Social Cognition: Theory and Neuroscience in Fetal Alcohol Spectrum Disorders

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
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Abstract

Children with fetal alcohol spectrum disorders (FASD) have deficits across many cognitive, behaviour and social domains. However, despite social difficulty being proposed as a main deficit following prenatal alcohol exposure, the nature of their deficient social behaviour is largely unknown. One process that may underlie difficulties in social functioning is poor social cognition, which refers to one’s understanding of the self, others and social world. The primary goal of this dissertation was to determine whether social cognitive deficits represent a core disability underlying the socio-behavioural problems of FASD using a bottom-up approach. The first level of this approach is represented by face processing. Global and independent face feature processing was compared between FASD and normal controls (NC) using experimental and clinical measures. Eye gaze processing was investigated next using experimental and clinical tasks. At the highest level of the bottom-up approach, social perspective taking, including theory of mind and empathy were examined, along with how these abilities related to parent-rated behaviour. Finally, the lowest level consisted of specific aspects of the social neural network. White matter in three limbic pathways was investigated using diffusion tensor imaging (DTI).
Results generally supported the bottom-up approach of social cognition in FASD. These children showed impaired processing of face features, when matching mouth shapes and partially occluded identity, compared with NC. The FASD group was slower to process gaze and arrow cues, suggesting impaired attention shifting. Children with FASD also showed impairments in social perspective taking, including understanding false beliefs and empathy, and these impairments were related to parent-rated attention and social problems, and autistic-like traits. Deficits in theory of mind got worse with age in FASD and empathy showed distinct sex-related differences. Although no group differences were observed on DTI indices, groups did show different age-related changes in white matter. In conclusion, deficits at each level of the current bottom-up approach may underlie the social impairments in FASD and may contribute to their broader social behavioural phenotype. The results from this dissertation have potential to inform clinical practice and lead to more effective diagnostic and treatment approaches in FASD.
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List of Abbreviations

AD=Axial Diffusivity
ADHD=Attention Deficit Hyperactivity Disorder
AFNI=Analysis of Functional NeuroImages
ANOVA=Analysis of Variance
ARND=Alcohol Related Neurodevelopmental Disorders
B=Beta
CBCL=Child Behavior Checklist
CI=Confidence Intervals
DTI=Diffusion Tensor Imaging
FA=Fractional Anisotropy
FAS=Fetal Alcohol Syndrome
FASD=Fetal Alcohol Spectrum Disorders
FSIQ=Full Scale Intelligence Quotient
FSL=FMRIB Software Library
ILF=Inferior Longitudinal Fasciculus
IOM=Institute of Medicine
IQ=Intelligence Quotient
LD=Learning Disorder
MD=Mean Diffusivity
MNI=Montreal Neurological Institute
MRI=Magnetic Resonance Imaging
ms=Milliseconds
NC=Normal Controls
NEPSY=A Developmental NEuroPSYchological Assessment
ODD=Oppositional Defiant Disorder
PAE=Prenatal Alcohol Exposure
RD=Radial Diffusivity
RT=Reaction Time
SD=Standard Deviation
SES=Socioeconomic Status
SickKids=The Hospital for Sick Children
SPSS=Statistical Package for the Social Sciences
SSIS=Social Skills Improvement System
UF=Uncinate Fasciculus
WASI=Weschler Abbreviated Scale of Intelligence
Chapter 1
Introduction

Fetal alcohol spectrum disorders (FASD) are a set of developmental conditions that arise from prenatal exposure to alcohol, a powerful teratogen with severe consequences for brain development. As a result of prenatal alcohol exposure (PAE) children with FASD have significant deficits across a variety of domains, with their executive function abilities being especially affected. Indeed, their executive function difficulties are considered a hallmark deficit in this population (Kodituwakku, 2007). In addition, children with FASD show marked social and behaviour problems, which are reported mainly using standardized parent questionnaires. However, the processes that underlie and contribute to these deficiencies remain largely unknown.

One potential set of processes underlying the difficulties of FASD in these domains is deficient social cognition. Social cognition refers to the specialized aspect of cognition that pertains to one’s understanding of the self, others, and the social world (see Lewis & Carpendale, 2004). Importantly, social cognition is fundamental for social and behavioural functioning (Dodge, Laird, Lochman & Zelli, 2002; Herrmann, Call, Hernández-Lloreda, Hare & Tomasello, 2007) and the field of social cognitive neuroscience has emerged to further our understanding of how biological systems relate to this functioning (Cacioppo et al., 2007). Thus, it is not only important to understand the characteristics of abnormal social behaviour following PAE, it is also critical to investigate the neuroanatomical mechanisms relating to these characteristics.

It is well established that the developing brain is a major target of PAE and that the executive function deficits of children with FASD have their roots in abnormal brain structure and function.
Evidence also suggests PAE affects the neural substrates underlying social abilities; however this relationship has received limited investigation. The present thesis will therefore adopt a bottom-up approach to examine several specific aspects of social cognition that are deficient in children with FASD and the neuroanatomical determinants of these deficiencies. By identifying the processes underlying the social problems following PAE we will gain further understanding of the nature of behavioural symptoms. This knowledge is essential for identifying the core deficits in FASD.

1.1 History, Definitions and Diagnosis of FASD

The adverse effects of alcohol on the developing fetus have long been known. Some of the first references on the negative influences of PAE appeared in ancient Greek and Roman literature, with the belief alcohol intoxication during pregnancy resulted in damage to the unborn child (Abel, 1999; Jones & Smith, 1973). Several articles have also quoted Aristotle’s admonishment: ‘Foolish, drunken and harebrained women most often bring forth children like unto themselves, morose and languid’ (Calhoun & Warren, 2007). However, clinical recognition of the disorder known as fetal alcohol syndrome (FAS) is far more recent, with the seminal scientific publication by Lemoine and colleagues in 1968. These clinicians described a consistent constellation of abnormalities seen in children born to mothers who drank heavily during pregnancy. These abnormalities included (i) abnormal facial features, such as short palpebral fissures, poorly developed or absent philtrum and a thin upper lip, (ii) growth retardation affecting weight and height, and (iii) behavioural and cognitive deficits indicating central nervous system delay and neurological abnormalities (Lemoine, Harousseau, Borteyru & Menuet, 1968).
Several years later in the United States, a research team headed by Kenneth Jones coined the term ‘fetal alcohol syndrome’ to describe the negative effects of heavy alcohol exposure in children (Jones & Smith, 1973). In recognition of the growing concern for the poor outcomes in these children, the United States Congress mandated the Institute of Medicine (IOM) (Institute of Medicine, 1990) to investigate FAS and its related birth defects. The IOM published a classification scheme for FASD, which is the umbrella term describing the negative consequences following PAE. Around the same time, a research team from Washington State, who were conducting follow-up studies on the long term effects of PAE, set out to formulate a diagnostic system that became known as the Washington 4-Digit Diagnostic Code (Astley & Clarren, 2000). The four digits in this code represent the magnitude of expression of the four key diagnostic features of FAS, including growth deficiency, physical facial features, central nervous system damage, and alcohol exposure prenatally. Each feature and its magnitude is ranked independently on a 4-point Likert scale with 1 reflecting absence of the FAS feature and 4 reflecting a strong presence of the FAS feature (Astley & Clarren, 2000). Based on the 4-Digit Code, diagnoses under the FASD umbrella included FAS, partial FAS, alcohol related birth disorders, and alcohol related neurodevelopmental disorders (ARND) (Clarren & Smith, 1978). ARND, which is the most prevalent condition among children with PAE, involves only the neurobehavioural manifestations and none of the identifying physical features (Riley & McGee, 2005). However, since both the IOM and Washington systems lacked specificity, neither was satisfactory in diagnosing children with ARND.

In Canada, the prevalence is 4 in 1000 births for FAS, and 40 in 1000 births for ARND (Canadian Society of Pediatrics, 2002), and as high as 20% in some Aboriginal communities (Davies & Bledsoe, 2005). The costs are estimated at $1 million per person, making FASD a
serious public burden for Canadians (Stade, Ungar, Stevens, Beyen & Koren, 2007). In fact, these figures may underestimate the true prevalence of FASD, as ARND is physically invisible (i.e., no facial dysmorphia or growth deficiency) and thus many children are un- or mis-diagnosed (Ritchie, 2004). In an attempt to better address the needs of all individuals affected prenatally by alcohol, the Canadian government in 2002 set up a team to deal with the lack of proper diagnostic criteria for ARND and to examine the problems related to FASD diagnosis. Following from the initial attempts of the IOM and Washington 4-Digit Diagnostic Code, the Canadian team published a set of clinical diagnostic guidelines (Chudley et al., 2005). Under these guidelines, the diagnostic process for ARND involved first excluding alternative diagnoses and then establishing evidence of impairment in three or more of the following central nervous system domains: hard and soft neurologic signs (e.g., fine motor skills), brain structure, cognition, communication, academic achievement, memory, executive function, abstract reasoning, attention deficit/hyperactivity, adaptive behaviour, social skills and communication; along with confirmation of PAE (Chudley et al., 2005). By integrating current approaches to diagnoses, the Canadian guidelines represent an important step forward in reaching a standard of diagnosis and assessment for FASD.

1.2 Cognition, Behaviour and Social Deficits in FASD

It is well established that a broad range of cognitive sequelae are seen in children with FASD. These include impairments in attention (Coles et al., 1997; Streissguth et al., 1986), memory (Mattson, Riley, Delis, Stern & Jones, 1996; Willoughby, Sheard, Nash & Rovet, 2008), language (Coggins, Olswang, Olson & Timler, 2003; Coggins, Timler & Olswang, 2007; McGee, Bjorkquist, Riley & Mattson, 2009) and notably, executive functions (Connor, Sampson, Bookstein, Barr & Streissguth, 2001; Kodituwakku, Handmaker, Cutler, Weathersby &
Handmaker, 1995; Mattson, Goodman, Caine, Delis & Riley, 1999). In addition, children and adolescents with FASD are at high risk for behaviour problems, which often lead to psychopathology, most commonly conduct disorder, oppositional defiant disorder (ODD), attention deficit hyperactivity disorder (ADHD), and autism (Bishop, Gahagan & Lord, 2007; Fryer, McGee, Matt, Riley & Mattson, 2007; Mukherjee, Layton, Yacoub & Turk, 2011; Schonfeld, Mattson & Riley, 2005). The pattern of deficits and clinical profiles of FASD are unique and distinct from those seen in children diagnosed with psychiatric conditions but who were not prenatally exposed to alcohol. For example, children with FASD exhibit attention deficits (Coles et al., 1997), social cognitive difficulties (Greenbaum, Stevens, Nash, Koren & Rovet, 2009), and sociopathic behaviours (Nash et al., 2006) that are more severe and slightly different in character than those seen in ADHD. Notably, children with FASD have fewer internalizing problems, but more severe externalizing problems and are at higher risk of social impairment than ADHD (Greenbaum et al., 2009). These behaviour problems can lead to serious secondary disturbances later in life such as trouble with the law and disrupted school experience, inappropriate sexual behaviours, and alcohol and drug problems (Streissguth et al., 2004).

Moreover, as many as 90% of adults with FASD have mental health problems and the risk of suicide is high (Streissguth et al., 2004). In addition to the cognitive and behaviour deficits, the severe secondary disabilities seen in FASD highlight the difficulty these individuals have integrating and adapting to the social demands of society.

Children with FASD also typically show striking delays in adaptive and social functioning (Thomas, Kelly, Mattson & Riley, 1998; Whaley, O'Connor, & Gunderson, 2002), which are said to plateau at the 6 year age level (Thomas et al., 1998). In addition, they show difficulties in social judgment and communication (Kodituwakku, 2007), are unable to anticipate the
consequences of their actions (Caldwell, 1993), and behave inappropriately in social situations (Hinde, 1993). Children with FASD also show lower levels of moral maturity than their peers (Schonfeld et al., 2005), and these lower levels are associated with increased behaviour problems and compromised social relationships. Impaired social adaptive functions exist even when compared with groups who have similar levels of verbal intelligence (Thomas et al., 1998), suggesting their social deficits extend beyond their cognitive delay. Furthermore, sex differences have been reported in parent-rated social behaviour in children with FASD, with females being rated as having more severe social problems than males (Rasmussen, Becker, McLennan, Urichuk & Andrew, 2011; Schonfeld, Paley, Frankel & O’Connor, 2006). Children with FASD also have a number of other associated difficulties including poor problem solving, difficulty generating and implementing favourable strategies and producing relevant responses when solving social dilemmas, as well as greater reliance on adult assistance during these tasks (McGee, Bjorkquist, Price, Mattson & Riley, 2009; McGee, Fryer, Bjorkquist, Mattson & Riley, 2008).

In summary, children with FASD have poor social skills in addition to their impairments in cognitive and behaviour domains, all of which lead to poor peer relations and negative socialization later in life. It is essential to understand these difficulties and, in order to be able to offer appropriate interventions, it is also necessary to investigate the processes related to these difficulties. The underlying processes of social symptoms observed in FASD are suggestive of specific PAE-related deficits in social cognition and related neuroanatomy. However, a comprehensive picture of the social cognitive profile in FASD is lacking.
1.3 Social Cognition: A Bottom-Up Approach

Social cognition refers to the specialized domain of cognition that underlies mental representations of the self, others, and the social world (Lewis & Carpendale, 2004). Social cognitive abilities are used in social interactions, and influence the development of social skills and behaviour (Staub & Eisenberg, 1981; Dodge et al., 2002). As previously discussed, social skills are crucial for multiple aspects of daily functioning and are disturbed in populations with PAE (Coggins et al., 2007; Greenbaum et al., 2009; Rasmussen, Wyper & Talwar, 2009; Thomas et al., 1998; Whaley et al., 2002). Importantly, the social deficits observed in FASD are suggestive of impaired social cognition and related neuroanatomy. However, as research to date is based on understanding cognitive and behavioural difficulties of this population, the processes underlying their deficient social skills specifically are largely unknown. Also lacking is knowledge of how social cognition deficits relate to daily behaviour, or how neuroanatomy related to social processing is influenced following PAE. Thus the present thesis will address these knowledge gaps by adopting a bottom-up perspective of social cognition (Figure1). Bottom-up approaches have been used to describe development in other behavioural domains such as shared attention (Emery, 2000; Itier & Batty, 2009), theory of mind (Baron-Cohen, 1995), and self-regulation (Williams & Shellenberger, 1996). These bottom-up approaches propose that lower level base functions or foundation skills are necessary to support the development of higher order functions, or more complex skills (Ayres, 1979).

Within the current bottom-up approach there is the issue of task complexity. For the purposes of this thesis, I define a simple task as one that has few elements and few cognitive demands. For example, an immediate recognition task may be considered simple because all stimuli are presented until a response is made and there are few elements to integrate and cognitive demands
(e.g., no working memory or manipulation). By comparison, a complex task has multiple elements to be integrated and requires recruiting many different cognitive processes. For example, an N-back task requiring one to remember previously presented items in a sequence would be a complex task since multiple elements need to be integrated and many cognitive processes are required (e.g., hold information in mind, manipulation, short term memory). Within the present bottom-up approach, complexity increases from low to high levels (e.g., face processing to social perspective taking). In addition to complexity increasing between levels, complexity can also vary within each level (e.g., simple reaction time responses to cued reaction time responses).

For the present thesis, the bottom-up approach defines face processing as one of the lower level base functions, as this is a universal preference present from birth. The next level in the bottom-up perspective is eye gaze processing, which is a specific and more complex aspect of face processing. Next, it is proposed that adequate face and gaze processing are required for the development of higher order social perspective taking, namely theory of mind and empathy, which represent the top level of this approach. Importantly, underlying these three levels is the neuroanatomy related to social functioning, which is represented in the lowest level (Figure 1). Research supports the current bottom-up perspective of social cognition, as face and eye gaze processing are related to theory of mind and empathy development (Balconi, 2008; Baron-Cohen, 1995; Staub & Eisenberg, 1981; Yeates et al., 2007), and each of these processes are subserved by common brain regions and white matter pathways (Baron-Cohen, 1995; Calder et al., 2002; Castelli, Frith, Happe & Frith, 2002; Wicker, Michel, Henaff & Decety, 1998). However, this approach has not been used to describe social cognition and related impairments in FASD. The present thesis therefore builds on previous knowledge and uses this bottom-up
perspective to examine the influence of PAE on social cognition. Each component of this
perspective will be discussed in subsequent sections and then related to FASD.

**Figure 1.** Bottom-up approach used to examine social cognition

1.3.1 Face Processing

The human face is one of the most important visual stimuli people process on a daily basis and is
essential for social communication (Chung & Thomson, 1995; Cohen Kadosh & Johnson, 2007;
Frischen, Bayliss & Tipper, 2007; Kinzler & Shutts, 2008). Accordingly, face processing
represents the first stage in the current bottom-up approach (Figure 1). Face perception is critical
for social interactions and, based on both human and animal research, requires specialized neural
networks for face processing (Cohen Kadosh & Johnson, 2007; Kanwisher, 2010; Perrett &
Rolls, 1982). Newborn human infants show interest in faces immediately after birth (Goren,
Sarty & Wu, 1975) and by two days of age can reliably discriminate their mother’s face from
that of a stranger’s (Bushnell, Sai & Mullin, 1989; Fagan, 1979). Furthermore, typically
developing infants demonstrate preference towards certain aspects of the face at different ages:
one month olds, for example, prefer to look at external features such as the hair line and chin,
whereas two month olds prefer internal features such as the eyes and mouth (Maurer &
Salapatek, 1976). Sex differences in face processing development are also observed. Male
infants at 12 months of age orient towards faces less than female infants, suggesting early sex
differences in face preference and development (Connellan, Baron-Cohen, Wheelwright, Batki &
Ahluwalia, 2000). Also, by approximately 12 to 18 months, maternal face expressions are shown
to influence a child’s behaviour (Klinnert, 1984), but it is not until the second year of life that a
child is able to interpret the specific consequences of the emotions in faces (Pons, Lawson,
Harris & De Rosnay, 2003). Further developmental improvement in face identification skills is
seen between three to four years of age (Bruce et al., 2000; Ellis, 1992), with some adult-like
skills observed as early as 8 to 11 years (Ellis, 1992; Feinman & Entwisle, 1976). However, the
neurophysiological correlates underlying face processing continue to develop throughout
adolescence and into young adulthood (Batty & Taylor, 2006).

One influential cognitive model of face processing proposed by Bruce and Young (1986) posits
that independent processing pathways serve to extract different types of information and
meaning from face stimuli. According to their model, facial features and configural information
are processed using structured encoding mechanisms that extract information about the
individual components of the face (e.g., identity, expression, gaze). From these encoding
mechanisms, face expressions are proposed to be processed independent of face identity, while
the processing of facial speech is independent of other face categorizations such as emotion and
eye gaze (Bruce & Young, 1986; Bruce et al., 2000; Campbell, Landis & Regard, 1986).
Unfortunately, the majority of research to date has focused on face identification or facial expressions in children, but has not examined other critical components such as the mouth and eye gaze (Bruce et al., 2000). By investigating the specific aspects of face development, we can further understand how individuals acquire identification skills and extract meaningful information from different facial components. Because of the fundamental role that face processing plays in guiding social interactions and communication, it is believed that deficits in any component may lead to atypical social development (Bruce et al., 2000; Dawson, Webb & McPartland, 2005). Therefore by investigating global and individual components of face processing in FASD we can determine what aspects may underlie any potential impairment and examine whether these impairments are related to social and behavioural difficulties.

1.3.2 Eye Processing

Although the human face is arguably one of the most important visual stimuli people process, details within the face, specifically the eyes, are thought to be most critical for social functioning (Emery, 2000; Itier & Batty, 2009; Kobayashi & Kohshima, 1997). Compared to other mammals, the human eye has unique morphology represented by the high contrast of white sclera and coloured iris (Csibra & Gergely, 2005; Kobayashi & Kohshima, 1997), which allows for easy discrimination of eye gaze. Thus, the unique morphology of the human eye makes it critical for social communication and understanding (Maurer & Salapatek, 1976). Infants as young as two months of age spend more time looking at the eyes than external face features such as the hairline and chin (Maurer & Salapatek, 1976). At 5 months of age, infants are able to discriminate between small horizontal deviations of gaze (Symons, Hains & Muir, 1998), supporting the use of eye direction as a form of communication. Sex differences in sensitivity to
eye gaze are also observed at approximately 12 months of age, reflecting less eye contact made by males than females (Lutchmaya, Baron-Cohen & Raggatt, 2002). Overall, not only is the eye region important in non-verbal communication, the eyes also play a critical role in attentional orienting and social processing. Therefore, the second level of the current bottom-up approach to social cognitive development is eye processing (Figure 1).

One of the main communicative functions of eye gaze is to direct attention towards specific locations or objects in the environment. If someone is looking directly at us, we are the object of their attention; however, when eye gaze is averted away from us, we are no longer the object of interest and the person is attending to something or someone else (Baron-Cohen, 1995; Emery, 2000; Itier & Batty, 2009). Researchers in the field of spatial attention have adopted a social cognitive approach for investigating the mechanisms of social attention. Specifically, averted eye gaze cues are commonly used in adaptations of Posner cuing paradigms to demonstrate reflexive attentional orienting in response to eye gaze direction (Driver et al., 1999; Ristic, Friesen & Kingstone, 2002; Stevens, West, Al-Aidroos, Weger & Pratt, 2008). In these spatial cuing paradigms, an eye gaze cue is presented in the centre of the computer screen with gaze directed to the left or right, followed by a peripheral target. It is commonly observed that reaction times (RT) are faster for targets that appear in the gazed-at, or valid location, compared to the location opposite the gazed direction, or invalid location (Driver et al., 1999; Friesen & Kingstone, 1998). This robust eye gaze following has been demonstrated successfully in infants as young as three months of age (Farroni, Csibra, Simion & Johnson, 2002; Hood, Willen & Driver, 1998), children three to five years old (Ristic et al., 2002), as well as clinical populations such as autism (Kylläinen & Hietanen, 2004; Senju, Tojo, Dairoku & Hasegawa, 2004). Furthermore, eye gaze following is observed even when the gaze cue is counter-predictive of the target location.
(Friesen, Ristic & Kingstone, 2004), supporting the idea that gaze following is reflexive (Laidlaw & Pratt, 2010; Ristic, Wright & Kingstone, 2007; Stevens et al., 2008).

The eye region also has a main role in social functioning. Reflexive orienting to eye gaze contributes to the development of joint attention, which is the ability to determine whether one is attending to the same object or event as someone else (i.e., using eye direction) (Bruner, 1985; Emery, 2000; Itier & Batty, 2009). Joint attention typically emerges around 9 to 14 months of age (Baron-Cohen, Baldwin & Crowson, 1997) and is observed earlier in female infants than male infants (Olafsen et al., 2006). It is not until approximately 18 months that shared attention is developed. Shared attention occurs when two individuals are aware of each other’s object of attention and each use the other’s eye direction to ensure both are attending to the same target, incorporating mutual gaze and gaze orienting (Butterworth, 1991; Perrett & Emery, 1994). Thus, due to the importance of the eye region and gaze in social functioning and development, any impairment in processing or understanding may lead to atypical social cognition.

One clinical population where atypical social cognitive processing has been observed is autism. It is their impairments in social processing, specifically eye gaze processing, which is believed to underlie their social deficits (Baron-Cohen, 1995). Children with autism tend to avoid eye contact (Pelphrey et al., 2002) and have deficient attentional orienting in response to eye gaze (Kylliäinen & Hietanen, 2004; Senju et al., 2004). It has also been proposed that impaired social and attentional understanding of eye gaze may result in the deficient social processing observed in autism, such as their impairments in theory of mind and joint attention (Baron-Cohen, 1995; Baron-Cohen, Wheelwright, Hill, Raste & Plumb, 2001; Dawson et al., 2004). Deficient eye
gaze processing and understanding may contribute to atypical social cognitive development in clinical populations, such as FASD; however this has not been examined.

1.3.3 Social Perspective Taking

The highest level of the current bottom-up approach is represented by social perspective taking (Figure 1), which is a fundamental determinant of children’s moral and social development (Selman, 2003), referring to one’s understanding of another person’s point of view (Selman, 1971). Within the current dissertation, this includes theory of mind, empathy and related behaviour.

1.3.3.1 Theory of Mind

Theory of mind is the ability to infer and comprehend the mental states of others, including deceptions, intentions and beliefs (Premack & Woodruff, 1978). This ability develops rapidly during the preschool years and by the age of four most children are able to understand another’s perspective and pass simple false belief tasks (Mitchell & Lacohee, 1991; Wellman, Cross & Watson, 2001). Sex differences are also observed in theory of mind, with females demonstrating higher performance than males on these tasks (Happe, 1995).

The eye region, in addition to providing salient information about another’s attention, also functions in complex forms of social cognition including theory of mind by conveying key information about mental states and emotions (Baron-Cohen, 1995; Frischen et al., 2007). According to Baron-Cohen (1995), the development of theory of mind involves understanding and interpreting eye gaze and shared attention. In his model, he proposed several specialized
modules that subserve these abilities. The first two modules are the eye direction detector, which identifies the presence of eyes and their direction and the intentionality detector, which assigns goal directed motion to an agent. Baron-Cohen suggested these two modules both contribute to the development of the shared attention mechanism, which determines whether you and another individual are both attending to the same object or event in the environment. Because it requires higher order processing, the shared attention mechanism is believed to be specific to humans and higher primates. Notably, the shared attention mechanism is thought to be necessary for higher order theory of mind development (Baron-Cohen, 1995), since it allows one to use information about eye gaze and the intentions of others to infer their mental states and desires. Eye direction is therefore critical to the attribution of mental states and development of theory of mind (Baron-Cohen, 1995; Baron-Cohen et al., 2001). Taken together, the pervasive role of eye gaze in social cognition develops from simple preference towards viewing eye stimuli and eye direction to complex social knowledge and elaborate theory of mind.

1.3.3.2 Empathy

Empathy is another key aspect of social perspective taking and it refers to the response that stems from understanding another’s emotional state (Eisenberg, Spinrad & Sadovsky, 2006). Empathy also develops during the preschool years, with children three years of age capable of differentiating between emotional responses in other people and understanding that social outcomes are associated with these responses (Borke, 1971; 1973). As with theory of mind, empathy is also reportedly lower in boys than girls, suggesting sex differences in this component of social perspective taking (Bryant, 1982; Marton, Wiener, Rogers, Moore & Tannock, 2009).
Importantly, young children are capable of empathic responses and these responses play a critical role in social cognition.

Empathy development occurs as a continuous process that is first manifested as a conscious awareness that other people have their own feelings that can differ from one’s own, and is followed by the act of putting oneself in another person’s place and viewing the world from their perspective (Borke, 1973). Furthermore, empathy consists of both cognitive and affective components. The cognitive aspect represents a child’s ability to comprehend and assume the perspective of another person (Zahn-Waxler, Robinson & Emde, 1992); while the affective aspect represents a child’s understanding of and ability to experience vicariously the emotional responses of others and hence share their feelings (Shirtcliff et al., 2009; Zahn-Waxler et al., 1996). Both cognitive and affective aspects of empathy are not independent of each other (Hoffman, 1988), but instead develop as continuous processes together (Borke, 1973). Important for this thesis, empathy is believed to mature as the result of children’s improved social abilities and is implicated in the development of prosocial behaviours (Hoffman, 2000).

