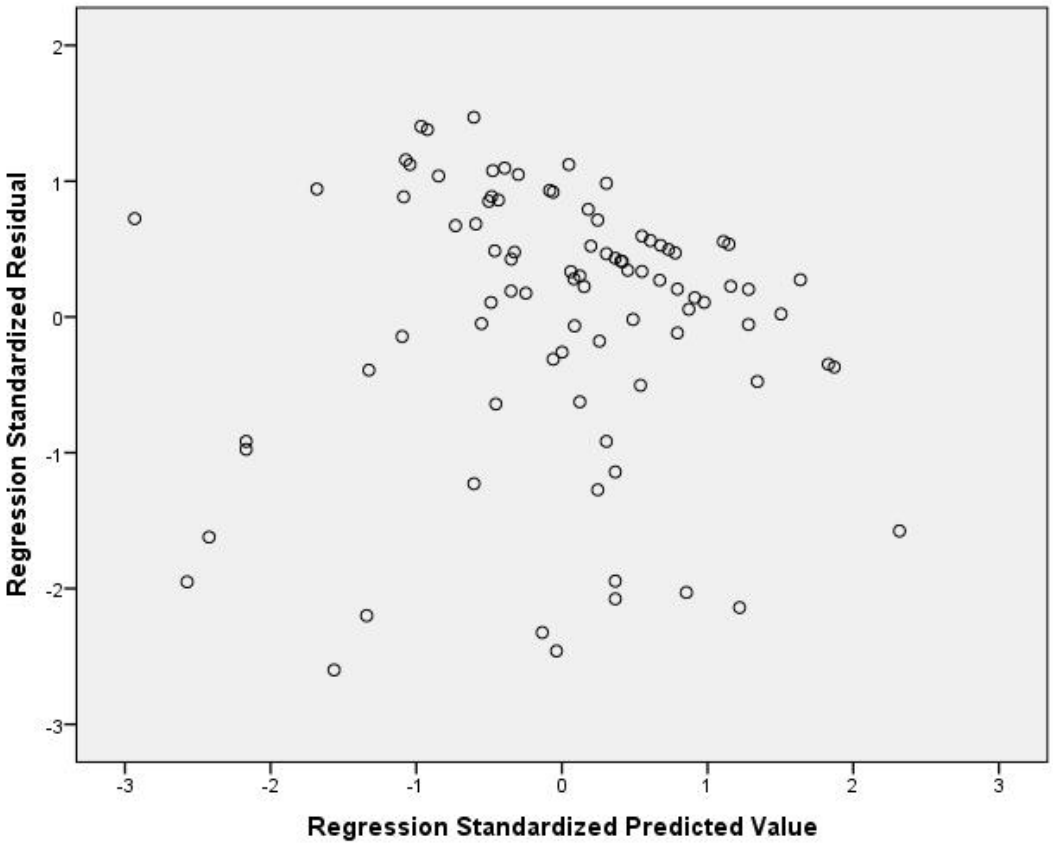

Figure I2. Scatterplot showing heteroscedasticity within Prospective Memory residual values in regression model 2.

