Effects of Methamphetamine on Prenatally Exposed Children in Cape Town: Cognition and intrinsic functional brain connectivity

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A dissertation submitted in fulfillment of the requirements for the award of the degree of Master of Arts (Clinical Neuropsychology).

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2014

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Declaration

This work has not been previously submitted in whole, or in part, for the award of any degree. Part of this thesis, the introduction, has already been published in the Journal of Metabolic Brain Disease; however, the introduction has been reworked for the purpose of this dissertation. 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.

Signature: **Date:**

Acknowledgements

I would like to express my deepest gratitude and thanks to my supervisor, A/Prof. Kevin Thomas, for his time, guidance, teaching, and support throughout this dissertation. His knowledge and commitment to the highest standards of academic research have inspired me to be a better writer, researcher, and clinician. Thank you for allowing me the space to speak freely during our supervision sessions, and pursue various projects without objection. I have grown both personally and professionally through this experience.

I am also grateful to my co-supervisors, Dr Annerine Roos and Dr Jonathan Ipser for their guidance and dedication to this project. Thank you for imparting me with a better understanding of the brain through the lens of imaging research – without your expertise, I could not have completed this dissertation. I would also like to thank Dr Kirsty Donald for her mentorship throughout this project – thank you for your confidence in me, words of wisdom, and always encouraging me to pursue my passion. I further wish to express my profound appreciation to the mothers, caregivers, and children who participated in this research.

This study was undertaken with generous support from the Harry Crossley Foundation, and Thuthuka funding from the National Research Foundation, obtained by the MRC Unit of Anxiety and Stress Disorders, Department of Psychiatry, Stellenbosch University.

Abbreviations

ACC	Anterior cingulate cortex
ADC	Apparent diffusion coefficient
ADHD	Attention-deficit/hyperactivity disorder
AFNI	Analysis of Functional Neuroimaging
BA	Brodmann areas
BNT-SA-SF	Boston Naming Test (South African Short Form)
BOLD	Blood oxygen level-dependent
CN	Caudate nucleus
CNS	Central nervous system
CPRS	Conners' Parent Rating Scale
Cr	Creatine
CUBIC	Cape Universities Brain Imaging Centre
DA	Dopamine
DMN	Default mode network
DTI	Diffusion tensor imaging
EPI	Echo planar imaging
ESE	Estimate of effect size
fMRI	Functional magnetic resonance imaging
fMRIb	Functional magnetic resonance imaging of the brain
FSL	Functional Magnetic Resonance Imaging of the Brain Software Library
GLM	General linear model
FWHM	Full width at half maximum
GLX	Glutamate + glutamine
GPT	Grooved Pegboard Test
HC	Healthy controls
HPCSA	Health Professionals Council of South Africa
ICA	Independent Component Analysis
IDEAL	Infant Development, Environment, and Lifestyle
IPC	Inferior parietal cortex
IQ	Intelligence quotient
KABC-II	Kaufman Assessment Battery for Children (Second Edition)
MA	Methamphetamine
MAO	L-Monoamine oxidase
MELODIC	Multivariate Exploratory Linear Decomposition into Independent Components
MP-RAGE	Magnetization-prepared rapid acquisition with gradient echo
MI	Myoinositol
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NA	N-acetyle
NE	Norepinephrine
NVI	Nonverbal Index
NVS	Nonverbal Scale
PAL	Paired Associate Learning
PCC	Posterior cingulate cortex
PME	Prenatal methamphetamine exposure

RA	Research Assistant
RS-fMRI	Resting state functional magnetic resonance imaging
RSNs	Resting state networks
RXH	Red Cross Children‟s Hospital
SA	South Africa
SACENDU	South African Community Epidemiology Network on Drug Use
SES	Socioeconomic status
sMRI	Structural magnetic resonance imaging
tCR	Total creatine
TH	tyrosine hydroxylase
UCT	University of Cape Town
VMI	Visual motor integration
WISC	Wechsler Intelligence Scale for Children
WM	White matter
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
ZAR	South African Rand
5HT	Serotonin

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Abstract

Methamphetamine use among pregnant women is an increasing problem in South Africa. The aim of this cross-sectional exploratory study was to examine the possible neurotoxic effects of prenatal methamphetamine exposure (PME) on cognition and the developing brain in a sample of affected children in Cape Town, South Africa. Thus, this is a two-part study: the first part examines the effects of PME on neuropsychological outcomes, and the second part examines the effects of PME on intrinsic functional brain connectivity. Children with PME (n = 23) and unexposed controls (n = 22) completed a battery of neurocognitive assessments, and a smaller sub-sample (n = 36; 19 children with PME, 17 unexposed controls) also underwent resting-state functional magnetic resonance imaging (RS-fMRI). Independent samples t-tests revealed that children with PME scored significantly more poorly on measures of IQ, learning and memory, confrontation naming, visual-motor integration, and fine motor co-ordination, when compared to controls. Hierarchical regression analyses confirmed that PME has a significant effect on cognitive performance, and that this effect largely withstands the effects of potentially confounding sociodemographic and anthropometric variables. Independent component analyses revealed significant between-group differences in functional brain networks detected in task-free RS-fMRI in children with PME. Specifically, there is evidence for compromised connectivity within and between the basal ganglia network and default mode network in children with PME. Overall, the findings contribute to the small but growing literature on the cognitive effects of PME. The current study is the first to document preliminary evidence indicating aberrant intrinsic functional brain connectivity in children with PME, and suggests that further investigation of potential associations between particular neurocognitive deficits and such aberrant connectivity might be warranted.

With over 250 million users worldwide, methamphetamine (MA) has become a significant public health concern (United Nations Office on Drugs & Crime, 2010). The global rise in MA abuse during pregnancy has rendered a large number of infants and children at risk for the adverse consequences of prenatal methamphetamine exposure (PME; Meredith, Jaffe, Ang-Lee, & Saxon, 2005). Emerging evidence suggests that PME affects fetal growth and may lead to a variety of developmental, behavioral, and neurological abnormalities (Abar et al., 2013a; Nguyen et al., 2010). However, outside of animal studies, very little is known about the extent of the medium- and long-term functional and structural effects of MA exposure in utero. This study aims to contribute to the small but accumulating body of research delineating the longer-term clinical outcomes of PME.

Methamphetamine Abuse in Cape Town: Epidemiology, risks, and consequences

MA abuse is the fastest growing illicit drug problem worldwide (Wouldes et al., 2013). In the United States, the Treatment Episode Data set that captures admissions to federally funded treatment centers reported that admissions for pregnant women using MA increased from 8% in 1994 to 23.7% in 2006 (Terplan, Smith, Kozloski, & Pollack, 2009). These findings are corroborated in Cape Town, the largest city in the Western Cape province of South Africa (population approximately 3 700 000), which has experienced a significant increase in MA abuse over the past decade (Meade et al., 2012).

Recently, the South African Community Epidemiology Network on Drug Use (SACENDU) reported that, since 2004, MA has become the primary drug of choice in the Western Cape, with 70% of MA users falling under the age of 20 (Van Heerden et al., 2009). Reports from treatment centers in Cape Town indicate that the proportion of patients with MA as their primary substance of abuse increased from less than 1% in 2000 to approximately 34% in 2010 (Plüddemann, Parry, Bhana, Dada, & Fourie, 2010).

Although MA use is cause for concern in both sexes, South African social history and structure (both socioeconomic and cultural) has facilitated a context that predisposes women, particularly those living in historically disadvantaged communities, to associated risks (Kapp, 2008; Morris & Parry, 2006; Wechsberg et al., 2008a, 2008b). For example, because MA users frequently engage in high-risk sexual behaviors (e.g., having unprotected sex with multiple partners, working in the sex trade), female users are at greater risk for unplanned pregnancy (Simbayi et al., 2006; Wechsberg et al., 2010). Once pregnant, their addiction, and subsequent chronic fetal exposure to MA, often continues (Petersen, Jordaan, Mathews, Lombard, & Parry, 2013).

In a recent study exploring drug use in pregnant and non-pregnant women in a community sample in Cape Town, Jones et al. (2011) found that 92% of the pregnant sample (n = 26; age range = 18-33 years, M = 22.70, SD = 3.60) reported recent use of MA; 67% of the non-pregnant sample (n = 356; age range = 18-33 years, M = 24.30, SD = 4.30) also reported recent use. Many of the pregnant women reported having made attempts to stop or to reduce their drug intake after learning that they were pregnant; however, more than 30% of them continued to use MA at the same level, or increased their use.

The consequences of continued MA use during pregnancy have been documented in earlier studies. Longitudinal data have revealed a greater number of complications in pregnancy (including low maternal weight gain, increased premature delivery, and neonatal mortality) of women who had been unable to discontinue MA use during the first trimester, relative to those who had terminated use (Eriksson et al., 1981). Speculated reasons for continued and/or increased drug use during pregnancy relate to psychiatric comorbidity, partner conflict or abuse, availability of social support, and utilization of treatment services (Roberts & Pies, 2011; Semple, Zians, Strathdee, & Patterson, 2007). A recent international study found that women who decreased their use of MA over the course of pregnancy

attended a greater number of prenatal care visits (Della Grotta et al., 2010). It is possible that prenatal care might have an impact on reducing MA use; alternatively, pregnant women who decrease their MA use are simply more likely to visit prenatal care providers.

Pregnant women who live in low-income communities in SA do not usually seek (or have access to) regular antenatal care, and often report that they are unaware of drug treatment options (Myer & Harrison, 2003). Moreover, lack of psychoeducation around, and awareness of, the potential effects of PME on the developing fetus is widespread. As clinical studies have demonstrated, these effects can include decreased weight, length, and head circumference upon birth (Little, Snell, & Gilstrap, 1988; Nguyen et al., 2010; Smith et al., 2006), as well as compromised neonatal behavioral outcomes (e.g., poor feeding, abnormal sleep patterns, under-arousal, and reduced movement scores; LaGasse et al., 2011; Smith et al., 2003, 2006). These deleterious effects may be compounded by the types of poor health behaviors, such as poor nutrition and increased likelihood of exposure to violence in utero, that are frequently associated with maternal drug use (Behnke et al., 2013). Thus, the effects of PME on the fetus, and on ongoing development, are of increasing concern.

Affective, Behavioral, and Cognitive Outcomes

There is a small literature on long- and short-term outcomes of PME in humans. The most extensive follow-up data on affective, behavioral, and cognitive outcomes following PME are provided by Swedish researchers who tracked a cohort of 65 MA-exposed children from birth to age 14 years. They have reported, in that cohort of children with continuous MA exposure throughout gestation, a variety of adverse physical, cognitive, emotional, and social effects, including increased prevalence of attention-deficit/hyperactivity disorder (ADHD), aggression, and learning difficulties attributed to deficits in attention, memory, and motivation (for a timeline of findings, see Eriksson et al., 1978, 1981, 1989, 1994, 1994a,

1994b, 2000). In that cohort, the first few months of life were marked by signs of drowsiness and lethargy (Billing, Eriksson, Larsson, & Zetterström, 1980). By the age of 1 year, the children began showing affective characteristics of autism, speech impediments, and signs of wariness of strangers. At age 4, IQ was lower than that of population controls (Billing, Eriksson, Steneroth, & Zetterström, 1988), and at age 8 prenatal exposure predicted aggressive behavior towards peers (Billing, Eriksson, Jonsson, Steneroth, & Zetterström, 1994). By the age of 14, the children showed delays in math and language performance, and difficulties with physical fitness appeared to affect academic advancement (Cernerud, Eriksson, Jonsson, Steneroth, & Zetterstrom, 1996). Despite the robust database of behavioral profiles generated by research on this Swedish cohort, issues around some key methodological aspects (e.g., lack of a control group and uncontrolled-for confounding drug exposures) limit the strength of possible interpretations.

Given the presence of those methodological issues with the Swedish research, the ongoing Infant Development, Environment, and Lifestyle (IDEAL) study (Della Grotta et al., 2010), is the first and largest systematically controlled study of neurobehavioral outcomes in prenatally MA-exposed children. The IDEAL study, which uses cohorts from New Zealand and America, was the first to publish dose-response and trimester-related effects (validated by meconium testing) in prenatally MA-exposed children (LaGasse et al., 2011). From birth to 36 months, heavy PME was related to lower arousal, increased lethargy, and greater levels of physiological stress. In particular, first-trimester MA use was associated with greater physiological and central nervous system (CNS) stress, and third-trimester use with more lethargy and hypotonicity.

Data from the IDEAL study have also been used to examine the effects of prenatal MA exposure on motor and cognitive development in children between the ages of 1 and 3 years (Smith et al., 2011). At 1 year, children with PME presented with subtly impaired fine

motor performance, with the greatest disturbances observed in children with heavy PME. At age 3, however, both high- and low-dose groups presented with no PME-related motor impairment. So far, these findings yield inconsistent results in relation to some of the cognitive-behavioral evidence from neuroimaging studies (discussed under *Structure-Function Correlations* below). For example, Chang et al. (2009) found significantly impaired performance on tasks of visuomotor integration in children with PME at the age of 4 years. It is possible that the reported differences are a factor of time, and that long-term follow-up of the visual-motor functioning of children in the IDEAL study will reveal comparable results.

Discrepancies in PME-related findings have also been observed within and across the IDEAL study in relation to behavioral outcomes. One recent IDEAL publication (LaGasse et al., 2012) reported on the behavioral assessment of an older cohort of prenatally MA-exposed children (ages 3 and 5 years). Controlling for normal developmental trajectories, PME was related to heightened emotional reactivity and more anxious/depressive symptoms at both ages, and with externalizing and ADHD problems at age 5. Both withdrawn behavior and attention problems were associated with heavy PME at ages 3 and 5. Although this research is consistent with data from the Swedish cohort, which reported aggressive behavior, attentional issues, and adjustment problems at the age of 8 years (Billing et al., 1994), LaGasse et al.‟s findings were not replicated in a follow-up IDEAL study that used an older (age = 7.5 years) cohort of children (Diaz et al., 2014). In fact, Diaz et al. found no association between PME and behavioral problems, as measured by indices of oppositional behavior, hyperactive behavior, and ADHD.

Diaz et al. (2014) proposed that the behavioral and attention difficulties identified by LaGasse et al. (2012) could have dissipated with age or environmental factors. However, this explanation does not account for the confounding findings in Billing et al.‟s (1994) cohort, aged 8 years, or a more recently published study (independent from the IDEAL study), which

reported that the frequency of an ADHD diagnosis was four-fold more common in children (aged 7-9 years) with PME (Piper et al., 2011). It is possible that the differences in findings can be accounted for, in part, by methodological inconsistencies. In particular, the latter IDEAL study derived data from parent reports, whereas the earlier IDEAL study used child-based measures.

Despite the noted incongruities in some of the studies discussed so far, there are some consistencies. PME has been associated with an increased incidence of cognitive problems, specifically on parental ratings of executive functioning (including working memory, impulse regulation, goal-setting, flexibility, and emotional control; Diaz et al., 2014; Piper et al., 2011). As mentioned earlier, PME is also associated with poor school performance (Cernerud et al., 1996), and so the identified cognitive impairments are likely contributing factors to the lack of academic success present in exposed children. Additionally, cognitive problems linked to inattention predict negative externalizing behaviors during childhood, possibly due to the relatively high levels of frustration, lack of motivation, and confusion that exposed children may experience (Hill, Degnan, Calkins, & Keane, 2006). Twomey et al. (2013) found that home environments that were more stable and sensitive to the emotional and developmental needs of children with PME were associated with decreased risk of internalizing and externalizing behavioral problems. This finding, however, was independent of MA exposure (the control group displayed similar behavioral challenges), thus placing the child‟s behavioral problems in the context of the larger family system.

Overall, evidence from the above studies suggests that the adverse developmental effects experienced by children with PME are due either to the effects of the drug, the environment in which these children are raised, or, most likely, a combination of these factors. Furthermore, it is clear that PME results in changes in affect, behavior, and cognition; the severity and extent of these changes is likely to be modulated by the timing, dose, and route

of MA exposure, however. To better understand the effects of PME on childhood development, the potential mechanisms of action and toxicity of MA (and how they translate to changes in developing neural circuitry) must be explored.

Effects of Methamphetamine on Developing Neural Circuitry

MA is one of a group of sympathomimetic drugs that stimulate the CNS. It passes readily through the placenta and the blood-brain barrier, and can have significant vasoconstrictive effects on the developing fetus, resulting in decreased uteroplacental blood flow and fetal hypoxia (Golub et al. 2005; Won, Bubula, McCoy, & Heller, 2001). Although the biochemical mechanisms of action and toxicity of MA for the adult brain have been well documented (see Cruickshank & Dyer, 2009; Kish, 2008; Scott et al., 2007), the effects of PME on the organization of developing neural circuitry, and whether/how subsequent recovery from those effects is possible, is unclear (Sowell et al., 2010). Furthermore, because of the multiple interactions among developing neuronal systems that determine the organization of brain circuitry, the effects of MA on neural connectivity in the immature CNS are likely to be different to those in adults.

The development of neural networks is influenced by numerous morphogenetic events, including proliferation, migration, differentiation and apoptosis, neurite growth, synaptogenesis, and neuronal pruning. These events are modulated by, among other factors, pre- and post-synaptic electrical activity, neurotrophic factor signaling, and multiple neurotransmitter systems (Frost & Cadet, 2000). With specific regard to the latter, the primary monoaminergic pathways (i.e., those using norepinephrine (NE), dopamine (DA), and serotonin (5HT)) project widely and develop early. This spatial and temporal arrangement allows these pathways to modulate the development of non-aminergic neural elements and the connections between them. Thus, damage to monoaminergic neurons in

utero may have a secondary effect on a wide variety of neural circuits (see Figure 1).

Regarding the effects of the acute and chronic MA exposure on mature serotonergic, dopaminergic, and glutaminergic axons, a substantial body of literature, encompassing both animal and human studies, suggests multiple mechanisms of action (Barr et al. 2006; Nordahl, Salo, & Leamon, 2003; Scott et al., 2007; Sulzer, Sonders, Poulsen, & Galli, 2005). The principal mechanism by which MA stimulates the excessive release of monoamines (primarily, DA) includes the redistribution of catecholamines from synaptic vesicles to the cytosol (Brown, Hanson, & Fleckenstein, 2001) and the reverse transport of neurotransmitters through plasma membrane transporters (Khoshbouei, Wang, Lechleiter, Javitch, & Galli, 2003). There is also evidence that MA blocks the catabolism of catecholamines by inhibiting the activity of mitochondrial monoamine oxidase (MAO), and by increasing the activity and expression of the dopamine-synthesizing enzyme tyrosine hydroxylase (TH) (Schmitz, Lee, Schmauss, Gonon, & Sulzer, 2001; Sulzer et al., 2005). As a result of these multiple mechanisms, MA acts as a highly potent releaser of monoamines, giving rise to MA-induced neurotoxicity. This neurotoxicity is evident in several neurotransmitter systems, but is most notable in the nigrostriatal dopaminergic pathways. Thus, it is possible that PME potentially alters the function of the dopamine-rich fronto-striatal-thalamocortical loops (Cass, 1997).

Given these effects of MA on mature monoaminergic pathways, it is reasonable to suggest that developing monoaminergic neurons may also be susceptible to MA-induced neurotoxicity (Cadet & Krasnova, 2009). In rat studies, TH (responsible for the conversion of L-tyrosine to L-DOPA, a precursor for DA) has been identified as an effective marker in assessing potential effects of MA on developing DA systems (Gomes-da-Silva et al., 2002). The action of TH early in CNS development is associated with the differentiation of neuronal groups, and with neurochemical processes that control axonal guidance, neuronal recognition,

and synaptogenesis (Flames & Hobert, 2011). Because TH levels appear to be reduced permanently following repeated MA administrations in rat pups, it is possible that the action of MA on TH gene expression early in development might affect critical processes related to dopaminergic activity (Graham et al., 2011, 2013). Specifically, MA-induced depletion of TH appears to alter the pattern of maturation of dopaminergic TH-containing neurons in the dorsal striatum, prefrontal cortex, nucleus accumbens, and substantia nigra (Kaewsuk, Sae-ung, Phansuwan-Pujito, & Govitrapong, 2009). Such findings have been replicated in several rat studies, suggesting that the functional consequences of PME might result from effects on the mesolimbic dopaminergic pathway (Bubenikova-Valesova et al., 2009; Suzuki et al., 2003).

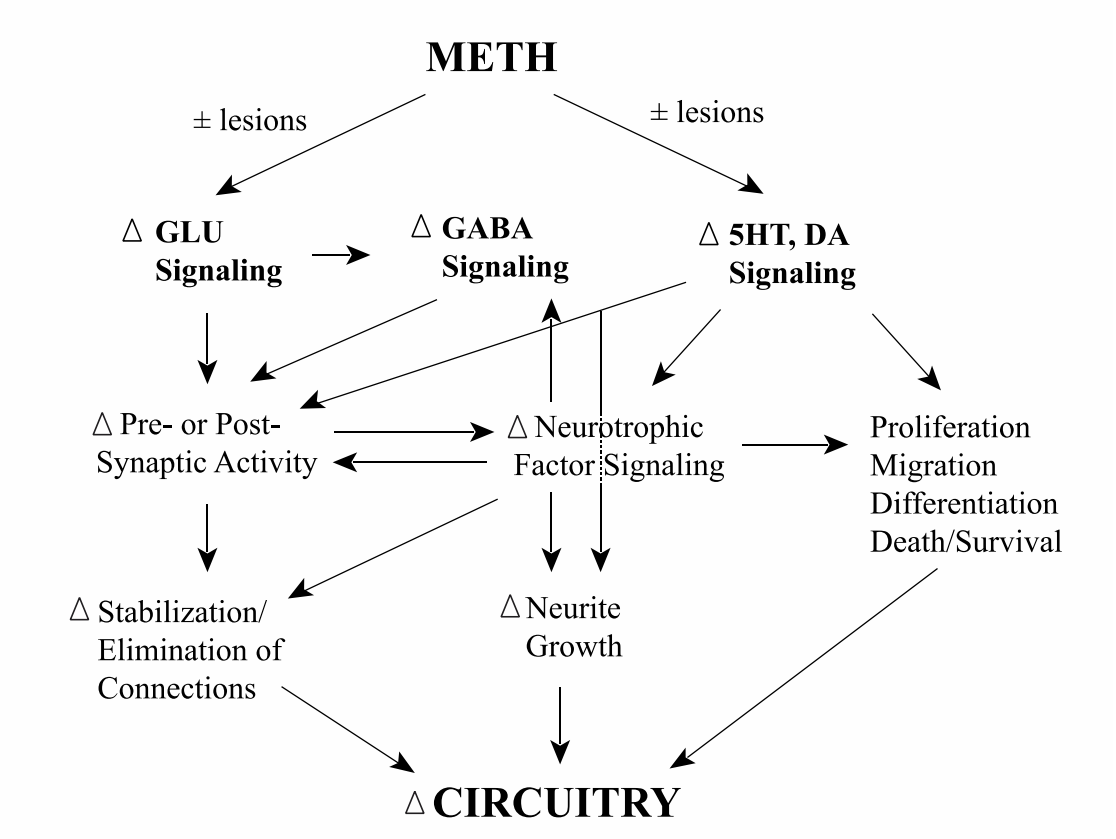

*Figure 1.*Schematic diagram of how methamphetamine, by virtue of its effects on the serotoninergic (5HT), dopaminergic (DA) or glutamatergic (GLU) systems, can modulate the development of non-aminergic neural circuitry. The notation „+/- lesions" indicates that methamphetamine-induced modulation of signaling in the glutamate, serotonin, and dopamine systems is not necessarily accompanied by overt destruction of neurons or their processes in these systems. Reproduced with permission from Frost and Cadet (2000).

The evidence reviewed above is drawn from rat studies involving multiple high-dose exposures to MA throughout periods of fetal development. However, even single-dose MA exposure in utero may have significant developmental consequences. Jeng, Wong, Ting-A-Kee, and Wells (2005) found that a relatively low dose (20 or 40 mg/kg ip, resulting in similar concentrations observed in premature infants born to MA-abusing mothers) of MA administered once-off during the embryonic or fetal period in pregnant rats caused oxidative DNA damage in the brain, and long-standing (potentially permanent) postnatal functional deficits. Of note here is that these functional deficits arose without any concomitant alterations in dopaminergic nerve terminal density (evidenced by staining for TH). Taken together, these results suggest that even single-dose PME may have negative developmental consequences, and that the mechanisms underlying these effects might be distinct from those arising from multiple-dose schedules.

