Infant Attention, Motor Activity and Cardiac Activity and the Effects of Prenatal Smoke Exposure

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Summary of Thesis

To advance our understanding of the association between maternal smoking during pregnancy and the development of ADHD in offspring, studies using a prospective and longitudinal design, beginning with the study of temperament during infancy are required. The aim of this thesis was to investigate domains of infant temperament that could be considered early precursors and correlates of ADHD and to examine the effect of prenatal smoke exposure on these domains. Attention together with motor activity and heart rate (HR), measured during cognitive and emotional challenge, were studied in a representative, community sample of 130 infants at 6 and 12 months. At 6 months infants exposed to prenatal smoke showed more sustained attention, increased motor activity and increased HR compared with non-exposed infants. However, at 12 months there was no evidence of an effect of prenatal smoke exposure on attention or motor activity but there was evidence of an effect on HR. Given the importance of understanding temperament in infants, we examined 50 infants in an intensive laboratory assessment, using measures of vagal tone (VT) as well as HR, to enhance our understanding of the relationship between temperament and physiology. Results supported the use of HR as an index of temperament and although VT results were ambiguous, the indication was that measures of VT reactivity may be useful in future research. Combining the novel and rigorous designs presented in this thesis to study the effects of prenatal smoke exposure on offspring development, beginning during the neonatal period and with several assessments during the first year of life, utilizing physiological measures in combination with parent reports and behavioural observations, both at home and in more intensive laboratory settings, will be an important task for the future to enhance our knowledge of potential pathways from prenatal smoke exposure to the development of behaviour disorders, such as ADHD.

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CHAPTER 1

GENERAL INTRODUCTION

1.1. Introduction

Externalizing behaviour problems are one of the most common reasons for children to come to the attention of clinicians and externalizing behaviour problems have been found to be the most common form of childhood psychiatric problems in the community (Frick, 1998). Externalizing behaviour problems are associated with a variety of adverse outcomes such as poor academic achievement, social problems, substance abuse and persistent aggressive behaviour (DeWolfe, Byrne & Bawden, 2000; DuPaul, McGoey, Eckert & VanBrakle, 2001; Egger, Kondo and Angold, 2006a; Fontaine et al., 2008; Hill, 2002; Hinshaw, 1992; McGee, Partridge, Williams, & Silva, 1991; McGee, Prior, Williams, Smart & Sanson, 2002; Merrel & Wolfe, 1998). The term externalizing behaviour problems is used to refer to Oppositional Defiant Disorder (ODD), Conduct Disorder (CD) and Attention Deficit Hyperactivity Disorder (ADHD) (Campbell, Shaw & Gilliom, 2000). There are two main classification systems used for the diagnosis of psychiatric disorders; the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV, American Psychiatric Association (APA), 1994) and the International Classification of Diseases, tenth edition (ICD-10, World Health Organisation, 1993). Both DSM-IV and ICD-10 describe CD and ODD but in ICD-10 the counterpart of ADHD, as described in DSM-IV, is hyperkinetic disorder (Kutcher et al., 2004). The criteria for hyperkinetic disorder as described in ICD-10 are stricter than the criteria described in DSM-IV and ICD-10 defines only one subtype, which refers to whether CD

is also present, in contrast with DSM-IV which defines several subtypes of ADHD (see section 1.2). However, in general terms hyperkinetic disorder and ADHD can be considered similar disorders and given that the DSM system has received more attention in research (Hill, 2002; Kutcher et al., 2004), in this thesis we will focus on ADHD, CD and ODD as described in DSM-IV (APA, 1994).

Externalizing behaviour problems are highly comorbid; for example between 30% and 50% of children with ADHD also meet criteria for CD (Biederman, Newcorn & Sprich, 1991), whilst in clinical samples up to 70% of children with CD are also diagnosed with ADHD (Klein, Abikoff, Klass, Ganeles, Seese & Pollack, 1997). A common pathway from ODD to CD has been proposed (Moffit et al., 2008) and 60% of children with CD also have ODD (Cohen et al., 1993). In the past the high comorbidity of externalizing behaviours led some researchers to suggest that they represented alternative manifestations of one underlying syndrome but today it is generally agreed that the disorders are, at least to an extent, distinct (Beauchaine, Katkin, Strassberg & Snarr, 2001; Kuhne, Schachar & Tannock, 1997; Sonuga-Barke, Thompson, Stevenson & Viney, 1997). For example, Gadow and Nolan (2002) carried out a study looking at the differences between preschool children with ODD, ADHD and ODD+ADHD symptoms and found that ratings made by teachers differentiated those children who exhibited symptoms of ODD+ADHD from those who only had symptoms of ADHD. The authors concluded that ODD and ADHD represent distinct clinical entities in preschool children.

However, there is evidence that comorbidity can increase the risk of adverse outcomes for an individual (Kuhne et al., 1997); for example early-onset antisocial behaviour that is accompanied by ADHD has been shown to be a particularly severe

combination and is associated with poor outcomes (Thapar et al., 2005a) and children with ADHD who also have co-occurring aggression or ODD have been shown to have more serious problems when followed up in adolescence (Barkley, Fischer, Edelbrock & Smallish, 1990) and adulthood (Weiss & Hechtman, 1993). In line with these findings, Sonuga-Barke et al. (1997) found that children with both hyperactivity and conduct symptoms, as rated by parents, were the most disadvantaged group. Shaw, Owens, Giovannelli and Winslow (2001) found that children with comorbid ADHD-ODD/CD were more temperamentally difficult, had more attention problems, were more oppositional and aggressive and had more chronic family and neighbourhood risk factors than those with only a diagnosis of ADHD or controls. Thapar, Harrington and McGuffin (2001) found that both genetic and non-shared environmental factors explained the overlap between ADHD and CD and although there was evidence that the disorders were at least in part distinct as additional environmental influences were found to contribute to CD, the authors concluded that ADHD+CD was a genetically and clinically more severe variant of ADHD.

Several studies suggest ADHD is a developmental precursor of persistent and severe CD (Loeber, 1988; Mannuzza, Klein, Abikoff & Moulton, 2004; Moffitt, 1993; Moffitt, Caspi, Dickson, Silva & Stanton, 1996). Indeed Moffitt et al. (2008) suggest that ADHD may be a key disorder that is responsible for the subgroup of individuals who show continuity from ODD to CD to antisocial personality disorder (ASPD). In line with this suggestion, Taylor, Chadwick, Heptinstall and Danckaerts (1996) found that hyperactivity in 6- and 7-year-olds placed the children at increased risk of developing psychiatric disorders, independently from the existence of conduct problems, at 16 and 18

years of age. Nagin and Tremblay (2001) found that boys who displayed high levels of hyperactivity and opposition during preschool were at high risk of persistent physical aggression from 10 to 15 years of age. Thus, ADHD could be considered an important disorder to study when investigating the development of severe behaviour problems in children.

Externalizing behaviour problems are characterised by a number of shared symptoms; for example ADHD is defined by problems with inattention and persistent hyperactivity and impulsivity but these symptoms are also present in children with the childhood-onset subtype of CD. Deficits in executive function have been shown to be common in both children with ADHD (Pennington & Ozonoff, 1996) and children with CD (Nigg & Huang-Pollock, 2003). Research has also shown that there are a number of common physiological correlates; for example heart rate (HR) during resting and challenge conditions has been robustly associated with conduct problems (Ortiz & Raine, 2004) and also with more global aggressive tendencies (Lorber, 2004). Externalizing behaviour disorders have a heritable component (Payton et al., 2001; Rhee & Waldman, 2002) but there is little evidence that specific genetic markers predict specific behaviour disorders; for example the dopamine receptor gene (DRD4), the dopamine transporter gene (DAT1) and a polymorphism in the monoamine oxidase A (MAOA) gene have been associated with both ADHD (Auerbach, Benjamin, Faroy, Geller & Ebstein, 2001a; Auerbach, Faroy, Ebstein, Kahana & Levine, 2001b; Thapar, O'Donovan & Owen, 2005b) and CD (Caspi et al., 2002; Holmes et al., 2002; Young et al., 2006). Thus, it is likely that individual genes are associated with particular disorders via complex pathways involving environmental influences (Kendler, 2005). These pathways are complicated

further by the findings that a number of environmental factors have been implicated in the development of externalizing behaviours. These include prenatal risk factors such as maternal smoking, obstetric complications and family adversity (e.g. Farrington & Loeber, 1998; Fergusson, Woodward & Horwood, 1998; Moffit, 1993).

We now focus on the specific disorder of ADHD and the symptoms, potential precursors and correlates of the disorder. We then examine prenatal smoke exposure, an environmental factor that has been implicated in the development of externalizing behaviour disorders, including ADHD. We review research examining the effect of prenatal smoke exposure on the developing foetus, which provides a mechanism through which smoking during pregnancy may affect the development of ADHD and other externalizing behaviours in offspring.

1.2. Attention Deficit Hyperactivity Disorder (ADHD)

ADHD is the most commonly diagnosed childhood disorder and a summary of epidemiologic studies in children between the ages of 6 and 12 years reported a prevalence rate of 4% to 12% (Brown et al., 2001). Egger et al. (2006a) report the prevalence of ADHD in preschool children, between the ages of 2 and 5 years, ranges from 2.0% to 7.9%. ADHD is more common in boys than girls both in epidemiological and clinical samples; epidemiological studies usually report a ratio of 2:1 (Arcia & Conners, 1998) and some research suggests that ADHD may be at least four times higher in boys than in girls (Biederman et al., 2002). For children to be diagnosed with ADHD, they must show developmentally inappropriate attentional problems, impulsiveness and motor hyperactivity, which persist for 6 months, occur across multiple settings and

interfere with developmentally appropriate functioning (APA, 1994). DSM-IV (APA, 1994) distinguishes three subtypes of ADHD: attention deficit hyperactivity disorder-combined type; attention deficit hyperactivity disorder – predominantly inattentive type; and attention deficit hyperactivity disorder – predominantly hyperactive-impulsive type. Egger et al. (2006a) found that the hyperactive-impulsive type and combined type were significantly more common than the pure inattentive type ADHD in preschoolers.

A diagnosis of ADHD is most commonly made when children reach middle childhood, at between 5 and 8 years of age (Applegate et al., 1997; Sonuga-Barke, Auerbach, Campbell, Daley & Thompson, 2005) and for a diagnosis of ADHD to be made symptoms should be present before the age of 7 years (Connor, 2002). Lavigne et al. (1996) showed that approximately 2% of children between the ages of 3 and 5 years have ADHD and children as young as 2 years have been prescribed stimulant medication for treatment of ADHD symptoms (Zito, Safer, dosReis, Gardner, Boles & Lynch, 2000). Lavigne et al. (1996) and Egger, Erkanli, Keeler, Potts, Walter and Angold (2006b) found the overall prevalence rate of ADHD in preschool children was similar to that found in other studies looking at school-age children (Costello et al., 1988). Confirming ADHD occurs in young children, Lahey et al. (1998) showed that all three DSM-IV subtypes are valid for children between the ages of 4 and 6 years and Egger et al. (2006b) concluded that ADHD is a reliable and valid diagnosis for 2- to 5-year-olds. However, children with the inattentive type of ADHD were found to be significantly older than children in the other groups (Lahey et al., 1998). ADHD has also been shown to continue into adolescence and persists into adulthood in approximately 80% of cases (Farone, Sergeant, Gillberg & Biederman, 2003).

1.3. ADHD and Associated Problems

ADHD has been associated with a number of severe adverse outcomes both during childhood and later in life (DeWolfe, Byrne & Bawden, 2000; DuPaul, McGoey, Eckert & VanBrakle, 2001; Egger et al., 2006a; Fontaine et al., 2008; McGee, Partridge, Williams, & Silva, 1991; McGee, Prior, Williams, Smart & Sanson, 2002; Merrel & Wolfe, 1998). For example, children as young as 3 to 5 years of age, classified as having ADHD, showed higher levels of problem behaviour and were less socially skilled than controls (DuPaul et al., 2001). Another study showed that children between the ages of 5 and 6 years, who were identified as having significant ADHD symptoms, had poor social skills, particularly social cooperation skills (Merrell & Wolfe, 1998). Cunningham and Boyle (2002) found that children at risk of ADHD were reported by teachers to work less, behave worse, present more problems in more situations and have more social problems than groups without ADHD symptoms. A study by DeWolfe et al. (2000) again found evidence of deficits in social skills in preschool children classified as having ADHD. The children with ADHD also showed more aggression, more demand for parental time, were less adaptable to change in routine and showed more non-compliance than controls. Poor social relationships in preschool can have wide-reaching implications. For example, research has shown that inadequate early peer relationships increases children's risk for poor functioning in social skills and relationships in later life, even if those individuals do not meet criteria for ADHD in adolescence and adulthood (Olson & Brodfeld, 1991; Weiss & Hechtman, 1993). In a study by Loe et al. (2008) it has been shown that children in the ADHD group had lower scores on cognitive and receptive language measures in

preschool as well as receiving higher scores by both parents and teachers on the Child Behavior Checklist (CBCL) and therefore the authors propose that ADHD should be considered as a cognitive as well as a behavioural disorder.

Research in a representative community sample has shown that by 16 years of age at least one in three children will have had one or more psychiatric disorders (Costello, Mustillo, Erkanli, Keeler & Angold, 2003). Once children, especially girls, develop a psychiatric disorder it has been shown that the chances of them continuing to have the disorder or developing an episode after remission is far greater than their normal peers (Costello et al., 2003). Evidence that deficits associated with ADHD can persist into adulthood was shown in a recent study; girls diagnosed as being hyperactive or hyperactive-aggressive between the ages of 6 and 12 years were significantly more likely to have poor psychosocial outcomes, including smoking, poor educational achievement and difficulties with intimate relationships, at 21 years of age (Fontaine et al., 2008). A similar result has also been found in a study by Young, Chadwick, Heptinstall, Taylor & Sonuga-Barke (2005). In this study, 6- and 7-year old girls identified as being hyperactive were found to have disrupted relationships with peers and the opposite sex at 14-16 years of age. These results provide support for studies which have previously found a similar relationship with males (e.g. Hansen, Weiss & Last, 1999; Mannuzza, Klein, Abikoff & Moulton, 2004). This highlights the importance of understanding the development of psychiatric disorders and that, if possible, it is important to prevent or treat the disorder at a young age.

The sole reliance on using parental reports when diagnosing ADHD has been cautioned by Gimpel and Kuhn (2000) who surveyed 253 mothers about ADHD

symptoms in their children, ranging in age from 2 to 6 years. Although, parental reports of low levels of hyperactivity, inattention and impulsivity were found to predict a non-ADHD diagnosis, parental reports of high levels of these behaviours was not found to be predictive of an ADHD diagnosis. Therefore, Gimpel and Kuhn (2000) suggest sole use of parental reports when diagnosing ADHD should be avoided because it may lead to over-identification of the disorder. Gimpel and Kuhn (2000) suggest when high levels of these behaviours are reported, further investigation is required before a diagnosis is given. This investigation should use full DSM-IV diagnostic criteria and standardised behaviour rating scales completed by multiple informants and across settings should be utilized. In conclusion, it is important that multiple measures and multiple informants are used where possible in research when identifying and investigating ADHD symptoms in individuals.

The impact of a diagnosis of ADHD is not just felt by the individual. Studies have shown that boys with hyperactivity are more demanding of their parents (Barkley, Karlsson, Pollard & Murphy, 1985) and the parents of ADHD children report more stress than those of non-ADHD children (DeWolfe et al., 2000; DuPaul et al., 2001). Research has also shown that mothers of children with ADHD have more negative patterns of communication, more conflict with the child, more controlling and negative management strategies and a higher intensity of anger than control mothers (Cunningham & Boyle, 2002; Offord et al., 1992). Therefore, it is possible that there is a reciprocal parent-child relationship, with children with ADHD symptoms being more demanding, resulting in an increase in stress in the parents and also higher levels of negative parenting (Calkins et al., 2000). Other research has shown that young children with ADHD are more likely to

use medical services than their normal peers, as a result of suffering a higher number of physical injuries (Lahey et al., 1998) and as a result of being prescribed medication (Zito et al., 2000), which can place additional demands on already stretched medical services.

In conclusion, the societal impact of ADHD is vast in terms of the adverse academic, vocational and social outcomes and the negative effect on self-esteem of those individuals diagnosed with ADHD and also in terms of the stress to families and the financial costs (Farone & Biederman, 1998). Given that ADHD is one of the most commonly diagnosed childhood disorders, that symptoms have been observed in preschool children, that outcomes are often severe, that interventions often result in a limited response at best and that the use of medical services is increased, it is vital that future research continues to investigate the occurrence of ADHD in children and considers potential precursors to ADHD which could be identified in very young children. Studying the symptoms of hyperactivity, impulsivity and inattention is crucial given that these symptoms have been shown to be strongly related to underachievement in early and middle childhood, whereas there is evidence that aggression is only related to achievement through its relation with inattention and hyperactivity (Mannuzza et al., 2004; Moffitt et al., 2008; Spira & Fischel, 2005).

1.4. Studying Precursors and Correlates of ADHD

In the past, research in child psychopathology has focused almost exclusively on school-aged children (Calkins et al., 2000). This probably reflected, at least in part, conceptual and methodological gaps in the field (Calkins et al., 2000). However, emerging theories in the last four decades have resulted in a renewed interest in early

precursors in the development of psychopathology. For example, the work on infant temperament by Thomas and colleagues (Thomas, Chess, Birch, Hertzig & Korn, 1963; Thomas, Chess & Birch, 1968; Thomas & Chess, 1977) was a key influence in renewing interest in individual differences in development (Calkins et al., 2000).

Studies investigating ADHD symptoms in preschoolers have found very similar behaviours across individuals; for example studies have found impaired attention, higher levels of activity and a higher frequency of changes in activity (McGee et al., 1991; McGee et al., 2002; Rabiner, Coie & the Conduct Problems Prevention Research Group, 2000), which supports the suggestion that ADHD is a neurodevelopmental disorder and as a result the symptoms of this disorder may be present well before school age (DeWolfe et al., 2000). Sonuga-Barke et al. (2005) suggest that there is now evidence that early precursors to disorder, shown in small variations in child characteristics, can be identified during infancy. Sonuga-Barke et al. (2005, p. 144) propose that these characteristics include "neurodevelopmental immaturity, increased activity level, emotional dysregulation, over-responsivity to environmental stimulation and lower cognitive functioning". Auerbach, Atzaba-Poria, Berger and Landau (2004) suggest that determining whether pathways to disorder are present in the first few months of life is one of the current challenges facing developmental psychopathology. However, when studying potential precursors to ADHD in young children, it is crucial to distinguish between normal, age-related behaviour and early symptoms and precursors to disorder (Barkley et al., 2000; Carter, Briggs-Gowan & Davis, 2004; Keenan & Wakschlag, 2000; Moffitt, Caspi, Dickson, Silva & Stanton, 1996; Sonuga-Barke et al., 2005; Spira & Fischel, 2005). It is also important to aim to identify which of the children who display

pre-clinical levels of ADHD symptoms during infancy and early childhood will go on to develop ADHD and other disorders (Sonuga-Barke et al., 2005). Despite these challenges, there is increasing recognition that it is important to detect the emergence of early social, emotional and behavioural problems (American Academy of Pediatrics, 2001).

We now review the main symptoms and correlates of ADHD and consider their role in the search for early precursors to ADHD.

Hyperactivity. Hyperactivity is one of the three symptoms necessary for a diagnosis of ADHD and hyperactivity can be observed during infancy making it a candidate for the study of early precursors to ADHD. Indeed, a number of studies have investigated the link between hyperactivity in infancy and a subsequent diagnosis of ADHD (Morrell & Murray, 2003). In a study by Becker, Holtman, Laucht and Schmidt (2004) it was found that children identified as suffering from multiple regulatory problems at 3 months of age had more hyperkinetic symptoms throughout childhood than a control group who did not have regulatory problems as infants. However, when factors of family adversity, such as one parent families and poor parental coping skills, were controlled, the association between regulatory problems and hyperkinetic symptoms became insignificant, suggesting that factors relating to family adversity are mainly responsible for the relation between multiple regulatory problems and subsequent hyperkinetic problems. A limitation of the study by Becker et al. (2004) was that the sample contained a large number of children born at risk of later developmental problems and psychopathology and therefore, the findings may not extend to a general population sample.

However, a number of studies have provided support for the results found by Becker et al. (2004); for example, Carlson, Jacobvitz and Sroufe (1995) found in a sample of 3.5-year-olds that the strongest predictors in explaining hyperactive and distractible behaviours, apart from hyperactivity itself, were measures of the relationship status of the mother at birth, social support for the parent and direct measures of parental overstimulation. Other research has also found that poor parent coping, the use of aggressive methods of discipline and lower rates of father-child communication were significantly associated with hyperactivity in the offspring (Keown & Woodward, 2002; McGee et al., 1991; Woodward, Taylor and Dowdney, 1998). Providing further support for the link between family adversity and psychopathology is a study by Keenan, Shaw, Walsh, Delliquadri and Giovannelli (1997), who found that there were higher rates of psychopathology in preschool children who came from low-income families than those children who came from middle-income families. However, a number of studies (Byrne et al., 1998; Cunningham et al., 1988; Johnston, 1996) have shown that ADHD symptoms only were not linked to family dysfunction and it is in fact ODD symptoms that are more closely related to family disadvantage (Barkley, Anastopoulos, Guevremont & Fletcher, 1992; Stormont-Spurgin & Zentall, 1995). Also, it is possible that the behaviours shown by parents, such as poor coping and aggressive parenting, are indicators of psychopathology in the parents. Clearly further research, using designs to examine gene-environment correlations, is needed to unravel these findings.

Auerbach et al. (2004) investigated activity level in boys using two methods; the first involved mother reports of activity level during the first month of life and at 7 months and the second method was observation of activity level at 7 months, during a

prone and supine placement episode in a laboratory. Mothers of the infants in the ADHD 'at risk' group, based on current paternal ADHD symptoms, reported their infants to be significantly more active than the control group. No difference in activity level between the two groups during the laboratory observation was observed. This task was taken from the Laboratory Temperament Assessment Battery (Lab-TAB-Prelocomotor version; Goldsmith & Rothbart, 1994). The infant was placed on a mat in a supine position for 30 seconds and then the infant was transferred into a prone position for a further 30 seconds. The 30 second trials were divided into 10 second epochs and the vigour of the infants' movement was coded for each epoch, using a scale ranging from 0 for extremely low vigour (i.e. "lying on the quilt with very little movement except for looking around") to 4, for extremely high vigour (i.e. "thrashing of arms and legs that leads to whole-body movements"). The reason for the lack of observed difference in activity level between the two groups in the laboratory may have been because the period of observation of 60 seconds in total was too short and only one measure of activity during this time was used which may have been too exclusive. The difference in mother reported activity level was present both neonatally and at 7 months, demonstrating stability in activity level during the first year of life. Subsequent studies could benefit from using a sample containing both males and females and from the use of an activity monitor to measure the activity levels of babies across a range of tasks.

Marakovitz and Campbell (1998) carried out a study in which a group of boys identified as hard to manage at age 4 were compared with age-matched controls. Those boys classified as hard to manage exhibited some behavioural problems at 9 years of age but were no more impulsive or inattentive than controls. Boys diagnosed with Attention

Deficit Disorder (ADD) at age 9 were more hyperactive, as measured by an actometer, out of seat behaviour and examiner ratings, were more inattentive as measured by Continuous Performance Test (CPT) omissions and were found to be more impulsive on the Matching Familiar Figures Test, than problem boys without ADD and controls. When the ADD group was compared with the hard to manage but non-ADD group at age 4, it was found that the two groups differed in poorer impulse control and the ADD group were rated as more inattentive/hyperactive. However, overall the two groups could not be distinguished from each other on most of the measures of inattention, impulsivity and hyperactivity at age 4 and so the authors concluded that symptoms which are specific to ADD emerged most clearly between the ages of 6 and 9 years. In general, the results from the studies reviewed here provide support for the proposal that problems with hyperactivity are stable from preschool to school age.

Impulsivity. Like hyperactivity, impulsivity is another symptom required for a diagnosis of ADHD to be made but unlike hyperactivity, symptoms of impulsivity are difficult to measure during infancy. Thus, the majority of studies focus on impulsive symptoms during the preschool period and beyond. The development of self-regulatory skills, such as the management of impulsivity and attention, are crucial during the preschool years and provide the child with an important foundation for the development of social and academic capabilities (Kochanska, Murray & Coy, 1997; Kochanska, Murray & Harlan, 2000; Kochanska, Coy & Murray, 2001). Caspi and Silva (1995) found that children identified as having a "lack of control", a measure of impulsivity, inattention and a lack of persistence, scored highly on measures of impulsivity, danger-seeking, aggression and interpersonal alienation at age 18 years. The results from this study

demonstrate the importance of developing self-regulatory skills during childhood and show that for those children who do not develop these skills, problems can persist for many years. Campbell (1994) found that boys identified as hard to manage during preschool, were rated two years later by mothers, fathers and teachers as having more impulsivity than controls. Olson, Bates, Sandy and Schilling (2002) investigated precursors of impulsivity in a sample of toddlers and found evidence that impulsivity is multidimensional in nature. The results showed that interaction between the caregiver and child, child temperament and child cognitive competence, during infancy and the toddler years, significantly predicted subsequent impulsive functioning at 8 years of age. Impulsivity was measured using the Matching Familiar Figures Test, the Draw-a-Star-Slowly procedure, the restricted task period, which involved colouring in shapes according to a certain colour code and the incentive task, which involved repeating the colouring task with the motivation of receiving a prize. The authors concluded that it is important that precursors of children's later self-regulatory competence are assessed during the toddler period.

Deficits in attention. Together with hyperactivity and impulsivity, inattention is the final symptom required in the diagnosis of ADHD. McGee, Prior, Williams, Smart and Sanson (2002) investigated both hyperactivity and inattention in a sample of children between the ages of 5 and 8 years. Results showed that those children identified as being inattentive-hyperactive were more likely to have problems with attention and reading in adolescence and as a result have a significant risk of further educational failure and poor psychosocial adjustment in later school years and after they left school. In general, the results showed that the greater the level of inattention-hyperactivity in childhood, the

poorer the outcome. The results by McGee et al. (2002) provide support for previous findings by McGee et al. (1991) and Fergusson, Lynskey and Horwood (1997). Rabiner et al. (2000) considered only problems of inattention and found that problems in attention during kindergarten predicted reading achievement at fifth-grade, even when prior reading achievement, IQ and other behavioural difficulties were controlled. Campbell (1994) also found that boys rated as having problems with attention had been identified during preschool years, two years earlier, as being hard-to-manage. In studies by Harper and Ottinger (1992) and Hooks, Milich and Lorch (1994) it was found that children with ADHD made more errors of omission and commission, indicating inattentiveness, on the CPT than controls. Evidence that problems with attention can be identified in infants was provided by a study by Auerbach et al. (2004). In this study sustained attention was investigated in 7-month-olds by measuring object interest, using a task taken from the Lab-TAB (Goldsmith & Rothbart, 1994). They found that those children in the ADHD 'at risk' group, based on ADHD symptoms in the father, showed significantly less interest in the task than the comparison group. This indicates that inattention during infancy could be considered as an early precursor in the study of the emergence of ADHD.

Temperament. Whilst not a precursor to ADHD itself, it is widely accepted that the temperamental profile a child exhibits can influence the child's functioning later in life, although the mechanisms through which this may happen are still debated (e.g. Rothbart & Bates, 1998; Thomas et al., 1968). Thomas et al. (1968) describe temperament as the "how" of behaviour and suggest it concerns the way in which an individual behaves. Temperament is defined by Rothbart and Bates (1998) as "constitutionally based individual differences in emotional, motor and attentional

reactivity and regulation" (p.109) and most major theories of temperament include scales to measure activity levels and attention (e.g. Diamond, 1957; Rothbart, 1981; Thomas et al., 1968). Individual differences in the display of positive and negative affect in response to environmental factors are considered to be a central component of temperament (Beauchaine, 2001) and indeed emotionality is widely accepted as a dimension of temperament by the main temperament theorists (Goldsmith, Buss, Plomin, Rothbart, Thomas, Chess, Hinde & McCall, 1987).

Based on findings from their longitudinal study investigating the dimensions of temperament, Thomas et al. (1963) classified children as having a "difficult" or "easy" temperament. Thomas and Chess (1977) observed that there were many examples of the children in their sample showing similar temperamental patterns at different ages, suggesting that temperamental traits were relatively stable. They went on to confirm, through qualitative and quantitative analyses, that features of temperament were often significant variables in the development of behaviour disorders and they proposed that healthy development depended to a large extent on the "goodness of fit between temperament and environment" (Thomas & Chess, 1977, p. 29). Since then clear links have been documented between children exhibiting behaviour problems and being rated as having a "difficult" temperament. For example, Kingston and Prior (1995) investigated patterns in the development of aggression in a group of children aged between 2 and 8 years of age. Results showed that teachers correctly identified 74% of children who developed aggression at school age, using ratings of temperament factors of task orientation and reactivity and ability ratings. Graham and Stevenson (1987) proposed that emotional disorder, hyperactivity and antisocial disorder could be considered to be severe

manifestations of ordinary, non-pathological behaviours. However, Frick (2004) suggests that the temperamental characteristics observed in infants and young children could in fact be symptoms of the disorder themselves. The overlap between items in both temperament and psychopathology measures raises a considerable problem when attempting to understand the relationship between temperament and disorder. As ADHD begins during childhood and is a diverse disorder, it is considered to be an important condition to study when researching the link between temperament and disorder (Bussing, Gary, Mason, Leon, Sinha & Garvan, 2003).

Bussing et al. (2003) investigated the link between temperament and ADHD, whilst also considering the suggestion that item overlap in measures could account for any relationship observed. In this study it was found that child self-report of specific temperament dimensions was linked with child psychiatric disorders and ADHD was specifically associated with lower scores on task orientation and higher scores of general activity level. The possibility of item overlap accounting for the relationship was ruled out because there were no significant similarities between the measures used. The authors conclude that those infants and young children who show low levels of task orientation and high levels of activity may be at risk of developing further behaviours which could lead to a diagnosis of ADHD. Another study looking at the link between temperament traits and ADHD was carried out by Martel and Nigg (2006). In this study it was found that problems with regulation contributed to the development of symptoms of inattention and disorganisation, whereas reactive or motivational problems contributed to the emergence of hyperactivity and impulsivity and therefore, it was concluded that

particular traits may predispose a child to develop the symptoms of ADHD or other behaviour disorders.

Hirshfeld-Becker, Biederman, Faraone, Violette, Wrightsman and Rosenbaum (2002) also investigated the link between temperament, specifically behavioural inhibition, and externalizing behaviours, particularly ADHD. High levels of approach behaviours, high novelty seeking, low harm avoidance and irritable distress are all characteristics of behavioural disinhibition (Egger & Angold, 2006). Previous research has found a robust association between behavioural inhibition and anxiety disorders (e.g. Biederman et al., 1991; Kagan, Reznick & Snidman, 1987). However, there is increasing evidence of an inverse relationship between behavioural disinhibition and externalizing behaviour disorders, including ADHD (Biederman et al., 2001). In the study by Hirshfeld-Becker et al. (2002) it was found that children with behavioural disinhibition were significantly more likely than nondisinhibited, noninhibited children to have ADHD and to have comorbid mood disorders and externalizing behaviour disorders. From the results, it was concluded that behavioural disinhibition may be a temperamental precursor to ADHD and possibly other externalizing behaviours.

Several studies have found links between negative emotionality and ADHD (Degangi, Porges, Sickel & Greenspan, 1993; Wolke, Rizzo & Woods, 2002). In a study of 7-month-old infants, Auerbach et al. (2004) found that there were significant differences between the ADHD 'at risk' group, which was based on current ADHD symptoms in the father, and the control group in measures of anger reactivity and directed anger. However, Auerbach et al. (2004) found that the degree of anger was small. The authors suggest that the barrier task, taken from the Lab-TAB (Goldsmith & Rothbart,

1994), which they used to elicit anger may not have been effective in eliciting anger given the age of the sample and so they propose that a task using physical restraint may be more appropriate in future research. In another study, Weiss and Hechtman (1993) found that mothers of children with ADHD reported that, as infants, these children were fussy and irritable, in contrast with controls. Indeed, studies have shown that problems with anger and anger regulation are associated with ADHD from preschool through to adulthood (Douglas & Parry, 1994; Mash & Johnson, 1982; Ramirez, Rosén, Deffenbacher, Hurst, Nicoletta, Rosencranz & Smith, 1997).

In contrast, Maziade, Cote, Bernier, Boutin and Thivierge (1989a) found that very difficult temperament as measured at 4 and 8 months had very little influence on clinical outcome at 4 years of age, whereas there was an association between temperament measured at 4 years and disorder. The authors proposed that temperament during infancy may indirectly affect clinical outcome through its association with temperament at age 4. In a follow-up study, Maziade Cote, Bernier, Boutin and Thivierge (1989b) concluded that measuring temperament at several points in the first years of life and considering the direction of any change in temperament could be more useful in the prediction of disorder than considering only one assessment of temperament taken at one time point.

Despite the importance of studying infant temperament, there have been a number of limitations with previous research, the main one being a heavy reliance on parent reports of infant temperament. A number of researchers have criticised the validity of parent reports of infant temperament. For example, some researchers suggest that maternal reports may be biased because they reflect maternal as well as infant characteristics (Crockenberg & Acredolo, 1983; Leerkes & Crockenberg, 2003;

Mangelsdorf, Gunnar, Kestenbaum, Lang & Andreas, 1990). Kagan (1998) suggests that parents may not report their child's behaviour accurately because they lack sufficient knowledge of other children for comparison and their responses may be biased because of a desire to present their children in a positive way. Also, it is suggested that parents can perceive the same behaviours in different ways. For example, not all mothers will interpret a child's shyness as fearful behaviour but consider it sensitivity or caution. Observations of behaviour enable the assessment of dimensions of temperament which cannot be measured using questionnaires (Kagan, 1994). However, this method also has a number of limitations, for example, in naturalistic settings (i.e. in the home) there is limited control over the conditions in which the child's behaviour is recorded and observers may miss specific reactions that are part of a whole range of behaviours that make up a child's temperament. However, behavioural observations in the laboratory using measures such as the Lab-TAB developed by Goldsmith and Rothbart (1999) can help to overcome some of these problems. As with observation, physiological measures can be used to reveal aspects of infant and children's temperament that cannot be obtained through questionnaires. Physiological responses, such as changes in heart rate (HR) and skin conductance, are regarded as important physiological correlates of temperament (Strelau, 1998) and there is increasing recognition that an accurate understanding of the relationship between temperament and physiology is important in our understanding of infant temperament (Nachmias, Gunnar, Mangelsdorf, Parritz & Buss, 1996).

Cardiac activity. One of the most reliable, sensitive and well validated physiological measures used in infant research is the measurement of HR (Campos, 1976;

Nigg, 2006). Heart rate can be measured relatively unobtrusively making it a useful physiological measure when studying infants and it also has the feature of bidirectional responding, meaning it can increase or decrease in response to stimulation (Campos, 1976). Heart rate is controlled by the sympathetic and parasympathetic branches of the autonomic nervous system (ANS). The ANS regulates homeostatic function (Rosenzweig, Leiman & Breedlove, 1999). In general the sympathetic nervous system is said to prepare the body for action as a result of challenges from outside the body e.g. blood pressure increases, pupils dilate and HR quickens. In contrast the parasympathetic nervous system promotes processes involved with growth and restoration e.g. pupil constriction, vesical and rectal sphincter relaxation and a decrease in HR (Lovallo, 1997). The vagus is the primary parasympathetic pathway to the heart and vagal tone (VT) is a measure of the amount of neural influence on the heart (Stifter & Fox, 1990). Vagal tone has two roles (Porges, Doussard-Roosevelt, Portales & Greenspan, 1996): (1) to promote physiological homeostasis when there is low environmental demand and (2) during periods when there is environmental challenge the vagus acts as a brake to rapidly regulate cardiac output and therefore metabolic output. The "vagal brake" increases vagal output to the heart and actively inhibits sympathetic influences which results in keeping HR slow (Levy, 1984). As the vagal brake is released, vagal inhibition on the sino-atrial node is reduced and HR increases. Respiratory sinus arrhythmia (RSA) is the name given to the variability in HR as a result of respiration. Quantifying RSA is a relatively accessible way of measuring the vagal control of the sino-atrial node of the heart.

Eppinger and Hess (1910) were some of the first researchers to suggest a relationship between the sympathetic and parasympathetic branches of the autonomic

nervous system with behaviour. Since the work of Eppinger and Hess, VT has continued to become a psychophysiological marker for emotion regulation and other aspects of behavioural functioning, in children and adults (Graziano, Keane & Calkins, 2007). Several studies have made the connection between dimensions of temperament and the regulation of the autonomic system (e.g. Huffman, Bryan, del Carmen, Pedersen, Doussard-Roosevelt & Porges, 1998; Kagan, 1982; Rothbart, 1989) and polyvagal theory, as described by Porges (1995, 1997) provides justification, both at a neuroanatomical and neurophysiological level, for studying VT as an index of temperament.

Raine (2002, p. 417) proposed that "low resting heart rate is the best replicated biological correlate of antisocial and aggressive behaviour in children and adolescent populations". Many studies have investigated the link between HR and externalizing behaviour disorders. For example, van Goozen, Matthys, Cohen-Kettenis, Gispen-de Wied, Wiegant, and van Engeland (1998) found that a group diagnosed with ODD had significantly lower HR levels during baseline compared with controls. However, the HR levels of the ODD group during frustration and provocation tasks were higher. Rogeness, Cepeda, Macedo, Fischer and Harris (1990) found that male and female participants with CD had lower HR than those without a diagnosis of CD. Raine and Venables (1984) found a group of males classified as "antisocial" had significantly lower HR than a "prosocial" group. Davies and Maliphant (1971), Wadsworth (1976), West and Farrington (1977), Raine, Venables and Williams (1990) and Patrick (1994) have all also found evidence of low resting HR in individuals classified as being antisocial. In 1997, Raine, Venables and Mednick confirmed the relationship using a prospective study

design. In this study it was found that those children classified as aggressive at 11 years, had lower HR at 3 years of age than nonaggressive children. In a meta-analysis carried out by Lorber (2004), it was found that children with aggressive and conduct problems had a lower resting HR but increased HR reactivity.

In contrast to the hypothesis put forward by Raine (2002), Zahn and Kruesi (1993) found that boys identified as being disruptive, which was based on persistent problems at home and school with figures of authority, problems with aggression and impulsivity, had higher resting HR than controls. However, further analysis showed that the elevated HR was largely as a result of those participants without a diagnosis of CD. Jennings, van der Molen, Pelham, Debski and Hoza (1997) also found that during baseline the ADHD group had shorter inter-beat intervals than the controls, however, this difference was not found to be significant. Iaboni, Douglas and Ditto (1997) found that there was no significant difference in HR during baseline between the ADHD and control groups. Herpertz, Wenning, Mueller, Qunaibi, Sass and Herpetz-Dahlman (2001) found that resting HR was not significantly lower in children with both ADHD+CD, compared with controls, although it did tend to be lower, but boys with ADHD+CD showed low autonomic responses to orienting and aversive startle stimuli compared with children with only ADHD and controls. However, the majority of the literature confirms the suggestion put forward by Raine (2002) that low resting HR is associated with antisocial and aggressive behaviours. Raine (2002) concludes that future research needs to identify the specific cardiovascular processes, for example sympathetic versus parasympathetic processes, which are involved in the relationship between low HR and antisocial and aggressive behaviour.

Börger, van der Meere, Ronner, Alberts, Gueze and Bogte (1999) suggest the 0.10Hz component of HR variability can be considered a psychophysiological index of motivation. Thus, a greater 0.10Hz component indicates the participant is allocating less effort or motivation. Factors of motivation and effort are considered to be the main components accounting for the deficit in attention observed in children with ADHD (Börger et al., 1999). Börger et al. (1999) assessed HR variability in a sample of children with ADHD and found that ADHD participants had a greater 0.10-Hz component, which was associated with poor performance over time. Luman, Oosterlaan, Hyde, van Meel and Sergeant (2007) also found evidence of motivational deficits in children with ADHD when they studied HR parameters in response to feedback associated with reward and response cost. Iaboni et al. (1997) investigated HR in ADHD children and controls during a repetitive motor task with reward and extinction conditions. The results showed that ADHD children habituated more quickly to reward than controls, with a lower HR responsivity to reward conditions over successive trials and therefore, showed a reduced psychophysiological responding. Beauchaine, Katkin, Strassberg and Snarr (2001) also investigated HR during a repetitive motor task. The ADHD+CD group was found to have longer cardiac preejection periods (PEPs) than the ADHD only or control groups and also showed less PEP reactivity than the control group. Also, during baseline the ADHD+CD group showed reduced respiratory sinus arrhythmia (RSA) than the ADHD and control groups. However, Shibagaki and Furuya (1997) found that participants with ADHD had lower RSA than normal controls.

Van Lang, Tullen, Kallen, Rosbergen, Dieleman and Ferdinand (2007) found that following a task designed to elicit stress, ADHD participants showed less HR reactivity

and comorbid ODD/CD did not account for this relationship. The authors conclude this may be related to stronger activation of the parasympathetic than the sympathetic system. Crowell, Beauchaine, Gatzke-Kopp, Sylvers, Mead and Chipman-Chacon (2006) found evidence that cardiac activity was similar in both preschoolers and older children. In this study, children, between the ages of 4 and 6 years, with ADHD and ODD were found to have lengthened PEPs at baseline and during reward. No group differences were found in baseline RSA between the two groups. However, HR changes among ADHD and ODD participants were found to be moderated entirely by parasympathetic withdrawal, with no independent sympathetic contribution, whereas, in controls both branches of the autonomic nervous system were found to contribute to changes in HR.

Thus, evidence suggests that disrupted patterns of cardiac activity correlate with ADHD and other externalizing behaviour disorders. Cardiac activity can be measured relatively easily in infants and young children and thus could be measured when investigating the emergence of problem behaviours in early development.

In conclusion, studying temperament in infants is the first step in understanding the development of ADHD and other behaviour disorders. Most major theories of temperament include scales to measure infant activity levels and attention (e.g. Diamond, 1957; Rothbart, 1981; Thomas et al., 1968) and problems in these domains are characteristic of individuals with ADHD. However, current infant temperament research has a number of limitations. For example, there has been a heavy reliance on parent reports and although most definitions of temperament suggest that there is a biological basis to temperament, it is only recently that the importance of having an accurate

understanding of the relationship between temperament and physiology has been recognised in aiding our understanding of infant temperament (Nachmias et al., 1996). Thus, the aim of this thesis was to study domains of infant temperament (using behavioural observations, parent reports and physiological measures) that could be considered in the search for early precursors of the development of ADHD. As reviewed above there are several domains of temperament that can be studied in infants, such as attention, activity levels and emotionality, and evidence suggests that individual variations in these domains during infancy may influence functioning later in life (Auerbach et al., 2004; Bussing et al., 2003; Degangi et al. 1993; Kingston & Prior, 1995; Lara, Pinto, Akiskal & Akiskal, 2006; Lawson & Ruff, 2004; Weiss & Hechtman, 1993). Researchers studying emotionality have measured a range of constructs including negative affectivity, fear, soothability, irritability and anger. In the current thesis, we chose to focus on the domains of attention and activity level because inattention and excessive activity levels are key symptoms in individuals diagnosed with ADHD. We also chose to study HR because of the importance of recognising that there is a biological basis to temperament and HR has been shown to be one of the most sensitive, reliable and well validated physiological measures used in infant research (Campos, 1976; Nigg, 2006). Next, we review research examining the effects of maternal smoking during pregnancy, a prenatal risk factor associated with the development of ADHD, on offspring outcomes.