University

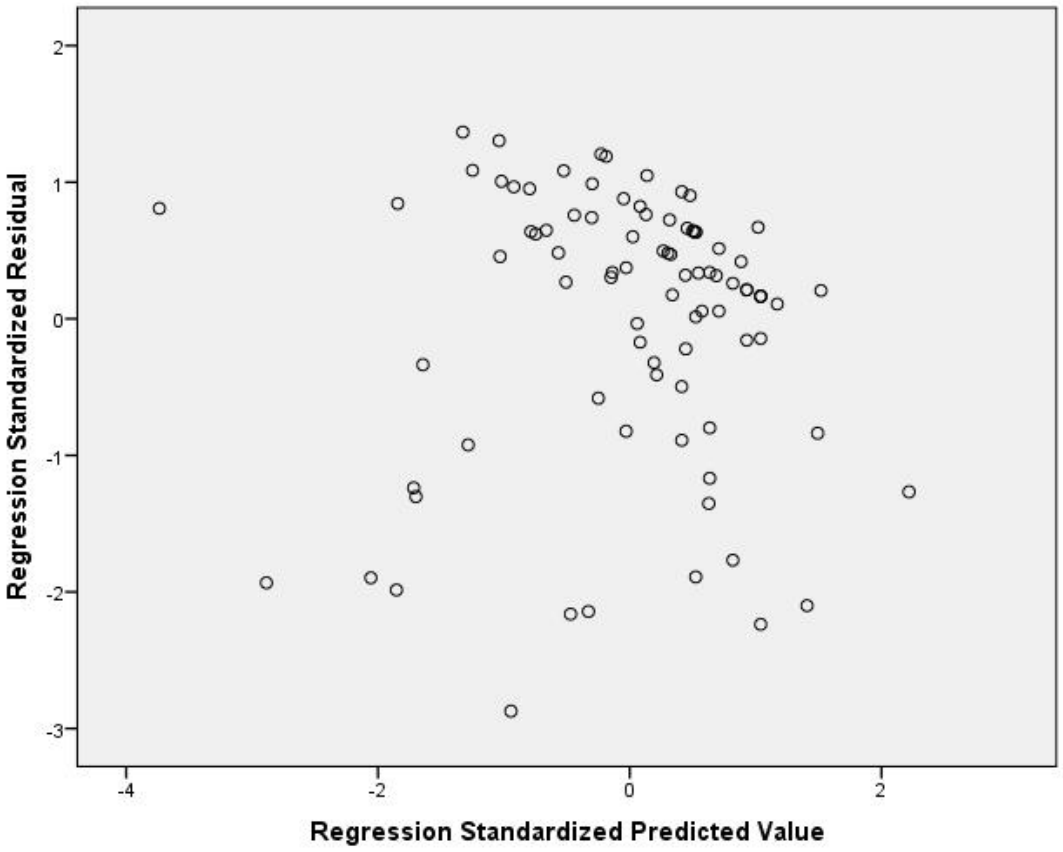

Figure I3. Scatterplot showing heteroscedasticity within Prospective Memory residual values in regression model 3.