Given the plasticity of the developing brain (Andersen, 2003; Johnston et al., 2009), one may infer that neurological insult associated with PME would be compensated for more effectively than that associated with adult exposure. However, the molecular and morphological changes that take place during development seem to bring about windows of selective vulnerability, even while allowing compensatory repair mechanisms to function (Jeng et al., 2005; Stanwood & Levitt, 2004; Vaccarino & Ment, 2004). For example, it is possible that striatal dopaminergic neurons may continue to develop even after PME, but that their development may occur aberrantly. This aberrant development might involve atypical processes of neural patterning and/or remodeling in addition to, or instead of, dopaminergic cell loss (Jeng et al., 2005). Although further research is needed to validate these claims, it seems clear that the mechanisms of action in PME are a combination of the interaction of MA with monoaminergic neurotransmitter systems in the developing fetal brain, as well as with changes in brain morphogenesis (Cui et al., 2006; Won et al., 2001).

Human Magnetic Resonance Imaging Studies of Prenatal Methamphetamine Exposure

To investigate the above-mentioned changes in brain morphogenesis in children with PME, several studies have used magnetic resonance imaging (MRI). MRI is a safe, non-invasive technology that is often used to study brain structure and function. It uses magnet and radio waves to measure signals from protons (water) within the brain (Lebel, Roussotte, & Sowell, 2011). The signal measured is dependent on various tissue properties, including density, local environment, blood oxygenation, water movement, and relaxation properties (i.e., T1- and T2-weighted images). Different contrast mechanisms allow for several different types of imaging modalities, including structural MRI (sMRI), functional MRI (fMRI), diffusion tensor imaging (DTI), and magnetic resonance spectroscopy (MRS; see Roussotte, Soderberg, & Sowell, 2010 for a summary of MR-based imaging techniques). Each study discussed in the sections below features the use of at least one of these imaging techniques; however, there is little consistency in the outcomes reported by these papers, the results of which cannot be easily synthesized. For this reason, the end of this part of the review is followed by a discussion of the challenges associated with research in the area of PME.

Structural and metabolic neuroimaging findings. A literature search revealed six studies that reported the use of structural and metabolic MRI to examine the effects of PME on brain structure and function. The first of these was published in 2001. These studies range in sample size from 12-49 prenatally methamphetamine-exposed subjects, and they use a variety of analytic methods. Table 1 presents the basic methodological details and the findings of each of the six studies.

Because striatal structures have the highest densities of dopaminergic synapses, one might predict that the neurotoxic effects of MA would be pronounced in these regions (Chang, Alicata, Ernst, & Volkow, 2007). Using sMRI, Chang et al. (2004) confirmed this prediction: They found that, compared to unexposed age-matched controls, children exposed

to MA in utero showed significant regional volumetric reductions in the globus pallidus and putamen, and marginal decreases in caudate size. They also found significant volumetric reductions in the hippocampus bilaterally. Sowell et al. (2010) replicated these findings in an sMRI study that compared the brain morphometry of children with PME to that of children with prenatal alcohol exposure. They found that, although both groups of children showed widespread volumetric reductions (including in striatal, thalamic, prefrontal, and occipitoparietal regions) and some volumetric increases in limbic structures, MA-exposed children showed more severe volume reductions in the striatum, and more pronounced volumetric increases in limbic structures such as the anterior and posterior cingulate and the inferior frontal gyrus.

A recent publication using a sub-sample from the present study found significant increases in left putamen volume (Roos, Jones, Howells, Stein, & Donald, 2014), which is consistent with findings on adult MA exposure (Change et al., 2005). Although the above findings are contradictory in terms of directionality of volumetric changes found by Chang et al. (2004) and Sowell et al. (2010), these data suggest aberrant processes in the dopaminergic system. Thus, cumulatively, these findings are not only generally consistent with predictions derived from the rat studies reviewed above, but they are also consistent with research showing that striatal and limbic structures are sites of neurotoxicity in adult MA users (Sulzer et al., 2005).

Table 1
Structural and Metabolic MRI Findings in PME

First Author, year	Imaging Modality	*N*	Age (years)	Frontal	Temporal	Parietal	Subcortical structures	Correlations with neuropsychological measures
Smith et al., 2001	MRS	12 PME	7-8 (*M* = 8.10, *SD* = 0.80)				↑tCr in striatum	
		14 HC	7-8 (*M* = 7.30, *SD* = 1.10)					
Chang et al., 2004	sMRI	13 PME	3-16 (*M* = 6.9, *SD* = 3.50)				↓V putamen, ↓V globus pallidus, ↓V hippocampus, ↓V caudate	Poorer performance on measures of visual motor integration, attention, verbal memory, and long-term spatial memory
		15 HC	3-15 (*M* = 7.8, *SD* = 3.20)					
Chang et al., 2009	MRS	49 PME	3-4 (*M* = 3.91, *SD* = 1.07)	↑tCR, NA, GLX in frontal WM			↓MI in thalamus	↓MI in thalamus correlated with poor performance on a task of visual-motor integration
		49 HC	3-4 (*M* = 3.76, *SD* = 0.99)					
Cloak et al., 2009	DTI	29 PME	3-4 (*M* = 4.03, *SD* = 1.20)	↓ADC in WM tracts		↓ADC in WM tracts	↑Ch in striatum	
		37 HC	3-4 (*M* = 3.98, *SD* = 1.40)					
Sowell et al., 2010	sMRI	21 PME	5-15 (*M* = 9.66, *SD* = 1.85)	↓V inferior frontal gyrus, ↑V anterior cingulate	↑V inferior and medial	↓V dorsal, ↑V posterior cingulate	↓V striatum, ↓V thalamus	A negative correlation was found between full-scale IQ and caudate volume
		27 HC	5-15 (*M* = 10.12, *SD* 2.90)					
Roos et al., 2014	sMRI	18 PME	6 (*M* = 6.45, *SD* = 0.42)	↓cortical thickness of the pars opercularis		↓cortical thickness of inferior parietal and precuneus areas	↑V putamen	
		18 HC	6 (*M* = 6.51, *SD* = 0.33)					

Note. Only significant results are included in the table. MRS = magnetic resonance spectroscopy; sMRI = structural magnetic resonance imaging; DTI = diffusion tensor imaging; PME = prenatal methamphetamine exposure, HC = healthy controls, V = volume, ADC = apparent diffusion coefficient, WM = white matter, tCr = total creatine, NA = N-acetyle compounds, GLX = glutamate + glutamine, MI = myoinositol

To my knowledge, the three studies reviewed above are the only published sMRI studies investigating the effects of PME on the brain. Despite some consistency in findings, the etiology of the observed changes in volume (both reductions and increases) is not entirely clear. For instance, it is possible that volume increases in the anterior and posterior cingulate and other associated limbic cortices may serve as a compensatory mechanism for PME-associated reductions in the dopamine-rich striatal and thalamic structures (Sowell et al., 2010). Alternatively, the PME-related volume increases observed by Roos et al. (2014) may represent an aberrant process due to inadequate synaptic pruning and/or reduced myelination – processes that are known to continue throughout childhood to facilitate more efficient cognitive processing (Sowell et al., 2004).

To date, only one published study has examined microstructural brain changes following PME in humans. Cloak, Ernst, Fujii, Hedemark, and Chang (2009), using DTI, found that, compared to age-matched controls, prenatally MA-exposed children had lower diffusion in frontal and parietal white matter tracts (as measured by the apparent diffusion coefficient). Although the exact mechanism of how PME may lead to lower brain diffusivity is unknown, lower white matter diffusivity typically reflects, among other outcomes, more compact axonal fibers. Reduced myelination and higher dendritic density have also been reported in rat pups prenatally exposed to MA (Melo, Moreno, Vázquez, Pinazo-Durán, & Tavares, 2006).

The findings of lower diffusivity in frontal and temporal white matter are consistent with those of two MRS studies (Chang et al., 2009; Smith et al., 2001). Smith et al. (2001) found elevated levels of creatine (Cr) in the striatum in children with a history of prenatal MA exposure. Chang et al. (2009), using a much larger sample, found higher metabolite concentrations of total Cr, as well as of N-acetyle (NA), and of glutamate and glutamine (GLX), in the frontal white matter and thalamus. Because the three metabolites NA, Cr, and

GLX are present in neurons, their higher white-matter concentrations suggest increased axonal density or compactness in MA-exposed children (as confirmed by the DTI results presented by Cloak et al. (2009)).

As with the sMRI findings, an etiology for the increased metabolite concentrations in children with PME is not clear. It is possible that the higher metabolite levels suggest accelerated growth patterns in these children. Previous MRS studies of normally developing children (Kreis, Ernst, & Ross, 1993), and of healthy mice (Weiss, Melkus, Jakob, & Faber, 2009), found age-dependent increases in total CR, NA, and GLX, similar to the levels observed in the MRS studies discussed above. Alternatively, it is possible that the known vasoconstrictive effects of PME could result in altered cell energy metabolism in exposed children (Golub et al., 2005; Won et al., 2001).

Functional neuroimaging findings. Again, this is a small body of literature, featuring only two published studies (see Table 2). Those studies do, however, report results that one might interpret as being broadly consistent with those from sMRI and animal studies: They also identify limbic and striatal regions as being particularly vulnerable to the effects of PME.

In a design similar to that of Sowell et al."s (2010) sMRI study, Lu et al. (2009) compared functional activation in response to a verbal memory task in three groups of children: those with prenatal exposure to both MA and alcohol, those with prenatal exposure to alcohol alone, and age-matched non-exposed controls. Although both exposure groups showed similarly impaired performance on the memory tasks, children with PME recruited more diffuse areas in the bilateral medial temporal lobes than the alcohol-exposed and control groups. The authors interpreted these findings as suggesting that children with PME may need to allocate additional (and more diffuse) resources to achieve the same level of medial temporal lobe function and to compensate for a less efficient verbal memory network.

Table 2
Functional MRI Findings in PME

First Author, year	*N*	Age (years)	Measures	Results
Lu et al., 2009	14 PME+ALC	7-15 (*M* = 9.50, *SD* = 1.91)	Paired Associate Learning (PAL) Task	↑ activation of diffuse brain regions for PME+ALC group on PAL task than ALC group
	9 ALC	7-15 (*M* = 11.33, *SD* =2.65)		
	20 HC	7-15 (*M* = 2.56)		
Roussotte et al., 2011	19 PME+ALC	7-15 (*M* = 9.16, *SD* =1.83)	N-back task	↓ activation in striatal and frontal regions for the PME+ALC group on N-back task than HC group. ↓ activation in right caudate and putamen in ALC group compared to PME+ALC group
	13 ALC	7-15 (*M* = 11.46, *SD* = 2.44)		
	18 HC	7-15 (*M* = 10.28, *SD* = 2.61)		

Note. Only significant results are included in the table. PME+ALC = prenatal methamphetamine exposure with concomitant alcohol exposure; ALC = alcohol; HC = healthy controls.

The other published fMRI study in this area of research (again, using the same study design as the one described above) found more severe functional alterations in children with prenatal MA and concomitant alcohol exposure than those with alcohol exposure alone, compared to age-matched non-exposed controls (Roussotte et al., 2011). Specifically, decreased activation was observed in several fronto-striatal circuits in children with prenatal MA+alcohol exposure as they completed a visuospatial working memory task, relative to the control group. This finding is consistent with the evidence of structural and metabolic abnormalities of the striatum and fronto-striatal connections, discussed in the previous section of this review (i.e., Chang et al., 2004, 2009; Roos et al., 2014; Smith et al., 2001). However, Roussotte et al., instead of observing the hypothesized negative correlations between activation in the caudate nucleus (implicated in working memory) and task accuracy, observed no correlation between cognitive performance and caudate activation. Unexpectedly, their statistical analyses revealed a negative correlation between task accuracy and activation in the putamen, bilaterally, in the prenatal MA+alcohol exposed group.

One possible interpretation for this finding may be offered by way of understanding the potential interactions between the basal ganglia-thalamocortical circuits and their regional connections. Each circuit is organized in parallel and underlies specific motor, cognitive, or affective functions (Cummings, 1993; Middleton & Strick, 2000). For example, the dorsolateral prefrontal loop (implicated in working memory) engages the dorsolateral caudate (Lewis, Dove, Robbins, Barker, & Owen, 2004), whereas the putamen is involved in the motor loop (Seger, 2009). Because striatal dopamine depletion (such as that observed in rat studies on PME; e.g., Bubenikova-Valesova et al. (2008)) appears to result in changes in cortico-striatal network properties, it is possible that this depletion may lead to a remapping of cerebral connectivity (in particular, reduced spatial segregation) and may ultimately result in increased interaction between the different cortico-striatal loops (Helmich et al., 2010).

Similar patterns of data occur in patients with Parkinson‟s disease, which features reduced levels of striatal DA (Morrow, Roth, Redmond, & Elsworth, 2011). Therefore, it is possible that a mechanism similar to the one occurring in Parkinson‟s disease may occur in children with PME. That is to say, damage to DA terminals in the striatum during ontogeny may affect the development of neural circuits and lead to a comparable remapping phenomenon, as suggested by Cadet and Krasnova (2009). Thus, in children with PME, it is possible that the dorsolateral prefrontal loop (activated during working memory tasks) may engage the putamen (rather than the dorsolateral caudate), due to reduced spatial discrimination between the motor and dorsolateral prefrontal loops (Roussotte et al., 2011).

Because the body of research described above is small, the postulated explanations for the effects observed and described in the reviewed studies are largely speculative, with little supporting evidence. Moreover, although the functional connectivity data reveal specific task-related changes in blood oxygen level-dependent (BOLD) response in prenatally MA-exposed children, they do not examine the possibility of altered underlying global attentional

modulation. The recent discovery of regions that are consistently more active during resting periods than during cognitive demand (see Fox & Greicius, 2010; Greicius, Krasnow, Reiss, & Menon, 2003) suggests scope for examining resting state data in those with PME. However, to date there are no published data on resting state connectivity in prenatally MA-exposed individuals, and only one study (Ahmadlou, Ahmadi, Rezazade, & Azad-Marzabadi, 2013) has examined global organization of functional brain connectivity in adult MA users.

Resting-state neuroimaging. Resting-state fMRI (RS-fMRI) is a relatively novel technique that offers potential for exploring PME-associated abnormalities in functional connectivity. In RS-fMRI, the neurophysiological index is the BOLD signal, which exhibits low-frequency spontaneous fluctuation in the brain at rest (i.e., no task is performed during the scan – rather, the participant is instructed to remain still with eyes closed or open; Greicius, 2008). Numerous studies have suggested that variations in BOLD signal, temporally correlated across the brain, are of neuronal origin and correspond to functional resting-state networks (RSNs; Beckmann, DeLuca, Devlin, & Smith, 2005; Damoiseaux et al., 2006; Fox & Raichle, 2007). Together, these RSNs characterize the neuronal baseline activity of the human brain in absence of task-based or externally stimulated neuronal activity, and may reflect functionally distinct networks.

The last 15 years have witnessed a steady increase in the number of RS-fMRI studies (Cole, Smith, & Beckmann, 2010). The growing popularity of RS-fMRI can be ascribed to several factors: (1) It provides a measure of the intrinsic connectivity of neural networks that is highly reliable across both subjects (including children) and scans (Shehzad et al., 2009; Thomason et al., 2011; Van Dijk et al., 2010); (2) its minimal task demands and scanner time (a full dataset can be collected in as little as 5 minutes) encourage compliance in difficult-to-scan populations, such as children, without the need for sedation; and (3) it is sensitive to brain abnormalities across a range of clinical disorders (Rosazza & Minati, 2011). Thus, RS-

fMRI provides an opportunity to offer new insights on the effects of PME on brain activity, as well as the relationship between RSNs and the cognitive and behavioral outcomes that have been described in affected individuals.

Structure-function correlations. The studies reviewed thus far present evidence of structural and functional deficits, and of clinical cognitive and behavioral phenotypes, in PME. While such research contributes to our knowledge of the seemingly multifaceted manifestations of PME, correlational analyses investigating brain-behavior relationships provide opportunity for a clearer understanding of the neurobehavioral and neuroanatomical tenets that underlie developmental outcomes in PME. Among the studies described in the section headed *Structural and Metabolic Neuroimaging Studies*, three have reported correlations between structural or metabolic brain abnormalities and neurocognitive performance in children with PME.

Chang et al. (2004) found that the smaller size of the putamen and globus pallidus in children with PME was associated with relatively impaired performance on a task of sustained attention. In the same study, reduced hippocampal volume was also associated with relatively impaired performance on a verbal memory task. These correlations of performance on attention and memory tasks with volumetric reductions in subcortical structures are also consistent with reports linking smaller striatal brain volume (and deficits in the dopaminergic system) with impaired learning in children with PME (Thompson, Levitt, & Stanwood, 2009).

In the second correlational study, investigating potential interactional effects of prenatal MA and alcohol exposure on cognitive outcomes, Sowell et al. (2010) found volumetric reductions in striatal and thalamic regions for both prenatal MA+alcohol and prenatal alcohol-only groups, compared to controls. For the prenatal MA+alcohol group, reduced volumes in the caudate nucleus (a structure associated with mental processes such as memory, learning, motor control, and punishment and reward) were negatively correlated

with IQ. This effect was not observed in the alcohol-only group, suggesting that children with prenatal methamphetamine and alcohol exposure may have more severe cognitive deficits than those exposed to alcohol alone. Given the prevalence of concomitant alcohol exposure in PME research, as indicated by several of the studies reviewed here (Lu et al., 2009; Roussotte et al., 2011), such findings warrant further replication.

In terms of metabolic correlates, one MRS study (Chang et al., 2009) found that decreased metabolic activity in the frontal white matter and thalamic regions was correlated with poor performance on tasks assessing visuomotor integration. Consistent with some of the behavioral findings presented in previous human research (e.g., Chang et al., 2004), as well as in animal studies (Šlamberová, Pometlová, & Charousová, 2006), it is possible that PME results in altered psychomotor development via changes to the dopaminergic system in fronto-striatal or thalamocortical pathways.

Challenges in Prenatal Drug Exposure Research

All the studies reviewed thus far have been subject to numerous ethical and methodological restrictions. Regarding research ethics, views on what constitutes an appropriate response to drug-exposed infants vary due to the many complex issues endemic to perinatal substance use. For example, reporting pregnant illicit drug users to child welfare authorities is often argued to be an ethical obligation; however, research shows that pregnant women who fear prosecution and loss of custody as a result of their drug use are less likely to seek help or essential prenatal care (Poland, Dombrowski, Ager, & Sokol, 1993; Roberts & Nuru-Jeter, 2010). Although the scope of this review does not cover the aforementioned complexities, an appropriate response in terms of research on prenatal drug exposure and social policy is an important consideration, and I refer the reader elsewhere (see Lester,

Andreozzi, & Appiah, 2004; Ondersma, Simpson, Brestan, & Ward, 2000; Thompson et al., 2009). My focus here, instead, is on methodological constraints pertinent to research on PME.

From a methodological perspective, research on the effects of PME is problematic and has, to date, been limited. One challenging aspect is that prevalence statistics are difficult to establish and often fluctuate from site to site. Variations in prevalence rates may be attributed to differing sampling and drug detection methods (e.g., immunoassay vs. meconium testing), screening women in different settings (e.g., community samples vs. targeted samples, such as drug rehabilitation centers or prisons), and obtaining data at various points in time (Behnke et al., 2013). For example, many of the existing PME studies feature retrospective designs, and thus data pertaining to the quantity, frequency, and combinations of drugs used, and at what points they were used during pregnancy, is often inaccurate or unavailable (Kaltenbach & Finnegan, 1993; Maisto, McKay, & Connors, 1990).

In direct relation to the challenges outlined above, a frequently cited limitation of PME research is that documentation of MA use by women during pregnancy is typically based on self-report measures, without verification by toxicological analysis. Moreover, information from the primary source is often inaccessible. This is because many child participants in PME studies have been removed from the custody of their biological mothers due to the presence of drugs, violence, and neglect in the home (Smith, Johnson, Pears, Fisher, & De Garmo, 2007). Therefore, information regarding the mother‟s substance use history is often collected by way of medical and legal records, and/or reports from adoptive or foster parents. Consequently, establishing whether there is a dose-response curve in terms of neurocircuitry and behavioral outcomes, and the shape of that curve, is problematic.

The issue of accuracy of maternal drug exposure histories is further compounded by the prevalence of polysubstance abuse. Children with PME are at high risk of in utero exposure to other substances, including alcohol, tobacco, cocaine, marijuana, and opiates

(Smith et al., 2006). Abuse of each of these substances has its own particular consequences for brain structure and function (Salisbury, Ponder, Padbury, & Lester, 2009; Smith et al., 2006; Sowell et al., 2010). Hence, in polysubstance abusing mothers, it is difficult to tease apart the effects of MA from that of (an)other drug(s). One way of resolving the confounding effects of polydrug abuse in PME research might be to recruit samples without concurrent polydrug exposure; however, such samples are rare. Therefore, research on children with PME might be more ecologically valid if, in fact, one did not try to recruit those with "pure" exposure to MA alone. A more viable solution, then, might be to recruit larger samples in order to isolate the effects of a specific drug. With a large enough sample size, there may be enough statistical power and variability among various combinations of drugs to be able to covary or adjust the effects of the drug of interest for the effects of other drugs.

Summary and Conclusion

I have summarised findings from the cognitive, affective and neuroimaging literature in infants and children exposed to MA prenatally. I have also discussed, using findings from animal studies, some of the underlying neuroteratogenic mechanisms of PME.

The teratogenic effects of PME appear likely to result from interference with the neurotropic roles of monoaminergic transmitters (particularly DA) during brain development (Frost & Cadet, 2000). This interference with the DA system is, in turn, postulated to have a significant effect on cortical neuronal development, and may lead to morphologic deviations in several brain structures (particularly the striatum and several limbic structures). Overall, there are too few published neuroimaging studies on the effects of PME in humans to draw any definitive conclusions regarding the brain systems most affected by PME. However, despite the limited evidence, diverse methodology, and small sample sizes, some consistent patterns of abnormalities have emerged: It appears that the development of areas of the brain

responsible for the regulation of attention, memory, visual-motor integration, and executive functioning are particularly vulnerable to PME. The striatum, specifically, seems to be susceptible to structural and metabolic alterations as a result of PME (Chang et al., 2004; Smith et al., 2001).

Recently, the IDEAL study has begun systematic documentation of some of these functional and behavioral deficits in infants with PME. Findings include poor movement quality, decreased arousal, increased stress, and attention difficulties (LaGasse et al., 2011). Support for the clinical significance of these abnormalities is also beginning to surface: There are suggestions that PME may have significant neurocognitive effects even beyond that of frequently co-occurring alcohol exposure (Sowell et al., 2010). Unfortunately, long-term developmental data for older controlled cohorts is scarce; however, existing research suggests that children with PME may be more vulnerable to disorders of executive function, manifested by externalizing behavioral problems and aggression (Diaz et al., 2014; LaGasse 2012).

In conclusion, study of the effects of PME is still evolving and further investigation is needed to confirm existing findings. The reviewed literature suggests that children exposed to MA in utero may experience a range of neurotransmitter and neurostructural alterations, with potential long-term cognitive and behavioral sequelae. Currently, we do not know how data from different imaging modalities relate to each other in this literature, and we know little about how imaging findings correspond to child affective, behavioral, and cognitive functioning.

Rationale, Specific Aims, and Hypotheses

An extensive literature search yielded no evidence of published South African research that has examined functional and neurobiological imaging data alongside

neurocognitive profiles in children exposed to MA in utero. Moreover, globally, there are few studies that have examined resting state connectivity specifically in pediatric populations in low and middle-income countries.

The proposed study is nested within an ongoing prospective longitudinal cohort study investigating the structural and cognitive correlates of prenatally MA-exposed children in Cape Town. The aim of this larger study is to investigate: (1) whether cognitive functioning is impaired in children with a history of PME and, if it is, (2) whether there are any significant correlations with impairments/defects, detected via sMRI, DTI, and MRS, in the associated areas.

Given the known impact of MA exposure on striatal structures in adult users, and limited evidence for the same in children, the design of the current study allowed for the exploratory testing of these specific hypotheses:

1. Children with a history of PME will show impaired performance on measures of IQ, memory, language, and visual-motor integration and co-ordination when compared to typically developing, demographically-matched controls.

2. Deficits in IQ, memory, language, and visual-motor integration and co-ordination will be related to the effects of PME and not to the effects of potential confounding variables, such as prenatal alcohol exposure and maternal level of education.

3. Children with a history of PME will show disrupted functional intrinsic connectivity in frontal cortical, visuomotor and striatal networks when compared to typically developing, demographically-matched controls.

Methods

Design and Setting

The study featured a cross-sectional quasi-experimental case-control design. As noted earlier, this study forms part of a larger prospective longitudinal research programme. The aim of that programme is to investigate the effects of PME on neurodevelopment and cognition by gathering, across several testing occasions stretching over several years, neuropsychological and neuroimaging data from the same cohort of children with PME.

Participants

The sample comprised 45 children, between the ages of 6 and 7 years. Participants were assigned to either the PME group (n = 23; 10 boys, 13 girls) or the control group (n = 22; 10 boys, 12 girls).