1.5. Smoking during Pregnancy

In 2005, 24% of adults, over the age of 16 years, reported smoking in the UK (http://www.statistics.gov.uk, retrieved July 2008). Between 2000 and 4000 chemical compounds are thought to be comprised in cigarette smoke (Johnson et al., 2000; Julien, 1998). Of these compounds, it is nicotine which has received the majority of focus in both animal and human studies. The effects of nicotine are primarily as a result of its action on nicotinic acetylcholine receptors in the central nervous system (Navarro et al., 1989). The nicotinic acetylcholine receptors are located on the presynaptic nerve terminals of dopamine- and serotonin-secreting neurons and therefore activation of these receptors results in the release of dopamine and serotonin (Julien, 1998). Even in low concentrations nicotine has been found to increase the activity of these receptors. As the brain tries to compensate for the artificial stimulation brought about by the intake of nicotine, there is a down-regulation of the production of dopamine and other stimulatory neurotransmitters. Also, the sensitivity of nicotinic acetylcholine receptors decreases, which results in a further compensatory process, whereby the brain upregulates the number of receptors. This results in an increase in reward pathway sensitivity (Julien, 1998). The neuronal brain alteration has been shown to persist for months after nicotine administration stops and indeed DiFranza and Wellman (2005) propose the "sensitization-homeostasis" model which suggests that dependence on nicotine results in neural circuitry being reprogrammed with the result that a return to apparently normal behavioural function does not necessarily mean there has been a return to the brain state prior to exposure. Instead, it is suggested that there have been long-term adaptive and counteracting synaptic changes.

Despite these findings, it was found that in the year 2000, 20% of pregnant women in the UK reported smoking (http://www.statistics.gov.uk, retrieved Jan 2008). In the same year, 26% of women from the "unskilled" work group reported smoking whilst pregnant compared with 4% of pregnant women in the "professional class". Smoking has been shown to affect neurotransmitter pathways and perhaps produce long-term changes in adults who smoke, so what are the consequences for the developing foetuses in women who smoke whilst pregnant?

1.6. Prenatal Smoke Exposure and the Developing Brain

When women smoke during pregnancy it has been found that there is a decrease in intervillous placental blood flow (Lehtovirta & Forss, 1978) and maternal smoking during pregnancy adversely affects the ability of both the foetal and maternal blood to carry oxygen (Cole, Hawkins & Roberts, 1972). Nicotine has also been shown to have vasoconstrictive effects (Morrow, Ritchie & Bull, 1988), which may affect the blood flow in the placenta, and this combined with a nitric oxide and prostacyclin deficiency may contribute to impaired foetal nutrition and an increase in perinatal mortality of infants born to mothers who smoke (Ulm, Plöckinger, Pirich, Gryglewski & Sinzinger, 1995). Women who smoke during pregnancy have also been found to have persistent endothelial dysfunction (Quinton, Cook & Peek, 2008). Protein metabolism and enzyme activity in the cord blood have also been shown to be affected by persistent smoking (Jauniaux, Biernaux, Gerlo & Gulbis, 2001) and could contribute towards poor foetal growth. Roy, Andrews, Seidler and Slotkin (1998) found that even when embryos were exposed to low doses of nicotine there was destruction of cells in the forebrain, midbrain and hindbrain.

This destruction was evidenced by vacuoles forming in the cytoplasm of cells, an increase in the intercellular spaces in cells and a dramatic increase in the occurrence of cell death. With exposure to high concentrations of nicotine, these irregularities were found to be present in the majority of cells. Roy et al. (1998) also found an increase in cell mitosis.

Nicotinic acetylcholine receptors and ChAT, an enzyme necessary for the synthesis of acetylcholine, have been identified in the brain as early as the eighth week of gestation (Ernst, Moolchan & Robinson, 2001) and nicotine receptor proteins and gene transcripts for the different nicotine receptor subunits have been shown to be present in the human foetus as early as four to five weeks of gestation (Hellström-Lindahl, Seiger, Kjældgaard & Nordberg, 2001). These findings suggest the importance of nicotinic receptors in controlling dendrite growth, the establishment of neuronal connections and the formation of synapses (Ernst et al., 2001; Hellström-Lindahl et al., 2001). Also, several studies have provided evidence for the role of nicotinic acetylcholine receptors in the regulation of neuronal migration and growth cone direction (Ernst et al., 2001), which is the tip of growing dendrites and is thought to be responsible for the guidance of axons and dendrites and also synaptic transmission (Landmesser, 1994). An increase in receptor density of foetal and neonatal cerebral nicotinic acetylcholine receptors has been shown after pregnant rats were exposed to chronic nicotine treatment (Miao, Liu, Bishop, Gong, Nordberg & Zhang, 1998; Slotkin, 1998; Van de Kamp & Collins, 1994). Van de Kamp and Collins (1994) found that exposure to nicotine prenatally resulted in an increase in levels of nicotine binding at birth in the hypothalamus, hippocampus and also possibly the cortex. At 20 to 30 postnatal days nicotine binding was found to be heightened in the

hippocampus, the hindbrain, striatum, midbrain and again possibly the cortex. Van de Kamp and Collins (1994) suggest that these changes are unlikely to be simply as a result of upregulation, considering that in adults there is a return to control levels within 7 days of exposure. Therefore, the authors suggest that the changes seen in the offspring of animals exposed to nicotine prenatally reflect a teratological effect of nicotine on development.

There are widespread functional interactions between cholinergic and catecholaminergic systems, with nicotinic cholinergic receptors being closely involved in the regulation of catecholaminergic function within the central nervous system and therefore, exposure of the developing foetus to nicotine is expected to affect multiple neurotransmitter pathways and the programming of synaptic competence (Slotkin, 1998). Slotkin, MacKillop, Rudder, Ryde, Tate and Seidler (2006a) found that both acetylcholine and serotonin synaptic function was permanently affected following prenatal exposure to nicotine in rats. Further studies have shown that the interaction of nicotine with nicotinic acetylcholine receptors in the brain of the foetus results in interference of neural cell replication and differentiation, impaired synaptogenesis and abnormal synaptic function, concluding eventually in neurobehavioural deficits (Law, Stroud, LaGasse, Niaura, Liu & Lester, 2003; Slotkin, Cho & Whitmore, 1987; Slotkin, 1998; Slotkin, Ryde & Seidler, 2007). Unsurprisingly, given the close association between cholinergic and catecholaminergic systems, long-lasting modifications in dopamine and norepinephrine activity have been found in rats, which had been exposed to nicotine prenatally (Ribary & Lichtensteiger, 1989; Richardson & Tizabi, 1994). Also, Oncken, Henry, Campbell, Kuhn, Slotkin and Kranzler (2003) found that the

concentration of epinephrine and norepinephrine was significantly lower in the cord blood of the offspring of smokers compared with the concentration in the cord blood of the offspring of non-smokers. A further study found that serotonin transporter expression was increased in the forebrain of offspring who had been exposed to nicotine prenatally (Muneoka, Ogawa, Kamei, Mimura, Kato & Takigawa, 2001). These findings support the results from animal studies that catecholamine concentrations may be affected by prenatal nicotine exposure. In conclusion, nicotine has been shown to have adverse effects on both cholinergic and catecholaminergic systems.

Causing further concern are the studies which show that exposure prenatally to environmental tobacco smoke can cause changes in brain development. For example, in a study with rhesus monkeys, Slotkin, Pinkerton, Auman, Qiao and Seidler (2002) found in those animals which had been exposed as foetuses to environmental tobacco smoke in late pregnancy and the early neonatal period, there was a marked upregulation of the nicotinic acetylcholine receptors and the effect was specific to those receptors. The upregulation of nicotine receptors is an indicator of chronic cell stimulation and is a characteristic of neuroteratogeneis caused by nicotine (Slotkin et al., 2002). In another study by Slotkin, Pinkerton, Tate and Seidler (2006b), prenatal exposure to environmental tobacco smoke was found to result in serotonin (5HT) receptor dysregulation, the overexpression of the $5HT_{1A}$ receptor changes future synaptic and behavioural 5HT responses.

In conclusion it can be seen that maternal smoking during pregnancy has negative effects on the foetus through two main pathways (Law et al., 2003). Firstly, normal placenta functioning is affected by cigarette smoke, which results in a reduction of

uterine blood flow and therefore, the infant is deprived of nutrients and oxygen. Secondly, nicotine acts as a neuroteratogen which interferes with the development of the foetus, specifically the developing nervous system. Differences have been observed in the developmental profiles of nicotine binding between species and strains and therefore this suggests that there may be genetic factors which help to regulate the maturation of nicotinic receptors and this may explain the differences in sensitivity observed among individuals, when exposed to nicotine prenatally (Ernst et al., 2001; Van de Kamp & Collins, 1994).

1.7. Prenatal Smoke Exposure and Health Problems

Prenatal exposure to tobacco has been shown to be related to many health problems including increased rates of miscarriage (George, Granath, Johansson, Olander & Cnattingius, 2006), lower birth weight (Hardy & Mellits, 1972; Kleinman & Madans, 1985; Kline, Stein & Hutzler, 1987; Pollack, Lantz & Frohna, 2000; Simpson, 1957; Wang et al., 2002; Windham, Hopkins, Fenster & Swan, 2000), change in maternal and foetal thyroid function (Shields et al., 2009) and increased rates of sudden infant death syndrome (SIDS) (Slotkin, Lappi, McCook, Lorber & Seidler, 1995). Miscarriage is believed to occur in between 12% to 15% of all recognised pregnancies (Stirrat, 1990; Wilcox et al., 1988) and George et al. (2006) have found that smoking during pregnancy increases the risk of a woman having repeated miscarriages. Maternal smoking during pregnancy has also been found to be associated with an increased risk of premature delivery, especially for women carrying twins (Pollack et al., 2000). Simpson (1957) was one of the first researchers to identify an association between smoking and low birth

weight. This finding has since been confirmed by Hardy and Mellits (1972) and Wang et al. (2002), amongst others. Hardy and Mellits (1972) carried out a longitudinal pair-matched study which found that there was significant intrauterine growth retardation in the babies of smokers. At birth, the babies of mothers who smoked were 250 grams lighter and also shorter than the babies of mothers who did not smoke and at 1 year of age the babies of smokers remained shorter than those of non-smokers. Wang et al. (2002) confirmed the findings of Hardy and Mellits (1972), showing that there was a mean reduction of 377 grams in birth weight in the offspring of mothers who had smoked continuously during pregnancy compared with those who had never smoked during pregnancy. Studies have also found a direct dose response relationship between smoking and low birth weight, for example Kleinman and Madans (1985) found that for every five additional cigarettes smoked per day the odds of offspring having low birth weight increases by 26%, a finding supported in a study by Kline et al. (1987). These findings are particularly worrying given that in the United States 65% of all infant deaths occur among low birth weight infants (Guyer, Hoyert, Martin, Ventura, MacDorman & Strobino, 1999). Maternal smoking during pregnancy has also been linked with subsequent offspring smoking behaviour. For example, Roberts et al. (2005) found that maternal smoking during pregnancy was associated with an increased risk of female but not male offspring smoking later in life with similar findings also reported by Oncken, McKee, Krishnan-Sarin, O'Malley and Mazure (2004). However, in contrast a study by Munafò, Wileyto, Murphy and Collins (2006) found evidence that maternal smoking during late pregnancy was associated with an increased likelihood of male offspring being non-smokers but there was no association for females.

1.8. Nicotine Exposure and Cardiac Activity

It is proposed that SIDS may result from cardiorespiratory failure of the infant during a hypoxic episode (Oncken et al., 2003; Slotkin, Saleh, McCook & Seidler, 1997). Nicotine exposure may lead to an increase in the risk of SIDS through its effect on cell differentiation within the adrenal medulla. Mediation of circulating catecholamines by the adrenal medulla is thought to help the infant survive hypoxic challenge (Oncken et al., 2003; Slotkin, 1998). It is suggested that further cell differentiation caused by stimulation of the nicotinic cholinergic receptors results in the disappearance of this mechanism and as nicotine mimics acetylcholine, exposure to nicotine results in this foetal/ neonatal response being lost prematurely (Oncken et al., 2003). Slotkin (1998) found that when exposed to a hypoxic environment normal control rats secreted almost 40% of the catecholamine content of the adrenal. However, it was found that rats which had been exposed to nicotine prenatally secreted almost no catecholamines and also showed a reduced sinoatrial response to adrenergic stimulation. Rats exposed to nicotine also showed changes in brainstem noradrenergic processes which, it is suggested, are likely to assist in cardiorespiratory control (Slotkin et al., 1995). Exposure to nicotine prenatally also reduces cardiac reactivity to circulating catecholamines and to sympathetic neuronal stimulation and may promote cell damage which in turn affects the reactivity to periods of hypoxia (Slotkin et al., 1997). During hypoxia control rats showed a small increase in cardiac activity followed by a slight decrease in HR; nicotine exposed rats showed an immediate and rapid decline in HR (Slotkin et al., 1997). Slotkin et al. (1997) suggest that the impairment of infants' ability to withstand hypoxic episodes, caused by nicotine,

could also explain the stable relationship between smoking and perinatal injury as child birth, like SIDS, involves hypoxic episodes. The results from these studies suggest that as the adverse effects only emerge during hypoxia and not under normal resting conditions, it is important to test the effects of exposure of the foetus to drugs and other substances using conditions which challenge physiological processes (Slotkin et al., 1997).

A number of other areas of research have also shown that cardiac activity is affected in the foetus and infant following exposure to nicotine. Ginzel et al. (2007) carried out a study looking at the effect of nicotine on both foetal HR and the adult's HR. In this study it was found that it is the effect of nicotine on the nicotinic acetylcholine receptors in the peripheral nervous system which affects heart and blood vessels, causing a change in adult HR and rhythm and an acceleration of foetal HR. Morrow, Ritchie and Bull (1988) found that after mothers smoked one cigarette during late pregnancy there was an increase in the HR of the foetus as well as a very significant rise in the systolic/diastolic velocity ratio of the umbilical artery. Browne, Colditz and Dunster (2000) found that there was a difference in blood pressure responses to tilting at postnatal days 2 and 3 and at 3 months of age between those infants that had been exposed to smoking prenatally and those that had not had prenatal nicotine exposure. Franco, Chabanski, Szliwowski, Dramaix and Kahn (2000) found that infants whose mothers had smoked during pregnancy had significantly lower high frequency powers, high frequency normalized powers and higher high frequency/low frequency power ratios in active sleep than the offspring of non-smokers. Søvik, Lossius and Walløe (2001) found that increasing the number of cigarettes smoked by the mother was correlated with deeper HR declines during hyperoxia and smaller HR rises during hypoxia and hypercapnia. Joseph,

Jackson, Westaway, Taub, Petersen and Wailoo (2007) found that infants living with at least one parent who smoked excreted higher levels of cotinine, a metabolite of nicotine, than infants in households where neither parent smoked. The authors proposed that this may have a detrimental effect on the cardiorespiratory system of the infants.

However, there are a few studies which provide contradictory findings. For example, Galland, Hayman, Taylor, Bolton, Sayers and Williams (2000) looked at HR and HR variability in infants at 1 to 4 weeks and 11 to 14 weeks of age and found that there was no difference between the smoking and non-smoking groups. Tuladhar, Harding, Cranage, Adamson and Horne (2003) also found no difference in baseline HR, maximum HR at arousal or change in HR during either active or quiet sleep state between the offspring of mothers who smoked prenatally compared with those who did not smoke. However, there were a number of limitations in these studies, such as small sample sizes and low levels of smoking in the smoking groups. Schuetze and Eiden (2006) suggest that there is sufficient evidence to suggest that measures of HR may be useful when investigating the effect of prenatal smoke exposure on autonomic functioning during early infancy.

1.9. Prenatal Smoke Exposure and Behavioural Problems

As exposure to nicotine has been shown to affect cell signalling pathways used by multiple neurotransmitters it is likely that there will be a wide range of behaviour disorders resulting from prenatal nicotine exposure (Slotkin et al., 2006a). Also, as a result of the interaction of nicotine with multiple transmitter pathways, it has been found that prenatal nicotine exposure affects the ultimate programming of synaptic capability as

well as direct developmental events in the foetal brain (Slotkin, 1998). Therefore, it is possible that problems arising as a result of exposure to nicotine may not appear until childhood or adolescence (Slotkin, 1998).

One of the first studies to investigate a possible link between maternal smoking and behaviour problems in children was carried out in 1992 by Weitzman, Gortmaker and Sobel. In this study 2256 children taking part in the National Longitudinal Survey of Youth were investigated between the ages of 4 and 11 years. Weitzman et al. (1992) considered three levels of exposure to maternal smoke: those children that had been exposed to smoke prenatally, those that had been exposed postnatally and finally those whose mothers had smoked both whilst pregnant and after the birth. The authors found that there was an increase in the rate of children's behaviour problems which was associated with all three levels of exposure to maternal smoking, providing evidence for a dose-response relationship. Fergusson, Horwood and Lynskey (1993) also compared the effect of prenatal smoking and postnatal smoking on the development of the offspring. They found evidence that smoking during pregnancy resulted in an increase in the risk of problem behaviours during childhood. Ashford, van Lier, Timmermans, Cuijpers and Koot (2008) found that the children of mothers who had smoked during pregnancy had increased levels of internalizing and externalizing problems between the ages of 5 and 8 years of age, when compared with the children of mothers who did not smoke during pregnancy. The authors found that these associations remained significant when potential confounding variables were controlled and when internalizing problems were controlled for externalizing problems and vice versa. Rasanen, Hakko, Isohanni, Hodgins, Jarvelin and Tiihonen (1999) found that at the age of 26 years, the offspring of women who

smoked during their pregnancy showed a twofold increase in violent criminal offending and Gibson and Tibbets (2000) found that maternal smoking during pregnancy interacted with absence of parents in predicting early onset offending in offspring. Nigg and Breslau (2007) found that prenatal smoking was associated with the development of ODD and CD in the offspring, even when confounding variables were controlled.

However, in contrast to the results found by Weitzman et al. (1992), smoking during pregnancy was not found to be significantly associated with an increase in childhood behaviour problems, after adjustment for confounding variables in a study by Maughan, Taylor, Taylor, Butler and Bynner (2001). Although Maughan et al. (2001) found a strong-dose response relationship between smoking during pregnancy and childhood-onset conduct problems, when controlling for a range of social background factors and maternal characteristics, they found that the pattern of results was modified, when controlling for the mother's subsequent smoking behaviour. Maughan et al. (2001) concluded that it may be persistent maternal smoking that is associated with risk for early-onset conduct problems as opposed to solely smoking during pregnancy. However, further support for a relationship between maternal smoking and the development of behaviour problems in the offspring was provided by Williams, O'Callaghan, Najman and Bor (1998). In this study evidence of a dose-response relationship was found, with higher levels of maternal smoking associated with higher levels of externalizing behaviour problems in the offspring at 5 years of age. Results from this study showed that smoking at the beginning of pregnancy was associated with subsequent behaviour problems and smoking in the later stages of pregnancy did not seem to add to the risk of the development of externalizing behaviours. Williams et al. (1998) propose that the

suggestion that mothers who smoke report the behaviours of their children differently is unlikely given that the relationship between smoking and behaviour is only observed for externalizing behaviours and not other behaviours.

Maughan, Taylor, Caspi and Moffitt (2004) used data from the Environmental Risk Longitudinal Twin Study to further investigate the relationship between maternal smoking and antisocial behaviour in offspring. Results from this study showed a strong dose-response relationship between maternal smoking and child conduct problems at ages 5 and 7 years. However, when antisocial behaviour in both parents, depression in mothers, family disadvantage and genetic influences were controlled, estimates of the effects of prenatal smoking were dramatically reduced. Rantakallio, Läärä, Isohanni and Moilanen (1992) suggested that although in their sample of 5966 males they found a higher incidence of delinquency (measured by possession of a criminal record) in the offspring of mothers who had smoked (10.3%) than those mothers who had not smoked during pregnancy (4.6%), maternal smoking may in fact be a marker of a certain life-style as opposed to having a direct causal role. Hill, Lowers, Locke-Wellman and Shen (2000) found a strong and significant positive association between maternal smoking and CD and ODD. However, when Hill et al. (2000) used a confounder score approach, these associations were not supported. When the confounding effects of both socioeconomic status and parental antisocial personality disorder were evaluated, the only relationship that remained significant was that between familial risk for alcohol dependence and ADHD. This suggests that there was not a causal relationship between prenatal smoke exposure and externalizing behaviour disorders and thus, prenatal smoke exposure was a marker of an association between familial risk for alcohol dependence and behaviour

disorders. However, there were a number of limitations of this study, the main one being that the parents and relatives of the children were selected because of problems with substance dependence and so the sample was not representative of the general population.

In a study by Fergusson, Woodward and Horwood (1998), evidence was found of a consistent dose-response relationship with an increase in cigarette exposure during pregnancy, associated with steadily increasing rates of psychiatric symptoms. When social and contextual factors were controlled, the association between maternal prenatal smoking and offspring reports of anxiety, depression, nicotine dependence, alcohol misuse and illicit drug abuse was reduced. However, maternal smoking during pregnancy remained significantly associated with conduct symptoms reported by the offspring at 18 years of age, even when the potential confounding variables were controlled. In a recent study, using a novel design, Rice, Harold, Boivin, Hay, van den Bree and Thapar (2009) found that the association between prenatal smoking and antisocial behaviour in the offspring was dependent on inherited factors. In this study, children born through IVF were studied. Children conceived through IVF can be genetically related to both parents, genetically related to only one parent or not genetically related to either parent. This allows the effect of prenatal conditions to be considered. Results from this study showed that the association between prenatal smoking and offspring antisocial behaviour was only present in mothers and offspring who were related. In contrast, low birth weight was found to be associated with prenatal smoking in both related and unrelated offspring. A similar finding has also been reported using the same novel design to investigate the relationship between prenatal smoking and ADHD (Thapar et al., in press).

Wasserman, Liu, Pine and Graziano (2001) investigated the effects of maternal smoking in a sample in Yugoslavia, in order to try and overcome the problem of studies in Western settings where smoking co-occurs with social disadvantage. In contrast to the study by Maughan et al. (2004), who found that smoking was related to social adversity, Wasserman et al. (2001) found in their sample that smoking was not related to social adversity. Results showed that maternal smoking was found to be associated with childhood behaviour problems, after controlling for a number of confounding variables, adding further evidence that the association between maternal smoking and child behaviour problems is not simply a marker for social adversity or other problems. Pickett, Wood, Adamson, D'Souza and Wakschlag (2008) carried out a study looking at women who quit smoking during their pregnancy in an attempt to untangle whether the association between maternal smoking during pregnancy and the development of problem behaviours in offspring reflects a teratological effect or is in fact a marker of maternal characteristics. Results from this study showed that women who gave up smoking during pregnancy had infants with the highest scores of easy temperament, measured using the Carey Infant Temperament Scale, and in contrast infants born to women who were heavy smokers during their pregnancy showed a more difficult temperamental profile. Therefore, the authors conclude that both maternal characteristics, which distinguish persistent smoking from quitting, and teratological effects may be operating in the association. Also, this study was carried out on 9-month-old infants suggesting that atypical behaviour as a result of persistent heavy smoking may occur during the first year of life. Support for this finding was provided by Tremblay, Nagin, Séguin, Zoccolillo, Zelazo, Boivin and Pérusse (2004). In this study it was found that infants born to women

who smoked during pregnancy showed high levels of physical aggression between the ages of 17 and 42 months, even when confounding variables were controlled. Wakschlag and Hans (2002) propose that prospective studies with measures of behaviour which are developmentally based are essential for investigating pathways from prenatal cigarette exposure to the development of clinical disorder.

Nicotine, behaviour disorders and gender. A number of researchers have only studied males when investigating the relationship between maternal smoking and problem behaviours in the offspring (Brennan, Grekin & Mednick., 1999; Rantakillo et al., 1992; Wakschlag, Pickett, Kasza & Loeber, 2006). For example, Wakschlag et al. (2006) studied males in a cohort of the Pittsburgh Youth Study. Results from this study revealed that boys who had been exposed to smoking prenatally were significantly more likely to develop ODD and comorbid ODD/ADHD but were not at an increased risk of developing ADHD on its own. Boys in this sample were also found to have an earlier onset of significant delinquent behaviour if they had been exposed to smoking in utero. Brennan et al. (1999) also investigated a male-only sample and found a dose-response relationship between the amount of prenatal smoking by mothers and arrests for both non-violent and violent crimes in the offspring.

Other studies, for example that by Weissman, Warner, Wickramaratne and Kandel (1999), have found maternal smoking has different effects on males and females. Weissman et al. (1999) found that there was a greater than fourfold increase in the risk of prepubertal-onset conduct disorder in boys and a five-fold increase risk of adolescent onset drug dependence in girls whose mothers smoked 10 or more cigarettes a day during pregnancy. In order to try and untangle any gender differences, Orlebeke, Knol and

Verhulst (1999) investigated the effect of maternal smoking on males and females. Results from this study provided further support for the finding that maternal smoking is related to externalizing behaviour problems in the offspring and also showed that although males had higher externalizing scores than females at 3 years of age, the effect of maternal prenatal smoking was the same for both genders. Maughan et al. (2001) also found that maternal smoking and its association with early-onset conduct problems was as clear for girls as it was for boys. Gibson, Piquero and Tibbetts (2000) aimed to extend previous work looking at gender differences associated with exposure to smoking, by investigating criminal behaviour, measured by age at which the participant first had contact with the police, and prenatal smoking. Results from this study showed that maternal smoking had a significant effect on the age at which offspring had their first police contact. For male offspring, maternal smoking was found to significantly predict early onset of offending but this was not found for females. However, odds ratios suggest that the effect of maternal smoking is similar across genders but the small sample size of females may have meant the effect was not detected in this sample. Biederman (2005) suggests that girls with ADHD may be under-identified and therefore, under-treated as a result of possible gender discrepancies. For example, Biederman et al. (2002) found that boys with ADHD are more at risk for comorbid disruptive behaviour disorders than girls and because referrals are usually made as a result of disruptive behaviour, this may explain why the ratio of boys to girls is higher in clinic than community samples.

1.10. Prenatal Smoke Exposure and ADHD

As cited above maternal smoking has been identified as a possible environmental cause or risk factor in the development of ADHD (Sonuga-Barker et al., 2005). There has been much research linking smoking with ADHD (Button, Thapar & McGuffin, 2005; Kotimaa et al., 2003; Linnet, Wisborg, Obel, Secher, Thomsen, Agerbo & Henriksen, 2005; Mick, Biederman, Faraone, Sayer, & Kleinman, 2002; Rodriquez & Bohlin, 2005; Thapar et al., 2003). Mick et al. (2002) carried out a case control study with 280 ADHD cases and 242 non-ADHD controls, including both males and females, and found that ADHD cases were 2.1 times more likely to have been exposed to nicotine in utero than non-ADHD controls, controlling for important potential confounders, including a comorbid diagnosis of CD. This study adds support to results found in previous studies carried out by Milberger, Biederman, Faraone, Chen and Jones (1996) and Milberger, Biederman, Faraone and Jones (1998), who found maternal smoking was associated with a 2.7-fold increase in the risk for ADHD. Another study which supports the finding by Mick et al. (2002) of a link between maternal smoking and ADHD in the offspring, which remains significant when CD is controlled, was carried out by Thapar et al. (2003). This study used a population-based twin sample and the results suggest that maternal prenatal smoking shows an association with ADHD symptoms in the offspring which are in addition to genetic factors and are not attributed to shared rater effects, clinical referral biases or covariation with antisocial behaviour. However, the design of the study meant that the intra-uterine environment shared by monozygotic twins was not controlled and this may be more similar for monozygotic than dizygotic twins. Bastra, Hadders-Algra and Neeleman (2003) found that after adjusting for confounding variables, children born to mothers who smoked during their pregnancy showed more symptoms of attention

deficit problems and exhibited higher levels of externalizing behaviours than children born to women who did not smoke during their pregnancy.

As previous studies have found evidence for a link between maternal smoking and antisocial behaviour (Brennan et al., 1999; Button et al., 2005; Wakschlag, Pickett, Cook, Benowitz & Leventhal, 2002) and hyperactivity is known to be shown in an individual before antisocial behaviour (Rutter, Giller & Hagell, 1998), Thapar et al. (2003) suggest that the link between prenatal smoking and antisocial behaviour may be mediated through hyperactivity. Thapar et al. (2003) suggest that longitudinal studies are needed to test this hypothesis. A study by Button et al. (2005) provides further data investigating the link between smoking and antisocial behaviour and whether this link is mediated by ADHD. In this study it was found that maternal smoking during pregnancy independently influences both ADHD symptoms and antisocial behaviour in the offspring, suggesting that the association of smoking during pregnancy with antisocial behaviour is not mediated through the covariation with ADHD. However, a limitation of the studies carried out by Mick et al. (2002), Thapar et al. (2003) and Button et al. (2005) was that retrospective reports of nicotine exposure were used. These reports are susceptible to recall bias, with mothers of ADHD cases potentially providing qualitatively different information from those of the controls.

To address the problem of retrospective reports of nicotine exposure, Rodriguez and Bohlin (2005) carried out a prospective study, the results of which continue to provide support for the findings by Mick et al. (2002), Milberger et al. (1996, 1998) and Thapar et al. (2003). In Rodriquez and Bohlin's (2005) study four assessments of smoking were collected on six occasions during pregnancy and the children were

followed up at 7 years of age. Results showed that prenatal exposure to smoking was associated with symptoms of ADHD in the offspring, particularly for boys, and this was independent from the finding of an association between maternal stress and subsequent ADHD symptoms in the offspring. The multiple assessments during pregnancy allowed the authors to investigate whether the timing of exposure to nicotine during pregnancy had an effect on ADHD symptoms. It was found that significant associations were present only for exposure to nicotine during the first half of the pregnancy and that later exposure did not account for any additional individual variance. Kotimaa et al. (2003) also carried out a longitudinal, prospective population based study obtaining data during pregnancy and when the children were 8 years old. Again maternal smoking during pregnancy was found to be associated with hyperactivity in the offspring, after controlling for a number of confounding variables. The results showed that there was a positive dose-response relationship between maternal smoking and hyperactivity.

Kahn et al. (2003) carried out a prospective study following infants from 6 to 60 months. Results from this study showed that those children who had been exposed to prenatal smoke and possessed the dopamine transporter (DAT) polymorphism (DAT +/+) had significantly higher hyperactive-impulsive scores. However, scores of inattention were not found to be affected. Neuman, Lobos, Reich, Henderson, Sun and Todd (2007) found that in genetically susceptible children, i.e. children who had inherited the DAT1 440 allele, maternal smoking during pregnancy was associated with specific subtypes of ADHD. Huijbregts, Séguin, Zoccolillo, Boivin and Tremblay (2007) found that although maternal prenatal smoking was not related with hyperactivity-impulsivity when it was examined as a separate variable, maternal prenatal smoking was found to predict high

levels of physical aggression, especially when it was co-occurring with high levels of hyperactivity-impulsivity. This is an important finding, given previous research which has shown that multiple behaviour problems, co-occurring at a young age are associated with a higher risk of persistent antisocial problems (Nagin & Tremblay, 1999; Lahey et al., 2000; Moffit, Caspi, Dickson, Silva & Stanton, 1996). Clearly, as suggested above, when investigating disorders such as ADHD it is important to consider the individual symptoms such as hyperactivity, impulsivity and inattention and potential precursors to disorder. This remains true when considering the link between nicotine and ADHD and other behavioural disorders, which is something few previous studies have considered.

1.11. The Effect of Prenatal Smoke Exposure on Symptoms of ADHD

Hyperactivity and impulsivity. Nicotine and its effect on activity levels in offspring has been investigated in human (Fried, Watkinson & Gray, 1992; Kristjansson, Fried & Watkinson, 1989; Naeye & Peters, 1984) and animal studies (Richardson & Tizabi, 1994; Schlumpf, Hwiler, Ribary & Lichtensteiger, 1988; Thomas, Garrison, Slawecki, Ehlers & Riley, 2000; Tizabi, Popke, Rahman, Nespor & Grunberg, 1997). Human studies have found prenatal nicotine exposure results in increased activity levels (Kristjansson et al., 1989), hyperactivity (Naeye & Peters, 1984) and increased impulsive behaviour (Fried et al., 1992). A study by Langley, Holmans, van den Bree and Thapar (2007) found that maternal smoking during pregnancy was significantly associated with greater hyperactive-impulsive symptom severity in offspring, when significant covariates were controlled. Further analysis of the results revealed a dose dependent effect with children born to mothers who smoked 10 or more cigarettes a day during their pregnancy

having more hyperactive-impulsive symptoms than those children whose mothers smoked less than 10 cigarettes a day.

Much research has investigated the link between nicotine and hyperactivity in animals. One of the first experimenters to do so was Schlumpf et al. (1988), who investigated early motor development, using an activity meter, in rats which had been exposed prenatally to nicotine. In controls, both male and females showed an increase in motor activity between postnatal days 4 and 11 which then levelled out. However, for those pups which had been exposed to nicotine prenatally, the motor activity of the male pups was significantly different from controls between postnatal days 5 and 15. In the first 7 days there was a delayed rise in motor activity of prenatally treated rats and then from day 15 the motor activity of these rats was above that of controls. This finding was supported by another study using rats by Thomas et al. (2000). In this study it was found that those offspring which were exposed to nicotine were significantly more active compared with controls. Johns, Louis, Becker and Means (1982) obtained a similar finding when studying guinea pigs which had been exposed to nicotine in utero. Richardson and Tizabi (1994) also found that exposure to nicotine prenatally resulted in a dose-dependent stimulation of locomotor activity in selective offspring. However, it was only those offspring that had been exposed to the highest dose of nicotine that showed continued hyperactivity throughout test periods. In a follow-up to this study, Tizabi et al. (1997) found no overall effect of treatment, on mean activity scores, between those groups exposed to nicotine compared with those not exposed and Paulson, Shanfeld, Vorhees, Sweazy, Gagni, Smith and Paulson (1993) also found that activity levels were not affected by exposure to prenatally administered tobacco. However, Tizabi et al.

(1997) did find that in hyperactive male offspring, which had been exposed to nicotine, there was an association with an increase in neuronal nicotinic receptors in the cortex and possibly the striatum. These results suggest that certain offspring are susceptible to behavioural and neurochemical effects of nicotine exposure in utero.

Attention. There is evidence that prenatal nicotine exposure affects attention in offspring (Cornelius, Ryan, Day, Goldschmidt & Willford, 2001; Leech, Richardson, Goldschmidt & Day, 1999; Naeye & Peters, 1984; Noland, Singer, Short, Minnes, Arendt, Kirchner & Bearer, 2005; Streissguth, Martin, Barr, Sandman, Kirchner & Darby, 1984), although other studies have found no association (Huijbregts, Séguin, Zelazo, Parent, Japel & Tremblay, 2006; Langley et al., 2007). For example, Leech et al. (1999) found that smoking during the second and third trimester predicted increased omission errors, a measure of inattentiveness, on the CPT in offspring at 6 years of age. Naeye and Peters (1984) also found that prenatal smoking resulted in a decrease in attention span in offspring and Streissguth et al. (1984) found that the use of cigarettes by mothers during pregnancy resulted in poor attention during a vigilance task in 4-year-old children. In a study by Noland et al. (2005) it was found that prenatal smoke exposure was associated with increased commission errors, which indicates poor selective attention, in a group of 4-year-olds. Cornelius et al. (2001) found maternal smoking during pregnancy was associated with an increase in perseverative errors on the Wisconsin Card Sorting Test, which is an indicator of inattentiveness.

Huijbregts et al. (2006) investigated the relationship between maternal smoking and cognitive abilities in children aged 3.5 years. Prenatal smoking was found to be associated with performance on the Wechsler Preschool and Primary Scale of

Intelligence-Revised, the Peabody Picture Vocabulary Test and the Visually Cued Recall task; an increase in prenatal smoking was associated with a decrease in performance level on the tasks. However, when maternal education was controlled, maternal smoking did not independently predict any cognitive ability. Results from this study also showed that birth weight had a small but significant effect on short-term memory and the authors suggest that prenatal smoking may effect cognitive development through birth weight. Whilst finding an association between maternal pregnancy smoking and increased hyperactivity-impulsive symptoms in their sample, Langley et al. (2007) did not find an association between maternal smoking and symptoms of inattention. However, this study was carried out on a clinical sample of children with ADHD and thus, it is not clear whether these findings generalise to a non-clinical population. Clearly more research is needed to investigate the links between nicotine and the symptoms and precursors to ADHD.

Having reviewed the current literature regarding ADHD and the possible adverse effects that may result following exposure of the foetus to nicotine, the potential link between nicotine exposure and ADHD will now be considered.

1.12. The Link between Prenatal Smoke Exposure and the Development of ADHD

One piece of evidence suggesting that there are biological mechanisms which could explain the association between prenatal nicotine exposure and ADHD, is the finding from functional and structural imaging studies that children with ADHD have a dysfunction in the fronto-subcortical pathways, which control attention and motor behaviour, and have high concentrations of catecholamines (Blum, Sheridan, Wood,

Braverman, Chen & Comings, 1995; Ernst, Zametkin, Matochik, Pascualvaca, Jons & Cohen, 1999; Farone & Biederman, 1998; Farone & Biederman, 1999), which is consistent with the finding that nicotine causes impairment of the dopaminergic system (Richardson & Tizabi, 1994; Robary & Lichtnesteiger, 1989). Wasserman et al. (2001) suggest that nicotine's interaction with brain monoamine systems could cause impairments in impulsive behaviour through the role of monoamines in the development of prefrontal-striatal circuits, specifically in the ventral-prefrontal-cortical region, which together with the striatum are thought to be involved in the inhibition of impulses and the effect of nicotine on monoamine systems could produce defects in the amygdala which in turn alters its input to the prefrontal cortex, which results in lower levels of inhibition. The reduction in noradrenergic functioning caused by nicotine would also be expected to disrupt the activity of the sympathetic nervous system (Raine, 2002). This is in line with evidence which has shown that antisocial individuals have reduced sympathetic arousal (Raine, 1996). Adding further evidence for the link between prenatal smoke exposure and the development of ADHD is the finding by Slotkin, Epps, Stenger, Sawyer and Seidler (1999) that when pregnant rats are exposed to nicotine there is an increase of cardiac M2-muscarinic cholinergic receptors. These receptors inhibit autonomic functions and therefore this may explain the link between low resting HR and externalizing behaviour disorders (Raine, 1993).

ADHD is a heritable disorder and research in recent years has begun to identify potential genes associated with the development of ADHD (Auerbach et al., 2001a, 2001b; Caspi et al., 2008; Langley et al., 2004; Payton et al., 2001; Schmidt et al., 2001; Thapar et al., 2005). However, it is important to remember that genetics cannot provide

the complete picture, as genetic factors only account for a portion in the risk of developing ADHD (Hechtman, 1994; Thapar et al., 2007a). If the genetic components of behavioural problems are linked autosomally to smoking, then they should be passed from smoking mothers and smoking fathers, to their offspring, equally (Weitzman, Byrd, Aligne & Moss, 2002). However, current research suggests that it is maternal smoking, as opposed to paternal smoking, which has a higher association with adverse outcomes in the offspring (Bastra et al., 2003; Trasti, Vik, Jacobsen & Bakketeig, 1999; Weitzman et al., 2002). If smoking by parents was simply an indicator for behavioural problems, which are genetically driven, in children, then studies should have found that both maternal smoking and paternal smoking contribute in equal amounts to negative outcomes in offspring and this has not been consistently found (e.g. Bastra et al., 2003; Weitzman et al., 2002). Therefore, as Rutter (2003) and Thapar et al. (2007b) propose it is likely that the development of ADHD in individuals is as a result of a complex interaction between gene and environment.

In conclusion, the majority of the literature supports an association between maternal smoking and subsequent behaviour disorder in offspring. The findings from several studies show that exposure to nicotine during gestation results in extensive alterations to brain structures and neurotransmitter networks and thus, highlights nicotine as a neuroteratogen (Law et al., 2003; Miao et al., 1998; Richardson & Tizabi, 1994; Robary & Lichtnesteiger, 1989; Slotkin, 1998; Slotkin et al, 1987; 1998; 2002; 2006a; 2006b; 2007; Van de Kamp & Collins, 1994). Roy et al. (1998) conclude that their results provide a precise means for linking maternal smoking with adverse neurobehavioural outcomes and that it is nicotine itself, and not psychosocial factors associated with

smoking, which is exclusively responsible for the damage observed in offspring. Evidence of structural brain abnormalities in individuals with an ADHD diagnosis (Faraone & Biederman, 1998; 1999) adds further support to the link between nicotine and ADHD.

1.13. Aims of the Thesis

In summary, there is evidence that exposure of the foetus to levels of nicotine that do not affect the survival of the foetus may lead to behavioural and attentional problems in childhood and could lead to the development of behavioural disorders, such as ADHD, with adverse effects persisting for many years. Further prospective and longitudinally designed studies are required to investigate pathways from prenatal cigarette exposure to the development of clinical disorder (Wakschlag & Hans, 2002).

Current research indicates there is a relationship between prenatal smoke exposure and the development of ADHD. When investigating pathways from prenatal smoke exposure to ADHD, the first step is to identify symptoms characteristic of children with ADHD, which can also be observed in infants during the first year of life but surprisingly, research on the early development of children who subsequently develop ADHD is scarce (Auerbach et al., 2004; 2008; Bussing et al., 2003). It is suggested that studying infant temperament is the first stage in understanding the development of ADHD (Bussing et al., 2003; Wakschlag & Hans, 2002) and it follows that the study of infant temperament is a necessary step when examining potential pathways from prenatal smoke exposure to the development of behaviour problems (Wakschlag & Hans, 2002). However, there are a number of limitations with current infant temperament research. For

example, research has been dominated by the widespread use of parent reports and although most definitions of temperament make reference to the fact that temperament has a biological basis; it is only relatively recently that the importance of having an accurate understanding of the relationship between temperament and physiology has been recognised (Nachmias et al., 1996).

Excessive motor activity and symptoms of inattention are key symptoms required for a diagnosis of ADHD and individuals with behaviour problems, including ADHD, have been shown to have disrupted cardiac activity profiles. Each of these symptoms can be observed during infancy and preschool years and so could be considered for the study of early precursors of the development of ADHD. Most major theories of temperament include scales to measure activity levels and attention and cardiac activity has been shown to be a useful index of infant temperament. Evidence from animal and human studies suggests that prenatal smoke exposure can affect attention, motor activity and cardiac activity in offspring. Thus, the goal of this thesis was to investigate domains of infant temperament that could be considered early precursors to ADHD and to examine the effect of prenatal smoke exposure on these domains.

In the first three chapters we examine the effect of prenatal smoke exposure on attention (Chapter 2), motor activity (Chapter 3) and HR (Chapter 4) in infants at 6 and 12 months. Infants were taking part in a prospective, longitudinal study; the Cardiff Child Development Study (CCDS). This sample was a large, representative, community sample recruited from antenatal clinics with assessments carried out in the home and laboratory. Attention was measured using a task adapted from the Lab-TAB (Goldsmith & Rothbart, 1999) and motor activity and HR were recorded during resting conditions and in response

to cognitive and emotional challenge. *A priori* power calculations were performed, which showed that to achieve the minimum power ($\beta = .80$) recommended by Cohen (1988), with alpha = .05 and to detect a medium effect size, a minimum sample size of 128 participants was required (Faul et al., 2007). Thus, a sample size of 130 infants was used in Chapters 2, 3 and 4. In Chapter 5 we present data from a sample who took part in a high-intensity lab-based assessment utilising more complex physiological measures; thus, enabling ECG recordings of cardiac activity to be made during resting conditions, attention, emotional challenge and a recovery period. In this chapter we focus on the study of temperament in infants, specifically using measures of cardiac activity, to enhance our understanding of the relationship between temperament and physiology and as a direction for future research of the effects of prenatal smoke exposure on infant development. Again, *a priori* power calculations were performed, which indicated a minimum sample size of 24 participants was required to achieve $\beta = .80$, alpha = .05 and to detect a medium effect size (Faul et al., 2007). Thus, a sample size of 50 infants was used in Chapter 5. The main questions this thesis set out to address were:

- Is there an effect of prenatal smoke exposure on infant attention? (Chapter 2)
- Is there an effect of prenatal smoke exposure on infant motor activity? (Chapter 3)
- Is there an effect of prenatal smoke exposure on infant HR? (Chapter 4)
- What is the role of vagal tone in the study of infant temperament? (Chapter 5)

Our subsidiary goals were (a) to examine gender differences and (b) to examine the role of parent reports in the study of infant temperament.