Low levels of empathy are commonly observed in childhood disorders characterized by impairments in social cognition, such as disruptive behaviour disorders (Marton et al., 2009; de Wied, de Wied & van Boxtel, 2010). Both low levels of empathy and theory of mind are believed to be risk factors in the development of aggressive and violent behaviour (Freshbach, 1997). Acquiring strong social skills and adaptive behaviour therefore requires an understanding of other people’s mental and emotional states, and applying this understanding to social interactions. Overall, because social skills and adaptive behaviour are poor in children with
FASD, they too may show underlying impairments in empathy and theory of mind. The present thesis therefore investigated these two components of social perspective taking in FASD and NC.

1.3.4 Social Neural Network in Typical Development

1.3.4.1 Typical Grey and White Matter Development

At the base of the current bottom-up approach are the neural networks underlying social cognitive processing (Figure 1). It is imperative that the neuroanatomic underpinnings of behaviour and social cognition be investigated, as both diagnostic and intervention approaches would benefit from increased understanding of the teratogenic effects of alcohol on the brain and related social function. In typical development, cortical grey matter follows a functional maturation sequence that begins in the dorsal aspect of the parietal cortex, particularly the primary sensorimotor areas, and then spreads rostrally over the frontal cortex, followed by lateral spread over the parietal, occipital and temporal cortices (Gogtay et al., 2004). While the frontal and occipital poles mature early, the superior temporal gyrus and dorsal lateral prefrontal cortex mature somewhat later in development (Gogtay et al., 2004). The sequence in which the cortex matures relates to cognitive and functional development. For example, regions associated with basic functions such as motor and sensory processing mature before regions associated with spatial orientation, speech and attention (Gogtay et al., 2004).

It is well established that by 6 years of age the total size of the brain reaches approximately 90% its adult size, with male brains approximately 12% larger on average than those of females (Giedd, 2004). Although total brain size remains relatively stable across the ages of 6 to 20 years, various brain regions do undergo distinct maturational changes. For example, non-linear
changes in grey matter volume are observed in the frontal and parietal lobes; grey matter reaches peak volumes in these areas by approximately 11 to 12 years (12 years for males and 10 to 11 years for females), followed by reductions after puberty and into post-adolescence. The development of temporal lobe grey matter is also non-linear, peaking in volume around 17 years of age and declining thereafter (Giedd et al., 1999).

In addition to the non-linear changes in grey matter, steady increases in white matter are also seen during childhood to adolescence, although considerable regional variation exists (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). For example, the corpus callosum and inferior longitudinal fasciculus (ILF), which are two of the most rapidly developing white matter tracts, reach 90% of their development by 11 years of age. In comparison, the uncinate fasciculus (UF), a fronto-temporal connection, only reaches 90% of its development by approximately 25 years of age (Lebel, Walker et al., 2008). The grey and white matter developmental changes are believed to reflect synaptic pruning and use-dependent strengthening of neural networks, as well as increased myelination of neurons (Bourgeois, Goldman-Rakic & Rakic, 1994; Woo, Pucak, Kye, Matus & Lewis, 1997). Importantly, disruption to any of these processes can lead to disturbed cognitive and social development (Blakemore & Choudhury, 2006).

1.3.4.2 Brain Regions Comprising the Social Neural Network

Social cognitive neuroscience is an emerging field devoted to understanding how brain regions and systems implement social processes and behaviour (Cacioppo et al., 2007). Within social neuroscience, a distributed neural network has been proposed to support a variety of social cognitive processes (Adolphs, 2001). The brain regions that form the social cognitive network include the inferior temporal regions such as the fusiform gyrus, which is implicated in face
perception and recognition (Kanwisher, 2010; McCarthy, Puce, Gore & Allison, 1997; Puce, Allison, Asgari, Gore & McCarthy, 1996), and the superior temporal sulcus, which is involved in analysing biological motion cues (e.g., eyes and hands) (Pelphrey, Morris, Michelich, Allison & McCarthy, 2005). The amygdala is a limbic area that is also essential in the social cognitive network, involved in processing and recognizing emotions, as well as labeling stimuli with emotional content and processing gaze direction (Adolphs, 1999; Kawashima et al., 1999).

The social neural network also includes specific parietal and frontal regions. Parietal regions such as the temporal parietal junction are engaged when one considers what another person is thinking (Kanwisher, 2010; Saxe & Kanwisher, 2003), and during eye gaze processing (Calder et al., 2002). The temporal parietal junction acts as an interface between the ventral and dorsal visual streams, allowing individuals to recognize and interpret objects in relation to motion and intention, an important prerequisite to perspective taking abilities (Frith & Frith, 2001). Specific frontal regions involved in the social neural network include orbital frontal and ventromedial prefrontal cortices, which play critical roles in theory of mind, regulating and recognizing emotions, processing rewards and punishments, and understanding gaze (Amodio & Frith, 2006; Frith & Frith, 2001; Vecera & Rizzo, 2006; Vuilleumier, Armony, Driver & Dolan, 2001). The anterior cingulate, a key paralimbic region is also involved in these social processes (e.g., emotion, rewards, theory of mind) (Allman, Hakeem, Erwin, Nimchinsky & Hof, 2001; Carter et al., 2000). Importantly, studies report that the regions involved in theory of mind overlap extensively with those involved with gaze perception and face processing, giving rise to the possibility of a neural link between the components of the proposed social cognitive approach (Baron-Cohen, 1995; Calder et al., 2002; Castelli et al., 2002; Wicker et al., 1998). Sophisticated
forms of social cognition arise from enhanced connectivity and integration between brain structures involved in the social neural network (Adolphs, 2001; Pelphrey & Carter, 2008).

### 1.3.4.3 White Matter Pathways in the Social Neural Network

Three important limbic white matter pathways that may represent neural links between regions within the social network include the UF, cingulum, and ILF. The UF is a ventral anterior association bundle that originates from the anterior temporal area (i.e., amygdala and hippocampus) and connects to the frontal lobes (i.e., orbital frontal and frontal polar regions) (Catani, Howard, Pajevic & Jones, 2002; Klingler & Gloor, 1960). Fibres in the UF are shown to be critical for emotional regulation (Carmichael & Price, 1995), evaluation and regulation of affective stimuli (Petrides & Baddeley, 1996), as well as the socioemotional and behavioural difficulties observed in children with socioemotional deprivation (Eluvathingal et al., 2006). Notably, the UF is disturbed in patients with autism (Pugliese et al., 2009) and schizophrenia (Kawashima et al., 2009), populations that are known to have deficient social perspective taking ability (Lee, Farrow, Spence & Woodruff, 2004). The second white matter tract that will be investigated in the current thesis is the cingulum, which connect with multiple brain regions including specific frontal and temporal areas (Pandya, Hoesen & Mesulam, 1981). This pathway allows for communication and relay of information between important limbic structures (Catani et al., 2002), and plays a critical role in theory of mind, empathy, and emotional processing (Mayberg, 1997; Singer et al., 2004). The third tract that will be examined is the ILF, which is a ventral association bundle with long and short fibres that connects sensory areas to limbic regions. This white matter pathway runs through the temporal lobe and connects the temporal pole with the occipital pole (Catani et al., 2002), including visual areas, amygdala and
hippocampus (Catani, Jones, Donato & Ffytche, 2003). The ILF is involved in processes related to visual perception (Ffytche & Catani, 2005), with reduced connectivity associated with impaired face processing in autistic populations (Kleinhans et al., 2008).

Together, these limbic pathways are involved in neural functioning related to social processing and represent the root of the present bottom-up approach (Figure 1). Disruption in any of these white matter connections may lead to disturbed social behaviours, such as those observed in children with FASD. To determine whether limbic white matter is impaired following PAE, the current thesis will investigate the microstructure of the UF, cingulum, and ILF in children with FASD.

1.4 Social Cognition in Children with FASD

According to the current bottom-up approach for studying social cognition, face processing and eye processing are seen as lower level skills that are required for the development of higher order social perspective taking (e.g., theory of mind and empathy). The neural network that supports these three levels, including the UF, cingulum and ILF is also integral for social cognitive functioning (Figure 1) and makes up the bottom level of this approach. Each component of the present bottom-up perspective will now be discussed in relation to current understanding of social functioning in FASD. From this discussion, gaps in current knowledge will be highlighted and aims of the present thesis will be stated.
1.4.1 Face Processing in FASD

To date, research on the face processing abilities of children with FASD has been relatively limited. Several studies have examined face memory, but results have been varied. Some researchers fail to observe deficits in face memory (Autton-Ramo et al., 2002; Uecker & Nadel, 1996), while others have reported below average performance on tasks of immediate and delayed memory for faces (Rasmussen, Horne & Witol, 2006; Wheeler, Stevens, Sheard & Rovet, 2011). These findings suggest children with FASD may have deficits in processing and remembering certain types of face stimuli. However, these previous results may have been influenced by the memory component of the tasks, making it difficult to discern whether the group differences were the result of deficient face processing or memory impairments, which are common in FASD (Mattson, Riley et al., 1996; Willoughby et al., 2008). Furthermore, these tasks failed to indicate what specific aspects of face processing are specifically impaired. Relevantly, more recent research has shown children with FASD have difficulties in more complex aspects of face processing, such as impaired identification of face emotions in social contexts (Greenbaum et al., 2009). However, because these findings were limited to a single published article, it is important to examine multiple aspects of face processing more thoroughly in children with FASD and to determine what aspects of their face recognition difficulties underlie the social behavioural deficits that are commonly observed following PAE.

1.4.2 Eye Processing in FASD

As with face processing, research on understanding eye gaze has also been limited in FASD. One study reports 60% of children with FASD have abnormalities in direct gaze and 25% show deficits in eye contact (Bishop et al., 2007). The results from this study, however, were limited
due to reliance on caregiver reports and measures specific to autism. Due to the significant role of eye gaze processing in social cognition development (Baron-Cohen, 1995; Emery, 2000; Itier & Batty, 2009), examining the understanding and use of eye gaze following PAE is critical to further our understanding of the social and adaptive impairments in this population. If impairments in processing and understanding face and eye gaze stimuli are found to underlie the poor social skills and behaviour in FASD, not only will we gain further understanding of their social difficulties, we will also be able to use this information to appropriately structure treatment approaches, as has been done in other clinical populations (e.g., autism) (Tanaka et al., 2010).

1.4.3 Social Perspective Taking in FASD

Although much is known about the social skill and behaviour difficulties following PAE, far less is understood about the social perspective taking abilities that may underlie these difficulties. Preliminary reports indicate school age children with FASD perform poorly on tasks of theory of mind. Specifically, they are unable to convey how story characters feel in certain situations (Coggins, 1997; Greenbaum et al., 2009; Kodituwakku et al., 1997; Rasmussen et al., 2009) and they have difficulty with social communication (Coggins et al., 2003) and identifying emotions in photographed faces (Greenbaum et al., 2009). Since these impairments are also predictive of caregiver- and teacher-rated behavioural problems in FASD (Greenbaum et al., 2009), this suggests their social behavioural impairments may stem from a breakdown in these social cognitive domains.

Additionally, children with FASD show inadequate understanding and use of mental state words when referring to other people’s perspectives (Timler, Olswang & Coggins, 2005). Rasmussen et
al. (2009) found that deficient performance on theory of mind tasks in 4- to 8-year old children with FASD was correlated with their inhibition deficits. Interestingly, older children with FASD performed worse on theory of mind tasks than younger children. Similar age-related declines are also observed in other aspects of social and adaptive functioning in these children (Thomas et al., 1998; Whaley et al., 2002) and are suggestive of an arrest in social development. Caregiver reports are consistent with these findings, indicating children with FASD fail to take into account the perspectives of other people during conversations (Timler & Olswang, 2001). Indeed, two of the core social deficits in children with FASD are proposed to be their inability to understand the mental states of others and their difficulty selecting emotions that accompany these states (Greenbaum et al., 2009). However, these claims are limited, as they are based on few published studies.

To our knowledge, no studies to date have directly investigated empathy in FASD. However, clinical descriptions provided by caregivers suggest children with FASD may have difficulty empathizing and anticipating the consequences of their actions (Caldwell, 1993). Because these children are at risk for aggressive behaviour, conduct problems, and attention problems (Fryer, McGee, Matt et al., 2007), empathy may also be compromised.

Taken together, preliminary findings support the notion that children with FASD have difficulties with theory of mind, related emotion processing and empathy. Moreover, these domains of social perspective taking are essential for social cognitive development and may underlie the observed behaviour and social problems experienced following PAE (Denham et al., 2001; Hoffman, 2000). However, because of the limited evidence and heavy reliance on caregiver reports, the profile of social perspective taking following PAE, and how these
difficulties relate to behaviour, is not known. Therefore, in order to fully understand the teratogenic impact of PAE on these social domains, and to ensure informed clinical practice is maintained, the current thesis examined both theory of mind and empathy in FASD and NC.

1.4.4 Social Neural Network in FASD

Even though the teratogenic effects of alcohol on the brain are seen to be widespread, there is mounting evidence that certain brain regions may be more vulnerable than others. For example, the occipital lobes appear to be relatively spared (Lebel, Roussotte & Sowell, 2011), while several areas of particular vulnerability appear to be those belonging to the social neural network. Recent studies have shown abnormalities in the temporal cortex, reflecting increased gray matter (Sowell et al., 2001) and activational differences (Sowell et al., 2007). Likewise, reduced volumes in the amygdala region were described in older, compared with younger children with FASD (Nardelli, Lebel, Rasmussen, Andrew & Beaulieu, 2011). Structural and functional abnormalities in the orbital and medial frontal cortices (Fryer, Tapert et al., 2007; Sowell et al., 2002) may reflect abnormal engagement of the orbital frontal area during emotional and inhibitory tasks (Fryer, Tapert et al., 2007; Kodituwakku, May, Clericuzio & Weers, 2001). Accordingly, some researchers have posited the orbital and medial frontal cortices as ‘hot-spots’ of PAE (Kodituwakku et al., 2001). In addition, structural impairments have also been observed in other frontal regions such as the inferior and middle frontal areas (Fryer, Tapert et al., 2007; Nash et al., 2006), while functional differences have been noted in the dorsal frontal cortex (Sowell et al., 2007). These structural and functional abnormalities represent a critical first step in understanding the teratogenic influence of PAE on the developing social brain, however
further research is warranted on the white matter connections that also comprise the social neural network.

It is well established that the neural network involved in social processing also includes critical white matter tracts that connect key regions within the network. However, in FASD, the pathology of the white matter connections between these regions has not been specifically examined, particularly in relation to their social cognition difficulties. Since white matter appears to be a main target of alcohol teratogenesis (Chiappelli, Taylor, Espinosa de los Monteros & de Vellis, 1991; Guerri, Pascual & Renau-Piqueras, 2001; Riikonen, Salonen, Partanen & Verho, 1999; Watari, Born & Gleason, 2006), investigating white matter tracts following PAE is critical for further understanding the neural mechanisms underlying the social disturbances in these children.

One neuroimaging tool for examining white matter is diffusion tensor imaging (DTI). DTI is a non-invasive technique based on magnetic resonance imaging (MRI) that provides information about tissue microstructure and orientation properties of the diffusion process of water molecules (Basser, Mattielo & LeBihan, 1994). The main indices provided by DTI are fractional anisotropy (FA), which is a measure of water diffusion in a single direction within a tensor, and mean diffusivity (MD), which represents the average dispersion of water molecules in multiple directions in the tensor (Basser et al., 1994). DTI also provides several secondary indices, known as eigenvectors, which are scalar measures derived from the diffusion tensor matrix. The first eigenvalue ($\lambda_1$) is the largest and represents diffusivity parallel to the axons, referred to as axial (or parallel) diffusivity (AD). The second and third eigenvalues represent diffusivity in the planes orthogonal to the axons and are generally averaged ($(\lambda_2 + \lambda_3)/2$), resulting in radial or
perpendicular diffusivity (RD) (Basser, 1995). When brain development is abnormal or acquired brain damage occurs, FA values are typically lower and MD values typically higher in regions of affected white matter, compared with typically developing white matter (Neil, Miller, Mukherjee & Huppi, 2002).

A number of studies have used DTI to examine white matter in FASD. The majority of reports have highlighted poor fibre integrity (i.e., poor myelination and white matter disorganization) in the corpus callosum (Fryer et al., 2009; Lebel, Rasmussen et al., 2008; Li, Coles, Lynch & Hu, 2009; Ma et al., 2005; Sowell, Johnson, Kan et al., 2008; Wozniak et al., 2006; Wozniak et al., 2009). DTI studies have also reported poor fibre integrity in other white matter pathways including bilateral cingulum (Lebel, Rasmussen et al., 2008; Sowell, Johnson, Kan et al., 2008), temporal pathway regions (ILF) (Lebel, Rasmussen et al., 2008; Sowell, Johnson, Kan et al., 2008), frontal pathway regions (superior longitudinal, inferior fronto-occipital and UF) (Fryer et al., 2009; Lebel, Rasmussen et al., 2008; Sowell, Johnson, Kan et al., 2008), parietal and occipital pathway regions (Fryer et al., 2009), internal capsule (Fryer et al., 2009; Sowell, Johnson, Kan et al., 2008), globus pallidus, putamen and thalamus (Lebel, Rasmussen et al., 2008), brainstem (Sowell, Johnson, Kan et al., 2008) and cerebellar pathways (Lebel, Rasmussen, Wyper, Andrew & Beaulieu, 2010).

In summary, white matter pathology has been reported in many areas including, but not limited to the social neural network. The majority of DTI studies, however, have focused on the neuroanatomy related to cognitive processing, with no study focusing specifically on limbic pathology or discussing how limbic pathology may relate to social cognitive difficulties in FASD. Because social difficulties are proposed to be a core deficit following PAE (Greenbaum et al., 2009), and because key regions in the social neural network are believed to be ‘hot spots’
of PAE (i.e., orbital and medial frontal regions) (Kodituwakku et al., 2001), it is necessary to study white matter pathology in specific social limbic pathways in children with FASD.

1.5 Rationale for Proposed Research

1.5.1 Investigating Social Cognition in FASD

Children with FASD experience significant difficulty in a variety of domains, with cognitive processing being among the most widely researched (Kodituwakku, 2007; Kodituwakku, Kalberg & May, 2001). In addition, children with FASD show marked social difficulties (Greenbaum et al., 2009; Rasmussen et al., 2009; Thomas et al., 1998; Wheeler et al., 2011), leading some researchers to suggest social cognitive impairment represents a core deficit in this population (Greenbaum et al., 2009). Notably, social deficits in FASD are reported almost as frequently as their most common cognitive impairment, namely attention deficits (Steinhausen, 1996). However, the specific nature of social cognitive difficulties and the processes that underlie them have not been fully established. There is limited knowledge on how children affected by PAE perform in key aspects of social cognition such as face and eye gaze processing, theory of mind and empathy, and how difficulty in these areas relate to parent-ratings of behaviour and social dysfunction. Additionally, our understanding of the impact of PAE on neural structures comprising the social neural network is limited to a few studies. Therefore, to investigate the core components of social cognition dysfunction in FASD the present thesis used a bottom-up approach to examine social components starting with lower level base skills (e.g., face processing and eye gaze processing) and advancing to higher order social cognitive skills (e.g., theory of mind and empathy). A further goal of this thesis was to use DTI to better
characterize the underlying neuroanatomy relating to social dysfunction following PAE. Thus, the primary goals of the present thesis were to identify the core social cognitive deficits and related neuroanatomic abnormalities in children with FASD and examine whether these abnormalities account for observed deficits in parent-ratings of behaviour and social skills. I believe that by identifying the processes underlying the social and behavioural problems in children with FASD we will gain further understanding of the root causes of their behavioural phenotype and obtain information on how to help design greatly needed treatment approaches.

1.5.2 Research Questions

1. Do children with FASD show deficits in face processing?
   To address this question, individual face features and global face processing were investigated in children with FASD and normal controls (NC) using experimental and standardized measures. Age effects and relations between face processing and parent-rated social skills were also examined (Chapter 3).

2. Do children with FASD adequately orient attention in response to social eye gaze cues and are they able to use information of eye expression to understand other people’s mental states?
   To address this question an adaptation of the classic spatial cuing paradigm with central eye gaze and arrow cues was used. In addition, theory of mind was assessed using an experimental measure known as the Reading the Mind in the Eyes task (Chapter 4).
3. Do children with FASD show specific weaknesses in social perspective taking and do these change with age and differ by sex?

To address this research question, social cognition was investigated in children with FASD and NC (Chapter 5) using a neuropsychological test battery assessing social perspective taking. The relation between theory of mind and empathy, and parent-rated behaviour and social skills was also investigated. Additionally, age-related changes and sex differences in social perspective taking were examined.

4. Do children with FASD show impairments in a neural network involved in social functioning?

To examine the underlying neural mechanisms that support social cognition, DTI was used to investigate specific limbic white matter pathways. The DTI parameters in the UF, cingulum and ILF pathways were compared between children with FASD and NC (Chapter 6).

1.5.3 Hypotheses

1. Previous research indicates global face processing develops to a normal level following PAE (Uecker & Nadel, 1996; Autti-Ramo et al., 2002). However, certain aspects of face processing, such as eye gaze and emotion appear to be compromised (Bishop et al., 2007; Greenbaum et al., 2009). In addition, children with FASD have difficulty processing and integrating complex information (Kodituwakku, 2007; Simmons, Thomas, Levy & Riley, 2010). From this it was expected that compared to NC, children with FASD would not show significant impairments in accuracy when matching global face identity, but would
show lower accuracy scores when matching facial expression and eye-gaze. Furthermore, because face stimuli are highly complex in nature, I also hypothesized children with FASD would have slower overall processing speed (RT) when matching face features, compared to the NC group, and would not show improvements in accuracy and RT with age. Finally, I hypothesized any accuracy or RT impairments in the FASD group would correlate with parent-rated social problems.

2. Children with FASD show intact processing on simple RT measures, while displaying impaired processing with more complex RT tasks (Simmons et al., 2010; Simmons, Wass, Thomas & Riley, 2002) and, based on caregiver reports, they have abnormal use of eye gaze (Bishop et al., 2007). Furthermore, these children also have impaired performance on theory of mind measures (Greenbaum et al., 2009; Rasmussen et al., 2009), which are highly complex in nature. Based on these social processing impairments, I hypothesized children with FASD would not have difficulty on simple processing task (i.e., detecting stimulus onset with no central cues). They would, however, show significantly slower responses on complex tasks, such as detecting peripheral targets following central gaze and arrow cues. Because parental reports have indicated abnormal eye gaze processing in FASD, it was also predicted children would show a larger validity effect (i.e., a larger difference in RT between invalid and valid cues) to arrow cues than gaze cues. In addition, I hypothesized that the FASD group would show poorer theory of mind performance on the Reading the Mind in the Eyes, compared to NC.

3. Parents consistently rate children with FASD as having more behaviour problems and poorer social skills than parents of typically developing children (Caldwell, 1993;
Greenbaum et al., 2009; Kodituwakku, 2007; Thomas et al., 1998). In line with parental reports, children with FASD display poorer performance on tasks of theory of mind (Greenbaum et al., 2009; Rasmussen et al., 2009). Age-related effects have been observed on theory of mind and related social abilities, with older children with FASD performing below that of younger children with FASD (Rasmussen et al., 2009; Thomas et al., 1998; Whaley et al., 2002). Sex differences in children with FASD have also been reported in social skills, with females being rated by parents as having lower social skills than males (Rasmussen et al., 2011; Schonfeld et al., 2006). From this, I expected to find significant parent-rated behaviour and social problems in the FASD compared to NC group. I hypothesized children with FASD would have poorer performance on child measures of theory of mind and empathy, supporting previous caregiver and child rated findings, and any weaknesses in social perspective taking would be related to parent-rated social and behavioural problems. In addition, I hypothesized children with FASD would show increasingly impaired social perspective taking with age relative to NC. Furthermore, I hypothesized that females in the NC group would show higher levels of empathy than males in the NC group (Bryant, 1982; Marton et al., 2009), whereas females in the FASD group would show lower empathy levels than males in the FASD group (Rasmussen et al., 2011; Schonfeld et al., 2006).

4. The UF, cingulum and ILF are important white matter pathways involved in social cognitive processing (Ffytche & Catani, 2005; Mayberg, 1997; Petrides & Baddeley, 1996; Singer et al., 2004), and are compromised in other pediatric populations with social impairments similar to FASD (e.g., autism and schizophrenia) (Eluvathingal et al., 2006; Kleinhans et al., 2008; Pugliese et al., 2009). Research indicates children with FASD
have abnormalities in white matter pathways including, but not limited to the social neural network (Fryer et al., 2009; Lebel, Rasmussen et al., 2008; Sowell, Johnson, Kan et al., 2008; Wozniak et al., 2008), however, no study has focused on specific limbic pathways. Based on this research, I hypothesized that children with FASD would show compromised white matter integrity in the UF, cingulum and ILF, compared with NC. I hypothesized that white matter integrity in these social pathways would improve with age in the NC group, and would be distinct from the age-related changes observed in the FASD group.

The following chapters will address each of the main research questions. The research described herein is comprised of four studies presented in journal manuscript format.
Chapter 2
Methods

2.1 General Procedures

All assessments were completed in the Psychology and Diagnostic Imaging Departments at The Hospital for Sick Children (SickKids). Informed consent was obtained from parents or legal guardians, while assent was obtained from the children. Testing was divided over two days. Day 1 was devoted to clinical and experimental testing (Chapters 3, 4, 5). Clinical testing was administered by two trained psychometrists, Kelly Nash (KN) and Sara Stevens (SS) and scored by three psychometrists (Dragana Ostojic, KN and SS). Clinical psychometrists (KN, SS) were not blind to the group of each participant due to the nature of the larger experimental treatment study and accommodations of families’ schedules with therapists and availability of psychometrists. Nevertheless, all psychometrists were blind to the group of each participant when scoring and double scoring protocols. The Day 1 clinical neuropsychological battery used for the present thesis was part of a larger study involving an intervention program for the FASD group. Due to the requirements of the larger study, several additional clinical measures were administered, but are not reported in this thesis. Clinical measures that will be presented in the current thesis include Weschler Abbreviated Scale of Intelligence (WASI) (Weschler, 1999), two subtests from the Developmental NEuroPSYchological Assessment-II (NEPSY-II) (Korkman, Kirk & Kemp, 2009), namely the Affect Recognition and Theory of Mind, and four subtests from the Test of Social Cognition (Saltzman-Benaiah & Lalonde, 2007), namely False Beliefs, Strategic Control of Emotions, Personalized Emotions and Personalized Thoughts, and the Index of Empathy (Bryant, 1982). In addition, standardized caregiver questionnaires were administered to parents/caregivers. These included the Child Behavior Checklist (CBCL) (Achenbach, 2001).
and Social Skills Improvement System (SSIS) (Gresham & Elliot, 2008). Experimental measures used in this thesis included the Face Processing task (Bruce et al., 2000), the Gaze and Arrow Cuing tasks, and the Reading the Mind in the Eyes task (Baron-Cohen et al., 2001). The research team consisting of Dr. Rovet, KN and myself, was involved in all aspects of experimental design and choice of measures.