University

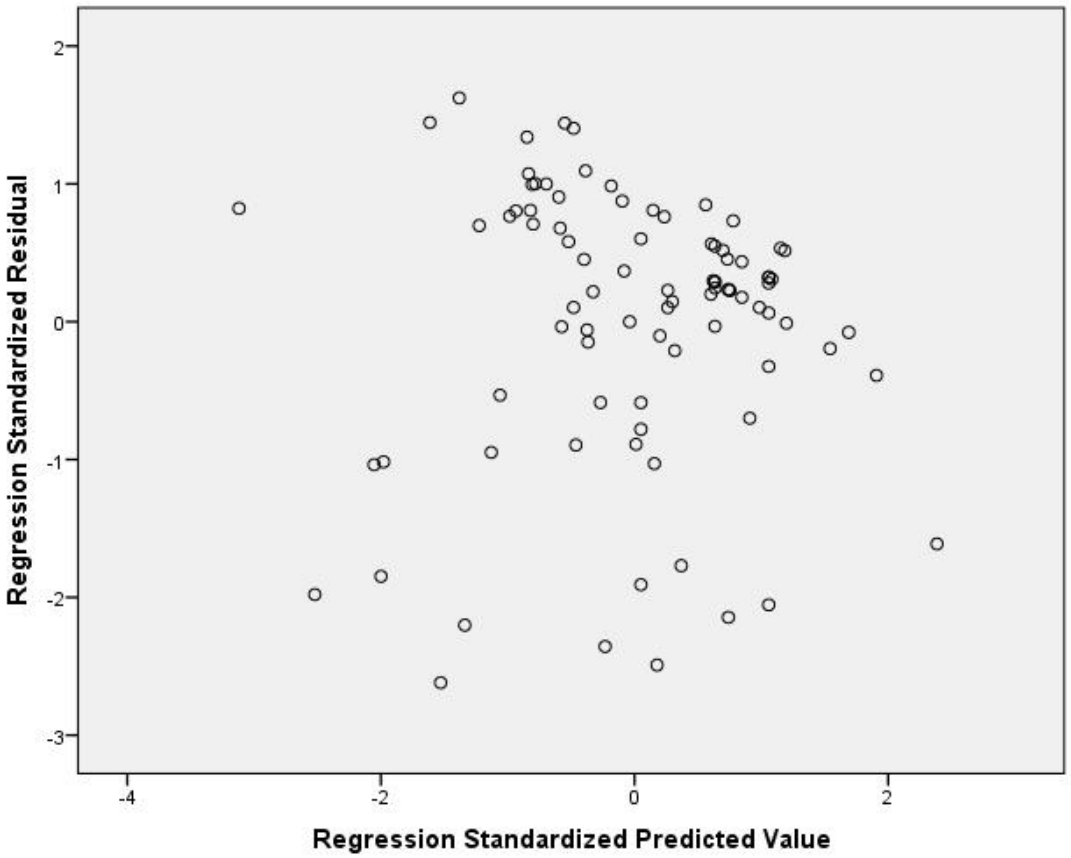

Figure I4. Scatterplot showing heteroscedasticity within Prospective Memory residual values in regression model 4.

University

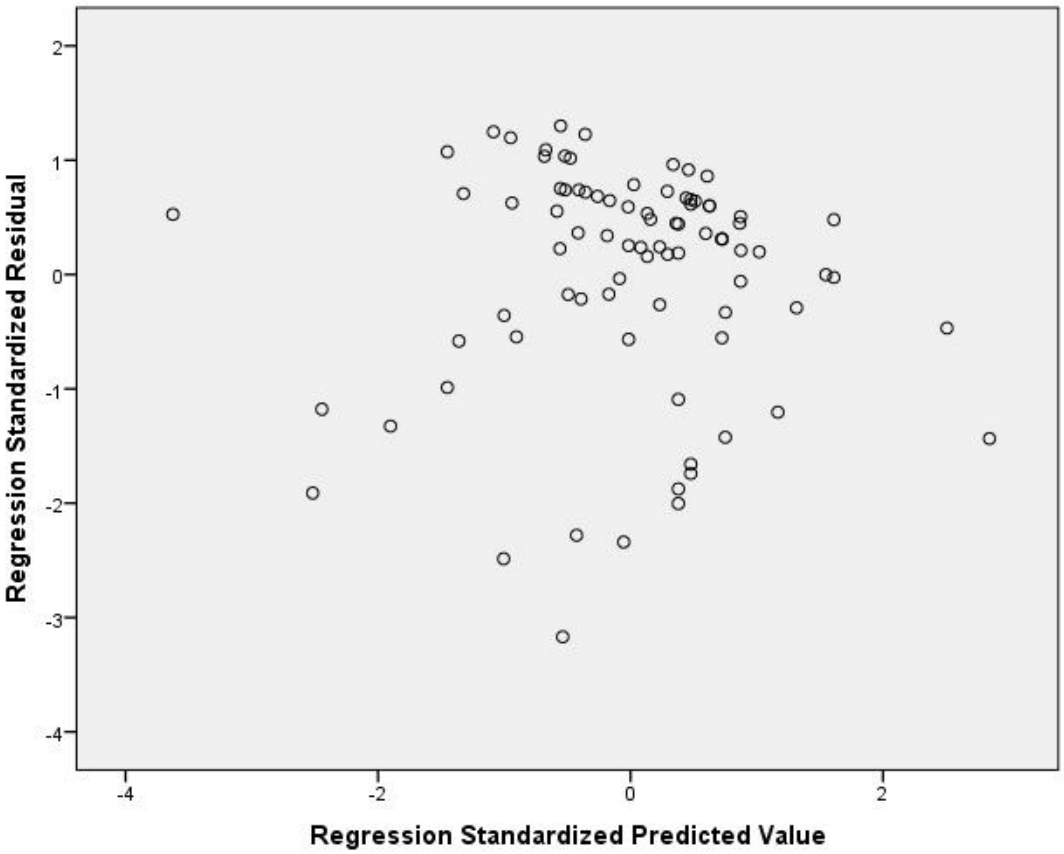

Figure I5. Scatterplot showing heteroscedasticity within Prospective Memory residual values in regression model 5.