Recruitment and eligibility criteria. Mothers of the 45 children included in this study were recruited by means of telephonic interviews, with assistance from the local school and care center, and resident social worker. The PME group comprised children whose mothers had disclosed that they had used MA during pregnancy. The control group was aggregate matched to the PME group on the following variables: age, sex, background, birth circumstances, gestation, and schooling. Both the PME and control groups comprised children who were born to women residing in a low socioeconomic status (SES), predominantly Cape Coloured (i.e., mixed ancestry) area of Cape Town.

Participants were excluded from the study if they, in the past or at the time of the assessment, had a pathology that might have influenced their neurocognitive functioning. These pathologies included: prematurity (i.e., a gestational age of less than 36 weeks); severe cases of neonatal jaundice, bacterial meningitis, or hypoglycemia; head injury; pre- or postnatal insults such as hypoxic ischemic encephalopathy; and other syndromes/illnesses

with known associated developmental delay. Because the parent study contained a neuroimaging component, participants with a declared presence of implanted metal in the body were also excluded.

In view of the limitations of research based on prenatal polysubstance exposure, participants whose birth mothers admitted to regularly abusing recreational drugs other than MA (e.g., cannabis, cocaine, opiates) during pregnancy were excluded from the study.

Measures

Although the standardized measures included in this study have been widely used in South African clinical research and practice, most of them have few or no published South African norms. This lack of locally appropriate normative data did not affect the aims, design, or power of the project, because performance for participants with a history of PME was compared to that of non-exposed control participants, and not to published normative data.

All tests were administered to participants in the language of instruction used at school (viz., either English or Afrikaans). Where standardized Afrikaans test instructions were not available, the original English instructions were translated by an first-language Afrikaans-speaking Clinical Psychology Master‟s student and checked by a bilingual (English and Afrikaans) doctoral-level neuroscientist at the Cape Universities Brain Imaging Centre (CUBIC) with extensive experience of the children in this cohort. Table 3 summarizes the cognitive domains assessed by each neuropsychological measure.

Sociodemographic questionnaire. This 41-item instrument (see Appendix A), created specifically for the larger study within which this one is nested, includes questions pertaining to various demographic variables (e.g., participant‟s and parent‟s age, sex, health history, home language, and educational attainment). The last section of the questionnaire includes items pertaining to the participant‟s birth details (such as gestation period and birth

weight), current anthropometrics (weight, height, head circumference, etc.), and medical history.

Table 3
Cognitive Outcome Variables

Domain / Variables	Definition
KABC-II General Intellectual Functioning	
Non-Verbal Index	Non-verbal IQ derived from performance of 5 subtests
Hand Movements	Total correctly copied hand sequences
Block Counting[a]	Total correctly counted block sequences
Conceptual Thinking[b]	Total correctly identified pictures
Triangles	Total correctly constructed geometrical shapes
Story Completion	Total correctly completed picture sequences
Pattern Reasoning	Total correctly identified pattern sequences
KABC-II Learning Ability	
Atlantis[c]	Number of correctly identified items on immediate recall trial
Atlantis Delayed[c]	Number of correctly identified items on the delayed recall trial
Language	
BNT-SA-SF	Total number of correctly named items
Visuospatial and Psychomotor Ability	
Beery VMI	Total correctly copied designs
Visual perception	Total correctly matched designs
Motor Coordination	Total correctly drawn designs
Grooved Pegboard Test	
Insertion times DH	Total correctly inserted pegs (dominant hand)
Insertion times NDH	Total correctly inserted pegs (non-dominant hand)
Drops DH	Total drops (dominant hand)
Drops NDH	Total drops (non-dominant hand)

Note. KABC-II = Kaufman Assessment Battery for Children (Second Edition); BNT-SA-SF = Boston Naming Test (South African Short Form); Beery VMI = Beery Test of Visual-Motor Integration; DH = dominant hand; NDH = non-dominant hand.
[a]Only 6-year-olds completed the Conceptual Thinking subtest for the KABC-II NVI.
[b]Only 7-year-olds completed the Block Counting subtest for the KABC-II NVI.
[c]The KABC-II Atlantis and Atlantis Delayed subtests were added to the battery as a means to assess learning and memory. These subtests are not part of the KABC-II NVI.

Drug intake questionnaire. This 24-item questionnaire (see Appendix B), created specifically for the larger study within which this one is nested, assesses the duration, frequency, and severity of MA use by mothers during pregnancy. It also screens for use of alcohol, cigarettes, and other recreational drugs during pregnancy.

The Beery Developmental Test of Visual-Motor Integration. The Beery VMI (4th edition; Beery, 1997) is a 27-item paper-and-pencil test designed to assess the extent to which

children aged 2 years and older are able to integrate their visual and motor abilities. The participant is asked to copy 27 geometrical designs as accurately as possible. The designs range in complexity from very simple (e.g., a straight line) to quite complicated (e.g., cubes, overlapping circles). The VMI also includes two supplemental tests (each featuring as stimuli the same 27 geometric forms as the main test) that are used to assess, respectively, aspects of visual perception and motor coordination. The Visual Perception Test requires the child to identify, from a selection of similarly-shaped targets, the exact match for each of 27 geometric forms. The Motor Coordination Test requires the child to trace the stimulus forms, using a pencil, without going outside double-lined paths.

Although cross-cultural validity for the Beery VMI has not yet been established, the test is, on the face of it, virtually culture-free, utilizing geometric shapes instead of letters and numbers. The test does have strong content, concurrent, and predictive validity, however (Beery, 2004). An average of Anastasi"s (1988) three major reliability error sources (inter-scorer, internal consistency, and test-retest) indicated overall reliability estimates of .92 (VMI), .91 (Visual Perception), and .90 (Motor Coordination; Beery, 2004). Furthermore, there are no statistically significant effects of sex, ethnicity, socioeconomic status, and place of residence (urban versus rural) on test performance (Brown & Rodger, 2008).

Kaufman Assessment Battery for Children - Second Edition. The KABC-II (Kaufman, 2004), designed for use in children and adolescents between the ages of 3 and 18 years, yields an IQ measure that reflects overall processing and cognitive abilities. It is divided into three levels: subtests appropriate for children aged 3, aged 4-6, and aged 7-18.

The set of KABC-II subtests used here were, with one exception, those that constitute the instrument"s Nonverbal Scale (NVS). The NVS permits valid assessment of children who have limited English proficiency, and is comprised of only those subtests that can be administered in pantomime and responded to motorically. The NVS measures three broad

cognitive domains in children aged 4-18: sequential processing, simultaneous processing, and planning ability. The sum of performance across the different subtests/domains within the NVS yields a global functioning score, the Nonverbal Index (NVI).

The NVS is fairly stable; the developers report average test-retest coefficients of .72 and .87 for the NVI at ages 3-6 and 7-18, respectively. Internal consistency coefficients for the NVI are reported as .90 and .92 at ages 3-6 and 7-18, respectively. Construct validity of the KABC-II is supported by factor-analytic studies described in the test manual (Kaufman, 2004). In South Africa, the KABC-II appears in a survey of instruments utilized by South African psychologists (Foxcroft, Paterson, Le Roux, & Herbst, 2004). Although there are no published local normative data for the KABC-II, it remains one of the less culturally loaded IQ tests available (Greenop, Fry, & de Sousa, 2012). Below, I give basic information about each KABC-II subtest used in the current research.

Hand Movements. This subtest allows for the assessment of sequential processing and short-term memory solely in the visual-motor channel. The child is requested to copy the examiner‟s precise sequence of taps on a table with the fist, palm, or side of the hand.

Block Counting. This subtest provides a measure of both simultaneous and visual processing with regard to spatial relationships, and it assesses conceptualization as well as visualization. The child counts the exact number of blocks in pictures of stacks of blocks that are configured so one or more of the blocks is partially or completely hidden from view.

Conceptual Thinking. This subtest assesses classification and induction abilities. The child is presented with a set of four pictures, and is asked to identify the one that does not belong in the set. Some items in the pictures are meaningful stimuli, while others are more abstract.

Triangles. This subtest assesses spatial relations and visualization. The child is first requested to assemble a set of various colorful plastic shapes, matching a model constructed

by the examiner. Then, for the more challenging items, the child is given two or more foam triangles (colored blue on one side, and yellow on the other) and asked to assemble them to match a picture of an abstract design.

Pattern Reasoning. This subtest requires the manipulation of abstract designs and symbols, thus assessing induction and visualization abilities. The child is presented with a series of stimuli (either abstract or meaningful) that form a logical, linear pattern, with one stimulus missing. The child is then required to complete the pattern by selecting the correct stimulus from a range of four to six options.

Story Completion. This subtest assesses induction, visualization, and general sequential reasoning by asking the child to sequence pictures in a logical, narrative order. The child is shown a booklet with a set of pictures that tell a story; however, one to three pictures are missing. A set of pictures is then given to the child, from which only the ones that are needed to complete the story must be selected and placed in the correct locations.

The KABC-II subtests listed above are those that constitute the NVS. To assess memory and learning ability, the KABC-II Atlantis and Atlantis Delayed subtests were added to the current battery.

Atlantis. This subtest is designed to measure a child‟s ability to learn new information (through associative memory) using colorful, interesting stimuli. The examiner teaches the child a set of nonsense names for pictures of four fish, four plants, and four shells. The child is then asked to point to the specified picture (out of an array of similar or previously presented targets) when it is named. During the assessment, the examiner provides feedback each time the child makes an error, as each picture has no symbolic relationship to its paired nonsense word. Because the subtest provides no context for learning cues, the feedback for each error prevents the child from getting locked into incorrect learning.

Atlantis Delayed. This subtest is administered 15-25 minutes after Atlantis, and the child is not forewarned that it is coming. The child demonstrates delayed recall of paired associations made earlier by pointing to a picture of the fish, plant, or shell that is named by the examiner. This subtest assesses the ability to retrieve newly encoded information after a filled delay.

Boston Naming Test (South African Short Form). The BNT-SA-SF is a test of confrontation naming ability, based on the original 60-item BNT (Kaplan, Goodglass, & Weintraub, 1983, 2001). The BNT-SA-SF consists of 15 black-and-white drawings that are presented in order of increasing difficulty, ranging from simple everyday objects (e.g., *comb*) to less familiar objects (e.g., *sphinx*). Upon presentation of the stimulus, participants are given 20 seconds to produce a spontaneous response, after which a semantic cue (e.g., „it is used on hair" for *comb*) is given. If the participant is still unable to answer, a phonemic cue is offered (e.g., „it starts with the sound |*ko*|"). After the full test is administered, the examiner returns to the items that were failed, and asks the participant to select a correct answer from four multiple-choice options that are read aloud.

A recent study of the BNT-SA-SF's psychometric properties found good test-retest reliability (Spearman's $r = .39$, $p = .033$), and good correlation with the full 60-item test (Spearman's $r = .54$, $p = .002$; Baerecke, 2010).

Grooved Pegboard Test. The GPT (Trites, 1977) is a manipulative dexterity test that is used to assess complex visual-motor coordination. The equipment consists of a pegboard with 25 holes, with randomly positioned slots. Pegs with a key on one side must be rotated to match the slot at a hole before they can be inserted. Participants are instructed to place all pegs into the 25 holes, picking up one at a time, and using just one hand (dominant hand first, and then non-dominant hand). The examiner records time of completion for the first line, total completion time, number of drops, and number of pegs placed.

The GPT‟s validity and reliability are well established through generous research in both healthy and patient populations (see, e.g., Maj et al., 1993; Ruff & Parker, 1993). For instance, it has good test-retest reliability (.91 and .85 for right and left hands, respectively; Wang et al., 2011). Cross-cultural validity for the GPT has been verified for South African children and adolescents, with no significant between-race, -language, or -sex differences (Ferrett et al., 2014).

Procedure

The research assistant (RA) at CUBIC carried out the recruitment, screening, data gathering, and data capturing for Phase I of the study (described below). Similarly, the imaging team at CUBIC was responsible for all scanning procedures (described below under the heading *Image Acquisition*). I was responsible for all the procedures outlined in Phase II of the study (described below).

Phase I. The RA contacted each potential participant‟s parent/caregiver telephonically, informed him/her about the study, and screened the participant according to the eligibility criteria outlined previously. Upon verbal agreement and expressed willingness to participate in the study, the RA scheduled an appointment for each individual participant and his/her caregiver.

On arrival at CUBIC, the RA reintroduced the parent to the study, explained the purpose of the study, and obtained verbal assent (from the child) and written consent (from the parent). The parent also provided a detailed demographic, medical and socio-economic history. In cases where the birth mother was absent or unable to attend, collateral information was gathered from the family member(s) present (n = 19), and followed up with a telephonic interview with the mother (where possible). Anthropometrics (including weight, height, and head circumference of the child) were also determined. As some of the MA-exposed children

recruited into this study were no longer living with their biological mother, the term „mother" and „parent" (used interchangeably) will, from here onwards, denote both caregiver and/or biological mother.

After the interview with the mother, participants were accompanied to a separate room to prepare, using a mock scanner, for image acquisition. Due to the loudness of the scanner and anticipated anxiety of the child in scanning situations (Malisza, Martin, Shiloff, & Yu, 2010), the RA was trained to familiarize the participant with the procedure. The scan process was simulated to encourage minimal distress and movement – this entailed a demonstration of positioning in the mock scanner, as well as familiarization with the audio environment via prerecorded sound snippets.

As no functional tasks were administered during the scan, each participant was provided with the option of selecting an animated movie (visible through a head-coil-mounted mirror) which was played after the completion of the resting state sequence. Parents were asked to sit alongside their children throughout the scan.

Image acquisition. Resting-state fMRI (RS-fMRI) echo planar imaging (EPI) data were acquired for 6 minutes from a 3T Allegra Siemens scanner (MAGNETOM Allegra, Erlangen, Germany) at CUBIC (slice thickness 4 mm; TR 2000 ms; TE 30 ms; voxel size: 3.4×3.4×4.0 mm). Participants were asked to close their eyes and relax during the resting state sequence. A high resolution motion-navigated T1 multiecho magnetization-prepared rapid acquisition with gradient echo (MP-RAGE) structural scan (repetition time of 2,530 ms; 4 echo times of 1.5 ms, 3.2 ms, 4.8 ms and 6.5 ms; flip angle of 7°; matrix size of 224×224×144; field of view of 224 mm; voxel size of 1.3×1.0×1.0 mm) was then acquired for anatomical localization. Other scan sequences, including DTI and MRS, were also obtained. Analyses of data from those sequences are not reported here. Total scan time was approximately 35 minutes.

Phase II. Within 8-20 weeks of the scan, I contacted each participant‟s parent telephonically and scheduled an appointment for a cognitive assessment at Red Cross Children‟s Hospital (RXH). Where possible, and to increase reliability of the data, I requested the presence of the birth mother so that an additional substance intake questionaire (described under *Measures*) could be administered.

On the day of testing, I reminded the attending parent of the purpose of the study and of their child‟s role in it. In consideration of privacy and confidentiality, I accompanied the participant to a separate desk to watch a children‟s television show for the duration of the parent‟s interview. I then interviewed the parent using the timeline follow-back method, a valid and reliable means of gathering retrospective data on the duration, frequency, and severity of alcohol and drug exposure during pregnancy (Jacobson, Chiodo, Sokol, & Jacobson, 2002). Post-interview, I requested that the parent leave the room for the duration of the child‟s neurocognitive assessment. Snacks and refreshments were provided in the waiting area.

Neurocognitive assessment. Prior to the commencement of the formal assessment, I talked each participant through the procedure and gave him/her information regarding its content, duration, and purpose (within reason; see *Ethical Considerations* section below) so as to ameliorate any distress or anxiety s/he may have experienced. I then gave the participant an opportunity to ask questions. I administered all instructions in the child‟s language of educational instruction (either English or Afrikaans). Two fairly recent South African studies suggest that even if the home language and the medium of instruction are not the same, the more reliable language for the individual to be tested in is that in which s/he has received formal education (Bethlehem, de Picciotto, & Watt, 2003; Shuttleworth-Edwards, Donnelly, Reid, & Radloff, 2004).

To facilitate rapport building and familiarity, I administered the cognitive tests in the following order: Beery VMI, KABC-II subtests, BNT-SA-SF, and the GPT. The Beery VMI is straightforward and interactive, the KABC-II is more time-consuming and has a higher cognitive demand, and the BNT-SA-SF and GPT are both quick and fairly simple to complete. Depending on the individual needs and concentration span of the participant, I provided two to three breaks throughout the course of the assessment. Snacks and refreshments were also supplied during these breaks.

Upon completion of testing, I escorted each participant to his/her parent, who was fully debriefed and thanked for cooperating and participating. Prior to leaving, I gave participants and their parents an opportunity to discuss any concerns or express opinions regarding the research experience. In cases where commentary on the participant‟s performance was requested, I arranged telephonic feedback sessions.

Ethical Considerations

This study adhered to the protocols and ethical guidelines for research as outlined by the Health Professionals Council of South Africa (HPCSA) and the University of Cape Town‟s (UCT) Codes for Research involving Human Subjects, as well as the guidelines contained in the Declaration of Helsinki (World Medical Association, 2008). Ethical approval for the parent study was granted by the Human Research Ethics Committee of UCT‟s Faculty of Health Sciences (Ref#: 235/2009; see Appendix C).

Due to the stigma associated with MA use and exposure, and the young age of the participants, I only fully debriefed the parents of child participants as to the topic and purpose of the research. I told child participants that they were participating in a „brain study,‟ rather than a study on the effects of PME. Informed consent and assent were obtained as part of the parent study prior to commencement of Phase I (see Appendices D and E, respectively). I

informed children and their parents that their participation was entirely voluntary, and that they had the right to withdraw at any point during the study.

To ensure confidentiality, all the imaging data collected at CUBIC was anonymized prior to analysis, and archived on a research-dedicated database at the Centre for High Performance Computing in Cape Town. No unauthorized access to study data was permitted. All the information and test results that were gathered during the interview and assessment, respectively, were kept strictly confidential. Furthermore, to ensure anonymity, I allocated each participant a code number under which all his/her data were stored.

Parents were informed in the consent form, however, that parental consent may be requested for access to additional medical records and/or transfer of obtained data to a medical expert should such a need be identified. Thus, in instances where significant social, psychological, or learning problems were identified (which, in the current study, happened once), I notified the principal investigators of the larger study, and a referral to the relevant organization was made.

There were no significant risks attached to participation in this study. In instances where participants experienced substantial distress or anxiety, as was occasionally the case during the MRI scan, the procedure was stopped. The parents and children who participated in this research incurred no financial costs pertaining to their involvement. In instances where the parent and/or child had to take leave from work/school to participate, I provided a letter to account for their absence. Transport to and from all appointments at both CUBIC and RXH was arranged and paid for by the parent study. Participants and their parents also received remuneration in the form of school supplies (to the value of ZAR80) and supermarket gift vouchers (to the value of ZAR70), respectively, for both Phase I and Phase II**.**

Data Management and Statistical Analyses

Neuropsychological data preprocessing and analysis. Prior to any formal statistical analyses, I checked and cleaned the data. For the Beery VMI, KABC-II, BNT-SA-SF, and GPT, I followed standard scoring procedures as set out in the respective test administration manuals. With the exception of the BNT-SA-SF and GPT (where raw scores were converted to *z*-scores), age-adjusted scaled scores (with a mean of 10 and a standard deviation of 3) were used in the final analyses. I used SPSS version 22.0.0 to analyze the data. No missing data were identified for the cognitive outcome variables. In instances where outliers (i.e., scores falling more than 3 *SD* from the mean) were identified ($n = 3$), these data were inspected and thought to represent the true performance within the population of scores, and thus left unadjusted.

The analysis began with an exploration of the data and testing of assumptions that underlie inferential statistical analyses. Unless otherwise stated in the Results section, all assumptions for the relevant analyses were upheld. In instances where data were not normally distributed, I employed non-parametric statistical measures. Then, to examine whether the PME and control groups were well matched on a specific set of sociodemographic variables, I used a series of one-tailed *t*-tests to compare scores on all continuous variables (i.e., age and mother‟s level of education), and a series of chi-square analyses to compare scores on all categorical variables (i.e., sex, language, grade, handedness).

At the next data analytic step, independent sample *t*-tests (one-tailed), or, where appropriate, Mann-Whitney *U* tests (one-tailed), sought to detect between-group differences on the neurocognitive outcome variables. I used the Šídák multiple comparison correction (Abdi, 2007) to protect against inflated Type I error resulting from multiple pairwise comparisons. Finally, linear regression modeling sought to indicate to what extent the

relation between PME and each neurocognitive outcome variable was influenced by potentially confounding sociodemographic and anthropometric variables.

For all analyses, the threshold for statistical significance (α) was set at .05. To allow for meaningful interpretations of significant results, I also reported an estimate of effect size (in this case, *r*), thresholded as follows: small (*r* = .10), medium (*r* = .30), large (*r* = .50), and very large (*r* = .70; Rosenthal, 1996).

fMRI data preprocessing and analysis. RS-fMRI BOLD data were preprocessed and analyzed using the Analysis of Functional Neuroimaging (AFNI) toolkit (http://afni.nimh.nih.gov/; Cox, 1996) and tools from the Functional MRI of the Brain (fMRIb) Software Library (FSL; Smith et al., 2004; Woolrich et al., 2009).

Preprocessing. Figure 2 is a flow diagram outlining each of the preprocessing steps. The first 4 volumes of the EPI were removed to account for magnetic inhomogeneity effects. The EPIs were placed into standard space through application of a warping matrix generated by the linear registration of the T1 dataset into Talairach space, using the template for 4.5 – 8.5 year olds provided by the McConnell Brain Imaging Centre (Fonov et al., 2011). To minimize spatial smoothing, motion parameters (generated from aligning each volume of the EPI time series to the last volume), the warping matrix (generated from transforming the T1 into Talairach space), and the EPI to T1 co-registration matrix were simultaneously applied to the BOLD. EPI voxels were then resampled to 3mm isotropic, and spatially blurred using a 6mm full width at half maximum (FWHM) Gaussian kernel. A bandpass filter was applied to restricted BOLD time series data to the low frequency (0.01-0.1 Hz) range.

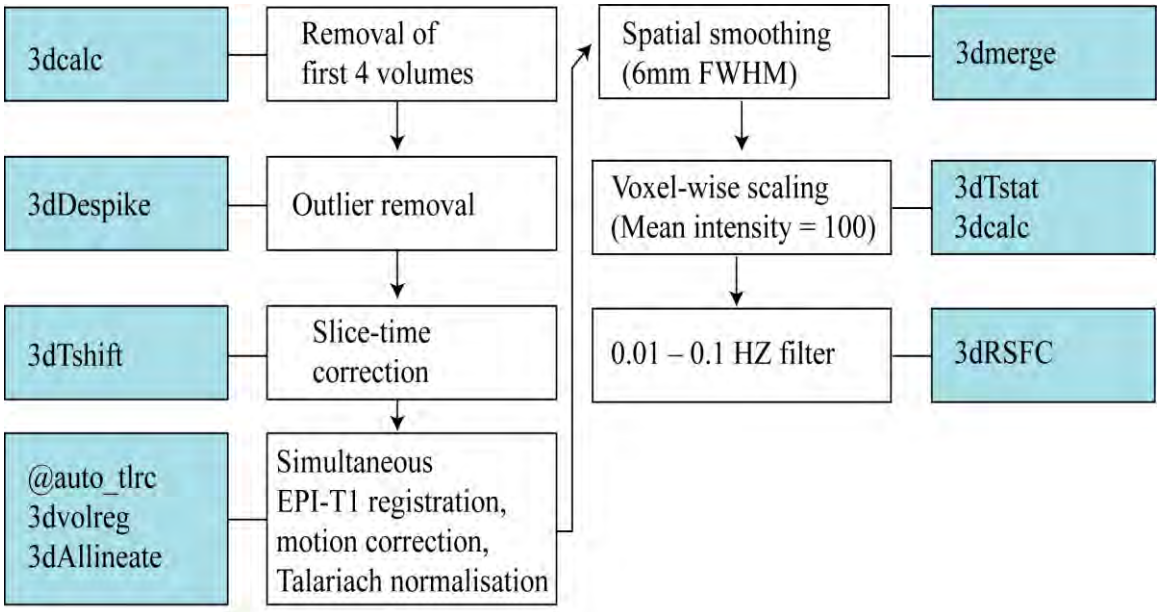

Figure 2. Schematic of RS-fMRI preprocessing pipeline – sequence and AFNI tools employed for each of the preprocessing steps.