Day 2 consisted of a one-hour MRI session (Chapter 6). As the neuroimaging component of the present thesis was also part of the larger intervention study, all children received structural and functional scans (Go/NoGo task), as well as the DTI sequences. Only the DTI findings will presented in the current thesis. All neuroimaging was acquired using the research scanner in Diagnostic Imaging. All data were collected with a 1.5T MRI System (Signa EXCITE HD, GE Medical) using a standard eight-channel receive-only head array coil. Whole brain anatomical scans were acquired using an inversion recovery prepared 3D-FSPGR sequence: FA=20°, TR/TE/TI=10.3/4.2/400ms, FOV=24x18 cm, 256 x 256 matrix, slice thickness=1.5mm, 116-124 slices, ~7 minutes scan times. DTI data were acquired using an EPI sequence with the following parameters: 31 directions plus 4 images with b=0, FA=90°, TR/TE=15000/83.3ms, FOV=320mm, 128x128 matrix, slice thickness=2.5, and 50 slices. Total DTI acquisition time was approximately 9 minutes. During the scans children watched a movie through fibre-optic goggles to help limit motion. Conventional T2-weighted and FLAIR scans were also obtained for all children to detect gross brain abnormalities. Neuroimaging data were collected by DO, KN and SS. I was responsible for analyses of all DTI data, with the support of a MRI analyst. After Day 2 all children received a CD with pictures of their brain and a movie pass. Parents were reimbursed for travel and parking. All procedures were approved and in accordance with the Research Ethics Board guidelines of both SickKids and the University of Toronto.
2.2 Participants

Children in the FASD group were recruited between December 2009 and February 2010. All children had previously received a diagnosis along the fetal alcohol spectrum through either the Motherisk Clinic at SickKids (n =16) or another accredited FASD diagnostic facility in Ontario (n =9) prior to participating in this study. Children were brought to the clinic by caregivers who were concerned that the child’s current learning and behaviour problems were from the biological mothers’ consumption of alcohol during pregnancy. Included in the present study were children who had received a diagnosis along the fetal alcohol spectrum based on a detailed assessment by a team which consisted of a pediatrician, psychologist, psychometrist, and speech language pathologist, who saw the child and family over several days, following which a final collaborative diagnosis was made. The approach at Motherisk was based on the Canadian Diagnostic Guidelines system (Chudley et al., 2005), according to which all children had to have definite or strongly suspicious exposure to a significant amount of alcohol in pregnancy. Definite or strongly suspicious exposure was based on reliable clinical observation, self-report by the biological mother, reports by a reliable source (i.e., biological relative), medical records documenting positive blood alcohol or alcohol treatment, or other social, legal or medical problems related to drinking during pregnancy (Chudley et al., 2005). For the majority of cases, level and timing of prenatal alcohol exposure was unknown. Those children with facial dysmorphology and growth retardation with or without cognitive/behavioural features were considered to have FAS, whereas those without physical symptomatology were assigned a score of 1 to 4 based on assessment results. A ‘4’ was given if a child had an intelligence quotient (IQ) at and below 70 and three areas of deficit; a ‘3’ for an IQ score above 70 and three deficit areas; a ‘2’ for IQ above 70 and two significant deficit areas; and ‘1’ for an IQ above 70 and 1 or 0
deficit areas. Only those children with scores above 3 were considered to have ARND. For the present study, all children diagnosed at Motherisk had scores of ‘3’ and none had a ‘4’. For those children diagnosed elsewhere, five were diagnosed with partial FAS and 4 with ARND. To avoid the influence of additional confounding variables, children in the FASD group were excluded if their exposure history was unconfirmed or their primary exposure was to a substance other than alcohol (e.g., cocaine, heroin, marijuana). These exclusionary criteria were based on each child’s clinical records.

The NC group was recruited from through community and hospital postings or were biological children of a participating adoptive or foster parent. Children in the NC group were screened to ensure they did not have any clinical diagnoses or exposure to prenatal teratogens, which may bias results. Children were excluded if they had any psychiatric diagnosis (e.g., ADHD), an identified learning disability (LD) or exposure to any teratogenic substance. In addition, due to the neuroimaging component of this study, general exclusionary criteria for both NC and FASD groups were: a head injury or other neurological or brain abnormality, or a debilitating or chronic medical condition (e.g. cerebral palsy).
Chapter 3
Face Processing Skills in Children with Fetal Alcohol Spectrum Disorders

The face is arguably the most important visual stimulus one processes on a daily basis (Chung & Thomson, 1995; Cohen Kadosh & Johnson, 2007; Itier & Batty, 2009), and is an essential component for social behavior (Adolphs, 2002). Right from birth, newborns show considerable interest in faces (Goren et al., 1975) and by two days of age, they can discriminate their mother’s face from a stranger’s (Bushnell et al., 1989; Fagan, 1979). While face identification skills show improvement between three and four years of age (Bruce et al., 2000; Ellis, 1992), children at this age continue to show difficulty processing the spatial relations among internal features (Mondloch, 2003). In order to develop mature face perception and processing, however, children must gain understanding of the internal facial features, their configural arrangements, and the more global aspects of the face itself (Bruce et al., 2000; Mondloch et al., 2002).

It is well established from a broad and diverse literature that the internal and external aspects of a face not only provide critical information about a person’s identity such as sex and age, these also convey key social information including the person’s feelings and mental states (Adolphs, 2002; Balconi, 2008; Emery, 2000; Itier & Batty, 2009). For example, children's ability to recognize emotional faces improves with age (Herba, Landau, Russell, Ecker & Phillips, 2006), with matching and discriminating happy emotions being observed by age four, fear by age six and surprise by the age eight (Markham & Adams, 1992). Also, children’s use of facial information to understand the mental states of others undergoes age-related improvement, developing by approximately four years (Leslie, 1987; Wellman et al., 2001). Accordingly,
social aspects of face processing and recognition can serve to indicate whether children’s face processing skills are age-appropriate or impaired.

Because of the social importance of the face and accompanying age-related maturation, impairments in any aspect of facial processing may be a marker of potential atypical social development (Bruce et al., 2000). In autism, for example, children’s compromised social skills (Baron-Cohen, 1995; Baron-Cohen et al., 2001) are thought to reflect their poor face processing, given their reduced time spent looking at faces, more disorganized and variable face exploration, and impaired recognition of emotions (Balconi, 2008; Gepner et al., 1996; Pelphrey et al., 2002). Similarly, children with FASD not only show a broad array of cognitive deficits (Coggins et al., 2007; Kodituwakku, 2007; Mattson, Riley, et al., 1996; Mattson et al., 1999; Willoughby et al., 2008), particularly the processing of complex information (Kodituwakku, 2007; Simmons et al., 2010), these children also show deficient social and adaptive skills (Niccols, 2007; Thomas et al., 1998; Whaley et al., 2002;) reflecting significant immaturity (Schonfeld et al., 2005), inappropriate social behaviors and interactions (Thomas et al., 1998; Whaley et al., 2002), and slowed processing of social information (Simmons et al., 2010). One group of investigators has linked these difficulties to a limited understanding of social cues and consequences of actions (Streissguth & Giunta, 1988) while others attribute them to difficulties comprehending the mental states and emotions of others (Greenbaum et al., 2009; Rasmussen et al., 2009). However, unlike other clinical populations whose facial understanding has been extensively studied, this has received limited attention in children with FASD. To date, most studies of facial processing in FASD deal only with facial memory, with results ranging from no effect (Autti-Ramo et al., 2002; Uecker & Nadel, 1996) to suboptimal performance (Rasmussen et al., 2006; Wheeler et al., 2011). Although several recent studies have shown these children may have difficulties when
dealing with complex emotional face processing (Greenbaum et al., 2009) and eye gaze (Bishop et al., 2007), the impact of these difficulties on their social functioning has not been adequately examined. Since an investigation of the role of atypical face processing in the social difficulties of children with FASD can serve to inform both clinical practice and targeted treatment approaches, further research is warranted.

The present study therefore examined face processing abilities and the relations to social difficulties in children with FASD. I hypothesized these children would show intact matching of global face identity (Autti-Ramo et al., 2002; Uecker & Nadel, 1996) but would have reduced performance on tasks of facial expression and eye gaze (Bishop et al., 2007; Greenbaum et al., 2009). I further hypothesized that relative to NC, children with FASD would show slower processing speeds (RT) when matching face features and would not show similar age-related improvements in facial recognition accuracy. Moreover, I hypothesized that parent-rated social difficulties would be correlated with indices of impaired face processing in FASD.

3.1 Methods

3.1.1 Participants
This study included 42 children aged 8 to 12 years who belonged to one of two groups: FASD (n = 25; 13 males and 12 females) and NC (n = 17; 9 males and 8 females). The mean ages of the groups were 10.3 (± 1.5) years for FASD and 10.2 (± 1.2) years for NC.

All children in the FASD group had a diagnosis along the fetal alcohol spectrum through either the Motherisk Clinic at SickKids (n = 16) or another accredited FASD diagnostic facility in Ontario (n = 9). Please refer to Chapter 2 for a detailed description of the FASD diagnostic procedure. For the present study, all children diagnosed at Motherisk had scores of ‘3’ and none
had a ‘4’ or significant physical symptomatology to be considered FAS. For those children diagnosed elsewhere, five were diagnosed with partial FAS and four with ARND. Children in the FASD group were excluded if their exposure history was unconfirmed or their primary exposure was to a substance other than alcohol (e.g., cocaine, heroin, marijuana).

The NC group was recruited from through postings in the community or were the biological children of a participating adoptive or foster parent. Exclusionary criteria for our control group were any child with a psychiatric diagnosis (e.g., ADHD), an identified LD or exposure any teratogenic substance.

General exclusionary criteria included: head injury or other neurological or brain abnormalities, or a debilitating or chronic medical condition (e.g. cerebral palsy). Parents or caregivers provided written consent for participation in this study, and all participants provided assent.

3.1.2 Measures

Parents/guardians completed a structured case history form providing information on demographics and the child’s prenatal, birth and developmental history. The Hollingshead scale was used to determine current family socioeconomic status (SES) (Hollingshead, 1975) based on occupation and education of parents. A score of 1 to 2 signified high SES and 3, 4, 5 signified medium to low SES. Intelligence was evaluated using the Vocabulary and Matrix Reasoning subtests from the WASI (Weschler, 1999). A two-subtest full scale IQ (FSIQ) was estimated from these subtests.

3.1.2.1 NEPSY Affect Recognition

All children received the NEPSY-II Affect Recognition subtest, a standardized task appropriate for children 3 to 16 years of age. This task contained four parts examining children’s ability to
recognize emotions (i.e., happy, sad, anger, fear, disgust, neutral) in photographs of children’s faces. In the first part of the subtest, children stated whether two faces depicted the same emotion. In the second part, they were shown a set of three or four face pictures and had to select two faces conveying the same emotion. The third part showed a target face on top and four faces below; children were to select the lower face depicting the same emotion as the upper face. Part four briefly showed a photographed face, followed by a set of faces and the child had to select the two faces depicting the same emotion as the target face. Three scores were obtained from this subtest, a total scaled score, a binary score representing clinical impairment (i.e., 0 = at or above scaled score of 7 and 1 = below scaled score of 7), and emotion errors. The emotion error scores, represented as percentiles, are based on the emotion of the target face when an error occurred.

3.1.2.2 Face Processing Tasks

The face processing tasks were derived from the study by Bruce et al. (2000) in which a battery of tasks was used to explore how children of different ages process faces. Across tasks, face stimuli were 5.5° wide by 6.5° high, and for each trial, a target face was shown at the top of the computer screen with two choice faces below. The task was to select the face at the bottom of the screen matching the target face above based on certain specified criteria.

For the current thesis, four face matching subtests from Bruce et al. (2000) were chosen: Identity, Expression, Eye Gaze and Mouth Shape. In the Identity subtests, children had to pick the bottom face that was the same person as the top face. There were 16 trials, with eight unique face identities. There were four Identity subtests, namely, Non-Masked Similar Identity, Non-Masked Dissimilar Identity, Masked Similar Identity, and Masked Dissimilar Identity. In the Non-Masked Identity subtests, the entire face was presented. In the Masked Identity subtests, all faces were shown with the hair and ears concealed. Both the Non-Masked and Masked subtests had
Dissimilar (i.e., all face identities were dissimilar in appearance; different sex, age or general appearance) and Similar conditions (i.e., all faces were similar in appearance).

In the Expression subtest, children had to pick the bottom face conveying the same emotion as the upper face. There were 12 trials; four emotions with three trials each. On half of the trials both the face choices differed in identity from the target face; for the other half of the trials the correct face had a different identity and the incorrect face had the same identity as the target face. There were four emotions to match: sad, angry, surprise, happy.

The Eye-Gaze subtest required children to choose the bottom face that was looking in the same direction as the top face, which always looked forward. There were 20 trials in total. The orientation of the correct face could be left, right or straight. Head and eye orientation for the incorrect face choice could be head and eyes oriented left, head and eyes oriented right, or head straight and eyes directed left or right.

In the Mouth Shape subtests, children had to pick the bottom face that was making the same speech sound as the top face. There were two Mouth Shape subtests. In the first Mouth Shape subtest, all faces were shown in front view; on half of the trials the two face choices differed in identity from the target face and on the other half, the correct face had a different identity and the incorrect face had the same identity as the target face. There were four speech sounds to match (‘aa’, ‘oo’, ‘ee’, ‘ff’) with three trials each, resulting in a total of 12 trials. In the Mouth Shape 45degrees subtest, target faces were presented at a 45 degree angle to the right, which increased the matching difficulty. The same four speech sounds from the first Mouth Shape subtests were used, with six trials each, and three target face identity with eight trials each, for a total of 24 trials. Please see Figure 2 for examples from each of the conditions.
For all subtests, children were instructed to press the ‘z’ button on a standard keyboard, marked with a red sticker if the left choice face matched the target face, or the ‘/’ button, marked with a yellow sticker if the right face matched the target. Children were asked to press the response key as soon as they had made their decision and to be as accurate as possible. To ensure there were no memory requirements, all faces remained on the screen until the children made their response. For all tasks, the correct response was balanced (i.e., 50% correct responses on the right side of the screen and 50% correct responses on the left side of the screen). As per Bruce et al. (2000), all of the target face identities and choice face identities were balanced. Verbal and visual instructions were provided to all children, as well as practice trials on the computer to ensure understanding. Median RT (milliseconds; ms) and raw accuracy scores were calculated and used in subsequent analyses.

Figure 2. Face processing experiment conditions. 2a: Non-Masked Similar Identity, 2b: Non-Masked Dissimilar Identity, 2c: Masked Similar Identity, 2d: Masked Dissimilar Identity, 2e: Expression, 2f: Eye-Gaze, 2g: Mouth Shape, and 2h: Mouth Shape 45 degrees.

Note: Written consent was obtained to use the stimuli from Bruce et al. (2000).
3.1.2.3 Parent-Rated Questionnaires

Parent-rated behaviour and social profiles were measured using the standardized CBCL (Achenbach, 2001) and the SSIS (Gresham & Elliot, 2008). The CBCL is a widely used questionnaire for 4 to 18 years old children containing 118 items on which parents rated their child using a 3-point scale ranging from ‘not true’ to ‘often true’. Scores on multiple scales were provided as T-scores (mean=50, SD=10), with scores of 65 or above signifying the clinical range. For the present study, group comparisons were made on the broadband scales of Internalizing, Externalizing, Total and the narrowband scale of Social Problems, and correlations analyses were conducted on the CBCL Social Problems scale.

The SSIS is a standardized 60-item rating scale of social skills and behaviour problems for 3 to 18 year old children completed by parents. Scores were provided as standard scores (mean=100, SD=15). For present purposes, two SSIS subscales were used: Social Skills, which measures communication, cooperation, assertion, responsibility, empathy, engagement, self control and autism-like traits; and Behavior Problems, which measures externalizing problems, bullying tendencies, hyperactivity/ inattention, internalizing problems and autism-like behaviours. A high Social Skills scores signifies good ability, whereas a high Behaviour Problem score signifies more behaviour problems. The Autism subscale, which consists of 15 autistic-like characteristics and was standardized on autism diagnoses using the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000) was also examined. Raw scores were used, with a higher total score indicating more autistic-like characteristics. Analyses were conducted on SSIS Social Skills, Behaviour Problem and Autism scores.
3.1.3 Data Analyses

Groups were compared for demographic characteristics using one-way analyses of variance (ANOVA) for continuous variables and chi-square analyses for dichotomous variables. Dependent variables were inspected for normality using the Shapiro-Wilk test. Data were analysed by non-parametric Mann–Whitney tests when the conditions for normal distribution were not met. When normal distribution was met, ANOVA was used to determine group differences. Effect sizes were calculated for both Mann Whitney and ANOVA statistics. Chi-square analyses were also conducted on the dichotomous clinical scores from the Affect Recognition subtest. Bonferroni correction was applied to all analyses of dependent variables. Within group linear regressions were conducted to investigate age-related changes on significant face processing results. Unstandardized betas (B), $R^2$ and 95% confidence intervals (CI) were presented for significant regressions. To examine whether face processing ability was related to parent ratings of social problems (i.e., CBCL Social Problems, SSIS Social Skills and SSIS Autism subscale), within group Spearman correlations were conducted. Statistical Package for the Social Sciences (SPSS) 17.0 was used for all analyses.

3.2 Results

3.2.1 Demographics

Table 1 presents the demographic and abbreviated IQ data of FASD and NC groups. Groups did not differ in age or sex. Although significant group differences were observed on the WASI FSIQ index and SES, with lower scores in the FASD group for both measures, these variables were not covaried in subsequent analyses, as they reflect attributes commonly associated with FASD and so should not be a covariate when examining neurodevelopmental conditions (Dennis et al., 2009). Also, controlling for pre-existing group differences in nonrandom group design
violates the core assumption that covariates are statistically independent from the grouping variable in an analysis of covariance (Miller & Chapman, 2001).

Table 1 also contains additional background information on living status, exposure histories and comorbidities in the two groups. The majority of children in the FASD group were in adoptive or foster care, or living with a biological relative. Almost all of the NC children were living with their biological parents. Most of the FASD group had biological mothers who reportedly smoked cigarettes during pregnancy versus two children from the NC group; information on prenatal tobacco exposure was unavailable for six children in the FASD group and three in the NC group. Fifty-two percent of children with FASD were exposed to secondary teratogens prenatally (drugs unspecified) while 25% were exposed to cocaine and 15% to marijuana prenatally. Information was unavailable on other prenatal drug exposure for five children in the FASD group. None of the children in the control group were exposed to prenatal teratogens. Children in the FASD group also had more diagnoses of ADHD (64%), ODD (20%), LD (44%), sensory processing disorder (8%) and anxiety (8%) than the NC group. Although information was unavailable for one child in the NC group, available data indicated none of the children had a comorbid diagnosis. Seventy-two percent of the FASD group was taking attention medications. Information was unavailable on one child in the NC group; however, available data indicated none of the children were taking attention medication.
Table 1. Mean (Standard Deviation; SD) demographic characteristics for children in the NC and FASD groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>NC N=17</th>
<th>FASD N=25</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>10.2 (1.2)</td>
<td>10.3 (1.5)</td>
<td>ns</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>53</td>
<td>52</td>
<td>ns</td>
</tr>
<tr>
<td>WASI Full Scale IQ</td>
<td>112.3 (15.1)</td>
<td>89.6 (14.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Range: 75-132</td>
<td>Range: 60-116</td>
<td></td>
</tr>
<tr>
<td>SES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%high</td>
<td>82</td>
<td>56</td>
<td>&lt; 0.03</td>
</tr>
<tr>
<td>%medium/low</td>
<td>18</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Family Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% with biological parents</td>
<td>82</td>
<td>0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% with biological relative</td>
<td>6</td>
<td>24</td>
<td>ns</td>
</tr>
<tr>
<td>% adopted</td>
<td>12</td>
<td>64</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% in foster care</td>
<td>0</td>
<td>12</td>
<td>ns</td>
</tr>
<tr>
<td>Cigarette Exposure (% yes)</td>
<td>14</td>
<td>89</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Secondary Drug Exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Unspecified</td>
<td>0</td>
<td>52</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>% Cocaine</td>
<td>0</td>
<td>25</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>% Marijuana</td>
<td>0</td>
<td>15</td>
<td>ns</td>
</tr>
<tr>
<td>% ADHD</td>
<td>0</td>
<td>64</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% ODD</td>
<td>0</td>
<td>20</td>
<td>&lt; 0.06</td>
</tr>
<tr>
<td>% LD</td>
<td>0</td>
<td>44</td>
<td>&lt; 0.002</td>
</tr>
<tr>
<td>% Sensory processing deficits</td>
<td>0</td>
<td>8</td>
<td>ns</td>
</tr>
<tr>
<td>% Anxiety</td>
<td>0</td>
<td>8</td>
<td>ns</td>
</tr>
<tr>
<td>% on Attention Medication</td>
<td>0</td>
<td>72</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Note: WASI mean =100; SD = 15

3.2.2 NEPSY Affect Recognition

Affect Recognition subtest scaled scores were analysed using ANOVA. Groups differed significantly with the FASD group scoring below NC [F (1, 40) = 13.5, p < 0.001, \( n^2 = 0.3 \)]. However, mean scaled scores of both groups remained in the average range (Table 2). Chi-
square analyses on the dichotomous clinical scores approached significance \( (X^2 = 3.0, p < 0.08) \). Four children in the FASD group obtained scores in the clinical range, whereas scores for all children in the NC group fell in the normal range. The emotion errors from the Affect Recognition subtest were analysed using Mann-Whitney. The FASD group made more errors than NC on trials where the target face displayed Happy \([U = 170.0, p < 0.07, r = -0.3]\), Neutral \([U = 115.0, p < 0.01, r = -0.4]\) and Angry \([U = 123.5, p < 0.02, r = -0.4]\) facial emotions (Table 2). However, after Bonferroni correction \((0.05/6 = 0.008)\), none of these remained significant.

**Table 2. NEPSY II Affect Recognition Mean (SD) scores for NC and FASD groups**

<table>
<thead>
<tr>
<th></th>
<th>NC</th>
<th>FASD</th>
<th>p value</th>
<th>Group Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Affect Recognition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scaled scores</td>
<td>11.8 (2.7)</td>
<td>8.9 (2.4)</td>
<td>&lt; 0.001</td>
<td>FASD &lt; NC</td>
</tr>
<tr>
<td>Range</td>
<td>7 to 16</td>
<td>4 to 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Affect Recognition Emotion Errors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Happy</td>
<td>38.0 (0.0)</td>
<td>31.1 (14.1)</td>
<td>&lt; 0.07</td>
<td>FASD &lt; NC</td>
</tr>
<tr>
<td>Sad</td>
<td>53.1 (32.4)</td>
<td>35.2 (31.5)</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Neutral</td>
<td>57.5 (29.1)</td>
<td>30.6 (29.0)</td>
<td>&lt; 0.01</td>
<td>FASD &lt; NC</td>
</tr>
<tr>
<td>Fear</td>
<td>41.0 (22.5)</td>
<td>32.6 (21.3)</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Angry</td>
<td>59.4 (34.2)</td>
<td>30.5 (31.1)</td>
<td>&lt; 0.02</td>
<td>FASD &lt; NC</td>
</tr>
<tr>
<td>Disgust</td>
<td>41.8 (30.0)</td>
<td>40.2 (33.6)</td>
<td>ns</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** For the happy emotion errors, all children in the NC group made 0 errors, whereas 20 of the 25 children in the FASD group had 0 errors. Bonferroni correction for emotion errors \((0.05/6 = 0.008)\). Higher percentile scores = fewer errors.

### 3.2.3 Face Processing Accuracy

Because criteria for normality were not met, the raw accuracy scores were analysed using Mann-Whitney. Analyses for the Masked Similar Identity and Masked Dissimilar Identity subtests were conducted on 24 children in the FASD group and 16 children in the NC, respectively, as these subtests were not completed by one child in each group. Analyses on the Expression subtest
consisted of 15 children in the FASD group and 14 in the NC group. Results revealed the FASD group was outperformed by NC in only one task, Mouth Shape 45degrees [U = 114.0, p < 0.01, r = -0.4]. Contrary to expectation, the FASD group scored above the NC group on the Non-Masked Similar Identity subtest [U = 131.0, p < 0.03, r = -0.3]. After Bonferroni correction (0.05/8 = 0.006), no group differences remained significant, indicating similar accuracy performance for both groups (Table 3).

### 3.2.4 Face Processing RT

The median RTs were analysed using Mann-Whitney. The FASD group responded more slowly than the NC group on the Non-Masked Dissimilar Identity [U = 111.0, p < 0.009, r = -0.40] and Similar Identity [U = 128.0, p < 0.03, r = -0.3] subtests, Masked Dissimilar Identity [U = 91.0, p < 0.003, r = -0.5] and Similar Identity [U = 136.0, p < 0.07, r = -0.3] subtests at trend level, as well as on the Eye-Gaze at trend level [U = 138.0, p < 0.06, r = -0.3], Mouth Shape [U = 88.0, p < 0.001, r = -0.5] and Mouth Shape 45degree subtests [U = 104.0, p < 0.005, r = -0.4]. There was no group difference on the Expression subtest (p < 0.22). After Bonferroni correction (0.05/8 = 0.006), only the Masked Dissimilar Identity, Mouth Shape and Mouth Shape 45degrees subtests remained significant. See Table 3 for RTs for each group.
| Table 3. Face processing: Mean (SD) Accuracy and RT scores for NC and FASD groups |
|------------------------------------|-----------------|----------------|----------------|-----------------|
|                                    | NC              | FASD            | p value        | Group Differences |
| **Accuracy percentage (raw):**     |                 |                 |                |                 |
| Non-Masked Dissimilar Identity     | 94.9 (6.4)      | 95.5 (7.3)      | ns             |                 |
| Non-Masked Similar Identity        | 84.6 (8.6)      | 89.2 (12.3)     | < 0.03         | FASD > NC       |
| Masked Dissimilar Identity         | 80.1 (13.9)     | 70.3 (19.9)     | ns             |                 |
| Masked Similar Identity            | 78.4 (14.3)     | 70.8 (21.4)     | ns             |                 |
| Expression                         | 88.1 (9.1)      | 82.7 (14.6)     | ns             |                 |
| Eye-Gaze Direction                 | 81.8 (15.9)     | 80.4 (16.1)     | ns             |                 |
| Mouth Shape                        | 86.9 (11.4)     | 90.0 (12.9)     | ns             |                 |
| Mouth Shape 45degrees              | 89.3 (10.8)     | 82.0 (11.9)     | < 0.01         | FASD < NC       |
| **RT (ms):**                       |                 |                 |                |                 |
| Non-Masked Dissimilar Identity     | 738.1 (299.7)   | 1066.5 (441.9)  | < 0.009        | FASD > NC       |
| Non-Masked Similar Identity        | 1091.2 (481.3)  | 1557.7 (707.2)  | < 0.03         | FASD > NC       |
| Masked Dissimilar Identity         | 1492.3 (518.9)  | 2169.4 (711.2)  | < 0.003*       | FASD > NC       |
| Masked Similar Identity            | 1460.7 (535.0)  | 1827.6 (686.4)  | < 0.07         | FASD > NC       |
| Expression                         | 1650.0 (691.3)  | 2244.0 (1221.9) | ns             |                 |
| Eye-Gaze Direction                 | 2100.8 (1110.6) | 2865.8 (1418.8) | < 0.06         | FASD > NC       |
| Mouth Shape                        | 1329.4 (437.6)  | 2097.9 (1000.5) | < 0.001*       | FASD > NC       |
| Mouth Shape 45degrees              | 1277.4 (644.1)  | 1858.4 (728.2)  | < 0.005*       | FASD > NC       |

**Note:** *Survived Bonferroni correction (0.05/8 = 0.006). For RT, means of the median RTs are presented.

### 3.2.5 Parent-Rated Questionnaires

The FASD group obtained significantly higher scores than the NC group for CBCL Internalizing [U = 57.5, p < 0.001, r = -0.6], Externalizing [U = 21.5, p < 0.001, r = -0.8] and Total Problems [U = 2.5, p < 0.001, r = -0.8], as well as Social Problems [U = 31.0, p < 0.001, r = -0.7] analysed using Mann-Whitney (Table 4). All results survived Bonferroni correction (0.05/4 = 0.01). For the SSIS, one child in the NC group did not have a Behavior Problems score; this analysis was conducted on 16 children in the NC group. The SSIS, also analysed using Mann-Whitney. One child in the NC group did not have an Autism or Total Behaviour Problems score, therefore these analyses were calculated on 16 NC children. The FASD group attained lower scores than the NC group for Social Skills [U = 19.5, p < 0.001, r = -0.8], higher scores for Total Behavior Problems.
[U = 5.5, p < 0.001, r = -0.8], and higher scores on the Autism subscale [U = 6.0, p < 0.001, r = -0.8] (Table 4). These results remained significant after Bonferroni correction (0.05/3 = 0.02).