University

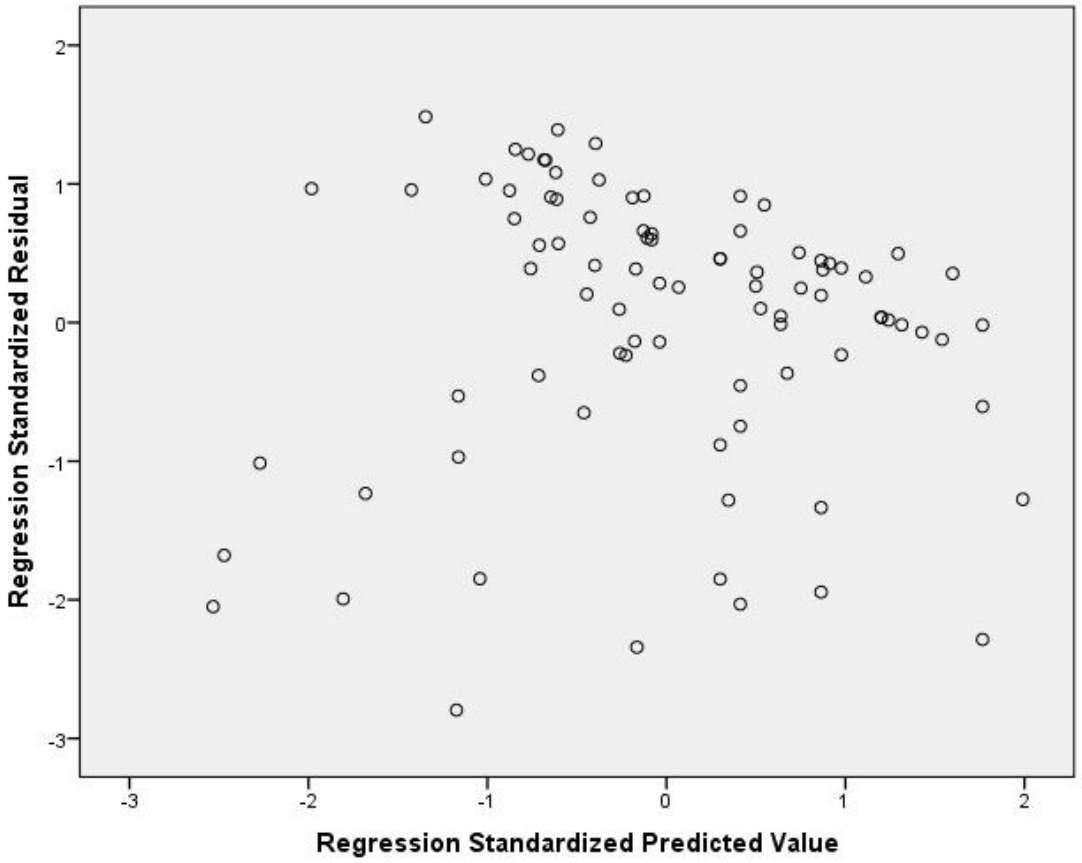

Figure I6. Scatterplot showing heteroscedasticity within Prospective Memory residual values in regression model 6.