CHAPTER 2

ATTENTION IN INFANCY AND THE EFFECT OF PRENATAL SMOKE EXPOSURE

2.1. Introduction

2.1.1. Attention and ADHD

As the name suggests, problems with attention are a key component in the diagnosis of ADHD. Inattention, together with hyperactivity and impulsivity, must be present in high levels, and must be shown to occur across multiple situations and persist across time in order for an individual to be given a diagnosis of ADHD (Hinshaw, 1994). Studies investigating ADHD symptoms in preschoolers have found evidence of attentional problems, similar to those observed in older children (McGee et al., 1991; McGee et al., 2002; Rabiner et al., 2000). Individuals with attentional difficulties present during the preschool and early school years have been shown to be at significant risk of suffering from problems with attention and reading achievement during adolescence, even when prior reading achievement, IQ and other behavioural difficulties were controlled (Rabiner et al., 2000) and these individuals are more likely to suffer educational failure and poor psychosocial adjustment in later school years and beyond (Fergusson et al., 1997; McGee et al., 1991, 2002). Rabiner et al. (2000) concluded that children with attention problems need to be identified and monitored at an early age so that any resulting problems can be prevented. Evidence has also been found that preschoolers classified as hard-to-manage, had higher levels of inattention and lower impulse control than a group of age-matched controls (Campbell, March, Pierce, Ewing

& Szumowski, 1991; Campbell, Pierce, Moore, Marakovitz & Newby, 1996). Clearly, research studying the emergence and development of attention problems in young children is required so that individuals at risk of developing serious educational and social problems can be identified and monitored and future problems prevented.

Evidence that problems with attention are present in infants at risk for ADHD was provided by Auerbach et al. (2004, 2008). In a sample of 7-month-old infants, sustained attention was investigated by measuring object interest, using a task taken from the Lab-TAB (Goldsmith & Rothbart, 1994), comparing infants 'at risk' of ADHD, based on ADHD symptoms in the fathers, with a control group. Results showed that children in the ADHD 'at risk' group showed significantly less interest in the task than the comparison group (Auerbach et al., 2004). In a follow up study, it was found that at 7, 12 and 25 months of age, infants 'at risk' for ADHD received significantly lower scores for attentional shift and appropriate allocation of attention and inhibitory control than the comparison group (Auerbach et al., 2008). The authors propose that the results provide support for the view that there is a link between early temperament and risk for ADHD (Auerbach et al., 2008). Further support for a link between ADHD and sustained attention, was provided in another study by Auerbach and colleagues (2001a). In this study it was found that 1-year-old infants with the 7-DRD4 allele showed less sustained attention and novelty preference than infants without the allele in a structured play situation and on an information-processing task. The 7-DRD4 polymorphism has been linked with ADHD with the seven-repeat allele occurring more frequently in children with ADHD. However, a major limitation of the study by Auerbach et al. (2004, 2008)

was that the sample consisted only of boys and further studies, which include girls, are required before firm conclusions can be drawn.

2.1.2. Attention in Infancy

Attention is a basic psychological process and in recent times attention has been considered a fundamental dimension of temperament in infants and children (Rothbart & Bates, 1998; 2006). In the work by Thomas et al. (1968), distractibility was identified as a dimension of temperament and Thomas et al. (1968, p. 109) described a distractible child as "one whose attention is easily drawn away from his ongoing activity by peripheral and chance stimuli". Since the beginning of experimental psychology, attention has been considered central to human performance (James, 1890). Since then, much evidence has been provided proving the role of attention in learning and cognitive development (Gaertner, Spinrad & Eisenberg, 2008). Skills involving attention have been shown to predict a wide range of outcomes including developmental level, IQ, problem solving and language skills (Bono & Stifter, 2003; Choudhury & Gorman, 2000; Dixon & Smith, 2000; Lawson & Ruff, 2004). Attentional abilities have also been linked with other domains of functioning in young children, for example effortful control (Kochanska, Murray & Harlan, 2000), compliance (Hill & Braungart-Rieker, 2002), delay of gratification (Mischel, Ebbesen & Raskoff Zeiss, 1972) and emotion regulation and social adjustment (Eisenberg, Fabes, Guthrie & Reiser, 2000). Emde and Robinson (1978) suggest that an infant's ability to shift visual attention is vital for the development of the infant's own control of sensory stimulation from the environment.

Research has shown that individual differences in attention can be clearly observed and measured during the first year of life (Auerbach et al., 2008). By 10 months of age, infants have been shown to display consistent individual differences in vigilant behaviour (Ruff, Capozzoli, Dubiner & Parrinello, 1990). Measures of duration of looking and facial expressions of interest are indicators of focused attention (Auerbach et al., 2004) and can be seen clearly when infants and young children explore and manipulate toys (Ruff & Rothbart, 1996). Measures of attention have been shown to be stable across time (Gaertner et al., 2008; Lawson & Ruff, 2001; Ruff & Dubiner, 1987) and parent reports of infant and toddler attention have been shown to be reliable and stable (Goldsmith, 1996; Rothbart, 1981; Rothbart, Derryberry & Hershey, 2000). O'Sullivan and Berthier (2003) investigated the relationship between visual attention, action and heart rate (HR) during a reaching task in 7.5-month-old infants. They found that during reaching and looking trials infants showed prolonged looking and large HR decelerations. From these results the authors conclude that the autonomic and behavioural changes seen in attention to simple visual displays are not prevented by overt action itself and attention is maintained throughout the act of reaching.

2.1.3. Effect of Prenatal Smoke Exposure on Attention

Several studies have shown that maternal smoking during pregnancy results in a decrease in performance on a range of tasks designed to measure attention in the offspring (see Chapter 1, section 1.11). Leech et al. (1999), Naeye and Peters (1984), Noland et al. (2005) and Streissguth et al. (1984) all found that children who had been exposed to prenatal maternal smoking had poorer performance on measures of attention

than children who had not been exposed to smoking during pregnancy. Schmitz et al. (2006) found that children born to women who smoked 10 or more cigarettes a day during pregnancy were significantly more likely to develop ADHD, predominantly inattentive subtype than children with no smoke exposure. Huijbregts et al. (2006) found that exposure to prenatal smoking resulted in a decrease in performance on a series of cognitive tasks in a sample of 3.5-year-olds. However, when education of the mother was controlled it was found that maternal smoking during pregnancy did not independently predict cognitive ability. Weissbluth and Liu (1983) studied attention in infants and found that maternal smoking during pregnancy did not affect attention span. Langley et al. (2007) also found no association between maternal smoking and inattention symptoms; however, this was a clinical sample of children between the ages of 6 and 16 years and therefore, it is not clear whether the results generalise to a normal population or whether the same pattern of results would be observed in infants.

Attention is clearly an important symptom in the diagnosis of ADHD and there is a body of research which suggests that maternal prenatal smoking is associated with ADHD (see Chapter 1, section 1.10). However, studies investigating potential links between maternal smoking during pregnancy and attention symptoms in offspring have provided conflicting results and have largely focused on symptoms in preschoolers and older children, for example, the children in the study by Leech et al. (1999) were 6 years old and 4-year-olds were studied by Noland et al. (2005) and Streissguth et al. (1984). Therefore, in order to fully investigate the potential link between maternal smoking during pregnancy and the development of ADHD in offspring, studies need to compare

attention in infants who have been exposed to smoke in utero with infants who have not had prenatal smoke exposure.

2.1.4. The Current Study

The aim of the current chapter was to study infants' attention at 6 and 12 months, with specific interest in the role of prenatal smoke exposure and the effect this has on infants' attention. A task adapted from the Lab-TAB (Goldsmith & Rothbart, 1999) was used to measure infant attention. The Lab-TAB has been described as a crucial development for research studying individual differences (Kagan, 1992) and several researchers have used episodes from the interest section of the Lab-TAB to successfully measure attention in infants and young children (e.g. Auerbach et al., 2004, 2008; Gaertner et al., 2008; Kochanska, Coy, Tjebkes & Husarek, 1998). For the purposes of the current study the 'toy interest game' was used and this was carried out in the home at 6 months and in the laboratory at 12 months. The 'duration of orienting' subscale from the IBQ was included at 6 months as a measure of individual differences in infant attention reported by mothers, fathers and a third person who knew the infant well.

Studies examining the link between prenatal smoke exposure and attention in offspring have found mixed results and have generally focused on preschool and older children (see sections 1.11. and 2.1.3.). Therefore, the current study was one of the first studies to examine the development of attention in infants comparing those infants born to women who smoked during pregnancy with those infants born to women who did not smoke during pregnancy. This is important given that more research is needed which uses a prospective design to study the pathways from prenatal smoke exposure to the

development of a clinical disorder (Wakschlag & Hans, 2002). In the current study, it was hypothesised that infants born to mothers who reported smoking during pregnancy would have lower scores on both the Lab-TAB measure of attention at 6 and 12 months and the IBQ measure of 'duration of orienting' at 6 months compared with infants whose mothers did not smoke during pregnancy. There is some evidence from animal research that the quantity and timing of the exposure of the offspring to nicotine in utero may affect developmental outcomes. Therefore, two additional analyses were carried out. In the first of these we created 'heavy smoking' and 'light smoking' groups based on the number of cigarettes the women reported smoking during their pregnancy and compared these two groups with the 'non-smoking' group. It was hypothesised that infants in the 'heavy smoking' group would show poorer attention than infants in the 'light smoking' group who in turn would show poorer attention than infants in the 'non-smoking' group, based on previous studies showing a dose-response association (Fried, Watkinson & Gray, 1992). In the second set of analyses, the timing of the smoke exposure was considered and the smoking group was split into two groups based on whether the woman had smoked only in the first trimester or had smoked throughout her pregnancy. It was predicted that infants who had been exposed to nicotine throughout the pregnancy would show lower attention scores than infants in the other groups because previous research has indicated that exposure during the later stages of pregnancy is especially harmful (e.g. Day, Richardson, Goldschmidt & Cornelius, 2000; Leech et al., 1999).

A review of the literature found that research investigating gender differences in attention in infants was scarce. Therefore, the current study was one of the first to examine whether there was a difference in attention between girls and boys at 6 and 12

months. In the 1970s, Gallas and Lewis (1977) found no sex differences on the Mental Development Index (MDI) of the Bayley Scales of Infant Development in infants at 12 weeks of age. More recently, Karass, Braungart-Rieker, Mullins and Lefever (2002) found no gender differences in infants at 4, 8, 12 and 16 months on the 'duration of orienting' subscale of the IBQ and on a composite measure of manipulative exploration, which was taken from the Infant Behaviour Record of the Bayley Scales of Infant Development and included a measure of attention span. In a meta-analysis of studies of children ranging in age from 3 months to 13 years, Else-Quest et al. (2006) found that in two of the four attention span dimensions studied, girls scored higher than boys and overall the results indicated that girls may be better at regulating and allocating attention compared with boys. Thus, we examined whether there was evidence of gender differences in infant attention at 6 and 12 months.

It was predicted that attention scores on the Lab-TAB would increase between 6 and 12 months of age. During the first year of life, attentional orienting has been described as following a U-shape (Ruff & Rothbart, 1996). For example, Carranza, Perez-Lopez, Gonzalez and Martinez-Fuentes (2000) found that scores on the 'duration of orienting' subscale of the IBQ decreased between 6 and 9 months but increased between 9 and 12 months. Posner and Rothbart (1991) and Gartstein and Rothbart (2006) propose that maturational changes occurring in the executive attention system during the end of the first year of life may contribute to the plasticity of orienting reactions, which in turn may account for the changes seen in infant attention during the second half of the first year of life.

The Lab-TAB was designed to fit closely with Rothbart's view of temperament and research suggests that temperamental subscales of the IBQ and the Lab-TAB are correlated. For example, Bridges et al. (1993) found positive correlations between the 'distress to limitations' subscale of the IBQ and a Lab-TAB measure of anger. Similar positive correlations were found between the 'smiling and laughter' and 'duration of orienting' subscales of the IBQ and the facial pleasure expression measure of the Lab-TAB. Hane, Fox, Polak-Toste, Ghera and Guner (2006) also found evidence that maternal and observer ratings of infant negativity were correlated when infants displayed high levels of negative affect during routine activities at home. These findings suggest that laboratory observations and maternal reports of temperament provide important but non-overlapping information about infant behaviour (Mangelsdorf, McHale, Diener, Goldstein & Lehn, 2000). However, Mangelsdorf et al. (2000) found few associations between temperament observed in the laboratory and maternal ratings of temperament. The current study aims to investigate these discrepancies. Given the similarities of the method used in the current study with that used by Bridges et al. (1993), it was hypothesised that in the current study there would be positive correlations between the 'duration of orienting' scale of the IBQ and Lab-TAB attention measure at 6 months.

2.2. Method

2.2.1. Participants

Participants were taking part in the Cardiff Child Development Study (CCDS), a prospective longitudinal study of 332 first-time parents, followed from the third trimester of pregnancy until the child reached pre-school years. In total 5 assessments took place; the first during the third trimester of pregnancy, the second when the child was 6 months of age, the third when the child was 12 months of age, the fourth when the child was between 18 and 24 months of age and the final assessment took place when the child was between 30 and 36 months of age.

Recruitment took place in hospital and general practice antenatal clinics in South East Wales between the 1st November 2005 and 31st July 2007. In the UK, women attend hospital antenatal clinics at 12 and 20 weeks of pregnancy for antenatal scans and therefore recruitment was predominantly focussed at 4 hospitals in the Cardiff and Vale and Gwent NHS trusts. In order to increase the diversity of the sample, additional recruitment was also carried out by a team of midwives who supported families who were vulnerably housed.

At the antenatal clinics, trained researchers approached first-time mothers and their partners, if they were present. The researchers briefly outlined the study and gave the mothers a detailed brochure, which provided further information about the aims and procedures used in the study. A short DVD, containing clips of the methods used in the study, was also available for researchers to show prospective participants. If the women expressed an interest in the study, they were asked to provide their contact details and the

project administrator called them within 2 weeks of the initial contact to answer any further questions. Parents who wanted more time to read the brochure and discuss their participation, were given a stamped addressed envelope upon which they could provide their contact details and post to the project administrator. If the families agreed to take part when called by the project administrator, an appointment was made for researchers to visit the family during the third trimester of the pregnancy to carry out the antenatal interview.

No exclusion criteria were used in the study, except for miscarriage or infant death. Translators were used for families who were not able to speak English and for those participants whose hearing was impaired. All analyses presented here focus on a subsample of 130 families taking part in the CCDS; selected because the infants turned 12 months of age before a specified cut-off date, with an over-sample of mothers who reported smoking during pregnancy. Fifty-nine mothers reported smoking during pregnancy and 71 mothers reported not smoking during pregnancy. In the complete CCDS sample there were 76 women who reported smoking. The smoking group used in the current study did not differ from the smokers not included in the sample on a variety of socio-demographic variables (see Table 2.1). Analyses reported will focus on data collected from the 6 month and the 12 month assessments, with maternal smoking data collected at the antenatal assessment.

Characteristics of the sample are in line with those found in the UK population. In the current sample, the mean age at first birth was 27.5yrs (SD = 6.26; range from 16.6 to 41.8), which is close to the UK average in 2002 of 27.3 years (http://www.statistics.gov.uk, retrieved Jan 2009). In the UK, 44.3% of births occur

outside of marriage (http://www.statistics.gov.uk, retrieved Jan 2008) and again the current sample lines up with this, with 55.4% of births occurring outside marriage. Based on the Standard Occupational Classification 2000 (http://www.statistics.gov.uk, retrieved Jan 2008), 50.8% of the current sample was classified as middle class.

Comparing women who reported smoking during pregnancy with women who did not smoke during pregnancy in the current sample, it was found that smoking mothers were significantly younger, were less likely to be married and more likely to be working class than non-smoking mothers. There were no differences in ethnicity between the smoking and non-smoking groups (see Table 2.2.).

Of the 130 women in the current sample, 2 women gave birth to twins. For the purposes of the current study, one twin was randomly selected to take part. Of the infants, 73 were male and 57 were female.

Table 2.1: Socio-demographic Variables for Smokers in Sample and Smokers not included in Sample

	Smokers in Sample (n=59)	Smokers not in Sample (n=17)	Test Statistics
Maternal age at 1st birth	24.04	21.94	t (74) = -1.36, p=.18
Married (%)	11.9	11.8	χ^2 = 0.76, p=.94
Working class (%)	72.9	82.4	χ^2 = 0.63, p=.54
British (%)	93.1	100	χ^2 = 1.24, p=.54

Table 2.2: Socio-demographic Variables for Non-Smokers and Smokers in Sample

	Non-smokers (n=71)	Smokers (n=59)	Test Statistics
Maternal age at 1st birth	30.34	24.04	t (128) = 6.59, p<.001
Married (%)	71.8	11.9	χ^2 = 52.40, p<.001
Working class (%)	29.6	72.9	χ^2 = 24.18, p<.001
British (%)	85.9	93.1	χ^2 = 3.84, p=.44

2.2.2. Measures

Nicotine during pregnancy. In the questionnaire given as part of the antenatal assessment, women were asked to report whether they had smoked cigarettes during their pregnancy. In the current study, 59 participants reported that they smoked during their pregnancy ('smoking' group) and 71 women reported that they did not smoke during their pregnancy ('non-smoking' group). Research suggests that self-report measures of smoking are as effective as more complicated and expensive measures incorporating biological assays of smoking (Pickett et al., 2009).

Women who reported smoking during their pregnancy were asked to specify on average the number of cigarettes smoked per day for each of the 3 trimesters of their pregnancy. It was necessary to obtain a figure for each of the 3 trimesters because maternal smoking during pregnancy has been shown to fluctuate substantially (Pickett, Wakschlag, Dai & Leventhal, 2003). The number of cigarettes smoked per day was correlated across the 3 trimesters (minimum $r = .46$, $p<.001$) and a composite measure of the mean number of cigarettes smoked per day throughout the pregnancy was created. Since there are no government guidelines describing how to classify the number of cigarettes smoked per day during pregnancy as heavy or light smoking, 3 groups were created consistent with literature in this area (e.g. Fergusson et al., 1998; Pickett, Wood, Adamson, DeSouza & Wakschlag, 2008; Schmitz et al., 2006). Based on the composite measure of mean number of cigarettes smoked per day during pregnancy, mothers in the 'smoking' group were classified as either 'light smoking' (mothers who smoked between 1 and 9 cigarettes a day; $n = 39$) or 'heavy smoking' (mothers who smoked an average of 10 or more cigarettes per day; $n = 17$). The 'light smoking' and 'heavy smoking' groups

were compared with the 'non-smoking' group. Three participants had missing data for these variables and so could not be included in the composite measure. One participant had missing data for the questionnaire item "number of cigarettes smoked during late pregnancy" and therefore this item was prorated and the participant included in the composite measure.

As different patterns of smoking were observed, for example, some women smoked low numbers of cigarettes throughout pregnancy and others smoked heavily during early pregnancy, an additional variable was created based on the timing of the cigarette use within pregnancy. For this variable the 'smoking' group was subdivided into 2 groups: '1st trimester' (mothers who only smoked in the first trimester, n = 15) and 'all trimester' (mothers who smoked in all 3 trimesters, n = 33). The '1st trimester' and 'all trimester' groups were compared with the 'non-smoking' group. Eight participants could not be classified into one of these 3 groups and a further 3 participants had missing data; all of these women were excluded for the analyses involving this variable.

Thus, the study factor (smoking during pregnancy) was defined in three ways; the first variable was dichotomous (non-smoking/ smoking) and the other two variables were categorical (non-smoking/ light smoking/ heavy smoking and non-smoking/ 1st trimester/ all trimester). Although there was inevitably some overlap between participants in the light smoking/1st trimester and heavy smoking/all trimester groups, it was not the case that the groups were exact replicas and the creation of smoking groups based on quantity and timing of smoke exposure allowed more detailed analysis of the effect of smoke exposure on offspring development.

Attention. This task was used at both the 6 and 12 month visit. The task was adapted from the 'toy interest game' task described in the interest/ persistence episodes section of the Laboratory Temperament Assessment Battery [Lab-TAB] manual (Goldsmith & Rothbart, 1999). The Lab-TAB was designed with the aim of providing a standardized instrument for the laboratory assessment of early temperament. The Lab-TAB was originally designed to be carried out in the laboratory. However, for the purposes of the current study, this task has been adapted so that it could be used in the home at the 6 month visit. Previous researchers have conducted items from the Lab-TAB successfully at home (e.g. Clark, Kochanska & Ready, 2000; Forman, O'Hara, Larsen, Coy, Gorman & Stuart, 2003) and indeed Clark et al. (2000, p. 276) report that they "consulted with Goldsmith and learned that the *(Lab-TAB)* paradigm had been conducted at home with good results".

The rationale for this task is that an object elicits interest with an electronic sound and light display, which is novel but not threatening. In this study an age-appropriate turtle toy was used at 6 months and a rocket toy was used at 12 months. Both the turtle and rocket toy emit sound and light when manipulated. The researcher placed the toy in front of the child and said "Look what I have for you to play with. Let me show you how it works." The researcher then pressed the toy so that sound and light were emitted. The child was then left undisturbed and allowed to manipulate the toy for 3 minutes. Parents were asked to be minimally responsive throughout the task.

The task was coded from the video, using the Lab-TAB scoring procedure by 2 researchers who were blind to the group status of the infants. The 3 minute task was divided into 3, 1 minute intervals, which were then subdivided into 10 second epochs.

The infant variables coded were 'intensity of facial interest' and 'duration of looking'. 'Intensity of facial interest' was coded on a 3-point scale ranging from (0) "no facial region shows codable interest, infant is not looking at stimulus" to (2) "a definite facial indication of interest occurs or coder otherwise has impression of strong facial interest". 'Duration of looking' was coded on a 4-point scale ranging from (0) "does not look at all" to (3) "child spends 9-10 seconds looking at item". At the 6 month assessment the intra-class correlations were .72 for 'duration of looking' and 'intensity of facial interest' and at the 12 month assessment the intra-class correlations were .83 for 'duration of looking' and .72 for 'intensity of facial interest'. Since the variables were found to be highly correlated (6 mths $r = .51$, $p<.001$; 12 mths $r = .65$, $p<.001$) they were added together to form a composite variable called "attention". Therefore, the 'attention' variable used in the current study ranged from (0) no attention to stimulus to (5) maximum level of attention.

Infant Behavior Questionnaire (IBQ). The current chapter focused on the 'duration of orienting' subscale of the IBQ, which is described as "the child's vocalization, looking at, and/or interaction with a single object for extended periods of time when there has been no sudden change in stimulation" and is accepted as a measure of attention (Rothbart, 1981, p. 573). The 'duration of orienting' subscale consisted of 11 items with a Cronbach's α .80 for mothers, .79 for fathers and .86 for significant others. The subscale was created by taking the mean of the items, which made up the subscale and therefore, the subscale ranged from (0) no duration of orienting to (7) maximum level of duration of orienting. The responses of the mother, father and significant other on the IBQ were found to be positively correlated (minimum $r = .40$, $p<.01$) and therefore,

composite scores were created by calculating a mean, using the mother, father and significant other scores, which allowed the sample size to be increased.

2.2.3. Procedure

The School of Psychology Cardiff University Ethics committee and the Multi-Centre Research Ethic Committee for Wales approved all of the procedures used in the CCDS. At each assessment, fully-informed written consent was obtained from all participants in the study. Participants also gave consent at each assessment to be contacted again for the next assessment. All assessments were conducted by research assistants who held a first degree in Psychology.

The antenatal assessment. The antenatal assessment took place in the participants' home, where this was not possible arrangements were made for the visit to take place in the School of Psychology, Cardiff University. The interview was carried out during the third trimester of pregnancy and lasted for approximately 2 hours. Each family was given £20 in gift vouchers for their involvement at this stage of the study. Following the interview, participants were asked to complete a questionnaire and return it to the university in a stamped addressed envelope. A telephone number and email address were also given, which could be used if participants needed help completing the questionnaire. The questionnaire included questions regarding socio-demographic information, relationship status and the use of substances (e.g. nicotine).

The 6 month assessment. The 6 month assessment was scheduled to take place when the infant was between 6 and 9 months of age (M = 6.55, SD = 0.76, range 5.30 to 9.87). The assessment took place in the participants' home and lasted for approximately 2

hours. Families were given £20 in vouchers for their participation at this stage of the study. The visit took place with the primary caregiver of the infant. The visit consisted of two parts; the baby assessment and an interview with the primary caregiver. The baby assessment lasted for approximately 20 minutes and consisted of a series of tasks, which included: toy interest game and restraint in a car seat task (adapted from the Lab-TAB; Goldsmith & Rothbart, 1999). All tasks were recorded using a handheld camera mounted on a tripod. Throughout the baby assessment an ActiTrainer was attached to the infants, which measured HR and motor activity.

The 12 month assessment. The 12 month assessment was scheduled to take place when the infant was between 11 and 16 months of age (M = 12.98, SD = 1.14, range 11.07 to 16.17). For this assessment participants were invited to the School of Psychology at Cardiff University, Wales. Participants were offered a taxi to transport them to the visit or had their parking or public transport costs reimbursed as well as receiving £20 in vouchers for taking part in this assessment. Three participants were invited to each assessment. If a mother was not able to accompany her child to the visit, the father or another caregiver were invited to attend. The visit took the theme of a birthday party. Throughout the visit the infants wore an ActiTrainer, measuring HR and motor activity. The initial part of the visit consisted of approximately 20 minutes of individual cognitive assessments, administered by a trained researcher, which included the toy interest game (adapted from the Lab-TAB; Goldsmith & Rothbart, 1999). All tasks were recorded using a handheld camera mounted on a tripod.

In the second part of the visit all 3 infants plus their caregivers were invited into a playroom. The infants were given approximately 10 minutes to adjust to being in the

room before the birthday lady entered. The birthday lady was a trained researcher dressed in a medieval costume. The birthday lady announced the start of the party and began setting out a picnic, consisting of play food items. The birthday lady asked all infants to sit around the picnic blanket and all parents to return to one of the sofas in the room. A researcher dressed in a full bear costume then entered the picnic. The birthday lady and bear performed a dance whilst singing "Round and Round the Garden" before offering each infant, with the help of their parent, the opportunity to dance with them and tickle the bear at the end of the song. Once each baby had danced with the birthday lady and bear, the bear offered to shake hands with each baby in turn and then left the play room. Throughout the procedure, parents were instructed to act as they normally would when their baby came into contact with a novel character or event. The visit concluded with a lucky dip, in which the infants were each given an age appropriate book. The whole procedure was filmed using two wall mounted cameras which were controlled from behind a one way mirror.

2.2.4. Data analysis

At the 6 month assessment, there were no participants with missing data on the Lab-TAB attention measure and for the IBQ measure there were 107 infants with at least one informant and therefore, 23 participants had missing data on this measure. The reasons for the missing IBQ data were either participant refusal or the questionnaires were misplaced in the postal system. At the 12 month assessment, 16 participants had missing data on the Lab-TAB attention measure; 13 of these did not attend the assessment and the remaining 3 could not be coded because of a fault with the video

recording. Table 2.3 shows the total number of participants in each of the smoking subgroups for the Lab-TAB and IBQ measures.

Table 2.3: Number of Participants in Smoking Groups for Lab-TAB and IBQ Attention Measures

	Attention (Lab-TAB)		Duration of orienting (IBQ)
	6 mth	12 mth	6 mth
Non-smoking	71	67	67
Smoking	59	47	40
Light smoking	39	29	29
Heavy smoking	17	12	8
1st trimester	15	15	10
3 trimester	33	25	22

The data were screened for violations in the assumptions of parametric tests, i.e. it was verified that the data in each of the cells were normally distributed and the variances in each of the cells were not different from each other. Extreme outliers were removed from analyses and in analyses where the homogeneity of variance assumption was violated a more conservative F-test was used (Greenhouse-Geisser). The LSD test was used to follow up any significant ANOVA results. A significance level of $p<.05$ was adopted throughout this paper but trends up to $p<.10$ were also indentified.

Age of infant was not correlated with attention as measured by the Lab-TAB at the 6 ($r = -.11$, $p=.36$) or 12 ($r = .01$, $p=.95$) month assessments. There was a low correlation between age of infant and attention as measured by the IBQ ($r = -.25$, $p<.05$).

2.3. Results

2.3.1. Analyses at 6 Months

Effect of prenatal smoke exposure. In the first set of analyses, infants born to mothers who reported smoking during pregnancy were compared with infants born to mothers who did not smoke during pregnancy. An independent samples t-test revealed there was a significant difference between the 'smoking' ($M = 3.64$, $SD = 0.72$) and 'non-smoking' ($M = 3.16$, $SD = 0.75$) groups ($t(128) = -3.73$, $p<.001$), with the 'smoking' group having a higher mean score on the Lab-TAB attention measure. No correlation was found between behavioural observations and parental reports of infant attention ($r = -.01$, $p=.92$). The analysis was repeated comparing scores on the duration of orienting subscale of the IBQ between the 'smoking' and 'non-smoking' groups. An independent samples t-test revealed that there was a marginal difference between the 'smoking' ($M = 4.62$, $SD = 1.00$) and 'non-smoking' ($M = 4.26$, $SD = 0.95$) groups ($t(105) = -1.83$, $p=.07$), with the 'smoking' group having a higher score than the 'non-smoking' group.

In the second set of analyses the number of cigarettes the mother reported smoking during her pregnancy was considered. The 'smoking' group was divided into the 'light smoking' and 'heavy smoking' groups and these two groups were compared with the 'non-smoking' group (see section 2.2.2. for full explanation). A one-way ANOVA revealed there was a significant difference between the 3 smoking groups ($F(2, 124) = 8.77$, $p<.001$) on the Lab-TAB measure of attention. Planned comparisons showed that there was a significant difference between the 'non-smoking' and 'light smoking' groups ($p<.001$) and a significant difference between the 'light smoking' and 'heavy smoking'

groups ($p<.05$). Table 2.4 shows that the 'light smoking' group had a higher mean score on the Lab-TAB attention measure than the 'non-smoking' and 'heavy smoking' groups. When looking at the duration of orienting subscale of the IBQ, a one-way ANOVA revealed there were no significant differences between the three smoking groups ($F(2, 101) = 2.27$, $p=.11$; see Table 2.4).

Table 2.4: Mean Attention Scores for Lab-TAB and IBQ for 'Non-Smoking', 'Light Smoking' and 'Heavy Smoking' Groups at 6 Months[a]

	Non-smoking (n=71)		Light smoking (n=39)		Heavy smoking (n=17)	
	M	SD	M	SD	M	SD
Attention (Lab-TAB)	3.16	0.75	3.77	0.78	3.33	0.53
Duration of orienting (IBQ)	4.26	0.95	4.60	0.19	4.88	0.99

[a] The n varies for Lab-TAB and IBQ variables because of missing data

In the third set of analyses, the timing of the smoke exposure during the pregnancy was considered. As described in section 2.2.2, the 'smoking' group was divided into the '1st trimester' and 'all trimester' smoking groups, which were compared with the 'non-smoking' group. A one-way ANOVA revealed that there was a significant difference between the 3 groups ($F(2, 116) = 9.35$, $p<.001$). Planned comparisons revealed that there was a significant difference between the 'non-smoking' and '1st trimester' groups ($p<.001$) and a significant difference between the 'non-smoking' and 'all trimester' groups ($p<.01$), with the 'non-smoking' group having a lower mean attention score than the '1st trimester' and 'all trimester' smoking groups (see Table 2.5). A one-way ANOVA revealed that there was no significant difference between the 3

groups on the duration of orienting subscale of the IBQ (F (2, 96) = 1.82, p=.17; see Table 2.5).

Table 2.5: Mean Attention Scores for Lab-TAB and IBQ for 'Non-Smoking', '1st Trimester' and 'All Trimester' Groups at 6 Months[a]

	Non-smoking (n=71)		1st trimester (n=15)		All Trimester (n=33)	
	M	SD	M	SD	M	SD
Attention (Lab-TAB)	3.16	0.75	3.95	0.77	3.6	0.65
Duration of orienting (IBQ)	4.26	0.95	4.79	1.05	4.58	1.07

[a] The n varies for Lab-TAB and IBQ variables because of missing data

2.3.2. Analyses at 12 Months

Effect of prenatal smoke exposure. When comparing infants born to smokers with infants born to non-smokers, an independent samples t-test revealed there was no significant difference between the 'non-smoking' (M = 3.88, SD = 0.74) and 'smoking' (M = 3.99, SD = 0.83) groups (t (111) = -0.71, p=.48) on the Lab-TAB attention measure.

In the second analysis, the quantity of cigarettes consumed by the mother during pregnancy was considered. A one-way ANOVA showed that there was no significant difference between the 'non-smoking' (M = 3.88, SD = 0.74), 'light smoking' (M = 4.04, SD = 0.94) and 'heavy smoking' (M = 3.87, SD = 0.70) groups (F (2, 107) = 0.46, p=.64).

In the third analysis, the timing of the smoke exposure during pregnancy was considered. A one-way ANOVA revealed that there was no significant difference between the smoking groups (non-smoking: M = 3.88, SD = 0.74; 1st trimester: M = 3.70, SD = 0.90; all trimester: M = 4.10, SD = 0.71; F (2, 100) = 1.27, p=.29)

2.3.3. Attention at 6 and 12 Months

Effect of time. When considering only infants born to non-smoking women, infant attention was not correlated at 6 and 12 months ($r = .18$, $p=.15$). A paired samples t-test revealed that there was a significant difference between attention at 6 ($M = 3.15$, $SD = 0.77$) and 12 ($M = 3.88$, $SD = 0.74$) months ($t(65) = -6.15$, $p<.001$), with infants at 12 months receiving a higher score on the Lab-TAB measure of attention than infants at 6 months. When considering only infants born to women who smoked during their pregnancy, it was again found that attention was not correlated at 6 and 12 months ($r = .15$, $p=.31$). A paired samples t-test confirmed that there was a significant difference in attention between infants at 6 and 12 months (6 mths: $M = 3.61$, $SD = 0.72$; 12 mths: $M = 3.99$, $SD = 0.83$; $t(46) = -2.57$, $p<.05$).

Effect of gender. Looking only at infants in the non-smoking group, independent t-tests showed there were no significant differences in attention between girls and boys at 6 months (girls: $M = 3.08$, $SD = 0.85$; boys: $M = 3.22$, $SD = 0.67$; $t(69) = -0.77$, $p=.44$) but a marginal difference was found at 12 months (girls: $M = 3.70$, $SD = 0.80$; boys: $M = 4.05$, $SD = 0.65$; $t(64) = -1.93$, $p=.06$), with boys receiving higher scores on the Lab-TAB attention measure than girls. Next, we looked only at infants in the 'smoking' group and independent t-tests showed that there was no significant difference in attention between girls and boys at 6 (girls: $M = 3.64$, $SD = 0.64$; boys: $M = 3.65$, $SD = 0.78$; $t(57) = -0.06$, $p=.95$) and 12 (girls: $M = 4.06$, $SD = 0.96$; boys: $M = 3.94$, $SD = 0.75$; $t(45) = 0.51$, $p=.61$) months.

2.4. Discussion

The aim of the current chapter was to investigate attention in infants at 6 and 12 months of age and to examine the effect of prenatal exposure to nicotine on attention development. Attention was measured using the 'toy interest game' adapted from the Lab-TAB (Goldsmith & Rothbart, 1999). At 6 months we also included the IBQ, which allowed us to compare infant attention as reported by observers with parent reports. The hypotheses were that (a) infants born to mothers who smoked during their pregnancy would show lower levels of attention compared with infants born to non-smoking mothers, (b) there would be a positive correlation between the Lab-TAB and IBQ measures of attention at 6 months, (c) are there gender differences in infant attention? and (d) scores on the Lab-TAB measure of attention would increase from 6 to 12 months.

Does prenatal smoke exposure affect infant attention? As reviewed in the Introduction (see section 2.1.3), previous research has found mixed findings when looking at the effect of maternal smoking during pregnancy on attention in offspring. Studies by Leech et al. (1999), Naeye and Peters (1984), Noland et al. (2005), Schmitz et al. (2006) and Streissguth et al. (1984) found decreased attention in children born to mothers who smoked during their pregnancy compared with controls. However, other studies suggest that there may be no association between maternal prenatal smoking and offspring attention (e.g. Langley et al., 2007; Weissbluth & Liu, 1983) or that maternal smoking during pregnancy does not independently predict cognitive ability (Huijbregts et al., 2006). Langley et al. (2007) concluded that their finding was in line with prior twin studies, which have shown that common environmental factors, such as maternal smoking during pregnancy, exert a greater influence on hyperactive-impulsive symptoms

than symptoms of inattention (Hay, Bennett, Levy, Sergeant & Swanson, 2007). Langley et al. (2007) suggest that these results provide support for the distinction of subtypes of ADHD and they suggest that both environmental and genetic factors may contribute to the heterogeneity in phenotypes of ADHD. However, Schmitz et al. (2006) found that children whose mothers smoked 10 or more cigarettes a day during pregnancy showed higher inattentive scores and were more likely to develop ADHD, predominantly inattentive type, than children with no smoke exposure. A limitation of past research is that the majority of studies have focused on preschoolers and older children and only the study by Weissbluth and Liu (1983) looked at attention in infants during the first year of life.

It was hypothesised that infants who had been exposed to nicotine in utero would show lower levels of attention compared with infants with no prenatal nicotine exposure. However, the results did not support our hypothesis. At the 6 month assessment, we found that infants born to women who smoked during pregnancy received higher scores on the Lab-TAB and IBQ measures of attention and at 12 months there was no difference between the 'non-smoking' and 'smoking' groups. We also predicted that there would be a dose-response effect with infants in the 'heavy smoking' group showing poorer attention than infants in the 'light smoking' and 'non-smoking' groups. At 6 months we found that infants in the 'light smoking' group received higher attention scores on the Lab-TAB measure of attention than infants in the 'non-smoking' and 'heavy smoking' groups and at 12 months there were no significant differences between the smoking groups. When the timing of the smoke exposure was considered, we predicted that infants exposed to nicotine throughout gestation would show poorer attention than infants with

early and no smoke exposure. In contrast, our results showed that at 6 months the infants born to women who did not smoke during pregnancy received lower scores on the Lab-TAB attention measure than infants born to women who smoked only in the first trimester and women who smoked throughout pregnancy and at 12 months there were no significant differences between the smoking groups.

The finding that infants born to smokers showed higher attention scores at 6 months than infants born to non-smokers conflicts with previous research suggesting there is no link between maternal smoking during pregnancy and offspring attention (e.g. Langley et al., 2007; Weissbluth & Liu, 1983) and contradicts with studies suggesting that prenatal smoke exposure results in decreased attention in offspring (e.g. Leech et al., 1999; Naeye & Peters, 1984; Streissguth et al., 1984). The sample size of the smoking groups was relatively small and so it is possible that this was not a true result given that small sample sizes can lead to false positive findings (Field, 2000). Therefore, before drawing any firm conclusions the current study should be replicated using a larger sample size. However, if the result is replicated then one possible reason for the better attention scores observed in the smoking groups is that in adults, nicotine exposure is widely regarded to enhance attention (Hasenfratz, Michel, Nil & Bättig, 1989; Kassel, 1997; Powell, Tait & Lessiter, 2002) and nicotine has been shown to pass from the blood stream of a lactating woman into her milk which could then pass into the feeding infant (Trundle & Skellern, 2008). At 6 months of age, many infants are still being breast fed and therefore, further research is required to investigate whether this could be a potential mechanism between maternal smoking and offspring attention. Future studies would need to obtain information regarding the smoking status of the mothers post partum and

whether the mothers breastfed their babies and if so, how old the infant was when breast feeding was terminated. Animal studies would also help to confirm whether there is a potential mechanism for nicotine to pass from mother to lactating infant, subsequently affecting infant attention. However, if this explanation was found to be true, then it would suggest that maternal smoking during pregnancy is a marker for offspring attention and does not appear to have a direct causal effect.

Previous research has indicated that offspring of mothers who stop smoking during pregnancy perform better than children born to women who smoked throughout pregnancy on general measures of cognitive functioning (Fried et al., 1992; Sexton, Fox & Hebel, 1990). This is in line with other findings which suggest that infants exposed to nicotine during the third trimester of pregnancy show greater adverse effects than infants only exposed during early pregnancy (e.g. Day, Richardson, Goldschmidt & Cornelius, 2000; Leech et al., 1999). Our results from the 6 month assessment partially support these previous studies. We found that infants born to light smokers received higher attention scores than infants born to heavy smokers. Although we found no significant difference between attention scores of infants with only first trimester nicotine exposure compared with infants exposed to nicotine throughout pregnancy, effect size and power calculations suggest that the sample size was too small and increasing the '1st trimester' and 'all trimester' groups to nearer 60 in each group would be sufficient (Faul et al., 2007).

At the 12 month assessment we found no significant differences between the smoking groups and the non-smoking group on the Lab-TAB measure of attention, which although contrary to our hypothesis, is in line with findings by Langley et al. (2007) and Weissbluth and Liu (1983). The current sample size was small and there was a limited

number of smoking women, particularly heavy smokers. In the study by Schmitz et al. (2006) significantly higher inattentive scores were observed in children born to mothers who smoked 10 or more cigarettes a day during pregnancy. Leech et al. (1999) found that tobacco exposure in the second and third trimesters of pregnancy resulted in an increase in omission errors in a sample of 6-year-olds. However, the low number of smokers in our sample meant that the subdivision of smoking women into groups based on individual trimester exposure was not possible. In the study by Cornelius et al. (2001) 54.3% of the 593 women smoked during the first trimester of pregnancy and 53.3% of the sample smoked during the third trimester. Therefore, before firm conclusions are drawn we suggest the current study should be replicated using a larger sample size.

Longitudinal studies of ADHD provide evidence that there are distinct subtypes of the disorder which can be identified by the pattern of onset of symptoms during the preschool period (Sonuga-Barke, 2003). Following these findings, Noland et al. (2005) proposed that longitudinal studies examining the development of attention skills from infancy through to school age are required in order to provide a complete picture of the effects of prenatal nicotine exposure on attention. Therefore, the current sample should be followed longitudinally through the preschool and into school years.

Are parental reports and observer reports of infant attention related? Previous studies have found mixed results when investigating whether observer and parent reports of infant temperament are correlated, with some studies suggesting a positive correlation between observer and parent reports (e.g. Bridges et al., 1993; Hane et al., 2006) and other studies finding no correlation (e.g. Mangelsdorf et al., 2000). In the current study, it was hypothesised that there would be a positive correlation between the two measures

given that both the Lab-TAB and the IBQ were designed to follow Rothbart's view of temperament (Rothbart, 1981). However, results from the current study did not support this prediction, with the finding that there was no correlation between the Lab-TAB and IBQ measures of attention at 6 months but this finding is in line with some other studies (e.g. Mangelsdorf et al., 2000). Mangelsdorf et al. (2000) suggest that the lack of correlation between observer and parent reports might be because the contexts in which the behaviours are observed are very different. For example, parents rate behaviours seen across a 1 or 2 week period, whereas observers rate behaviour during a limited time in a specific context. When looking at the effect of prenatal smoke exposure on infant attention both the Lab-TAB and IBQ measures indicated that at 6 months infants born to smokers had better attention than infants born to non-smokers. However, the Lab-TAB measure of attention indicated differences between smoking groups when the quantity and timing of the smoke exposure was considered, whereas the IBQ measure did not indicate differences between the smoking groups. As mentioned above the sample size was small and therefore, the study should be replicated using a larger sample size before firm conclusions are drawn.

Is there an effect of gender on attention? We investigated whether there was evidence of gender differences in infant attention. At the 6 month assessment we found no differences between boys and girls but at the 12 month assessment we found a marginally significant result in the 'non-smoking' group, indicating that boys had higher attention scores than girls. As mentioned in the Introduction (section 2.1.4), few previous studies have investigated whether there are gender differences in attention but one of the few studies to do so found no differences between boys and girls at 12 months on

parental reports and observer-reported measures of attention (Karass et al., 2002). Given that the gender difference was only marginally significant at 12 months and no difference was found in the 'smoking' group, the study should be replicated before firm conclusions can be drawn.