**Table 4.** Means (SD) for NC and FASD group on CBCL and SSIS

<table>
<thead>
<tr>
<th>Parent-Rated Measure</th>
<th>NC</th>
<th>FASD</th>
<th>p value</th>
<th>Group Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CBCL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internalizing</td>
<td>47.9 (10.6)</td>
<td>64.6 (10.8)</td>
<td>&lt; 0.001</td>
<td>FASD &gt; NC</td>
</tr>
<tr>
<td>Externalizing</td>
<td>47.7 (9.2)</td>
<td>70.5 (8.8)</td>
<td>&lt; 0.001</td>
<td>FASD &gt; NC</td>
</tr>
<tr>
<td>Total</td>
<td>45.4 (10.5)</td>
<td>71.8 (6.7)</td>
<td>&lt; 0.001</td>
<td>FASD &gt; NC</td>
</tr>
<tr>
<td>Social Problems</td>
<td>53.7 (8.7)</td>
<td>71.1 (9.5)</td>
<td>&lt; 0.001</td>
<td>FASD &gt; NC</td>
</tr>
<tr>
<td><strong>SSIS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social Skills</td>
<td>98.9 (9.4)</td>
<td>67.3 (13.9)</td>
<td>&lt; 0.001</td>
<td>FASD &lt; NC</td>
</tr>
<tr>
<td>Behavior Problems</td>
<td>93.1 (10.8)</td>
<td>136.6 (14.7)</td>
<td>&lt; 0.001</td>
<td>FASD &gt; NC</td>
</tr>
<tr>
<td>Autism Subscale</td>
<td>6.1 (3.3)</td>
<td>20.2 (4.5)</td>
<td>&lt; 0.001</td>
<td>FASD &gt; NC</td>
</tr>
</tbody>
</table>

**Note:** CBCL lower T scores indicate fewer problems (scores over 65 indicate clinical significance); SSIS Social Skills higher standard scores indicate fewer problems; SSIS Behavior Problems lower standard scores indicate fewer problems. SSIS Autism subscale is presented in raw scores with higher scores indicating more autism-like characteristics. All results survived Bonferroni correction.

### 3.2.6 Regressions with Age and Performance

Within group linear regressions with age were conducted to examine age-related changes on significant face processing subtests (RTs on the Masked Identity Dissimilar, Mouth Shape and Mouth Shape 45degrees subtests, and NEPSY II Affect Recognition subtest). There were no significant relations between age and face processing in the FASD or NC groups.

### 3.2.7 Correlations between Child Performance and Parent-Ratings

Within group Spearman correlations were conducted to examine whether performance on significant face processing subtests (RTs on the Masked Identity Dissimilar, Mouth Shape and Mouth Shape 45degrees subtests) was related to parent ratings of social problems (CBCL Social problems, SSIS Social Skills and SSIS Autism traits). Within the FASD group, median RT on the Masked Dissimilar Identity ($r_s = +0.4, p < 0.03$) and Mouth Shape subtests ($r_s = +0.4, p <$
0.03) were positively correlated with parent-rated autistic behaviours on the SSIS; an increase in face processing RT was associated with increased parent-rated autistic traits. These correlations did not remain significant after Bonferroni correction (0.05/6 = 0.008). There were no significant correlations between face processing and parent-rated social abilities in the NC group.

3.3 Discussion

The present study used two techniques for examining face processing in children with FASD and NC. For the standardized test of face processing using the NEPSY-II, results revealed no group differences on accuracy, after Bonferroni correction. On the experimental tasks, results revealed no group differences on accuracy, but significant group differences on RT measures for specific face processing subtests. The FASD group responded more slowly than the NC group when matching face identity that was masked and dissimilar in appearance, and when matching mouth shapes. Importantly, increased RTs on the Masked Dissimilar Identity and Mouth Shape matching tasks were significantly related to increased parent-rated autistic-like behaviours in the FASD group. This was not observed in the NC group. There were no age-related changes on any of the significant face processing subtests in the FASD or NC groups.

The main findings of the present chapter are represented through the RT results; children with FASD showed slower processing of incomplete face identity and mouth shape. It was recently proposed that a core deficit in FASD was impaired processing and integration of complex information (Kodituwakku, 2007). Previous research supports this view, as children with FASD show difficulty with complex skills such as executive functions (e.g., planning and inhibition) (Kodituwakku, May et al., 2001), planning complex movements (Simmons et al., 2010), language (Coggins et al., 2007; McGee, Bjorkquist et al., 2009), and social cognitive processing
Greenbaum et al., 2009; McGee, Bjorkquist et al., 2009; McGee et al., 2008). The current findings provide further support for impaired processing of complex information, as face stimuli are complex and require high level detailed social processing and integration of features (Adolphs, 2002; Bruce & Young, 1986; Kanwisher, 2010). Moreover, children with FASD displayed significantly slower RTs on face processing subtests requiring the highest level of detailed processing, namely matching face identity when information was missing and matching subtle mouth shapes. It is argued that these subtests required more processing and integration of local features, which are believed to more difficult, or complex, than processing global stimuli (Navon, 1977). In comparison, the expression and completed identity matching subtests required more global face processing, which is believed to be less difficult than local feature processing (Navon, 1977). These findings corroborate Mattson and colleagues who found that when presented with stimuli consisting of large global letters constructed from smaller local letters, children with PAE were impaired at recalling and re-constructing the local features, with no impairments for global features. From this it was proposed these children do not have general visuospatial impairments, but instead have select deficits in visual processing of local, detail features (Mattson, Gramling, Riley, Delis & Jones, 1996). Similarly, the FASD group in the current study displayed significantly slower RTs when detailed, not global, face processing was required. Of note, both the FASD and NC groups had slow RTs on the Eye Gaze subtest, which also involves local feature processing and appeared to be one of the most difficult tasks for both groups. Thus, current findings support the idea that processing local facial features and complex social information are impaired in FASD.

Slow response times have been related to less mature brain development and the recruitment of more brain regions in children compared with adults. During childhood, brain development is
characterized by synapse proliferation and ongoing myelination, as well as the recruitment of
many brain regions for task performance (Batty & Taylor, 2006; Blakemore & Choudhury, 2006;
Giedd, 2004; Gogtay et al., 2004). This immature neurodevelopment is believed to account for
slower RT in children (Blakemore & Choudhury, 2006). Over the course of typical development
from childhood to adulthood, increased synaptic pruning, increased myelination, and more focal
task-related cortical activation, are reported (Casey et al., 1997; Tamm, Menon & Reiss, 2002),
which contribute to the decreased RTs observed with age (Blakemore & Choudhury, 2006).
Specific brain regions are believed to be critical for integrating information across sensory
modalities. These regions, termed association areas, include the superior temporal sulcus,
inferior parietal and frontal areas (Mesulam, 1999), which continue to mature late in
development (Gogtay et al., 2004). Interestingly, the teratogenic effects of PAE appear to
resemble the immature stages of brain development; being exposed to alcohol prenatally can
result in disrupted synaptic pruning (Guerri et al., 2001), reduced myelination and abnormal
white matter (Chiappelli et al., 1991; Fryer et al., 2009; Lebel, Rasmussen et al., 2008; Riikonen
et al., 1999; Watari et al., 2006). Prenatal alcohol exposure can also result in abnormal
recruitment of brain regions during certain tasks (i.e., go no-go), leading to more extensive
activation and poorer performance (Fryer, Tapert et al., 2007). Furthermore, children with FASD
have structural and functional abnormalities in specific association areas (Archibald et al., 2001;
Fryer, Tapert et al., 2007; Sowell et al., 2001; Sowell, Mattson et al., 2008; Sowell et al., 2002).
Together, the teratogenic effects of PAE may negatively impact children’s ability to process and
integrate complex stimuli, such as faces, in a timely manner, supporting the current results.
Future work would benefit from investigating specific neural underpinnings related to face
processing in FASD.
The present study did not observe accuracy impairments in children with FASD in face recognition, after Bonferroni correction. These findings corroborate previous research where children with FASD did not show deficits in memory for face identity (Autti-Ramo et al., 2002; Uecker & Nadel, 1996). However, the present findings are not consistent with our hypotheses or with Greenbaum et al. (2009) and Bishop et al. (2007), who reported deficits in understanding face expression and eye gaze in FASD. The discrepancies between these studies and the present findings are likely due to differences in task requirements. Greenbaum et al. (2009) presented children with a series of emotional faces and instructed them to touch the face depicting the emotion generated verbally by the computer. Deficits on this task could have been due to the limited verbal understanding of children with FASD (McGee, Bjorkquist et al., 2009; Timler et al., 2005). In contrast, the present study eliminated all language demands, resulting in similar performance between FASD and NC groups. Bishop et al.’s (2007) results were based on parental reports of eye contact and eye gaze understanding in FASD. In contrast, the present study measured children’s performance on face matching tasks in a laboratory setting, and did not observe specific impairments in eye gaze matching. Both groups did, however, show increased RTs on the eye gaze subtest, suggesting this was one of the more difficult matching tasks. Overall, children with FASD do not show accuracy impairments when faces were presented in isolation, without social context. However, impairments are observed in FASD when faces are presented in a social context requiring complex understanding and processing (Bishop et al., 2007; Greenbaum et al., 2009).

Similarly, non-significant findings were observed in the Affect Recognition subtest. As there were no time constraints on this subtest, the findings support the idea that children with FASD display adequate face and emotion recognition when given sufficient processing time. Before
Bonferroni correction, however, the FASD group did show weakness in matching happy, neutral and angry face emotions. Despite differing in emotional valence (Adolphs, 2002), both angry and happy facial emotions are ‘approach emotions’ and are responded to more quickly when presented with direct gaze (Adams & Kleck, 2003). In comparison, fear and sadness are ‘avoidance emotions’, and are responded to more quickly when presented with averted gaze (Adams & Kleck, 2003). All faces presented in the Affect Recognition subtest had direct eye gaze. Viewing approach emotions, which indicate potential for social interactions, coupled with poor social skills and complex processing commonly observed in FASD, may have resulted in increased error rates to these specific expressions. It may, therefore, be the case that children with FASD had increased aversion to these approach emotions, failing to process the facial features adequately. Additionally, neutral face expressions are reported to be highly complex in nature. In their investigation of neuronal activity in emotion processing, Thomas et al. (2001) found increased amygdala activity in adults while viewing fearful face expressions. In contrast, increased amygdala activity was observed in children while viewing neutral expressions. It was suggested children process neutral expressions as more complex and ambiguous due to their limited understanding of the emotional representation presented in a neutral face, as well as increased decoding required to understand the neutral expression (Thomas et al., 2001). We can speculate that children with FASD find neutral expressions to be more complex than do NC children, which may indicate abnormalities in underlying neural structure or function, resulting in increased errors. Notably, although previous research indicates emotion and face recognition improve with age (Herba et al., 2006; Markham & Adams, 1992), the present study did not observe age-related changes.
The present study found a significant relationship between slower RTs when matching mouth shapes and identity that was dissimilar and partially occluded and increased parent-ratings of autistic-like behaviour in FASD. Case study reports have estimated the incidence rate of autism in FASD to be 1 in 54 (Nanson, 1992). Previous reports also reveal behaviour similarities among children with FAS and autism, including difficulty relating to people, resistance to change in daily routines and abnormal sensory responses (e.g., hypersensitivity to noise); suggesting there may be some overlap between these disorders (Harris, MacKay & Osborn, 1995; Nanson, 1992). Recently, Mukherjee and colleagues (2011) supported the idea that PAE was associated with autism, with 72% of their sample of FASD meeting diagnostic criteria for autism. Children with autism are commonly reported to show impairments in face processing, spending less time looking at a face and more disorganized face exploration, when compared with NC (Balconi, 2008; Gepner et al., 1996; Pelphrey et al., 2002). Face processing impairments are also believed to underlie the compromised social skills observed in autism (Baron-Cohen, 1995; Baron-Cohen et al., 2001). Thus, similarities may exist between autism and FASD profiles in social processing, specifically face processing and its relation with social abilities. Further research investigating the similarities and differences between these two clinical groups is warranted.

In conclusion, the present study found children with FASD were significantly slower to process face stimuli than NC children. These findings have real life implications for children with FASD, as quick and adequate face processing is crucial for mature social cognition and understanding (Adolphs, 2002). Impaired face processing may underlie the social difficulties experienced by children with FASD. Overall, the present results have potential to influence treatment approaches for children with FASD. Because they demonstrated slow, yet accurate processing of complex
face stimuli, children affected by PAE may benefit from additional processing time to ensure adequate understanding and integration of social information.
Chapter 4
Attentional Orienting by Eye Gaze and Links to Theory of Mind:
An Investigation of Children with Fetal Alcohol Spectrum Disorders

The human face is arguably one of the most important stimuli people process on a daily basis, making the ability to recognize and understand the face essential for social development (Itier & Batty, 2009; Kinzler & Shutts, 2008). It has been argued that details within the face, specifically the eyes, are critical for social interactions and communication due to the unique morphology of white sclera and coloured iris (Csibra & Gergely, 2005; Kobayashi & Kohshima, 1997). Impressively, the eyes fascinate us from the day we are born, with the neonatal visual system having great sensitivity to eye gaze (Batki, 2000; Farroni et al., 2002). For example, infants as young as two months spend more time looking at the eyes than any other region of the face (Maurer & Salapatek, 1976). Furthermore, at five months, infants are able to discriminate between small horizontal deviations of gaze (Symons et al., 1998). It is clear that preferential sensitivity to eye gaze develops early and relates to subsequent communicative and social cognitive skill (Baron-Cohen & Cross, 1992; Charman et al., 1997; Itier & Batty, 2009).

One social cognitive skill believed to rely heavily on eye gaze processing is theory of mind. Theory of mind is the ability to infer and comprehend the mental states of others, including deceptions, intentions and beliefs (Premack & Woodruff, 1978), and develops after skills of joint attention and shared attention are acquired (Baron-Cohen, 1995). Joint attention aids in determining whether one’s self and another are both attending to the same object in the environment and typically emerges between 9 to 14 months of age (Baron-Cohen, Baldwin, et al., 1997; Bruner, 1985; Emery, 2000; Itier & Batty, 2009). By approximately 18 months of age
children develop shared attention, which is the ability for two individuals each to have knowledge of the direction of the other’s attention and have a shared experience over an object (Butterworth, 1991; Perrett & Emery, 1994). Importantly, joint attention at 20 months of age can predict theory of mind abilities at 44 months (Charman et al., 2000), demonstrating the importance of eye gaze sensitivity in the development of social cognition. By four years of age, children learn the eyes provide information about mental states of others (Baron-Cohen, 1992; Leslie, 1987) and are important cues for theory of mind (Baron-Cohen et al., 1997; Baron-Cohen et al., 2001).

Importantly, atypical eye gaze processing are observed in some clinical populations, such as children with autism, and are proposed to underlie their accompanying social cognitive and communication deficits. For example, these children tend to avoid eye contact (Pelphrey et al., 2002) and have impaired joint attention (Dawson et al., 2004). Furthermore, children with autism perform poorly on tasks of theory of mind (Baron-Cohen, 1989), possibly due to impaired eye gaze processing (Baron-Cohen, 1995; Baron-Cohen et al., 2001). They also perform below that of typically developing children on the Reading the Mind in the Eyes task, a task where photographs of isolated eye regions are presented to children and they are asked to pick from four mental state words the one that best describes what the person in the photograph is thinking or feeling (Baron-Cohen et al., 2001). Results from this task support the role of eye processing in theory of mind. Due to the importance of the eye region in social cognition, impairments in gaze processing or understanding may lead to atypical social development.

Another clinical population where eye gaze processing may underlie social cognitive impairment is FASD, as these children show social and adaptive behaviour difficulties (Thomas et al., 1998;
Whaley et al., 2002). Children with FASD have deficits in a wide range of social domains including social problem solving (McGee, Bjorkquist, et al., 2009; McGee et al., 2008), moral maturity (Schonfeld et al., 2005), as well as anticipating the consequences of their actions (Caldwell, 1993). Furthermore, impairments in processing complex information have also been observed in this population (Kodituwakku, 2007; Simmons et al., 2010), which may impact their social skill development. More recently, it was reported that children with FASD have poor understanding and use of mental state words (Timler et al., 2005), difficulty conveying how story characters feel in certain situations (Coggins, 1997; Greenbaum et al., 2009; Kodituwakku et al., 1997; Rasmussen et al., 2009), and selecting emotions that accompany other’s mental states (Greenbaum et al., 2009). Relevantly, abnormalities have also been reported in the understanding of direct gaze and eye contact (Bishop et al., 2007). However, these claims are based on few published studies, making it unknown whether children with FASD show deficits in eye gaze processing, which may be related to their poor social cognitive processing. It may be the case that poor social skill and behaviour observed in FASD stem from, or are at least linked to, an inability to process and understand eye stimuli. Therefore, the aim of the present study was to investigate social eye processing and its relation to higher order social cognition in FASD.

One method of examining attentional orienting to gaze is through an adaptation of the classic spatial cuing paradigm (Posner, 1980). In this adaptation, an eye gaze cue is presented in the centre of the computer screen with gaze directed to the left or right, followed by a peripheral target. It is commonly observed that RT are faster for targets that appear in the gazed-at, or valid location (i.e., the location the eye gaze is directed), compared to the location opposite the gazed direction, or invalid location (i.e., the location opposite to where the eye gaze is directed) (Driver et al., 1999; Friesen & Kingstone, 1998). This result is known as the validity effect, representing
the RT benefit received from a valid cue compared to an invalid cue. Impressively, reflexive eye gaze following has been successfully demonstrated in infants as young as three months of age (Farroni et al., 2002; Hood et al., 1998) and children three to five years old (Ristic et al., 2002).

To investigate attention orienting to eye gaze, as well as the underlying mechanisms of joint attention in children with FASD, the present study used a standard cuing paradigm with central gaze cues, as well as central arrow cues, which are non-biologically relevant cues that show similar cuing effects (Hommel, Pratt, Colzato, & Godijn, 2001; Pratt & Hommel, 2003; Ristic et al., 2002). In addition, the present study examined the ability to use eye information to understand higher order social cognition using the Reading the Mind in the Eye task (Baron-Cohen et al., 2001). Based on reports from Bishop et al. (2007) and Greenbaum et al. (2009), it was predicted that children with FASD would show a larger validity effect to arrow cues than gaze cues. It was also hypothesized that the FASD group would show poorer theory of mind performance on the Reading the Mind in the Eyes, compared to NC (Greenbaum et al., 2009; Rasmussen et al., 2009). Furthermore, because children with FASD have difficulty on complex processing tasks (Kodituwakku, 2007; Simmons et al., 2010), I hypothesized they would have significantly slower responses when required to detect peripheral targets following central gaze and arrow cues, compared to when no central cues were present and they simply had to detect the onset of a stimulus.

4.1 Methods

4.1.1 Participants

This study included 42 children between the age of 8 to 12 years; 25 in the FASD group (13 males and 12 females) and 17 in the NC group (9 males and 8 females). The mean ages of the
groups were 10.3 (± 1.5) years for FASD and 10.2 (± 1.2) years for NC. A more detailed description of the FASD and NC groups, as well as inclusion and exclusion criteria were described previously, please refer to Section 3.1.1.

4.1.2 Measures

Information on developmental history, SES and IQ measures was previously described, please refer to Section 3.1.2.

4.1.2.1 Gaze and Arrow Cuing Experiments

For the Gaze Cuing experiment, a photograph of a male or female face was used as the gaze cue. The photographs were 5.0° wide and 6.5° high. The same photographs were used for the gazing-left cue and the gazing-right cue, with only the eye regions differing between these two cues by a mirror reflection. This was to ensure that no asymmetric properties of the face other than the direction of the gaze could be responsible for any differences in orienting produced by the cues. There were six unique face cue identities, each presented 16 times during the experiment. For the Arrow Cuing experiment, a picture of an arrow was used as the directional cue, pointing to the left or right. The arrow stimuli were 3.5° wide and 1° high. There were two arrow identities (left and right pointing) and each presented 48 times. The target for both cuing experiments was a snowflake (~1° in size). A central fixation cross was used as the fixation point (1° in size). Each experiment (gaze, arrow) had 4 blocks of 24 trials for a total of 96 trials, with breaks in between each block. Within each block, valid (48 trials total) and invalid (48 trials total) trials were equiprobable, and were crossed with the two equiprobable cue lengths, 200 ms (24 valid trials, 24 invalid trials) and 400 ms (24 valid trials; 24 invalid trials), to avoid anticipation of cue onset.
The sequence of events for each trial was as follows: a fixation cross appeared in the centre of the screen for 500 ms. The cross was replaced by a face/arrow cue, which was equally likely to gaze or point towards the left or right. After a variable delay, depending on the cue length (200 or 400 ms), the peripheral target appeared to the left or right, remaining present along with the face/arrow cue until the child responded or 3000 ms elapsed (Driver et al., 1999; Ristic et al., 2002). A blank screen (intertrial interval) of 1000 ms was presented between each trial. Please see Figure 3. No response feedback was provided. Both the Gaze and Arrow Cuing experiments were localization tasks; children were asked to localize the target as quickly and accurately as possible by pressing the ‘z’ button on a standard keyboard (red sticker) if the target was on the left side, and the ‘/’ button (yellow sticker) if the target was on the right. It was emphasized to the children that the central face/arrow was irrelevant to the location of the snowflake, and that they were to fixate at the center of the screen for each trial. All children received detailed verbal and visual instructions, as well as practice trials on the computer to ensure understanding. The order of the gaze and arrow experiments was counterbalanced between participants. Both RT and accuracy scores were recorded and used in subsequent analyses. Reaction times less than 100 ms and greater than 3000 ms were excluded from analyses (Senju et al., 2004).
Figure 3. Cuing paradigm.

NOTE: In addition to arrow cue displayed above, a gaze cue with eyes averted to left or right was also used (stimuli not shown).

4.1.2.2 Sorting Control Task

To ensure children understood and perceived the directional information presented in the gaze and arrow cues used in the cuing experiments, all children were given sorting cards with either arrows or faces with averted gaze. The faces were the same and arrows were similar (multiple arrow designs were used for variety) to those used in the Gaze and Arrow Cuing tasks. Children were instructed to sort the two groups of cards into piles, depending on the direction of eye gaze, or the direction the arrow was pointing. The sorting task was given following the two cuing experiments, and the order of the sorting sub-task (gaze or arrows) was counterbalanced across participants. There were 24 trials for the gaze and arrow sorting tasks, with a total of 48 trials. Raw error scores were used in subsequent analyses.

4.1.2.3 Reaction Time Control Task

A Reaction Time Control task was also given to the children. This task was the same as the cuing experiments except that there was no central cue. A fixation cross appeared in the centre of the screen for 500 ms and was followed by a square peripheral target to the left or right of fixation.
Children pressed the ‘z’ button on a standard keyboard (red sticker) if the target was on the left side, and the ‘/’ button (yellow sticker) if the target was on the right. Children were asked to localize the target as quickly and accurately as possible. There were 96 trials total in the Reaction Time Control task. RT and accuracy scores were used in the analyses.

4.1.2.4  Reading the Mind in the Eyes Task

This is a 28-item task that measures processing of the eye region and mental states. Children saw photographs of the eye region of a face conveying a specific emotion. Around each face were four words, one of which corresponded to the mental state of the person in the photograph. The task was to identify the word best identifying what the person was thinking or feeling. Two control tasks were included: (i) a Gender Control task requiring children to indicate the gender of the person in the photo (12 trials) and (ii) a Language Control task requiring children to provide a example of each mental state word used in the Reading the Mind in the Eyes task to ensure understanding and familiarity for all of the presented words (43 trials). Analyses were conducted on the Language and Gender Control tasks. For the Reading the Mind in the Eyes task, analyses were completed on the ‘total number of trials completed’, which included only trials where children understood the mental state word (maximum 28 trials) based on the Language Control task. Of these trials, the ‘correct raw’ score represents the total number of correct trials on the Reading the Mind in the Eyes task.

4.1.3  Data Analyses

Groups were compared for demographic characteristics using one-way ANOVA for continuous variables and chi-square analyses for dichotomous variables. Groups were compared on Gaze and Arrow Cuing RTs using a mixed design ANOVA with three within-participant factors: cue
type (gaze or arrow), validity (valid or invalid), and cue length (200 or 400 ms), and Group as the between subject factor. Sphericity was not investigated for the cuing experiments due to the number of levels in the present ANOVA (Field, 2009). Overall accuracy performance on both Arrow and Gaze Cuing experiments were analysed using a single multivariate ANOVA to account for multiple comparisons. Separate univariate ANOVAs were conducted on the Gaze and Arrow Sorting Tasks and Reaction Time Control tasks, as well as the Reading the Mind in the Eyes (total trials completed and total correct raw score), Language Control and Gender Control (raw scores) tasks, comparing the two groups. Wilks Lambdas and effect sizes were reported for all analyses. Correlation analyses were conducted using within group Pearson correlations. Significance was set at $p < 0.05$. SPSS 17.0 was used for all analyses.

4.2 Results

4.2.1 Demographic Characteristics

Please see Section 3.2.1 and Table 1 for the demographic and IQ data, as well as additional background information for the FASD and NC groups.

4.2.2 Gaze and Arrow Cuing

A four-way repeated measures ANOVA was conducted on RTs. One child in the NC group did not complete the cuing tasks; therefore analyses were conducted on 25 children in the FASD group and 16 in the NC group. Overall, there was a main effect of Group [$F (1, 39) = 10.3, p < 0.003, n^2 = 0.2$] with the FASD group (587.1 ms) having slower RTs than the NC group (442.1 ms). There were also significant main effects of Cue [$F (1, 39) = 4.5, p < 0.04, n^2 = 0.1$] with slower RTs for Arrow (528.4 ms) than Gaze cues (500.8 ms); Validity [$F (1, 39) = 22.5, p < 0.001, n^2 = 0.4$] with Invalid cues (530.6 ms) slower than Valid cues (498.5 ms); and Cue Length
With 200 ms cues (540.0 ms) having slower RTs than 400 ms cues (489.2 ms). The Group x Validity interaction was significant \([F (1, 39) = 6.8, p < 0.02, n^2 = 0.2]\) indicating the overall Validity effect (benefit of valid compared to invalid cues) was greater in the FASD group (49.8 ms across both cue lengths and cue types) than the NC group (14.4 ms; Figure 4a & b). ANOVA revealed this interaction was driven by the larger difference in the FASD group between total invalid and valid trials for Gaze, at trend level \((p < 0.1)\) and Arrow \((p < 0.05)\) cues, compared to the NC group. There were no significant Group x Cue, Group x Cue Length, Cue x Validity, Cue x Cue Length interactions, or any three-way interactions. Using MANOVA, no group differences were observed on accuracy scores \((p < 0.6)\). See Table 5.