Independent components analysis (ICA). A probabilistic group-level ICA (Beckmann & Smith, 2004) was then implemented in MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components), part of FSL (see Figure 3 for a schematic of ICA of fMRI data). The ICA is a statistical technique that separates a set of signals into independent spatiotemporal components (Beckmann & Smith, 2004). Currently, there is little consensus on how to select the optimal number of components; however, methods to do so have been proposed (i.e., Calhoun et al., 2001; Li, Adali, & Calhoun, 2007).

The number of components identified by the ICA was set to 20, 25 and 35, in keeping with the typical dimensionality of resting-state ICA studies reported in the literature. After visual inspection of the resulting networks by MK and JI, the output of the 35-network ICA was selected for further group comparisons, based on the correspondence of the networks with canonical networks reported in the literature (Beckmann et al., 2005; Smith et al., 2009). The melodic ICA applies a high-pass filter setting of 100 sec (full width at half maximum) which was used to reduce very-low frequency artifact such as scanner drift.

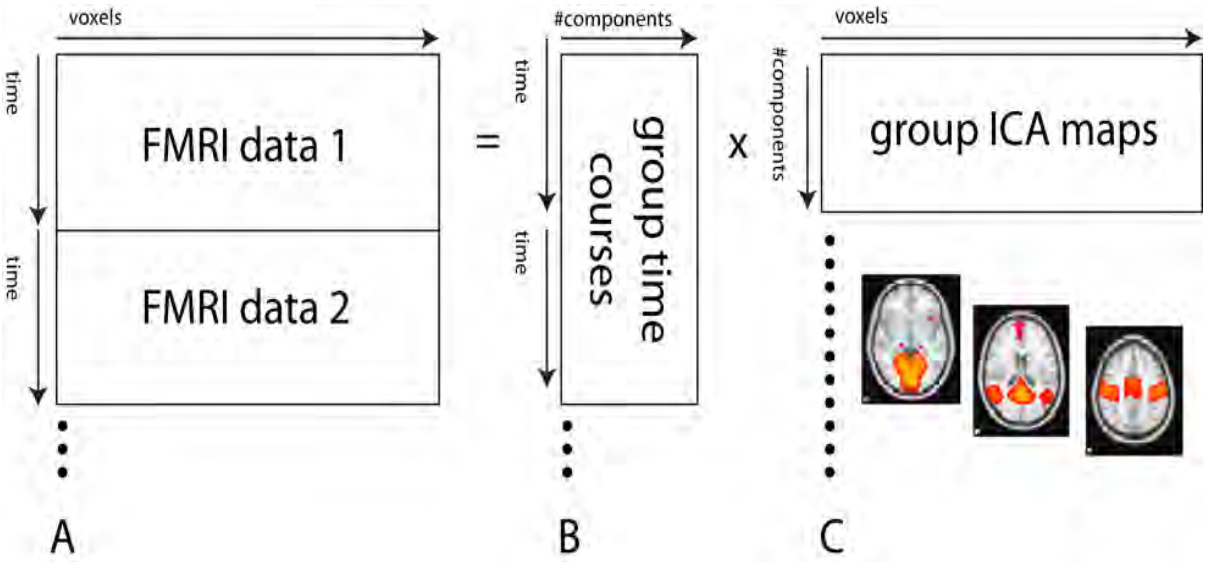

Figure 3. Schematic of independent components analysis of fMRI data. In A, individual fMRI data sets are temporally concatenated. The ICA then combines these and converts them into a new data set comprising group time courses (B) and group spatial maps (C) for all the components. The RSNs are selected from the group spatial maps. Reproduced from Beckmann, Mackay, Filippini, and Smith, 2009.

The BOLD from each of the 26 participants was temporally concatenated, with variance normalization applied to the BOLD, prior to extracting 35 spatially orthogonal networks for the entire sample. The group spatial maps for these RSNs were then utilized as input for the dual regression, as outlined below.

Dual regression analysis. The order of the spatiotemporal components extracted using ICA is arbitrary. To conduct comparisons between networks for the PME and control participants, it was therefore necessary to identify networks at the individual-subject level that corresponded to those extracted from the group ICA. This identification was achieved for this dataset using the dual regression methodology (Beckmann et al., 2005). FSL was used to carry out this step in a two-stage process. At the first stage, group-level components were regressed against the BOLD for each participant to identify corresponding subject-level time courses for each of the group ICA components (Cole et al., 2010). At the second stage, time courses from stage one were subsequently regressed once again from each participant's BOLD, to identify spatial maps for each participant that corresponded to the group-level maps (Cole et al., 2010; Zuo et al., 2010).

Between-group comparisons. The randomize tool in FSL was then used to perform comparisons between the control group and the PME group for all RSNs of interest (Winkler, Ridgway, Webster, Smith & Nichols, 2014**)**. This analysis used the spatial map images produced in stage two of the dual regression analysis to identify areas in the brain where the measure of RSN integrity was greater/weaker in the control group than in the PME group. To specify the desired comparisons, a general linear model (GLM) was incorporated into the randomize instruction by means of a design matrix specifying these particular contrasts: A > B (areas in which the PME group showed greater network integrity than the control group) and B > A (areas in which the control group showed greater network integrity than the PME group). Both of these contrasts adjusted for the average motion per participant, as well as the mean network *Z* scores, as specified in the design matrix. The null distribution was simulated for each contrast by means of Monte Carlo estimation, using 5000 permutations (Bellec, Rosa-Neto, Lyttelton, Benali, & Evans, 2010).

Results

Child Sample Characteristics

Table 4 presents the sociodemographic and anthropometric information for the two groups, as well as maternal sample characteristics. For all continuous data, I used Levene‟s test to assess homogeneity of variance across the two groups, and examined the residual plots to check for departures from normality. Unless otherwise indicated, the assumptions of normality and homogeneity were upheld for all data distributions. Hence, I compared the sociodemographic and anthropometric differences between the PME and control groups using the Pearson Chi-square test and independent samples *t*-tests, as appropriate.

Sociodemographic variables. Regarding age at testing, a two-tailed independent samples *t*-test detected a significant between-group difference, associated with a moderate

effect size. Specifically, children in the control group were slightly older than those in the PME group. Regarding sex distribution, Pearson‟s chi-squared test detected no significant between-group differences, although girls outnumbered boys in both the PME and control groups.

Regarding language, Afrikaans was the mother tongue of all participants. The language data recorded in Table 4, however, are those relating to medium of school instruction (and, hence, language used in the assessment). Again, Pearson‟s chi-squared test detected no significant between-group differences in terms of language distribution, although the proportion of Afrikaans-administered participants was higher than that of English-administered participants in both the PME and control groups.

Regarding level of education, I defined this variable as the grade in which the participant was enrolled on the date of testing. As Table 4 shows, most participants were in Grade 1, and the ratio of Grade R to Grade 1 to Grade 2 participants varied slightly across both groups. However, Pearson‟s chi-squared test detected no significant between-group differences.

Anthropometric variables. Independent samples *t*-tests detected no significant between-group differences regarding handedness, height, or head circumference. However, participants in the PME group weighed significantly less than those in the control group, a difference associated with a very large effect size (see Table 4).

Table 4
Demographic and Anthropometric Sample Characteristics for Participants and Mothers (N = 45)

	Group				
Variable	PME (n = 23)	Control (n = 22)	t / X^2	p	ESE
Child					
Age	6.91 (0.42)	7.24 (0.38)	2.79	.008**	.85
Sex (M:F)	10:13	10:12	0.02	.89	.02
Language (Eng:Afr)	5:18	7:15	0.58	.45	.11
Education (GrR:Gr1:Gr2)	10:12:1	6:14:2	1.47	.48	.18
Handedness (L:R)	1:22	0:22	0.93	.34	.15
Weight (kg)	18.67 (2.44)	20.65 (3.45)	2.17	.04*	.68
Height (cm)	92.50 (8.32)	90.50 (7.04)	-0.83	.41	.27
Head circumference (cm)	51.41 (2.00)	52.63 (2.09)	1.98	.06	.61
Mother					
Education (years)[a]	8.71 (1.35)	10.35 (2.30)	2.79	.008**	.89
Employment status (yes/no)[b]	4:17	12:4	5.80	.02*	-.38
Income brackets[c]	12:3:1:0	10:2:4:4	5.81	.12	.40
<10 000 (n, %)	12 (75.00)	10 (50.00)			
10 000 – 20 000 (n, %)	3 (18.75)	2 (10.00)			
20 000 – 40 000 (n, %)	1 (6.25)	4 (20.00)			
40 000 – 60 000 (n, %)	0	4 (20.00)			
Marital status[d]	17:1:0:2:0	12:6:1:0:2	9.42	.05	.48
Single (n, %)	17 (85.00)	12 (60.00)			
Married (n, %)	1 (5.00)	6 (28.57)			
Living with partner (n, %)	0	1 (4.76)			
Divorced (n, %)	2 (10.00)	0			
Widowed (n, %)	0	2 (9.52)			
Cigarette use (yes/no)[e]	18:4	6:16	13.21	< .001**	.55
Alcohol use (yes/no)[f]	6:16	1:21	4.25	.04*	.31

Note. In some cells, means are presented with standard deviations in parentheses; otherwise, data are presented in raw numbers/percentages. PME = prenatal methamphetamine exposure; ESE = estimate of effect size (r); M = male; F = female; Eng = English; Afr = Afrikaans; Gr = grade; L = left; R = right. The estimate of effect size was calculated using either r or ϕ, depending on whether an independent samples t-test or a Chi-square test was employed.
[a]Data missing for 2 mothers in PME group, and 2 mothers in the control group.
[b]Data missing for 2 mothers in PME group, and 6 mothers in the control group.
[c]Data missing for 7 mothers in PME group, and 2 mothers in the control group.
[d]Data missing for 2 mothers in the PME group, and 1 mother in the control group.
[e]Data missing for 1 mother in the PME group.
[f]Data missing for 1 mother in the PME group.
*p < .05. **p < .01. ***p < .001.

Maternal Sample Characteristics

Analyses detected significant between-group differences regarding years of completed education, employment status, cigarette use, and alcohol use (see Table 4). Specifically, mothers of children in the control group had reached a higher level of education than those in the PME group (although, on average, mothers in both groups had attained no more than a high school education); this difference was associated with a large effect size. Similarly, a significantly greater number of mothers in the control group (compared to the PME group) were employed. Again, this difference was associated with a very large effect size.

Regarding level of alcohol and cigarette exposure during pregnancy, there were, as expected, significant between-group differences. An important note here is that these data were categorical in nature. As stated earlier, the aim of the study was to collect information regarding the duration, frequency, and amount of drug, alcohol, and cigarette exposure during pregnancy; however, due to the difficulty in collecting accurate retrospective reports, a substantial number of participants simply answered "yes" or "no" to questions about prenatal substance use. Hence, I was only able to use categorical data in this case. Analyses of those data suggested that, overall, significantly more mothers in the PME group smoked cigarettes and drank alcohol during pregnancy. These between-group differences were associated with large and medium effect sizes, respectively.

Cognitive Outcomes

Hypothesis 1. I predicted that, compared to controls, children in the PME group would be impaired on measures of IQ, memory, language, and visual-motor integration and co-ordination. To test this prediction, I explored the descriptive statistics for all cognitive tasks and then assessed between-group differences.

Across the entire dataset (i.e., the two groups‟ data collapsed together), the assumption of independence was met for all cognitive outcome variables. Inspection of the Q-Q plots, however, revealed potential departures from normality for several of those variables. I then ran Shapiro-Wilk tests to assess whether these departures from normality were statistically significant. The assumption of normality was not upheld for four of the KABC-II subtests (Hand Movements, Pattern Reasoning, Atlantis, and Atlantis Delayed) and for the GPT outcome variables. When examining the data distributions for each group separately, however, the analyses revealed that the assumption of normality was not upheld for several other outcome variables (see Table 5). Such within-group analysis was necessary because, given that subsequent analyses involved comparing the groups against one another, what is important is not the overall distribution of the data set, but rather the distribution in each group (Field, 2009).

Table 5
Results for Tests of Normality and Homogeneity of Variance for Cognitive Variables (N = 45)

	Shapiro-Wilk Test		
Cognitive Measure	PME	Control	Levene‟s test
KABC-II NVI	.04*	.82	.87
Sequential Processing			
Hand Movements	.03*	.58	.03*
Simultaneous Processing			
Conceptual Thinking	.23	.69	.76
Block Counting	.34	.07	.26
Triangles	.16	.36	.74
Planning Ability			
Story Completion	.14	.02*	.85
Pattern Reasoning	.05	.13	.79
KABC-II: *Learning Ability*			
Atlantis	.15	.93	.06
Atlantis Delayed	.07	.003**	.52
BNT-SA-SF	.08	.03	.96
Beery VMI	.59	.75	.40
Visual score	.22	.10	.66
Motor score	.03*	.61	.98
Grooved Pegboard Test			
Insertion time DH	.03	.26	< .001***
Insertion time NDH	< .001***	.05*	.01*

Note. Data presented are *p*-values. PME = prenatal methamphetamine exposure; KABC-II = Kaufman Assessment Battery for Children – Second Edition; NVI = Non-Verbal Index; VMI = visual motor integration; BNT-SA-SF = Boston Naming Test (South African Short Form); DH = dominant hand; NDH = non-dominant hand. *$p < .05$. **$p < .01$. ***$p < .001$

Similarly, the assumption of homogeneity, as determined by Levene"s statistic, was not upheld for one of the KABC-II subtests (Hand Movements), and for the GPT dominant and non-dominant insertion time scores for the GPT, respectively (see Table 5). Because the data were not consistently normally distributed, I used the non-parametric Mann-Whitney *U*-test to investigate between-group differences where appropriate. Otherwise, I used independent sample *t*-tests (in instances where the assumption of homogeneity was not upheld, I used separate estimates of variance). To control for inflated familywise error rate as a result of multiple pairwise comparisons, I calculated a Šídák multiple comparison correction [$\alpha_{PC} = 1.0 - (1.0 - \alpha_{FW})^{1/K}$], which resulted in a critical value of $p = .003$ (there were 15 cognitive outcome variables in total).

Table 6 presents descriptive statistics and results of between-group comparisons for the cognitive outcome variables. There were significant between-group differences across most of the KABC-II subtests (constituting sequential processing, simultaneous processing, planning ability, and learning ability), which were associated with large to very large effect sizes (ranging from $r = .55$ to $r = .74$), with the exception of one. Analyses of data from the Conceptual Thinking subtest (which assesses simultaneous processing) detected no significant between-group differences at the corrected *p*-value; these differences neared significance, however ($p = .005$). Overall, as expected, children in the PME group performed more poorly than those in the control group. Moreover, scores on the global IQ index, the NVI, also differed significantly between groups; this difference was associated with a large effect size. Again, children in the PME group achieved a significantly lower score on this measure than did those in the control group.

Regarding performance on the BNT-SA-SF, the analysis detected significant between-group differences that were associated with a large effect size. On average, children with PME named fewer items correctly than did those in the control group.

Table 6
Cognitive Outcome Variables: Descriptive statistics and between-group comparisons (N = 45)

	Group					
Cognitive Measure	PME (n = 23)	Control (n = 22)	t / U	df	p	ESE
KABC-II NVI[a]	27.87 (6.79)	46.23 (7.52)	17.00	43	< .001***	.80
Sequential Processing						
Hand Movements[a]	7.04 (1.49)	10.64 (2.48)	56.52	43	< .001***	.67
Simultaneous Processing						
Conceptual Thinking[b]	5.33 (2.39)	9.50 (2.65)	2.95	14	.005**	.62
Block Counting[c]	6.27 (3.38)	9.72 (1.97)	3.49	27	< .001***	.56
Triangles	5.43 (2.25)	8.77 (2.32)	4.89	43	< .001***	.60
Planning Ability						
Story Completion[a]	4.96 (1.69)	8.23 (1.44)	37.5	43	< .001***	.74
Pattern Reasoning	4.65 (1.87)	8.77 (2.00)	7.13	43	< .001***	.74
KABC-II:*Learning Ability*						
Atlantis	5.65 (1.77)	8.82 (2.97)	4.36	43	< .001***	.55
Atlantis Delayed	6.74 (1.94)	9.59 (2.48)	93.00	43	< .001***	.55
BNT-SA-SF	5.78 (1.67)	8.27 (1.49)	91.50	43	< .001***	.55
Beery VMI	6.78 (2.95)	8.82 (2.59)	2.45	43	.009**	.35
Visual score	6.78 (2.94)	9.59 (2.58)	3.40	43	< .001***	.46
Motor score[a]	7.09 (1.86)	10.18 (1.84)	52.50	43	< .001***	.69
Grooved Pegboard Test						
Insertion time DH[a]	75.00 (24.36)	45.36 (7.35)	42.50	43	< .001***	.71
Insertion time NDH[a]	98.04 (41.18)	54.05 (14.90)	89.00	43	< .001***	.66

Note. Data are scaled score means, with standard deviations in parentheses, except for the BNT and Grooved Pegboard Test, where raw scores are presented. Similarly, the t/U and p values presented here are based on analyses of scaled scores for most variables, and of z-scores for the BNT-SA-SF and Grooved Pegboard Test. PME = prenatal methamphetamine exposure; KABC-II = Kauffman Assessment Battery for Children – Second Edition; NVI = Non-verbal Index; BNT-SA-SF = Boston Naming Test (South African Short Form); VMI = visual-motor integration; DH = dominant hand; NDH = non-dominant hand; ESE = estimate of effect size (in this case, r). Test statistics were either t or U, depending on whether data were normally distributed or not.
[a]The assumption of normality was violated, so the Mann-Whitney U test was used.
[b]Data unavailable for 11 children in the PME group and 18 children in the control group as composite tests for the NVI varied for children aged 6 and those aged 7; specifically, Conceptual Thinking was only administered to children aged 6 years.
[c]Data unavailable for 12 children in the PME group and 4 children in the control group as composite test for the NVI varied for children aged 6 and those aged 7; specifically Block Counting was only administered to children aged 7 years.
*p < .05. **p < .01. ***p < .001

Similarly, children in the PME group generally performed significantly more poorly than those in the control group on the Beery VMI. Specifically, they committed a greater number of errors when asked to copy the series of geometric shapes. The between-group difference for the Beery VMI score was not significant at the corrected p-value; however, it

neared such significance (p = .009). This pattern of performance was repeated at a significant level on both the visual perceptual and motor subtests of the Beery, and was associated with medium and large effect sizes, respectively.

Finally, regarding the GPT, children in the PME group performed significantly more poorly than those in the control group, for both dominant and non-dominant hand removal times. These between-group differences were both associated with very large effect sizes.

Secondary Analyses

Given the discrepancy between home language and language of test administration (Barac & Bialystok, 2012), and the potentially confounding effects of sex (Halpern, 2013) on cognitive outcomes, I conducted secondary analyses to explore the potential impact of within-group differences in language and sex on test performance. I used the non-parametric Mann-Whitney *U*-test to investigate between-group differences where data were not normally distributed. Otherwise, I administered independent sample *t*-tests. Of note here is that the corrected *p*-value (p = .003), adjusted for multiple comparisons, was retained.

There were no significant within-group differences in cognitive performance when comparing English-administered to Afrikaans-administered children: For the control group, *p* ranged from .01 to .44, and for the PME group, *p* ranged from .03 to .50. Similarly, there were no significant within-group differences in cognitive performance when comparing boys to girls: For the control group, *p* ranged from .01 to .48, and for the PME group, *p* ranged from .01 to .46.

Hierarchical Regression Analysis

Hypothesis 2. I predicted that the cognitive deficits observed in the PME group would be related to the effects of drug exposure, and not to the effects of potential confounding variables.

Examination of the relationship between PME, cognitive outcomes, and potential confounding variables began with construction of a correlation matrix (see Table 7). The aim of this analytic step was to assess associations between all the cognitive outcomes and the following potential confounding variables: child‟s age at testing, child‟s weight, maternal education level, maternal employment status, maternal cigarette use, and maternal alcohol use. To increase the strength of PME-related interpretations, variables that were even weakly related (at $p < .10$) to a given cognitive outcome were considered for inclusion in the regression models.

Based on the results of tests of normality, the Pearson *r* coefficient was used for correlations involving child‟s age at testing and weight, whereas Spearman‟s ρ coefficient was used for correlations involving maternal education level, maternal employment status, and maternal cigarette and alcohol use. As Table 7 shows, all of the above-mentioned potential confounders correlated significantly with several cognitive outcomes.

Due to considerations of sample size in relation to the reliability (and power) of the regression model, I selected five predictors (guided by both theory and the correlation matrix data) for inclusion in subsequent regression models: child‟s age at testing, child‟s weight at testing, maternal education level, maternal alcohol exposure, and the main variable of interest, PME status. I included maternal level of education in the models because the between-group differences for that variable were significantly greater than those related to employment status (see Table 4). Furthermore, maternal level of education is highly correlated with employment status, and previous research has found maternal level of education to have a

significant influence on child development (see, e.g., Bornstein & Bradley, 2014). To conserve statistical power, I could not include both cigarette and alcohol exposure in the regression models. I decided to exclude the former because all the mothers in the PME group who used alcohol also smoked, and thus it would be problematic to separate out the effects of the two variables. A recent study corroborates this observed trend, reporting that maternal smoking is associated with an increased risk of prenatal alcohol exposure (Williams, Nkombo, Nkodia, Leonardson, & Burd, 2014).

Table 7
Correlations for Cognitive Outcomes and Potential Confounding Variables (N = 45)

	Child		Mother			
Cognitive Measure	Age[a]	Weight[a]	Education	Employ-ment	Alcohol Use	Cigarette Use
KABC-II NVI	.26 †	.48***	.57***	.41**	-.24	-.58***
Sequential Processing						
Hand Movements	.30*	.41**	.58***	.33*	-.06	-.46**
Simultaneous Processing						
Conceptual Thinking	-.12	.36	.29	.32	.10	-.68**
Block Counting	.03	.40*	.29	.22	-.27	-.36*
Triangles	.24	.45**	.47**	.26 †	-.30*	-.43*
Planning Ability						
Story Completion	.05	.34*	.49***	.45**	-.19	-.53***
Pattern Reasoning	.22	.37*	.53***	.32*	-.32*	-.51***
KABC-II: *Learning Ability*						
Atlantis	.10	.31*	.60***	.47**	.06	-.34*
Atlantis Delayed	.27 †	.14	.22	.28 †	-.18	-.31*
BNT	-.03	.35*	.49**	.45**	-.14	-.37*
Beery VMI	.37**	.41**	.34*	.003	-.04	-.31*
Visual score	.30*	.27 †	.18	-.02	-.12	-.33*
Motor score	.30*	.28*	.30 †	.21	-.22	-.56***
Grooved Pegboard						
Insertion time DH	-.34*	-.26 †	-2.70 †	-.23	.14	.36*
Insertion time NDH	-.09	-.16	-.16	-.11	.06	.30*

Note. Statistics presented are Spearman correlation coefficients (ρ) unless otherwise stated. All tests are 2-tailed. KABC-II = Kaufman Assessment Battery for Children - Second Edition; BNT-SA-SF = Boston Naming Test (South African Short Form); VMI = visual-motor integration; DH = dominant hand; NDH = non-dominant hand.
[a]Statistic presented is Pearson correlation coefficient (r).
†$p < .10$. *$p < .05$. **$p < .01$. ***$p < .001$.

To examine the degree to which the above-mentioned potential confounding variables influenced the association between PME and cognitive outcomes, I conducted a separate hierarchical regression analysis for each of the 15 outcome variables of interest. The confounding variables I wished to control for (child‟s age at testing, child‟s weight at testing, maternal level of education, maternal alcohol exposure) were entered as a block at the first step in the model, and exposure status (PME group versus control group) was entered at the second step.

All assumptions underlying the regression models (viz., multicollinearity [determined by tolerance statistics and the mean VIF value for each model], independence of model residuals [determined by the Durbin-Watson statistic], homoscedasticity [determined by the plot of standardized residuals against standardized predicted residuals], and normality of standardized residuals [determined by visual inspection of the histogram and normal probability plot]) were upheld for each model, unless otherwise specified. Regarding regression model diagnostics, unless otherwise specified Cook‟s distance was within acceptable limits (i.e., < 1), and Mahalanobi‟s distance was below the conventional cut-off of 15, indicating no multivariate outliers (Field, 2009).

Model 1: Predicting performance on the KABC-II Non-Verbal IQ score. At step 1 of the hierarchical multiple regression, I entered the following four predictors: child‟s age at testing, child‟s weight at testing, maternal level of education, and maternal alcohol exposure during pregnancy. Table 8 shows that, at this step, the model was statistically significant, explaining 48.2% of the variance in the KABC-II NVI scores, $F(4, 35) = 8.16$, $p < .001$. The introduction of group status (PME versus control) at step 2 explained an additional 25.6% of the variance in the NVI scores. In the final model, only maternal level of education and group status remained significant predictors of the non-verbal IQ score.