University

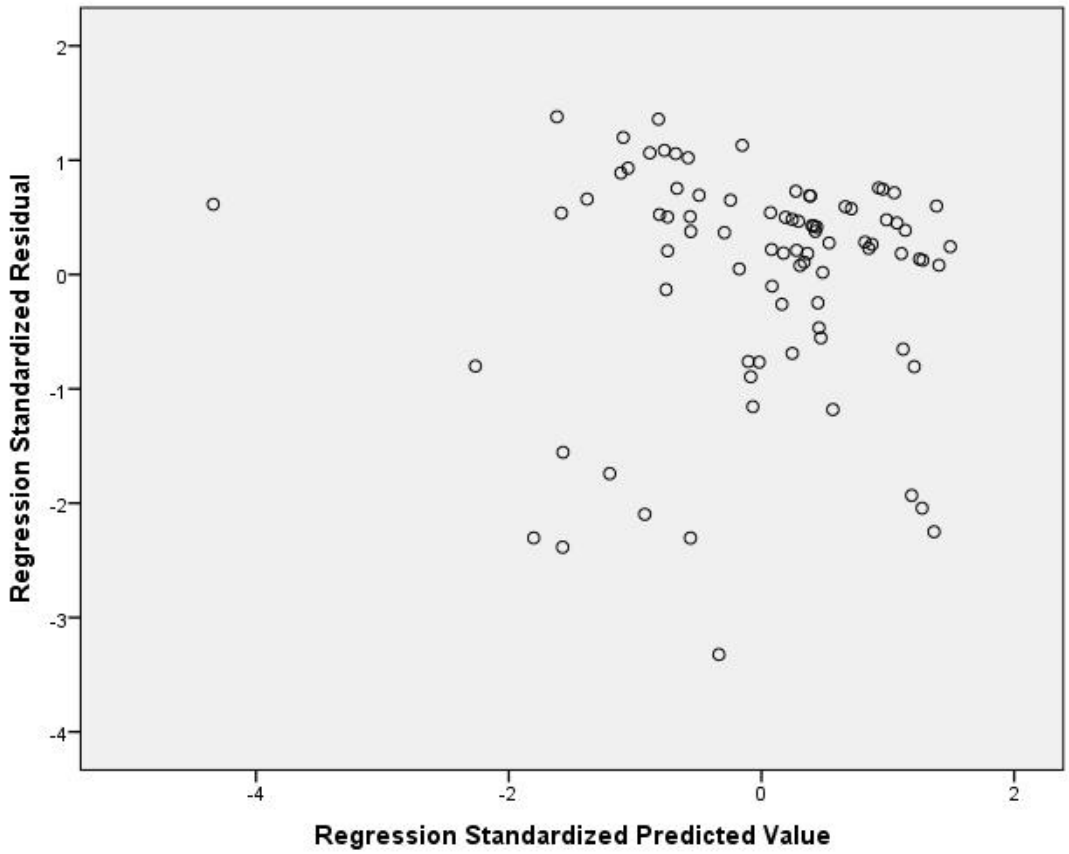

Figure I7. Scatterplot showing heteroscedasticity within Prospective Memory residual values in regression model 7.