Is there an effect of age on attention? Based on the findings of Carranza et al. (2000) and Ruff and Rothbart (1996), it was hypothesised that attention scores would increase between 6 and 12 months and our results supported this hypothesis. During the first year of life infant attention evolves as neurological development occurs. During early infancy, infants have been shown to be selective in their attention, focusing initially on intensity of stimulation such as the size and brightness of stimuli and then focusing on aspects such as pattern and form (Fantz & Fagan, 1975; Ruff & Turkewitz, 1975). Infants then become interested in the novelty of objects and at around 3 and 4 months of age infants become aware of the properties of objects (Ruff & Rothbart, 1996). By 4 months of age infants become better at shifting attention as well as initiating and sustaining attention (Johnson, Posner & Rothbart, 1991). As the infant moves into toddlerhood, attention becomes more related to planned and self-generated activity with objects rather than simply object exploration. In line with these behavioural changes, neurological development is taking place. At first the brain stem controls general arousal in the cortex. During the first year of life, the spatial orienting network in the parietal cortex (Posner & Peterson, 1990) and the object recognition pathway in the temporal cortex become fully functional (Clohessy, Posner, Rothbart & Vecera, 1991). The third system to develop is a complex system involving areas of the frontal cortex (Posner & Peterson, 1990), which is important in the development of planned and goal directed behaviour and this system

becomes functional towards the end of the first year of life and continues to develop over the coming years (Diamond, 1991). Posner and Rothbart (1981) and Gartstein and Rothbart (2006) suggest that these maturational changes are responsible for the increase in attention seen towards the end of the first year of life.

Conclusions. The results indicate that at 6 months infants exposed to nicotine in utero show higher levels of attention than infants with no nicotine exposure but at 12 months no effect of prenatal smoke exposure on infant attention was observed. However, given the small sample size, caution should be used in interrupting the data. An alternative explanation of the results is that higher scores on the attention measures reflect poorer not better attention and thus at 6 months prenatal smoke exposure may be related to adverse attention outcomes. Therefore, before firm conclusions can be drawn the study should be replicated using a larger sample size and follow-up assessments will help clarify whether high scores on the attention measures are related to better cognitive outcomes. Future studies could also benefit by including variables regarding maternal smoking postpartum and infant feeding. It is possible, as suggested by Langley et al. (2007), that maternal smoking during pregnancy exerts varying influences on infant outcomes; so for example, hyperactivity and impulsivity symptoms are affected by prenatal smoke exposure to a greater extent than inattention symptoms. No gender differences were found at 6 months but a marginal gender difference was found at 12 months in the 'non-smoking' group, with boys showing higher attention scores than girls. This finding contradicts previous research and replication of the current study with a larger sample size will allow us to confirm whether gender differences in attention develop towards the end of the first year of life. Infant attention was found to increase

between 6 and 12 months of age, which is in line with previous findings, and maturational changes may account for the increase in attention seen at the end of the first year of life as suggested by Posner and Rothbart (1981) and Gartstein and Rothbart (2006).

CHAPTER 3

INFANT MOTOR ACTIVITY AND THE EFFECT OF PRENATAL SMOKE EXPOSURE

3.1. Introduction

3.1.1. Activity Level and ADHD

Activity level is a domain of reactivity which is clearly important in the development of ADHD (Auerbach et al., 2008). As stated in Chapter 1 (section 1.2), over activity or hyperactivity is one of the three symptoms required for a diagnosis of ADHD to be made. In order for excessive activity levels to be considered a component of ADHD, an individual must show high levels of activity, with extreme deviation from developmental norms, which persist across both time and situations (Hinshaw, 1994).

Several studies have been carried out investigating the possibility that high levels of activity observed in infants and young children could serve as a marker for the subsequent development of ADHD (e.g. Auerbach, 2004, 2008; Sonuga-Barke et al., 2005; see Chapter 1 section 1.4 for review). In 1968, Thomas, Chess and Birch commented that children who showed symptoms of behavioural disturbance were significantly more active than those children who did not show symptoms of behavioural disorder. At age 4, extreme levels of hyperactivity have been shown to predict the early onset of ADHD (Sonuga-Barke et al., 2005). Auerbach et al. (2004, 2008) found that mothers of infants in the ADHD 'at risk' group (based on ADHD symptoms in the father) reported their infants had a higher level of activity than infants in the control group, at 7, 12 and 25 months of age. Buss et al. (1980) carried out a longitudinal study investigating

activity levels between 3 and 7 years of age. In this study activity levels were measured at 3 and 4 years of age using an actigraph. Results showed that children measured as being highly active, were less inhibited, more aggressive, more assertive, more competitive, more restless and less cautious at 3, 4 and 7 years of age, than children who were measured as being less active. There is also evidence that active children tend to oppose peers more than less active children (Halverson & Waldrop, 1973, 1976) and that very active children are often not liked by their peers (Eaton, 1994). These findings have been supported by other research which has shown that activity levels during preschool years are predictive of activity levels at school-age, both in normal and at-risk samples (Campbell, Pierce, March, Ewing & Szumowski, 1994; Lemery, Essex & Smider, 2002; Thomas, Chess & Birch, 1968). This led Auerbach et al. (2008) to conclude that activity levels could be a useful early behavioural marker of risk for ADHD, because it has been found that activity levels are consistently higher in infants at risk for ADHD and preschool activity levels predict subsequent activity level in normal and clinical populations. Therefore, prospective longitudinal studies designed to measure activity using mechanical measures together with parent reports are required to study the development of activity level in infants and to investigate the link between high levels of motor activity and the development of ADHD.

Some research, for example studies by Becker et al. (2004), Carlson et al (1995), Keenan et al. (1997), Jacobvitz and Sroufe (1987), Olson et al. (2002) and Woodward et al. (1998), suggest that factors of family adversity, such as one-parent families, poor social support and coping skills, and negative parenting are significant in predicting preschool and later hyperactivity. One suggestion is that there is a reciprocal relationship

with the behaviour of the child influencing the behaviour of the adult, which in turn aggravates the behaviour of the child (Sonuga-Barke et al., 2005). However, there is evidence that factors of family adversity are in fact related to conduct symptoms and when pure ADHD is considered there is no link with family disadvantage (Barkley et al., 1992; Byrne et al., 1998; Cunningham et al., 1988; Goodman & Stevenson, 1989; Johnston, 1996; Stormont-Spurgin & Zentall, 1995). Clearly, regardless of whether family factors are implicated in the development of ADHD and/or other disorders, activity level is an important symptom to investigate.

Although excessive motor activity is clearly an important and striking feature of ADHD, very little research has been carried out investigating motor activity in children with ADHD and as a result very little is known about the underlying impairment. Ben-Pazi and colleagues designed a study in 2003 with the aim of investigating the motor abnormalities that characterise children with ADHD (Ben-Pazi, Gross-Tsur, Bergman & Shalev, 2003). An experimental motor paradigm previously used with patients suffering from Parkinson's disease was used on a sample of 6- to 14-year-olds, diagnosed with ADHD. The paradigm involved a tapping test which was used to assess pacing. Results from this study showed that most children with ADHD responded with a pattern that was constant and faster than the input frequency. This is in line with the pattern of response seen in patients with Parkinson's disease and may reflect an underlying oscillatory pathology in subcortical circuits (Logigian, Hefter, Reiners & Freund, 1991). This study highlights the need to investigate the development of excessive motor activity in young children in order to understand the underlying impairment.

3.1.2. Activity Level in Infants

Activity level is an important factor in normal development and forms a large part of young children's behaviour (Campbell, Eaton & McKeen, 2002). Activity level provides a channel through which infants can explore their environment and develop skills in social and cognitive domains, as well as leading to enhanced motor functioning (Angulo-Kinzler, Peirano, Lin, Garrido & Lozoff, 2002). Activity level is also a basic and important component of children's play (Campbell et al., 2002). Typical activity levels have been shown to change with age, probably reflecting in an inverted U-shape, with a peak some time between 2 and 5 years of age (Eaton, 1994).

With regard to gender differences in activity level there have been mixed findings. In a study looking at 13-month-olds, Goldberg and Lewis (1969) found that boys played more vigorously with toys than girls. This finding was supported by Pedersen and Bell (1970) who found that during the preschool years, boys were more active than girls. These findings have been supported by a number of studies looking at activity levels in preschool and school-aged children (Baranowski, Thompson, DuRant, Baranowski & Puhl, 1993; Riddoch et al., 2004; Trost et al., 2002). A meta-analytic review carried out by Eaton and Enns (1986) found that boys were more active than girls, a finding supported by Campbell et al. (2002), although in this study the difference was found to be non-significant. However, several studies have found no gender differences in activity levels in infants and preschoolers. In a study by Buss et al. (1980), in a sample of 3- and 4-year-olds, comparisons between genders were made at five points during the study and in two of the comparisons boys were found to be more active than girls and in three comparisons no significant gender differences were found. In an attempt to explain the

discrepancy in findings, Maccoby and Jacklin (1974) proposed that some situations may provoke activity in boys and not in girls and other situations may suppress activity in girls and not in boys. Halverson and Waldrop (1973) assessed play using mechanical activity recorders in a group of 2- and 3-year-olds and found that there was no difference in activity levels between girls and boys when they were playing alone. However, when playing in a group boys displayed higher levels of activity. Eaton and Keats (1982) found that higher levels of motor activity occurred when 2- to 7-year-olds were in a group situation and that boys were generally more active than girls. A meta-analysis by Else-Quest et al. (2006) found that males showed a small but significantly greater level of activity than girls. Clearly, studies investigating gender differences in activity levels of young children have found contradicting results and future studies are required to help untangle the conflicting results found previously. There has also been a lack of studies investigating gender differences in infants and therefore, future studies should begin studying activity levels during the first year of life.

In infancy and childhood, activity levels have been shown to be a key individual difference variable (Saudino & Zapfe, 2008) and most major theories of temperament have included activity level as a core domain of temperament (Goldsmith et al., 1987). One of the first studies to identify activity level as an aspect of temperament was that carried out by Thomas, Chess and colleagues (Thomas & Chess, 1977; Thomas et al., 1968; Thomas, Chess, Birch, Hertzig & Korn, 1963). Since this time, motor activity level has probably been the most extensively studied characteristic of temperament in young children (Rothbart, 1981; Rothbart & Derryberry, 1981).

As highlighted by the studies described above (e.g. Crockenberg & Acredolo, 1983; Eaton, 1994; Eaton & Dureski, 1986; Kagan & Snidman, 1991; Rothbart, 1989), individual differences in activity level can be identified in the first months of life. This finding has been supported by numerous studies including a study carried out by Auerbach et al. (2005). In this study differences in activity level were found to emerge in the neonatal period, with the group identified as being at risk of ADHD showing higher activity levels than a comparison group. The individual differences identified in activity level have been found to be stable across time (e.g. Auerbach et al., 2004, 2005, 2008; Buss et al., 1980; Campbell et al., 1994; Lemery et al., 2002; Thomas et al., 1968). However, there is some research which suggests that preschool hyperactivity is stable in only a proportion of cases (Lavigne et al., 1996; Mathiesen & Sanson, 2000). Therefore, for early identification and intervention to be successful, a crucial step is to predict which children displaying pre-clinical patterns of early hyperactivity will subsequently develop ADHD and other disorders (Sonuga-Barke et al., 2005). This highlights the need for prospective longitudinal studies designed to study activity profiles of children.

In newborns, high levels of activity have been linked with distress (Rothbart, 1989). In 6-month-olds, activity levels measured at home for 48 hours have been found to be positively correlated with reports of crying and fussing (Eaton, 1994). Kagan and Snidman (1991) carried out a longitudinal study looking at motor activity and temperamental profiles in infants. The authors found that infants who at 4 months showed a combination of high motor activity and frequent crying to stimulation were more fearful to unfamiliar events at 9 and 14 months of age, compared with infants who at 4 months displayed low motor activity and infrequent crying. However, limitations of the Kagan

and Snidman (1991) study include the sample consisting of white, middle-class mothers who had been screened for consumption of alcohol, cigarettes and caffeine consumption, exclusion of all infants with pre- and postnatal complications and also motor activity was assessed using observations by researchers. Therefore, to confirm these findings future studies are required using a more representative sample and including mechanical measures of motor activity.

There is evidence from both human and non-human animal studies that activity level may be highly heritable (Fuller & Thompson, 1978; Matheny, Dolan & Wilson, 1976; Saudino & Eaton, 1995; Saudino & Zapfe, 2008; Thapar, Hervas, & McGuffin, 1995; Willerman, 1973; Willerman & Plomin, 1973; Wood, Saudino, Rogers, Campbell, Asherson & Kuntsi, 2007). For example, Saudino and Eaton (1995) found in a study of twins that activity level, measured mechanically, showed a genetic influence during early childhood. Support for this finding was provided by Wood et al. (2007). In this study, actigraphs were used with twin pairs aged between 7 and 9 years in two situations. Results provided evidence that there is a moderate degree of genetic influence on activity levels. In another study, Saudino and Zapfe (2008) used actigraphs to assess activity level in 312 twin pairs aged 2 years old, in the home and in the laboratory. Results showed that there was significant genetic variation in activity level across three situations (i.e. home, laboratory test and laboratory play situations) and that actigraph scores were significantly correlated across the situations. The authors concluded that although genes largely account for the similarities among activity level between the three situations, the situation is also important, as long as the situations are sufficiently dissimilar.

In the past, there have been a number of problems when attempting to measure motor activity in infants and young children. These include having to rely on self-report or observer-reported measures of activity level and/or the use of time-consuming, intrusive and complicated physiological measures (Kohl, Fulton & Caspersen, 2000; Sirad & Pate, 2001; Welk, Corbin & Dale, 2000). However, recent advances in technology have led to the development of reliable, unobtrusive and ecologically valid activity monitors, which have good memory capacity and sensitive accelerometers (Puyau, Adolph, Vohra & Bute, 2002; Trost, 2001). Pate et al. (2006) used the same actigraph device to that used in the current study to compare actigraph output with a metabolic criterion measure of physical activity; oxygen consumption (VO_2). Results showed that accelerometer counts from the actigraph were highly correlated with VO_2 in children between the ages of 3 and 5 years and the authors concluded that accelerometers can be used appropriately with young children. Kelly, Reilly, Fairweather, Barrie, Grant and Paton (2004) compared the actigraph used in the current study with another accelerometer and compared both devices with direct observations in 3- to 4-year-olds. Results from this study showed that the actigraph used in the current study was significantly correlated with direct observation, providing evidence for the validity of the actigraph and adding support for findings from a small scale study carried out by Fairweather, Reilly, Grant, Whittaker and Paton (1999). The sensitivity of actigraphs has also been proved with infants and very young children. For example, Angulo-Kinzler et al. (2002), attached actigraphs to the right ankles of infants at 6, 12 and 18 months of age in a study investigating iron deficiency anaemia (IDA). Results showed that there were differences in overall activity level between infants with IDA compared with normal

controls at all three ages. Actigraphs have also been used successfully with children displaying behaviour disorders. For example Corkum, Tannock, Moldofsky, Hogg-Johnson and Humphries (2001) used actigraphs to investigate sleep behaviour in participants aged 7 to 11 years with ADHD.

3.1.3. Effect of Prenatal Smoke Exposure on Activity Level

The effect of prenatal exposure to smoking, specifically exposure to nicotine (the main psychoactive chemical in cigarettes), on the activity levels of offspring has been investigated in both non-human animal (Richardson & Tizabi, 1994; Schlumpf, Hwiler, Ribary & Lichtensteiger, 1988; Thomas, Garrison, Slawecki, Ehlers & Riley, 2000; Tizabi, Popke, Rahman, Nespor & Grunberg, 1997) and human research (Fried, Watkinson & Gray, 1992; Kristjansson, Fried & Watkinson, 1989; Naeye & Peters, 1984; see Chapter 1 section 1.11 for full review). Generally findings from animal research suggest that exposure to nicotine prenatally results in a change in normal activity level in the offspring, usually shown as an increase in activity level (e.g. Schlumpf et al., 1988; Thomas et al., 2000). There is evidence that this may be a dose-dependent effect, with a higher dose of nicotine resulting in an increase in activity level (Richardson & Tizabi, 1994). Research also suggests that certain offspring are more susceptible to the behavioural and neurochemical effects of exposure to nicotine in utero. For example, Tizabi et al. (1997) found that in offspring selected as being hyperactive and which had also experienced prenatal nicotine exposure, there was an increase in nicotinic receptors in certain areas of the brain. However, in hyperactive offspring born to rats which had been saline-treated, there was no significant change in the density of nicotinic receptors

compared with low- or middle-activity groups. However, a few studies have found no effect of nicotine exposure on activity levels in offspring (Paulson et al., 1993; Tizabi et al., 1997).

Human research investigating potential links between prenatal nicotine exposure and activity levels has generally found that exposure to nicotine prenatally results in an increase in activity levels (Kotimaa et al., 2003; Kristjansson et al., 1989; Makin, Fried & Watkinson, 1991; Naeye & Peters, 1984) and an increase in impulsive behaviour (Fried et al., 1992). Romano, Tremblay, Farhat and Côté (2006) found that maternal prenatal smoking together with maternal depression, hostile parenting and the child being male, were significant predictors for persistently high levels of hyperactivity from 2 to 7 years. Martin, Dombrowski, Mullis, Wisenbaker and Huttunen (2006) found a marginal non-significant relationship between prenatal maternal smoking and parent-reported infant activity level at 6 months; this relation was significant at 5 years of age. Denson, Nanson and McWatters (1975) found that mothers who had children with hyperkinesis reported smoking two to three times as many cigarettes as mothers of dyslexic and normal controls. Langley et al. (2007) also found an increase in severity of hyperactive-impulsive symptoms in offspring, aged between 6 and 16 years, who had been exposed to smoking in utero and this was found to be a dose dependent effect. Although many studies have shown prenatal smoking is associated with an increase in activity levels in offspring, the results are not conclusive with some studies suggesting that there is no effect. As many human studies have focused on older children, it is not clear whether the effects found emerge in early development and as a result the potential pathways between smoking and development of disorder are unclear.

3.1.4. The Current Study

The aims of the current chapter were to investigate motor activity levels in infants at 6 and 12 months, during a baseline period and an attention and an emotional challenge task, and to examine the role of prenatal maternal smoking on activity levels. Activity levels were recorded using an accelerometer. It was hypothesised that activity levels would be lower during attention compared with baseline because a novel and non-threatening stimulus was presented, which would engage the infants' attention. It was hypothesised there would be an increase in activity levels during the emotional challenge, based on the findings by Eaton (1994), Kagan and Snidman (1991) and Rothbart (1989).

There has been a lack of research studying changes in activity levels during the first year of life. We predicted that at the 12 month assessment the participants would be more active than at the 6 month assessment, based on work carried out by Eaton (1994). With regards to gender differences in activity levels, there have been mixed findings and again very few studies have looked at gender differences in infants. Based on the findings of Goldberg and Lewis (1969), who studied 13-month-olds, and Pedersen and Bell (1970), Else-Quest et al. (2006) and Eaton and Enns (1986), it was hypothesised that there would be gender differences in motor activity, with boys showing higher levels of activity than girls.

In the current study, mothers, fathers and a third person who knew the infant well were asked to complete the Infant Behavior Questionnaire (IBQ), an instrument developed by Rothbart (1981) to measure temperament in infancy. In line with theories of temperament, this questionnaire includes items relating to infant activity, which formed

an activity subscale. Dane, Schachar and Tannock (2000) and Saudino, Wertz, Gagne and Chawla (2004) found that actigraph measures correlated around 0.3 with parent reports of activity as reported on the Colorado Childhood Temperament Inventory. However, Eaton and Dureski (1986) found that maternal IBQ reports of activity level did not correlate with actigraph measures of behaviour and proposed that this may be because the IBQ focuses on caretaking situations such as dressing and eating, and therefore, may miss social interactions which elicit activity in the infants. As the measures used in the current study overlap with those used by Eaton and Dureski (1986), we expected to find no correlation between parental reports and actigraph measures of activity level.

The current study investigated the effect of prenatal smoking on activity levels in offspring in three ways. The first of these was to compare offspring of women who smoked during pregnancy with offspring of women who did not smoke during pregnancy. In line with findings by Kristjansson et al. (1989), Naeye and Peters (1984) and Kotimaa et al. (2003), it was predicted that infants exposed to smoking prenatally would exhibit higher levels of activity as measured by the actigraph and as reported on the IBQ. The second set of analyses aimed to investigate if the quantity of cigarettes consumed during pregnancy affected activity levels in offspring, with the aim of determining whether there was a dose-response relationship. To investigate this, women who smoked during pregnancy were spilt into two groups; a 'light smoking' group and a 'heavy smoking' group and these two groups were compared with the 'non-smoking' group. Based on findings from the non-human animal literature of a dose-response relationship between prenatal nicotine exposure and activity level (e.g. Richardson & Tizabi, 1994), it was expected that infants born to mothers in the 'heavy smoking' group would show higher

activity levels than those infants born to mothers in the 'light smoking' group and the 'non-smoking' group. The final set of analyses aimed to investigate if the timing of the smoke exposure affected activity levels in offspring. For these analyses, the smoking group was divided into infants born to women who smoked only in the first trimester of pregnancy and infants born to women who smoked throughout their pregnancy. These two groups were compared with the 'non-smoking' group. Few studies have investigated whether the timing of smoke exposure affects offspring activity levels but it was predicted that infants born to women who smoked throughout pregnancy would show higher levels of motor activity than infants born to women who smoked only in the first trimester, who in turn would show higher levels of motor activity than infants born to women who did not smoke. This is based on the findings that nicotine affects foetal brain development and function from as early as 4 or 5 weeks gestation (Ernst et al., 2001; Hellström-Lindahl et al., 2001; Miao et al., 1998; Slotkin, 1998; Van de Kamp & Collins, 1994).

3.2. Method

3.2.1. Participants

As described in Chapter 2 (section 2.2.1) a subsample of 130 participants taking part in the CCDS were selected. Of the 130 participants, 59 women reported smoking during pregnancy and the remaining 71 women did not smoke during pregnancy. A full description of the recruitment of the sample and sample characteristics are reported in Chapter 2.

3.2.2. Measures

Nicotine during pregnancy. This variable has been described in detail in Chapter 2 (section 2.2.2). Smoking during pregnancy was defined in three ways; the first variable was dichotomous (non-smoking/ smoking) and the other two variables were categorical (non-smoking/ light smoking/ heavy smoking and non-smoking/ 1st trimester/ all trimester).

Attention. See Chapter 2 (section 2.2.2) for a full description of this variable.

Negative emotion challenge. To create a negative emotion challenge for infants we used a restraint task at 6 months and a bear procedure at 12 months. Both tasks were designed to be distress provoking challenges but it was not expected that all children would show distress in these situations, rather we were presenting situations that may induce distress in some children.

The restraint in car seat task was adapted from the Lab-TAB (Goldsmith & Rothbart, 1999) and the rationale for the task was that being physically restrained against

one's wishes can elicit anger and the use of a car seat for this task provided some ecological validity, given that car seats are required by law. The procedure for this task involved placing the car seat on the floor in front of the camera and the mother was asked to place the child into the car seat. The mother was asked to stand to the side of the seat to avoid obstructing the camera, while strapping the child into the seat. Once the child was strapped in the mother was asked to stand next to the researcher, who was standing to the side and slightly behind the car seat. The child was then left in the car seat for 30 seconds. Parents were instructed that they could end the procedure at any point if they felt their child became too distressed.

The 12 month assessment was designed with the premise of a simulated birthday party with a teddy bears' picnic theme. Thus, for the bear paradigm a researcher dressed in full bear costume entered the party room and joined the birthday lady (another researcher dressed in medieval costume) to perform a series of actions, designed to be emotionally challenging. The bear procedure was divided into 4 parts; the bear arriving at the picnic, the bear taking part in the picnic and offering each baby a piece of pretend cake, the bear dancing with each baby in turn and finally the bear leaving and shaking hands with each baby in turn. Before the bear entered, the birthday lady asked the parents to position the infants around the picnic rug at the front of the room and parents were asked to sit on sofas at the back of the room. Parents were instructed that they could approach and interact with their infant, at any time, if they felt the infant had become too distressed. The entire procedure lasted for approximately 6 minutes.

Infant Behavior Questionnaire (IBQ). In the current chapter we focussed on the 'activity level' subscale from the IBQ, defined as "*the* child's gross motor activity,

including movement of arms and legs, squirming and locomotor activity" (Rothbart, 1981, p. 573). The 'activity level' subscale consisted of 17 items with a Cronbach's α .81 for mothers, .73 for fathers and .81 for significant others. The 'activity level' subscale was created by calculating a mean from the responses given to each of the items, which made up the subscale. The responses of the mother, father and significant other on the 'activity scale' were found to be positively correlated (minimum $r = .25$, $p<.01$) and a composite score was created by calculating a mean score, using the mother, father and significant other scores, which allowed the sample size to be increased.

Activity. The ActiGraph ActiTrainer (Manufacturing Technology, Inc, MTI) was selected as the accelerometer used in the current study because a number of studies have shown the validity and reliability of the device (e.g. Eisenmann, Strath, Shadrick, Rigsby, Hirsch & Jacobson, 2004; Esliger, Tremblay & Copeland, 2003; Kelly et al., 2004; Puyau et al., 2002; Trost, Ward, Moorehead, Watson, Riner & Burke, 1998). The ActiGraph ActiTrainer contains an activity monitor with a built-in single axis accelerometer, which is designed to measure and record time varying accelerations ranging in magnitude from approximately 0.05 to 2 G's. Although tri-axial monitors are available, Freedson et al. (2005) carried out a review of accelerometers, including the one used in the current study, and concluded there was no evidence to suggest tri-axial monitors were better. The output from the accelerometer is digitized by a twelve-bit Analog to Digital Converter (ADC) at a rate of thirty times per second (i.e. 30 Hertz (Hz)). When the signal has been digitized, it passes through a digital filter which band-limits the accelerometer to the frequency range of 0.25Hz to 2.5Hz. These limits have been chosen carefully to allow detection of normal human motion but reject motion from other sources. Each sample was then

summed over a specified epoch, defined by the researcher, which can range from between 30 times per second to 4 minutes. In this study a 15 second epoch was used throughout. A short epoch length is recommended when collecting activity data from young children because they tend to perform physical activity in short bursts rather than in prolonged bouts (Bailey, Olson, Pepper, Porszasz, Barstow & Cooper, 1995; Pate, Pfeiffer, Trost, Ziegler & Dowda, 2004; Pate, et al., 2006).

The accelerometer was packaged in a plastic enclosure which is attached to the infants' leg with a Velcro strap. The ActiGraph ActiTrainer weighs approximately 1.8 ounces and has dimensions of 8.6cm x 3.3cm x 1.5cm. The ActiGraph ActiTrainer was attached to the infants' left leg. Puyau et al. (2002) and Nilsson, Ekelund, Yngve and Sjoestroem (2002) found that similar results were obtained whether the actigraph was attached to the hip or the leg. The ActiGraph ActiTrainer has an integrated USB plug, which allows fast and convenient downloading of data. The collected data were stored in ASCII format which was then converted into a Microsoft Excel file, using the ActiLife Software (www.theactigraph.com, December 2008). The activity data were downloaded and stored simultaneously with the HR data (see Chapter 4 for HR data). Baseline and attention were 3 minutes and negative emotion challenge lasted for 30 seconds at the 6 month assessment and the duration of the negative emotion challenge at the 12 month assessment was analysed, which ranged from 3 to 6 minutes. Thus, there were 12 15 second epochs for baseline and attention, 2 15 second epochs for negative emotion challenge at 6 months and between 12 and 24 15 second epochs for negative emotion challenge at 12 months. The data were cleaned and divided into 30 second epochs and for

analyses a mean activity score was calculated for each condition, after first checking that there was no significant effect of time on activity levels within each condition.

3.2.3. Procedure

The procedure has been explained in Chapter 2 (section 2.2.3).

3.2.4. Data Analysis

At the 6 month assessment, there were missing data for 13 participants during baseline, for 11 participants during the attention task and for 14 participants during the emotional challenge. The reasons for the missing data were either equipment malfunction, extreme anomalies or the task not being completed. At the 12 month assessment, 13 participants did not attend the assessment. As a result of equipment malfunction, extreme anomalies in the data or the task not being completed, a further 12 participants had missing data during baseline, 10 during attention and 10 during negative emotion challenge (see Table 3.1).

Table 3.1: Number of Participants in Each Smoking Group at Baseline, Attention and Negative Emotion Challenge

	Baseline		**Attention**		**Negative Emotion**	
	6 mth	12 mth	6 mth	12 mth	6 mth	12 mth
Non-smoking	67	60	68	61	67	62
Smoking	50	45	51	46	49	45
Light smoking	31	27	32	28	31	27
Heavy smoking	16	15	16	15	15	15
1st trimester	12	12	13	12	12	12
3 trimester	29	23	29	24	28	23

Mean activity levels at baseline, attention and negative emotion challenge were used for analyses. A measure of reactivity was calculated as the percentage change in activity levels from baseline to attention and from baseline to negative emotion challenge. The following equation was used to calculate reactivity: ((Activity level $_{condition}$ – Activity level $_{baseline}$) / Activity level $_{baseline}$) * 100. Thus, reactivity represents a change in activity level that is comparable between conditions because it takes into account baseline state.

The data were screened for violations in the assumptions of parametric tests, i.e. it was verified that the data in each of the cells were normally distributed and the variances in each of the cells were not different from each other. These assumptions were found to be violated for the activity data and data transformations did not improve skewness or kurtosis. Therefore, non-parametric tests were used throughout this chapter, with the exception of the IBQ. With respect to the IBQ t-tests and ANOVAs were used where appropriate. A significance level of $p<.05$ was adopted throughout this paper but trends up to $p<.10$ were also indentified.

At the 6 month assessment, there were no significant correlations between age of infant in months and activity levels at baseline ($r_s = -.04$, $p=.77$), attention ($r_s = -.03$, $p=.78$.) or negative emotion challenge ($r_s = -.07$, $p=.60$). At the 12 month assessment, there were no significant correlations between age of infant in months and activity levels at baseline ($r_s = .02$, $p=.86$), attention ($r_s = -.10$, $p=.43$) or negative emotion challenge ($r_s = -.12$, $p=.35$).

3.3. Results

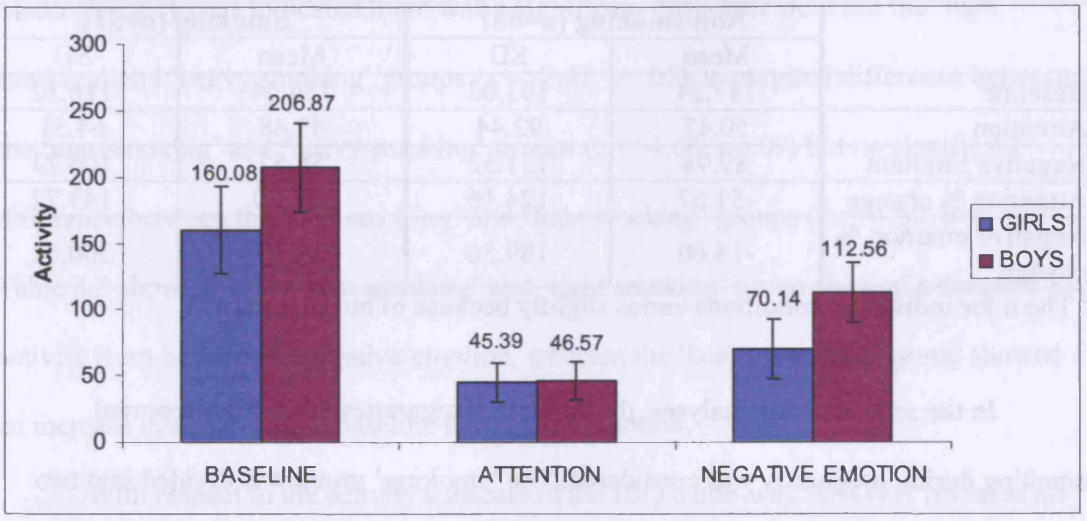
3.3.1. Analyses at 6 Months

Effect of condition and gender. The effect of condition on activity levels was investigated only in children who had not been exposed to smoke prenatally, as this group formed the comparison group for the study. A Friedman test revealed that there was a significant difference in activity levels between conditions (χ^2 (2) = 27.78, p<.001). Wilcoxon tests revealed there was a significant difference between baseline and attention (z = -5.83, p<.001), baseline and negative emotion challenge (z = -3.52, p<.001) and attention and negative emotion challenge (z = -2.56, p<.05). Figure 3.1 shows that activity levels were higher during baseline than both attention and negative emotion challenge tasks.

The effect of gender on activity in each of the conditions was investigated. Mann-Whitney tests revealed there was no significant difference in activity levels between girls and boys during baseline (z = -0.72, p=.47), attention (z = -0.35, p=.73) or negative emotion (z = -0.32, p=.75; see Figure 3.1). An independent t-test also revealed that there was no significant gender difference on the activity subscale of the IBQ (Girls: M = 4.02, SD = 0.72; Boys: M = 3.93, SD = 0.69; t (105) = 0.71, p=.48).

Spearman rho correlations revealed that IBQ-reported infant activity levels did not correlate with objectively measured activity levels at baseline (r_s = .10, p=.45), or during attention (r_s = -.01, p=.93) or negative emotion challenge (r_s = .05, p=.69).

Figure 3.1: Mean Activity Levels during Baseline, Attention and Negative Emotion Challenge for Girls and Boys at 6 Months (n=68)



Effect of prenatal smoke exposure. In the first set of analyses infants born to mothers who reported smoking during pregnancy were compared with infants born to mothers who did not smoke during pregnancy. Mann-Whitney tests revealed no significant differences between smoking groups at baseline ($z = -1.04$, $p=.30$), attention ($z = -0.25$, $p=.80$) or negative emotion ($z = -1.16$, $p=.25$; see Table 3.2). When change in activity level from baseline to condition was considered, Mann-Whitney tests again revealed no significant differences between the non-smoking and the smoking groups for attention ($z = -0.51$, $p=.61$) or negative emotion ($z = -0.59$, $p=.55$). However, an independent t-test revealed that the 'non-smoking' group ($M = 3.90$, $SD = 0.71$) had a marginally lower IBQ activity score than the 'smoking' group ($M = 4.14$, $SD = 0.64$; $t(104) = -1.75$, $p=.08$).

Table 3.2: Activity Levels during Baseline, Attention and Negative Emotion Challenge for 'Non-Smoking' and 'Smoking' Groups at 6 Months[a]

	Non-smoking (n=68)		Smoking (n=51)	
	Mean	SD	Mean	SD
Baseline	187.24	193.02	134.64	116.32
Attention	50.47	92.44	43.48	64.51
Negative Emotion	89.98	131.32	58.52	106.73
Attention % change	-51.67	124.16	-23.20	143.72
Negative emotion % change	-14.60	189.56	14.30	300.61

[a] The n for individual conditions varies slightly because of missing data

In the second set of analyses, the number of cigarettes the mother reported smoking during pregnancy was considered. The 'smoking' group was divided into two groups: the 'light smoking' and 'heavy smoking' groups, which were compared with the 'non-smoking' group (see Chapter 2 section 2.2.2 for full explanation). Kruskal-Wallis tests indicated that there were no significant differences between the smoking groups at baseline (χ^2 (2) = 0.80, p=.67) or attention (χ^2 (2) = 0.43, p=.81). However, there was a marginal difference between the smoking groups during negative emotion challenge (χ^2 (2) = 5.00, p=.08). Mann-Whitney tests indicated there was a significant difference between the 'light smoking' and 'heavy smoking' groups (z = -2.13, p<.05), a marginal difference between the 'non-smoking' and 'light smoking' groups (z = -1.77, p=.08) and no difference between the 'non-smoking' and 'heavy smoking' groups (z = -0.79, p=.43). Table 3.3 shows that the 'heavy smoking' group had the highest level of activity and that the 'light smoking' group had the lowest level of activity during negative emotion challenge.

When considering changes in activity levels compared with baseline, Kruskal-Wallis tests indicated that there were no significant differences between the smoking groups during attention (χ^2 (2) = 0.85, p=.66). However, there were significant

differences between the smoking groups during negative emotion (χ^2 (2) = 6.39, p<.05). Mann-Whitney tests indicated there was a significant difference between the 'light smoking' and 'heavy smoking' groups (z = -2.41, p<.05), a marginal difference between the 'non-smoking' and 'heavy smoking' groups (z = -1.66, p=.09) but no significant difference between the 'non-smoking' and 'light smoking' groups (z = -1.50, p=.13). Table 3.3 shows that the 'non-smoking' and 'light smoking' group showed a decrease in activity from baseline to negative emotion, whereas the 'heavy smoking' group showed an increase in activity from baseline to negative emotion.

With respect to the activity subscale of the IBQ a one-way ANOVA revealed no significant differences between the smoking groups (non-smoking: M = 3.90, SD = 0.71; light smoking: M = 4.08, SD = 0.67; heavy smoking: M = 4.37, SD = 0.58; F (2, 100) = 2.06, p=.13).

Table 3.3: Mean Activity Levels at Baseline, Attention and Negative Emotion Challenge for 'Non-Smoking', 'Light Smoking' and 'Heavy Smoking' Groups at 6 Months[a]

	Non-smoking (n=67)		**Light smoking (n=31)**		**Heavy smoking (n=15)**	
	Mean	SD	Mean	SD	Mean	SD
Baseline	187.24	193.02	136.17	112.78	144.78	130.55
Attention	50.47	92.44	38.20	60.35	45.49	58.53
Negative emotion	89.98	131.32	36.90	55.26	113.34	166.39
Attention % change	-51.67	124.16	-45.69	126.37	-22.38	123.79
Negative emotion % change	-14.60	189.89	-40.33	131.41	150.61	496.22

[a] The n for individual conditions varies slightly because of missing data

In the third set of analyses, the timing of the smoke exposure during the pregnancy was considered. As described in Chapter 2 (section 2.2.2), the 'smoking' group was divided into the '1st trimester' and 'all trimester' smoking groups, which were

compared with the 'non-smoking' group. Kruskal-Wallis tests revealed that there were no significant differences in activity levels between the smoking groups at baseline (χ^2 (2) = 1.75, p=.42), attention (χ^2 (2) = 1.86, p=.40) or negative emotion (χ^2 (2) = 3.13, p=.21; see Table 3.4.).

When considering changes in activity levels compared with baseline, Kruskal-Wallis tests revealed that there was a marginal difference between the smoking groups during attention (χ^2 (2) = 5.73, p=.06). Mann-Whitney tests indicated that there was a significant difference between the '1st trimester' and 'all trimester' smoking groups (z = -2.23, p<.05) but no significant differences between the 'non-smoking' and '1st trimester' (z = -1.57, p=.12) and the 'non-smoking' and 'all trimester' smoking groups (z = -1.49, p=.14). Table 3.4 shows that the decrease in activity levels from baseline to attention was smaller in infants from the 'all trimester' smoking group than in infants from the '1st trimester' smoking group. When looking at negative emotion challenge, there were no significant differences between the smoking groups (χ^2 (2) = 1.08, p=.58).

When looking at the activity subscale of the IBQ, a one-way ANOVA revealed there were no significant differences between the three smoking groups (Non-smoking: M = 3.90, SD = 0.71; 1st trimester: M = 3.96, SD = 0.76; All trimester: M = 4.26, SD = 0.65; F (2, 96) = 2.25, p=.11).

Table 3.4: Mean Activity Levels at Baseline, Attention and Negative Emotion Challenge for 'Non-Smoking', '1st Trimester' and 'All Trimester' Smoking Groups at 6 Months[a]

	Non-smoking (n=68)		1st trimester (n=13)		All trimester (n=29)	
	Mean	SD	Mean	SD	Mean	SD
Baseline	187.24	193.02	121.67	109.30	127.11	112.41
Attention	50.47	92.44	31.02	49.82	49.16	67.55
Negative emotion	89.98	131.32	38.69	73.70	76.66	130.71
Attention % change	-51.67	124.16	-84.08	36.88	-10.17	148.52
Negative emotion % change	-14.60	189.56	13.21	212.87	46.75	269.23

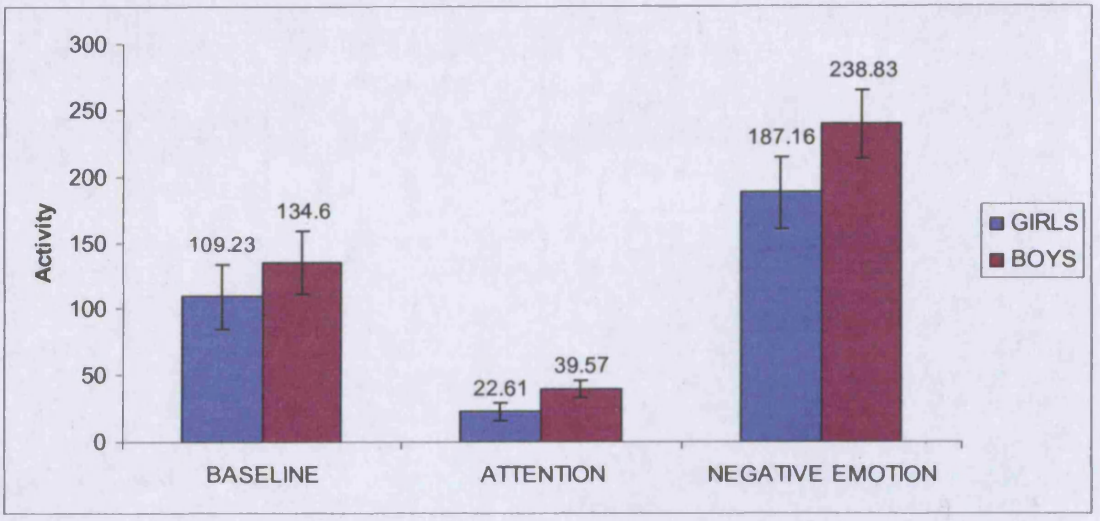
[a] The n for individual conditions varies slightly because of missing data

3.3.2. Analyses at 12 Months

Effect of condition and gender. A Friedman test revealed there was a significant difference in activity levels between conditions (χ^2 (2) =59.26, p<.001). Wilcoxon tests revealed that there was a significant difference between baseline and attention (z = -5.54, p<.001), between baseline and negative emotion (z = -3.20, p<.01) and between attention and negative emotion (z = -6.55, p<.001). Figure 3.2 shows that activity levels were higher during negative emotion challenge than during baseline and attention, and that activity levels during baseline were higher than during attention.

The effect of gender on activity in each of the conditions was investigated. Mann-Whitney tests revealed there was no significant difference in activity levels between girls and boys during baseline (z = -0.38, p=.70), attention (z = -1.13, p=.26) or negative emotion (z = -1.36, p=.17; see Figure 3.2).

Figure 3.2: Mean Activity in Baseline, Attention and Negative Emotion Challenge for Girls and Boys at 12 Months (n=62)



Effect of prenatal smoke exposure. When comparing the smoking group with the non-smoking group, Mann-Whitney tests revealed there were no significant differences in activity levels between smoking groups at baseline ($z = -0.19$, $p=.85$), attention ($z = -0.38$, $p=.71$) or negative emotion ($z = -0.06$, $p=.96$). When considering changes in activity levels compared with baseline, Mann-Whitney tests revealed there were no significant differences between the 'non-smoking' and 'smoking' groups for attention ($z = -0.42$, $p=.67$) or negative emotion ($z = -0.40$, $p=.69$; see Table 3.5).

Table 3.5: Activity at Baseline, Attention and Negative Emotion Challenge for 'Non-Smoking' and 'Smoking' Groups at 12 Months[a]

	Non-smoking (n=62)		Smoking (n=46)	
	Mean	SD	Mean	SD
Baseline	129.10	127.58	125.56	143.35
Attention	31.04	36.09	38.14	48.54
Negative emotion	209.88	138.47	199.48	108.18
Attention % change	-2.16	203.92	-6.78	166.59
Negative emotion % change	589.59	1170.74	373.24	484.63

[a] The n for individual conditions varies slightly because of missing data

With respect to the quantity of cigarettes consumed by the mother Kruskal-Wallis tests revealed that there were no significant differences between smoking groups at baseline (χ^2 (2) = 0.53, p=.77), attention (χ^2 (2) = 0.16, p=.92) or negative emotion (χ^2 (2) = 1.41, p=.49). When considering changes in activity levels compared with baseline, Kruskal-Wallis tests revealed there were no significant differences between the 'non-smoking', 'light smoking' and 'heavy smoking' groups as a result of attention (χ^2 (2) = 0.70, p=.71) or negative emotion (χ^2 (2) = 0.05, p=.97; see Table 3.6).