Overall, the final inclusive model accounted for 74.1% of the variance in NVI scores, $F(5, 34) = 19.41$, $p < .001$.

Table 8
Hierarchical Regression Model 1: Performance on the KABC-II NVI[a], predicted by potential confounding variables and group status (N = 45)

Variable Entered	*B*	*SE B*	*β*
Step 1			
Constant	-50.44	24.68	
Child age at testing	6.59	3.38	0.24
Child weight at testing	0.73	0.53	0.20
Maternal education	2.81	0.81	0.49***
Maternal alcohol exposure	-4.25	3.90	-0.14
Step 2			
Constant	20.43	21.63	
Child age at testing	-0.24	2.71	-0.01
Child weight at testing	0.58	0.38	0.15
Maternal education	1.51	0.62	0.26*
Maternal alcohol exposure	0.55	2.93	0.02
Group status	-14.95	2.59	-0.065***

Note. KABC-II NVI = Kauffman Assessment Battery for Children – Second Edition, Non-verbal Index; $R^2 = .48$ for Step 1, $\Delta R^2 = .26$ for Step 2 ($p < .001$).
[a]The Non-verbal Index of the KABC-II constitutes the following subtests: Hand Movements, Conceptual Thinking (for 6-year-olds only), Block Counting (for 7-year-olds only), Triangles, Story Completion, and Pattern Reasoning.
*$p < .05$. **$p < .01$. ***$p < .001$.

Model 2: Predicting performance on the KABC-II Sequential Processing subtest.

I entered the aforementioned potential confounding variables and PME as two separate steps into this hierarchical regression model. Table 9 shows that age at testing, weight at testing, maternal level of education, and alcohol exposure explained 49.7% of the variance in Hand Movements scores, $F(4, 35) = 8.65$, $p < .001$. The introduction of group status at step 2 of the model explained an additional 13.6% of the variance in the outcome scores. In the final model, only maternal level of education and group status remained statistically significant predictors of sequential processing abilities. Overall, the final inclusive model accounted for 63.3% of the variance in Hand Movement scores, $F(5, 34) = 11.72$, $p < .001$.

Table 9
Hierarchical Regression Model 2: Performance on the KABC-II Sequential Processing subtests, predicted by potential confounding variables and group status (N = 45)

Variable Entered	*B*	*SE B*	*β*
Step 1			
Constant	-13.94	5.65	
Child age at testing	1.93	0.77	0.31*
Child weight at testing	0.07	0.12	0.08
Maternal education	0.81	0.18	0.60***
Maternal alcohol exposure	0.23	0.89	0.03
Step 2			
Constant	-1.96	5.95	
Child age at testing	0.78	0.75	0.12
Child weight at testing	0.04	0.11	0.05
Maternal education	0.59	0.17	0.44**
Maternal alcohol exposure	1.04	0.81	0.14
Group status	-2.53	0.71	-0.47***

Note. KABC-II = Kaufman Assessment Battery for Children – Second Edition. R^2 = .50 for Step 1, ΔR^2 = .14 for Step 2 ($p < .001$).
*$p < .05$. **$p < .01$. ***$p < .001$.

Models 3-5: Predicting performance on the KABC-II Simultaneous Processing subtests. I entered the aforementioned potential confounding variables and group status as two separate steps, respectively, into hierarchical regression models for the three KABC-II subtests that measure simultaneous processing ability: Conceptual Thinking, Block Counting, and Triangles.

Model 3: Conceptual Thinking. Table 10 shows that the set of potential confounding variables had no significant predictive value for Conceptual Thinking scores, $F(4, 9) = 0.60$, $p = .67$. The introduction of group status at step 2, however, explained 50.9% of the variance in Conceptual Thinking scores, $F(5, 8) = 4.12$, $p < .01$. In the final model, only child's age at testing and group status were statistically significant predictors of conceptual thinking abilities.

Of note here is that the Conceptual Thinking subtest was administered to 6-year-olds only (as per manual specifications), and so the results from this regression model must be interpreted with caution as the power of the regression analysis was compromised by the reduced sample size ($n = 16$). The effects of small sample size (and, thereby, unequal

distribution of data between exposure groups) were further evidenced by the plot of standardized residuals against standardized predicted residuals, which indicated that the assumption of homoscedasticity was not upheld. Hence, one should exercise caution when attempting to generalize this model beyond this sample (Field, 2009).

Model 4: Block Counting. Table 10 shows that the set of potential confounding variables had no significant predictive value for Block Counting scores, $F(4, 22) = 1.52$, $p = .23$. The introduction of group status at step 2 of the model, however, explained 20.5% of the variance in Block Counting scores, $F(5, 21) = 3.07$, $p < .01$. In the final model, only group status was a statistically significant predictor of block counting abilities.

Of note here is that the Block Counting subtest was administered to 7-year-olds only (as per manual specifications), and so the results of this regression model must be interpreted with caution as the power of the regression analysis was compromised by the reduced sample size ($n = 29$). Visual inspection of the P-P plot of standardized residuals suggested that the assumption of normality was violated. Hence, one should exercise caution when attempting to generalize this model beyond this sample (Field, 2009).

Model 5: Triangles. Table 10 shows that the set of potential confounding variables explained 38.8% of the variance in the *Triangles* subtest scores, $F(4, 35) = 5.56$, $p < .001$. The introduction of group status at step 2 of the model explained an additional 9% of the variance in the outcome. In the final model, only PME status remained a statistically significant predictor of abstract constructional abilities. Overall, the final inclusive model accounted for 47.8% of the variance in Triangles scores, $F(5, 34) = 6.23$, $p < .001$.

Table 10

Hierarchical Regression Models 3-5: Performance on the KABC-II Simultaneous Processing subtests, predicted by potential confounding variables and group status

Variable Entered	*B*	*SE B*	*β*
Model 3: Conceptual Thinking ($N = 16$)[a]			
Step 1			
Constant	5.85	15.49	
Child age at testing	-1.19	2.12	-0.17
Child weight at testing	0.31	0.33	0.32
Maternal education	0.27	0.51	0.18
Maternal alcohol exposure	1.30	2.45	0.16
Step 2			
Constant	31.61	11.89	
Child age at testing	-3.68	1.49	-0.53*
Child weight at testing	0.25	0.21	0.26
Maternal education	-0.20	0.34	-0.14
Maternal alcohol exposure	3.05	1.61	0.37
Group status	-5.44	1.43	-0.91**
Model 4: Block Counting ($N = 29$)[b]			
Step 1			
Constant	2.28	10.02	
Child age at testing	-0.23	1.37	-0.03
Child weight at testing	0.32	0.22	0.33
Maternal education	0.18	0.33	0.12
Maternal alcohol exposure	-1.69	1.58	-0.21
Step 2			
Constant	18.88	10.71	
Child age at testing	-1.83	1.34	-0.26
Child weight at testing	0.28	0.19	0.29
Maternal education	-0.13	0.31	-0.09
Maternal alcohol exposure	-0.57	1.45	-0.07
Group status	-3.50	1.28	-0.58**
Model 5: Triangles ($N = 45$)[c]			
Step 1			
Constant	-11.00	6.49	
Child age at testing	1.34	0.89	0.21
Child weight at testing	0.21	0.14	0.23
Maternal education	0.49	0.21	.036*
Maternal alcohol exposure	-1.59	1.03	-0.21
Step 2			
Constant	-0.86	7.40	
Child age at testing	0.37	0.93	0.06
Child weight at testing	0.19	0.13	0.21
Maternal education	0.31	0.21	0.22
Maternal alcohol exposure	-0.90	1.00	-0.12
Group status	-2.14	0.89	-0.38*

Note. KABC-II = Kaufman Assessment Battery for Children – Second Edition.

[a] $R^2 = .21$ for Step 1, $\Delta R^2 = .51$ for Step 2 ($p < .05$).

[b] $R^2 = .22$ for Step 1, $\Delta R^2 = .21$ for Step 2 ($p < .05$).

[c] $R^2 = .39$ for Step 1, $\Delta R^2 = .09$ for Step 2 ($p < .001$).

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

Models 6-7: Predicting performance on the KABC-II Planning Ability subtests. I created similar hierarchical regression models as above for two KABC-II subtests that measure planning ability: Story Completion and Pattern Reasoning.

Table 11
Hierarchical Regression Models 6-7:Performance on the KABC-II Planning Ability subtests, predicted by potential confounding variables and group status (N = 45)

Variable Entered	*B*	*SE B*	*β*
Model 6: Story Completion[a]			
Step 1			
Constant	-1.40	5.61	
Child age at testing	0.22	0.77	0.04
Child weight at testing	0.09	0.12	0.12
Maternal education	0.51	0.18	0.45**
Maternal alcohol exposure	-0.58	0.89	-0.09
Step 2			
Constant	14.68	4.92	
Child age at testing	-1.33	0.62	-0.25*
Child weight at testing	0.05	0.09	0.07
Maternal education	0.21	0.14	0.19
Maternal alcohol exposure	0.52	0.67	0.08
Group status	-3.39	0.59	-0.76***
Model 7: Pattern Reasoning[b]			
Step 1			
Constant	-11.20	6.37	
Child age at testing	1.44	0.87	0.22
Child weight at testing	0.08	0.14	0.09
Maternal education	0.67	0.21	0.48**
Maternal alcohol exposure	-1.64	1.01	-0.22
Step 2			
Constant	4.42	6.28	
Child age at testing	-0.07	0.79	-0.01
Child weight at testing	0.04	0.11	0.05
Maternal education	0.38	0.18	0.28*
Maternal alcohol exposure	-0.58	0.85	-0.08
Group status	-3.30	0.75	-0.59***

Note. KABC-II = Kaufman Assessment Battery for Children – Second Edition.
[a]R^2 = .30 for Step 1, ΔR^2 = .35 for Step 2 ($p < .001$).
[b]R^2 = .41 for Step 1, ΔR^2 = .21 for Step 2 ($p < .001$).
*$p < .05$. **$p < .01$. ***$p < .001$.

Model 6: Story Completion. Table 11 shows that the set of potential confounding variables explained 29.5% of the variance in the Story Completion subtest scores, $F(4, 35) = 3.67$, $p < .05$. The introduction of group status at step 2 of the model explained an additional 34.7% of the variance in the outcome. In the final model, only child's age at testing and

group status remained statistically significant predictors of sequential reasoning ability. Overall, the final inclusive model accounted for 64.3% of the variance in Story Completion scores, $F(5, 34) = 12.24$, $p < .001$.

Model 7: Pattern Reasoning. Table 11 shows that the set of potential confounding variables explained 34.6% of the variance in the Pattern Reasoning subtest scores, $F(4, 35) = 6.16$, $p < .001$. The introduction of group status at step 2 of the model explained an additional 21.2% of the variance in the outcome. In the final model, only maternal level of education and group status remained statistically significant predictors of abstract reasoning ability. Overall, the final inclusive model accounted for 62.5% of the variance in Pattern Reasoning scores, $F(5, 34) = 11.33$, $p < .001$.

Models 8-9: Predicting performance on the KABC-II Learning Ability subtests. I created similar hierarchical regression models as above for two KABC-II subtests that measure learning and delayed recall ability: Atlantis and Atlantis Delayed.

Model 8: Atlantis. Table 12 shows that the set of potential confounding variables explained 45.1% of the variance in the Atlantis subtest scores, $F(4, 35) = 7.20$, $p < .001$. The introduction of group status at step 2 of the model explained an additional 11.3% of the variance in the outcome. In the final model, only maternal level of education and group status remained statistically significant predictors of learning ability. Overall, the final inclusive model accounted for 56.5% of the variance in Atlantis scores, $F(5, 34) = 8.83$, $p < .001$.

Model 9: Atlantis Delayed. Table 12 shows that the set of potential confounding variables was not a significant predictor of Atlantis Delayed subtest scores, $F(4, 35) = 1.97$, $p = .12$. The introduction of group status at step 2 of the model, however, explained 14.1% of the variance in outcome, $F(5, 34) = 3.27$, $p < .01$. In the final model, only group status remained a statistically significant predictor of delayed recall ability. However, the plot of standardized residuals against standardized predicted residuals indicated that the assumption

of homoscedasticity was not upheld for this model, and so one must exercise caution when generalizing this finding beyond this sample (Field, 2009).

Table 12
Hierarchical Regression Models 8-9: Performance on the KABC-II Learning Ability subtests, predicted by potential confounding variables and group status (N = 45)

Variable Entered	*B*	*SE B*	*β*
Model 8: Atlantis[a]			
Step 1			
Constant	-7.89	6.29	
Child age at testing	0.87	0.86	0.13
Child weight at testing	-0.03	0.14	-0.03
Maternal education	0.98	0.21	0.69***
Maternal alcohol exposure	0.81	0.99	0.10
Step 2			
Constant	3.80	6.91	
Child age at testing	-0.26	0.87	-0.04
Child weight at testing	-0.05	0.12	-0.06
Maternal education	0.77	0.20	0.54***
Maternal alcohol exposure	1.60	0.94	0.21
Group status	-2.47	0.83	-0.43**
Model 9: Atlantis Delayed[b]			
Step 1			
Constant	-7.14	6.97	
Child age at testing	1.79	0.96	0.29
Child weight at testing	-0.07	0.15	-0.08
Maternal education	0.43	0.23	0.33
Maternal alcohol exposure	-0.71	1.10	-0.10
Step 2			
Constant	4.69	7.82	
Child age at testing	0.64	0.98	0.11
Child weight at testing	-0.10	0.14	-0.11
Maternal education	0.21	0.23	0.17
Maternal alcohol exposure	0.09	1.06	0.01
Group status	-2.50	0.94	-0.48**

Note. KABC-II = Kaufman Assessment Battery for Children – Second Edition.
[a]R^2 = .45 for Step 1, ΔR^2 = .11 for Step 2 ($p < .001$).
[b]R^2 = .18 for Step 1, ΔR^2 = .14 for Step 2 ($p < .001$).
*$p < .05$. **$p < .01$. ***$p < .001$.

Model 10: Predicting performance on the BNT-SA-SF. Table 13 shows that the set of potential confounding variables explained 29.9% of the variance in BNT-SA-SF scores, $F(4, 35) = 3.73$, $p < .05$. The introduction of group status at step 2 of the model explained an additional 20.3% of the variance in the outcome. In the final model, only group status remained a statistically significant predictor of confrontation naming ability. Overall, the

final inclusive model accounted for 50.2% of the variance in BNT-SA-SF scores, $F(5, 34) = 6.85$, $p < .001$.

Table 13
Hierarchical Regression Model 10: Performance on the BNT-SA-SF, predicted by potential confounding variables and group status (N = 45)

Variable Entered	*B*	*SE B*	*β*
Step 1			
Constant	-5.09	3.09	
Child age at testing	0.02	0.42	0.01
Child weight at testing	0.11	0.07	0.27
Maternal education	0.22	0.10	0.35*
Maternal alcohol exposure	-0.16	0.49	-0.05
Step 2			
Constant	1.70	3.21	
Child age at testing	-0.64	0.40	-0.22
Child weight at testing	0.09	0.06	0.23
Maternal education	0.09	0.09	0.15
Maternal alcohol exposure	0.30	0.44	0.09
Group status	-1.43	0.39	-0.58***

Note. BNT-SA-SF = Boston Naming Test (South African Short From). $R^2 = .30$ for Step 1, $\Delta R^2 = .20$ for Step 2 ($p < .001$).
*$p < .05$. **$p < .01$. ***$p < .001$.

Models 11-13: Predicting performance on the Beery VMI subtests. I created similar hierarchical regression models as above for the Beery VMI primary score, and the two subtest scores: the Visual Perception Test score and the Motor Co-ordination Test score.

Model 11: Beery VMI. Table 14 shows that the set of potential confounding variables explained 32.7% of the variance in Beery VMI subtest scores, $F(4, 35) = 4.26$, $p < .05$. The introduction of group status at step 2 of the model explained an additional 0.2% of the variance in the outcome. In the final model, only child"s age at testing remained a statistically significant predictor, suggesting that PME was not a significant predictor of performance on this task of visual-motor integration. Overall, the final inclusive model accounted for 32.9% of the variance in Beery VMI scores, $F(5, 34) = 3.33$, $p < .05$.

Table 14
Hierarchical Regression Models 11-13: Performance on the Beery VMI, predicted by potential confounding variables and group status (N = 45)

Variable Entered	*B*	*SE B*	*β*
Model 11: Beery VMI[a]			
Step 1			
Constant	-17.05	7.09	
Child age at testing	2.37	0.97	0.35*
Child weight at testing	0.20	0.15	0.22
Maternal education	0.43	0.23	0.29
Maternal alcohol exposure	0.18	1.12	0.02
Step 2			
Constant	-15.58	8.72	
Child age at testing	2.23	1.09	0.33*
Child weight at testing	0.20	0.15	0.21
Maternal education	0.40	0.25	0.28
Maternal alcohol exposure	0.28	1.18	0.04
Group status	-0.31	1.05	-0.05
Model 12: Visual Perception[b]			
Step 1			
Constant	-10.58	8.32	
Child age at testing	1.98	1.13	0.28
Child weight at testing	0.17	0.18	0.17
Maternal education	0.17	0.27	0.11
Maternal alcohol exposure	-0.56	1.32	-0.07
Step 2			
Constant	0.47	9.70	
Child age at testing	0.91	1.22	0.13
Child weight at testing	0.14	0.17	0.14
Maternal education	-0.04	0.28	-0.03
Maternal alcohol exposure	0.19	1.32	0.02
Group status	-2.33	1.16	-0.38*
Model 13: Motor Co-ordination[c]			
Step 1			
Constant	-7.59	6.19	
Child age at testing	1.64	0.85	0.29
Child weight at testing	0.05	0.13	0.07
Maternal education	0.38	0.20	0.32
Maternal alcohol exposure	-0.59	0.98	-0.09
Step 2			
Constant	5.51	6.53	
Child age at testing	0.38	0.82	0.07
Child weight at testing	0.02	0.12	0.03
Maternal education	0.14	0.19	0.12
Maternal alcohol exposure	0.30	0.89	0.05
Group status	-2.77	0.78	-0.58***

Note. Beery VMI = Beery Developmental Test of Visual-Motor Integration.
[a]R^2 = .33 for Step 1, ΔR^2 = .002 for Step 2 ($p < .05$).
[b]R^2 = .16 for Step 1, ΔR^2 = .09 for Step 2 ($p = .07$).
[c]R^2 = .24 for Step 1, ΔR^2 = .21 for Step 2 ($p < .001$).
*$p < .05$. **$p < .01$. ***$p < .001$.

Model 12: Beery Visual Perception Test. Table 14 shows that at neither the first nor the second modeling step was there a significant set of predictors for scores on the Beery Visual Perception Test, $F(4, 35) = 1.63$, $p = .19$, and $F(5, 34) = 2.23$, $p = .07$, respectively. Group status, however, trended strongly toward significance in the final model ($p = .05$).

Model 13: Beery Motor Co-ordination Test. Table 14 shows that the set of potential confounding variables explained 23.5% of the variance in Beery Motor Co-ordination subtest scores, $F(4, 35) = 2.68$, $p < .05$. The introduction of group status at step 2 of the model explained an additional 20.6% of the variance in the outcome. In the final model, only group status remained a significant predictor of motor coordination performance. Overall, the final inclusive model accounted for 44.0% of the variance in Beery Motor Co-ordination scores, $F(5, 34) = 5.35$, $p < .001$.

Models 14-15: Predicting performance on the GPT outcome variables. I created similar hierarchical regression models as above for two GPT variables: Insertion Time (dominant hand) and Insertion Time (non-dominant hand).

Model 14: GPT insertion time, dominant hand. Table 15 shows that the set of potential confounding variables was not a significant predictor of GPT dominant hand insertion times, $F(4, 35) = 2.36$, $p = .07$. The introduction of group status at step 2, however, explained 18.8% of the variance in the outcome, $F(5, 34) = 3.27$, $p < .01$. In the final model, only group status remained a statistically significant predictor, demonstrating the independent effect of PME on dominant-hand fine motor co-ordination. However, the plot of standardized residuals against standardized predicted residuals indicated that the assumption of homoscedasticity was not upheld for this model, and so one must exercise caution when generalizing this finding beyond this sample (Field, 2019).

Model 15: GPT insertion time, non-dominant hand. Table 15 shows that the set of potential confounding variables was not a significant predictor of GPT non-dominant hand

insertion times, $F(4, 35) = 0.43$, $p = .79$. The introduction of group status at step 2 of the model, however, explained 23.8% of the variance in the outcome, $F(5, 34) = 2.71$, $p < .05$.

Table 15
Hierarchical Regression Models 14-15: Performance on the GPT, predicted by potential confounding variables and group status (N = 45)

Variable Entered	*B*	*SE B*	*β*
Model 14: Insertion Time – Dominant Hand[a]			
Step 1			
Constant	25.99	8.74	
Child age at testing	-2.64	1.20	-0.34*
Child weight at testing	-0.09	0.19	-0.08
Maternal education	-0.38	0.29	-0.23
Maternal alcohol exposure	0.75	1.38	0.08
Step 2			
Constant	8.55	9.39	
Child age at testing	-0.96	1.17	-0.12
Child weight at testing	-0.05	0.17	-0.04
Maternal education	-0.06	0.27	-0.04
Maternal alcohol exposure	-0.43	1.27	-0.05
Group status	3.68	1.13	0.56**
Model 15: Insertion time – Non-dominant Hand[b]			
Step 1			
Constant	7.59	8.61	
Child age at testing	-0.31	1.18	-0.05
Child weight at testing	-0.14	0.19	-0.15
Maternal education	-0.13	0.28	-0.08
Maternal alcohol exposure	0.24	1.36	0.03
Step 2			
Constant	-9.99	9.20	
Child age at testing	1.39	1.15	0.20
Child weight at testing	-0.10	0.16	-0.10
Maternal education	0.20	0.27	0.14
Maternal alcohol exposure	-0.95	1.25	-0.12
Group status	3.71	1.10	0.63**

Note. GPT = Grooved Pegboard Test.
[a]$R^2 = .21$ for Step 1, $\Delta R^2 = .19$ for Step 2 ($p < .05$).
[b]$R^2 = .05$ for Step 1, $\Delta R^2 = .24$ for Step 2 ($p < .05$).
*$p < .05$. **$p < .01$. ***$p < .001$.

In the final model, only group status remained a statistically significant predictor, demonstrating the independent effect of PME on non-dominant hand fine motor co-ordination. However, visual inspection of the P-P plot of standardized residuals suggested

that the assumption of normality was violated, and so one must exercise caution when generalizing this finding beyond this sample (Field, 2009).

Imaging Analysis

Sample characteristics. Of the 45 participants originally enrolled in this study (see Table 4), 80% (n = 36; 19 PME, 17 controls) completed the scanning procedure. In all instances where no scanning sequences were acquired, the participants (within the rights of their consent agreements) refused to continue with the scan due to anxiety and/or fear of the scanner. Of the 36 scans obtained, 72.22% (n = 26; 13 PME, 13 controls) had successful structural and resting state sequences; scans from the other 10 participants were unusable due to motion and/or noise artifacts.

To ensure that the whole-sample trends described in the *Cognitive Outcomes* section were similar in this sub-group of participants, I re-ran similar between-group comparisons as described above for this sub-sample's demographic, anthropometric, and cognitive outcome variables. The relevant data are presented in Tables 16 and 17.

Regarding the child demographic and anthropometric variables, there were no significant between-group differences in this sub-sample. Regarding maternal demographic variables, there were significant between-group differences in the distribution of marital status. Notably, most mothers (84.62%) in the PME group were single, and the rest were divorced; in contrast, less than half (46.15%) of the mothers in the control group were single, and none were divorced. As was the case in the larger sample, significantly more mothers in the PME group than in the control group were exposed to nicotine during pregnancy.

Regarding cognitive outcomes, the data were not consistently normally distributed. Hence, I used the non-parametric Mann-Whitney U-test to investigate between-group differences where appropriate. Otherwise, I administered independent sample t-tests.