University

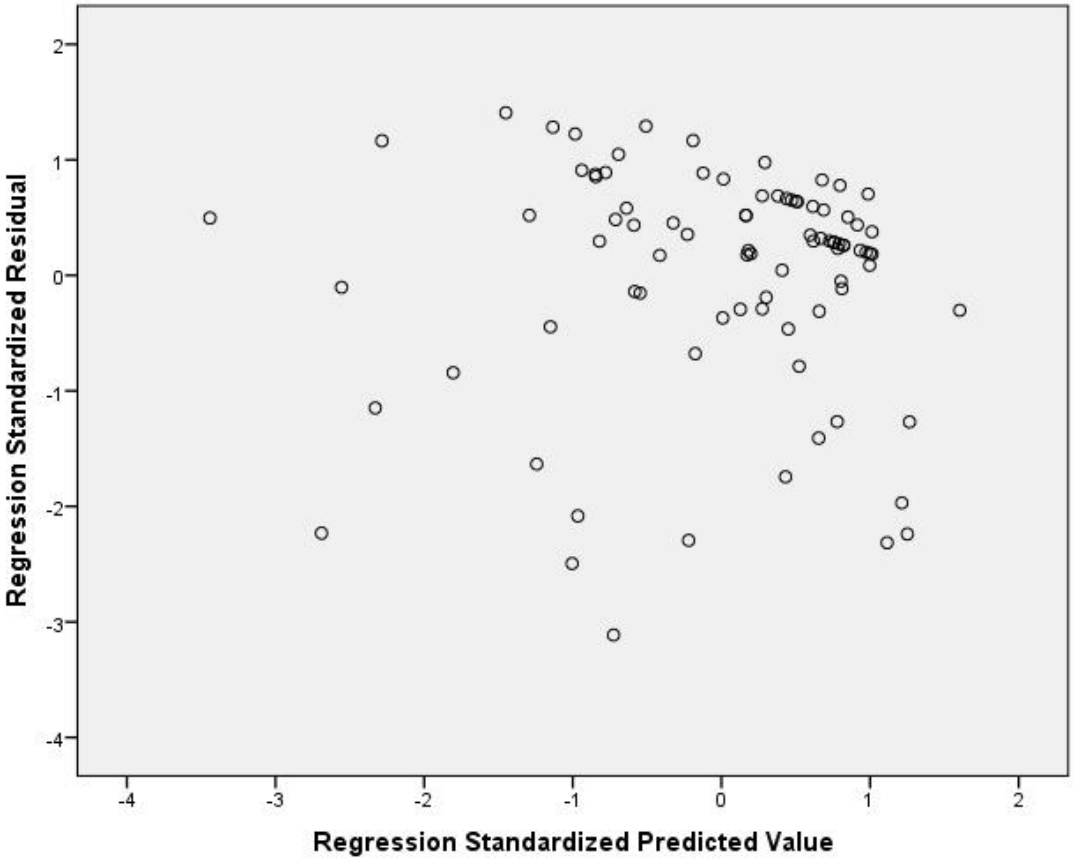

Figure I8. Scatterplot showing heteroscedasticity within Prospective Memory residual values in regression model 8.

University

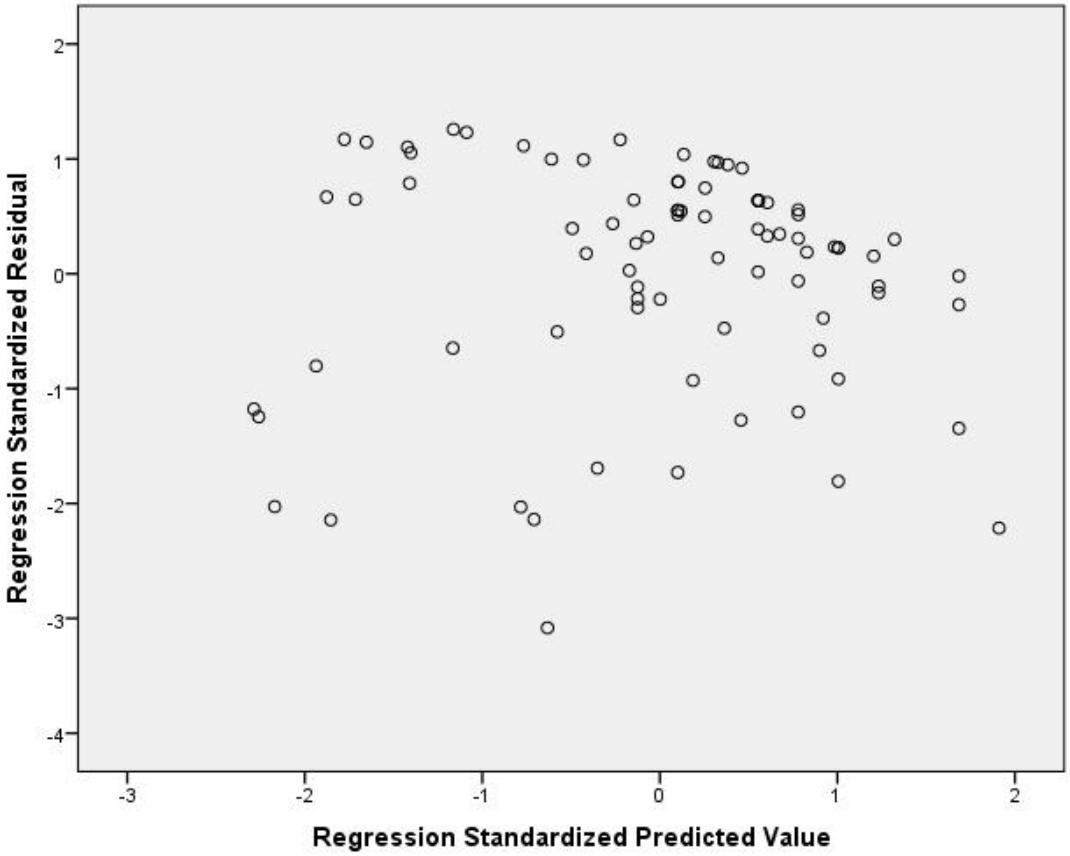

Figure I9. Scatterplot showing heteroscedasticity within Prospective Memory residual values in regression model 9.

University