Table 3.6: Activity at Baseline, Attention and Negative Emotion Challenge for 'Non-Smoking', 'Light Smoking' and 'Heavy Smoking' Groups at 12 Months[a]

	Non-smoking (n=62)		Light smoking (n=28)		Heavy smoking (n=15)	
	Mean	SD	Mean	SD	Mean	SD
Baseline	129.10	127.58	124.49	146.54	144.40	150.84
Attention	31.04	36.09	44.32	57.36	30.68	31.29
Negative emotion	209.88	138.47	173.51	89.76	215.52	110.99
Attention % change	-2.16	203.92	27.74	210.82	-57.02	51.01
Negative emotion % change	589.59	1170.74	383.12	527.20	256.22	377.01

[a] The n for individual conditions varies slightly because of missing data

With respect to timing of the cigarette smoking Kruskal-Wallis tests revealed there were no significant differences between the smoking groups at baseline (χ^2 (2) = 1.59, p=.45), attention (χ^2 (2) = 0.34, p=.85) or negative emotion (χ^2 (2) = 0.62, p=.73). When considering changes in activity levels compared with baseline, Kruskal-Wallis tests revealed there were no significant differences between the smoking groups at attention (χ^2 (2) = 0.83, p=.66) or negative emotion (χ^2 (2) = 0.81, p=.67; see Table 3.7).

Table 3.7: Activity at Baseline, Attention and Negative Emotion Challenge for 'Non-Smoking', '1st Trimester' and 'All Trimester' Smoking Groups at 12 Months[a]

	Non-Smoking (n=62)		1st trimester (n=12)		All trimester (n=24)	
	Mean	SD	Mean	SD	Mean	SD
Baseline	129.10	127.58	31.04	36.09	35.13	39.95
Attention	31.04	36.09	35.13	39.95	40.76	52.58
Negative emotion	209.88	138.47	174.87	112.83	202.27	97.86
Attention % change	-2.16	203.92	5.31	128.89	-0.87	209.36
Negative emotion % change	589.59	1170.74	428.16	588.27	260.44	415.69

[a] The n for individual conditions varies slightly because of missing data

3.3.3. Activity Levels at 6 and 12 Months

Infant activity levels at 6 and 12 months in infants born to non-smoking mothers were not correlated at baseline (r_s = .13, p=.34) nor during attention (r_s = .11, p=.43) or negative emotion challenge (r_s = .14, p=.28). The same applies when considering change in activity levels from baseline to condition (attention: r_s = .18, p=.23; negative emotion provocation: r_s = -.18, p=.25), or when investigating these relations in infants born to smoking mothers (baseline: r_s = -.08, p=.62; attention: r_s = -.16, p=.32; negative emotion challenge: r_s = -.13, p=.44). When considering changes in activity level compared with baseline in the 'smoking' group, there was no correlation during attention (r_s = -.21, p=.21) and a marginal correlation during negative emotion challenge (r_s = -.31, p=.07).

Next, Wilcoxon tests were carried out to establish whether there was significantly more activity in 12 months olds as compared with when these children were 6 months old. For infants in the non-smoking group results showed that there were no differences in motor activity between 6 and 12 months during baseline (6 mth: M = 179.98, SD =

198.54; 12 mth: M = 120.78, SD = 126.50; z = -1.06, p=.29) or attention (6 mth: M = 49.82, SD = 90.23; 12 mth: M = 31.09, SD = 36.85; z = -0.17, p=.87). When considering changes in activity level compared with baseline, there was no difference between the age groups during attention (6 mth: M = -46.90, SD = 135.44; 12 mth: M = -20.45, SD = 178.95; z = 1.07, p=.29). For infants in the smoking group, results showed the same pattern as that for the non-smoking group (baseline: 6 mth: M = 134.27, SD = 114.89; 12 mth: M = 135.76, SD = 149.31; z = -0.26, p=.80; attention: 6 mth: M = 41.27, SD = 61.29; 12 mth: M = 39.85, SD = 51.64; z = -0.14, p=.89). When considering changes in activity level compared with baseline, there was no significant difference between age groups during attention (6 mth: M = -24.60, SD = 129.40; 12 mth: M = -16.06, SD=175.84; z = -0.06, p=.95).

3.4. Discussion

A review of the literature suggested that further research was needed investigating activity profiles in young children and the relationship between these profiles and temperament and subsequent risk for disorder, specifically ADHD. The link between prenatal smoking and the development of hyperactivity, as a precursor and symptom of ADHD, is also unclear as very few studies have examined activity levels in young infants. Therefore, the main goals of the current chapter were to investigate motor activity levels, using an accelerometer, during an attention task and a negative emotion challenge task. It was hypothesised that activity levels would be lower during attention and higher during negative emotion compared with baseline levels. Potential gender differences were also considered, as previous studies have found conflicting results. The second main goal was to examine the effect of prenatal exposure to smoke on activity levels during three situations; baseline, attention and negative emotion challenge. It was hypothesised that offspring exposed to smoke in utero would show increased levels of motor activity compared with infants with no smoke exposure.

Is there a reduction in activity level during sustained attention? There has been a lack of research investigating the motor activity levels of infants during tasks designed to measure interest and attention and a review of the literature found no such studies. Therefore, this study is one of the first to report activity levels of infants during an attention task. It was hypothesised that activity levels would be lower during attention than baseline. During baseline infants were seated either on the floor or on their mothers' laps and were not presented with any specific toys or stimuli. We predicted that the presentation of a novel stimulus during attention would engage the infants' interest and

hence reduce restlessness, which may be present during baseline. The stimulus was non-threatening meaning there was no need for infants' to attempt to move from the stimulus. The results at both 6 and 12 months supported our hypothesis, as activity levels were lower during the attention task than during baseline.

During the baseline period, infants may have been reacting to seeing new people (the experimenters) and being in a new place and this may have caused their activity levels to be relatively high. Therefore, with the introduction of a new toy the infants may have settled and thus their activity levels were lower during attention than baseline. To investigate whether this explanation is true, observers could code infant behaviour during the baseline period so that a direct comparison of behaviours during baseline and attention can be made. Future studies could include a longer baseline period and also include a task such as watching a video during the baseline period to settle the infants prior to the start of testing, as has been done in some other studies. As the stimuli were manipulated using the arms, future studies could investigate individual differences in activity levels as a result of direct manipulation of the toy by attaching actigraphs to each of the four limbs, as has been done in some previous studies (e.g. Saudino & Zapfe, 2008).

Is there an effect of emotion induction on activity levels? In line with findings by Rothbart (1989), Eaton (1994) and Kagan and Snidman (1991), it was predicted that activity levels during the negative emotion challenge tasks would be higher than during baseline. At 12 months, the results from the current study supported our prediction, with the finding that activity levels were significantly higher during the bear paradigm compared with baseline. Both Eaton (1994) and Kagan and Snidman (1991) found a link

between high activity levels and distress in infants but their children were younger (i.e., between 4 and 6 months of age). However, at 6 months the results did not support our prediction, with the finding that activity levels were significantly lower during the car seat task compared with baseline. In a study by Morier and Cossette (2006) it was found that when infants showed facial movements of anger they displayed high levels of motor activity but when they showed facial movements of sadness they showed low levels of activity. Therefore, it is possible that in the current study the car seat task elicited sadness in the infants at 6 months. The car seat task was adapted from the anger section of the Lab-TAB (Goldsmith & Rothbart, 1999) and although there is evidence that anger can be identified in infants as young as 6 months of age (Sroufe, 1995), previous studies have found that it is difficult to provoke anger as an emotion in infants during the first half of the first year of life (e.g. Auerbach et al., 2005) and indeed anger has been shown to increase between 7 and 12 months of age (Auerbach et al., 2008).

In general, the actigraph data were found to be positively skewed during baseline, attention and negative emotion tasks at 6 and 12 months, which is consistent with previous studies (Saudino & Eaton, 1991; Wood et al., 2007), but unfortunately data transformation did not create a more normal distribution. Although past research has established that actigraphs are valid measures of motor activity (Angulo-Kinzler et al., 2002; Fairweather et al., 1999; Kelly et al., 2004; Pate et al., 2006; Puyau et al., 2001), there is still some debate about the reliability of actigraph measures of motor activity over short measurement durations because human activity is inherently variable. Previous research has suggested that the reliability and validity of actigraph measures can be increased by attaching actigraphs to two or more limbs or body parts and aggregating the

data collected (Eaton, 1983). Wood, Kuntsi, Asherson and Saudino (2008) found that activity data collected using actigraphs during a single laboratory session can have good reliability and factors such as the research assistant fitting the device, inter-machine differences and the effect of battery life did not have a significant effect on the data collected. However, Wood et al. (2008) found that the reliability of actigraphs was increased when data were averaged across limbs and tasks. This may be because the effects of unrepresentative influences or artifacts in the data, such as the child knocking or playing with the actigraph or the potential confound of infant with parent movement, were reduced. In the current study, we tried to overcome the effects of such artifacts by placing the actigraph under the infants' clothes so that it was less likely they would be distracted by the actigraph and the videos were screened for evidence of such artifacts and where such incidences were found to occur, the data were not used in analyses. However, Wood et al. (2008) suggest that when investigating differences in activity level between tasks, as in the current study, researchers should aggregate data measured at several body loci and/or aggregate data collected across tasks that are theoretically linked. Thus, future research should consider these points to increase the reliability of activity data collected using actigraphs.

Is there an effect of gender on activity levels? Previous research has provided mixed results when looking at potential gender differences in activity levels. Most studies investigating gender differences in activity levels have focused on preschool and older children and the current study is one of the few studying gender differences in the first year of life. One study in 13-month-old infants found that boys played more vigorously with toys than girls (Goldberg & Lewis, 1969). Based on this finding and the findings of

Pedersen and Bell (1970) and Eaton and Enns (2002), we predicted that there would be a gender difference with boys showing higher levels of activity than girls. However, results indicated that in the current study there were no differences in motor activity between girls and boys during baseline, attention or negative emotion provocation at 6 or 12 months. One reason why our findings did not match the findings of Goldberg and Lewis (1969) is because they focused primarily on play behaviour, whereas we focused specifically on activity levels in response to cognitive and emotional challenge. However, our results are in line with some other studies, for example, Halverson and Waldrop (1973) found no differences in activity levels between girls and boys when they were playing alone. However, their sample was older (the children were between 2 and 3 years of age). In another sample of preschoolers, Buss et al. (1980) assessed activity levels at five time points and found no significant gender differences in three of the situations.

There is clearly mixed evidence when studying gender differences in activity levels in preschoolers. One reason for this may be the way in which activity levels were measured with some studies using actigraphs (e.g. Halverson & Waldrop, 1973), others using parental report and still others using observed behaviour. The current study combined parental reports and actigraph measures and future studies would benefit from including two or more measures to help clarify findings. The current study measured activity levels at two time points during the first year of life. Following these infants longitudinally will allow us to investigate whether gender differences do emerge during preschool years, providing additional evidence to help clarify the results which have been found in previous studies.

Is there an effect of age on activity levels? Results indicated that there were no differences in activity levels between 6 and 12 months at baseline and attention. We predicted that activity levels would be higher at 12 months compared with 6 months and so our prediction is not supported. There has been a lack of research investigating whether activity levels change with age and our hypothesis was based on the work of Eaton (1994) who suggested that activity levels change with age in an inverted U-shape, with a peak between 2 and 5 years of age. However, our results suggest that in the first year of life activity levels may be more stable and replication of the current study would help confirm this.

Is there an effect of maternal smoking in pregnancy on activity levels? It was predicted that infants who had been exposed to smoke prenatally would show increased activity levels in each of the three situations, i.e. baseline, attention and negative emotion challenge at 6 and 12 months. The results from the current study show that infants born to mothers who smoked during pregnancy and infants born to mothers who did not smoke during pregnancy did not differ in motor activity (as measured by actigraphs) at baseline, during attention or negative emotion challenge, neither at 6 or 12 months. However, there was a marginal difference in parent reported activity (subscale of the IBQ) with the 'non-smoking' group having lower reported activity levels.

We considered whether the quantity of cigarettes smoked affected infant outcomes by subdividing the 'smoking' group into women who smoked between 1 and 9 cigarettes per day ('light smoking') and women who smoked 10 or more cigarettes per day ('heavy smoking'). The 'light smoking' and 'heavy smoking' groups were compared with the 'non-smoking' group. Results revealed there was a significant difference

between the smoking groups during the negative emotion task at 6 months, with the 'heavy smoking' group having significantly higher activity levels than the 'light smoking' group. However, this difference was not found at 12 months. When considering changes in motor activity at 6 months, both the 'non-smoking' and the 'light smoking' groups showed a decrease in activity from baseline to negative emotion, whereas the 'heavy smoking' group showed an increase in motor activity from baseline to negative emotion and this difference was found to be significant between the 'heavy smoking' and 'light smoking' groups and marginally different between the 'heavy smoking' and 'non-smoking' groups. Again this difference was not observed at 12 months. No significant differences in motor activity were observed between the smoking groups during attention at 6 or 12 months.

The finding that the 'heavy smoking' group had significantly higher activity levels than the 'light smoking' group during negative emotion and that the 'heavy smoking' group showed an increase in activity from baseline to negative emotion compared with the 'non-smoking' and 'light smoking' groups who showed decreases, suggests that there may be a threshold at which prenatal smoke exposure affects the offspring. The fact that this difference was only found during the negative emotion task and not during baseline provides evidence that when investigating the effects of prenatal smoke exposure on offspring, potential outcomes should be investigated under a range of conditions and not just under resting ones.

We don't know why this result was not replicated at 12 months. Given that heightened activity levels are a key symptom required for a diagnosis of ADHD and as many studies suggest there may be a link between prenatal smoke exposure and the

development of ADHD in offspring (e.g. Denson et al., 1975; Kotimaa et al., 2003; Kristjansson et al., 1989), we would expect symptoms such as high activity levels to be present throughout infancy and into toddler and preschool years. One reason why we failed to find an effect at 12 months of age might be the nature of the task used. At 6 months we used the car seat task, whereas at 12 months the bear paradigm was used as an emotionally challenging task. Before firm conclusions can be drawn about whether there are differences in activity levels between smoking groups throughout infancy, the experiment should be replicated using the same negative emotion task designed to elicit a discrete negative emotion at both 6 and 12 months. These infants should then be followed longitudinally to investigate whether differences in activity levels persist into toddlerhood and preschool years. A final assessment should take place when the infants reach school and an assessment of ADHD symptoms can be made.

To investigate whether the timing of the smoke exposure during pregnancy affected the activity levels of the infants, the 'smoking' group was divided into women who smoked only during the first trimester of pregnancy ('1st trimester') and women who smoked throughout pregnancy ('all trimester'). These groups were created to account for different patterns of smoking, for example, some mothers smoked low numbers of cigarettes throughout pregnancy, while others smoked in large quantities during early pregnancy and only classifying women into 'light' and 'heavy' smoking may have missed these subtle differences.

When considering the timing of the smoke exposure, it was found there was a marginal difference between the smoking groups during attention at 6 months. In the attention task, the infants born to mothers who smoked throughout pregnancy were found

to show a smaller decrease in activity from baseline than those infants born to women who smoked only in the first trimester. These findings provide further evidence that prenatal smoke exposure affects activity levels of infants at 6 months of age and that to fully understand the range of effects infants must be examined under a range of cognitive and emotional challenges. However, this finding was not repeated at 12 months of age. In order to clarify our results, the study should be replicated using a larger sample size and the infants should be followed longitudinally.

The role of parental reports of activity levels. This study found that parental reports of activity levels, as reported on the IBQ, were not correlated with actual motor activity levels as measured by using an actigraph during resting and cognitive and emotional challenge situations. This is in line with the findings of Eaton and Dureski (1986). However, some previous studies have found correlations between parental reports and actigraph measures of activity levels (Dane et al., 2000; Saudino et al., 2004) albeit modest ones (in the region of 0.30). The reasons for the lack of correlation between parental reports of activity levels and actigraph measures in the current study may be because parents are reporting on behaviours they observe every day for a one week period, whereas the actigraph is measuring motor activity for short periods of time, up to 3 minutes for each task. A second reason may be as Eaton and Dureski (1986) suggested that the IBQ focuses on caretaking situations such as eating and dressing the infant, whereas the actigraph is measuring activity in response to discrete stimuli. The IBQ revealed that there was a difference in activity levels between the 'non-smoking' and 'smoking' groups, with the 'smoking' group receiving a higher score than the 'non-smoking' group. However, the actigraph measure did not reveal a difference between

these two groups and when the actigraph measure revealed a significant difference when looking at the quantity and timing of the smoke exposure, the IBQ did not. Therefore, we conclude that when investigating the effect of prenatal smoke exposure on infant activity levels, both parental report and actigraph measures should be combined to fully examine the pattern of effects.

Conclusions. Activity levels decreased from baseline to attention at 6 and 12 months. At 12 months activity levels increased and at 6 months activity levels decreased from baseline to negative emotion challenge. No gender differences in activity levels were found at either 6 or 12 months. At 6 months, a dose-dependent effect of prenatal smoke exposure was found with evidence that the 'heavy smoking' group had higher levels of activity during negative emotion than the other groups and there was also evidence that the timing of the smoke exposure may have affected infant motor activity levels, with results showing that infants born to women who smoked throughout their pregnancy showed a smaller decrease in activity from baseline to attention than infants who had been exposed only in the first trimester. However, these results could not be replicated at 12 months. To investigate whether this pattern of results reflects a true effect of prenatal smoke on motor activity in one year olds, the current study should be replicated with a larger sample and the infants should be followed longitudinally until they reach school age. Moreover, the same emotional challenges should be used at the different assessment points.

The results tentatively suggest that prenatal smoke exposure affects infant motor activity levels at 6 months but future studies will have to determine whether these effects persist into childhood. Infants with high levels of activity during infancy and preschool

years have been found to be at risk of developing ADHD (e.g. Auerbach et al., 2004, 2008; Sonuga-Barke et al., 2005). If it is the case that elevated motor activity levels occur as a result of prenatal smoke exposure and persist throughout childhood then measuring activity levels in infancy with actigraphs could help to identify children at risk for hyperactivity problems, and interventions could be put in place to reduce the negative effects of persistently high activity levels. Measures designed to help women who smoke during their pregnancy, particularly women who smoke heavily and throughout pregnancy, reduce or stop their cigarette consumption may also be beneficial.

CHAPTER 4

INFANT HEART RATE AND THE EFFECT OF PRENATAL SMOKE EXPOSURE

4.1. Introduction

4.1.1. Heart Rate and ADHD

As reviewed in Chapter 1 (section 1.4), there has been much research investigating the link between heart rate (HR) and externalizing behaviour disorders. In 2002, Raine stated that low resting HR was the "best replicated biological correlate of antisocial and aggressive behaviour in children and adolescent populations" (Raine, 2000, p. 417). Many studies have provided support for this statement (e.g. Davies & Maliphant, 1971; Patrick, 1994; Raine et al., 1997; Raine & Venables, 1984; Rogeness et al., 1989; van Goozen et al., 1998; Wadsworth, 1976; West & Farrington, 1977). Further support was provided by Crowell et al. (2006) and Cole et al. (1996), who found evidence that the pattern of cardiac activity identified in children, adolescents and adults with externalizing behaviour problems, was similar in preschool children with externalizing symptoms. Therefore, evidence suggests that low HR during resting conditions is associated with aggressive and antisocial behaviours.

Snoek, van Goozen, Matthys, Buitelaar and van Engeland (2004) investigated the effects of stress on cortisol, HR and skin conductance level in children with Oppositional Defiant Disorder (ODD), Attention Deficit Hyperactivity Disorder (ADHD), comorbid ODD/ADHD and normal controls. It was found that during both the baseline and stressful conditions the ODD group had a significantly lower HR than the ODD/ADHD and ADHD groups and the normal controls. However, further analyses revealed that the

higher HR levels in the ADHD and ODD/ADHD groups were a result of these participants receiving methylphenidate (MPH) treatment and there were in fact no differences in HR between children in the ODD group compared with children in the ADHD or ADHD/ODD group who were not on (MPH). In another study, Herpertz et al. (2001) found that resting HR was not significantly lower in children with both ADHD and conduct disorder (CD), compared with controls, although it did tend to be lower. Iaboni et al. (1997) found that there was no significant difference in HR during baseline between the ADHD and control groups. However, the ADHD children were found to show lower HR responsivity to reward conditions and therefore showed reduced psychophysiological responding, indicating that they had habituated more quickly than controls to reward. Jennings et al. (1997) found that during baseline the ADHD group had shorter inter-beat intervals (thus higher HR) than the controls but this difference was not found to be statistically significant. In a study of 18 children diagnosed with ADHD and 49 normal controls, Shibagaki and Furuya (1997) found that participants diagnosed with ADHD had lower respiratory sinus arrhythmia (RSA) than controls. Van Lang et al. (2007) found that after completing a task, which had been designed to elicit stress, participants with ADHD had less HR reactivity and comorbid ODD/CD was not found to account for this relationship.

4.1.2. Heart Rate in Infants

Measuring HR in infants has been found to be one of the most reliable, sensitive and well validated physiological measures (Campos, 1976; Nigg, 2006). Heart rate is a useful physiological measure when studying infants because it can be measured relatively

unobtrusively and it also has the characteristic of bidirectional responding, meaning it can increase or decrease in response to stimulation (Campos, 1976). A number of studies have shown that HR shows stable individual differences. For example Fracasso, Porges, Lamb and Rosenberg (1994) investigated normative developmental changes and the reliability and stability over time of individual differences in heart period and cardiac vagal tone. They found that infants have established characteristic patterns of cardiac activity towards the end of the first year of life. Calkins and Keane (2004) also found that cardiac activity shows continuity over time. Several studies have shown that cardiac activity is associated with control of attention, emotion, behaviour and effortful control in preschool and school-aged children (Calkins, 1997; Calkins & Keane, 2004; Eisenberg, Fabes, Bustamante, Mathy, Miller & Lindholm, 1988; Huffman et al., 1998; Porges et al. 1994a; Porges et al.1996; Suess, Porges, & Plude, 1994).

Ruff and Rothbart (1996) suggest that changes in HR are a primary indicator of attention. It is suggested that when HR decelerates it is reflecting attention directed outwards, for example as during the processing of novel stimuli. However, HR acceleration reflects attention directed inwards, for example during problem solving tasks. A number of studies have shown that during sustained attention, HR levels decline (e.g. Colombo et al., 2001; Lansink & Richards, 1997; Richards & Casey, 1991; Richards & Gibson, 1997), which supports the suggestion by Ruff and Rothbart (1996). Calkins and Dedmon (2000) suggest that it might be useful to study changes in HR as an indicator of individual differences in the ability to control attention and see if this is related to early behaviour problems.

Provost and Gouin-Decarie (1979) investigated the relationship between cardiovascular reactions and specific emotions in 9- and 12-month-old infants. The experiment included six 3 minute situations which were designed to trigger one of five basic emotions: interest, fear, anger, distress and joy. It was found that HR associated with negative emotions was significantly different from HR associated with positive emotions. Emotions generally considered as being negative such as anger and distress were found to produce significant cardiac acceleration. However, emotions such as interest and joy, which are usually considered as positive, were associated with a small deceleration in HR. Support for the results obtained in this study was provided by Buss et al. (2005), who examined changes in HR, RSA and preejection period (PEP) in 24-month-olds in four increasingly challenging, emotion eliciting tasks. Results showed that as distress increased across the tasks HR increased. No gender differences were found for cardiac activity and the authors concluded that there are no gender differences in underlying physiology.

4.1.3. Effect of Prenatal Smoke Exposure on Heart Rate

Research suggests that the ability of an infant to survive a hypoxic episode may be controlled by the cardiorespiratory system (for review see Chapter 1, section 1.8). It is suggested that sudden infant death syndrome (SIDS) and perinatal injuries may occur as a result of the failure of the cardiorespiratory system of an infant during a hypoxic episode (Oncken et al., 2003; Slotkin et al., 1997). The control of catecholamines by the adrenal medulla is understood to facilitate an infant's survival during hypoxic challenges and as nicotine exposure has been shown to affect cell differentiation within the adrenal

medulla, it is suggested that exposure to nicotine results in the foetal and neonatal response to hypoxia being lost prematurely (Oncken et al., 2003; Slotkin, 1998). Exposure to nicotine prenatally, even at relatively low levels, has been shown to cause changes in the noradrenergic neurotransmitter system, which assists in cardiorespiratory control (Slotkin et al., 1995). Prenatal nicotine exposure has also been found to reduce cardiac reactivity to circulating catecholamines and to sympathetic neuronal stimulation, affecting reactivity to periods of hypoxia, (Slotkin et al., 1997) and it has also been found to affect neuronal development in the cerebellum, which is involved in cognitive functioning (Raine, 2002). Raine (2002) suggests that the effects of prenatal smoke exposure on the functioning of the noradrenergic neurotransmitter system may be particularly important when considering the deficits in autonomic functioning seen in antisocial individuals. Reduced noradrenergic functioning may disrupt the activity of the sympathetic nervous system, which fits with evidence that antisocial individuals have reduced sympathetic arousal (Raine, 1996). Also, the finding that rat pups that have been exposed to nicotine in utero have an increase in cardiac M2-muscarinic cholinergic receptors, which inhibit the functioning of the autonomic system (Slotkin et al., 1999), helps explain the finding that antisocial individuals have low resting HR (Raine, 2002).

Few studies have investigated the effect of prenatal nicotine exposure on cardiac activity in humans. Ginzel et al. (2007) and Morrow et al. (1988) carried out studies looking at the effect of nicotine exposure on foetuses. They found that exposure of the foetus to nicotine resulted in an increase in foetal HR. Browne et al. (2000) assessed autonomic functioning of infants at 2-3 days and 3 months, using blood pressure responses to a passive head-up tilt. The results showed that those neonates, which had

been exposed to smoke prenatally, showed a difference in blood pressure compared with those infants who had not had prenatal smoke exposure, indicating that maternal smoking affects cardiovascular responses of the infant, which are mediated autonomically. Franco et al. (2000) investigated the affect of maternal smoking on offspring cardiac activity by studying infants between 6- and 16-weeks of age. Infants born to non-smoking women were compared with infants born to women who smoked 10 or more cigarettes a day and spectral analyses of HR were evaluated as a function of sleep stages. Results revealed that infants in the smoking and non-smoking groups were characterised by different ratios of the low-frequency and high-frequency components of spectral analysis of HR. Infants in the smoking group were characterised by significantly lower high-frequency powers, which are related to parasympathetic tone, and higher low-frequency (related to sympathetic and parasympathetic system)/ high-frequency ratios than the non-smoking group. This indicated that maternal smoking during pregnancy affects autonomic control and maturation in infants. Søvik et al. (2001) investigated the change in HR during episodes of hyperoxia, hypoxia and hypercapnia in infants between 2 and 82 days of age. Infants born to smokers were compared with infants born to non-smoking mothers and results revealed that the number of cigarettes smoked by the mother was correlated with deeper HR decline and smaller HR rises. The authors concluded that maternal smoking during pregnancy affected the size and time of the HR response in a dose-dependent manner.

Schuetze and Zeskind (2001) found that infants born to mothers who smoked during their pregnancy were more likely to have higher HR in general and higher HR during quiet and active sleep states. This was supported by Schuetze and Eiden (2006)

who found that at 2-4 weeks of age, infants who had been exposed to maternal smoking or environmental tobacco smoke during pregnancy had higher HR and lower RSA than infants with no smoke exposure. A gender effect was also found, with boys in the exposure groups having a higher HR and lower RSA than girls in the exposure groups. The authors propose that their finding of an increase in HR at baseline suggests that the exposed infants may have a change in their neurobehavioural functioning, which may be particularly important when considering other research which has shown that infants at high risk, such as infants born prematurely, have an increased HR and lower RSA (DiPietro, Caughy, Cusson & Fox, 1994; Porges, 1992). Previous research suggests that baseline RSA is a marker of the infant's ability to react both physiologically and behaviourally to external stimuli (Porges et al., 1994b; Stifter, 1989). Therefore, the authors conclude that the increase in physiological arousal observed in exposed infants may alter their interactions with external stimuli (Schuetze & Eiden, 2006). The authors call for further studies to investigate if these changes are observed after the first month of life, as a limitation of this study was that infants were only studied during the first month of life and therefore, it is not clear whether these effects persist beyond this time. Raine (2002) reviews evidence which suggests that prenatal smoke exposure may result in lower resting HR in antisocial adolescents and adults. Therefore, longitudinal studies are required to investigate whether the cardiac profiles of infants exposed to nicotine prenatally are transient or stable. Another limitation of the study by Schuetze and Eiden (2006) was that it only measured cardiac activity when the infants' were asleep and therefore, future studies should include cardiac measures during both resting and challenging situations in order to fully investigate the effects of prenatal smoke exposure.

In contrast to the studies reviewed above, Galland et al. (2000) and Tuladhar et al. (2003) found that there was no difference in HR between infants who had been exposed to nicotine prenatally compared with those who had not. Like Browne et al. (2000), Galland et al. (2000) investigated HR responses following a head-up tilt procedure. Infants were tested at 1 and 3 months of age and results revealed that maternal smoking status was not related to changes in the cardiac indices. However, the smoking group contained only mothers who had smoked 5 or more cigarettes per day during the second trimester of pregnancy and the authors conclude that if a group of infants who had been exposed to heavier levels of smoke had been included, a difference in autonomic responsiveness may have been found. Tuladhar et al. (2003) investigated the cardiac responses of sleeping infants when they were aroused in order to investigate whether sleeping position or maternal smoking had an effect on autonomic functioning. Twenty-four infants were studied at 2-3 weeks and 5-6 months and results showed that there were no differences in cardiac activity between infants born to non-smokers compared with infants born to smokers. However, this was a small sample size and the procedure unique. Therefore, before firm conclusions can be drawn about whether prenatal smoke exposure affects cardiac activity, more research is needed, which studies infants longitudinally and assesses HR during resting conditions and also during cognitive and emotional challenge.

4.1.4. The Current Study

The aim of the current study was to measure HR in infants at 6 and 12 months, across a range of situations, and to consider the role of prenatal smoke exposure on infant HR. The 6 month visit was carried out in the home and the 12 month visit was carried out

in the laboratory. The situations were: (1) a baseline period when the child was sitting quietly, (2) an attention task, where the child was given a novel toy to play with for 3 minutes, and finally (3) a negative emotion challenge paradigm. Heart rate data were collected throughout the tasks. It was hypothesised that firstly, HR would be lower during attention than during baseline, in line with findings by Colombo et al. (2001), Lansink and Richards (1997), Provost and Gouin-Decarie (1979), Richards and Gibson (1997), Richards and Casey (1991) and Ruff and Rothbart (1996) and secondly, HR would be higher during negative emotion challenge than during baseline, in line with the results found by Buss et al. (2005) and Provost-Decarie (1979). Fracasso et al. (1994) and Calkins and Keane (2004) have found HR to be relatively stable in infants and therefore, we expected to find correlations in HR between 6 and 12 months. Stifter and Jain (1996), Alkon et al. (2006) and Richards, Alexander, Shinebourne, de Swiet, Wilson and Southall (1984) found evidence that HR decreases during the first year of life and therefore, we expected that HR at 12 months would be lower than HR at 6 months.

Buss et al. (2005) found that there was no difference in cardiac activity between boys and girls in a sample of 2-year-olds. However, in a study by Calkins and Dedmon (2000), also in a sample of 2 year-olds, it was found that boys had a lower HR than girls. Scarpa, Raine, Venables and Mednick (1997) also found a significant gender difference in HR with boys having a lower HR. However, this study used a sample of 3 year-olds. Another study found that during the neonatal period male infants had a lower HR during baseline than female infants (Nagy, Orvos, Bardos & Molnar, 2000). However, Richards et al. (1984) found that males had higher HRs than females in the first 6 months of life but this difference was most marked in the first 6 weeks of life. However, Alkon, Lippert,

Vujan, Rodriquez, Boyce and Eskenazi (2006) found no gender difference in HR or RSA in 6 and 12 infants. Campos, Emde, Gaensbauer and Henderson (1975) also found no gender effect when looking at infants aged 5 and 9 months of age. Given previous conflicting findings, we aimed to examine the question: are there gender differences in HR at 6 and 12 months during baseline, attention and negative emotion?

The literature examining an association between prenatal maternal smoking and infant cardiac activity is fairly limited. Most studies have focused on the neonatal period and therefore, it is not clear whether the results found persist beyond the first weeks of life. Therefore, prospective, longitudinally designed studies are urgently needed in this area. Also, a review of the literature revealed that no previous studies, investigating the effects of prenatal smoke exposure, have included measures of HR under resting and cognitive and emotional challenge situations. Very few studies looking at cardiac activity in general, particularly following prenatal smoke exposure, have included measures of HR reactivity (Alkon et al., 2006; Calkins & Keane, 2004). This is a limitation of previous studies because measures of reactivity take account of resting state when assessing the response of an individual to a discrete stimulus or challenge (Matthews, 1986). Previous studies investigating the link between maternal smoking during pregnancy and infant HR have reported mixed results. Some studies suggest that maternal prenatal smoking results in a change in offspring cardiac activity (Browne et al., 2000; Franco et al., 2000; Søvik et al., 2001), which is largely supported by studies carried out with animals (Oncken et al., 2003; Slotkin et al., 1995, 1997; Slotkin, 1998). However, some other studies suggest there is no link between maternal smoking during pregnancy and cardiac activity in the offspring (Galland et al., 2000; Tuladhar et al., 2003).

The current study aimed to address some of these conflicting results by examining the effect of prenatal smoke exposure on infant HR during both resting and challenging situations and by using a prospective, longitudinal design. The current study examined the effect of prenatal smoke exposure by comparing offspring born to smokers with offspring born to non-smokers, but we also considered the quantity of cigarettes smoked in pregnancy and the timing of the smoke exposure. It was hypothesised that infants, who had been exposed to smoke in utero would show higher HR than infants with no prenatal smoke exposure (Schuetze & Eiden, 2006; Schuetze & Zeskind, 2001) and that there would be a dose dependent effect, in line with findings by Søvik et al. (2001) and Franco et al. (2000). No previous studies have investigated whether the timing of the smoke exposure affects infant cardiac activity, but it was predicted that infants born to mothers who smoked throughout pregnancy would show higher HR than infants born to women who smoked only in the first trimester, who in turn would have higher HR than infants born to mothers who did not smoke at all. This is based on the findings that nicotine affects foetal brain development and function from as early as 4 or 5 weeks gestation (Ernst et al., 2001; Hellström-Lindahl et al., 2001; Miao et al., 1998; Slotkin, 1998; Van de Kamp & Collins, 1994).

4.2. Method

4.2.1. Participants

As described in Chapter 2 (section 2.2.1) a subsample of 130 participants taking part in the CCDS were selected. Of the 130 participants, 59 women reported smoking during pregnancy and the remaining 71 women did not smoke during pregnancy. A full description of the recruitment of the sample and sample characteristics are reported in Chapter 2.

4.2.2. Measures

Nicotine during pregnancy. This variable has been described in Chapter 2 (section 2.2.2). Smoking during pregnancy was defined in three ways; the first variable was dichotomous (non-smoking/ smoking) and the other two variables were categorical (non-smoking/ light smoking/ heavy smoking and non-smoking/ 1st trimester/ all trimester).

Attention. See Chapter 2 (section 2.2.2) for a full description of this variable.

Negative emotion challenge. See Chapter 2 (section 2.2.2) for a full description of this variable.

Heart rate. Heart rate data was collected using the ActiGraph ActiTrainer (Manufacturing Technology, Inc, MTI) worn in conjunction with a Polar Wearlink T31 device connected to a chest strap. Before use the electrode areas of the Polar strap were moistened with water. The Polar strap was attached around the infants' sternum and secured so that it was a snug fit, with the Polar logo on the connector positioned in a central and upright position. The ActiGraph ActiTrainer was attached to the infants' leg.

Once the Polar strap was attached securely it created a unique coded communication link with the ActiGraph ActiTrainer. This unique link prevented data from other Polar straps corrupting the HR data. The ActiGraph ActiTrainer collected and stored the HR data transmitted from the Polar strap (ActiTrainer User Manual, 2007). Heart rate data were stored as the average beats-per-minute per epoch (ActiLife Users Manual, 2008); with an epoch defined as a 15 second block in this study. The HR data were downloaded and stored simultaneously with the activity data (see Chapter 3 for activity data). Baseline and attention were 3 minutes and negative emotion challenge lasted for 30 seconds at the 6 month assessment and the duration of the negative emotion challenge at the 12 month assessment was analysed, which ranged from 3 to 6 minutes. Thus, there were 12 15 second epochs for baseline and attention, 2 15 second epochs for negative emotion challenge at 6 months and between 12 and 24 15 second epochs for negative emotion challenge at 12 months. The data were cleaned and divided into 30 second epochs and for analyses a mean HR score was calculated for each condition, after first checking that there was no significant effect of time on HR within each condition.

4.2.3. Procedure

The procedure has been explained in Chapter 2 (section 2.2.3).

4.2.4. Data analysis

At the 6 month assessment, the HR data for 13 participants were not collected because of a delay in the delivery of the ActiTrainer ActiGraphs from the manufacturers, meaning only activity data could be collected for these participants. One infant had a

heart condition and the mother of the participant requested that the Polar Wearlink strap was not worn. As a result of equipment malfunction, extreme anomalies in the data or the task not being completed, 18 participants had missing data during baseline, 13 during attention and 17 during negative emotion (see Table 4.1). At the 12 month assessment, 13 participants did not attend the assessment and 1 infant did not wear the Polar Wearlink strap because of a severe heart condition. Seventeen participants had missing data during baseline and 15 during attention and negative emotion tasks, as a result of equipment malfunction, extreme anomalies in the data or the task not being completed (see Table 4.1).

Table 4.1: Number of Participants in Each Smoking Group at Baseline, Attention and Negative Emotion Challenge

	Baseline		**Attention**		**Negative emotion**	
	6 mth	12 mth	6 mth	12 mth	6 mth	12 mth
Non-smoking	62	59	66	59	64	60
Smoking	37	41	38	43	36	42
Light smoking	25	25	26	26	25	26
Heavy smoking	11	13	11	14	10	14
1st trimester	9	11	9	11	9	11
All trimester	22	22	22	23	22	22

Mean HR levels at baseline, attention and negative emotion challenge were used for analyses. The importance of studying HR reactivity in addition to mean HR was highlighted by Althaus, Gomarus, Wijers, Mulder, van Velzen and Minderaa (2005) and Alkon et al. (2006). Therefore, a measure of reactivity was calculated as the percentage change in HR from baseline to attention and from baseline to negative emotion task. The following equation was used to calculate reactivity: $((HR_{condition} - HR_{baseline}) / HR_{baseline})$

* 100. Thus, reactivity represents a change in HR that is comparable between conditions because it takes into account baseline state.

At the 6 month assessment, age of infant was not correlated with HR at baseline ($r = -.05$, $p=.72$), attention ($r = -.12$, $p=.35$) or negative emotion ($r = -.15$, $p=.24$) and this pattern was repeated at the 12 month assessment (baseline: $r = .03$, $p=.85$; attention: $r = -.10$, $p=.44$: negative emotion: $r = .03$, $p=.81$). Therefore, there was no need to control for age within the 6 and 12 month analyses.

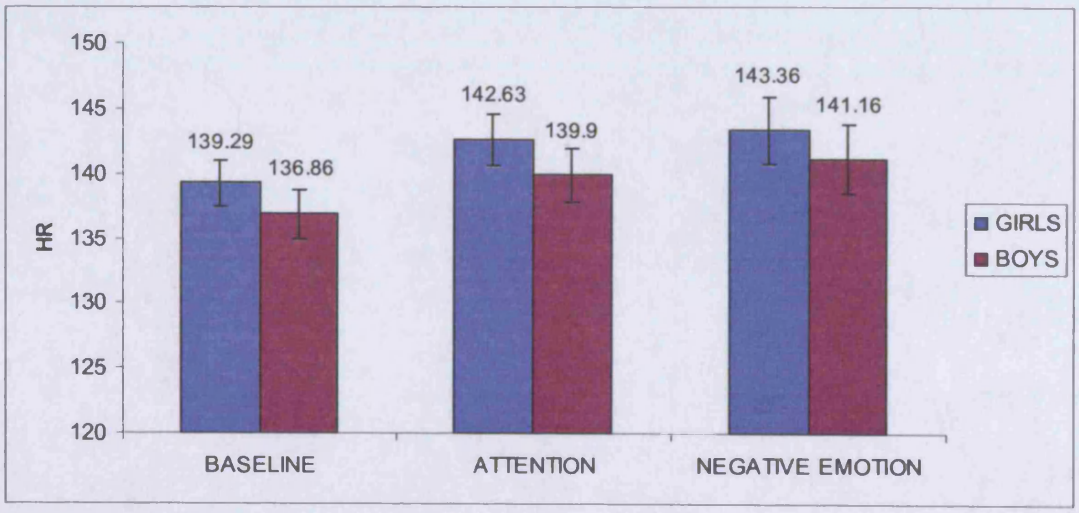
The data were screened for violations in the assumptions of parametric tests, i.e. it was verified that the data in each of the cells were normally distributed and the variances in each of the cells were not different from each other. Extreme outliers were removed from analyses and in analyses where the homogeneity of variance assumption was violated a more conservative F-test was used (Greenhouse-Geisser). The LSD test was used to follow up any significant ANOVA results. A significance level of $p<.05$ was adopted throughout this paper but trends up to $p<.10$ were also indentified.

4.3. Results

4.3.1. Analyses at 6 Months

Effect of condition and gender. The effect of condition on HR was only investigated in children who had not been exposed to prenatal smoke, as this group formed the comparison group for the study. A repeated measures ANOVA showed there was a significant main effect of condition ($F(1.56, 89.17) = 6.69$, $p<.01$), no effect of gender ($F(1, 57) = 0.79$, $p=.38$) and no interaction between condition and gender ($F(1.56, 89.17) = 0.03$, $p=.95$; see Figure 4.1). Planned comparisons of the main effect revealed there was a significant difference between baseline and attention (baseline $M = 138.13$, $SD = 9.90$; attention $M = 141.33$, $SD = 10.99$; $p<.001$) and between baseline and negative emotion (negative emotion $M = 142.31$, $SD = 14.18$; $p<.01$) but there was no significant difference between attention and negative emotion ($p=.46$). Thus, baseline HR was lower than negative emotion HR, but also lower than attention HR, which was unexpected.

Figure 4.1: Mean HR during Baseline, Attention and Negative Emotion Challenge for Girls and Boys at 6 Months (n=59)



Effect of smoking on HR and condition. In the first analysis, infants born to mothers who reported smoking during pregnancy were compared with infants born to mothers who did not smoke during pregnancy. A repeated measures ANOVA revealed that there was a main effect of condition on HR ($F(1.58, 148.90) = 7.68$, $p<.01$) but no effect of smoking group ($F(1, 94) = 0.23$, $p=.63$), nor was there an interaction between condition and smoking group ($F(1.58, 148.90 = 2.48$, $p=.10$; see Table 4.2). When changes in HR compared with baseline were considered, independent samples t-tests revealed that there was no difference between the 'non-smoking' and 'smoking' groups for attention ($t(91) = -1.20$, $p=.23$) or negative emotion ($t(91) = 1.53$, $p=.13$; see Table 4.2).