Table 16
Demographic and Anthropometric Sample Characteristics, for Participants and Mothers (N = 26)

Variable	Group: PME (n = 13)	Group: Control (n = 13)	t / X^2	p	ESE
Child					
Age at testing	6.99 (.41)	7.23 (.27)	1.71	.10	.69
Sex (M:F)	5:8	6:7	0.16	.69	.08
Language (Eng:Afr)	2:11	3:10	0.25	.62	.10
Education (GrR:Gr1:Gr2)	5:8:0	4:8:1	1.11	.57	.21
Handedness (L:R)	0:13	0:13			
Weight (kg)	19.16 (2.75)	19.87 (3.45)	0.62	.54	.25
Height (cm)	91.42 (7.84)	90.46 (8.01)	-0.31	.76	.13
Head circumference (cm)	51.85 (1.95)	52.10 (1.96)	0.33	.74	.13
Mother					
Education (years)[a]	8.92 (1.44)	10.00 (2.45)	1.35	.19	.56
Employment status (yes/no)	3:10	7:6	2.60	.11	-.32
Income brackets[b]	8:2:0:0	6:1:3:2	5.48	.14	.50
<10 000 (n, %)	8 (80.00)	6 (50.00)			
10 000 – 20 000 (n, %)	2 (20.00)	1 (8.33)			
20 000 – 40 000 (n, %)	0	3 (25.00)			
40 000 – 60 000 (n, %)	0	2 (16.67)			
Marital status	11:0:0:2:0	6:5:1:0:1	10.47	.03*	.64
Single (n, %)	11 (84.62)	6 (46.15)			
Married (n, %)	0	5 (38.46)			
Living with partner (n, %)	0	1 (7.69)			
Divorced (n, %)	2 (15.38)	0			
Widowed (n, %)	0	1 (7.69)			
Cigarette use (yes/no)	11:2	4:9	7.72	.005**	.55
Alcohol use (yes/no)	4:9	1:12	2.23	.14	.29

Note. In some cells, means are presented with standard deviations in parentheses; otherwise, data are presented in ratios. PME = prenatal methamphetamine exposure; ESE = estimate of effect size; M = male; F = female; Eng = English, Afr = Afrikaans; Gr = grade; L = left, R = right. The estimate of effect size was calculated using either r or ϕ, depending on whether an independent samples t-test or Chi-square test was employed.
[a]Data missing for 1 mother in the control group.
[b]Data missing for 3 mothers in the PME group, and 1 mother in the control group.
*p < .05. **p < .01. ***p < .001.

Table 17
Cognitive Outcome Variables: Descriptive Statistics and Between-Group Comparisons (N = 26)

	Group					
Cognitive Measure	PME (n = 13)	Control (n = 13)	t / U	df	p	ESE
KABC-II NVI	27.92 (7.74)	44.31 (6.81)	5.73	24	< .001***	.76
Sequential Processing						
Hand Movements	7.23 (1.69)	10.00 (2.68)	3.15	24	.002**	.54
Simultaneous Processing						
Conceptual Thinking[ac]	4.67 (.82)	9.00 (1.41)	0.00	6	.04*	.73
Block Counting[b]	7.29 (3.30)	9.45 (1.97)	19.00	16	.04*	.42
Triangles	5.31 (2.56)	8.54 (1.81)	3.72	24	< .001***	.60
Planning Ability						
Story Completion[c]	4.46 (1.71)	8.00 (1.53)	11.00	24	< .001***	.77
Pattern Reasoning[c]	4.85 (1.91)	8.15 (1.95)	20.00	24	< .001***	.66
Learning Ability						
Atlantis	5.54 (1.51)	8.08 (2.57)	3.08	24	.003**	.53
Atlantis Delayed[c]	6.62 (1.90)	9.31 (1.49)	19.50	24	< .001***	.67
BNT-SA-SF	6.08 (1.75)	8.31 (1.75)	3.17	24	.002**	.54
Beery VMI	7.46 (3.26)	8.85 (2.91)	1.14	24	.13	.23
Visual score	7.38 (2.96)	9.31 (2.56)	1.77	24	.04*	.34
Motor score	7.23 (1.48)	9.62 (1.56)	4.00	24	< .001***	.63
Grooved Pegboard Test						
Insertion time DH[c]	69.62 (19.89)	48.77 (7.19)	25.00	24	.001***	.60
Insertion time NDH[c]	99.38 (45.02)	54.31 (13.31)	36.50	24	.006**	.48

Note. Data are scaled score means, with standard deviations in parentheses, except for the BNT and Grooved Pegboard Test, where raw scores are presented. Similarly, the t/U and p values presented here are based on analyses of scaled scores for most variables, and of z-scores for the BNT-SA-SF and Grooved Pegboard Test. PME = prenatal methamphetamine exposure; KABC-II = Kauffman Assessment Battery for Children – Second Edition; NVI = Non-Verbal Index; BNT-SA-SF = Boston Naming Test (South African Short Form); VMI = visual-motor integration; DH = dominant hand; NDH = non-dominant hand; ESE = estimate of effect size (in this case, r).
[a]Data unavailable for 7 children in the PME group and 11 children in the HC group as composite tests for the NVI varied for children aged 6 years and those aged 7 years; specifically, Conceptual Thinking was only administered to children aged 6 years.
[b]Data unavailable for 6 children in the PME group and 2 children in the HC group as composite test for the NVI varied for children aged 6 years and those aged 7 years; specifically, Block Counting was only administered to children aged 7 years.
[c]The assumption of normality was violated, so the Mann-Whitney U test was used

Similar trends as for the whole sample were observed for most of the cognitive outcome variables. That is to say, participants in the PME group performed significantly more poorly than those in the control group on most cognitive tests. However, between-group differences on the following variables were no longer significant at the corrected p-value (p = .003): KABC-II Block Counting, Beery Visual Perception Test, and the GPT insertion time

for the dominant hand. The aforementioned variables neared significance within the 95% confidence interval (i.e., ranging from $p = .006$ to $p = .04$). There were no significant between-group differences only for the Beery VMI scores in this sub-sample.

Independent Component Analysis outcomes. Based on a comparison with the standard resting state networks (RSNs) identified in previous work (Beckmann et al., 2005; Bressler & Menon, 2010; Damoiseaux et al., 2006; De Luca, Beckmann, De Stefano, Matthews, & Smith, 2006), two raters (MK and JI) visually identified 14 3D spatial map output components from the 35-component ICA as being artifactual, and potentially with a vascular and/or motion-related origin. By consensus, the raters identified the remaining 21 components as potentially functionally relevant, though a number likely consisted of a mixture of RSNs and artifactual sources. To reduce the possibility of spurious results, the raters only considered the components classified as RSNs that were potentially relevant to PME exposure (as guided by literature). I describe these below, with Brodmann areas (BA) presented in parentheses (see Figure 4):

1. Visual network (see Figure 4a): incorporating, bilaterally, the lingual gyrus (BA 18), cuneus (BA 7, 17, 18, 19), and precuneus (BA 31).

2. Sensorimotor network (see Figure 4b): incorporating, bilaterally, the inferior frontal gyrus, medial frontal gyrus, pre-central gyrus (BA 3, 4), paracentral lobule (BA 31), post-central gyrus extending into the precuneus (BA 7), superior temporal gyrus (BA 41), the posterior aspect of insula (BA 13), and the left thalamus.

3. Basal ganglia network (see Figure 4c): incorporating, bilaterally, the thalamus, lentiform nucleus, putamen, caudate nucleus, pulvinar, lateral globus pallidus, nucleus accumbens, subthalamic nucleus, cuneus (BA 17), and the left insula.

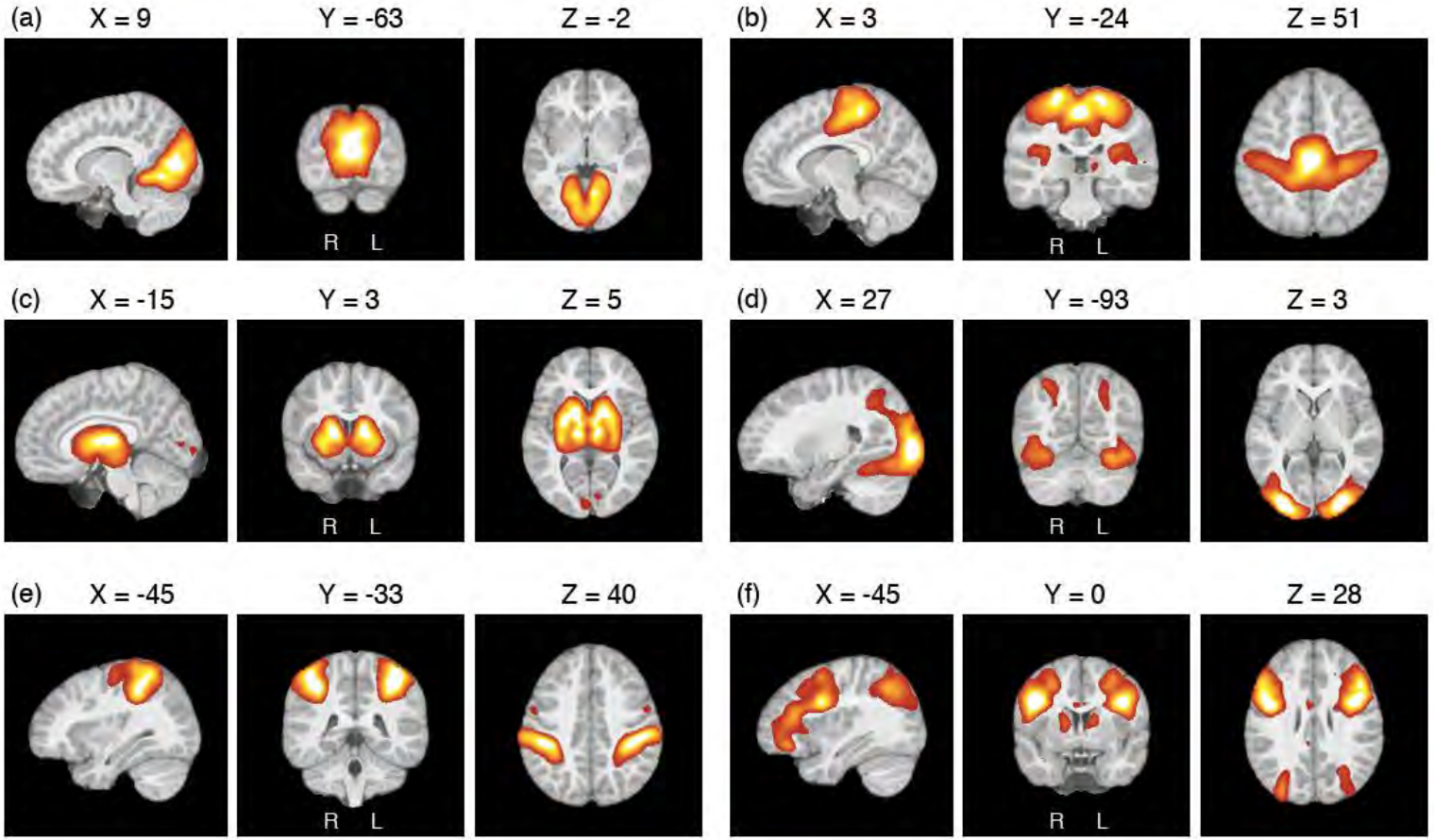

Figure 4. RSNs of interest identified in the 35-component ICA: (a) visual network; (b) sensorimotor network; (c) basal ganglia network; (d) visuo-spatial network; (e) dorsal attention network; (f) fronto-parietal/central executive network. The coordinates refer to millimeter distances from the anterior commissure. Images are shown in radiological convention.

4. Visuospatial (occipitoparietal) network (see Figure 4d): incorporating, bilaterally, the inferior temporal gyrus (BA 22), middle occipital gyrus (BA 19), extending into the cuneus, and the superior parietal lobule (BA 7).

5. Dorsal attention network (see Figure 4e): incorporating, bilaterally, the post-central gyrus (BA 3, 2), precentral gyrus (BA 6), inferior parietal lobule (BA 40), superior parietal lobule, and the middle occipital gyrus (BA 19).

6. Fronto-parietal (central executive control) network (see Figure 4f): incorporating, bilaterally, the middle frontal gyrus (BA 9, 46), inferior frontal gyrus, inferior parietal lobule (BA 40), superior parietal lobule, and the medial frontal gyrus (BA 8).

Testing for between-group differences in motion. In addition to correcting data for motion (see complete description in the Methods section), the raters performed a between-group comparison to test for any potential remaining systematic group differences in motion. An independent samples *t*-test revealed no significant effect for motion, $t(23) = -1.26$, $p = .22$. However, on average, participants in the PME group experienced greater motion ($M = 0.16$, $SD = 0.12$) than those in the control group ($M = 0.11$, $SD = 0.08$). Because head motion can change the results of resting state functional connectivity (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012), the raters included motion as a covariate in the design matrix in order to reduce systematic sources of error variance.

Examining between-group differences in network connectivity. The raters identified significant between-group differences for two of the above-mentioned RSNs of interest. In the group contrast for the sensorimotor network, participants in the PME group showed increased network functional connectivity ($p < .05$) in a single voxel in the right post-central gyrus (see Table 18 and Figure 5a). In the group contrast for the basal ganglia network, decreased connectivity for participants in the PME group was observed in two clusters: the

right posterior cingulate gyrus (BA 31), extending into the precuneus, and the right inferior parietal cortex (BA 40; see Table 18 and Figure 5b).

Visual inspection of these clusters suggested they form part of the posterior default mode network (DMN; Greicius et al., 2003) identified in this sample across all participants (and not initially included as one of the six RSNs of interest). This interpretation was confirmed by overlaying a component corresponding to the posterior DMN, thresholded at $Z = 3$, onto the cluster map (see Figure 5b). No further between-group differences were observed in any of the remaining four RSNs of interest at the 95% confidence interval. Of note here is that the between-group comparisons were corrected on a voxel-wise level, but not for comparisons across networks, due to concerns regarding the limited power (given the small sample size) of these comparisons.

Table 18
Clusters Differing in Connectivity Between Groups for RSNs of Interest (N = 23)

Anatomical cluster locations	Network of interest	Cluster size (voxels)	*p*	Primary peak location (x, y, z)
PME > Controls				
R post-central gyrus[a]	Sensorimotor	1	.04	31.5, -31.5, 43
Controls > PME				
R posterior cingulate gyrus[a]	Basal Ganglia	12	.02	10.5, -43.5, 37
R inferior parietal cortex[a]	Basal Ganglia	10	.03	40.5, -52.5, 49
R post-central gyrus[a]	DMN	1	.04	34.5, -25.5, 46
R pre-central gyrus[b]	DMN	13	.05	31.5, -10.5, 61
R caudate nucleus[b]	DMN	20	.06	19.5, 1.5, 19
R anterior cingulate cortex[b]	DMN	18	.07	19.5, 25.5, 16

Note. PME = prenatal methamphetamine exposure; R = right.
[a]Height and extent thresholds of $p < .05$ were used to determine significant clusters.
[b]Height and extent thresholds of $p < .10$ were used to determine significant clusters as part of the post-hoc analysis.

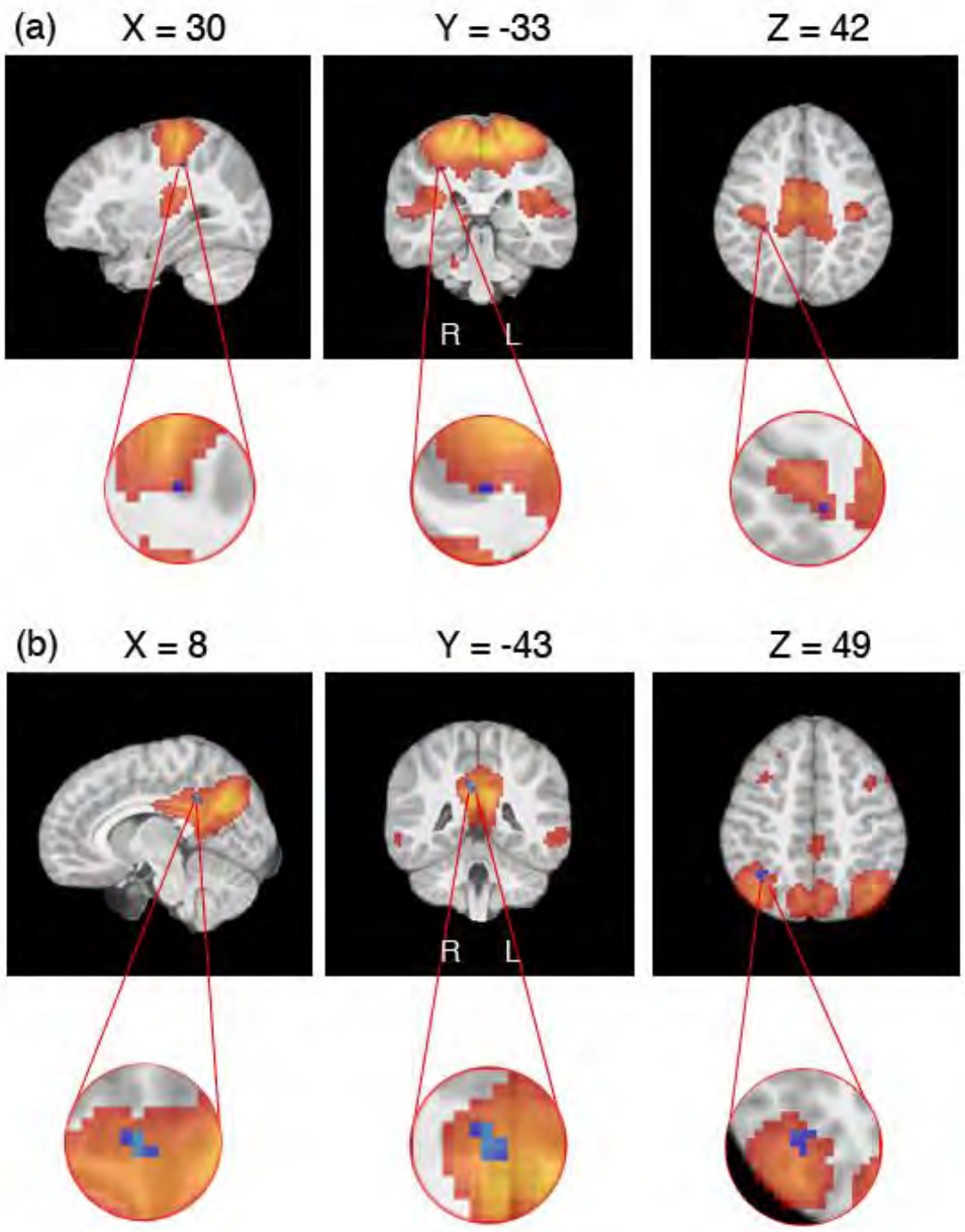

Figure 5. Significant between-group differences identified in the RSNs of interest: (a) Increased sensorimotor network connectivity in the right post-central gyrus in the PME group. (b) Decreased DMN connectivity in the right posterior cingulate gyrus (planes X and Y), and the right inferior parietal cortex (plane Z). R = right; L = left.

Because the clusters identified in the right posterior cingulate gyrus and right inferior parietal cortex were thought to form part of the DMN, a post-hoc between-group contrast was run for this network. Although the aforementioned findings were not replicated, a single cluster of decreased connectivity in the right post-central gyrus (closely located to the cluster of increased connectivity in the sensorimotor network in the initial analysis) was observed in the PME group (see Table 18 and Figure 6a). As the second cluster identified in the right post-central gyrus forms part of the sensorimotor network, this finding of decreased connectivity in the PME group suggests compromised connectivity between the sensorimotor network and the DMN in methamphetamine-exposed children.

To further characterize group differences in DMN connectivity, clusters of at least 10 voxels were identified that differed at the group level at a less stringent alpha of 0.1 (see Table 18). Using the lowered threshold, the raters identified three clusters of decreased connectivity in the PME group: the right precentral gyrus (BA 6, which forms part of the sensorimotor network [Mayka, Corcos, Leurgans, & Vaillancourt, 2006]; see Table 18 and Figure 6b), the right caudate nucleus (which forms part of the basal ganglia network [Robinson et al., 2009]; see Table 18 and Figure 6c), and the right anterior cingulate cortex (which forms part of the salience network [Menon & Uddin, 2010]; see Table 18 and Figure 6d).

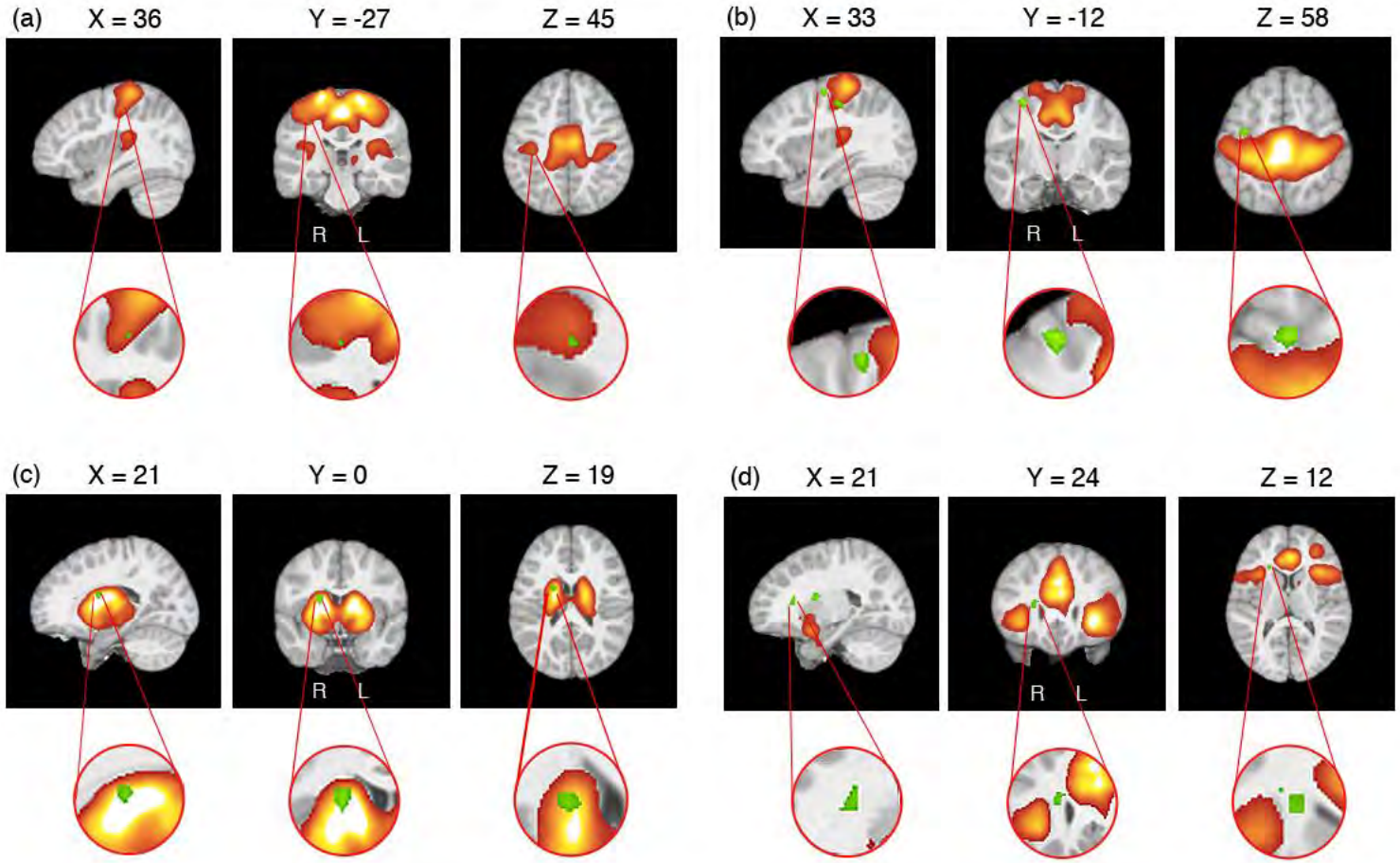

Figure 6. Significant between-group differences for the DMN revealing decreased connectivity for the PME group in the following areas: (a) right post-central gyrus (sensorimotor network used as underlay); (b) right pre-central gyrus (sensorimotor network used as underlay); (c) right caudate nucleus (basal ganglia network uses as underlay); (d) right anterior cingulate cortex (salience network used as underlay).

Discussion

The primary aim of this study was to determine whether cognitive functioning is impaired in children with a history of prenatal methamphetamine exposure (PME). The secondary aim, relating to the resting-state component of this study, was two-fold: (a) to identify intrinsic functional networks in children with a history of PME, and (b) to determine whether intrinsic functional connectivity within and between these networks might be compromised in children with PME. This study is the first of its kind to examine functional resting-state connectivity in this population, and as such that component of the study is properly regarded exploratory.

In this section, I discuss the outcomes of each hypothesis within the context of relevant, previously published literature. The section begins with a discussion of the results of the between-group analyses (i.e., those relating to Hypothesis 1), and the findings from the regression-based analyses that assessed the association between PME and performance on neuropsychological tasks when potentially confounding variables were controlled for (i.e., Hypothesis 2). I then discuss the results from the Independent Component Analysis (ICA) that examined the between-group differences in intrinsic functional connectivity resulting from PME (i.e., Hypothesis 3). Lastly, I address the limitations of this study, suggest directions for future research, and comment on the clinical significance of the results reported.