Within group Pearson correlations were conducted to investigate any relation with IQ. For both groups, the validity effect (i.e., difference between invalid and valid cues) for both cue types was not correlated with IQ scores.

**Figure 4a.** Gaze cue reaction times (ms): Means (SD) for NC and children with FASD
Figure 4b. Arrow cue reaction times (ms): Means (SD) for NC and children with FASD

![Arrow Cues Graph](image)

Table 5. Gaze and arrow cuing: Mean accuracy scores and SD for NC and FASD groups

<table>
<thead>
<tr>
<th></th>
<th>NC</th>
<th>FASD</th>
<th>Group Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td><strong>Gaze Cues</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valid Cue 200ms</td>
<td>98.0 (3.3)</td>
<td>95.9 (5.8)</td>
<td>ns</td>
</tr>
<tr>
<td>Valid Cue 400ms</td>
<td>97.0 (3.7)</td>
<td>95.8 (6.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Invalid Cue 200ms</td>
<td>97.0 (3.1)</td>
<td>97.4 (5.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Invalid Cue 400ms</td>
<td>97.1 (5.7)</td>
<td>95.0 (6.0)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Arrow Cues</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valid Cue 200ms</td>
<td>98.0 (3.6)</td>
<td>96.4 (5.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Valid Cue 400ms</td>
<td>94.4 (7.2)</td>
<td>95.0 (6.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Invalid Cue 200ms</td>
<td>95.9 (5.1)</td>
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</tr>
<tr>
<td>Invalid Cue 400ms</td>
<td>93.6 (7.7)</td>
<td>91.8 (7.8)</td>
<td>ns</td>
</tr>
</tbody>
</table>

4.2.3 Sorting Control Task and Reaction Time Control Tasks

For the Sorting Control tasks, two ANOVAs were conducted on 25 children in the FASD group and 16 in the NC group. There were no significant group differences for gaze ($p < 0.52$) or arrow ($p < 0.43$) sorting. Only a subset of participants completed the Reaction Time Control task;
ANOVA was conducted on 15 children in the FASD group and 14 in the NC group. There were no significant group differences on RT ($p < 0.16$) or accuracy ($p < 0.47$) scores (Table 6).

### Table 6. Sorting and reaction time control tasks: Mean scores and SD for NC and FASD groups

<table>
<thead>
<tr>
<th>Sorting Control Tasks</th>
<th>NC Mean (SD)</th>
<th>FASD Mean (SD)</th>
<th>Group Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw error scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gaze Sorting</td>
<td>0.2 (0.8)</td>
<td>0.1 (0.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Arrow Sorting</td>
<td>0.0 (0.0)</td>
<td>0.2 (1.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Reaction Time Control Task</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction Time</td>
<td>447.6 (126.2)</td>
<td>534.2 (187.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Accuracy</td>
<td>97.0 (3.3)</td>
<td>96.0 (4.3)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Note: Sorting tasks had 24 trials each. Reaction Time Control task had 96 trials total.

### 4.2.4 Reading the Mind in the Eyes Task

One child from each group did not complete the Reading the Mind in the Eyes task, therefore analyses were conducted on 24 children in the FASD and 16 in the NC group. Results from the ANOVA on the Language Control task revealed a significant main effect of Group [$F (1, 38) = 16.2, p < 0.001, n^2 = 0.3$], indicating the FASD understood fewer mental state words than the NC group. An ANOVA was then conducted on total number of trials completed, which represented the number of trials completed on the Reading the Mind in the Eyes task where children understood the mental state words based on the Language Control task. Results revealed a significant main effect of Group [$F (1, 38) = 23.6, p < 0.001, n^2 = 0.4$]. Finally, results from the ANOVA investigating the correct raw score of the Reading the Mind in the Eyes task indicated a significant effect of Group [$F (1, 38) = 22.2, p < 0.001, n^2 = 0.4$], with the FASD group performing below the NC group. Although the FASD group understood fewer mental state words than NC on the Language Control task, significant group differences were still observed on the
Reading the Mind in the Eyes task when analyses only included trials where children understood the meaning of the mental state word. There was no group difference on the Gender Control task ($p < 0.88$).

Within group Pearson correlations were conducted to investigate the relationships between performance on the Reading the Mind in the Eyes and the validity effect for arrow and gaze cues. There were no significant correlations within either group.

| Table 7. Reading the Mind in the Eyes Task: Mean raw scores and SD for the Reading the Mind in the Eyes, Language Control and Gender Control task for NC and FASD groups |
|---------------------------------|----------|-----------|-------|-------------------|
|                                 | NC      | FASD      | $p$ value | Group Differences |
| **Reading the Mind in the Eyes Task** |         |           |       |                   |
| Language Control                | 41.7 (1.2) | 37.5 (4.1) | $< 0.001$ | FASD < NC         |
| Total Number of Trials Completed | 26.1 (1.5) | 19.2 (5.5) | $< 0.001$ | FASD < NC         |
| Reading the Mind in the Eyes    | 16.6 (3.0) | 10.6 (4.4) | $< 0.001$ | FASD < NC         |
| Correct raw score               | 10.9 (0.7) | 10.8 (0.9) | ns      |                   |
| Gender Control                  |          |           |       |                   |

*Note:* Language control task had 43 trials, the Reading the Mind in the Eyes task had 28 trials, and the Gender control task had 12 trials. Total number of trials completed represents the number of trials children completed on the Reading the Mind in the Eyes task based on understanding of the mental state words (max 28 trials) on the Language control task. Correct raw score represents the total number of trials children got correct on the Reading the Mind in the Eyes task.

### 4.3 Discussion

In the present study, children with FASD and NC children were evaluated on attentional cuing paradigms and a measure of theory of mind. Results revealed that children with FASD were significantly slower than NC on both gaze and arrow cuing paradigms, with no differences in accuracy (cuing or sorting). On the cuing tasks, the FASD group had an overall larger validity effect than NC. This larger validity in the FASD group was driven by the larger difference between the total invalid and valid trials. Notably, children with FASD performed below the NC group on Reading the Mind in the Eyes task, which required integration of emotional eye
information and mental state understanding. In addition, arrow cues were responded to more slowly than gaze cues, invalid cues more slowly than valid cues, and 200 ms cue lengths more slowly than 400 ms cue lengths, with no differences between groups. Overall, these results suggest children from both groups were able to discriminate the direction of eye gaze and use this information to orient their attention, with FASD displaying slower processing speed than NC. The FASD group, however, had a significant weakness using eye information to understand others’ mental states.

The present findings corroborate previous work showing standard validity effects in children, with faster RTs for valid than invalid cues (Farroni et al., 2002; Hood et al., 1998; Ristic et al., 2002). The overall RTs in the present study were faster for cues presented for 400 ms, compared to 200 ms, which is a typical result reflecting factors such as the influence of arousal and expectancy on RT after any cued event (Niemi & Naatanen, 1981). The present results are therefore consistent with previous cuing literature reporting shorter RT as a function of increased cue length (Driver et al., 1999; Friesen & Kingstone, 1998; Friesen et al., 2004), reflecting a standard foreperiod effect (Bertelson, 1967). In addition, the present study found overall RTs were slower following arrow cues than gaze cues in both FASD and NC groups, signifying all groups had more difficulty engaging their attention in response to central arrow cues than the gaze cues. Because this effect was observed for both valid and invalid trials, it suggests children may have found it harder to decode the information presented in the arrow cues and disengage their attention following arrows compared to gaze cues, resulting in slower RTs to the peripheral targets. Slower RTs following arrow cues have been observed previously (Ristic et al., 2002; Senju et al., 2004) and have been suggestive of difficulties disengaging attention following high
contrast arrow cues in ASD (Senju et al., 2004). In the present study, both FASD and NC groups showed this pattern.

The results from the present study are also consistent with previous reports in the FASD literature. Children with FASD had slower overall RTs to both gaze and arrow cues; however, they did not have slower RT on the Reaction Time Control task that required a simple response to the onset of a target. This is similar to reports that, compared to simple RT tasks, children with FASD have significantly slower responses on complex RT tasks (Simmons et al., 2010, 2002), suggesting impairments in the integration and processing of complex information (Kodituwakku, 2007). In the current study, understanding central eye gaze and arrow cues required additional processing compared to the control task, where no central cues were present, supporting the idea children with FASD display difficulty when processing becomes more complex. Importantly, group differences were not observed in the Gaze and Arrow Sorting tasks indicating the cuing results were not due to an inability in perceiving and discriminating eye gaze and arrow direction. The present study also found the overall validity effect was greater in the FASD compared to the NC group, as indicated by a significant group by validity interaction, which reflected the larger difference between total invalid and valid trials in the FASD group compared to the NC group. Although the FASD group had longer overall response times, RTs were even longer for invalid trials compared to the NC group. This finding suggests possible differential attentional processes in the two groups. For example, children with FASD may have deficits in voluntary or endogenous attention, which resulted in difficulty detecting targets on the invalid, or uncued, side following the central cues. In line with this interpretation, Green and colleagues found that compared with controls, children with FASD have deficits on antisaccade tasks, requiring them to make voluntary saccades towards the uncued side (Green et al., 2009). The
larger validity effect in the FASD group may also be due to difficulty in their shifting attention, as commonly reported in this population (Coles, Platzman et al., 1997). Because the central cues remained on the screen until a response was made, these children may have had more difficulty disengaging attention from the central cue and then shifting attention to the uncued location, significantly slowing their RTs.

The present study also hypothesized that children with FASD would show a larger cuing effect to arrow cues than gaze cues; however, current results did not support this expectation. One reason may be that the central face cues appeared on the screen with eye direction already averted to the periphery. Eye gaze cues in other cuing studies have been presented first with direct gaze and then with eyes are averted. If children with FASD have difficulty processing direct gaze, impairments may be observed after first viewing a face with straight eye gaze and then orienting attention to the periphery. The present results demonstrate children with FASD do not have difficulty on simple RT tasks, similar to NC, and that both groups located peripheral targets faster in the cued location compared to the uncued location, regardless of cue type. Importantly, however, when information processing and integration became more complex with the addition of central cues, children with FASD had significantly slowed processing speed compared to NC.

In addition to slowed processing of both gaze and arrow cues, the children with FASD performed more poorly than NC children on the Reading the Mind in the Eyes task, a task which requires making inferences about other people’s mental states based on expression information from the eyes. This finding suggests that as the need for understanding eye information and complementary mental states is increased, children with FASD show greater impairments than NC, and this persisted even when there were not time requirements. One interpretation of this
finding is that these children had difficulty comprehending the mental states of others, as previously shown by Timler et al. (2005). Although the FASD group understood fewer mental state words, compared to the NC group, this interpretation cannot account for all of the results, as significant group differences were still observed when analyses only included trials where children understood the meaning of the word. Importantly, the present findings also cannot be the result of poor attending, as there were no significant deficits on the Gender Control task, indicating children from both groups attended to the eye region well enough to make a judgment about gender. It is therefore proposed that when higher level social cognitive processing is required, as in the Reading the Mind in the Eyes task, the FASD group is unable to adequately process and integrate the complex information. Children with FASD show impairments in theory of mind, as presented previously (Greenbaum et al., 2009; Rasmussen et al., 2009), which may result from poor processing and integration of complex social eye expression with mental state information.

Similar to the present findings, gaze and theory of mind deficits have also been observed in children with autism, suggesting potential overlap between these two populations (Harris et al., 1995; Landgren, Svensson, Strömland & Andersson Grönlund, 2010; Mukherjee et al., 2011; Nanson, 1992). Senju et al. (2004) observed that children with autism automatically shifted their attention in response to both gaze and arrow direction, failing to show preferential sensitivity to the social gaze cue. The autism group also had slower overall RTs and greater validity effects than the NC children, suggestive of difficulty in disengaging attention (Casey, Gordon, Mannheim & Rumsey, 1993) and trouble with strategic attention orienting (Minshew, Goldstein & Siegel, 1997). Kyllianen and Hietanen (2004) also reported children with autism were able to recognize the direction of another’s eye gaze and trigger automatic attentional shifts in response
to gaze. The findings from Senju et al. (2004) and Kyllianen and Hietanen (2004) are similar to the present results on FASD. Children with autism have also been shown to have impairments on the Reading the Mind in the Eyes task (Baron-Cohen et al., 2001), relative to NC, with no differences on the Gender Control task. These findings indicate those with autism have difficulty in processing and integrating eye expression information with mental state information, similar to what the present study on children with FASD found.

In addition, children with autism are believed to have abnormal neural processing in response to face and eye gaze processing. Baron-Cohen et al. (1999) reported abnormal amygdala activation in individuals with autism while performing the Reading the Mind in the Eyes task, compared to NC. Abnormalities have also been observed in the superior temporal sulcus and orbital frontal cortex in this population (Pelphrey, Singerman, Allison, & McCarthy, 2003; Schmitz, Daly, & Murphy, 2007). Similar abnormalities have also been observed in FASD, including structural abnormalities in the amygdala, superior temporal sulcus and orbital frontal cortex (Archibald et al., 2001; Nardelli et al., 2011; Sowell et al., 2001; Sowell et al., 2002). Taken together, although the clinical profiles of autism and FASD are clinically distinct, it appears there may be similarities in their social cognitive processing, specifically attentional orienting to eye gaze, its links to theory of mind and the underlying neuroanatomy. Further research comparing the profiles of these two clinical groups would be of value to ensure appropriate differential diagnoses are achieved and relevant treatment approaches are made available.

In conclusion, the present study found that children with FASD do not have difficulty on simple RT tasks, similar to NC, while both groups showed reflexive orienting to peripheral locations, regardless of whether cued by an eye gaze or arrow. Children with FASD only showed impairments when processing became more complex, as indicated by their longer RTs on both
cuing tasks, relative to NC. Furthermore, children with FASD had significant weakness in understanding the mental states of others when presented with limited information from the eye region. Taken together, the present study supports the idea that children with FASD show deficits in processing complex information (Kodituwakku, 2007), especially within the social cognitive domain. As processing demands increased from a simple RT task, to attention orienting and understanding of gaze and arrow cues, to high level theory of mind based on eye information, children with FASD showed increased RT and decreased performance compared with NC children. Overall, children with FASD require a significantly longer time to process and integrate complex social information, a finding which may provide critical information to future treatment approaches.
Chapter 5
Social Perspective Taking and Empathy in Children with Fetal Alcohol Spectrum Disorders

Fetal alcohol spectrum disorders is the umbrella term used to denote the conditions arising from prenatal exposure to alcohol and is associated with increased risk of cognitive and behavioral impairments (Coggins et al., 2003; Coggins et al., 2007; Mattson et al., 1996; Mattson et al., 1999; McGee et al., 2009; Niccols, 2007; Willoughby et al., 2008), as well as significant social deficits (Thomas et al., 1998; Niccols, 2007). Typically, children with FASD have poor interpersonal and peer relationships (O’Connor et al., 2006; Keil et al., 2010) and they lack social judgment (Kodituwakku, 2007). In addition, they show low moral maturity (Schonfeld et al., 2005) and ineffective social problem solving skills (McGee et al., 2009; McGee et al., 2008). Furthermore, sex differences have been reported in parent-rated social behaviour in children with FASD, with females being rated as having more severe social problems than males (Rasmussen et al., 2011; Schonfeld et al., 2006). However, the determinants of the social deficits are not well understood. One set of abilities that may be particularly compromised in these children is their social perspective taking, which is critical for proper social development (Selman, 2003). While limited evidence exists on social perspective taking in children with FASD, several recent reports do indicate these abilities may be compromised (Greenbaum et al., 2009; Rasmussen et al., 2009). However, as previous studies were narrow in their focus, a more comprehensive investigation of social perspective taking is required.

Two fundamental components of social perspective taking are theory of mind and empathy (Davis, 1996; Ruby & Decety, 2004). Theory of mind, which refers to comprehending the mental states of others (Premack & Woodruff, 1978), typically develops during the preschool years
(Wellman et al., 2001) and is generally stronger in females than males (Happe, 1995). Among children with FASD, recent investigations show they exhibit impairments in this domain, with limited capacity to understand the mental states (Coggins 1997; Kodituwakku et al. 1997; Greenbaum et al. 2009; Rasmussen et al. 2009) or the emotions of others (Greenbaum et al., 2009). In addition, their impairments in theory of mind predict parent- and teacher-reported behavioral problems (Greenbaum et al., 2009) and their inhibitory control deficits (Rasmussen et al., 2009). Moreover, according to Rasmussen et al. (2009), these deficits may increase with age since older children with FASD performed below younger children on theory of mind tasks. A second critical component of social perspective taking is empathy, which refers to the affective response one experiences from understanding another’s emotional state (Eisenberg et al., 2006). Empathy is also found to be weaker in boys than girls (Bryant, 1982; Marton et al., 2009) and is positively associated with social skills and negatively associated with aggressive behaviors (Eisenberg et al., 1998; Hoffman, 2000). Indeed, empathy is weaker in some populations such as conduct disorder and ADHD (Marton et al., 2009; de Wied et al., 2010). To our knowledge, however, empathy has never been examined in children with FASD, who are not only at risk for externalizing behavior problems (Fryer et al., 2007) but according to their parents, also have difficulty understanding other’s emotions (Caldwell, 1993).

The present study was designed to comprehensively examine both components of social perspective taking in children with FASD by using measures that assess multiple aspects of theory of mind and empathy. A second goal was to determine whether poor social perspective taking contributes to the sociobehavioural deficits seen in FASD based on parent ratings of behaviour and social skills. Finally, we also sought to examine sex differences and to determine whether the developmental trajectories of these abilities differed for FASD versus NC children.
In light of past research, I hypothesized that parents of children with FASD would rate them as having more behaviour and social problems compared to the NC group. I also hypothesized children with FASD would have poorer performance on child measures of theory of mind and empathy, and any weaknesses in social perspective taking would be related to parent-rated problems. In addition, I hypothesized children with FASD would show increasingly impaired social perspective taking with age relative to NC, and that females in the NC group would show higher levels of empathy than males in the NC group (Bryant, 1982; Marton et al., 2009), whereas females in the FASD group would show lower empathy levels than males in the FASD group (Rasmussen et al., 2011; Schonfeld et al., 2006).

5.1 Methods

5.1.1 Participants

Included in this study were 42 children between the ages of 8 to 12 years; 25 in the FASD group (13 males, 12 females) and 17 in the NC group (9 males; 8 females). The mean ages of the groups were 10.3 (± 1.5) years for FASD and 10.2 (± 1.2) years for NC. A detailed description of the FASD and NC groups, as well as inclusion and exclusion criteria were described previously, please refer to Section 3.1.1.

5.1.2 Measures

Information on developmental history, SES and IQ measures was previously described, please refer to Section 3.1.2.
5.1.2.1 Parent-Ratings

Parent rated behaviour and social profiles were measured using the CBCL (Achenbach, 2001) and the SSIS (Gresham & Elliot, 2008). The CBCL is a widely used standardized questionnaire for 4 to 18 years old children containing 118 items on which parents rated their child using a 3-point scale ranging from ‘not true’ to ‘often true’. Scores on multiple scales were provided as T-scores (mean=50, SD=10), with scores of 65 or above signifying the clinical range. For present purposes, broadband scales of Internalizing, Externalizing and Total Problem, as well as the Social Problem scores were used. In addition, Attention Problem scores were also included in correlation analyses.

The SSIS is a standardized 60-item scale of social skills and behaviour problems for 3 to 18 year old children completed by parents. Scores were provided as standard scores (mean=100, SD=15). For present purposes, two subscales were used: Social Skills, which measures communication, cooperation, assertion, responsibility, empathy, engagement and self control; and Behavior Problems, which measures externalizing problems, bullying tendencies, hyperactivity/inattention, internalizing problems, and autism-like behaviours. High Social Skills scores signify good ability, whereas high Behaviour Problem scores signify more behaviour problems.

5.1.2.2 Theory of Mind Measures

To assess social perspective taking abilities, the NEPSY-II Theory of Mind subtest was used (Korkman et al., 2009). This standardized subtest assesses children’s understanding of other’s mental states such as beliefs, deception and emotions, as well as their understanding that others have their own thoughts and feelings. In the Verbal task, children were read scenarios that required them to understand the knowledge of another individual. In the Contextual task, they
were shown a picture that depicted a social situation and had to select from a set of photographed faces the one best depicting an appropriate emotional response to the scenario. The combined Verbal and Contextual scores provided a total Theory of Mind score. Percentile scores were used from the Verbal task and Total Theory of Mind subtests; however, percentile scores were not provided for the Contextual scores, therefore raw scores were examined for this task.

In addition, I also used four of the five subtests from the Test of Social Cognition (Saltzman-Benaiah & Lalonde, 2007), which assessed theory of mind. These subtests included False Beliefs, Strategic Control of Emotions, Personalized Emotions and Personalized Thoughts. In False Beliefs, the examiner read aloud eight stories that depicted situations of false belief, sarcasm or deception and provided an accompanying picture for each. Children had to make a prediction and provide an explanation about one of the character’s beliefs; one point was provided for each story for a maximum score of eight. The Strategic Control of Emotions subtest contained four stories read aloud by the examiner, each of which described a situation involving a person hiding his or her true emotions about a particular event. Two of the four stories were designed to elicit prosocial rules (e.g., protecting other people) and two, self-protection (e.g., from embarrassment). Children had to decide what the character in each story would say by selecting from a set of face drawings, the one best matching how the character would feel. The maximum score was four, one point being given for a ‘display rule’ response for each story. In the Personalized Emotions subtest, children heard short stories describing a character involved in two distinct events, with the first event potentially influencing the character’s feelings towards the second event (e.g., seeing a scary movie about snakes and then being scared of a snake in real life). Children had to predict and explain the character’s feelings during the second event (e.g., How did the character feel when he saw the snake? Why?). For each story, a single point was
Given if the character’s emotion reflected the influence of the first event for a maximum of three. Finally, the Personalized Thoughts subtest involved four brief verbally presented scenarios using dolls and props. In each case, a child doll gave information about the location of a hidden prize to another adult or infant doll, which could be either ambiguous or unambiguous. Based on the information given by the child doll, children had to state whether the adult or infant knew where the prize was hidden. They had to understand that the adult doll would benefit from unambiguous information, whereas the infant would not. One point was assigned for each correct answer, for a total of four. Z scores were calculated based on normative data provided by Saltzman-Benaiah and Lalonde (2007). All of the verbal stories presented in these subtests were brief (i.e., few sentences) and were accompanied by visual pictures to aid understanding and limit the need to rely solely on language.

5.1.2.3 Empathy Measures

Empathy was measured using the child-rated Index of Empathy for Children and Adolescents (Bryant, 1982) and the parent-rated SSIS Empathy Index (Gresham & Elliot, 2008). The Index of Empathy is a 22 dichotomous item (true/false) measure developed to assess empathy in children six years and older. This scale measured the understanding of feelings towards familiar and unfamiliar people, emotional responsiveness to others’ emotions, and sympathy. The measure was scored by assigning ‘yes’ responses a score of 1 and a ‘no’ responses, a score of 0 (except reverse scored items). Raw scores were used in analyses, with higher scores indicating higher empathy levels. In a standardized sample, Bryant (1982) reported a Cronbach’s alpha of 0.68 for fourth graders and 0.83 for seventh graders.
The SSIS Empathy scale examined child’s empathy from the parent’s perspective. Raw scores from the SSIS Empathy scale were used in subsequent analyses, with higher scores indicating high empathy levels.

### 5.1.3 Data Analyses

Groups were compared for demographic characteristics using one-way ANOVA for continuous variables and chi-square analyses for dichotomous variables. Groups were then compared on dependent variables using MANCOVA (CBCL and SSIS, NEPSY Theory of Mind subtests, and Test of Social Cognition subtests), or ANCOVA (Index of Empathy, SSIS Empathy) using Group and Sex as independent factors and Age as a covariate. Effect sizes were also calculated. When significant effects of Age were indicated by MANCOVA, within group linear regressions were conducted to further investigate the effects of age on social perspective taking measures. Unstandardized B, R², and 95% CI were presented for regressions. Within group Pearson correlations were also conducted to examine whether performance on tasks of theory of mind and empathy (i.e., NEPSY Theory of Mind Total, False Beliefs, Strategic Control of Emotions and Index of Empathy measures) was related to parent ratings (i.e., CBCL Social Problems, CBCL Attention Problems, SSIS Empathy, and SSIS Social Skills). SPSS 17.0 was used for analyses.

### 5.2 Results

#### 5.2.1 Demographic Characteristics

Please see Section 3.2.1 and Table 1 for the demographic and IQ data, as well as additional background information for the FASD and NC groups.
5.2.2 Parent-Rated Behaviour and Social Skills

A MANCOVA with Group and Sex as factors and Age as a covariate was used to analyse the CBCL and SSIS subscales. One child in the NC group did not have a score for the SSIS Behaviour Problems subscale; therefore analyses were conducted on 25 children with FASD and 16 NC children. Results revealed an overall effect of Group \[F (6, 31) = 43.7, \ p < 0.001, \ n^2 = 0.9\], but not Sex, Age, or Group by Sex interaction. Univariate analyses revealed significant Group effects for the CBCL Internalizing \[F (1, 36) = 25.6, \ p < 0.001, \ n^2 = 0.4\], Externalizing \[F (1, 36) = 63.9, \ p < 0.001, \ n^2 = 0.6\], Total \[F (1, 36) = 105.2, \ p < 0.001, \ n^2 = 0.7\] and Social Problems scales \[F (1, 36) = 59.9, \ p < 0.001, \ n^2 = 0.6\], as well as SSIS Social Skills \[F (1, 36) = 88.4, \ p < 0.001, \ n^2 = 0.7\] and Behaviour Problems scales \[F (1, 36) = 106.3, \ p < 0.001, \ n^2 = 0.7\] (see Table 8). Children with FASD had poorer parent-rated social skills and behaviour problems compared to NC.

**Table 8.** Means (SD) for NC and FASD groups on CBCL and SSIS

<table>
<thead>
<tr>
<th>Parent-Rated Measure</th>
<th>NC</th>
<th>FASD</th>
<th>(p) value</th>
<th>Group Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBCL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internalizing</td>
<td>47.3 (10.7)</td>
<td>64.6 (10.8)</td>
<td>&lt; 0.001</td>
<td>FASD &gt; NC</td>
</tr>
<tr>
<td>Externalizing</td>
<td>47.1 (9.1)</td>
<td>70.5 (8.8)</td>
<td>&lt; 0.001</td>
<td>FASD &gt; NC</td>
</tr>
<tr>
<td>Total</td>
<td>44.4 (10.0)</td>
<td>71.8 (6.7)</td>
<td>&lt; 0.001</td>
<td>FASD &gt; NC</td>
</tr>
<tr>
<td>Social Problems</td>
<td>51.8 (10.0)</td>
<td>71.1 (9.5)</td>
<td>&lt; 0.001</td>
<td>FASD &gt; NC</td>
</tr>
<tr>
<td>SSIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social Skills</td>
<td>99.9 (8.7)</td>
<td>67.3 (13.9)</td>
<td>&lt; 0.001</td>
<td>FASD &lt; NC</td>
</tr>
<tr>
<td>Behavior Problems</td>
<td>93.1 (10.8)</td>
<td>136.6 (14.7)</td>
<td>&lt; 0.001</td>
<td>FASD &gt; NC</td>
</tr>
</tbody>
</table>

**Note:** CBCL lower T scores indicate fewer problems (scores over 65 indicate clinical significance); SSIS Social Skills higher standard scores indicate fewer problems; SSIS Behavior Problems lower standard scores indicate fewer problems.