Table 4.2: HR during Baseline, Attention and Negative Emotion Challenge for 'Non-Smoking' and 'Smoking' Groups at 6 Months[a]

	Non-smoking (n=62)		Smoking (n=37)	
	Mean	SD	Mean	SD
Baseline	137.62	10.58	137.69	11.29
Attention	141.04	11.13	141.50	10.42
Negative emotion	142.68	14.33	139.06	10.70
Attention % change	2.14	4.26	3.27	4.42
Negative emotion % change	3.00	7.29	0.76	5.71

[a] The n for individual conditions vary slightly because of missing data

In the second set of analyses, the number of cigarettes the mother reported smoking during her pregnancy was considered. The 'smoking' group was subdivided into 'light smoking' and 'heavy smoking' groups, which were compared with the 'non-smoking' group (see Chapter 2 section 2.2.2. for a full explanation). A repeated measures ANOVA showed that there was again a main effect of condition ($F(1.57, 144.20) = 4.93$,

p<.01), no effect of smoking group (F (2, 92) = 1.16, p=.32) and no interaction between condition and smoking group (F (3.14, 144.20) = 1.45, p=.23; see Table 4.3).

When changes in HR compared with baseline were considered, one-way ANOVAs revealed that there was a marginally significant difference between the 3 smoking groups for attention (F (2, 89) = 2.58, p=.08) and a significant difference for negative emotion (F (2, 89) = 3.73, p<.05). Analysis of the simple effects for attention showed that the 'heavy smoking' group had a significantly larger increase in HR from baseline than the 'non-smoking' (p<.05) and 'light smoking' groups (p<.05; see Figure 4.2). When looking at the simple effects for negative emotion, it was revealed that the 'non-smoking' (p<.05) and the 'heavy smoking' (p<.05) groups had a larger increase in HR from baseline than the 'light smoking' group. Figure 4.2 indicates that the 'light smoking' group showed a decrease in HR from baseline to negative emotion and that the 'non-smoking' and 'heavy smoking' groups both showed an increase in HR.

Figure 4.2: HR Reactivity during Attention and Negative Emotion Challenge for 'Non-Smoking', 'Light Smoking' and 'Heavy Smoking' Groups at 6 Months (n=92)

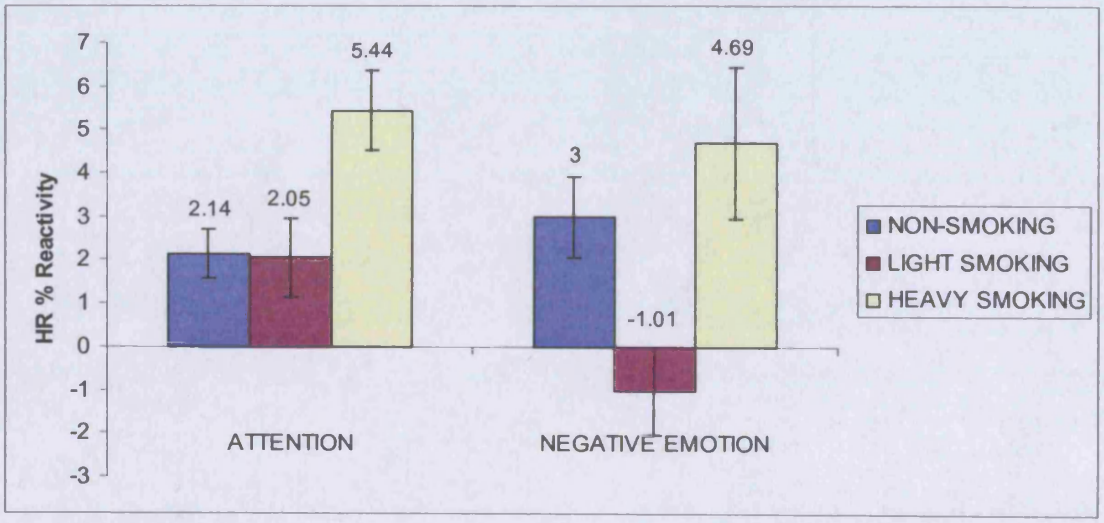


Table 4.3: HR during Baseline, Attention and Negative Emotion Challenge for 'Non-Smoking', 'Light Smoking' and 'Heavy Smoking' Groups at 6 Months

	Non-smoking (n=60)		Light smoking (n=25)		Heavy smoking (n=10)	
	Mean	SD	Mean	SD	Mean	SD
Baseline	137.62	10.58	136.78	10.89	140.33	12.05
Attention	141.04	11.13	139.58	9.72	145.48	11.61
Negative emotion	142.68	14.33	136.96	10.03	144.00	11.67

In the third set of analyses, the timing of smoke exposure during pregnancy was considered. As described in Chapter 2 (section 2.2.2), the 'smoking' group was subdivided into the '1st trimester' and 'all trimester' groups, which were compared with the 'non-smoking' group. A repeated measures ANOVA revealed there was a main effect of condition ($F(1.52, 131.92) = 5.72$, $p<.01$), no effect of timing of smoke exposure ($F(2, 87) = 0.70$, $p=.50$) and no interaction between condition and timing of smoke exposure ($F(3.03, 131.92) = 1.58$, $p=.20$; see Table 4.4). When considering changes in HR compared with baseline, one-way ANOVAs revealed that there were no significant differences between the 3 smoking groups for attention ($F(2, 85) = 1.03$, $p=.36$) or negative emotion ($F(2, 84) = 1.10$, $p=.34$).

Table 4.4: HR at Baseline, Attention and Negative Emotion Challenge for 'Non-Smoking', '1st Trimester' and 'All Trimester' Smoking Groups at 6 Months[a]

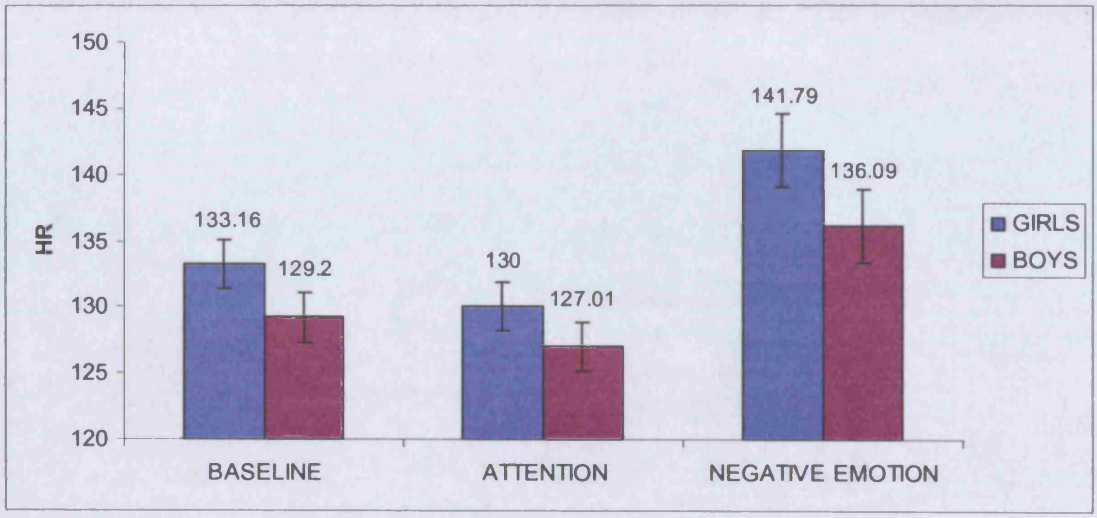
	Non-smoking (n=62)		1st trimester (n=9)		All trimester (n=21)	
	Mean	SD	Mean	SD	Mean	SD
Baseline	137.62	10.58	133.03	11.87	139.48	14.33
Attention	141.04	11.13	139.39	8.26	143.30	9.77
Negative emotion	142.68	14.33	136.44	11.29	139.83	11.76
Attention % change	2.14	4.26	3.56	4.39	3.53	4.11
Negative emotion % change	3.00	7.29	0.97	6.74	0.47	5.97

[a] The n for individual conditions varies slightly because of missing data

4.3.2. Analyses at 12 Months

Effect of condition and gender. A repeated measures ANOVA showed there was a significant main effect of condition ($F(1.37, 69.96) = 41.67$, $p<.001$), no effect of gender ($F(1, 51) = 2.26$, $p=.14$), nor an interaction between condition and gender ($F(1.37, 69.96) = 0.67$; $p= .46$; see Figure 4.3). Planned comparisons of the main effect revealed there was a significant difference between baseline and attention (baseline: $M = 131.21$, $SD = 9.77$; attention: $M = 128.53$, $SD = 9.72$; $p<.001$), baseline and negative emotion (negative emotion: $M = 138.99$, $SD = 14.34$; $p<.001$) and attention and negative emotion ($p<.001$). Therefore, as predicted, HR during baseline was lower than during negative emotion and HR during attention was lower than during baseline.

Figure 4.3: Mean HR in Baseline, Attention and Negative Emotion Challenge for Girls and Boys at 12 Months (n=53)



Effect of smoking on HR and condition. When comparing the 'smoking' with the 'non-smoking' groups a repeated measures ANOVA revealed that there was a main effect of condition ($F(1.45, 125.93) = 76.63$, $p<.001$), no main effect of smoking group ($F(1,$

87) = 0.00, p=.99) and no interaction between condition and smoking group (F (1.45, 125.93) = 1.47, p=.23; see Table 4.5). When considering change in HR from baseline to condition, independent samples t-tests revealed there were no differences between the 'non-smoking' and 'smoking' groups for attention (t (92) = 0.30, p=.77) or negative emotion (t (91) = -0.97, p=.34; see Table 4.5).

Table 4.5: HR at Baseline, Attention and Negative Emotion Challenge for 'Non-Smoking' and 'Smoking' Groups at 12 Months[a]

	Non-smoking (n=52)		Smoking (n=37)	
	Mean	SD	Mean	SD
Baseline	130.94	9.66	130.61	11.79
Attention	128.36	9.73	126.88	9.99
Negative emotion	138.29	13.53	140.07	10.09
Attention % change	-2.11	3.70	-2.36	4.57
Negative emotion % change	5.74	7.75	7.45	9.24

[a] The n for individual conditions varies slightly because of missing data

In the second set of analyses, looking at quantity of smoke exposure, a repeated measures ANOVA revealed there was again a main effect of condition (F (1.43, 120.31) = 59.13, p<.001), no main effect of smoking group (F (2, 84) = 0.04, p=.96) and no interaction between condition and smoking group (F (2.87, 120.31) = 0.85, p=.47; see Table 4.6). When considering changes in HR compared with baseline, one-way ANOVAs revealed there were no significant differences between the 'non-smoking', 'light smoking' and 'heavy smoking' groups for attention (F (2, 88) = 1.02, p=.37) or negative emotion (F (2, 88) = 0.44, p=.65, see Table 4.6).

Table 4.6: HR at Baseline, Attention and Negative Emotion Challenge for 'Non-Smoking', 'Light Smoking' and 'Heavy Smoking' Groups at 12 Months[a]

	Non-smoking (n=55)		Light smoking (n=24)		Heavy smoking (n=13)	
	Mean	SD	Mean	SD	Mean	SD
Baseline	130.94	9.66	130.49	12.09	130.69	12.74
Attention	128.36	9.73	127.38	8.96	125.22	12.42
Negative emotion	138.29	13.53	140.25	9.40	139.30	12.42
Attention % change	-2.11	3.70	-1.55	4.25	-3.51	4.77
Negative emotion % change	5.74	7.75	7.63	10.43	6.91	7.70

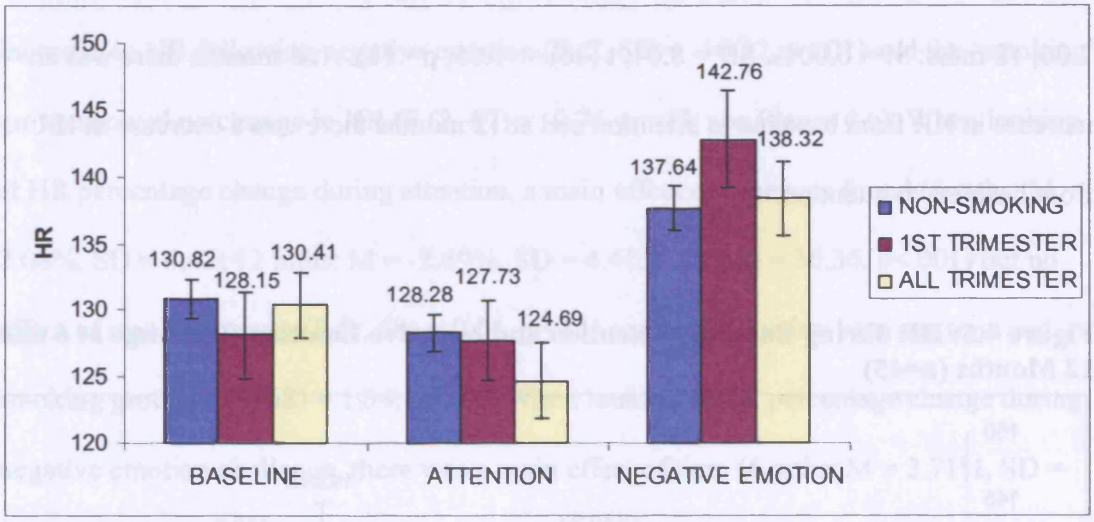
[a] The n for individual conditions varies slightly because of missing data

In the third set of analyses, looking at timing of smoke exposure, a repeated measures ANOVA showed there was again a main effect of condition ($F(1.48, 115.55) = 67.70$, $p<.001$), no main effect of smoking group ($F(2, 78) = 0.13$, $p=.88$) and a significant interaction between condition and smoking group ($F(2.96, 115.55) = 2.83$, $p<.05$; see Figure 4.4). Examining the interaction further, results revealed that there was a marginally significant difference between the 'non-smoking' and 'all trimester' smoking groups during attention, with the 'non-smoking' group having a higher HR than the 'all trimester' smoking group ($p=0.07$). The '1st trimester' group showed no significant difference in HR between baseline and attention ($p=0.81$), whereas both the 'non-smoking' ($p<0.01$) and 'all trimester' ($p<0.01$) smoking groups had significantly higher HRs during baseline than attention. However, there were no significant differences between smoking groups during baseline ($p=0.72$) or negative emotion ($p=0.39$).

When considering changes in HR compared with baseline, one-way ANOVAs revealed there were no significant differences between the smoking groups during attention ('non-smoking' $M = -2.01$, $SD = 3.77$; '1st trimester' $M = -0.29$, $SD = 3.15$; 'all trimester' $M = -3.56$, $SD = 5.68$; $F(2, 86) = 2.29$, $p=.11$), but there was a significant

difference between the 'non-smoking' (M = 4.82, SD = 6.13), '1st trimester' (M = 11.61, SD = 7.57) and 'all trimester' (M = 7.56, SD = 7.65) smoking groups during negative emotion (F (2, 80) = 5.10, p<.01). Planned comparisons showed a significant difference between the 'non-smoking' and '1st trimester' (p<.01) groups only, with the '1st trimester' smoking group showing a larger increase in HR from baseline to negative emotion than the 'non-smoking' group.

Figure 4.4: Mean HR at Baseline, Attention and Negative Emotion Challenge for 'Non-Smoking', '1st Trimester' and 'All Trimester' Smoking Groups at 12 Months (n=81)



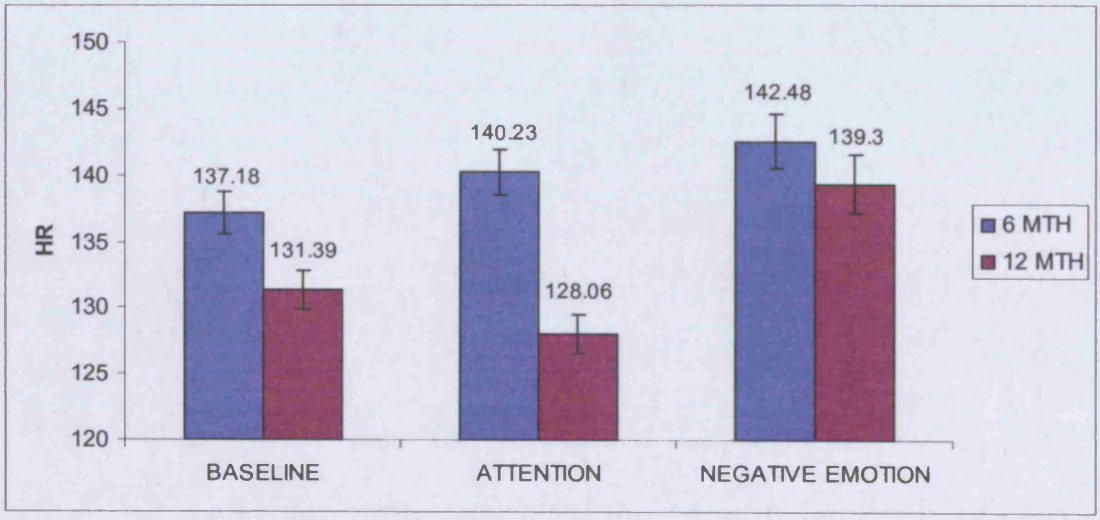
4.3.3. Comparing Heart Rate at 6 and 12 Months

Effect of time on HR. Infant HR at 6 and 12 months was positively correlated during baseline (r = .28, p<.05) and attention (r = .27, p<.05), but not during negative emotion challenge (r = .09, p=.53). A repeated measures ANOVA revealed that there was a main effect of condition (F (1.46, 64) = 30.11, p<.001), a main effect of time (F (1, 44) = 15.06, p<.001) and a significant interaction between condition and time (F (1.33, 58.35)

= 9.92, p<.01). Analysis of the simple effects revealed that baseline HR was higher at 6 months than at 12 months (p<.01) and the same applies for attention (p<.001), but not during negative emotion challenge (see Figure 4.5).

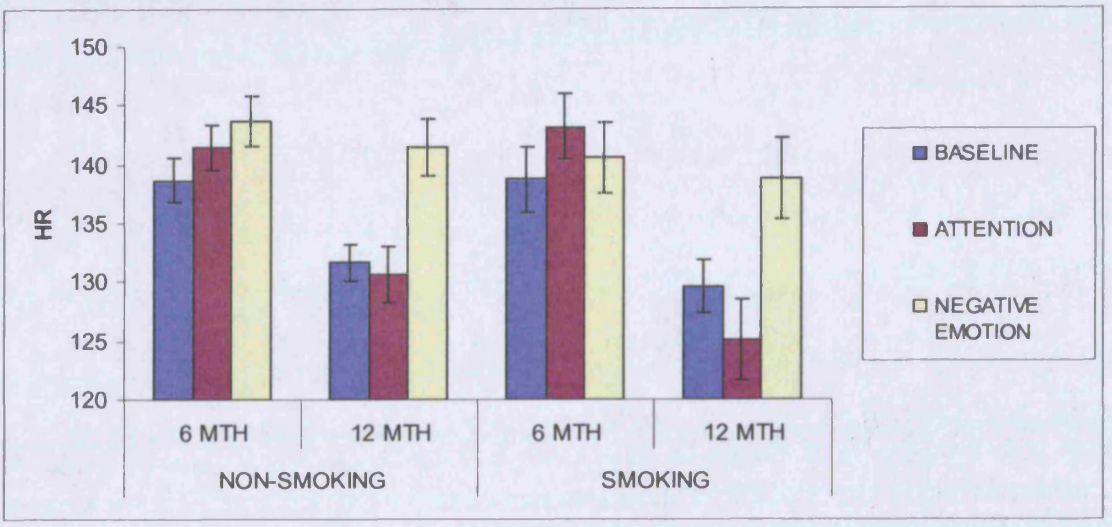
When considering changes in HR compared with baseline, there was no correlation between attention reactivity scores at 6 and 12 months (r = -.00, p=.99) and similarly for negative emotion challenge (r = -.15, p=.33). However, paired samples t-tests revealed that there was a significant difference in attention reactivity scores between 6 and 12 months (6 mths: M = 1.71%, SD = 4.18; 12 mths: M = -2.40%, SD = 3.68; t (46) = 5.06, p<.001) but not during negative emotion challenge (6 mths: M = 3.25%, SD = 7.06; 12 mths: M = 6.00%, SD = 8.04; t (46) = -1.65, p=.11). At 6 months there was an increase in HR from baseline to attention and at 12 months there was a decrease in HR from baseline to attention.

Figure 4.5: HR during Baseline, Attention and Negative Emotion Challenge at 6 and 12 Months (n=45)



Effect of condition, smoking group and time. When comparing the non-smoking with the smoking group, a repeated measures ANOVA showed that there was a main effect of condition ($F(1.80, 122.05) = 27.38$, $p<.001$), a main effect of time ($F(1, 68) = 17.23$, $p<.001$), an interaction between condition and time ($F(1.75, 119.13) = 16.93$, $p<.001$) and a marginally significant 3-way interaction ($F(1.75, 119.13) = 1.67$, $p=.08$). However, there was no interaction between smoking group and time ($F(1, 68) = 0.55$, $p=.46$) nor between smoking group and condition ($F(1.80, 122.05) = 0.47$, $p=.61$). Analysis of the simple effects only revealed a difference between the 'non-smoking' and 'smoking' groups at 6 months, where the 'non-smoking' group showed a significant increase in HR following negative emotion ($F(2, 67) = -10.32$, $p<.01$) and the 'smoking' group showed no change in HR ($F(2, 67) = -0.74$, $p=.43$; see Figure 4.6). When looking at HR percentage change during attention, a main effect of time was found (6 mths: M = 2.08%, SD = 4.42; 12 mths: M = -2.69%, SD = 4.41; $F(1, 68) = 36.36$, $p<.001$) but no effect of smoking group ($F(1, 68) = 0.04$, $p=.83$) and no interaction between time and smoking group ($F(1, 68) = 1.34$, $p=.25$). When looking at HR percentage change during negative emotion challenge, there was a main effect of time (6 mths: M = 2.71%, SD = 6.71; 12 mths: M = 6.48%, SD = 8.44; $F(1, 66) = 8.37$, $p<.01$) but no effect of smoking group ($F(1, 66) = 0.00$, $p=.95$) and no interaction ($F(1, 66) = 1.17$, $p=.28$).

Figure 4.6: Mean HR at Baseline, Attention and Negative Emotion Challenge at 6 and 12 Months for 'Non-Smoking' and 'Smoking' Groups (n=70)



With respect to the quantity of cigarettes consumed, a repeated measures ANOVA showed there was a main effect of condition ($F(1.51, 94.97) = 20.94$, $p<.001$), a main effect of time ($F(1, 63) = 25.71$, $p<.001$) and a significant interaction between condition and time ($F(1.48, 93.20) = 19.64$, $p<.001$). However, there was no interaction between time and smoking group ($F(2, 63) = 1.98$, $p=.15$), between condition and smoking group ($F(3.02, 94.97 = 0.17$, $p=.92$), nor was there a 3-way interaction ($F(2.96, 93.20) = 1.28$, $p=.29$; see Table 4.7). When considering change in HR from baseline to attention, a main effect of time was found ($F(1, 66) = 32.96$, $p<.001$), no effect of smoking group ($F(2, 66) = 0.96$, $p=.39$) and there was a marginally significant interaction between time and smoking group ($F(2, 66) = 2.72$, $p=.07$; see Table 4.7). Examining the interaction effect further, it became clear that at 6 months the 'heavy smoking' group had a larger increase in HR from baseline to attention than the 'non-smoking' ($p<.05$) and the 'light smoking' ($p<.05$) groups. However, at 12 months there were no differences between the groups. When considering change in HR compared with baseline during negative emotion

challenge, there was a main effect of time ($F(1, 64) = 5.01$, $p<.05$) but no effect of smoking group ($F(2, 64) = 1.05$, $p=.36$) nor was there an interaction between time and smoking group ($F(2, 64) = 0.92$, $p=.40$; see Table 4.7).

With respect to timing of smoke exposure, a repeated measures ANOVA revealed a main effect of condition ($F(1.48, 88.66) = 18.83$, $p<.001$), a main effect of time ($F(1, 60) = 16.14$, $p<.001$) and a significant interaction between condition and time ($F(1.50, 89.76) = 15.04$, $p<.001$). However, there was no interaction between time and smoking group ($F(2, 60) = 2.00$, $p=.14$), between condition and smoking group ($F(2.96, 88.66) = 0.87$, $p=.46$), or 3-way interaction ($F(2.99, 89.76) = 1.28$, $p=.29$; see Table 4.7). When considering change in HR from baseline to attention, there was a main effect of time ($F(1, 63) = 13.81$, $p<.001$), but no effect of smoking group ($F(2, 63) = 0.78$, $p=.46$) nor an interaction ($F(2, 63) = 1.75$, $p=.18$). When looking at HR compared with baseline during negative emotion challenge, a main effect of time was found ($F(1, 61) = 6.25$, $p<.05$ but no effect of smoking group ($F(2, 61) = 0.10$, $p=.90$) nor an interaction between time and smoking group ($F(2, 61) = 0.62$, $p=.54$).

Table 4.7: Mean HR at Baseline, Attention and Negative Emotion Challenge Tasks at 6 and 12 Months for Smoking Groups [a]

			Baseline	Attention	Negative emotion	Attention % change	Negative emotion % change
Non-smoking (n=71)	6 mth	M	136.93	140.1	142.22	1.71	3.25
		SD	10.77	11.42	13.83	4.18	7.06
	12 mth	M	131.07	127.84	138.48	-2.4	6
		SD	9.51	9.73	13.68	3.68	8.04
Light smoking (n=39)	6 mth	M	137.77	140.43	138.63	0.86	-0.43
		SD	11	11.02	10.17	4.51	5.1
	12 mth	M	131.04	127.03	139.87	-2.79	7.11
		SD	13.99	10.42	8.44	6.05	11.15
Heavy smoking (n=17)	6 mth	M	141.3	147.92	133.64	5.82	5.31
		SD	12.8	11.88	12.29	2.58	5.99
	12 mth	M	126.46	120.94	135.95	-4.11	8.35
		SD	12.39	13.49	12	5.59	5.42
1st trimester (n=15)	6 mth	M	134.34	140.14	139.5	2.23	1.39
		SD	13.04	7.81	8.96	5.25	6.16
	12 mth	M	129.45	129.8	141.96	0.39	8.97
		SD	9.67	11.09	7.62	2.85	8.68
All trimester (n=33)	6 mth	M	141.54	145.76	141.39	3.24	1.15
		SD	11.24	12.36	12.2	4.45	6.58
	12 mth	M	128.01	121.92	135.53	-4.06	6.95
		SD	14.97	11.34	10.13	6.72	10.21

[a] The n for individual conditions varies slightly because of missing data

4.4. Discussion

The main goals of the current chapter were to investigate changes in HR following procedures designed to elicit attention and induce negative emotion in infants at 6 and 12 months of age. Potential gender differences were also considered. The second main aim of the research was to establish the effect of prenatal smoke exposure on HR.

Is there a reduction in HR during sustained attention? It was predicted that HR would be lower during attention than during baseline in line with previous studies (Colombo et al., 2001; Lansink & Richards, 1997; Provost & Gouin-Decarie, 1979; Richards & Casey 1991; Richards & Gibson, 1997; Ruff & Rothbart, 1996). Results from the 6 month assessment showed that HR was higher during attention compared with baseline, but indeed lower at the 12 month assessment. One reason for the conflicting results is that the object used in the current study could be manipulated by the infant, whereas in previous studies measuring attention and HR, the stimulus is simply observed and this difference in object affordance may account for the discrepancy in findings. To confirm this, the task should be repeated with the current toy presented, in a counterbalanced order, with a stimulus which cannot be manipulated and is simply observed.

Is there an effect of emotion induction on HR? In line with previous research, it was predicted that HR during baseline would be lower than during negative emotion challenge at 6 months and 12 months (Buss et al., 2005; Provost & Gouin-Decarie, 1979). In a sample of 2-year-olds Buss et al. (2005) found that HR increased as distress increased across tasks and Provost and Gouin-Decarie (1979) found that HR accelerated when negative emotions, such as anger and fear, were induced. Results from the current

study showed that HR was significantly higher during the negative emotion induction tasks, compared with baseline, at both 6 and 12 months, providing support for our prediction and also providing evidence that the car seat and bear tasks can be used as valid procedures when measuring negative emotion in infants.

Is there an effect of gender on HR? Previous studies investigating gender differences in cardiac activity have provided conflicting results. For example, Buss et al. (2005) and Alkon et al. (2006) both reported no gender differences in cardiac activity. However, Calkins and Dedmon (2000) and Scarpa et al. (1997) found that boys had lower HR than girls. In the current study we investigated the question: are there gender differences in HR at 6 and 12 months during resting conditions and cognitive and emotional challenge? Results from the current study showed no gender differences during baseline, attention or negative emotion challenge at 6 and 12 months. Both Calkins and Dedmon (2000) and Scarpa et al. (1997) found gender differences in preschoolers. Therefore, it is possible that gender differences in cardiac activity develop after the first year of life. In order to investigate this, the current sample should be studied again during preschool years and HR should be compared between boys and girls during baseline and cognitive and emotional challenge.

Is there an effect of age on HR? It was predicted that there would be a positive correlation between HR at 6 and 12 months of age for each of the conditions, in line with previous results, indicating that individual differences in HR are stable (Calkins & Keane, 2004; Fracasso et al., 1994). When considering HR at baseline and attention, results from the current study supported our prediction. However, contrary to our prediction, we found no correlation during negative emotion challenge, indicating that individual differences in

HR during negative emotion were not stable. This is in line with previous studies, which suggest that negative emotions are not stable in infants. For example, one study found that the continuity of classifying an infant as temperamentally difficult from 6 to 24 months was only about 50% (Lee & Bates, 1985) and Belsky, Fish and Isabella (1992) suggest that negative emotionality may be unstable during infancy and preschool years and factors such as family conditions may account for some or all of the variability (Crockenberg, 1986). The use of a different task to elicit negative emotion at 6 and 12 months may also explain the finding. However, given that previous studies have found HR increases during a range of negative emotions, including distress, anger and fear (e.g. Buss et al., 2005; Provost & Gouin-Decarie, 1979), we suggest that this is unlikely to be the reason but replication of the study using the same negative emotion procedure at 6 and 12 months would confirm this hypothesis.

We predicted that HR at 12 months would be lower than HR at 6 months and results supported our hypothesis, with the finding of a main effect of time on HR. Post-hoc analyses revealed that HR was lower at 12 months than at 6 months during baseline and attention, providing evidence that during the first year of life, HR decreases, which supports results from previous studies (e.g. Alkon et al., 2006; Harper, Hoppenbrouwers, Sterman, McGinty & Hodgman, 1976; Richards et al., 1984; Stifter & Jain, 1996). We also found a difference in HR reactivity between 6 and 12 months during attention, with an increase in HR from baseline to attention at 6 months and a decrease in HR at 12 months. Alkon et al. (2006) found that both HR and RSA changed from 6 to 12 months, which provides evidence that the parasympathetic nervous system undergoes developmental changes during the first year of life, with an increase in parasympathetic

activation and a subsequent decrease in HR. To confirm these findings future studies should include measures of parasympathetic (e.g. RSA) and sympathetic (e.g. preejection period, PEP) activity.

However, in the current study there was no significant difference in HR or HR reactivity between 6 and 12 months during stress inducing situations. Previous research suggests that negative emotionality increases during the first year of life (Auerbach et al., 2008; Campos, Emde, Gaensbauer & Henderson, 1975; Gartstein & Rothbart, 2006; Rothbart, 1981; Scarr & Salapatek, 1970) and the finding that there was no age difference in HR during negative emotion induction but there was an age difference during baseline and attention, adds some support to these findings. Scarr and Salapatek (1970) found that at around 12 months of age infants become fearful of new people and strange objects and the bear procedure incorporates these elements, making it a useful measure for studying negative emotion in 12-month-olds.

Is there an effect of maternal smoking in pregnancy on HR? As discussed in the Introduction to this chapter (section 4.1.3), there have been very few studies investigating the effect of prenatal smoke exposure on cardiac activity in offspring, especially in humans, and of those that have been carried out most have focused on the neonatal period and none have measured HR during cognitive and emotional challenge. The studies that have looked at cardiac activity in infants exposed to smoke whilst in the womb have provided conflicting results, with some studies suggesting there is no effect (Galland et al., 2000; Tuladhar et al., 2003) and others suggesting there may be an effect (Browne et al., 2000; Franco et al., 2000; Søvik et al., 2001). In the first set of analyses, we compared infants born to mothers who smoked during their pregnancy with infants born to mothers

who did not smoke during pregnancy. At 6 and 12 months, results from this analysis revealed there were no differences in HR between the two groups during baseline, attention and negative emotion provocation. However, Franco et al. (2000) found that infants born to smokers were characterised by different ratios of the low- and high-frequency components of spectral analysis of HR compared with non-smokers, indicating that maternal smoking affects autonomic control and maturation in infants. However, the smoking group consisted of women who smoked 10 or more cigarettes a day, suggesting that there may be a dose dependent relationship between maternal smoking and infant outcomes. Søvik et al. (2001) also found evidence of a dose-dependent relationship; with the number of cigarettes smoked by the mother correlating with deeper declines in HR and smaller rises in HR.

Therefore, in the second set of analyses we considered whether the quantity of smoke exposure affected infant HR. When looking at mean HR during baseline, attention and negative emotion induction we found that there was no difference between the smoking groups. However, at 6 months, we found that when a measure of reactivity was used (i.e. percentage change in HR from baseline to condition) there were significant differences between the 'non-smoking', 'light smoking' and 'heavy smoking' groups during attention and negative emotion challenge. Our results showed that during attention the 'heavy smoking' group showed a larger increase in HR from baseline than either the 'non-smoking' or the 'light smoking' group. In normal populations, HR usually decreases from baseline to attention (Colombo et al., 2001; Lansink & Richards, 1997; Provost & Gouin-Decarie, 1979; Richards & Casey 1991; Richards & Gibson, 1997; Ruff & Rothbart, 1996). Therefore, the finding that infants born to mothers who smoked 10 or

more cigarettes a day during pregnancy had a significantly larger increase in HR from baseline to attention than the 'non-smoking' and 'light smoking' groups suggests that heavy smoking during pregnancy interferes with attention in infants at 6 months of age and suggests that there may be a dose-dependent relationship between prenatal smoke exposure and cardiac activity during cognitively challenging situations. Schuetze and Eiden (2006) suggest that an increase in physiological arousal, observed in infants with prenatal smoke exposure, might alter the infants' interaction with external stimuli.

During negative emotion challenge, a different pattern of results was seen, with the 'light smoking' group showing a decrease in HR from baseline to negative emotion, whereas the 'non-smoking' and the 'heavy smoking' groups showed an increase in HR from baseline to negative emotion. In normal populations, it has widely been found that HR increases during situations designed to provoke negative emotion (Buss et al., 2005; Levenson, Ekman & Frieson, 1990; Provost & Gouin-Decarie, 1979). Therefore, both the 'non-smoking' and 'heavy smoking' groups showed the expected pattern. However, the 'light smoking' group showed the reverse trend with a decrease in HR from baseline to negative emotion. This result suggests that prenatal smoking interferes with infant cardiac activity during a task designed to evoke negative emotion. However, in contrast to the results found during attention, in this case it was infants who had been exposed to relatively low levels of smoke, between 1 and 9 cigarettes a day, which show the altered cardiac response. Taken together, these results suggest that when considering the effect of prenatal smoke exposure on infant cardiac activity, the quantity of cigarettes consumed by the mother during pregnancy should be taken into account. Infants should also be studied under a range of conditions, not just during baseline, and measures of HR

reactivity should be used. Using a measure of reactivity allowed us to examine the cardiac response of the infant to the stimulus or challenge, while accounting for resting state.

However, the same patterns of results were not observed at 12 months. As mentioned, the previous studies that have been carried out investigating the effect of prenatal smoke exposure on infant HR have focused on young infants in the first weeks of life. The only study in the area, which examined infants past the first weeks of life, found no effect of smoke exposure, but the sample size was very small, with only 23 infants, and a unique procedure was used to investigate the main hypothesis of the effect of prenatal smoke on SIDS (Tuladhar et al., 2003). The current study was the first to examine the effect of prenatal smoke exposure on infant HR in the second half of the first year of life. Before firm conclusions are drawn the study should be replicated, using a larger sample size as previous studies have found an effect of prenatal smoke when using a larger sample size, albeit with younger infants, for example, Schuetze and Eiden (2006) included 62 infants in their smoking group.

In the third set of analyses the effect of timing of the smoke exposure was considered. At 6 months no differences in HR were observed between the smoking groups when comparing mean HRs between conditions or when considering reactivity measures. However, at 12 months an interaction between condition and smoking group was found with infants born to mothers who never smoked during pregnancy having higher HRs during attention than infants born to mothers who smoked throughout pregnancy. This finding is somewhat difficult to explain given that previous studies by Schuetze and Zeskind (2001) and Schuetze and Eiden (2006) found that infants at 2 to 4

weeks of age, who had been exposed to smoke in utero, had higher HR than non-exposed infants. However, both of these studies investigated younger infants compared with those studied in the current sample. In a study with rat pups, Slotkin et al. (1999) found that rat pups exposed to nicotine prenatally showed an increase in cardiac M2-muscarinic cholinergic receptors, which inhibit the autonomic system. However, in the current study HR was only lower for the 'all trimester' smoking group compared with the 'non-smoking' group during attention and based on the findings of Slotkin et al. (1999) we would expect to see lower HR in smoking groups across conditions. In order to interpret our findings, the current study should be replicated using a larger sample size and increasing the size of the smoking group.

When considering the HR reactivity measure and the effect of timing of smoke exposure, no differences between smoking groups were observed during attention at 12 months. However, there was a significant difference between smoking groups during negative emotion challenge at 12 months, with infants born to women who smoked only during the first trimester showing a larger increase in HR from baseline to negative emotion challenge than infants born to women who never smoked. As discussed above, negative emotions are variable in infants (Belsky, Fish & Isabella, 1992; Lee & Bates, 1985) and increase towards the end of the first year of life (Auerbach et al., 2008; Campos, Emde, Gaensbauer & Henderson, 1975; Gartstein & Rothbart, 2006; Rothbart, 1981; Scarr & Salapatek, 1970). Therefore, when investigating prenatal smoke exposure on offspring outcomes, measures of negative emotion should be included together with resting measures and measures of cognitive challenge.

Conclusions. This was one of the first studies to examine cardiac activity under a range of conditions in infants, who had been exposed to smoke prenatally, at 6 and 12 months. The results suggest that prenatal smoke exposure affects infant HR at 6 and 12 months. However, the pattern of results was not the same at both time points, nor was it easy to interpret. Whereas the quantity of cigarettes consumed seemed to affect infant HR at 6 months, the timing of the smoke exposure affected infant HR at 12 months. We know that cardiac activity changes over the first year of life, with a decrease in baseline HR, and previous studies have shown that negative emotionality can be variable during the first years of life. Therefore, to gain a complete picture of the effect of prenatal smoke on infant outcomes future studies need to examine infant cardiac activity during a range of challenging situations at several time points during the first year, using a larger sample and including measures of parasympathetic (e.g. RSA) and sympathetic (e.g. PEP) cardiac activity, to fully understand the differences observed in the current study at 6 and 12 months. The sample should also be followed during the preschool years to investigate whether the effects of prenatal smoke exposure become more pronounced beyond the first year of life and if so, whether the effect of exposure is to increase or decrease cardiac activity.

In conclusion, the current findings provide preliminary evidence that smoking during pregnancy may affect underlying physiological processes in the offspring. In order to understand the full extent of the adverse effects of prenatal smoke exposure, both the quantity and timing of the cigarettes consumed should be considered and infants should be studied during cognitive and emotional challenge, as well as during a baseline period. Moreover, different measures of cardiac reactivity should be included.

CHAPTER 5

THE ROLE OF HEART RATE AND VAGAL TONE IN THE STUDY OF INFANT TEMPERAMENT

5.1. Introduction

As discussed in Chapter 1, it is generally believed that the temperamental style displayed by a child can affect how the child behaves and functions later in life (Rothbart & Bates, 1998; Thomas et al., 1968). Several studies have shown evidence of a child being described as having a "difficult" temperament and subsequently developing behaviour disorders (e.g. Kingston & Prior, 1995). However, the progression between a particular temperamental profile and the development of disorder is unclear and is complicated by the overlap between items in temperament measures and measures of disorder (Frick, 2004). This led Bussing et al. (2003) to suggest that Attention Deficit Hyperactivity Disorder (ADHD) may be a useful disorder to study when investigating the link between temperament and the development of behaviour disorders because it is a diverse disorder, which is present in early childhood.

To begin to understand the pathways through which behaviour disorders, in this case ADHD, develop, we need to study temperamental profiles in infants and young children. Behavioural observations together with parent reports are useful measures and go some way to help us study temperament in young children. However, physiological measures such as heart rate (HR) and vagal tone (VT) allow extra depth in the examination of temperament. Polyvagal Theory, as described by Porges (1995, 1997) provides justification, both at a neuroanatomical and neurophysiological level, for

studying VT as an index of temperament and several studies have made the connection between dimensions of temperament and the regulation of the autonomic system (e.g. Huffman, Bryan, del Carmen, Pedersen, Doussard-Roosevelt & Porges, 1998; Kagan, 1982; Rothbart, 1989).

5.1.1. The Role of Psychophysiological Measures

Psychophysiological measures can be useful in the study of the human infant for a number of reasons. Firstly, they are very sensitive to changes in psychological state. Secondly, because physiological responses are non-verbal they are particularly useful when studying infants, who are non-verbal participants. Thirdly, physiological responses have been used extensively in studies investigating learning, habituation, psychophysics and emotion and therefore the factors which affect these responses are often quite well understood. Finally, physiological responses can be used in longitudinal studies with infants in a way in which behavioural responses cannot because infants cannot communicate with speech and are limited in the behavioural tasks in which they can engage (Campos, 1976). Campos (1976) suggests that of all the physiological responses that have been used in studies of infants, HR has been found to be the most sensitive and reliable.

The beating of the heart is an electromechanical event and the transmission of electrical activity through the various parts of the heart creates an electrical field which can be easily measured by placing electrodes on the surface of the body (Papillo & Shapiro, 1990). The stereotypic pattern of electrical activity generated by the heart during

each beat can be displayed as a graphical representation known as the electrocardiogram or ECG.

The autonomic nervous system (ANS) regulates homeostatic function and spans both the central and the peripheral nervous system. It is divided into two components: the sympathetic nervous system and the parasympathetic nervous system (Rosenzweig, Leiman & Breedlove, (1999). The parasympathetic nervous system and the sympathetic nervous system contribute to the regulation of a number of organs, including the eyes, salivary and sweat glands, blood vessels, heart, lungs, stomach and the bladder (Porges, Doussard-Roosevelt & Maiti, 1994a). In general the sympathetic nervous system is said to prepare the body for action as a result of challenges from outside the body e.g. blood pressure increases, the pupils dilate and HR quickens. In contrast, the parasympathetic nervous system promotes processes involved with growth and restoration e.g. pupil constriction, vesical and rectal sphincter relaxation and a decrease in HR (Lovallo, 1997).

Among the first researchers to suggest a relationship between the sympathetic and parasympathetic branches of the autonomic nervous system with behaviour were Eppinger and Hess (1910). Through their clinical work and the case studies they described, Eppinger and Hess suggested that high levels of VT may be related to psychopathology. Since then VT, as an index of the parasympathetic influence on the heart, has continued to become a psychophysiological marker for emotion regulation and other aspects of behavioural functioning, in children and adults (Graziano, Keane & Calkins, 2007). The sympathetic branch of the ANS is believed to adjust preejection period (PEP) and thus, an increase in PEP is the result of increased sympathetic influence on the heart (Berntson, Cacioppo & Quigley, 1994). Research studying cardiac activity

and the sympathetic nervous system, for example PEP, is relatively scarce (Buss, Goldsmith & Davidson, 2005).