Impaired Cognitive Functioning in Children with PME

Hypothesis 1. The prediction was that, compared to controls, children with PME would perform significantly more poorly on measures of general intellectual functioning, memory, language, and visual-motor integration and fine motor co-ordination. This prediction was confirmed. The findings for each cognitive domain assessed are discussed below.

General intellectual functioning. Overall, the current findings of lower scores on the KABC-II Non-Verbal Index (an IQ equivalent) in the PME group are largely consistent with previous studies that have documented poor performance on both IQ measures and parent-rated cognitive problem subscales in children with PME (Billing et al., 1998; Cernerud et al. 1996; Chang et al., 2004; Diaz et al., 2014). Specifically, Chang et al. (2004) found a trend for lower verbal IQ scores on both the Wechsler Intelligence Scale for Children (WISC) and the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) in a group of 3-15 year old children with PME. More recently, Diaz et al. (2014) found increased cognitive problem scores in the PME group, aged 7.5 years, as assessed by Conners' Parent Rating Scale (CPRS).

Despite the apparent consistency between parent-rated and formally assessed cognitive problems reported in children with PME, IQ scores and indirect measures are crude indicators of cognitive functioning, and so may not provide sufficient insight into the nature of the cognitive deficits observed in children with PME. Although the current study did make use of a comprehensive cognitive battery, qualitative observations of the participants with PME in the current study (specifically, I noted general distractibility and difficulties in sustaining attention in exposed participants) warrant further investigation. More data on the affective, behavioral, attentional, and executive profiles of children with PME are needed in order to make meaningful interpretations regarding the lower IQ scores reported in the current study.

Accumulating evidence suggests a relationship between intelligence tests and measures of executive functioning (Ardila, Pineda, & Rosselli, 2000; Arffa, 2007; Friedman et al., 2006). Although the NVI is not a discrete measure of executive functioning, children with PME performed significantly worse across all measures of sequential and simultaneous processing, as well as measures of planning ability – all of which rely on aspects of executive

functioning (specifically, attention, planning, problem solving, self-monitoring, and mental flexibility; Anderson, 2001).

A small number of studies have explored the profile of executive deficits in children with PME. For example, Piper et al. (2011) observed pronounced deficits in executive functioning and mild impairments in spatial memory, suggestive of a selective profile of abnormalities in a sample of similar age to the present study. Furthermore, the four-fold incidence rate of attention-deficit/hyperactivity disorder (ADHD) diagnosis in children with PME (compared to controls), as reported by Piper et al., suggests that children with PME may be predisposed to a unique profile of executive dysfunction which may mediate performance on other cognitive measures. A study by Derauf et al. (2012a) supports this claim, proposing deficits in executive functioning related to inhibitory control in children with PME at 5.5 years of age.

Typically, deficits in executive functioning have been associated with behavioral changes such as distractibility, impulsivity, disinhibition, hyperactivity, social problems, and communication difficulties (Clark, Prior, & Kinsella, 2002; Semrud-Clikeman, Walkowiak, Wilkinson, & Butcher, 2010; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). In relation to PME research, the IDEAL study found increased emotional reactivity, and anxious/depressed problems, at the age of 3-5 years, externalizing and ADHD problems at the age of 5 years (LaGasse et al., 2011), subtle differences in outcomes predictive of ADHD at 5.5 years (Kiblawi et al., 2013), and neurobehavioral disinhibition at 5 and 6.5 years of age (Abar et al., 2013b). It is therefore possible that existing research on the cognitive, affective, and behavioral outcomes in children with PME might be parsimoniously explained by considering deficits in executive functioning.

Despite a poor understanding of the etiology of the lower IQ scores reported in the current study, structural imaging studies provide evidence for a distinct neural basis for the

lowered IQ scores in children with PME. For example, volumetric reductions in the caudate nucleus in preschool children with PME have been significantly correlated with reduced cognitive control processes and lower IQ scores (Derauf et al., 2012b; Sowell et al., 2010). Although the consistency of these findings has not yet been established across many studies, the structural abnormalities reported above are functionally related to some of the deficits reported in children with PME in both the current and other studies. Furthermore, the structural findings shed light on the resting state data analyzed for the current study.

Learning and memory. Children in the PME group performed significantly more poorly than healthy controls on a task of visual-verbal associative learning (the KABC-II Atlantis subtest), as well as on the delayed recall component of that task (the KABC-II Atlantis Delayed subtest). This finding is consistent with research suggesting that structural and metabolic changes in striatal structures associated with MA use may be linked to abnormalities in verbal and visual memory in both prenatally exposed children (Chang et al., 2004) and adult MA users (Chang et al., 2007). For example, Change et al. (2004) found that decreased putamen, globus pallidus, and hippocampal volumes were significantly correlated with decreased performance on sustained attention and delayed verbal memory tasks, which may contribute to poor learning in children with PME (Chang et al., 2004).

Furthermore, the observed impairments in learning and delayed recall performance of children with PME are also consistent with the finding of decreased connectivity in the basal ganglia RSN observed in the current sample (discussed below, under *Disrupted Functional Connectivity in Children with PME*). Together, these findings have significant clinical implications. Because of the association between basal ganglia and executive functioning, structural abnormalities in the basal ganglia in children with PME might be functionally related to impairments in executive functioning, including impairments in learning ability (i.e., Derauf et al., 2012b; Roussotte et al., 2011).

Language. Confrontation naming ability (assessed by the BNT-SA-SF) was significantly impaired in children with PME. Chang et al. (2004) reported similar results in a group of 3-15-year-old children with PME whose performance on the Expressive One Word Picture Vocabulary Test was compared to that of an age-matched healthy control group. This finding was not replicated in a younger cohort, however (Chang et al., 2009).

A potential hypothesis for the naming deficit reported in some (but not all) children with PME is that the reduced bilateral hippocampal volumes identified by Chang et al. (2004) may be linked to reduced learning and encoding capacities, and may thereby affect confrontation naming ability (Lavenex & Lavenex, 2013). Intact confrontation naming ability depends on the integrity of the hippocampus and of the connecting frontotemporal networks (Bonelli et al., 2011). Hence, it might be useful for future studies to employ more extensive language and memory batteries to establish whether a specific naming deficit exists in children with PME, and, if so, whether it is attributable to a semantic memory deficit or to a retrieval deficit (i.e., a deficit related to executive dyscontrol of memory processes).

Visual-motor integration. In the current study, children in the PME group performed significantly more poorly than healthy controls on the Beery Visual and Motor subtests (and results neared significance on the Beery VMI measure), suggesting compromised visual sensory input, motor output, and their integration. These observations are consistent with reports from previous studies that used the same measure (Chang et al., 2004, 2009; Colby et al., 2012).

In adult MA users, the striatum, which contains the highest density of dopaminergic synapses, appears particularly vulnerable to the effects of MA (Chang et al., 2007). Because the dopaminergic system regulates motor pathways and cognitive functions that require attention, it is possible that children with PME may show similar deficits to those observed in adult users (including psychomotor slowing; see Salo et al., 2007, 2009; Scott et al., 2007).

This hypothesis has been partly corroborated by studies showing that structural and metabolic striatal abnormalities are associated with poor performance on tasks of visuomotor integration in both young cohorts (average age = 4 years; Chang et al., 2009) as well as school-aged children with PME (average age = 8 years; Chang et al., 2004). Furthermore, these findings suggest that early difficulties in visuomotor integration in children with PME may persist into later childhood.

Fine motor co-ordination. Consistent with the current findings, reported above, of poor visuomotor integration, children in the PME group showed significantly reduced speed on a task of fine motor co-ordination and dexterity (i.e., the Grooved Pegboard Test, using both dominant and non-dominant hands). These findings of compromised motor functioning are consistent with previous literature on prenatally MA-exposed children throughout childhood development. For instance, some studies report hypotonia in the newborn period (LaGasse et al., 2010; Smith et al., 2008), and others report poorer performance on tasks measuring physical fitness and activities by age 14 years (Cernerud et al., 1996).

Data from structural and metabolic neuroimaging studies provide evidence for a distinct neural basis for the above-mentioned deficits. Specifically, Chang et al. (2004) found that poorer visuomotor integration, as measured by the Beery VMI, was associated with smaller globus pallidus volumes in school-aged children with PME. A subsequent study by the same group revealed that lower thalamic myoinositol levels were associated with poorer visuomotor performance in children, aged 3-4 years, with PME (Chang et al., 2009). The globus pallidus is responsible for mediating increases and decreases in excitatory thalamic input to the motor cortex by way of direct and indirect pathways, respectively (Desmurget & Turner, 2010). Therefore, it is possible that reduced globus pallidus volumes and altered metabolic activity in the thalamus of children with PME contribute to poor performance on tasks of motor control.

Similar neuroimaging findings have been reported in adult MA users. Chang et al. (2005) found enlarged striatal (putamen and globus pallidus) volumes in adults who recently abstained from MA use. However, those with greater cumulative MA use, or longer duration of use, had smaller striatal volumes (as observed in most studies of PME). These reduced striatal volumes were associated with poorer performance on a measure of fine motor co-ordination (specifically, the GPT).

Relationship between PME and Neuropsychological Outcomes when Controlling for Potential Confounding variables

To determine whether PME is a primary mechanism underlying cognitive impairments described in the present sample, it was necessary to consider the potentially confounding contribution of child and maternal sociodemographic and anthropometric variables to the observed between-group differences (Jacobson & Jacobson, 2005).

Hypothesis 2. The prediction was that the cognitive deficits observed in the PME group would be related to the effects of PME, and not to the effects of potential confounding variables (viz., child‟s age at testing, child‟s weight at testing, maternal level of education, and maternal alcohol exposure). This prediction was partially confirmed using 15 separate hierarchical regression models. Child‟s weight at testing and maternal alcohol exposure were found to have no significant predictive value for the cognitive outcomes assessed. Below, I discuss only the potential confounding variables that were found to be significant predictors of some of the cognitive outcomes investigated in the current study.

Child's age at testing. Child‟s age at testing had a significant effect on one of the KABC-II simultaneous processing subtests (Conceptual Thinking). However, this subtest was only administered to 6-year-olds (the Block Counting subtest was administered as the age-appropriate equivalent to 7-year-olds). Hence, age was already controlled for, indirectly,

making meaningful interpretations of these results problematic. Furthermore, because of the age-specific cut-off for this subtest, the sample size used in modeling was quite small, thus further compromising the reliability of results.

Child‟s age at testing was also a significant predictor of one of the KABC-II planning ability subtests (Story Completion). However, it was only a significant predictor of performance on that subtest after group status was entered into the regression model. Given that children in the PME group were significantly younger than those in the control group, it is possible that children in the PME group performed more poorly not only because of their exposure to the drug, but also due to relatively immature development. Cognitive control develops gradually over childhood, and improvements in control across development make an important contribution to the kinds of higher cognitive function measured by, for instance, tests of planning ability (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002).

Finally, child‟s age at testing was the sole predictor of performance on the Beery VMI, and remained significant even after group status was entered into the regression model. Child‟s age at testing was not, however, a significant predictor of performance on either the Beery Visual or Beery Motor subtests (administered consecutively after the Beery VMI). It is likely that the Beery VMI (which integrates both the visual and motor aspects of the test) was more cognitively challenging than either the Beery Visual or Motor subtests, and therefore performance on the Beery VMI improved with age.

Overall, then, child‟s age at testing was the sole predictor of performance on only one measure: the Beery VMI. However, given the known effects of age on cognitive performance (Allaire & Marsiske, 1999; Bunge et al., 2002; Jones, Rothbart, & Posner, 2003), it remains an important factor to consider when interpreting data from studies such as this.

Maternal level of education. Given the proposed relationship between maternal level of education and socioeconomic status (SES; Luo, Wilkins, & Kramer, 2006), and the well-

established association between SES and cognitive ability and achievement in childhood (Hackman & Farah, 2009; Noble, McCandliss, & Farah, 2007), I investigated maternal level of education as a potential confounder of the relationship between group status and cognitive performance.

Consistent with existing research documenting the effects of lower SES environments and maternal level of education on child IQ and cognitive development (e.g., Kalil, Ryan, & Corey, 2012; Voss, Jungmann, Wachtendorf, & Neubauer, 2012), maternal level of education was a significant predictor of KABC-II NVI scores. Specifically, maternal level of education was a significant predictor of performance on some of the subtests which constitute the KABC-II NVI, including sequential processing (the Hand Movements subtest) and planning ability (the Pattern Reasoning subtest), as well as learning ability (the Atlantis subtest, a KABC-II measure independent of the NVI).

Recent research suggests that low SES is associated with various neurocognitive impairments differentially, with language and executive/attentional domains being most vulnerable to such effects (see Hackman & Farah, 2009, for a review). Although maternal level of education was not a sole predictor of any one cognitive outcome in the current study, it remains a significant potential confounder and should be considered when interpreting the effects of PME on cognitive outcomes. This is particularly true for the current sample, as the mothers in the control group, on average, had a higher level of maternal education than those in the PME group.

Disrupted Functional Connectivity in Children with PME

Hypothesis 3. The prediction was that children with PME would show disrupted functional connectivity in frontal cortical, visuomotor, and striatal networks when compared

to typically developing, demographically-matched controls. This prediction was partially confirmed using independent components analysis.

Overall, the present results suggest that, in the sub-group of children with PME for whom imaging data were available, there is evidence for compromised connectivity within and between the basal ganglia and default mode network (DMN) networks. It is important to note that this was an exploratory analysis and that, therefore, the resting state networks (RSNs) selected for the between-group analysis were chosen according to available knowledge on the behavioral and cognitive pathology of PME. In particular, methamphetamine exposure, in both adult and prenatally-exposed populations, has been linked to deficits in areas of the brain responsible for the regulation of attention, memory, visuomotor integration, and executive functioning, all of which rely on aspects of the six networks originally selected (i.e., the visual network, the sensorimotor network, the basal ganglia network, the visuospatial network, the dorsal attention network, and the central executive network). The DMN, although included in the post-hoc analysis, was not chosen as one of the original six RSNs because of considerations related to statistical power. For the sake of brevity, below I discuss only the RSNs for which the analyses detected significant between-group alterations in functional connectivity.

Basal ganglia network. Children with PME showed relatively reduced functional connectivity in two regions for the between-group basal ganglia network analysis, when compared to controls: the right posterior cingulate gyrus and the right inferior parietal cortex. Of note here is that, traditionally, these regions are not associated with the basal ganglia network; rather, they constitute aspects of the default mode network (DMN; Fransson & Marrelec, 2008; Greicius, Supekar, Menon, & Dougherty, 2009), and hence will be discussed in the sub-section that follows.

Given the above findings of reduced connectivity in areas typically associated with the DMN (for the between-group basal ganglia analysis), a post-hoc between-group ICA analysis was run on the DMN. A region of decreased connectivity was observed in the right caudate nucleus (CN) of the PME group, which traditionally forms part of the basal ganglia network. The CN provides input to the oculomotor, dorsolateral prefrontal, and lateral orbitofrontal circuits. Hence, it plays a role in reward, emotional, and cognitive regulation (Haruno et al., 2004; Robinson et al., 2009).

Consistent with the present findings, Roussotte et al. (2012) found decreased functional connectivity between the right dorsal caudate and most prefrontal areas during working memory tasks in children with PME (aged 7-15 years). As mentioned earlier, volumetric reductions in the caudate nucleus have also been significantly correlated with reduced cognitive control processes in preschool children with PME (Derauf et al., 2012b) and with lower full-scale IQ scores in school-aged children with PME (Sowell et al., 2010). The current findings are also consistent with literature on the effects of adult methamphetamine use. For example, Lee et al. (2009) found that reduced striatal dopamine receptor availability in the caudate nucleus was associated with increased impulsivity in MA-dependent adults.

It is plausible that a similar mechanism (i.e., reduced dopaminergic receptor availability due to PME in the caudate nucleus) contributes to the decreased connectivity found in the right caudate of the PME group in the present study. Furthermore, because decreased connectivity in the right caudate of the PME group was found in the between-group DMN analysis, this suggests compromised connectivity within and between the caudate nucleus (which is part of the basal ganglia network) and DMN.

Cumulatively, the MA-associated structural, metabolic, and functional brain changes in the striatum, as observed in both adults and prenatally exposed children, suggest the

potential for circuit-level alterations in the mesocorticoclimbic system**.** The consequences of such alterations have been linked to disruptions in cognitive, emotional, and reward regulation mechanisms (for a review see Sutherland, McHugh, Pariyadath, & Stein, 2012).

Default mode network. Participants in the PME group displayed decreased functional connectivity in the right posterior cingulate cortex (PCC) and right inferior parietal cortex (IPC) for the between-group basal ganglia network analysis. The aforementioned regions constitute the posterior DMN (Fransson & Marrelec, 2008). The DMN is typically associated with self-related and social cognitive processes, value-based decision making, and emotion regulation (Buckner, Andrew, Hanna, & Schacter, 2008). These affective and cognitive aspects of functioning have not yet been explored in detail in children with PME.

The PCC, a significant component of the DMN, plays a pivotal role in how intrinsic activity is mediated throughout the DMN (Fransson & Marrelec, 2008). Neuroimaging studies have implicated the PCC in a range of cognitive tasks that draw on various aspects of self-processing (i.e., self-reflection tasks, autobiographical memory tasks, emotional and moral judgment tasks; for reviews, see Buckner & Carroll, 2007; Cravanna & Trimle, 2006; Northoff & Bermpohl, 2004). Moreover, previous imaging studies in adult MA users have observed metabolic and volumetric changes in the PCC that are associated with higher levels of depression, anxiety, and aggression (London et al., 2004; Sekine et al., 2006). Increased PCC activation has also been associated with a choice of delayed reward rather than immediate reward choices in healthy controls (Wittmann, Leland, & Paulus, 2007). This piece of data suggests another potential mechanism for the increased inattention and impulsivity reported in children with PME (Chang et al., 2004; Kiblawi et al., 2013).

The right IPC has bidirectional connections to the right dorsolateral prefrontal and anterior cortex, and has been linked to the visuospatial orienting of attention and several aspects of decision-making, including: sustained and selective attention, switching from task-

relevant to global targets, voluntary attentional control, as well as the distinction between task irrelevant and task-relevant events (Ciaramelli, Grady, & Moscovitch, 2008; Naghavi & Nyberg, 2005). Therefore, the right IPC may be critical for the extraction and selection of task-relevant information, and it has been implicated in inhibitory control in several different paradigms (Garavan, Ross, & Stein, 1999; Kana, Keller, Minshew, & Just, 2007).

Moreover, an RS-fMRI study found that decreased activation in the right IPC (as well as in the dorsolateral prefrontal and temporal cortex, and in the insula) significantly predicted relapse rates in MA-dependent adults, thus further supporting the hypothesis that MA affects a network of structures that are critical for decision-making (Paulus, Tapert, & Schuckit, 2005). How these reductions in functional connectivity manifest at an affective, behavioral, or cognitive level in prenatally-exposed populations is not yet clear, however.

Salience network. Participants in the PME group displayed, relative to the control group, decreased functional connectivity, at a more lenient statistical threshold ($p < .10$), in the anterior cingulate cortex (ACC) for the DMN analysis. The ACC traditionally forms part of the salience network (Seely et al., 2007). This network is anchored by the paralimbic anterior cingulate and frontoinsular cortices, and has extensive connections to subcortical and limbic structures. The salience network connects areas in the brain responsible for conflict monitoring, reward-processing, and interoceptive-autonomic functioning.

The ACC itself plays a role in the processing of errors and conflict (Kerns et al., 2004), and is part of the attentional network previously shown to be deficient in children with PME (Chang et al., 2004). The ACC also has robust connections with dopamine-rich striatal, medial temporal, and thalamic structures, all shown to be dysmorphic in children with prenatal drug exposure (Roussotte et al., 2011). In MA-dependent adults, reduced levels of N-acteyl-asparate, a marker for living neurons, have been reported in the cingulate (Nordahl et al., 2002). Further studies have provided evidence for reductions in glucose metabolism

(London et al., 2004), cerebral blood flow (Hwang et al., 2006), gray matter density (Thompson et al., 2004), and decision-making related to activation in the ACC in MA-abusing or -dependent adults (Paulus, Hozack, Frank, Brown, & Schuckit, 2003).

Although functional imaging research on children with PME is limited, and the results of extant studies somewhat inconsistent (e.g., Chang et al. [2004] found volumetric reductions in the ACC, whereas Sowell et al. [2011] found volumetric increases in the ACC), the abnormalities reported in striatal regions are largely consistent with MA‟s neurotoxic effect on dopaminergic neurons, which, in humans, innervate the ACC more densely than any other cortical structure (Paus, 2001). Furthermore, in light of (a) the observation of decreased connectivity in the right IPC, and (b) the fact that inferior parietal regions, in conjunction with co-activation with the ACC, have been related to error detection, response conflict, and visuospatial alerting and orientating (evidenced in healthy controls; Kana et al., 2007), one might suggest that synchronized connectivity between these two regions may be reduced in children with PME.

Sensorimotor network. In the initial group contrast for the sensorimotor network, the analysis detected a voxel-sized increase in functional connectivity in the post-central gyrus (i.e., the primary sensory cortex) for the PME group. Naturally, the interpretive value of this finding is limited due to the size of this cluster. Furthermore, a post-hoc contrast for the DMN revealed *decreased* connectivity in the right post-central gyrus (also 1 voxel in size). The latter analysis also revealed a larger area of decreased connectivity in the pre-central gyrus (i.e., the primary motor cortex) for the PME group at a less stringent statistical threshold ($p < .10$). The pre-central gyrus and post-central gyrus make up part of the sensorimotor RSN (Mayka et al., 2006; Smith et al, 2009); therefore, the finding of reduced connectivity in those regions suggests compromised connectivity within and between the DMN and sensorimotor network.

To date, no studies have documented metabolic or structural changes in the primary sensory and motor areas in children with PME. However, Chang et al. (2009b) found altered neurometabolites in the frontal white matter and thalamus of children with PME. These alterations were correlated to deficits in visuomotor integration. These findings suggest that PME may alter motor or psychomotor neurodevelopment via the frontostriatal or thalamocortical pathways. It is possible that the reductions in functional connectivity in the primary sensory and motor cortices relate to altered white matter integrity (and thereby, communication with cortical areas) in children with PME (Cloak et al., 2009b; Colby et al., 2012). Alternatively, these findings suggest localized cortical abnormalities in the primary motor and sensory cortex due to dopamine transporter reductions (Volkow et al., 2001). Evidence from research on the dopaminergic modulation of cortical function in patients with Parkinson‟s disease supports the latter hypothesis. That research reports increased activation in the right primary motor cortex after dopaminergic therapy (Mattay et al., 2002).

Interim summary. Taken together, the results of the between-group basal ganglia and DMN analysis suggest compromised connectivity within and between the two networks. Although there are no previously published RS-FMRI data for children with PME, the results of this study are largely consistent with the hypothesis that PME (a) affects the neurotropic roles of monoaminergic transmitters (particularly DA), and (b) leads to morphologic and metabolic alterations in several brain structures, particularly those constituting the striatum (Frost & Cadet, 2000). Although the hypotheses provided in this subsection are largely speculative, given the known functional disturbances associated with disruptions in frontostriatal circuitry (i.e., impaired capacity for self-regulatory control, decision-making and executive dysfunction; Caset, 2001; Chudasama & Robbins, 2006; Scott et al., 2007; Wu, Gau, Lo, & Tseng, 2014), the evidence provided by this study is generally consistent with existing research on the cognitive and functional outcomes following PME.

Limitations and Directions for Future Research

Several limitations of this study should be addressed by future research aiming to further delineate the structural and functional brain changes that might result from PME. Many of these limitations relate to issues discussed earlier, in the section titled *Challenges in Prenatal Drug Exposure Research;* however, although these limitations might have been anticipated, they were, for practical reasons, difficult to overcome.

The primary limitation of this study is that PME histories and dosages were generally unavailable given that many participants in the exposed group were being cared for by family members or foster care parents. Furthermore, even in instances where the birth mother was present, the retrospective data was limited to „yes/no" responses related to MA use. Hence, specific data pertaining to the period, duration, and frequency of MA use throughout pregnancy were largely unavailable. This is true of most retrospective studies of prenatal drug exposure given difficulties in accurately recalling drug histories years after use, a difficulty further compounded by the stigma of admitting to drug use during pregnancy (Kaltenbach & Finnegan, 1993).