5.2.3 Theory of Mind

The NEPSY-II Theory of Mind subtests were analysed using MANCOVA. Two children in the FASD group did not complete the Contextual subtest; therefore analyses were based on 23
children in the FASD and 17 in the NC group. Results revealed a main effect of Group [F (3, 33) = 4.2, \( p < 0.02, n^2 = 0.3 \)] and Age [F (3, 33) = 6.7, \( p < 0.001, n^2 = 0.4 \)], but not Sex or the Group by Sex interaction. Univariate analyses indicated the FASD group scored significantly below the NC group on the Verbal [F (1, 35) = 8.2, \( p < 0.007, n^2 = 0.2 \)] and Total scores [F (1, 35) = 4.4, \( p < 0.04, n^2 = 0.1 \)], but did not differ on the Contextual subtest. Scores on the Verbal and Total subscales for both groups, however, were in the average range. Univariate effects of Age were observed on the Contextual subtest, at trend level [F (1, 35) = 3.8, \( p < 0.06, n^2 = 0.1 \)] (see Table 9). Within group linear regressions were conducted on the raw scores from the Contextual subtest and Age. Regressions were not significant for the FASD or the NC group, due to the trend level significance of the univariate effect.

A separate MANCOVA was conducted on the Test of Social Cognition subtests. One NC child did not complete the Personalized Emotions subtest, therefore this analysis included 16 children in the NC group. Results revealed a main effect of Group [F (4, 33) = 5.8, \( p < 0.001, n^2 = 0.4 \)] and Age [F (4, 33) = 4.7, \( p < 0.004, n^2 = 0.4 \)], but not Sex or the Group by Sex interaction. Univariate analyses indicated the FASD group performed below the NC on the False Belief [F (1, 36) = 23.2, \( p < 0.001, n^2 = 0.4 \)], Strategic Control of Emotions [F (1, 36) = 6.0, \( p < 0.02, n^2 = 0.1 \)] and Personalized Emotions subtests [F (1, 36) = 4.4, \( p < 0.05, n^2 = 0.1 \)], with no group difference on the Personalized Thoughts subtests (p < 0.6). Univariate effects of Age were observed on the False Belief subtest [F (1, 36) = 15.2, \( p < 0.001, n^2 = 0.3 \)]. Please refer to Table 9. Within group linear regressions were then conducted on the raw scores of the False Belief subtest to further examine the effects of Age. Within the FASD group, performance on the False Belief subtest declined as a function of age, at trend level [F (1, 23) = 3.1, \( R^2 = 0.12, p < 0.09, \)
slope = -0.4, 95% CI = -0.8 to 0.1]. The regression results were not significant in the NC group [F (1, 15) = 1.0, R² = 0.06, p < 0.3, slope = +0.4, 95% CI = -0.4 to 1.2] (Table 10).

Table 9. Means (SD) for NC and FASD groups on the theory of mind measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>NC</th>
<th>FASD</th>
<th>p value</th>
<th>Group Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEPSY-ToM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal (%)</td>
<td>65.4 (26.1)</td>
<td>37.9 (31.7)</td>
<td>&lt; 0.007</td>
<td>FASD&lt;NC</td>
</tr>
<tr>
<td>Contextual (raw)</td>
<td>4.7 (1.0)</td>
<td>4.4 (1.3)</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Total (%)</td>
<td>58.2 (24.8)</td>
<td>37.5 (32.6)</td>
<td>&lt; 0.04</td>
<td>FASD&lt;NC</td>
</tr>
</tbody>
</table>

Test of Social Cognition (z scores)

<table>
<thead>
<tr>
<th>Measure</th>
<th>NC</th>
<th>FASD</th>
<th>p value</th>
<th>Group Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>False Belief</td>
<td>-0.8 (1.4)</td>
<td>-3.2 (2.1)</td>
<td>&lt; 0.001</td>
<td>FASD&lt;NC</td>
</tr>
<tr>
<td>Strategic Display of Emotions</td>
<td>-0.3 (1.2)</td>
<td>-1.3 (1.4)</td>
<td>&lt; 0.02</td>
<td>FASD&lt;NC</td>
</tr>
<tr>
<td>Personalized Emotions</td>
<td>-1.2 (2.1)</td>
<td>-2.8 (2.9)</td>
<td>&lt; 0.05</td>
<td>FASD&lt;NC</td>
</tr>
<tr>
<td>Personalized Thoughts</td>
<td>-0.1 (0.6)</td>
<td>-0.3 (1.1)</td>
<td>ns</td>
<td></td>
</tr>
</tbody>
</table>

Note: NEPSY higher percentiles scores indicate better performance. Test of Social Cognition higher z scores indicate better performance.

Table 10. Linear regressions with age as a predictor of theory of mind performance in the NC and FASD groups

<table>
<thead>
<tr>
<th>Measure</th>
<th>NC</th>
<th></th>
<th></th>
<th>FASD</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>95% CI</td>
<td>p value</td>
<td>B</td>
<td>95% CI</td>
<td>p value</td>
</tr>
<tr>
<td>False Belief</td>
<td>0.9</td>
<td>-7.7 to 9.5</td>
<td>ns</td>
<td>6.5</td>
<td>2.0 to 10.9</td>
<td>&lt;0.09</td>
</tr>
<tr>
<td>Constant</td>
<td>0.4</td>
<td>-0.4 to 1.2</td>
<td>ns</td>
<td>-0.4</td>
<td>-0.8 to 0.1</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.2.4 Empathy

An ANCOVA with Group and Sex as factors and Age as a covariate was conducted on the Index of Empathy. Results revealed the scores for the FASD group were lower than the NC group on the Index of Empathy [F (1, 37) = 5.4, p < 0.03, n² = 0.1] (Table 11). There was also a main effect of Sex [F (1, 37) = 10.1, p < 0.003, n² = 0.2], with males (11.2) scoring lower than females (15.0), and a trend level effect for Age [F (1, 37) = 4.0, p < 0.06, n² = 0.1]. There was no
significant Group x Sex interaction. Within group regressions to further investigate the effects of Age revealed no significant effects for the FASD or NC group, due to the trend level significance of the univariate effect.

A separate ANCOVA conducted on the SSIS Empathy subscale revealed a main effect of Group \( F (1, 37) = 28.7, p < 0.001, n^2 = 0.4 \], with the FASD group rated by parents as having lower empathy scores than NC (Table 11). There were no main effects of Sex or Age. There was, however, a significant Group x Sex interaction \( F (1, 37) = 5.8, p < 0.02, n^2 = 0.1 \), reflecting the higher empathy level ratings for males in the FASD group than females. In contrast, females in the NC group were rated by parents as having higher empathy levels than males in the NC group (Table 11).

### Table 11. Means (SD) for NC and FASD groups on the empathy measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>NC</th>
<th>FASD</th>
<th>( p ) value</th>
<th>Group Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index of Empathy</td>
<td>14.3 (4.1)</td>
<td>11.8 (4.1)</td>
<td>&lt; 0.03</td>
<td>FASD &lt; NC</td>
</tr>
<tr>
<td>SSIS Empathy Subscale</td>
<td>13.4 (2.8)</td>
<td>8.3 (3.6)</td>
<td>&lt; 0.001</td>
<td>FASD &lt; NC</td>
</tr>
<tr>
<td>Female raw scores</td>
<td>14.6 (1.1)</td>
<td>7.0 (0.91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male raw scores</td>
<td>12.4 (1.0)</td>
<td>9.5 (0.87)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note:* Raw scores were used for both measures. Higher scores indicate higher levels of empathy.

#### 5.2.5 Correlation between Social Perspective Taking and Parent-Rated Behaviour and Social Skills

Within group Pearson correlations were conducted to examine whether performance on theory of mind and empathy task (i.e., NEPSY Theory of Mind Total, False Beliefs, Strategic Control of Emotions and Index of Empathy measures) was related to parent ratings (i.e., CBCL Social Problems, CBCL Attention Problems, SSIS Empathy, and SSIS Social Skills). Within the FASD
group, child performance on the NEPSY Theory of Mind Total score was negatively correlated with parent-rated attention problems ($r = -0.5, p < 0.01$), reflecting higher scores on the Theory of Mind subtest by those with lower parent-rated attention problems. Within the NC group, child performance on the Index of Empathy was negatively correlated with parent-rated social problems (CBCL Social problems; $r = -0.6, p < 0.01$), reflecting higher scores on the empathy questionnaire related for those with lower parent-rated problems. The Index of Empathy was also positively correlated with parent-rated social skills (SSIS Social Skills; $r = +0.7, p < 0.005$) and empathy ($r = +0.5, p < 0.03$), with higher child reported empathy correlated with higher parent rated social abilities and empathy. After Bonferroni correction ($0.05/8 = 0.006$), only the relationship between the Index of Empathy and SSIS Social Skills in the NC group remained significant.

5.3 Discussion

The present study examined theory of mind and empathy in children with FASD and NC, processes that develop during childhood and are often abnormal in developmental conditions with social skills difficulties. Overall, children with FASD were rated by parents as having increased behaviour problems and poorer social skills than NC children. The FASD group also performed more poorly on various tests of theory of mind and had lower self- and parent-rated empathy. With regard to age, older children with FASD showed worse performance on one theory of mind task, the False Beliefs task. Sex differences were observed in both groups on the Index of Empathy, reflecting higher scores by females compared with males. In contrast, on the parent-rated empathy scale, males in the FASD group received higher scores than females in the FASD group, whereas females had higher scores than males in the NC group. Additionally,
higher theory of mind performance (i.e., NEPSY Theory of Mind subtest) was associated with decreased parent-rated attention problems in the FASD group; whereas higher self-reported empathy levels (i.e., Index of Empathy) was associated with increased parent-rated social skills in the NC group.

The present results indicate children with FASD have impairments in multiple aspects of theory of mind (i.e., false beliefs, understanding emotional control, and how emotions influence experience), consistent with previous findings (Greenbaum et al., 2009; Rasmussen et al., 2009). In addition, children’s performance on social perspective taking measures predicted caregiver-ratings of behaviour. Within the FASD group, higher performance on the NEPSY Theory of Mind subtest was related to lower parent-rated attention problems, whereas in the NC group, higher self-rated empathy levels were related to higher parent-rated social skills, including empathy. These findings suggest social perspective taking may be related to real world behaviour in children with FASD, with poorer theory of mind linked to attention problems. Understanding other’s mental states is a complex ability that requires intact attentional processes, such as joint attention (Charman et al., 2000). As a result, if children with FASD have difficulty understanding social interactions and other people’s intentions, these difficulties could present as impaired attention and a seeming lack of interest. Together, difficulties in theory of mind and attention could spill over into other domains, resulting in attention being one of the most commonly observed deficits in FASD (Fryer, McGee, Matt et al., 2007). Interestingly, children with ADHD also have severe difficulty in domains of social perspective taking (Marton et al., 2009). Because children with FASD often have comorbid diagnoses of ADHD this may further the view that attention deficits are related to impaired social perspective taking. Further work is
warranted to investigate the direct and bi-directional relationships between attention and social perspective taking.

Our findings also corroborate the work of Rasmussen et al. (2009), who observed impaired performance on a false belief task in FASD, where older children with FASD performed more poorly on false beliefs than younger children with FASD. Similarly, the present study also found that older children with FASD performed more poorly at trend level than younger children on false beliefs. Previous studies reporting similar age-related declines in social and adaptive abilities in FASD (Thomas et al., 1998; Whaley et al., 2002), suggest social perspective taking and socialization deficits become more pronounced with age. Arrested social cognition may negatively affect the development of prosocial behaviours and social skills, especially during early adolescence and adulthood. As children get older, their social interactions become more complex due to increased demands and expectations for peer relationships, as well as emotional and mental understanding. Therefore, if these social abilities are arrested, children may not interact appropriately in social contexts and instead display more maladaptive behaviours, as commonly observed in FASD. More specific conclusions about age-related changes, however, cannot be made in the present study as longitudinal data were not collected.

Importantly, children with FASD did not show impaired performance on the Personalized Thoughts subtest, which required them to understand basic information processing behaviours of adults and infants. Compared to the other social perspective taking subtests, this task did not require theory of mind or emotional understanding. This finding is critical, as it indicates children with FASD do not have deficits understanding basic information processing abilities of others. However, as social cognitive demands are increased and a larger amount of information needed to be integrated, as is the case in the other social perspective taking subtests, these
children do show significant impairments. This finding supports the claim that the behavioural phenotype of FASD is characterized by deficits in processing and integrating complex information (Kodituwakku, 2007), which is critical to social cognition.

The present study is one of the first to investigate empathy in children with FASD. My findings show that children with FASD and their parents both rated them as less empathic than NC. Lower empathy ratings by parents in FASD is similar to previous findings in children with ADHD (Marton et al., 2009), whose caregivers rated them as being less empathic than NC. The ADHD group, however, did not rate themselves as having lower empathy than NC. Further research is necessary to determine the overlapping characteristics between ADHD and FASD, and how they relate to the social profiles of these two clinical populations. Low empathy is believed to be a risk factor for aggressive and violent behaviour, as evident in other disorders (Freshbach, 1997; de Wied et al., 2010). However, empathy levels were not related to parent ratings of behaviour problems in the FASD group. In comparison, higher levels of empathy were positively related to increased social skills in the NC group, acting as a potential underlying mechanism for prosocial behaviour in typically developing children.

Sex differences in empathy were also observed in the current thesis, with females rating themselves as more empathic than males. Similar sex differences have been observed previously (Bryant, 1982; Marton et al., 2009), suggesting this is a consistent findings across different groups of children. Interestingly, parents rated males in the FASD group as having higher empathy than females in the FASD group, supporting previous research of more severe parent-rated social problems in females with FASD compared to males with FASD (Rasmussen et al., 2011; Schonfeld et al., 2006). These sex differences may be due to a reporting bias from parents of children with FASD, who rate females more negatively if they go against the commonly held
empathy stereotype. Because girls are often reported to be more empathic than boys (Baron-Cohen, Richler, Bisarya, Gurunathan & Sally Wheelwright, 2003; Bryant, 1982; Marton et al., 2009), any negative deviation from this perspective may be overrepresented by caregivers, as observed presently in the FASD group. Alternatively, these sex differences may reflect the more severe social symptoms experienced by females following PAE, as has been suggested in previous reports (Rasmussen et al., 2011; Schonfeld et al., 2006). Future work is required to further investigate these sex differences.

Studies have also reported females and males use different neural strategies when assessing their own emotions in response to others. Females have been shown to recruit brain regions (e.g., inferior frontal region and amygdala) to a higher degree than males when processing empathic stimuli (Derntl et al., 2010; Schulte-Rüther et al., 2008). Relevantly, children with FASD show atypical structure and function in these areas (Fryer, Tapert et al., 2007; Nardelli et al., 2011; Sowell, Mattson et al., 2008; Sowell et al., 2002), which may give rise to poor empathy ratings observed in the current study. However, sex differences in neuroanatomical regions have not been investigated in FASD. Overall, not only do children with FASD show difficulties understanding other’s perspectives, they also have impairments understanding and sharing another’s emotional state, which may be a result of abnormal neural recruitment.

The present study was unique in its approach of examining theory of mind and empathy in children with FASD. However, several limitations are noteworthy. I was not able to control for dose or timing of PAE in the FASD group, as is the case for many clinical studies that investigate prenatal teratogen exposure. There was also a lack of information on polysubstance exposure, which is an ongoing concern in research on all prenatal exposure to teratogens. I was also unable to measure the impact of other confounders such as maternal nutrition, parental
psychopathology, prenatal care and quality of home environment, which impact social
development and functioning (Henry, Sloane & Black-Pond, 2007; Henry, Richard-Yris,
Tordjman & Hausberger, 2009). Furthermore, there are believed to be strong relationships
between language, executive functions and theory of mind (Coggins et al., 2007; Marton et al.,
2009); however I did not investigate these relationships in the present study. It is important to
note that the present findings could not be solely due to language difficulties, as the FASD group
did not display impairments on all orally presented subtests (i.e., Personalized Thoughts). Future
work would benefit from comparing social perspective taking in FASD to other clinical
populations whose profiles are characterized by such impairments (i.e., autism).

In conclusion, the current study found that children with FASD have difficulties in multiple
domains of theory of mind and empathy, as rated by parents and by self-reports. Difficulties in
social perspective taking may underlie the attention problems commonly reported in this
population, as observed by the relation between poor theory of mind in children with FASD and
increase parent-rated attention problems. Moreover, social perspective taking deficits may
become more pronounced as these children get older and are faced with more complex social
situations. Because poorer social perspective taking performance during peer interactions is
associated with difficulty forming and maintaining friendships (Selman, 2003), it is plausible that
the lower theory of mind skills of children with FASD partially contribute to their difficulties in
social functioning and behaviour. If a child cannot understand another person’s mental state or
emotion, and has low levels of empathic understanding, they may have trouble comprehending
another person’s intentions and the social situation as a whole. Kodituwakku stressed the
importance of using neurobehavioural research to guide and direct intervention methods for
children with FASD (Kodituwakku, 2010), thus the present findings suggest these children may benefit from treatment approaches targeting specific aspects of social cognition.
Chapter 6
White Matter Pathology in Limbic Pathways: Investigation of Children with Fetal Alcohol Disorders

The adverse effects of alcohol on the developing human brain manifest as a spectrum of behavioural and neurocognitive disabilities most often referred to as FASD (Streissguth, 1997). Although children with FASD experience difficulties in many cognitive domains, particularly executive functioning (Kodituwakku, 2007; Mattson, Goodman, Caine, Delis & Riley, 1999), attention (Coles, Platzman et al., 1997), memory (Mattson et al., 1996; Willoughby et al., 2008), and language (Coggins et al., 2003, 2007; McGee, Bjorkquist et al., 2009), it has been proposed that one of the core deficits in FASD is deficient social cognition (Greenbaum et al., 2009). Indeed, the main social cognitive deficits described include their difficulty in understanding other people’s mental states and beliefs (Coggins, 1997; Kodituwakku et al., 1997; Rasmussen et al., 2009), and identifying emotions in faces (Greenbaum et al., 2009). These children also suffer from impairments in social communication (Coggins et al., 2003) and the use of mental state words (Timler et al., 2005). An important finding by Rasmussen et al. (2009) also showed that older children with FASD performed worse than younger children with FASD on theory of mind tasks, consistent with observations of declines in social and adaptive abilities with age (Thomas et al., 1998; Whaley et al., 2002). According to Thomas et al. (1998), these results suggest an arrestment in their social development. In light of findings that these social difficulties can lead to serious secondary disturbances later in life, such as trouble with the law, inappropriate sexual behaviour, suicide, and high rates of depression and other mental illness (Streissguth et al., 2004), it is important to identify the mechanisms contributing to the social difficulties of this population.
Recent studies using MRI have shown that prenatal alcohol exposure has a widespread teratogenic effect on the developing brain (Lebel et al., 2011). Compromised structures include the corpus callosum, caudate nucleus and cerebellum, all of which are associated with the executive disturbances observed in individuals with FASD (Riley & McGee, 2005). Importantly, several studies show regions involved in social cognitive processing, including the limbic system, are also targets of alcohol teratogenesis. Indeed, limbic structures such as the cingulate and orbitofrontal cortex, which are necessary for emotional decision making and theory of mind (Amodio & Frith, 2006; Mundy, 2003) appear to be structurally and functionally abnormal in FASD (Fryer, Tapert et al., 2007; Sowell, Mattson et al., 2008; Sowell et al., 2002). As the orbital and medial frontal regions are critical for social functioning, some researchers have posited these brain areas as 'hot-spots’ of PAE (Kodituwakku et al., 2001). Likewise, abnormalities in amygdala and hippocampus (Nardelli et al., 2011; Willoughby et al., 2008), which are critical for the storage of memories, emotional processing of visual cues and face processing (Cabeza & Nyberg, 2000; Kawashima et al., 1999), may also explain some of the social deficiencies in FASD. The many social functions attributed to limbic regions are impaired following PAE and suggest damage in limbic areas may give rise to social cognitive deficits observed in this population.

Although investigating the neural targets of alcohol teratogenesis represents an invaluable first step in identifying the mechanisms underlying social deficits in FASD, few studies to date have focused specifically on abnormalities within regions related to social processing. Several studies have reported regional differences in both grey and white matter, however, the impact of PAE on the white matter connections between regions has received less attention. More recently, there has been increased interest in white matter pathology following PAE, as findings from multiple
disciplines suggest white matter is a specific target of alcohol teratogenesis (Chiappelli et al., 1991; Riikonen et al., 1999; Watari et al., 2006). One procedure that has become increasingly popular in examining white matter pathology is DTI, a non-invasive technique using MRI to provide unique information about tissue microstructure and orientation properties of the diffusion process of water molecules (Basser et al., 1994). Two main DTI indices are FA, which assesses the degree of water diffusion in a single direction, and MD, which represents the average amount of dispersion across all directions (Basser et al., 1994). Calculations are also made on eigenvectors, from which scalar measures are derived based on the diffusion tensor matrix. The first and largest of the eigenvalues ($\lambda_1$) represents diffusivity parallel to the axons and is referred to as AD (Basser, 1995). The second and third eigenvalues represent diffusivity in the planes orthogonal to the axons and are generally averaged ($\frac{(\lambda_2 + \lambda_3)}{2}$), resulting in RD (Basser, 1995). When brain development is abnormal or acquired brain damage occurs, FA values are typically lower than normal white matter regions, while MD values are typically higher, signifying poor white matter integrity in affected regions (Neil et al., 2002).

A number of DTI studies have been conducted on individuals with FASD reveal poor fibre integrity in the corpus callosum (Fryer et al., 2009; Lebel et al., 2008; Li, Coles, Lynch & Hu, 2009; Ma et al., 2005; Sowell, Johnson et al., 2008; Wozniak et al., 2006; Wozniak et al., 2009), as indicated by low FA and high MD values. Studies have also shown reduced white matter integrity in the bilateral cingulate, temporal areas (ILF), frontal areas (superior longitudinal, inferior fronto-occipital and UF), parietal and occipital regions, the internal capsule, as well as globus pallidus, putamen and thalamus regions, brainstem and cerebellar pathways (Fryer et al., 2009; Lebel et al., 2010; Lebel, Rasmussen et al., 2008; Sowell, Johnson et al., 2008). Although these findings suggest white matter pathology in areas including, but not limited to limbic
structures, no study as of yet has focused specifically on limbic pathology related to social difficulties in FASD. Furthermore, few studies have investigated the secondary AD and RD eigenvalues in FASD populations.

The present study was designed to address the above knowledge gaps concerning the role of PAE in compromised white matter integrity in limbic pathways. Three main limbic tracts were investigated; the UF, cingulum, and ILF, all of which have been shown to play a role in various social cognitive processes. The UF, which is a ventral association bundle that originates from the anterior temporal area (i.e., amygdala and hippocampus) and connects to frontal regions (i.e., orbital frontal and frontal polar) (Catani et al., 2002; Klingler & Gloor, 1960), is important for social processing, particularly emotion regulation (Carmichael & Price, 1995) and affect processing (Petrides & Baddeley, 1996). The cingulum, which connects multiple brain regions including specific frontal and temporal areas (Pandya et al., 1981), allows for communication and relay of information between important limbic structures (Catani et al., 2002). The cingulum is believed to play a critical role in theory of mind, empathy, and emotional processing (Calarge, Andreasen & O’Leary, 2003; Singer et al., 2004). The third tract is the ILF, which is a ventral association bundle with long and short fibres running through the temporal lobe, and connects the temporal pole with the occipital pole, including visual areas, amygdala and hippocampus (Catani et al., 2003; Catani et al., 2002). The ILF has been linked to processes related to visual perception (Ffytche & Catani, 2005), including impaired face processing (Kleinhans et al., 2008). Given these tracts have important functions in processing social cognitive information, I hypothesized that children with FASD would show compromised white matter integrity in each of these pathways, relative to NC children. Furthermore, given that major age-related changes occur in white matter during typical childhood and adolescent development (Lebel, Walker et al.,
I hypothesized that white matter integrity would improve with age in the NC group, but would be distinct from the age-related changes observed in the FASD group.

6.1 Methods

6.1.1 Participants

Included in this study were 42 children between the ages of 8 to 12 years; 25 children were in the FASD group and 17 in the NC group. From this sample, one child in the FASD did not complete a scan, one child in the NC group was removed due to extensive motion, and three children in the FASD group and two children in the NC group were left handed. Therefore, the final sample consisted of 21 right handed children in the FASD group (age = 10.3 ±1.4; 10 males, 11 females) and 14 right handed children in the NC group (age = 10.5 ±1.1 years; 8 males, 6 females).

Please refer to Section 3.1.1 for a detailed description of the FASD and NC groups, as well as inclusion and exclusion criteria.

6.1.2 Procedures

Information on developmental history, SES and IQ measures was previously described, please refer to Section 3.1.2.

6.1.2.1 DTI Image Acquisition

All data were collected with a 1.5T MRI System (Signa EXCITE HD, GE Medical) using a standard eight-channel receive-only head array coil in SickKids Diagnostic Imaging unit. Whole brain anatomical scans were acquired using an inversion recovery prepared 3D-FSPGR sequence: FA = 20°, TR/TE/TI = 10.3/4.2/400ms, FOV = 24x18 cm, 256 x 256 matrix, slice thickness = 1.5mm, 116-124 slices, ~7 minutes scan times. DTI data were acquired using an EPI
sequence with the following parameters: 31 directions plus 4 images with $b=0$, $FA = 90^\circ$, TR/TE = 15000/83.3ms, FOV = 320mm, 128x128 matrix, slice thickness = 2.5, and 50 slices. Total DTI acquisition time was approximately 9 minutes. During both the structural and DTI scanning children watched a movie through fibre-optic goggles to help limit motion. Conventional T2-weighted and FLAIR scans were also obtained for all children to detect gross brain abnormalities.

6.1.2.2 Region of Interest Diffusion Measurements Image Acquisition

Average FA, MD (mm$^3$/s), RD and AD values were calculated for the UF, cingulum and ILF pathways using region of interest analyses. For each structure, left and right measurements were made and analysed separately. All data were visually inspected for artifacts and data quality before analyses. One dataset was discarded due to extensive motion. Following reconstruction the DTI data were corrected for interslice motion using a locally developed software and 2D motion correction (2dImReg, Analysis of Functional NeuroImages (AFNI); National Institute of Mental Health, Bethesda, MD) (Cox, 1996). Eddy current distortion correction was applied using eddycorrect (Oxford Centre for Functional MRI of the FMRIB Brain software library, FSL) (Smith et al., 2004). Diffusion tensors and estimates for FA, MD, AD and RD were generated using dtifit (FSL) (Smith et al., 2004). The resulting FA, MD, AD and RD maps were aligned into Montreal Neurological Institute (MNI) space using a 2-step non-linear transformation (fnirt, FSL) (Smith et al., 2004) between the average b=0 image, the anatomical image and the MNI-152 template (Evans, Collins & Milner, 1992). FA, MD, RD and AD values were calculated in the UF, cingulum and ILF pathways using the John Hopkins University white matter tractography atlas thresholded at 50%.
6.1.2.3 Data Analyses

Groups were compared for demographic characteristics using one-way ANOVA for continuous variables and chi-square for dichotomous variables. DTI analyses were as follows: (i) DTI variables (i.e., FA, MD, RD, AD) were each analysed using separate MANCOVAs with Group and Sex as independent factors, and Age as a covariate. Wilks Lambda and effect size are presented for each MANCOVA. (ii) Any significant effects of Age, as revealed through the individual MANCOVA were further investigated using within group linear regressions. Significant unstandardized B, $R^2$ and 95% CI were presented for all regressions. (iii) Bonferroni correction was applied to the significant regression analyses. All analyses were conducted using SPSS 17.0.