5.1.2. What is Vagal Tone?

Vagal tone is a measure of the amount of neural influence on the heart (Stifter & Fox, 1990). The vagus is the tenth cranial nerve and is a complex bidirectional system, which links the brain stem with target organs via myelinated branches (Porges et al., 1994a). The vagal input to the sino-atrial node is provided by the right nucleus ambiguus and this regulates atrial rate and determines HR. The vagal input to the atrio-ventricular node is provided by the left nucleus ambiguus and this regulates ventricular rate. The sino-atrial node is the primary pacemaker of the heart. Heart rate is slowed when the sino-atrial node is stimulated by the vagus, whereas HR is increased when there is vagal withdrawal at the sino-atrial node. Vagal tone has two roles (Porges, Doussard-Roosevelt, Portales & Greenspan, 1996). The first of its roles is to foster physiological homeostasis during times of low environmental demand. The second role occurs during periods when there is environmental challenge, the vagus acts as a brake to rapidly regulate cardiac output and therefore metabolic output. The 'vagal brake' increases vagal output to the heart and actively inhibits sympathetic influences which results in keeping the HR slow (Levy, 1984). As the vagal brake is released, vagal inhibition on the sino-atrial node is reduced and HR increases. Thus, the vagal brake represents vagal reactivity. The vagal brake does not completely determine HR and therefore, changes in VT are not always highly correlated with changes in HR (Porges et al., 1996)

Respiratory sinus arrhythmia (RSA) is the name given to the variability in HR as a result of respiration. Quantifying RSA is a relatively accessible way of measuring the vagal control of the sino-atrial node of the heart. Acetylcholine is the neurotransmitter involved at this site and changes in the tension of the vagus may be a result of changes in the peripheral and central cholinergic balance (Stifter & Fox, 1990). It is possible that the motor arousal system, which according to Porges (1976) responds to attention and approach behaviours to novel stimuli, is related to these differences in cholinergic activity. Porges (1985, 1986) has developed a method of analysing heart period data (i.e. the timing between heart beats) which extracts the portion of variance in HR which is due solely to RSA.

5.1.3. Vagal Tone and Reactivity

Porges et al. (1994a) propose that individual differences in VT are related to HR and behavioural reactivity in young infants. The central idea to this proposition is that VT is an indicator of the organization of the central nervous system that disposes an individual to be hypo- or hyper-reactive. Therefore, "subjects with higher levels of VT should have more organized (i.e. consistent) autonomic responses with shorter latency and greater magnitude autonomic responses" (p. 180, Porges et al., 1994a). In line with Porges' Polyvagal theory (1995), infants with good coping abilities should show strong fluctuations in vagal suppression in responses to the demands of a given task (Hastings, Sullivan, McShane, Coplan, Utendale & Vyncke, 2008). Several studies have investigated this hypothesis. For example, Porter, Porges and Marshall (1988) carried out a study which provided support for the idea that VT is an index of reactivity. Porter et al.

(1988) found that individual differences in VT in newborn infants were correlated with HR reactivity to circumcision.

In a study by Huffman, Bryan, del Carmen, Pedersen, Doussard-Roosevelt and Porges (1998), the relationship between temperament and cardiac activity was investigated in 12-week-old infants. The temperament of the infants was evaluated by observations in the laboratory and maternal ratings. Vagal tone was measured during a baseline period and during a laboratory assessment of temperament. Infants who had higher VT during baseline were observed in the laboratory as showing less negative behaviour and were also less disrupted by the experimental procedure. The authors suggest that low baseline VT in infants may be a marker for vulnerability or hypersensitivity to disruption of behavioural homeostasis. In support of this suggestion, a number of studies have shown that low baseline VT was related to anxiety problems in children (El-Sheik, Harger & Whitson, 2001; Fox & Field, 1989). In the study by Huffman et al. (1998) infants who showed a decrease in VT during the laboratory assessment were rated by mothers on a temperament questionnaire as being more easily soothed and showed higher levels of attention. Therefore, the authors propose that change in VT or regulation of the vagal brake may be an indicator of social and attentional behaviours. The authors conclude that when investigating the relationship between cardiac activity and temperament, it is important to measure VT during baseline and changes in VT as a result of challenge.

Stifter and Fox (1990) also investigated the relation between measures of heart period and VT and infant reactivity by carrying out a longitudinal study of infants from birth to 5 months of age. At 2 days of age a pacifier-withdrawal task was administered

and ECG was recorded. When the infants were 5 months, ECG was recorded and the infants and mothers took part in a laboratory session which included a peek-a-boo game with the mother, a peek-a-boo game with a stranger and an arm-restraint procedure. The tasks in the laboratory assessment were designed to elicit positive and negative reactivity. The mother's rating of the infant's temperament at 5 months was also collected. The findings suggested that infants with high VT at 5 months of age were more reactive to mildly frustrating events than infants with low VT. During the arm-restraint procedure the infants with high VT displayed more negative affect emotion expressions than the infants with low VT. These infants were also rated as displaying less positive affect, as being more active, less fearful of novel objects and were rated as less easily soothed upon distress. Therefore, in this study, a group of infants with high VT who displayed negative reactions when mildly frustrated but were highly active and fearless of novelty emerged. Newborn VT was not found to predict behavioural reactivity at 5 months of age. The authors suggest a possible reason for this is the maturational changes in parasympathetic control that occur over this period. Sachis, Armstrong and Becker (1982) provide data which suggest that during the first year of life there is an increase in myelination of the vagus nerve. Stifter and Fox (1990) conclude that "vagal tone may be a good index of individual differences in infant reactivity during the first year of life" (p. 586, Stifter & Fox, 1990).

Fox (1989) details results obtained from a longitudinal study in which two groups were selected based on their pattern of heart period variability. One group contained those with high VT and the other group contained those with low VT. These groups were defined based on the mean of seven recordings taken during the procedure. Therefore, the

high VT group displayed a VT above the mean and the low VT group displayed a VT below the mean for each of the seven recordings. At 5 months of age it was found that those infants with high VT were more reactive to both positive and negative events and at 14 months the same group of infants were more sociable and showed more approach behaviours. Fox (1989) concludes that during the first year of life infant reactivity to mildly stressful events seems to be a stable dimension and VT could prove to be an important measure of individual difference related to infant temperament. This pattern has also been found with 3-year-olds (Fox & Field, 1989). In this study it was found that those children with a high VT adapted faster to a new preschool environment and were rated as less difficult in their temperament than children with low VT.

Kagan, Reznick and Snidman (1987) carried out a longitudinal study looking at two cohorts of children who were selected at either 21 or 31 months of age to be either inhibited (extremely cautious and shy) or uninhibited (fearless and outgoing) to unfamiliar events and assessed them on a further two occasions up until 5.5 years of age. Kagan et al. (1987) measured the child's HR period and heart period variability at baseline and while undertaking cognitive tasks at each assessment. It was found that inhibited children had higher and more stable HR at every assessment compared with uninhibited children. The original indicator of inhibited behaviour when measured at 21 months predicted a higher and less variable HR at 5.5 years of age. Also, the inhibited children who had higher and more stable HR at the first two assessments were more likely to remain inhibited than the inhibited children who had lower and more variable HR.

The studies described above show that during the first year of life infants with high baseline VT and high VT reactivity show increased behavioural reactivity to both positive and negative events. These infants grow up to become sociable toddlers and preschoolers, possibly mediated through the infant-caretaker relationship, which will be reviewed in the next section. Infants with low VT have been found to exhibit inhibited and anxious behaviours (e.g. El-Sheik et al., 2001; Kagan et al., 1987). Therefore, it seems that VT is a sign of the infants' capacity to connect actively with their environment, which includes positive and negative responses in behavioural, attentional and emotional domains to external actions and challenges (Beauchaine, 2001). It can be concluded that VT can serve as a useful indicator of an infant's temperament.

5.1.4. Vagal Tone and Self-Regulation

As discussed above, it is important that infants are able to adjust to different sensory challenges and perform necessary homeostatic processes (DeGangi, DiPietro, Greenspan & Porges, 1991). Infants need to be able to regulate their sleep states, digest food and posses the ability to self-soothe in response to their changing environment. At first many infants have problems in one or more of these areas but as the infant gets older the problems are often resolved e.g. after 6 months of age colic occurs much less frequently in infants. Vagal tone has been found to be correlated with self-regulation (Porges et al., 1994a). In newborns it has been found that those infants with higher VT are more irritable and less able to self-soothe. However, those neonates with high VT have been shown to develop an increasing capacity to self-soothe. It is suggested that the mother of the newborn with high VT gives more appropriate care-giving as a result of her

offspring's reactivity and therefore, as the infant becomes more physiologically stable its ability to self-soothe is increased.

Porges, Doussard-Roosevelt, Portales and Suess (1994b) examined the relationship between behavioural reactivity, which was assessed using maternal report, and autonomic state which was assessed using VT, in a group of 9-month-old infants. It was found that high VT was related to greater behavioural reactivity interpreted by maternal reports as difficult temperament. However, VT at 9 months of age was related to maternal reports of less-difficult behaviour when the children were 3 years of age. The authors suggest that at 3 years of age the children had developed self-regulatory skills, which led the mothers to interpret them as being less difficult. Calkins and Fox (1992) suggest that high behavioural reactivity in infants is important for later sociability because of the effect it has on infant-caretaker interactions, as described above.

Studies have shown that those individuals with high VT consistently suppress VT in order to enhance their intake of information from the environment. Richards and Casey (1991) studied the variability of HR during a visual attention task in infants who were 4-, 20- or 26-weeks of age. The infants were presented with a recording of a Sesame Street programme and then a computer generated pattern replaced the Sesame Street display. They found that HR variability changed throughout attention; there was a decrease in variability during attention and then 5 seconds after termination of attention, variability returned to prestimulus levels. Also, infants with high VT have been found less likely to be distracted, when measured by gaze aversion towards an interrupting stimulus positioned peripherally (Richards, 1987). Donzella, Gunnar, Kruegar and Alwin (2000) found that the VT of 3- to 5-year-old children decreased as they took part in a

competition against a familiar adult and those children who were described as more tense and angry when they were losing showed additional suppression of VT as they began to lose the competition.

However, it is suggested that there is a subgroup of individuals who do not suppress VT during information processing despite having a high VT and therefore have difficulty self-soothing and are often described as fussy. DeGangi et al. (1991) suggest that infants who are older than 6 months of age and show irritability, fussiness, poor self-soothing, intolerance to change and a state of hyper-alert arousal should be described as "regulatory disordered" infants. The regulatory disordered infant shares many of the same characteristics as those described in the temperamental dimension of "difficult behaviour". Thomas, Chess and Birch (1968) describe the "difficult" infant as having the following attributes: a high proportion of negative emotions to new stimuli, being slow to adapt to changes in the environment, having a high frequency of expression of negative mood and having a high prevalence of intense reactions.

DeGangi et al. (1991) measured heart period and VT during baseline and during sensory and cognitive challenges in 24 normal and 11 regulatory disordered infants (selected through an extensive interview with the mother and diagnosed using criteria described by Greenspan and Lourie, 1981). The infants ranged in age from 8 to 11 months. They found that regulatory disordered infants tended to have higher baseline VT. During cognitive processing there was a significant suppression of VT across groups. It was also found that baseline VT was correlated with the suppression of VT during the cognitive task but only for normal infants. The findings support the vagotonic hypothesis, first described by Eppinger and Hess (1915). Eppinger and Hess (1915) described a

condition, which they called vagotonia, which was characterised by having high VT and hypervagal activity. The results from DeGangi et al.'s (1991) study also provide an indication that regulatory disordered infants are characterized by having higher baseline VT and exhibiting changes in VT which are not related to baseline VT.

In their study investigating the relationship between behavioural reactivity and autonomic state, Porges et al. (1994b) found that VT and difficult temperament were correlated from 9 months to 3 years of age and therefore, the authors concluded that VT is stable under steady state conditions. This finding adds support to the finding by Fracasso, Porges, Lamb and Rosenberg (1994) that individual differences in measures of VT were stable over 2 and 3 month periods. However the results conflict with those found by Stifter and Jain (1996), who found VT to be only slightly stable (0.30) from 5 to 18 months. The results of Porges et al. (1994b) also showed that VT at 9 months was related to difficultness at 3 years of age. It was found that higher VT at 9 months was related to less difficult behaviour at 3 years of age. As mentioned above, it is thought that it is the early behavioural reactivity of the infant that affects the development of the infant-caregiver interactions and leads to positive socialization in the infant as the caregiver has provided experiences which enhance self-regulatory skills. In support of this, Portales, Doussard-Roosevelt, Lee and Porges (1992) found that 9-month-olds who exhibited an inability to suppress VT were found to display higher levels of problem behaviours at 3 years of age.

Porges, Doussard-Roosevelt, Portales and Greenspan (1996) also suggest that the development of appropriate social behaviour depends upon an individual's ability to regulate VT. In this study 24 participants were tested between the ages of 7 to 9 months

and were then evaluated for behavioural problems at 3 years of age. It was found that infants who had the greatest decrease in VT during the Bayley test at 7 to 9 months had the fewest behavioural problems as measured on the Child Behaviour Checklist for Ages 2-3 years.

In conclusion, it can be seen that infants suppress VT in order to enhance information processing from their environment. However there seems to be a group of infants who do not suppress VT during information processing and DeGangi et al. (1991) describe these infants as being "regulatory disordered". As mentioned above, infants with high VT appear to be more reactive to stimuli than those with low VT. It seems that infants with high VT moderate the type of interaction from their caregiver and as a result are described as being less difficult during the preschool years than infants with low VT.

5.1.5. The Current Study

In a study by Buss et al. (2005) changes in HR, RSA and PEP in 68 24-month-olds, in 4 increasingly challenging, emotion eliciting tasks were examined. The study began with a baseline period during which the children watched a video, this was followed by a series of tasks designed to be cognitively challenging. The final tasks were 2 emotion eliciting tasks; the 1st task, Stranger Approach, was designed to elicit fear and the 2nd task, Toy Removal, was meant to induce anger or frustration. Results showed that as distress increased across the fear and frustration tasks HR increased and RSA decreased. The authors suggest that these changes occurred as a result of the withdrawal of the parasympathetic tone and the activation of the sympathetic system as the challenge and the stress of the visit increased. The decrease in RSA in response to stress or

challenge has been found to be related to lower frustration reactivity, the use of emotion regulation skills and fewer behaviour problems (Calkins, 1997; Calkins, Dedmon, Gill, Lomax & Johnson, 2002; Calkins & Dedmon, 2000; Eisenberg, Fabes & Murphy, 1996). There were no significant changes in PEP. Results showed that PEP had very little influence on HR reactivity and that it was only RSA that accounted for the significant variance in task HR and HR reactivity. The authors suggest that perhaps the sympathetic nervous system is still quite immature in 2-year-olds and this may explain why an effect of PEP was not found. Heart rate was also found to be associated with negative affect during all tasks. Heart rate and RSA were found to be negatively correlated during baseline, cognitive challenge, stranger approach and toy removal.

The aim of the current study was to replicate the study of Buss et al. (2005) by using a sample of younger infants, in order to further investigate the relationship between HR and VT during a series of increasingly challenging tasks in the laboratory. The current study aimed to examine the temperamental profiles of infants, focusing on HR and VT as markers, and also considering behavioural observations and parental reports. Studying infant temperament in detail is the first step in beginning to understand the development of ADHD and other behaviour disorders (Bussing et al., 2003).

The current study measured HR and VT during resting conditions and during cognitive and emotional challenges in a cohort of children in the age range of 6 to 14 months. Mothers reported that they did not smoke during pregnancy, which allowed HR and VT to be investigated in infants without noise introduced by potential effects of prenatal smoke exposure. The study began with a baseline period, which was followed by an attention task during which the infant was presented with a music box with a visual

display. The experiment finished with a procedure designed to elicit fear, which involved a remote controlled toy robot approaching the infant, which was operated by a stranger. It was predicted that during the attention procedure, there would be a decrease in HR and an increase in VT from baseline, as found in previous studies (e.g. Colombo et al., 2001; Lansink & Richards, 1997; Richards & Casey, 1991; Richards & Gibson, 1997). In line with the results obtained by Buss et al. (2005) it was also hypothesized that between baseline and fear infants would show an increase in HR and that VT would decrease. Previous studies have shown that the ability to withdraw vagal influence on the heart is important for infants' engagement with the environment (Porges, 1995; 1996). We also predicted that HR and VT would be negatively correlated during the baseline, attention and fear conditions, as found by Buss et al. (2005).

Buss et al. (2005) found no gender difference in cardiac activity in their sample of 2-year-olds. However, in a study carried out by Calkins and Dedmon (2000), also with a sample of 2-year-olds, it was found that there was a difference in HR with boys having lower HRs than girls. Scarpa, Raine, Venables and Mednick (1997) also found a significant difference in HR between boys and girls, with boys having slower HR than girls. However, this study used a sample of 3-year-olds. Alkon, Lippert, Vujan, Rodriquez, Boyce and Eskenazi (2006) found no significant differences in HR or RSA between boys and girls at 6 and 12 months, which was supported by the findings of Campos et al. (1975) in a sample of 5- and 9-month-olds. The aim of the current study was to examine whether there were any differences in cardiac activity between boys and girls.

Buss et al. (2005) and Calkins and Dedmon (2000) concluded that more research needs to be carried out in younger children, particularly to investigate the relationship between HR and emotion induction and temperament. Very few studies have been carried out which investigate HR and VT during baseline and fear in infants in the second half of the first year of life, and of the studies that have been carried out, most measured HR/VT during either resting or challenging conditions (e.g. Alkon et al., 2006; Calkins & Keane, 2004). Therefore, the results from the current study will add to the existing literature by focusing on infants reaching the end of the first year of life and including HR and VT measures during resting and cognitive and emotional challenges.

Campos et al. (1975) found that at 5 months of age infants' HR decelerated in the presence of a stranger, whereas at 9 months of age it accelerated and these accelerations were greater in frequency and magnitude when the infants' were tested with their mothers absent. Therefore, it was hypothesised, that in the current sample, during the fear challenge, older infants would show higher HR than younger infants. Previous studies have shown that baseline HR decreases and VT increases during the first year of life (e.g. Alkon et al., 2006; Stifter & Jain, 1996). Therefore, it was predicted that at baseline, the older infants would have lower HR and higher VT than the younger infants.

A major limitation of the Buss et al. (2005) study was that they did not measure HR and RSA levels at the end of the procedure and therefore, did not look at the recovery of the autonomic system following stressful events. In the current study, HR and VT were measured for 10 minutes following the end of the experiment in order to investigate the recovery of the autonomic system. A large body of animal research has focussed on stress recovery by examining the hypothalamic-pituitary-adrenal axis (HPA-axis) and the

effects of prenatal stress exposure. For example, Weinstock (1997) found that prenatally stressed monkeys and rodents were less able to cope with stressful situations and this was reflected in a dysregulation of the HPA axis. A number of researchers have also looked at the recovery of the HPA axis in children. For example, Zimmermann and Stansbury (2004) found that cortisol levels in groups of children described as either shy or bold had started to recover 15 minutes after their initial assessment. There are very few studies that have looked at the recovery of the autonomic nervous system in infants following stress. Seeman and Robbins (1994) and Kudielka, Buske-Kirschbaum, Hellhammer and Kirschbaum (2004) highlight the need to study autonomic activity in response to stress and during the recovery period following stress. In the current study it was predicted that HR and VT would return to baseline levels after stress termination and that there would be no gender differences in HR during recovery, in line with results by Kudielka et al. (2004).

Following the influential work of Thomas and colleagues (Thomas & Chess, 1977; Thomas, Chess & Birch, 1968) assessing infant temperament via parent report, a number of other researchers have devised parent report measures of infant temperament (e.g. Bates, Freeland & Lounsbury, 1979; Carey, 1970; Rothbart, 1981; Scarr & Salaptek, 1970). In 1981, Rothbart designed the Infant Behavior Questionnaire (IBQ) with the aim of creating a parent report instrument which would measure the dimensions of temperament identified by Thomas and colleagues but which would also measure other aspects of reactivity and self-regulation, whilst ensuring the conceptual independence of the individual dimensions (Rothbart, 1981). The questionnaire was designed to be completed by parents and measures temperament in infants between the ages of 3 and 12

months. In 2003, Gartstein and Rothbart created a revised version of the IBQ, known as the IBQ-R, which was used in the current study. A recent review has found that the temperament questionnaires developed by Rothbart have been the most frequently used measures in this area of research (Putnam & Stifter, 2008). Included in the IBQ-R is a scale called 'duration of orienting', which assesses individual differences in attention. The IBQ-R also includes a scale called 'fear', which has been designed to assess an infant's startle or distress to changes in stimulation and the presence of novel objects. The Lab-TAB (Goldsmith & Rothbart, 1999) was designed to fit closely with Rothbart's view of temperament and previous studies have found subscales of the IBQ and Lab-TAB to be correlated (e.g. Bridges, Palmer, Morales, Hurtado & Tsai, 1993; Hane, Fox, Polak-Toste, Ghera & Guner, 2006). In the current study, the infant's behaviour during fear challenge was scored using the Lab-TAB coding scheme. It was hypothesised that parental reports of attention and fear would correlate with physiological indices of HR and VT, and that behavioural observations of infants would also correlate with physiological indices and parental reports.

To summarise, VT is an index of the activity of the parasympathetic nervous system on the heart. An increase in parasympathetic nervous system influence on the heart results in an increase in VT and a decrease in HR. Thus, it follows that a decrease in parasympathetic nervous system influence on the heart results in a decrease in VT and a corresponding increase in HR. During times of environmental challenge, the influence of the parasympathetic nervous system and thus, vagal control of the heart is reduced, which allows HR to increase. During periods of sustained attention, vagal control of the heart is increased and HR decreases. Therefore, in the current study an increase in VT and a

decrease in HR was expected from baseline to attention task and during the fear task a decrease in VT and a corresponding increase in HR from baseline was predicted.

5.2. Method

5.2.1. Participants

Participants were 50 children aged between 6 and 14 months, who were recruited from local nurseries. Participants and their families were not selected for any behaviour or other characteristics. The majority of participants were Caucasian (43 Caucasian, 2 African, 2 African European, 3 Asian). The sample consisted of 46% females and 54% males. All mothers reported that they did not smoke during pregnancy. The study was approved by the School of Psychology's Research Ethics Committee (SREC) and parents gave written informed consent.

5.2.2. Measures

Attention. During the attention phase of the procedure, the child was presented with a novel stimulus, which was a music box with a moving picture. This was presented for 2 minutes. The stimulus was placed on a table in front of the infant but the infant could not reach the music box. The mother was asked to be minimally responsive to the child during this task.

Fear. For the fear challenge, an unfamiliar experimenter dressed in a white coat and laboratory glasses entered the playroom with a remote controlled toy robot which was placed 1.5 metres in front of the child. The experimenter operated the robot using the remote control and moved the robot towards the child where the robot stopped 15cm directly in front of the child. The robot remained in this position for 10 seconds whilst performing a series of rapid movements and noises before moving back to its starting

place where it remained stationary for 5 seconds. This procedure was repeated a further two times. The protocol was based on the procedure described in the Lab-TAB (Goldsmith & Rothbart, 1999). However, the current procedure was modified, with the aim of increasing stress, with the addition of a stranger, dressed in unfamiliar clothes and glasses, operating the robot and asking the mother to leave the room. These two additions combined with the child being strapped into a chair, produced an event which was deemed to be quite stressful for the infant, whilst still being ethically acceptable. When the robot reached its final position it was activated for a further 10 seconds during which time it made rapid movement and noises. In total this procedure lasted for approximately 3.5 minutes.

The procedure was scored using a coding system derived from the Lab-TAB (Goldsmith & Rothbart, 1999). The scoring began when the robot started moving and the task was divided into 10 second epochs. The infant variables coded in this task included 'intensity of facial fear', 'intensity of facial sadness', 'intensity of distress vocalizations' and 'intensity of bodily fear'. 'Intensity of facial fear' and 'intensity of facial sadness' were scored on a 4-point scale ranging from (0) "no facial region shows codable fear/ sadness movement" to (3) "an appearance change occurs in all 3 facial regions or coder otherwise has impression of strong facial fear/sadness". 'Intensity of distress vocalizations' was coded on a 6-point scale ranging from (0) "no distress" to (5) "full intensity cry/ scream (child is losing control)". Intensity of bodily fear was scored on a 4-point scale ranging from (0) "no sign of bodily fear" to (3) "freezing and trembling: tensing of the entire body with no motion, or trembling due to extreme muscular tension". Four coders scored the episodes independently and intra-correlation coefficients between

coders ranged between .70 - .99 across variables. Strong correlations were found between the following items: 'intensity of facial fear', 'intensity of facial sadness', 'intensity of vocal distress' and 'intensity of bodily fear' (minimum r =.87, p<.01). Therefore, these items were combined to form a composite measure of observed distress behaviour during the robot task, ranging from (0) no distress to (14) maximum distress.

Infant Behavior Questionnaire Revised (IBQ-R). The IBQ-R assesses 14 domains of infant temperament and the current study focused on the domains of 'duration of orienting' and 'fear'. The 'duration of orienting' subscale consisted of 12 items with a Cronbach's α .74 and the 'fear' subscale consisted of 16 items with a Cronbach's α .88. Each item was rated by the frequency with which it had been observed over the last week (or in some cases 2 weeks) on a 7-point scale from (1) never to (7) always. There was also the option to respond "does not apply" to each item. The items were deliberately constructed so that parents rated observed behaviours and did not have to make comparisons or global judgements or recall past behaviours (Rothbart, 1981).

Cardiac activity. The HR recording and analysis software programme were custom made using the PSYLAB programme (PSYLAB, 2005). The electrodes placed on the participant were attached to a PSYLAB Stand Alone Monitor (SAM) which is powered by 12 volt universal power units which run on any voltage between 100 and 250V, 50/60Hz. PSYLAB records HR as the interval between successive heart beats (I.B.I.). IBI is inversely related to HR by the equation HR = 60000 / IBI. The PSYLAB Interval Timer responds directly to the electrical signal produced by EKG or the Peripheral Pulse amplifier. It has an internal clock, which increases in one millisecond intervals. Each time a heart beat occurs, a self-adjusting circuit in the Interval Timer

converts the electrical shape of the heart wave into a discrete 'trigger' (http://www.psylab.com, retrieved July 2007).

The IBI files obtained from the PSYLAB programme were entered into CardioEdit (CardioEdit software. Brain-Body Center, University of Illinois at Chicago. 2007) for editing. 180 Seconds of data for the baseline period were analysed (except for 4 participants when 90, 110, 130 and 162 seconds of data were analysed), 120 seconds of data for the attention condition were analysed and the duration of the robot condition was analysed, ranging from 90 seconds to 300 seconds. The recovery period was divided into 3 120-second sections; recovery 1 included seconds 1 to 120, recovery 2 included seconds 240 to 360 and recovery 3 included seconds 480 to 600. For analysis of the recovery period, a mean of the 3 recovery sections was taken. The data files were scanned for points which were outliers relative to surrounding data and such points were divided or summed so that they were consistent with adjacent data. The data were entered into CardioBatch (CardioBatch software. Brain-Body Center, University of Illinois at Chicago. 2007) and VT was calculated using a moving 21-point polynomial filter to detrend periodicities in heart period data which were slower than VT (Porges, 1985; Porges & Bohrer, 1990). A band-pass filter then extracted the variance of heart period within the frequency band of spontaneous respiration for infants: 0.30-1.30Hz. Thirty second epochs were used to calculate VT and the mean estimate of VT of the 30 second epochs was used in all subsequent analyses.

5.2.3. Procedure

The procedure took place in a laboratory playroom and lasted for approximately 1 hour. Mothers were asked to accompany their child to the laboratory where the infants were assessed individually using several procedures designed with the consideration of building an increasingly novel and challenging situation for the infants. The infant was given time to adjust to being in the laboratory and allowed to play with some age-appropriate toys, whilst the procedure was explained to the mother. Three electrodes were then placed in a triangle across the heart on the infant's back to measure the infant's HR.

After a baseline period of approximately 4 minutes, the infant was strapped into a seat, which was placed on the floor and all toys were removed. The first task was designed to measure attention and lasted for 2 minutes. Throughout these tasks the experimenter sat at the computer facing away from the infant, to avoid distracting the infant.

For the final task the mothers were asked to leave the laboratory playroom and watch their infant from behind a one-way window. The fear challenge procedure was then carried out which involved an experimenter entering the playroom and operating a remote controlled robot. In total this procedure lasted for approximately 3.5 minutes. The mothers were told they could stop the procedure at any time if they felt their child was becoming too distressed. Following this episode the mother and infant were reunited and were asked to play in the laboratory playroom for a further 10 minutes whilst HR continued to be monitored. The entire laboratory assessment was recorded by video camera.

5.2.4. Data Analysis

The cardiac data for 2 participants were not collected because of equipment malfunction and the cardiac data for an additional 2 participants were not collected during baseline. A further 2 participants did not have cardiac data analysed because of excessive movement artefact, which meant appropriate editing could not be carried out. Therefore, there were complete cardiac data for 44 participants in the baseline, attention and robot conditions. At recovery 1, 43 participants had complete data, at recovery 2, 39 participants had complete data and at recovery 3, 34 participants, complete data. Therefore, for the recovery variable there were 32 participants with complete data.

Cardiac data for the analyses were HR and VT for baseline, attention, fear and recovery. A measure of reactivity was calculated as the percentage change in HR and VT between baseline and attention and baseline and fear. The following equations were used to calculate reactivity: $((HR_{condition} - HR_{baseline}) / HR_{baseline}) * 100$ or $((VT_{condition} - VT_{baseline}) / VT_{baseline}) * 100$. Thus, reactivity represents a change in HR or VT that is comparable between conditions because it takes into account baseline state.

When looking at the effect of age, the size of the sample meant that individual ages could not be compared and therefore, the sample was divided into 2 groups; those aged 6 to 9 months (n = 22), labelled the "younger" group, and those aged 10 to 14 months (n = 22), labelled the "older" group.

The data were screened for violations in the assumptions of parametric tests, i.e. it was verified that the data in each of the cells were normally distributed and the variances in each of the cells were not different from each other. Extreme outliers were removed and in those instances where the homogeneity of variance assumption was violated a

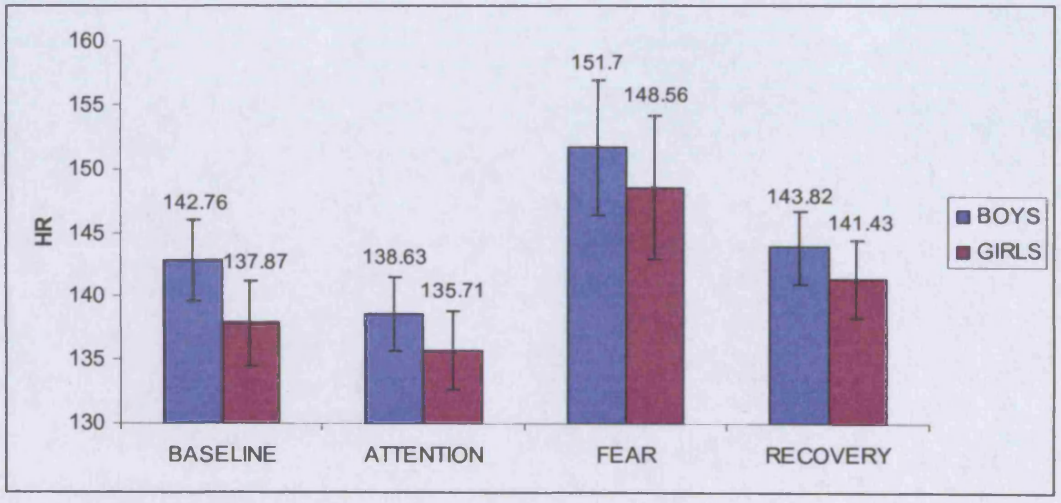
more conservative F-test was used (Greenhouse-Geisser). The LSD test was used to follow up any significant ANOVA results. A significance level of $p<.05$ was adopted throughout this paper but trends up to $p<.10$ were also identified.

5.3. Results

5.3.1. Effect of Condition and Gender

Heart rate. A repeated measures ANOVA showed there was a main effect of condition on HR ($F(1.67, 50.11) = 10.33$, $p<.001$) but no main effect of gender ($F(1, 30) = 0.57$, $p=.56$), nor was there an interaction between condition and gender ($F(1.67, 50.11) = 0.13$, $p=.85$). Planned comparisons of the main effect revealed that there was a significant difference in HR between baseline and attention ($p<.05$), between baseline and fear ($p<.01$), between attention and fear ($p<.001$), between attention and recovery ($p<.05$) and between fear and recovery ($p<.05$). Figure 5.1 shows, as predicted, that HR during attention was lower than during baseline and that HR during fear was higher than during baseline. HR during recovery was not significantly different from baseline but was lower than during fear.

Figure 5.1: Mean HR at Baseline, Attention, Fear and Recovery



We also examined whether HR changed across the visit by calculating the percentage change in HR from baseline to condition, as a measure of reactivity. A paired samples t-test revealed that changes in HR from baseline to attention (M = -2.06, SD = 4.53) were smaller than changes from baseline to fear (M = 8.45, SD = 14.04; t (43) = -4.96, p<.001). When looking at gender differences in change in HR from baseline to condition, it was found that there were no differences between girls and boys for attention (Girls: M = -0.94, SD = 4.38; Boys: M = -2.99, SD = 4.38; t (42) = -1.52, p=.14) and fear (Girls: M = 10.15, SD = 15.41; Boys: M = 7.03, SD = 12.96; t (42) = -0.73, p=.47).

Vagal tone. A repeated measures ANOVA revealed there was no main effect of condition (F (2.34, 70.05) = 0.43, p=.68), no main effect of gender (F (1, 30) = 0.01, p=.94), nor was there an interaction between condition and gender (F (2.34, 70.05) = 0.88, p=.44; see Table 5.1).

Table 5.1: Mean VT at Baseline, Attention, Fear and Recovery

	Boys		**Girls**		**Total**	
	Mean	SD	Mean	SD	Mean	SD
Baseline	4.23	0.99	3.95	1.44	4.10	1.21
Attention	4.04	1.08	3.85	1.42	3.95	1.24
Fear	3.82	1.31	3.98	1.17	3.90	1.23
Recovery	3.83	1.09	4.03	1.28	3.93	1.17

We also examined changes in VT as a result of our cognitive and emotional challenges relative to baseline levels. Paired samples t-tests revealed that there was no difference in VT change from baseline to attention (M = -0.05, SD = 19.33) and baseline to fear (M = -2.57, SD = 22.27; t (43) =0.64, p=.53). When looking at gender differences in change in VT from baseline to condition, it was found that there were no differences between girls and boys for attention (Girls: M = -2.11, SD = 13.01; Boys: M = 1.66, SD

= 23.49; t (42) = 0.64, p=.53) and fear (Girls: M = 3.33, SD = 19.75; Boys: M = -7.48, SD = 23.44; t (42) = -1.63, p=.11).

Relations between HR and VT. The bivariate associations between HR and VT were analyzed. HR and VT were not significantly correlated during baseline (r = -.21, p=.17), fear (r = -.19, p=.21) or recovery (r = -.13, p=.48). However, HR and VT were found to be negatively correlated during attention (r = -.44, p<.01).

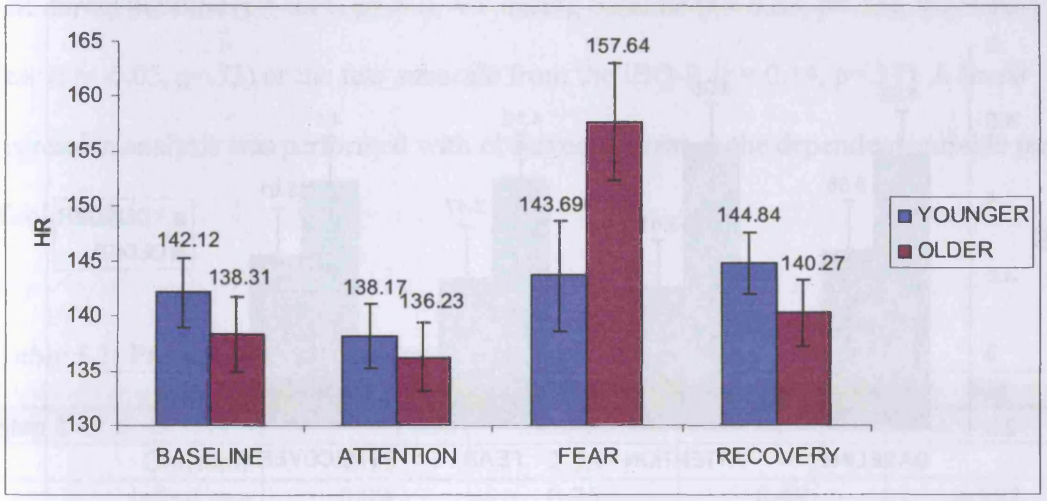
Cross-task correlations of HR and VT. Correlations among the tasks were carried out for both HR and VT. Significant correlations were found between HR at baseline and attention (r = .89, p<.001), baseline and fear (r = .50, p<.01), baseline and recovery (r = .75, p<.001), attention and fear (r = .46, p<.01), attention and recovery (r = .61, p<.001) and fear and recovery (r = .71, p<.001). Significant correlations were also found between VT at baseline and attention (r = .82, p<.01), baseline and fear (r = .77, p<.01), baseline and recovery (r = .71, p<.001), attention and fear (r = .72, p<.01), attention and recovery (r = .59, p<.001) and fear and recovery (r = .83, p<.001). This indicates that individual differences were stable across the tasks and is in line with findings from previous studies (e.g. Buss et al., 2005).

5.3.2. Effect of Age

Heart rate. A repeated measures ANOVA revealed there was a main effect of condition (F (1.79, 53.59) = 14.20, p<.001), no main effect of age (F (1, 30) = 0.04, p=.84) and a significant interaction between condition and age (F (1.79, 53.59) = 8.19, p<.01). Analysis of the simple effects showed that there was a marginal difference in HR between younger and older groups during fear (F (1, 30) = 3.60, p=.07), with the older

group having a higher HR than the younger group (see Figure 5.2). However, there were no differences between the age groups in baseline ($F(1, 30) = 0.66$, $p=.42$), attention ($F(1, 30) = 0.21$, $p=.65$) or recovery ($F(1, 30) = 1.24$, $p=.28$).

Figure 5.2: Mean HR at Baseline, Attention, Fear and Recovery for Younger and Older Groups

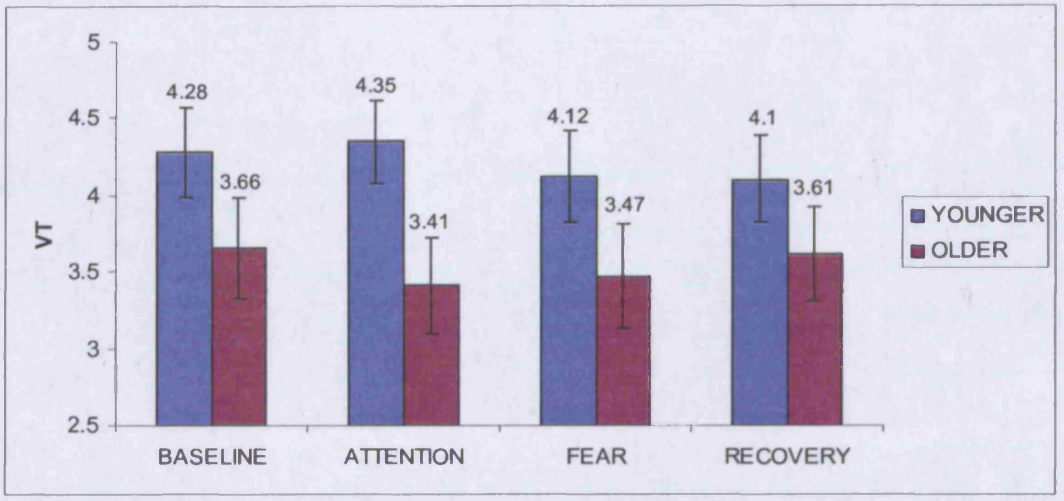


When considering percentage change in HR from baseline to condition, independent t-tests revealed there was no significant difference between age groups for attention (Younger: $M = -3.07$, $SD = 4.76$; Older: $M = -1.06$, $SD = 4.15$; $t(42) = -1.49$, $p=.14$) but there was a significant difference between age groups for fear (Younger: $M = 1.54$, $SD = 8.23$; Older: $M = 15.36$, $SD = 15.36$; $t(32.14) = -3.72$, $p<.01$), with the older group showing a larger increase in HR from baseline to fear than the younger group.

Vagal tone. A repeated measures ANOVA revealed there was no main effect of condition ($F(3, 84) = 0.36$, $p=.78$), a marginally significant main effect of age ($F(1, 28) = 3.28$, $p=.08$) and no interaction between condition and age ($F(3, 84) = 0.60$, $p=.62$). Analysis of the simple effects revealed that there was a significant difference between

older and younger groups in attention ($p<.05$) but not in baseline ($p=.16$), fear ($p=.16$) or recovery ($p=.25$). Figure 5.3 shows that the younger group had a higher VT during attention compared with the older group.

Figure 5.3: Mean VT at Baseline, Attention, Fear and Recovery for Younger and Older Groups



When considering change in VT from baseline to condition, independent t-tests revealed that there was a marginal difference between age groups for attention (Younger: $M = 5.58$, $SD = 18.49$; Older: $M = -5.69$, $SD = 18.89$; $t(42) = 2.00$, $p=.05$) and for fear (Younger: $M = 2.48$, $SD = 20.25$; Older: $M = -6.93$, $SD = 14.21$; $t(40) = 1.73$, $p=.09$). For both attention and fear the younger group showed a small increase in VT between baseline and condition, whereas the older group showed a decrease in VT between baseline and condition.

5.3.3. Behavioural Observations

Observed distress was found to be positively correlated with mean HR level during fear ($r = 0.76$, $p<.001$), with change in HR from baseline to fear ($r = 0.77$, $p<.001$) and with infant age ($r = 0.46$, $p<.01$) and negatively correlated with change in VT from baseline to fear ($r = -0.41$, $p<.01$). However, observed distress was not correlated with HR during baseline ($r = 0.11$, $p=.50$), VT during baseline ($r = 0.23$, $p=.13$), VT during fear ($r = -0.05$, $p=.73$) or the fear subscale from the IBQ-R ($r = 0.14$, $p=.37$). A linear regression analysis was performed with observed distress as the dependent variable (see Table 5.2).

Table 5.2: Predictor Variables for Observed Distress

	B	SE B	β	Sig
Step 1				
Constant	-2.15	2.55		
Infant age	0.89	0.25	0.48	p<.01
Step 2				
Constant	-14.17	4.28		
Infant age	0.43	0.18	0.23	p<.05
HR level fear	0.11	0.03	0.51	p<.001
HR reactivity fear	0.07	0.04	0.24	p=.09
VT reactivity fear	-0.03	0.02	-0.14	p=.11

Note: $R^2 = .23$ for Step 1, $\Delta R^2 = .52$ for Step 2 ($p<.001$).

5.3.4. Parent Reports

The duration of orienting subscale of the IBQ-R was not found to correlate significantly with any HR or VT measure (with correlations ranging from $r = .00$, $p=.99$ to $r = -.24$, $p=.12$) or with infant age ($r = .24$, $p=.12$).

The fear subscale of the IBQ-R was found to be significantly correlated with infant age ($r = .32$, $p<.05$) but not with any cardiac parameter (with correlations ranging

from r = -.05, p=.79 to r = .23, p=.15). Simple regression was carried out with the fear subscale as the dependent variable and infant age as the predictor variable and a significant model emerged ($F(1, 42) = 4.77$, $p<.05$), explaining 10% of the variance ($\beta=0.32$, $p<.05$).

5.4. Discussion

The main aim of the current chapter was to investigate temperamental profiles in infants, with particular focus given to the physiological measures of HR and VT during an attention and a fear provocation procedure and during recovery from challenge.

Is there a change in cardiac activity during sustained attention? It was predicted that there would be a decrease in HR and an increase in VT during the attention task and results partially supported this hypothesis. Results showed that there was a decrease in HR during attention from baseline, in line with previous findings (e.g. Richards & Gibson, 1997). However, a corresponding increase in VT was not observed. One possible reason why the expected increase in VT was not observed, may be that the sample size of 44 infants was too small and the variance within the sample too large. For example, Colombo et al. (2001) had a sample size of 68 infants. Therefore, before firm conclusions regarding VT can be drawn, the study should be repeated with a larger sample size.