The second major limitation of this study involves the issue of polydrug exposure. More than one-third of the subjects with PME also had concomitant prenatal alcohol exposure. Although alcohol exposure was controlled for in the regression analysis in an attempt to describe the effects of PME more accurately, it is possible that higher-order interaction effects between alcohol and PME may account for some of the cognitive and resting state outcomes observed in this sample. Furthermore, even though maternal smoking status was indirectly controlled for (i.e., all the mothers in the exposed group who drank alcohol also smoked), nicotine exposure might also have contributed uniquely to the observed differences between the PME and control groups. For instance, there is some evidence that

striatal volumetric reductions in MA-dependent adults may be a consequence of nicotine exposure (Morales, Lee, Hellemann, O'Neill, & London, 2012**)**

In addition to the potential confounding variables controlled for in this study, it is possible that other unaccounted-for variables (e.g., emotional trauma and abuse, neglect, multiple family placements, or differing parenting styles) may have contributed to the observed results (Davies & Bledsoe, 2005). For example, a high prevalence of depressive symptoms in MA-using mothers has been associated with neonatal effects, including decreased arousal and increased stress in infants with PME (Paz et al., 2009). Therefore, high levels of PME may impact directly (or indirectly, via the effects of maternal depression) on neurological development in affected children. Given that this study is part of a larger research program with a prospective longitudinal design, future investigations ought to consider the possible impact of psychiatric comorbidities (diagnosed via formal assessment) both within the maternal sample (e.g., post-natal depression) and within the group of exposed participants (e.g., ADHD). Although in the current study general psychiatric and medical comorbidities were screened for using self-report health-status questionnaires, given the low-SES background of the participants (and thereby limited access to regular medical and mental health care), it is possible that they have been undetected (Moultrie & Kleinthies, 2006).

In terms of the study design, retrospective human studies of prenatal drug exposure are not ideal for isolating the effects of PME (unlike animal studies, which allow for better control over experimental conditions). Nevertheless, studying „pure" single-drug exposure might compromise the clinical relevance and ecological validity of PME studies. Therefore, it is important that future studies recruit larger samples in order to better isolate the specific affective, behavioral, and cognitive effects of PME.

A third major limitation of this study pertains to the interpretive value of the conclusions from the resting-state analysis. The exploratory nature of the study design and

the novelty of the presented data make meaningful interpretations problematic. Although resting state connectivity measures are reliable, even in children, the reliability varies depending on the preprocessing and data handling steps (Thomason et al., 2011; Zuo et al., 2013). Given the small sub-sample employed for ICA analysis, between-group comparisons were corrected on a voxel-wise level, but not for comparisons across networks. Therefore, it is possible that no between-group differences in functional connectivity would have been observed if the effect of multiple comparisons had been accounted for. However, due to concerns relating to the small sample size (which may have precluded the detection of possible sub-threshold differences), the threshold for statistical significance when conducting the post-hoc DMN analysis was lowered (i.e., $p < .10$). Although this step does limit the extrapolative value of the results, the fact that the findings were generally consistent with previous literature on PME warrants further investigation. One of the advantages of RS-fMRI data is that it allows for the achievement of larger samples through the synthesis of multiple data sets. Future studies might want to employ more collaborative approaches in determining the relevance and reliability of changes in intrinsic functional connectivity in children with PME.

The last major limitation relates to the known influence of in-scanner motion on resting-state connectivity (Satterthwaite et al., 2012). Increases in motion have been associated with both increases and decreases in intrinsic functional connectivity, depending on the RSN of interest. This concern was addressed by the implementation of motion correction, testing for between-group differences in motion (of which there were none), and eliminating data from participants who exceeded standard motion parameters. However, it is possible that the participants who displayed excessive motion (and whose datasets were therefore removed from the analysis) represent a unique subsample of children who may be more severely affected by PME. Given that I conducted no correlational analysis between the

RS outcomes and cognitive measures, one cannot assume that participants excluded from the RS-fMRI analysis were equally representative of the full sample in terms of differences in functional connectivity. Nevertheless, a secondary between-group analysis of the cognitive outcome data in the imaging sub-sample detected similar trends to the full sample (i.e., relatively poorer cognitive performance across most measures for the PME group), suggesting that the sub-sample may have been representative of the full sample.

In summary, many of the limitations of this study relate to a lack of statistical power. Specifically, the small sample size limits the ability to account for many of the above-mentioned potential confounding variables. However, given the profound neurotoxic effect of MA in both adult users and animal models, PME is a likely contributor to the observed between-group differences.

Conclusion and Clinical Significance

Evidence from the current study has contributed to, and is largely consistent with, previously published literature on PME exposure. The current study found that PME affects areas of the brain responsible for the regulation of domain-specific cognitive functions, including learning and memory, confrontation naming, visuomotor integration, and fine motor co-ordination. Furthermore, children with PME had lower IQ scores than demographically-matched controls. Although this finding is not consistent across studies, it warrants further investigation in light of the presented evidence suggesting deficits in the frontostriatal systems (i.e., attentional and inhibitory control systems). As argued earlier, it is possible that children with PME present with a unique profile of abnormalities in lower and higher-order aspects of attention, representative of executive dysfunction. Extended follow-ups into late childhood, encompassing a broad number of outcome measures, might help elucidate the developmental trajectory of neuropsychological dysfunction in PME.

Despite the purely exploratory nature of the imaging component of this study (and, thereby, minimal assumptions of the dataset), the results suggest abnormal functional connectivity within and between the DMN and basal ganglia networks in children with PME. To date, RS-fMRI has been used in only a handful of addiction-related studies, and none have been conducted on children with PME. Although a few functional MRI studies have provided insights into the potential brain regions activated by particular tasks in children with PME, a systematic understanding of dysfunctional brain circuits has remained elusive. This is likely due to the variability in the locus of deficits identified in children with PME, as well as a general lack of consistency in the experimental paradigms used to investigate them. The RSNs explored in this study provide a useful framework through which alterations of functional connectivity in PME can be explored further. Specifically, follow-up correlational analysis (on larger samples) are needed to determine how the identified areas of decreased functional connectivity in children with PME relate to cognitive outcomes.

Overall, the current data suggest that PME has a unique effect on cognitive performance and functional connectivity in a sample of South African children with PME, and that this effect largely withstands the effects of potentially confounding sociodemographic and anthropometric variables. These findings are important because they provide a novel contribution to the definition of neuropsychological profiles of children with PME. Additionally, the finding of cognitive impairments specific to children with PME (i.e., deficits present beyond the effects of comorbid maternal alcohol exposure), alongside preliminary data showing disruptions in intrinsic functional connectivity in a sub-sample of these children, supports the inclusion of targeted interventions into programs for children with a history of PME.

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Appendix A

Sociodemographic Questionnaire

Background questionnaire

Mother / Principal caregiver details

1	Name of primary caregiver:	
2	Relationship of primary caregiver to child e.g. grandmother:	
3	Name of mother:	
4	Person answering questionnaire:	
5	Address of child:	
6	Contact details:	a. Home no: _____ b. Work no: _____ c. Cell: _____
7	Date of birth of mother:	_ _ / _ _ _ / _ _ _ _ DD / MMM / YYYY
8	Ethnicity of mother (tick one):	☐ African/Black ☐ Asian ☐ Caucasian/White ☐ Coloured ☐ Other; please specify _____
9	Highest level of education of mother (circle one):	a. Primary school 1 2 3 4 5 6 7 High School 8 9 10 11 12 College / University 1 2 3 4 5 6 7 8 b. Total of a: _____ c. Diploma / Degree obtained_____
10	Is the mother currently employed:	☐ Yes ☐ No
	If YES:	
11	Name her occupation:	_____
12	How long has she been at this job:	_____DD _____ MM _____ YY
13	Is she the "breadwinner":	☐ Yes ☐ No
14	How many hours does she work a week (tick one)?	☐ 20 to 40 hours / week ☐ 40 to 60 hours / week ☐ 60 to 80 hours / week

15 Marital status (tick one):

- ☐ Single
- ☐ Married
- ☐ Living with partner
- ☐ Divorced
- ☐ Separated
- ☐ Widowed

16 Household income *per year* of household where the child lives (tick one):

- ☐ <R10 000
- ☐ R10 000 - R20 000
- ☐ R 20 000 - R40 000
- ☐ R40 000 - R60 000
- ☐ R60 000 - R100 000
- ☐ >R100 000

17 How many people live in the house where the child lives: _____ people

18 How many rooms are in the house where the child lives: _____ rooms

19 Medical history of mother; any illnesses or conditions:

20 Surgical history of mother; any operations (list, if any):

21 Birth history/complications of mother (list, if any):

22 Number of life siblings born: _____

23 Number of siblings still alive: _____

24 Was this a planned pregnancy:

- ☐ Yes
- ☐ No

Child details		
Demographics		
25	Full name:	
26	Date of birth:	_ _ / _ _ _ / _ _ _ _ DD / MMM / YYYY
27	Age:	_____Y _____M
28	Gender:	☐ Male ☐ Female
29	Level of education (grade):	
30	How long in school:	a. Preschool: _____Y_____M b. Primary school: _____Y_____M c. Total years _____
Anthropometrics		
31	Weight:	_____g
32	Length:	_____cm
33	Head circumference (HC):	_____cm
34	Upper arm circumference (UAC):	_____cm
Birth details of child		
35	Gestation period:	a. _____Weeks b. _____Days
36	Birth weight:	_____g
37	Apgar score:	a. _____1 min b. _____5 min
38	Length:	_____cm
39	Head circumference:	_____cm
40	Birth complications (list, if any):	
41	Operations / illnesses (list, birth to present, if any):	

Appendix B

Drug Intake Questionnaire

Methamphetamine and Alcohol Exposure Questionnaire

42 Person answering questionnaire:

43 Contact details of **mother**:

(Preferably, the mother should answer the questions that follow i.e. Questions 44-59.)

a. Home no: _____
b. Work no: _____
c. Cell: _____

44 How many months was the mother pregnant (according to the clinic records), when she first found out that she was pregnant?

a. _____ months
b. _____ weeks

METHAMPHETAMINE EXPOSURE

FIRST TRIMESTER (0-12 weeks) *Tick the most appropriate answer.*

45 Did you use any methamphetamine?

(If "yes", proceed to Question 46.
If "no", skip Question 46; continue with Question 47.)

☐ Yes
☐ No

46 If yes, how many times did you use methamphetamine per week?

☐ Once per week or less
☐ Two to three times per week
☐ Four to six times per week
☐ Daily

SECOND TRIMESTER (13-24 weeks) *Tick the most appropriate answer.*

47 Did you use any methamphetamine?

(If "yes", proceed to Question 48.
If "no", skip Question 48; continue with Question 49.)

☐ Yes
☐ No

48 If yes, how many times did you use methamphetamine per week?

☐ Once per week or less
☐ Two to three times per week
☐ Four to six times per week
☐ Daily

THIRD TRIMESTER (24-40 weeks) *Tick the most appropriate answer.*

49 Did you use any methamphetamine?

(If "yes", proceed to Question 50.
If "no", skip Question 50; continue with Question 51.)

☐ Yes
☐ No

50 If yes, how many times did you use methamphetamine per week?

☐ Once per week or less
☐ Two to three times per week
☐ Four to six times per week
☐ Daily

ALCOHOL EXPOSURE

FIRST TRIMESTER (0-12 weeks) *Tick the most appropriate answer.*

51 Did you drink any alcohol?

(If "yes", proceed to Question 52.
If "no", skip Questions 52-53; continue with Question 54.)

- ☐ Yes
- ☐ No

52 If yes, how many times did you drink per week?

- ☐ Once per week or less
- ☐ Two to three times per week
- ☐ Four to six times per week
- ☐ Daily

53 How many drinks did you have per episode?

- ☐ < 2
- ☐ 2 to 3
- ☐ 4 or more

If > 4, please specify average number: _____

SECOND TRIMESTER (13-24 weeks) *Tick the most appropriate answer.*

54 Did you drink any alcohol?

(If "yes", proceed to Question 55.
If "no", skip Questions 55-56; continue with Question 57.)

- ☐ Yes
- ☐ No

55 If yes, how many times did you drink per week?

- ☐ Once per week or less
- ☐ Two to three times per week
- ☐ Four to six times per week
- ☐ Daily

56 How many drinks did you have per episode?

- ☐ < 2
- ☐ 2 to 3
- ☐ 4 or more

If > 4, please specify average number: _____

THIRD TRIMESTER (24-40 weeks) *Tick the most appropriate answer.*

57 Did you drink any alcohol?

(If "yes", proceed to Question 58.
If "no", skip Questions 58-59; continue with Question 60.)

- ☐ Yes
- ☐ No

58 If yes, how many times did you drink per week?

- ☐ Once per week or less
- ☐ Two to three times per week
- ☐ Four to six times per week
- ☐ Daily

59 How many drinks did you have per episode?

- ☐ < 2
- ☐ 2 to 3
- ☐ 4 or more

If > 4, please specify average number: _____

SMOKING

FIRST TRIMESTER (0-12 weeks) *Tick the most appropriate answer.*

60 Did you smoke?

(If "yes", proceed to Question 61.
If "no", skip Question 61; continue with Question 62.)

- ☐ Yes
- ☐ No

61 If yes, how many cigarettes did you smoke per day?

- ☐ 10 or less
- ☐ 11 to 20
- ☐ 21 to 30
- ☐ More than 30

SECOND TRIMESTER (13-24 weeks) *Tick the most appropriate answer.*

62 Did you smoke?

(If "yes", proceed to Question 63.
If "no", skip Question 63; continue with Question 64.)

- ☐ Yes
- ☐ No

63 If yes, how many cigarettes did you smoke per day?

- ☐ 10 or less
- ☐ 11 to 20
- ☐ 21 to 30
- ☐ More than 30

THIRD TRIMESTER (24-40 weeks) *Tick the most appropriate answer.*

64 Did you smoke?

(If "yes", proceed to Question 65.
If "no", skip Question 65.)

- ☐ Yes
- ☐ No

65 If yes, how many cigarettes did you smoke per day?

- ☐ 10 or less
- ☐ 11 to 20
- ☐ 21 to 30
- ☐ More than 30

Appendix C

Ethical Approval: Letter of confirmation

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Amendment Form

Date	15 April 2011
HREC REF Number	235/2009
Protocol number (if applicable) & Protocol title	STRUCTURAL NEURO-IMAGING AND NEURO-COGNITIVE CORRELATES IN PRENATALLY METHAMPHETAMINE EXPOSED CHILDREN IN CAPE TOWN.
Principal Investigator	Dr K Donald
Department / Office Internal Mail Address	Room 420, ICH building, School of Child and Adolescent Health, RXH

List of Proposed Amendments with Revised Version Numbers and Dates

No amendments to number of study participants and numbers or recruitment.

The reason the imaging was not included in the original protocol is that the children were too young to be able to lie still for the MRI scan. The children are now older and a moton-correction sequence has also been added to improve the quality of scans of unsedated children (see amended protocol). New additions to the protocol have been highlighted with different colour text. As we haven't changed the initial phase of the project, I haven't "removed" sections of the previous protocol.

Children will be provided with transport to and from Red Cross to CUBIC for the scan as well as transport money from home for the visit.

HREC office use only (FWA00001637; IRB00001938)

☐ Approved ✓	☐ Type of review: Expedited ✓	☐ Full committee

This serves as notification that all changes and documentation described above are approved.

Signature Chairperson of the HREC		Date	18/4/11.

Appendix D

Informed Consent Form

PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM FOR USE BY PARENTS/LEGAL GUARDIANS
Children Control Version

TITLE OF THE RESEARCH PROJECT:
STRUCTURAL NEURO-IMAGING AND NEURO-COGNITIVE CORRELATES IN PRENATALLY METHAMPHETAMINE EXPOSED CHILDREN IN CAPE TOWN.

REFERENCE NUMBER: HREC 235/2009

PRINCIPAL INVESTIGATOR: Dr Kirsty Donald

ADDRESS: School of Child and Adolescent Health, Red Cross Children's Hospital and the University of Cape Town

CONTACT NUMBER: (021) 6585322
Your child is being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how your child could be involved. Also, your child's participation is **entirely voluntary** and you are free to decline to participate. If you say no, this will not affect you or your child negatively in any way whatsoever. You are also free to withdraw him/her from the study at any point, even if you do initially agree to let him/her take part.

This study has been approved by the **Committee for Human Research at the University of Cape Town** and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

This study looks at the structure of your child's brain using a brain scan (Magnetic resonance imaging) and by doing some tests of learning. By doing so we hope to get a better understanding of how the brain looks and also what goes wrong in certain disorders so (in the long term) we can identify problems and develop better treatments.

Why has your child been invited to participate?

Previously we tested your child's development and we would now like to look at the structure of his/her brain as well as to do some further tests of learning and behaviour.

What will your responsibilities be?

You would be required to bring your child to the unit so we can get the images and wait with your child while we are scanning. Your child will also be given an assessment of learning on a different day at the Red Cross Children's Hospital. Each session will take 1-2 hours in total. There will be one set of assessments this year and another (similar) set in a year's time.

Will your child benefit from taking part in this research?

An assessment of your child's learning will be done and brain scanned. Possible problems may be picked up early and your child will be referred for treatment.

Are there any risks involved in your child taking part in this research?

No. Your child may become bored and not find this enjoyable but they will experience no pain. If at any time they become upset and do not wish to continue, the task will be stopped.

Who will have access to your child's medical records?

Only members of the research team will have access to the data gathered here. All information will remain confidential and if the results of this study are published no participant will be identified.

Will you or your child be paid to take part in this study and are there any costs involved?

You or your child will not be paid to take part in the study, but your/your child's transport and meal costs will be covered for each study visit. There will be no costs involved for you if your child does take part.

Is there any thing else that you should know or do?

- You should inform your family practitioner or usual doctor that your child is taking part in a research study.
- You can contact Dr Kirsty Donald at tel 021-6585322 if you have any further queries or encounter any problems.
- You can contact the Committee for Human Research if you have any concerns or complaints that have not been adequately addressed by your child's study doctor.
- You will receive a copy of this information and consent form for your own records.

Assent of minor

I (*Name of Child/Minor*)……. have been invited to take part in the above research project.

- The study doctor/nurse and my parents have explained the details of the study to me and I understand what they have said to me.
- They have also explained that this study will involve. I also know that I am free to withdraw from the study at any time if I am unhappy.
- By writing my name below, I voluntary agree to take part in this research project. I confirm that I have not been forced either by my parents or doctor to take part.

.....

Name of child **Independent witness**

(To be written by the child if possible)

Declaration by parent/legal guardian

By signing below, I *(name of parent/legal guardian)* …….. agree to allow my child (name of child) …….. who is ……. years old, to take part in a research study entitled *(insert title of study)*

I declare that:

- I have read or had read to me this information and consent form and that it is written in a language with which I am fluent and comfortable.
- If my child is older then 7 years, he/she must agree to take part in the study and his/her ASSENT must be recorded on this form.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to let my child take part.
- I may choose to withdraw my child from the study at any time and my child will not be penalised or prejudiced in any way.
- My child may be asked to leave the study before it has finished if the study doctor or researcher feels it is in my child's best interests, or if my child does not follow the study plan as agreed to.

Signed at (*place*) ..... on (*date*) …….. 2013.

……

Signature of parent/legal guardian **Signature of witness**

Declaration by investigator

I *(name)* …… declare that:

- I explained the information in this document to ……..
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understand all aspects of the research, as discussed above
- I did/did not use a translator (i*f a translator is used, then the translator must sign the declaration below).*

Signed at (*place*) ..... on (*date*) …….. 2013.

……

Signature of investigator **Signature of witness**

Declaration by translator

I *(name)* …… declare that:

- I assisted the investigator (*name*) …….. to explain the information in this document to (*name of parent/legal guardian*) …….. using the language medium of Afrikaans/Xhosa.
- We encouraged him/her to ask questions and took adequate time to answer them.

- I conveyed a factually correct version of what was related to me.
- I am satisfied that the parent/legal guardian fully understands the content of this informed consent document and has had all his/her questions satisfactorily answered.

Signed at (*place*) .....…….…….. on (*date*) ……..…….. 2013.

……

Signature of translator **Signature of witness**

Appendix E

Informed Assent Form

PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM FOR USE BY PARENTS/LEGAL GUARDIANS
Children Patient Version

TITLE OF THE RESEARCH PROJECT:
STRUCTURAL NEURO-IMAGING AND NEURO-COGNITIVE CORRELATES IN PRENATALLY METHAMPHETAMINE EXPOSED CHILDREN IN CAPE TOWN.

REFERENCE NUMBER: HREC 235/2009

PRINCIPAL INVESTIGATOR: Dr Kirsty Donald

ADDRESS: School of Child and Adolescent Health, Red Cross Children's Hospital and the University of Cape Town

CONTACT NUMBER: (021) 6585322

Your child is being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how your child could be involved. Also, your child's participation is **entirely voluntary** and you are free to decline to participate. If you say no, this will not affect you or your child negatively in any way whatsoever. You are also free to withdraw him/her from the study at any point, even if you do initially agree to let him/her take part.

This study has been approved by the **Committee for Human Research at University of Cape Town** and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

This study looks at the structure of your child's brain using a brain scan (Magnetic resonance imaging) and by doing some tests of learning and behaviour. By doing so we hope to get a better understanding of how the brain looks as well as how a child learns and also what goes wrong in certain disorders so (in the long term) we can identify problems and develop better treatments.

Why has your child been invited to participate?

We would like to get a better understanding of brain structure as well as the way children learn and behave who have been exposed to a substance such as Methamphetamine ('Tik'), with the aim of eventually improving diagnosis and treatment options.

What will your responsibilities be?

You would be required to bring your child to the unit so we can get the images and wait with your child while we are scanning. Your child will also be given an assessment of learning on a different day at the Red Cross Children's Hospital. Each session will take 1-2 hours in total. There will be one set of assessments this year and another (similar) set in a year's time.

Will your child benefit from taking part in this research?

Your child will receive a new type of brain scan as well as a report from the tests of learning. Any information obtained will be sent to your child's doctor (with your consent). This may or may not aid in your child's treatment.

Are there any risks involved in your child taking part in this research?

No. Your child may become bored and not find this enjoyable but they will experience no pain. If at any time they become upset and do not wish to continue, the task will be stopped.

Who will have access to your child's medical records?

Only members of the research team will have access to the data gathered here. All information will remain confidential and if the results of this study are published no participant will be identified. We may require access to your child's medical records. We will only ask for access to these records with your written permission.

Will you or your child be paid to take part in this study and are there any costs involved?

You or your child will not be paid to take part in the study, but your/your child's transport and meal costs will be covered for each study visit. There will be no costs involved for you if your child does take part.

Is there any thing else that you should know or do?

- You should inform your family practitioner or usual doctor that your child is taking part in a research study.
- You can contact Dr Kirsty Donald tel 6585322 if you have any further queries or encounter any problems.
- You can contact the Committee for Human Research at if you have any concerns or complaints that have not been adequately addressed by your child's study doctor.

- You will receive a copy of this information and consent form for your own records.

Assent of minor

I (*Name of Child/Minor*)…… have been invited to take part in the above research project.

- The study doctor/nurse and my parents have explained the details of the study to me and I understand what they have said to me.
- They have also explained that this study will involve. I also know that I am free to withdraw from the study at any time if I am unhappy.
- By writing my name below, I voluntary agree to take part in this research project. I confirm that I have not been forced either by my parents or doctor to take part.

.....

Name of child **Independent witness**

(To be written by the child if possible)

Declaration by parent/legal guardian

By signing below, I *(name of parent/legal guardian)* …….. agree to allow my child (name of child) …….. who is ……. years old, to take part in a research study entitled *(insert title of study)*

I declare that:

- I have read or had read to me this information and consent form and that it is written in a language with which I am fluent and comfortable.
- If my child is older then 7 years, he/she must agree to take part in the study and his/her ASSENT must be recorded on this form.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to let my child take part.
- I may choose to withdraw my child from the study at any time and my child will not be penalised or prejudiced in any way.

- My child may be asked to leave the study before it has finished if the study doctor or researcher feels it is in my child's best interests, or if my child does not follow the study plan as agreed to.

Signed at (*place*) ..... on (*date*) ..... 2013.

.....
Signature of parent/legal guardian **Signature of witness**

Declaration by investigator

I *(name)* ..... declare that:

- I explained the information in this document to .....
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understand all aspects of the research, as discussed above
- I did/did not use a translator (i*f a translator is used, then the translator must sign the declaration below).*

Signed at (*place*) ..... on (*date*) ..... 2013.

....
Signature of investigator **Signature of witness**

Declaration by translator

I *(name)* ..... declare that:

- I assisted the investigator (*name*) ..... to explain the information in this document to (*name of parent/legal guardian*) ..... using the language medium of Afrikaans/Xhosa.

- We encouraged him/her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the parent/legal guardian fully understands the content of this informed consent document and has had all his/her questions satisfactorily answered.

Signed at (*place*) ..... on (*date*) ..... 2013.

....

Signature of translator **Signature of witness**

I declare that:

I grant/do not grant the researcher permission to make my child's results known to my treating doctor

Signed at (*place*).....on (*date*) 2013

....

Signature of Participant Signature of Witness.

I declare that:

I grant/do not grant the researcher permission to access my child's medical records.

Signed at (*place*).....on (*date*) 2013

....

Sigsnature of Participant Signature of Witness