6.2 Results

6.2.1 Demographic Characteristics

Table 12 presents the demographic and abbreviated IQ data of the FASD and NC groups. Groups did not differ in age and sex, with trend level differences in SES. Although significant group differences were observed on the WASI FSIQ index, with lower scores in the FASD group, IQ was not covaried in the subsequent analyses for two reasons. First, according to Dennis et al. (2009), because IQ represents an inherent attribute of FASD it should not be a covariate when examining neurodevelopmental conditions. Second, according to Miller and Chapman (2001), controlling for pre-existing group differences in non-random group design violates the core assumption that covariates are statistically independent from the grouping variable in an analysis of covariance.
Table 12 also contains additional background information on living status, exposure histories and comorbidities in the two groups. The majority of children in the FASD group were in adoptive or foster care, or living with a biological relative. Almost all of the NC children were living with their biological parents. Most children in the FASD group had biological mothers who reportedly smoked cigarettes during pregnancy; information was unavailable for five children in the FASD group. Although information on prenatal tobacco exposure was unavailable for three children in the NC group, available data indicated one mother in the NC group smoked during pregnancy. Fifty percent of children with FASD were exposed to secondary teratogens prenatally (drugs unspecified) while 28% were exposed to cocaine and 17% to marijuana prenatally. Information was unavailable on other prenatal drug exposure for three FASD children in the FASD group. None of the children in the NC group were exposed to prenatal teratogens. Children in the FASD group also had diagnoses of ADHD (71%), ODD (19%), LD (43%), sensory processing disorder (10%) and anxiety (10%). Although information was unavailable for one child in the NC group, available data indicated none of the children in the NC group had a comorbid diagnosis. Seventy-one percent of the FASD group was taking attention medications. Although information was unavailable for one child in the NC group, available data indicated none of the children were taking attention medication.
<table>
<thead>
<tr>
<th>Variables</th>
<th>NC Mean (SD)</th>
<th>FASD Mean (SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>10.5 (1.1)</td>
<td>10.3 (1.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>57</td>
<td>48</td>
<td>ns</td>
</tr>
<tr>
<td>WASI FSIQ</td>
<td>111.4 (15.2)</td>
<td>89.5 (13.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%high</td>
<td>79</td>
<td>57</td>
<td>&lt; 0.08</td>
</tr>
<tr>
<td>%medium/low</td>
<td>21</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Family Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% with biological parents</td>
<td>86</td>
<td>0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% with biological relative</td>
<td>0</td>
<td>28</td>
<td>&lt; 0.03</td>
</tr>
<tr>
<td>% adopted</td>
<td>14</td>
<td>62</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>% foster care</td>
<td>0</td>
<td>10</td>
<td>ns</td>
</tr>
<tr>
<td>Cigarette Exposure (% yes)</td>
<td>9</td>
<td>94</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Secondary Drug Exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Unspecified</td>
<td>0</td>
<td>50</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>% Cocaine</td>
<td>0</td>
<td>28</td>
<td>&lt; 0.06</td>
</tr>
<tr>
<td>% Marijuana</td>
<td>0</td>
<td>17</td>
<td>ns</td>
</tr>
<tr>
<td>% ADHD</td>
<td>0</td>
<td>71</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% ODD</td>
<td>0</td>
<td>19</td>
<td>&lt; 0.09</td>
</tr>
<tr>
<td>% LD</td>
<td>0</td>
<td>43</td>
<td>&lt; 0.006</td>
</tr>
<tr>
<td>% Sensory Processing Deficits</td>
<td>0</td>
<td>10</td>
<td>ns</td>
</tr>
<tr>
<td>% Anxiety</td>
<td>0</td>
<td>10</td>
<td>ns</td>
</tr>
<tr>
<td>Attention Medication (% yes)</td>
<td>0</td>
<td>71</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Note: WASI mean =100; SD = 15
6.2.2 DTI FA Values

The MANCOVA conducted on the FA values revealed only a significant covariate effect of Age [F (4, 27) = 2.9, \( p < 0.04, \eta^2 = 0.3 \)], but no group differences (\( p < 0.2 \)) (see Table 13). Sex and the Group x Sex interaction were also non-significant (\( p < 0.6 \) and 0.8, respectively). Univariate analyses of Age revealed a significant age effect on FA in the Left UF [F (1, 30) = 8.6, \( p < 0.006, \eta^2 = 0.2 \)], reflecting a significant increase in FA as a function of age in the Left UF in the FASD group [F (1, 19) = 7.5, \( R^2 = 0.28, p < 0.02 \), slope = +0.02, 95% CI = 0.005 to 0.04; Table 14], and a similar trend level effect in the NC group [F (1, 12) = 3.6, \( R^2 = 0.23, p < 0.08 \), slope = +0.02, 95% CI = -0.003 to 0.05; Table 14]. Since the FASD and NC groups had overlapping CI, this indicates FA values increased as a function of age in both groups (Figure 5). After Bonferroni correction (0.05/5 = 0.01; see Table 14), only the age effect in the FASD group remained at trend level.

Figure 5. Linear regressions with age: Left UF FA values with 95% confidence intervals
6.2.3 DTI MD Values

The MANCOVA conducted on the MD values revealed a significant covariate effect of Age \[F(4, 27) = 3.4, p < 0.02, n^2 = 0.3\], but no group differences on mean MD values \((p < 0.5; \text{Table 13})\). Sex and the Group x Sex interaction were also non-significant \((p < 0.7 \text{ and } 0.4, \text{ respectively})\). Univariate analyses of Age revealed a significant effect occurred on the MD values of the Left UF \[F(1, 30) = 8.9, p < 0.006, n^2 = 0.2\] and Right ILF \[F(1, 30) = 6.0, p < 0.02, n^2 = 0.2\]. For the Left UF, MD decreased significantly with age in the FASD group \[F(1, 19) = 9.6, R^2 = 0.34, p < 0.006, \text{slope} = -0.02, 95\% \text{CI} = -0.03 \text{ to } -0.005\] (See Table 14 and Figure 6), but not in the NC group \[F(1, 12) = 1.9, R^2 = 0.14, p < 0.19, \text{slope} = -0.02, 95\% \text{CI} = -0.04 \text{ to } 0.009\]. For the Right ILF, a significant decrease in MD was observed with age in the NC group \[F(1, 12) = 10.5, R^2 = 0.47, p < 0.007, \text{slope} = -0.02, \text{CI} = -0.03 \text{ to } -0.005\] (See Table 14 and Figure 7), but not in the FASD group \[F(1, 19) = 1.5, R^2 = 0.07, p < 0.24, \text{slope} = -0.007, 95\% \text{CI} = -0.008 \text{ to } 0.003\].
CI = -0.02 to 0.005]. All age-related effects remained significant after Bonferroni correction (0.05/5 = 0.01; see Table 14).

**Figure 6.** Linear regressions with age: Left UF MD values with 95% confidence intervals

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Figure 7. Linear regressions with age: Right ILF MD values with 95% confidence intervals
6.2.4 DTI RD Values

The MANCOVA conducted on the RD values revealed a significant covariate effect of Age \([F(4, 27) = 3.2, p < 0.03, r^2 = 0.3]\), but no group differences on RD values \((p < 0.4; \text{Table 13})\). Sex and Group x Sex interaction were also non-significant \((p < 0.7 \text{ and } < 0.9)\). Univariate effects revealed a significant effect of Age on the RD of the Left UF \([F(1, 30) = 9.6, p < 0.004, r^2 = 0.2]\) and Right ILF, at trend level \([F(1, 30) = 3.4, p < 0.08, r^2 = 0.1]\). For the Left UF, RD was observed to decrease significantly with age in the FASD group \([F(1, 19) = 9.5, R^2 = 0.33, p < 0.006, \text{slope} = -0.02, 95\% \text{ CI} = -0.04 \text{ to } -0.008]\), but not in the NC group \([F(1, 12) = 2.6, R^2 = 0.18, p < 0.14, \text{slope} = -0.02, 95\% \text{ CI} = -0.05 \text{ to } 0.008; \text{Table 14, Figure 8}\). There were no significant relationships between age and Right ILF RD values for either the FASD \([F(1, 19) = \ldots\)
2.8, \(R^2 = 0.13, p < 0.11\), slope = -0.008, 95% CI = -0.02 to 0.002] or NC group [\(F(1, 12) = 1.7, \quad R^2 = 0.12, p < 0.2\), slope = -0.01, 95% CI = -0.03 to 0.007]. All age-related effects remained significant after Bonferroni correction (0.05/5 = 0.01; see Table 14).

**Figure 8.** Linear regressions with age: Left UF RD values with 95% confidence intervals

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6.2.5 DTI AD Values

The MANCOVA conducted on the AD values did not reveal any significant effects of Group ($p < 0.6$), Age ($p < 0.4$), Sex ($p < 0.7$) or Group x Sex interaction ($p < 0.6$). No age-related regressions were conducted on AD values for the FASD or the NC groups. See Table 13 for mean AD values.
Table 13. Means (SD) for the FA, MD, RD and AD values for the ILF, UF and cingulum pathways in the NC and FASD groups

<table>
<thead>
<tr>
<th></th>
<th>NC</th>
<th>FASD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ILF</td>
<td>0.35 (0.06)</td>
<td>0.34 (0.07)</td>
<td>ns</td>
</tr>
<tr>
<td>Right ILF</td>
<td>0.34 (0.03)</td>
<td>0.35 (0.04)</td>
<td>ns</td>
</tr>
<tr>
<td>Left UF</td>
<td>0.41 (0.05)</td>
<td>0.44 (0.05)</td>
<td>ns</td>
</tr>
<tr>
<td>Left Cingulum</td>
<td>0.60 (0.03)</td>
<td>0.62 (0.03)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>MD (mm$^3$/s)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Left ILF</td>
<td>0.82 (0.03)</td>
<td>0.81 (0.02)</td>
<td>ns</td>
</tr>
<tr>
<td>Right ILF</td>
<td>0.86 (0.02)</td>
<td>0.84 (0.03)</td>
<td>ns</td>
</tr>
<tr>
<td>Left UF</td>
<td>0.78 (0.05)</td>
<td>0.77 (0.04)</td>
<td>ns</td>
</tr>
<tr>
<td>Left Cingulum</td>
<td>0.78 (0.03)</td>
<td>0.77 (0.04)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>RD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ILF</td>
<td>0.66 (0.04)</td>
<td>0.66 (0.05)</td>
<td>ns</td>
</tr>
<tr>
<td>Right ILF</td>
<td>0.70 (0.03)</td>
<td>0.68 (0.03)</td>
<td>ns</td>
</tr>
<tr>
<td>Left UF</td>
<td>0.60 (0.06)</td>
<td>0.58 (0.06)</td>
<td>ns</td>
</tr>
<tr>
<td>Left Cingulum</td>
<td>0.47 (0.03)</td>
<td>0.46 (0.04)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>AD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ILF</td>
<td>0.11 (0.01)</td>
<td>0.11 (0.01)</td>
<td>ns</td>
</tr>
<tr>
<td>Right ILF</td>
<td>0.12 (0.005)</td>
<td>0.12 (0.01)</td>
<td>ns</td>
</tr>
<tr>
<td>Left UF</td>
<td>0.11 (0.005)</td>
<td>0.12 (0.004)</td>
<td>ns</td>
</tr>
<tr>
<td>Left Cingulum</td>
<td>0.14 (0.004)</td>
<td>0.14 (0.01)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Note: MD and RD values were multiplied by 1000, and AD multiplied by 100.
Table 14. Linear regressions with age as a predictor of UF and ILF values in the NC and FASD groups

<table>
<thead>
<tr>
<th></th>
<th>NC</th>
<th>FASD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>95% CI</td>
</tr>
<tr>
<td>FA: Left UF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>0.2</td>
<td>-0.06 to 0.4</td>
</tr>
<tr>
<td>Age</td>
<td>0.02</td>
<td>-0.003 to 0.05</td>
</tr>
<tr>
<td>MD: Left UF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>0.9</td>
<td>0.7 to 1.2</td>
</tr>
<tr>
<td>Age</td>
<td>-0.02</td>
<td>-0.04 to 0.009</td>
</tr>
<tr>
<td>MD: Right ILF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>1.0</td>
<td>0.9 to 1.1</td>
</tr>
<tr>
<td>Age</td>
<td>-0.02</td>
<td>-0.03 to -0.005</td>
</tr>
<tr>
<td>RD: Left UF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>0.8</td>
<td>0.5 to 1.1</td>
</tr>
<tr>
<td>Age</td>
<td>-0.02</td>
<td>-0.05 to 0.008</td>
</tr>
<tr>
<td>RD: Right ILF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>0.8</td>
<td>0.6 to 1.0</td>
</tr>
<tr>
<td>Age</td>
<td>-0.01</td>
<td>-0.03 to 0.007</td>
</tr>
</tbody>
</table>

Note: **Survived Bonferroni correction (0.05/5 = 0.01), *Survived Bonferroni correction at trend level

6.3 Discussion

The present study examined white matter integrity in specific limbic pathways using DTI in children with FASD and NC. I hypothesized children with FASD would show reduced integrity in the UF, cingulum and ILF relative to NC. Contrary to expectation, I observed groups did not differ on these indices. Rather, age-related changes were observed in several of the indices in both groups, although the patterns for specific tracts differed between the groups. Increases in FA and decreases in MD and RD were observed in the Left UF with age in the FASD group; whereas decreased in MD in the Right ILF with age were observed in NC children. There were no age-related changes in AD values in either of the groups.
The main finding of the current chapter is reflected through the age-related changes in specific limbic white matter tracts, which differed between groups. These findings suggest white matter maturation may differ between the FASD and NC groups, potentially reflecting accelerated maturation in children with FASD compared with NC children, who undergo a prolonged phase of maturation in the preadolescent period. It has been proposed that prolonged brain maturation is beneficial for development since it extends critical periods and allows for the development of cortical networks involved in high level cognitive processing. Accelerated maturation, in comparison, may cause a truncated development (Shaw et al., 2006). For example, using cortical thickness measures in frontal regions, Shaw et al. (2006) found that compared with children who had average intelligence, children with superior intelligence had thinner cortex in early childhood. This thin cortex was followed by marked increases in thickness that peaked at 11 years of age and was followed by rapid cortical thinning. In comparison, children with average intelligence had rapid increases in cortical thickness, with peak levels reached early in development (e.g., approximately 8 years of age). This increase in cortical thickness was then followed by a slower rate of thinning, compared with children of superior intelligence (Shaw et al., 2006). Although not included in the study, children with below average intelligence, commonly observed in FASD, may reach peak cortical thickness earlier, or around the 8 year age. Indeed, research supports this hypothesis, as cortical thickness is increased in children with FASD (between ages of 8 to 22 years) relative to typically developing children, whose period of peak thickness occurs later (Sowell, Mattson et al., 2008; Yang et al., 2011). These findings are relevant for the current study since white matter maturation also appears to follow an accelerated time course in FASD, reaching a potential peak in development earlier than in NC. Similar findings are seen in other clinical populations, such as children with autism (Ben Bashat et al.,
who show evidence of accelerated brain growth within the first 2 to 4 years of life 
(Aylward, Minshew, Field, Sparks & Singh, 2002; Courchesne & Pierce, 2005; Courchesne et 
al., 2001). Since the pathways evaluated in the current study were related to social processing, 
our findings suggest accelerated white matter maturation may be contributing to the deficient 
social processing in children with FASD.

The present age-related changes in white matter also indicate FA values increased, and MD and 
RD values decreased with age in the FASD group. Whereas conditions of abnormal brain 
development or acquired brain damage are typically associated with lower FA and higher MD 
values in affected white matter regions compared with typically developing controls (Neil et al., 
2002), our findings are in the opposite direction, although these results are non-significant. 
Nevertheless, it must be highlighted that decreased FA and increased MD are not always 
observed in clinical populations. For example, Fryer et al. (2009) reported higher FA in children 
with FASD in the cingulum and internal capsule, as well as lower MD in the anterior corona 
radiate and forceps major. Lebel et al. (2008) also reported higher FA values in the bilateral 
globus pallidus and lower MD values in the genu of the corpus callosum in FASD compared 
with NC. Lower MD in frontal and parietal white matter has also been observed in children with 
prenatal methamphetamine exposure (Cloak, Ernst, Fujii, Hedemark & Chang, 2009); and 
increased FA, especially in frontal regions has been reported in young children with autism (Ben 
Bashat et al., 2007). Moreover, higher FA in children with William’s Syndrome has been 
associated with visuospatial deficits (Hoeft et al., 2007). The early negative effect of PAE on 
white matter maturation in the current findings may therefore signify that prenatal alcohol targets 
white matter development by having a negative impact on myelin based proteins, which in turn 
lead to later abnormal myelination and white matter maturation (Chiappelli et al., 1991; Riikonen
et al., 1999; Watari et al., 2006). Since PAE may also have detrimental effects on axon development and synapse formation (Cloak et al., 2009), these teratogenic effects can lead to disorganized and delayed cell migration (Pratt, 1984), abnormal glial cell (Guerri et al., 2001) and pre-synaptic protein development (Barr, Hofmann, Phillips, Weinberg & Honer, 2005), which lead to impaired synapse formation and pruning. In turn, higher cell densities and abnormal myelination may restrict water movement and abnormally enhance diffusion properties (McCaffery & Deutsch, 2005). In addition, inefficient synaptic pruning could lead to maladaptive formation of neural networks since unused connections are not properly eliminated, as observed in typical development (Bourgeois et al., 1994; Hensch, 2004; Huttenlocher & Dabholkar, 1997), resulting in less effective and specialized neuronal systems (Cohen Kadosh & Johnson, 2007; Shaw et al., 2006), as has been proposed in children with FASD (Fryer, Tapert et al., 2007). A final interpretation of the present findings is that white matter pathology may act differently in regions with crossing fibres, which normally have low FA and high MD (Virta, Barnett & Pierpaoli, 1999). This may be a factor in the present study, as the UF and ILF are tracts containing many crossing fibres (Neil et al., 2002). Taken together, the current findings suggest restricted diffusion within white matter is not necessarily an indication of suboptimal cognition in clinical populations. Clearly, future work to determine the specific pathological mechanisms that may be underlying these results is needed.

The current interpretation of neural development following PAE also supports literature on social functioning in FASD. These children are known to have difficulties in social cognition that reflect poor social communication (Coggins et al., 2003), difficulty conveying the mental states of others (Coggins, 1997; Greenbaum et al., 2009; Kodituwakku et al., 1997; Rasmussen et al., 2009), and identifying emotions in faces (Greenbaum et al., 2009), as well as poor use of mental
state words (Timler et al., 2005). Importantly, the early social problems following PAE become exacerbated in adolescence (Kelly, Day & Streissguth, 2000; Rasmussen et al., 2009; Thomas et al., 1998; Whaley et al., 2002), reflecting their arrested social development. These findings, coupled with the present results, suggest that the accelerated maturation that children with FASD experience may mean they plateau in both neural development and related social behaviour. The present findings report differences in white matter maturation with age between NC and FASD groups in tracts critical for social cognitive processing (UF and ILF). Moreover, increased cortical thickness in FASD has been observed in areas involved in social functioning, such as frontal, temporal and parietal regions (Sowell, Mattson et al., 2008; Yang et al., 2011).

Accelerated maturation of limbic regions and white matter connections may therefore lead to the arrested social development observed in FASD, where social skills and social understanding are halted. Indeed, as children with FASD get older they often display increased difficulties in social understanding (Greenbaum et al., 2009; Rasmussen et al., 2009) that can result from increased societal demands, as well as maladaptive development of related neural regions. Longitudinal investigations are required to further understand these age-related changes in social behaviour and related neuroanatomy.

Although the present study represents a critical first step in understanding the neural mechanisms that underlie social cognitive deficits in FASD, it is not without limitations. Our sample size was small and not age-matched, which may have led to the lack of significant group differences due to insufficient power. In addition, some children with FASD have many varying comorbidities, including prenatal exposure to other teratogens and adverse post natal environments, which may result in white matter damage. It is also possible that uncontrolled factors, such as IQ and comorbid conditions may have contributed to the present results. Furthermore, DTI does not
provide an accurate model for all white matter pathways, especially those with high levels of crossing fibres. Although there are techniques to accurately model voxels with crossing fibres, the risk of data loss is increased due to lengthy acquisition times. Finally, it must also be noted that social cognitive functioning is not the result of isolated tracts and regions, but instead arises from complex interactions between many areas and pathways. Furthermore, since FASD is also a complex condition that includes a diverse group of affected children, it may be overly simplistic to expect a one-to-one relationship between a single tract and specific cognitive deficit. Since the present study did not investigate the direct relation between social cognitive processing and white matter integrity in FASD, it may be the case that abnormalities in the regions and pathways that together comprise the social neural network give rise to the social cognitive deficits observed in this population. Further study is therefore warranted.

In conclusion, age-related differences in diffusion were observed between children with FASD and NC children, whereas groups did not differ overall in their properties of white matter. Although these findings suggest abnormalities in white matter maturation, which may be due to deficient synapse formation and pruning following PAE, the exact mechanisms are not known. Nevertheless, present findings showing atypical white matter maturation following PAE in specific limbic pathways represent an important first step in understanding the underlying neural mechanisms of social cognitive deficits in FASD.
Chapter 7
Discussion

7.1 General Discussion

The primary goal of this dissertation was to determine whether deficits in social cognition represent a core disability underlying the social and behavioural problems of children with FASD. To investigate this, I adopted a bottom-up approach that examined multiple levels of social cognition starting with lower level base skills and moving to relatively complex abilities within this domain. I began with face processing, due to the universal preference for orienting and attending to faces that is present from birth, and I followed this with eye processing, which represents a more advanced aspect of face understanding that is critical for social development. At the next level, I investigated higher order social perspective taking, including theory of mind and empathy, and how these abilities related to behaviour. I hypothesized that children with FASD would show impairments at each of these levels in the bottom-up approach, and these impairments would be related to parent-rated behaviour and social problems. Overall, I found partial support for these hypotheses. The lowest level of the present bottom-up approach was represented by neuroanatomy related to social functioning. Using this perspective, I examined a neural basis of the social cognitive difficulties following prenatal exposure to alcohol. I accomplished this using DTI, and compared FASD and NC groups on specific white matter pathways involved in social processing (i.e., UF, cingulum, ILF). My findings provide partial support for the hypothesis that children with FASD and NC would differ on the DTI indices for these pathways, mainly highlighting the age-related differences between groups.
In addition to the findings observed at each level, I also found children with FASD had an overarching deficit that crossed all levels of my bottom-up approach, specifically an inability to process and integrate complex information. This overarching deficit has been proposed previously by an eminent researcher in the FASD field and is not restricted to one domain of functioning (Kodituwakku, 2007). Specifically, I found if task requirements were simple, children with FASD performed comparably to unexposed typically developing children, but as complexity increased, the performance of the FASD group declined. Given that everyday social processing requires online complex understanding, it is not surprising that these children fail to act appropriately in many social situations, appear immature (Nash et al., 2006; Thomas et al., 1998; Whaley et al., 2002), and show arrested social development (Thomas et al., 1998). Unfortunately, this arrested development has serious ramifications for their functioning in later life, as evident by the secondary disabilities that affect most individuals with PAE (Streissguth et al., 2004).

In the following discussion I will describe the findings from each of the studies of my thesis. In addition, although not a formulated objective of the present dissertation, I will discuss how the current findings add to the proposed behavioural phenotype of FASD. Furthermore, since much literature on FASD has also investigated similarities between these children and children with autism, I will provide a discussion outlining the overlapping characteristics between FASD and autism profiles. Finally, I will highlight the clinical relevance of the current findings and will discuss study limitations and provide directions for future research.
7.2 Summary of Main Results

7.2.1 Do children with FASD show deficits in face processing?

Experimental and standardized measures were used currently to examine specific aspects of face processing in FASD, namely face identity, expression, eye gaze, and mouth shape. Significant group differences were observed on RT measures from some of the face processing subtests. Notably, the FASD group responded more slowly than NC when identifying faces that were partially occluded or when matching a specific face feature, specifically the shape of the mouth. There were no group differences on accuracy for the Face Processing and Affect Recognition subtests after Bonferroni correction. Importantly, slower RTs on the tasks where identity was occluded and matching mouth shapes was required were related to increased parent-rated autistic-like traits in the FASD group. There were no age-related changes in face processing in the FASD or NC groups.

7.2.2 Do children with FASD adequately orient attention in response to social eye gaze cues and are they able to use information of eye expression to understand other people’s mental states?

To investigate attentional orienting following central eye gaze and arrow cues, I used an adaptation of a standard cuing paradigm. The FASD group was observed to respond more slowly than the NC group to peripheral targets following both eye gaze and arrow cues. The FASD group also showed a larger overall validity effect, which reflected their larger differences between invalid and valid trials, than NC. There were no differences in accuracy (cuing or sorting) between groups. However, children in the FASD group did show poorer performance on the Reading the Mind in the Eyes task compared to NC. Since the group effects were not due to
differences in language or attention, this result suggests children with FASD have poorly
developed theory of mind skills relative to NC.

7.2.3 Do children with FASD show specific weaknesses in social perspective taking and do these change with age and differ by sex?

To assess two fundamental aspects of social cognition, namely theory of mind and empathy, I used a variety of measures to compare FASD and NC groups, and I also related these findings to parent ratings of behaviour and social skills. Children with FASD were observed to perform below NC on the NEPSY-II Theory of Mind Verbal and Total subtests, as well as the False Belief, Strategic Control of Emotions and Personalized Emotions, but not the Personalized Thoughts subtest from the Test of Social Cognition. Children in the FASD group also rated themselves as being less empathic than children in the NC group, as did their parents. In addition, whereas parents of the NC group rated females as more empathic than males on average, parents of the FASD group rated males as more empathic than females. Lower parent-rated attention problems were also related to increased theory of mind in the FASD group. In the NC group, lower caregiver-rated social problems were related to higher levels of self-reported empathy. Age-related differences were also investigated, with the FASD group showing poorer performance with age on the False Beliefs subtest at trend level.

7.2.4 Do children with FASD show impairments in a neural network involved in social functioning?

In the final study of this dissertation, I used DTI to examine white matter in three specific limbic pathways, the UF, cingulum and ILF. No overall group differences were observed on any of the DTI indices between FASD and NC children. However, groups were observed to show different age-related changes in two of these pathways. The FASD group showed increased FA and
decreased MD and RD values with age in the left UF, whereas the NC group showed only decreased MD values with age in the right ILF.

7.3 Bottom-Up Approach of Social Cognition: Effective Description of Deficits in FASD

Results from the current dissertation support a bottom-up approach for characterizing the social cognitive deficits arising from PAE. The findings from Chapter 3 indicated children with FASD had deficient processing of face stimuli, reflecting their significantly slower responses than NC in matching mouth shapes and occluded face identity. In typical development, face recognition relies on the processing of both individual face features (featural processing) and relations among these features (configural processing) (Bruce & Young, 1986; Mondloch, 2003). These abilities allow the recognition of a person’s face when features are presented in isolation and when certain features are concealed. Because processing the mouth region and masked face identity both require detailed understanding of independent face aspects, current results suggest children with FASD have deficient featural processing but sufficient global processing (i.e., full identity, expression). These findings support results from Mattson and colleagues (1996) who found that when presented with stimuli consisting of large global letters constructed from smaller local letters, children with PAE were impaired at recalling and re-constructing the local features, with no impairments for global features. Instead of having a general visuospatial impairment, these researchers proposed children with FASD had select deficits in visual processing of local, detail features (Mattson, Gramling et al., 1996), which relates to the current findings. In the real world, adequate face understanding relies on accurate and speeded processing of features and their global configuration. For children with FASD, they may rely more heavily on global face processing, showing severe difficulty with face recognition when certain aspects of a face are masked. When features are occluded or focus has to be directed to one specific face feature, their
processing declines due to their need to process specific local features. Relevantly, Navon (1977) reports processing local features is more difficult than processing global stimuli. Overall, results of impaired feature processing, coupled with the social complexity of face stimuli, may result in the currently observed difficulties following PAE. These results signify that one of the first levels of impairment in social cognition for FASD may be deficient face processing.

Chapter 4 investigated the next level of social cognition, namely attentional cuing and eye processing (Figure 1). Although children with FASD displayed reflexive orienting following both arrow and eye gaze cues, they were significantly slower to process these cues and shift attention accordingly, compared with NC. These findings signify greater deficits in orienting attention in FASD and may reflect difficulty disengaging and shifting their attention towards the cued locations (Coles, Platzman et al., 1997; Green et al., 2009). Relevantly, these features of attention play a key role in both cognitive and social processing. For example, joint and shared attention require understanding another’s direction of focus, as well as disengaging and reorienting one’s attention towards a common goal (Charman et al., 2000). Thus, deficits in shared attention and disengaging may have a negative impact on social processing and contribute to the impairments observed currently in FASD. Similarly, impairments in joint attention and orienting may have contributed to the poor performance of the FASD group on the Reading the Mind in the Eyes task. Understanding and integrating joint attention based on limited eye information, as well as mental state processing, is required for adequate performance on this task and for social interactions more generally. Overall, children with FASD showed impaired processing of both social and non-social cues, as well as weaker theory of mind, compared with NC. These attention deficits therefore represent another level of impairment observed following PAE.
Social impairments were also found at the top level of the present social cognitive approach, namely social perspective taking (Chapter 5). I observed that as social cognitive demands increased, children with FASD displayed significantly greater difficulty in tasks such as understanding false beliefs, emotional control and empathy. Interestingly, the observation of more impaired perspective taking with age in children with FASD corroborates with other evidence showing social development plateaus in this population (Rasmussen et al., 2009; Thomas et al., 1998; Whaley et al., 2002). Their atypical social development may be due to the increased social demands placed on children as they get older. For example, peer relationships become more complex with age, as the demands of social understanding, emotion processing and communication increase. This atypical development may also be occurring at a neuronal developmental level as observed in the DTI study in Chapter 6. Children with FASD showed increased FA (and decreased MD and RD) in the left UF, which signifies increased restricted diffusion, as well as accelerated abnormal maturation in white matter (Assaf & Cohen, 2000; Ben Bashat et al., 2007). This accelerated maturation may result in atypical social development during critical periods and thus contribute to maladaptive social behaviours following PAE, which have also been observed in other populations such as autism (Pugliese et al., 2009). In general, the abnormalities in limbic white matter pathways may represent the fundamental mechanism contributing to social cognitive deficits in FASD.

A final important feature of the present dissertation was the finding that deficient social cognitive processes correlated with parent ratings of attention and social problems, as well as autistic-like traits in the children with FASD. These findings provide strong evidence that impairments in lower levels of the present approach contributed to the social and cognitive difficulties observed behaviourally in FASD. By adopting this bottom-up perspective, I was able to provide insight
into the social difficulties that may result from PAE and potentially contribute to the understanding of social deficits observed in this population.

In the study by Greenbaum et al. (2009), the proposed core deficit in FASD was their difficulty in understanding other people’s mental states, as well as selecting emotions that accompany these states. Using a bottom-up approach, I not only found support for this view, but also advanced this claim by showing that children with FASD have difficulty understanding mental states and emotions of others and also display impaired face processing, attentional orienting and empathy. Furthermore, these difficulties were seen to adversely affect their social skills and behaviour. The present studies also provide evidence of atypical white matter maturation, which may be a factor in their social impairments. The present bottom-up approach may accurately portray the defective components that underlie social cognitive impairments in FASD. These impairments likely have wide reaching effects on behaviour, which in turn contribute to the significant and secondary difficulties of FASD in adolescence and adulthood.

7.4 Social-Behaviour Phenotype of FASD

Since the FAS condition was first described by Jones and Smith (1973), researchers have been involved in characterizing the unique behavioural phenotype of FASD. Despite making considerable progress in delineating the cognitive and behavioural characteristics, the question still remains whether this population has a unique phenotype. Recently, Kodituwakku (2007) proposed that the cognitive-behavioural phenotype of FASD may be better characterized by a generalized deficit in processing complex information. Included in this proposed phenotype are difficulties including planning and inhibitory control (Kodituwakku et al., 2001), spatial, verbal and visual memory (Hamilton, Kodituwakku, Sutherland & Savage, 2003; Mattson & Roebuck,
vigilance and attention shifting (Coles, Platzman et al., 1997; Streissguth et al., 1986), higher level numerical processing (Burden, Jacobson & Jacobson, 2005), and understanding language pragmatics and semantics (Coggins et al., 2007; McGee, Bjorkquist et al., 2009). Moreover, a study of children with FAS reported they had longer and more variable response times than typically developing children when programming complex motor movements, such as lifting their hand and touching three targets in specific sequence (Simmons et al., 2010). However, performance did not differ from NC on a simple RT measure requiring minimal motor programming (Simmons et al., 2010, 2002). Similarly, children with FASD perform adequately on tasks involving face recognition (Uecker & Nadel, 1996; Willford, Richardson, Leech & Day, 2004), number naming (Kopera-Frye, Dehaene & Streissguth, 1996), and cued-navigational learning (Hamilton et al., 2003), which are relatively simple in their demands. This explanation of impaired processing and integration of complex information, with relative sparing on simple processing fits well with the results observed in the current dissertation. Although not part of the original conceptualization of this thesis, Kodituwakku’s formulation is important for explaining the present results, as well as informing research and clinical practice in the area of FASD.

Thus, in addition to highlighting specific deficits in social cognition, the results from the current studies support the idea that children with FASD have impaired processing of complex information (Kodituwakku, 2007) and in this case, impaired processing of complex social cognitive information. For example, on the tasks of face processing in Chapter 3, the FASD group differed from NC only on conditions involving complex face matching such as matching identity when the face was partially occluded and matching mouth shapes. These subtests required complex processing of independent face features, whereas groups did not differ on other face tasks that could be solved using global processing such as matching expression and
complete face identity. Since responding to local features is thought to be more difficult than global processing, as reflected by the slower response times in the former condition (Navon, 1977), it may be that the complexity of the face stimuli coupled with added featural processing tip the balance for children with FASD leading to their significantly increased RTs. Taken together, these findings suggest these children have greater difficulty processing the individual component features of a face, but not the gestalt.

Results from the attentional orienting study in Chapter 4 also support the notion that a social behavioural phenotype arises from PAE. The measures used in chapter 4 showed that children with FASD did not have difficulty on simple RT and sorting tasks, but as the tasks demands increased from complex understanding and decoding of attention cues (gaze and arrows) to higher order theory of mind, those with FASD showed impaired performance relative to their typically developing peers. In fact, when total mean RTs were compared between the RT Control, Gaze and Arrow cuing tasks (total valid and total invalid), the FASD group had the shortest mean RTs on the RT Control task, in contrast to the NC group who showed the shortest mean RT on total valid trials following an eye gaze cue. The extra information provided by the central cues required additional information processing, resulting in significantly slower RTs in the FASD group. In comparison, the NC group benefited from valid social cues, a finding which has been reported previously in typically developing children (Farroni et al., 2002; Hood et al., 1998; Ristic et al., 2002). The most complex task in this chapter was the Reading the Mind in the Eyes task, which required children to integrate limited eye information with complex mental state descriptions. The FASD group performed significantly below NC on this task, despite the absence of a time restriction. Thus, it seems that as processing increases from simple to complex, the FASD group became increasingly impaired in their social processing, compared with NC.
The social perspective taking study in Chapter 5 also provides evidence that impaired processing of social information in FASD is most pronounced when complexity is increased. No differences were observed between groups when children were required to understand the basic information processing abilities of an adult compared with an infant (Personalized Thoughts). This finding indicates children with FASD do not have deficits in understanding the processing abilities of others, but as the social cognitive demands increased, they become significantly more impaired as reflected by their difficulties understanding the mental states, false beliefs, and accompanying emotions of others. Another important finding was the observation that the older children in the FASD group performed worse than the younger children with FASD on a task of theory of mind. This finding suggests that as social interactions become more complex with age, reflecting increased societal demands and expectations for peer relationships, as well as the need for greater emotional and mental understanding, this necessitates a deeper understanding and need for more integrated social information. Since these abilities are underdeveloped in children with FASD, they are likely not to interact appropriately in social contexts, and instead will display the maladaptive behaviours that characterize this population (Coggins et al., 2007; McGee et al., 2008; Schonfeld, 2002).

Finally, the DTI results from Chapter 6 provide further support for the notion that FASD have a characteristics social behavioural phenotype. The age-related changes observed in the FASD group suggested accelerated white matter maturation in the UF. Importantly, brain regions connected by the UF are association areas, which are extensively interconnected to other regions and involved in integrative functions (Goldman-Rakic, 1988; Mesulam, 1990). For example, along with the social role of temporal and frontal cortices, these regions are also involved in the integration of memory and object recognition (Mesulam, 1999). Through interconnections with
the limbic system, association networks combine cognitive functions with emotion, drive and motivation, highlighting the integrative role of social and cognitive functioning (Fuster, 1989). Importantly, structural and functional abnormalities have been reported in temporal and frontal regions in FASD (Fryer, Tapert et al., 2007; Sowell et al., 2001; Sowell et al., 2007, 2002), suggesting deficits in these association areas following PAE. Furthermore, evidence from studies of cortical thickness development following PAE showed early atypical development, which was maintained over adolescence and early adulthood (Sowell, Mattson et al., 2008; Yang et al., 2011). The early social problems from PAE that become exacerbated in adolescence (Kelly et al., 2000; Rasmussen et al., 2009; Thomas et al., 1998; Whaley et al., 2002) may be the result of accelerated maturation of association areas, and related white matter pathways, leading to inadequate processing of social information and atypical social development.

Overall, not only do the present findings support a bottom-up approach of social cognitive impairment following PAE, these hierarchical impairments also contribute to the social behavioural phenotype of FASD. The difficulty children with FASD have in integrating and understanding complex information has a major impact on their ability to function in social contexts.

7.5 Profiling the Similarities between FASD and Autism

Autism has of late received considerable attention as a possible comorbidity in FASD and several studies have attempted to directly examine the overlap between these two disorders. Regarding prevalence, the rates of co-association vary considerably within the literature ranging from two separate disorders (Fombonne, 2002) with no increased risk of autism following PAE
(Eliaisen et al., 2010), to significant overlap between autistic and FASD profiles. Nanson (1992) reported an estimated incidence of 1 in 54 or approximately 2%, and found the similarities between the two populations reflected their common difficulties in relating to other people, resistance to change in daily routines and abnormal sensory responses (e.g., hypersensitivity to noise) (Harris et al., 1995; Nanson, 1992). Landgren et al. (2010) reported an incidence rate of 9%, while Bishop et al. (2007) claimed that approximately 35% of children in their FASD sample met Autism Diagnostic Observation Schedule criteria for autism. According to Bishop et al. (2007), the only distinguishing factors between groups were the abnormal desire and reduced frequency for social interactions in the autistic group. More recently, Mukherjee et al. (2011) reported that 72% of their FASD sample met diagnostic criteria for autism, with both FASD and autistic groups having dysfunctional social and linguistic skills. However, whereas children with PAE were more likely to show the passive or active-but-odd profile of autism, the autistic group was more likely to show the withdrawn type in their approach to social interactions. High levels of prenatal alcohol exposure may therefore be an important association with the clinical consequences of autism.

Although a comparison of FASD and autism was not a main goal of the current dissertation, I did observe a number of behavioural features in the FASD group that were characteristics of autism. In the face processing study, I observed a significant relation between slow RTs in matching mouth shapes and occluded face identity, as well as elevated parent-ratings of autistic-like traits in FASD. These findings are consistent with previous research showing that children with autism typically exhibit impaired face processing and spend less time looking at a face or show more disorganized face exploration than NC (Balconi, 2008; Gepner et al., 1996; Pelphrey et al., 2002). These impairments are believed to underlie the compromised social skills observed in
autism (Baron-Cohen, 1995; Baron-Cohen et al., 2001), similar to that observed in FASD. However, one major difference between autism and FASD profiles revealed through the present findings is their processing preference. Whereas children with FASD were shown to have difficulty processing individual components of face features, with adequate global face processing, children with autism tend to have a processing bias for feature-based and detailed processing (e.g., parts of objects), and a relative inability to extract information about the whole object (Frith, 1989; Happé & Frith, 2006). The latter finding is attributed to individuals with autism having a weak central coherence (Frith, 1989; Frith & Happé, 1994), in contrast, children with FASD seem to have strong coherence at the expense of attention to details.

A study of attentional orienting in autism by Senju et al. (2004) reported that these children shifted their attention equally in response to gaze and arrow direction and failed to show preferential sensitivity to the social gaze cue. The slower overall RT and greater validity effects in autism than typically developing children has been described as reflecting difficulty in disengaging attention (Casey et al., 1993) or trouble with strategic attention orienting (Minshew et al., 1997), which was observed currently in FASD. Additionally, children with autism show impaired performance on the Reading the Mind in the Eyes task (Baron-Cohen et al., 2001), which was thought to reflect a basic difficulty processing and integrating eye expression and mental state information in this population. These results are similar to those in FASD, again supporting the potential overlap between these two clinical groups.

Likewise in the domain of theory of mind and empathy, children with FASD were currently found to show impaired performance, a finding also observed in autism. Children with autism show deficits in face processing, joint attention, and empathy and these findings have been
linked to their later problems in social understanding (Baron-Cohen, 1995; Leslie, 1994; Weeks & Hobson, 1987). Similarly, infants with autism look less at other’s facial expressions and fail to express concern in response to other’s distress (Charman et al., 1997), while older children perform poorly on false belief tasks (Roth & Leslie, 1991), suggesting difficulty with perspective taking (Baron-Cohen, 1995). Since similar findings were ascertained in the current thesis, this is further support that FASD and autistic profiles may contain some overlap.

Finally, reported limbic white matter abnormalities in autism are comparable to the present FASD findings. For example, Pugliese et al. (2009) did not observed mean differences in FA and MD corrected values between individuals with autism and NC in the UF, cingulum and ILF, as observed presently. Furthermore, increase FA values in frontal white matter have been reported in autistic populations (Ben Bashat et al., 2007), comparable to the current findings. Even more compelling, age-related decreases in MD of the left UF have been observed in individuals with Aspergers, to a greater extent than typically developing controls (Pugliese et al., 2009). The current DTI study reported similar age-related decreases in MD of the left UF, in addition to age-related changes in RD and FA values. The age-related changes observed in the current thesis were proposed to represent possible white matter acceleration in FASD, which may underlie their deficient social cognitive processing. This explanation has also been applied to the age-related changes in autism. Evidence of accelerated brain growth in autism has been reported within the first 2 to 4 years of life (Aylward et al., 2002; Courchesne & Pierce, 2005; Courchesne et al., 2001), as well as accelerated maturation of white matter in specific frontal regions (Ben Bashat et al., 2007), which may be a factor in their deficient social cognition.
Taken together, results from the current studies suggest that FASD and autistic groups may share similar clinical profiles, particularly in the areas of face processing, attentional orienting, social perspective taking and underlying limbic neuroanatomy. It is important to understand the overlap and distinctions between FASD and other clinical populations, as critical information is gained to ensure proper differential diagnoses are made and appropriate treatments are provided.

7.6 Clinical Relevance and Implications

It is well established that deficits in social cognition and complex social processing have real life implications for children with FASD. For example, being able to discriminate whether a person walking towards you is your friend or someone you do not get along with, and whether that person looks happy or angry will impact on how you interact with them. However, in the case of FASD, if another child on a busy playground displaying a happy facial expression approaches a child with FASD, he or she may fail to adequately process the approaching child’s expression in a timely manner. As a result, the child with FASD may fail to properly interpret the other child’s social cues, such as eye gaze and other face features, leading to impairments in joint and shared attention. Furthermore, as the child with FASD may unsuccessfully integrate social information and mislabel the intentions and desires of the approaching child, he or she may react inappropriately and even aggressively and, as a result, behave negatively in this social context. Maladaptive decision making and ineffective problem solving may also be observed, as is commonly reported in FASD (McGee, Bjorkquist et al., 2009; McGee et al., 2008).

The real life implications of the present findings thus have potential to inform clinical practice and treatment approaches for FASD. Using the findings from the present bottom-up perspective, treatment approaches could be structured around specific aspects of social cognition. For
example, intervention programs could focus on face processing; teaching children what to look for in a face and how to extract relevant information. Specific face recognition treatments have been successfully applied to other clinical populations. For example, Tanaka et al. (2010) implemented a computer based intervention for children with autism targeting face processing, including both identity and expression recognition using different features and viewpoints, and found reliable improvements in analytic face recognition skills and the use of global face strategies. These results indicate an extremely focused intervention program can produce measurable improvements in face recognition skills. Similar treatment approaches targeting specific social cognitive domains may also be applied to children with FASD.

Other training programs that focus on social skills and social behaviour have been effective for the FASD population. For example, O'Connor and colleagues used the Child Friendship Training program to teach children how to form social networks and interact better with peers through explicit instruction on information exchange, entering play groups and negotiating conflict through modeling and feedback. This training was found to increase their social skills knowledge and led to higher social skills ratings by parents in the treatment group versus the control group. The FASD treatment group also made fewer hostile attributions when approaching and entering peer groups than the delayed-treatment FASD group (Keil et al., 2010). Furthermore, these improvements continued and were observed at the 3 month post treatment assessment. Although FASD is a heterogeneous population and social skills vary from child to child, there is strong evidence that social skills training positively influences social knowledge and behaviour (O’Leary, 2011).
Therapies that target self-regulation are also beneficial for FASD and may provide spillover effects to improve social cognition. The Alert® Program for Self-Regulation (Williams & Shellenberger, 1996) uses the metaphor of a car engine to compare children’s brains to engines that run at high, low or just right levels. This program teaches children to recognize their own engine speeds and how to change them accordingly with various sensorimotor devices to regulate their arousal levels. A study by Wells and colleagues showed significant improvement in executive functioning skills following the Alert Program in children with FASD (Wells, Chasnoff, Schmidt, Telford, Schwartz, 2012), while more recently Nash (2011) reported improvement as measured by tests of emotion recognition and understanding, as well as emotion control. Thus, teaching children with FASD strategies to improve self-regulation has significant influence on social cognition.

A final future treatment recommendation for children with FASD concerns providing them with additional processing time to complete tasks. When presented with social stimuli, such as faces, children with FASD require an environment free from distractions, as well as a significant amount of extra time to adequately process the stimuli. In their intervention study, Timler et al. (2005) examined the impact of a social communication program that encouraged the use of mental state words. In this case study, one child with FASD was taught to stop and listen, review what she learned, put this information into action and evaluate consequences. By encouraging the child to pay attention to her surroundings and process information more slowly, Timler et al. were able to improve mental state understanding in the FASD child and increase her use of mental state verbs. Children with FASD may be able to show improved understanding of social information when given sufficient processing time.
Overall, treatment approaches that focus on specific aspects of social cognition, as well as providing additional processing time for children with FASD may have positive cascading effects on other aspects of social functioning. As modeled by the present bottom-up approach, if children with FASD show improved face processing and attentional orienting, accompanying decreases in social perspective taking may be observed. Thus, the present findings have potential to inform clinical practice in FASD.

7.7 Limitations

Although the present dissertation involved a novel and unique approach for examining social cognition in children with FASD, several limitations need to be noted. As is the case for many clinical studies that investigate PAE, dose and timing of alcohol exposure, as well as information on polysubstance exposure were not controlled for presently. Also, the impact of specific confounders, such as maternal nutrition, parental psychopathology, prenatal care and quality of home environment, were not controlled for. These confounders may influence social development and functioning (Henry et al., 2007; Henry et al., 2009; Paley, O’Connor, Frankel & Marquardt, 2006) and would benefit from future research.

The sample size for this thesis was small for behavioural and imaging studies, and covered a wide age range. However, the concurrent running of clinical, imaging and an intervention study within this same FASD group made it difficult to recruit a larger sample. Because children in the FASD group were also involved in a subsequent intervention study, there were greater restrictions and exclusion criteria for recruitment, and families were required to dedicate a large amount of time to the study. Children in the NC group were also difficult to obtain from hospital postings and siblings of the FASD group, as I wanted to ensure IQ levels were as close as
possible with FASD. In addition, the imbalance of sample size between my groups may have impacted the statistical power.

Although strong relations between language, executive functions and theory of mind have previously been found (Coggins et al., 2007; Marton et al., 2009), I did not investigate these factors in the present studies. Because the vocabulary subtest from the WASI is a measure of word knowledge and verbal concept formation, it is not an adequate language control for social processing and understanding. However, it is important to note that the present findings could not be solely the result of language difficulties in the FASD group. Children with FASD did not display impairments on all orally presented subtests (i.e., Personalized Thoughts), displayed similar accuracy performance as NC on tasks with orally presented instructions (e.g., cuing and face processing tasks) and continued to show impairments even when language difficulties were accounted for (i.e., Reading the Mind in the Eyes and Language Control tasks). In addition, Thomas et al. (1998) observed social skill impairments in children with FASD even when compared to verbally IQ matched controls that were not exposed to alcohol prenatally, suggesting that social cognitive impairments extend beyond cognitive deficits in FASD. It should also be noted that the lack of significant differences on accuracy performance for the Face Processing tasks (Chapter 3) may have been the result of low task demands. By contrast, more complex tasks may reveal most subtle face processing difficulties in FASD.

The present studies also did not include a clinical control group, such as autism, which would have been beyond the scope of this dissertation. Performance was only compared between children with FASD and typically developing children.
Lastly, the DTI study did not examine the relation between specific limbic pathways and social functioning. It was noted in Chapter 6 that social cognitive functioning is not the result of isolated tracts and regions, instead arising from complex interactions among many brain areas and pathways. Because it may be overly simplistic to expect a one-to-one relation between a single tract and specific cognitive deficit, especially in a heterogeneous population such as FASD, the present study did not pursue this. There were additional limitations within the DTI chapter, specifically relating to acquisition and data analysis, which relate to the influence of crossing fibres. Please refer to Chapter 6 for a further discussion of these technical limitations.

7.8 Future Directions

This dissertation established that children with FASD have significant deficiencies in social cognition, which were associated with some measures of atypical neuroanatomy and were correlated with parent-rated social and behavioural problems. It was demonstrated that there is a relation among social and behavioural difficulties and core deficits in social cognition of FASD. Furthermore, this dissertation showed that a bottom-up perspective characterized the social cognitive difficulties in this population. However, the present perspective was preliminary and limited to four levels. Undoubtedly, a broader model should be conceptualized that follows the current thinking in social cognition and related social neuroscience. Future research should determine whether additional components need to be added to the present bottom-up approach, as a more comprehensive social cognitive model may be essential to the development of focused treatment plans for FASD. In addition, future research would benefit from examining the relations between each level of the social cognitive model, not just relations within each level. An increased sample size and use of principal component analysis would assist this investigation.
Secondly, future research would also benefit from further examining the development of joint and shared attention in young children with FASD. A more thorough understanding of the teratogenic effects of alcohol on joint and shared attention will allow us to gain further knowledge of the development of theory of mind and related social functioning. Thirdly, due to the strong link between language and theory of mind, more detailed studies are needed to establish the directional relationship between these variables and their impact on social development. Future studies may benefit from using alternative clinical measures of social cognition that limit the reliance on language. This is especially important for tasks of theory of mind. A fourth future direction needs to compare aspects of social cognitive functioning in FASD directly with children who have autism. Because research on social functioning in autism has received a lot of attention, the field of FASD could capitalize on this knowledge and gain a more comprehensive understanding of the similarities and differences between these profiles. If we understand the overlapping characteristics of FASD and autism in areas such as face processing, attentional orienting, and social perspective taking, we will be able to provide more informed differential diagnoses and focused treatments. A fifth future direction may also include investigating social cognition in siblings from the same family environment, but different exposures (e.g., PAE vs. no PAE) to determine the influence of post natal factors on social processing.

Current findings of atypical age-related changes in social perspective taking and limbic pathway maturation in FASD also need further investigation, as this work may shed light on the mechanisms underlying these maturational abnormalities, such as atypical neuronal development, synaptic pruning and myelination. Thus, a sixth direction will be to study how abnormal plasticity affects social development in FASD. Animal work may further this
understanding. It is possible that one day targeted procedures to facilitate neuroplasticity in the brain structures responsible for social processing may help ameliorate the later social difficulties of many childhood disorders.

Another natural extension of the current study is to assess the complete structure, function and connectivity of social neural networks following PAE. Comprehensive analyses of neuroanatomy and development will provide critical insight on how neuronal abnormalities following teratogenic exposure give rise to social cognitive deficits. By examining association areas, mirror neurons and more extensive limbic connections, we will be able to gain a further understanding of the influence of PAE. Finally, because the present dissertation found social processing difficulties in FASD (i.e., slower RTs), examination of the temporal mechanisms using electroencephalography or magnetoencephalography are warranted. If we gain a better understanding of the temporal processing mechanisms, as well as structure and function within the social neural networks, we will be able to more fully comprehend the effects of PAE and how this impacts social cognition. It is possible that this work will identify potential neural markers to be used in earlier diagnosis and specific intervention following PAE. This is critical since according to Streissguth et al. (2004), these two factors, namely early diagnosis and treatment, are essential for preventing the later secondary deficits that plague individuals with FASD.

7.9 Conclusions

In summary, the present thesis used a bottom-up approach to assess social cognitive deficits in FASD in order to identify the most vulnerable aspects of social processing difficulties in these children. Specifically, their deficits reflected complex aspects of face processing, attentional orienting, and social perspective taking. Moreover, the developmental abnormality in white matter that was also observed may contribute to the social cognitive impairments that were
identified. Importantly, difficulties were not only revealed directly through aspects of children’s performance, they were also seen to influence daily behaviour leading to a number of significant behavioural problems, as rated by parents. In conclusion, impaired social cognition is a primary core deficit that has wide reaching effects on the behaviour of children with FASD. A bottom-up approach, as adopted in the present thesis, has the potential to inform clinical practice, leading to effective diagnoses and treatment for this highly challenging population.
References


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