Is there an increase in cardiac activity during fear? It was hypothesised that there would be an increase in HR and a decrease in VT during fear (Buss et al., 2005). Again, results partially supported the hypothesis with the expected increase in HR but no significant change in VT. The finding of an increase in HR from baseline to fear suggests that the procedure was successful in creating a challenging and stressful situation. In fact, in the current study, HR rose by 10.78 beats per minute (bpm) from baseline to fear, compared with a mere 3.72 bpm from baseline to stranger exposure and 7.95 bpm from baseline to the toy removal in the study by Buss et al. (2005), providing evidence that the procedure used in the current study was successful in arousing the autonomic system.

However, the absence of a significant change in VT from baseline to fear contradicts previous findings (e.g. Buss et al., 2005) and does not support the theory that as infants engage with their environment, vagal influence on the heart is withdrawn (Porges, 1995, 1996). The small sample size may go someway to explain the discrepancy, as other studies have used larger samples. For example, Buss et al. (2005) and Huffman et al. (1998) used sample sizes of between 60 and 70 infants and Alkon et al. (2006) used a sample size of 150 infants. Another possible explanation may be the age of the infants in the current sample. In the study carried out by Buss et al. (2005) the infants were approximately one year older than the infants in the current study. Therefore, it is possible that the parasympathetic system of the infants was not fully developed.

However, other studies have successfully investigated VT during resting and challenging conditions in younger samples. For example, Bornstein and Suess (2000) found individual differences in parasympathetic activity in infants at 2 months of age. Alkon et al. (2006) studied infants at 6 and 12 months of age across a range of conditions and found changes in RSA at both ages. When comparing mean VT during resting and challenge conditions in the Alkon et al. (2006) study (6 months: resting: M = 3.3, SD = 0.9; challenge: M = 3.2, SD = 0.7; 12 months: resting: M = 3.8, SD = 0.9; challenge: M = 3.7, SD=0.9) with mean VT in the current study (resting: M = 4.01, SD = 1.20; challenge: M = 3.84, SD = 1.25) it can be seen that the decrease in VT between baseline and challenge was actually smaller in the Alkon et al. (2006) study than in the current study. However, their sample size was larger and their SD smaller. This provides further evidence that with an increase in sample size we might be able to detect change in VT in response to emotional challenge, which is supported by power and effect size

calculations, which suggest a sample size of over 50 is required (Faul, Erdfelder, Lang & Buchner, 2007).

Also, the Alkon et al. (2006) study used smaller age ranges, with the 6 month group ranging from 4 to 8 months and the 12 month group ranging from 10 to 14 months. In the current study an age range of between 6 and 14 months was used and therefore, whilst also increasing the sample size, the age range of the infants should be narrowed. When looking at the measure of VT reactivity we found that there was a marginal difference between the younger and older age groups, with the older age group showing a decrease in VT from baseline to fear and the younger group showed a slight increase. This suggests that by narrowing the age range and increasing the sample size we might have a better chance to replicate past results. Decreasing the age range is important because whilst there is some evidence that resting VT stabilises towards the end of the first year of life (e.g. Fox, 1989; Fracasso et al., 1994; Porges et al. 1994b) there are less consistent findings with regards to the stability of VT during challenging conditions (e.g. Fox, 1989; Porges et al., 1994b; Stifter & Jain, 1996). Therefore, using a sample of children with a smaller age range who are followed longitudinally will help to reduce the variability at each time point and allow the stability of cardiac indices to be assessed in a better way.

DeGangi et al. (1991) described a group of infants who had high baseline VTs but did not suppress VT during information processing, unlike other infants (e.g. Richards & Casey, 1991). DeGangi et al. (1991) described this group as "regulatory disordered" because they are fussy and have difficulty to self-sooth and have low intolerance to change. It is possible that the current sample includes a group of infants who DeGangi et

al. (1991) would describe as "difficult" because VT remained high throughout all tasks. Unfortunately, the current sample size did not allow this to be investigated but future studies with a larger sample may be able to detect such a subgroup of infants, which has difficulties regulating their autonomic nervous system in order to support their behavioural state.

Is there a decrease in cardiac activity during recovery from stress? Studies examining autonomic activity during a recovery period following a stressor have been scarce and a review of the literature found no such studies in infants and young children and only one study examining older children and adults (Kudielka et al., 2004). It was expected that during the recovery period cardiac activity would return to baseline levels and would be significantly lower compared with levels during fear. The HR results supported this prediction: HR was significantly lower during recovery than during fear challenge and no significant difference was found between HR at baseline and during recovery. These results suggest that within 10 minutes of exposure to a stressor HR has returned to resting levels.

At the start of the recovery period the mother and infant were reunited and future studies could benefit from investigating the attachment status of the infant with the caregiver and whether this affects the rate of recovery. Previous research has found evidence that mother-infant attachment status can affect an infant's physiological response to separation (e.g. Spangler & Grossman, 1993). Maternal soothing styles could also be studied to examine whether there are subgroups of infants who recover at different speeds dependent on their mothers' behaviour. There is evidence that maternal responsiveness can affect infant regulatory behaviours following a social challenge such

as the still face paradigm (e.g. Haley & Stansbury, 2003). Future studies would also benefit from examining whether certain patterns of autonomic activity during the recovery period serve as a marker for the development of behavioural disorders later in life, which would mean subgroups of infants could be identified (Kudielka et al., 2004). No change in VT was observed and possible reasons for this have been discussed above.

Is there an effect of gender on cardiac activity? No significant differences between boys and girls in HR or VT were found, in line with findings by Alkon et al. (2006) and Campos et al. (1975), who used similar age groups to the one used in the current study. Therefore, this provides evidence that during the first year of life there are no differences between boys and girls in cardiac activity during resting conditions, during cognitive and emotional challenge and during a recovery period following a stressor. There is, however, some evidence for gender differences in cardiac activity in slightly older children (Calkins & Dedmon, 2000; Scarpa et al., 1997). Future research involving prospective, longitudinal designs need to establish whether and when gender differences in cardiac activity appear in childhood.

Is there an effect of age on cardiac activity? The current study was one of the first to investigate HR and VT in 6- to 14-month-old infants during a fear-inducing procedure. As a result of the relatively large age range it was investigated if there was a difference in cardiac activity between younger and older infants during baseline, attention, fear provocation and recovery. There was no significant difference in baseline HR between the younger and the older age group. This contradicts previous findings, which show that resting HR decreases, as infants get older (Alkon et al., 2006; Stifter & Jain, 1996). However, older infants had higher HRs during fear and showed a stronger increase in HR

compared with baseline; younger infants showed no significant change in HR as a result of fear induction. When looking at observed distress, infant age was positively correlated with distress behaviour and a significant predictor in the model with observed distress as the dependent variable. This supports our prediction and is in line with previous research which suggests that during the first year of life there is an increase in negative emotionality (Auerbach et al., 2008; Campos, Emde, Gaensbauer & Henderson, 1975; Gartstein & Rothbart, 2006; Rothbart, 1981; Scarr & Salapatek, 1970). Campos et al. (1975) and Scarr and Salapatek (1970) have shown that at the end of the first year of life infants become fearful of strange objects and new people and these are the type of fears that the robot procedure targeted.

Contrary to our prediction, we found a marginally significant main effect of age on VT, with younger infants having higher VT during attention. During resting conditions, both Stifter and Jain (1996) and Alkon et al. (2006) found that VT increased from 5-6 months to 10-12 months. In Stifter and Jain's (1996) study there was a mean increase in VT of 0.66 and in Alkon et al.'s (2006) study there was an increase of 0.5 from the younger to the older age groups. However, in the current study there was a decrease in VT of 0.62 during baseline and 0.94 during attention from the younger to the older age group. Few, if any, studies have previously investigated age differences during attention tasks, making it difficult to compare our results with previous findings. However, in line with the current findings, one study found that parasympathetic withdrawal increased from newborns to 5 months of age (Stifter & Fox, 1990) but this was a younger sample compared with that used in the current study. Both Alkon et al. (2006) and Stifter and Jain (1996) used a larger sample compared with that used in the

current study and both studies used a longitudinal design, in contrast to the current study, which utilised a cross-sectional design. Therefore, in order to fully understand the pattern of results found in the current study we need to replicate with a larger sample and using a longitudinal design.

Correlations between HR and VT. The relationship between HR and VT was also investigated. It was predicted that HR and VT would be negatively correlated during baseline, attention, fear and recovery. However a significant negative correlation between HR and VT was only found during attention and not during baseline or fear challenge. Again this result contradicts the results obtained by Buss et al. (2005) who found a negative correlation across all tasks, including the stress induced conditions. However, as stated by Porges et al. (1996), the vagal brake does not completely determine HR and as a result changes observed in VT are not always highly correlated with changes in HR. The finding that HR and VT were correlated across conditions suggests that individual differences were stable across tasks.

The role of behavioural observation. Distress ratings during fear challenge, scored using the Lab-TAB, were positively correlated with HR, change in HR from baseline to fear, and age; change in VT from baseline to fear was negatively correlated with distress observation, suggesting that as VT increases from baseline to fear, observed distress decreases, in line with previous findings (e.g. Buss et al., 2005). This provides evidence that measures of reactivity are important when studying VT in infants as it provides a more complete picture than VT taken during a given task with no reference to resting state.

Heart rate and age were found to be significant predictors in a regression model with observed fear behaviour as the dependent variable. The finding that more distressed infants were more likely to have higher HR is in line with predictions and supports the use of HR as a physiological measure when studying temperamental profiles in young children. The finding that as age increased, observed fear behaviour also increased supports the results described above that HR was higher for the older group compared with the younger group during the fear challenge. Taken together, the finding of increased observed distress and higher HR during fear in the older age group provides strong evidence that infants become more fearful of new objects and people towards the end of the first year of life and the beginning of the second year.

The role of parental reports of infant temperament. The duration of orienting subscale of the IBQ-R was used as a measure of attention. Interestingly, this measure of parental report of infant attention was not correlated with the physiological measures of HR and VT recorded during attention. This is surprising given that a significant decrease in HR was found during the attention task, suggesting that the infants were engaged in sustained attention. Therefore, we can conclude that perhaps the parental report, as measured using the IBQ-R, and physiological indices, in this case HR, are tapping different aspects of attention as a measure of temperament.

The IBQ-R also contains a subscale measuring fear. When looking at this subscale, again no correlations were found with either HR or VT recorded during the fear challenge. However, age was found to be positively correlated and in a model of regression age was found to be a significant predictor of the fear IBQ-R variable, explaining 10% of the variance. The finding that age and parental reports of infant fear

are positively correlated makes an addition to our previous findings and provides additional support that as infants get older they become more fearful of strange objects and people. This suggests that as infants' cognitive abilities increase they may evaluate situations and objects in different ways, therefore perhaps increasing their perception of the threat and leading to a higher fear response.

Conclusions. The results from this study support the use of HR as a physiological measure when investigating temperament in infants. Our results are more ambiguous when looking at VT as a physiological measure. However, we provide evidence that measures of VT reactivity may be useful in future studies. Our study is one of the first to include such a measure when studying infants and future studies would benefit from including reactivity, which reflects the infant's response to a discrete challenge or stimulus when compared with baseline state. Previous studies, which have found an effect of condition on VT, have used larger sample sizes and a smaller age range. Therefore, we suggest the current study should be replicated with a larger sample size and should be repeated longitudinally so that the infants can be studied at 6 and 12 months and followed up as they reach preschool years and beyond. This will allow us to examine developmental trajectories in children and establish whether the patterns of results seen during the first year of life are stable throughout infancy and early childhood.

In line with our predictions, HR was found to decrease during attention and to increase during fear. Replication of the current study with a larger sample size, would allow potential subgroups, such as regulatory disordered (DeGangi et al., 1991) and fearful infants, to be identified and studied. Within 10 minutes of termination of the fear procedure, the infants' HR had returned to resting levels. Future studies would benefit

from studying the role of infant attachment with the primary caregiver and the role of maternal soothing strategies during this period. No gender differences were found in the current age group but following up the sample longitudinally will allow us to explore whether gender differences emerge in the second year of life or beyond. Older infants were found to have a higher HR than younger infants during the fear procedure, supporting our hypothesis that as age increases, fear also increases. Behavioural observations, as measured using the Lab-TAB, and parental reports recorded on the IBQ-R also supported this prediction.

In conclusion, HR, measured across conditions, can be used as a valid and reliable measure to investigate temperamental profiles of infants. During infancy myelination of neurons is occurring and the nervous system is developing, making infancy an important time for the development of the ANS. However, during this period self-regulatory behaviours are not yet fully developed. The results from the current study in combination with those from well-designed future studies will ultimately lead to a better understanding of how early indices of infant temperament may ultimately lead to later behavioural disorders.

CHAPTER 6

GENERAL DISCUSSION

6.1. Goals of Thesis

The goal of this thesis was to investigate domains of infant temperament that could be considered early precursors and correlates of ADHD and to examine the effect of prenatal smoke exposure on these domains. There is evidence to suggest that the temperamental profile an individual displays during infancy and childhood can affect the way an individual behaves later in life and research suggests that an infant described as having a 'difficult' temperament is at risk of developing behaviour disorders (Auerbach et al., 2008; Crockenberg & Leerkes, 2006; Kingston & Prior, 1995; Rothbart & Bates, 1998; Thomas et al., 1968). Investigating infant temperament is the first stage in understanding the development of ADHD and other behaviour disorders but surprisingly, research on the early development of children who subsequently develop ADHD is scarce (Auerbach et al., 2004; 2008; Bussing et al., 2003). It follows that the study of infant temperament is a necessary step when examining potential pathways from prenatal smoke exposure to the development of behaviour problems (Wakschlag & Hans, 2002). However, there are a number of limitations with current infant temperament research. For example, although most definitions of temperament make reference to the fact that there is a biological basis to temperament, for a long time research has been dominated by the widespread use of parent reports of infant temperament. However, recently the importance of having an accurate understanding of the relationship between temperament

and physiology has been recognised to aid our understanding of infant temperament (Nachmias, Gunnar, Mangelsdorf, Parritz & Buss, 1996).

Previous research has suggested there is a relationship between prenatal smoke exposure and the development of ADHD. However, there has been a lack of prospective, longitudinal studies designed to examine pathways from prenatal smoke exposure to the development of behaviour disorders, such as ADHD, and few studies have examined the emergence of such behaviours early in development. When investigating pathways from prenatal smoke exposure to ADHD, the first step is to identify symptoms characteristic of children with ADHD, which can also be observed in infants during the first year of life (Auerbach et al., 2004; Sonuga-Barke et al., 2005). Excessive motor activity and symptoms of inattention are key components required for a diagnosis of ADHD and individuals with behaviour problems, including ADHD, have been shown to have disrupted cardiac activity profiles. Each of these symptoms can be observed during infancy and early childhood and hence could be considered for the study of early precursors of the development of ADHD. There is also evidence from animal and human studies to suggest that prenatal smoke exposure can affect attention, motor activity and cardiac activity in offspring.

Therefore, we examined the effect of prenatal smoke exposure on infant attention, motor activity and HR. We studied 130 infants taking part in a prospective longitudinal study; the Cardiff Child Development Study (CCDS). Infants were studied at 6 and 12 months and mothers reported on their smoking behaviour during pregnancy. For the studies described in this thesis, we took an over-sample of women who reported smoking in the CCDS sample and so of the 130 mothers in our sample, 59 reported smoking

during their pregnancy and the remaining 71 mothers did not smoke during pregnancy. Smoking during pregnancy was defined in three ways; the first variable was dichotomous (non-smoking/ smoking) and the other two variables were categorical (non-smoking/ light smoking/ heavy smoking and non-smoking/ 1st trimester/ all trimester). Thus, we were able to consider the quantity and the timing of the smoke exposure, as well as comparing the effect of any smoke exposure with no smoke exposure.

In the final chapter (Chapter 5), we focused on the study of temperament in infants, specifically using physiological measures of cardiac activity, to enhance our understanding of the relationship between temperament and physiology and as a direction for future research of the effects of prenatal smoke exposure on infant development. In this study we examined 50 infants in an intensive laboratory assessment, which allowed ECG recordings of cardiac activity to be made during resting conditions, attention, emotional challenge and a recovery period.

6.2. Infant Temperament and the Effect of Prenatal Smoke Exposure

The main research questions which this thesis set out to address were: is there an effect of prenatal smoke exposure on infant attention, infant motor activity and infant HR? What is the role of vagal tone in the study of infant temperament? Subsidiary goals were to examine gender differences and the role of parent reports in the study of infant temperament and cognition. Each of these goals will be addressed below.

Is there an effect of prenatal smoke exposure on infant attention? Previous research investigating whether there is an effect of prenatal smoke exposure on offspring attention has provided conflicting results; for example, Leech et al. (1999), Noland et al.

(2005) and Streissguth et al. (1984) all found a link between smoking during pregnancy and a decrease in offspring attention but in contrast Langley et al. (2007) and Weissbluth and Liu (1983) found no association. However, previous research has mainly studied preschoolers and older children and thus our aim was to examine whether there was an effect of prenatal smoke exposure on offspring attention during infancy. We measured infant attention at 6 and 12 months using the 'toy interest game' adapted from the Lab-TAB (Goldsmith & Rothbart, 1999) and at 6 months we included the 'duration of orienting' subscale from the IBQ.

At 6 months, we found infants exposed to nicotine in utero received higher attention scores on observer and parent reports of attention than infants with no prenatal smoke exposure, in contrast to our hypothesis. Examining this association further considering the quantity and timing of the smoke exposure revealed that on the Lab-TAB measure infants in the 'light smoking' group received higher attention scores than infants in the 'non-smoking' and 'heavy smoking' groups and when considering the timing of the smoke exposure infants with no smoke exposure received lower attention scores than infants in the '1st trimester' and 'all trimester' smoking groups. However, at 12 months we found no effect of prenatal smoke exposure on infant attention. The sample size of the smoking groups was relatively small and so it is possible that the result at 6 months was not a true result given that small sample sizes can lead to false positive findings (Field, 2000). Therefore, before drawing any firm conclusions the current study should be replicated using a larger sample size; for example Noland et al. (2005) studied over 300 children and Streissguth et al. (1984) studied 450 children.

Another reason why our results did not support our hypothesis may be because of the nature of the task used to study attention. In the current study, the turtle and rocket toys could be manipulated and it is possible that at the 12 month assessment, given infant attention has been shown to increase between 6 and 12 months (Carranza et al., 2000), the physical affordances of the toy were such that infants' attention was maintained regardless of group status and hence no differences were found between smoking groups. Therefore, the study should be replicated using a novel stimulus, which cannot be manipulated at 6 and 12 months. Auerbach et al. (2004) suggest that depending on the context of the attention task, children with ADHD can show normal levels of focused attention. However, as the duration of the task increases and if the stimulus or situation is not changed, then children with ADHD have problems responding correctly to the demands of the task. In the current study we followed the Lab-TAB (Goldsmith & Rothbart, 1999) manual guidelines and performed the task for 3 minutes but at 12 months we did not find any differences between smoking groups. Auerbach et al. (2004) also suggest that when investigating differences between ADHD 'at risk' groups and normal controls different aspects of attention may distinguish the groups. For example, Auerbach et al. (2004) found that although infants at risk of ADHD were not differentiated from normal controls on a measure of duration of looking, there were differences between the groups on measures of facial interest and duration of manipulation.

Selecting an appropriate task that can be used to measure attention in infants at 6 and 12 months requires careful consideration. Many tasks used to measure attention in young infants are not appropriate measures for infants in the second half of the first year of life. For example, during a pilot phase we presented 6-month-olds with checkerboard

habituation items, adapted from the Bayley Scales of Infant Development, but we observed ceiling effects. Other tasks that could be used to assess attention in infancy include the visual expectation paradigm (VExP), inhibition of return (IOR) and disengagement tasks (Johnson, 2005; van de Weijer-Bergsma et al., 2008).

The visual expectation paradigm (VExP) is used to measure the ability of infants to direct attention based on expectations. In this paradigm stimuli are presented on either the left- or on the right-hand side of the infant and the ability to form expectations and make anticipatory eye movements are measured. IOR is a phenomenon whereby the reaction time to detect a second stimulus, which is presented at the same location as the first stimulus is longer than when the second stimulus is presented at a new location. Thus, the IOR paradigm can be used to examine the tendency not to shift back attention to a recently attended location, by presenting the second stimulus more than 300 ms after the initial stimulus. In disengagement tasks the infant's ability to disengage attention by adding a peripheral stimulus to a central fixation stimulus is measured. Distracter tasks can also be used to measure infant attention. In this paradigm infants are presented with a stimulus and then after a period of time a distracter is presented. For example, Lansink and Richards (1997) presented a toy that was attached to the table in front of the infant and then a distracter (in this case computer-generated patterns presented on a screen to the right of the infant) was presented later. The paired-comparison paradigm can also be used to assess attention in infants during the first year of life. In this paradigm the infant is presented with a stimulus during a familiarisation period and then during the test period the familiar stimulus is paired with a novel stimulus. Attention can be assessed during the paired-comparison paradigm using measures of peak look duration, mean look duration,

number of shifts in gaze from one target to another and mean duration of all looks off-target. Executive attention in infants can be assessed using the A- not-B (AB) task (Diamond & Goldman-Rakic, 1989), which is a marker of dorsolateral prefrontal cortex (DLPC) functioning. However, a limitation of many of these tasks is that the equipment required is often sophisticated and the procedures are too complicated to be carried out in the home, especially when embedded within a battery of cognitive tests as in the current study and thus, they were not appropriate for use in the current study.

Another reason for the inconsistencies found in research studying associations between maternal smoking and offspring attention may be the suggestion that attention is multifaceted (Barkley, 1996; Denckla, 1996) and the variety of tasks used across studies require different attentional demands. It is also possible that deficits in attention may change with age (Barkley, 1997; Streissguth et al., 1984). Fried and Watkinson (2001) suggest that when investigating the effects of prenatal smoke exposure it is important to consider attention as a multidimensional model consisting of a variety of components. Thus, it follows that attention cannot be fully understood by the use of a single measure (Fried & Watkinson, 2001). Although there is still considerable debate about the precise components comprised in the model of attention, Fried and Watkinson (2001) investigated the effect of prenatal smoke exposure on attention, considering the five elements of attention proposed by Mirsky (1996). Mirsky's (1996) model considered attention processes to include: (1) the ability to assign attentional resources to a particular task while filtering out irrelevant stimuli, (2) the capacity to shift attention across stimuli, (3) the capability to sustain attention over time, (4) the ability to maintain information mentally while manipulating or using it (similar to the concept of working memory) and

(5) the stability and consistency of maintaining attention over time. Fried and Watkinson (2001) found, in a sample of 13 to 16 year olds, that exposure to nicotine prenatally was associated with the working memory component of attention and in the youngest participants in the sample it was associated with impulsivity/behavioural inhibition. The authors concluded that prenatal smoke exposure appears to affect the ability of an individual to hold information temporarily while processing other information and in younger children it is negatively related to impulse control. Therefore, future studies investigating the association between prenatal smoke exposure and the development of behaviour disorders should include measures of attention that reflect the multifaceted nature of attention.

Animal studies provide evidence that in utero nicotine exposure changes the pathways of neurodevelopment, meaning deficits as a result of nicotine exposure could appear throughout life (Slotkin, 2008). The frontal-striatal system in the brain is involved in attention and inhibitory control (Noland et al., 2005). This system receives input from dopaminergic, cholinergic, serotonergic and noradrenergic neurotransmitters, all of which have been shown to be adversely affected following in utero exposure to nicotine (Muneoka et al., 2001; Oncken et al., 2003; Ribary & Lichtnesteiger, 1989; Richardson & Tizabi, 1994; Slotkin et al., 2006a). Abnormalities in the frontal-striatal system have been implicated in the cognitive deficits observed in individuals with ADHD (Castellanos et al., 1996). Imaging studies show that the frontal-striatal system is involved in selective attention and inhibitory control by 4 or 5 years of age but as yet there is no clear evidence this system is involved in attention processes during the first year of life (Casey, Giedd & Thomas, 2000). Indeed Diamond (1991) suggests that the complex system involving

areas of the frontal cortex, involved in planned and goal directed behaviour, becomes functional towards the end of the first year of life and develops over the preschool years. Thus, it is possible that deficits in attention as a result of exposure to prenatal smoke may only begin to emerge after the first year of life, a suggestion also proposed by Fried (2002). This is supported by the finding that in most cases it is only studies examining preschool and school aged children that report a link between prenatal smoke exposure and attention deficits in offspring (e.g. Leech et al., 1999; Naeye & Peters, 1984; Noland et al., 2005; Streissguth et al., 1984). Currently there is a lack of knowledge about the developing human brain during early childhood, particularly with regards to cognitive development, but recent advances in magnetic resonance imaging (MRI) will help to further our knowledge (Casey et al., 2000). These advances will also help to elucidate the potential effects of prenatal smoke exposure on infant attention.

Is there an effect of prenatal smoke exposure on infant motor activity? Both human and non-human animal studies have investigated the effect of prenatal smoke exposure on offspring activity levels. The majority of studies have shown that in utero nicotine exposure results in an increase in motor activity in offspring (e.g. Fried et al., 1992; Kristjansson, Fried & Watkinson, 1989; Naeye & Peters, 1984; Richardson & Tizabi, 1994; Schlumpf et al., 1988; Thomas et al., 2000; Tizabi et al., 1997). However, the majority of human studies have focused on older children and so it was not clear if these effects emerge in early development. Therefore, the aim of the study was to examine motor activity, using an accelerometer, in infants at 6 and 12 months of age during resting conditions and cognitive and emotional challenge. At 6 months we also included a parent report measure of infant activity taken from the IBQ.

In line with our prediction parent reports indicated infants with prenatal smoke exposure showed higher levels of motor activity than infants with no smoke exposure at 6 months. A dose-dependent effect of prenatal smoke exposure was found at 6 months, with results showing that infants in the 'heavy smoking' group had higher levels of activity than the 'non-smoking' and 'light smoking' groups during negative emotion, as measured using the actigraph. There was also evidence that the timing of the smoke exposure affected infant motor activity, with infants whose mothers smoked throughout pregnancy showing a smaller decrease in activity from baseline to attention than infants whose mothers smoked only during the first trimester. However, these results were not replicated at 12 months. Further studies are required to investigate whether this pattern of results reflects a true effect of prenatal smoke exposure on motor activity at 6 months and if so, whether an increase in motor activity is seen during preschool years.

Is there an effect of prenatal smoke exposure on infant HR? In Chapter 4 we considered the role of maternal smoking during pregnancy on infant HR. Heart rate was measured during baseline, attention and negative emotion challenge at 6 and 12 months. Previous studies investigating the effect of prenatal smoke exposure on infant cardiac activity have provided conflicting results; for example some researchers have found in utero nicotine exposure disrupts offspring cardiac activity (Browne et al., 2000; Franco et al., 2000; Oncken et al., 2003; Slotkin et al., 1995, 1997; Slotkin, 1998; Søvik et al., 2001), whereas other researchers have found no effect (Galland et al., 2000; Tuladhar et al., 2003). This is one of the first studies to examine the effect of prenatal smoke exposure on infant cardiac activity beyond the neonatal period and to investigate changes in HR during cognitive and emotional challenge.

At 6 months we found significant differences between the 'non-smoking', 'light smoking' and 'heavy smoking' groups on measures of cardiac reactivity (i.e. percentage change in HR from baseline to condition) during attention and negative emotion challenge, suggesting there may be a dose-response effect, in line with previous studies (Franco et al., 2000; Søvik et al., 2001). At 12 months we found no effect of the quantity of cigarettes smoked during pregnancy but there was evidence that the timing of the smoke exposure affected infant HR. During attention infants in the 'non-smoking' group had higher HRs than infants born to women who smoked throughout pregnancy. When considering change in HR from baseline to emotional challenge, infants in the '1st trimester' group showed a larger increase in HR than infants in the 'non-smoking' group. In conclusion, our results indicate that there may be an effect of maternal smoking during pregnancy on infant HR but the pattern of results was not the same at 6 and 12 months and the pattern was not easy to interpret.

As discussed, the current study was one of the first to examine the effect of prenatal smoke exposure on infant HR at 6 and 12 months during resting conditions and cognitive and emotional challenge. The current study also included measures of cardiac reactivity, which is important as these measures allow an individual's response to challenge to be measured while taking into account baseline state. The use of the ActiGraph ActiTrainer meant that HR data could be collected relatively easily and unobtrusively from infants in the study, meaning that few participants refused to take part in the procedure. This allowed us to collect HR data from a large and representative sample, across conditions and time. Therefore, we recommend that future studies utilize this design and methodology, with the aim of clarifying the association between prenatal

smoke exposure and infant cardiac activity. Unfortunately it was beyond the limits of this thesis to follow the sample into preschool years but future follow-up studies will allow us to investigate if the effects of prenatal smoke exposure on cardiac activity persist or become more marked beyond the first year of life.

What is the role of vagal tone in the study of infant temperament? In Chapter 4 we examined the effect of prenatal smoke exposure on infant HR. The autonomic nervous system (ANS) regulates organs in the body, including the heart, and consists of two components: the parasympathetic nervous system and the sympathetic nervous system. Vagal tone is considered an index of the parasympathetic influence on the heart and in the early 1900s Eppinger and Hess (1910; 1915) indicated that high levels of VT may be related to psychopathology. Since then VT has become a psychophysiological marker for emotion regulation and other aspects of behavioural functioning (Graziano et al., 2007) and theories such as the Polyvagal Theory provide justification for the use of measures of VT as an index of infant temperament (Porges, 1995; 1997). A more complete understanding of the relationship between temperament and physiology is required to advance our knowledge of infant temperament (Nachmias et al., 1996). Thus, in Chapter 5 we examined the role of physiological measures of cardiac activity, particularly VT, in the study of infant temperament and as a direction for future research examining the effects of prenatal smoke exposure on infant temperament. Heart rate and VT were measured during a baseline period and during cognitive and emotional challenge in a cohort of children between the ages of 6 and 14 months. It was predicted that VT would increase during attention and decrease during emotional challenge, in contrast to HR which would show the reverse pattern. However, our results with regards to VT were

ambiguous and we found no effect of condition on VT but our results suggest that in a larger sample size, with a narrower age range of participants, measures of VT reactivity may be useful in future studies. Results showed that HR decreased from baseline to attention and increased from baseline to emotional challenge, in line with our hypothesis, and thus supports the use of HR, measured across conditions, as a valid and reliable physiological measure to investigate infant temperamental profiles. Infancy is an important time for the development of the ANS because myelination of neurons is occurring and self-regulatory skills are not yet fully developed. Thus, infancy is an essential period to examine the potential effects of prenatal smoke exposure on cardiac activity.

Bauer, Quas and Boyce (2002) suggest that it is important to consider how physiological systems interact and not treat an individual physiological variable as an independent predictor without considering the biological framework in which it occurs. Therefore, future studies examining the temperament-physiology relationship and the effect of prenatal smoke exposure could consider including measures of the sympathetic branch of the ANS, such as PEP, and other measures of stress reactivity, such as skin conductance and cortisol.

The development of attention, motor activity and HR in infancy. Measures of attention have been shown to be stable across time (Gaertner et al., 2008; Lawson & Ruff, 2001; Ruff & Dubiner, 1987). During early infancy, infants tend to focus on aspects such as the size and brightness of the stimuli. By 4 months of age infants develop skills in initiating and sustaining attention and as the infant moves into the second year of life attention becomes more related to planned and self-generated activity (Johnson et al.,

1991). Results from the current thesis support previous findings that scores on measures of attention increase between 6 and 12 months (Carranza et al., 2000; Ruff & Rothbart, 1996).

Activity levels have been identified as showing major individual differences during infancy (Saudino & Zapfe, 2008). Whilst some researchers have found individual differences in activity levels to be stable across time, this is not consistently found (e.g. Auerbach et al., 2004, 2005, 2008; Buss et al., 1980; Campbell et al., 1994; Lemery et al., 2002; Thomas et al., 1968). One possible explanation for the mixed findings with regards to stability of activity levels is that during infancy activity levels are linked to both positive and negative affectivity (Rothbart & Bates, 1998). For example, during early infancy high levels of activity usually occur during periods of distress but during later stages of infancy more neutral mood states, such as orienting towards novel objects, can lead to increases in activity level. Thus, it is important to identify and differentiate between the types of activity.

Heart rate has been found to show individual differences that are stable over time (e.g. Fracasso et al., 1994). Heart rate is associated with control of attention and changes in HR can also be observed as a result of motor activity. During sustained attention HR levels decline (e.g. Colombo et al., 2001; Lansink & Richards, 1997; Richards & Casey, 1991; Richards & Gibson, 1997) and Ruff and Rothbart (1996) suggest that changes in HR are a primary indicator of attention. Stifter, Fox and Porges (1989) found that 5-month-old infants with higher VT (thus lower HR) showed higher levels of interest than infants with lower VT but interestingly this pattern was not found at 10 months. Porges, Heilman, Bazhenova, Bal, Doussard-Roosevelt and Koledin (2007) examined the

relationship between measures of cardiac activity and motor activity and found that small increases in motor activity (e.g. reaching) were not related to changes in cardiac measures but larger increases in motor activity were related to an increase in cardiac activity. Stifter and Fox (1989) found that at 5 months of age infants with high baseline VT (thus low HR) were rated by their mothers as being more active than infants with lower VT.

Correlational analyses on attention, motor activity and HR measures were performed among the non-exposed infants in the current thesis. Results revealed that there were no correlations between the measures at 6 or 12 months. As reviewed above, correlations between measures are not consistently found during infancy (e.g. Stifter et al., 1989) and therefore, following the sample beyond the first 12 months of life and studying the concurrent development of attention, motor activity and HR would be an interesting extension to the current thesis.

Are there gender differences in infant temperament? Research studying gender differences in infant temperament has found mixed results. When looking at infant attention a meta-analysis by Else-Quest et al. (2006) of studies of children ranging in age from 3 months to 13 years revealed that in two of the four attention span dimensions studied, girls scored higher than boys and overall the results indicated that girls may be better at regulating and allocating attention compared with boys. However, studies of infants carried out by Gallas and Lewis (1977) and Karass et al. (2002) indicated that gender differences in attention were not apparent during the first year of life. Karass et al. (2002) used the 'duration of orienting' subscale of the IBQ and a composite measure of manipulative exploration adapted from the Bayley Scales of Infant Development and Gallas and Lewis (1977) used the Mental Development Index (MDI) of the Bayley Scales

of Infant Development. In the current study we found no evidence of gender differences in attention at 6 months but at the 12 month assessment we found that boys received marginally higher attention scores than girls and this result requires replication before firm conclusions can be drawn.

When considering sex differences in motor activity in infants, previous studies have provided conflicting results with some studies suggesting there are no differences (e.g. Halverson & Waldrop, 1973) and others suggesting boys have higher levels of motor activity than girls (e.g. Eaton & Enns 2002; Else-Quest et al., 2006; Goldberg & Lewis, 1969; Pedersen & Bell, 1970). Based on results from a study by Goldberg and Lewis (1969) who studied a similar age to that studied in the current sample, we predicted that boys would show higher levels of motor activity than girls. Results from Chapter 3 indicated that in the current study gender differences were not apparent during baseline and cognitive and emotional challenge, during the first year of life. However, the situation during which activity is recorded may be important; for example Goldberg and Lewis (1969) found that during play situations gender differences were apparent in a sample of 13-month-olds. In the current study we used actigraphs to measure activity at 6 and 12 months and also included parent reports at 6 months. However, the measurement of motor activity varies across studies, with measures used including parent reports, observer ratings and accelerometers, and the different methodologies used between studies may go some way in explaining the discrepancies in past results. It is also possible that gender differences emerge during the second year of life. Therefore, future studies assessing motor activity using a multi-method design across different settings and

following the children from infancy through to preschool years and beyond will help clarify findings.

Previous research examining gender differences in cardiac activity in children has provided mixed results (e.g. Alkon et al., 2006; Buss et al., 2005; Calkins & Dedmon, 2000; Campos et al., 1975; Scarpa et al., 1997). However, in general studies investigating cardiac activity in infants during the first year of life have shown no evidence of gender differences. Results from Chapters 4 and 5 indicated that there were no differences in cardiac activity between girls and boys during resting conditions or during cognitive and emotional challenge during the first year of life. Given that some previous studies examining cardiac activity in preschoolers suggest that there are gender differences (e.g. Calkins & Dedmon, 2000; Scarpa et al., 1997), it is possible that differences between girls and boys in cardiac activity emerge after the first year of life and future studies following up our samples into preschool years and beyond will allow us to explore this hypothesis.

In conclusion, results from the studies in this thesis indicate that there are no gender differences of note in attention, motor activity or cardiac activity during the first year of life, except for a marginal difference in attention at 12 months. Previous research suggests that gender differences in some temperament dimensions may emerge and increase with age (Eaton & Enns, 1986; Maccoby & Jacklin, 1974). Social factors are clearly important in the development of gender differences and it is therefore not surprising that gender differences are not pronounced during the first year of life (Hay, 2007). Researchers suggest that gender differences can develop and increase, as a result of a rise in social interactions as the individual gets older (Else-Quest et al., 2006;

Maccoby, 1990; Scarr & McCartney, 1983). There is also evidence that adults code an infant's ambiguous response to a stimulus differently depending on whether the infant is a boy or a girl (Condry & Condry, 1976). Following the sample longitudinally using a multi-method, multi-informant design will allow us to examine whether gender differences emerge in these temperamental domains after the first year of life, whilst considering the potential effects of factors such as stereotypes and observer bias.

In their meta-analysis of gender differences in temperament in children from 3 months to 13 years, Else-Quest et al. (2006) found that girls performed better than boys on measures of effortful control, particularly attention regulation, and previous studies have found an association between low scores on these measures and a greater incidence of externalizing behaviour disorders, including ADHD (Nigg, Goldsmith & Sachek, 2004). This provides evidence that gender differences in aspects of effortful control may in part account for gender differences in ADHD and may be an important link in the finding that ADHD is more common in boys than girls (Else-Quest et al., 2006). Effortful control develops from the end of the first year of life (Rothbart & Ahadi, 1994; Rothbart, Ahadi & Evans, 2000) and including measures of effortful control would be useful in the study of gender differences in the pathways to behaviour disorders.

The role of parent reports in the study of infant temperament. The vast majority of studies examining child temperament utilize parent and teacher reports, and behavioural observations and laboratory measures are used relatively infrequently, probably as a result of the expense and time required to administer such measures. We were interested in whether parent reports correlated with behavioural and objective measures of infant temperament and behaviour. Based on previous research, we expected to find a

correlation between maternal reports and behavioural observations of attention (e.g. Bridges et al., 1993) but we did not expect to find a correlation between parent reports and actigraph measures of motor activity (Eaton & Dureski, 1986). Our results showed that there were no correlations between parent reports and actigraph measures of motor activity, and between parent reports and behavioural observations of attention. Some previous studies have found modest correlations (in the region of .30) between parent reports and actigraph measures of activity levels (Dane et al., 2000; Saudino et al., 2004) and between parent reports and behavioural observations of infant temperament (Bridges et al., 1993; Hane et al., 2006). However, there have also been several studies which have found no correlations between parent reports and behavioural observations (e.g. Eaton & Dureski, 1986).

One reason for the lack of convergence between parent reports and other measures of temperament and infant behaviour may be because parents are usually reporting on behaviours they observe in their infants on a daily basis, whereas the actigraph or observer is measuring infant behaviour during a short time period, often of just a few minutes or even seconds. There is some evidence to suggest that maternal reports of infant temperament reflect maternal as well as infant characteristics, which may add bias to maternal reports (Crockenberg & Acredolo, 1983; Leerkes & Crockenberg, 2003; Mangelsdorf, Gunnar, Kestenbaum, Lang & Andreas, 1990). Kagan (1998) has argued that parents may not be able to report accurately on their child's behaviour because they lack sufficient knowledge of other children for comparison and their responses may be skewed because of an inclination to present themselves and their children in a positive way. The emotional state of the parent may also play a role; for

example, Forman, O'Hara, Larsen, Coy, Gorman and Stuart (2003) found that mothers who were depressed were less accurate reporters of their child's negative emotionality at 6 months of age than non-depressed women.

However, it is also important to note that observer reports of infant behaviour during laboratory tasks are subject to measurement error and bias as well (Rothbart & Bates, 1998) and thus, no one informant should be considered more valid than another (Hane et al., 2006; Kraemer, Measelle, Ablow, Essex, Boyce & Kupfer, 2003). Indeed, some researchers argue that parents spend large amounts of time and have a vast knowledge of their children, which is unmatched by anyone else, and as a result are in the best situation to report on their infant's temperament (Else-Quest et al., 2006; Rothbart & Bates, 1998). Rothbart and Bates (1998) argue that for both genetic and environmental reasons maternal characteristics and personality can be considered meaningful predictors of child temperament.

Eaton and Dureski (1986) found no correlation when looking at parent reports and actigraph measures of infant activity and suggest this may be because the IBQ focuses on caretaking situations such as dressing, bathing and mealtimes, whereas the actigraph measures motor activity in response to a discrete stimulus. A study by Worobey, Vetrini and Rozo (2009) used a novel design to investigate the use of accelerometers in the study of motor activity in infants. Worobey et al. (2009) attached an actigraph to a human infant and another actigraph to a doll and a research assistant mimicked with the doll the movements made by the mother with the infant. Results showed that whilst the infant was significantly more active than the doll (as would be expected) some movement was credited to the doll, which must be as a result of movement artefact from the caregiver.

Worobey et al. (2009) suggest because actigraph measures can be confounded by caregivers' movements this may explain, at least in part, why correlations between maternal reports and actigraph measures of infant motor activity are often low or not present. However, as each method of measuring infant temperament and behaviour has advantages and disadvantages, studies which utilize a multi-method and multi-informant approach can make important contributions to the field of temperament research.

6.3. Limitations and Implications for Future Research

As discussed above, the results from the studies carried out in this thesis show that at 6 months of age infants exposed to prenatal smoke show more sustained attention, increased motor activity and increased HR during cognitive and emotional challenge than non-exposed infants. There was also evidence of a dose-dependent relationship between the amount of smoke exposure and offspring attention, motor activity and HR, and some evidence that the timing of the smoke exposure during pregnancy may play a role in motor activity and attentional abilities. However, the same pattern of results was not observed at 12 months and the only relationship between prenatal smoke exposure and offspring development observed at this assessment point was for cardiac activity, with infants in the 'non-smoking' group showing higher HRs during attention and smaller increases in HR from baseline to emotional challenge than infants exposed to prenatal smoke. The observed effects were not always in the expected direction and were not consistent across variables and age. For example, when evidence of a dose-dependent relationship was found, sometimes the 'light smoking' group differed significantly from the other groups and in other cases it was the 'heavy smoking' group that was

significantly different and a similar pattern was observed when considering the timing of the smoke exposure.

We suggest that these results provide preliminary evidence that prenatal smoke exposure affects some aspects of infant temperament and behaviour during the first months of life. Attention and motor activity are key symptoms of ADHD and disrupted cardiac activity is a known correlate of ADHD, thus, these domains could be considered in the search for early precursors to ADHD. However, these results are not conclusive and further studies are required to help interpret the complex results found and to examine whether these effects are evident at 12 months of age and persist into childhood. Limitations and questions raised by this thesis, together with directions for future research, are discussed next.

Quantity of smoke exposure. It is suggested a dose-response relationship between prenatal smoke exposure and infant outcomes indicates a causal association (Button, Maughan & McGuffin, 2007) and the majority of studies investigating maternal smoking during pregnancy and ADHD symptoms in offspring have found such a relationship (e.g. Kotimma et al., 2003; Langley et al., 2007). Whilst results from this thesis provide some evidence of a dose-response relationship at 6 months, this is not consistent across the variables studied and there is no evidence of such a relationship at 12 months. One possible reason for this may be because of the relatively low numbers of heavy smokers in our sample even though we over-sampled smoking women from the CCDS sample. Of the women who smoked in our sample, 30.4% smoked 10 or more cigarettes a day and only 5.4% smoked 20 or more cigarettes a day during pregnancy. The typical threshold for finding effects of smoking during pregnancy on infant outcomes, including effects on

birth weight, is 10 cigarettes per day (Jacobson, Jacobson, Sokol, Martier & Chiodo, 1996). However, when controlling for confounding factors, Gilman et al. (2008b) found an association between prenatal smoke exposure and low birth weight, when the mothers smoked 20 or more cigarettes a day during pregnancy, which was also the quantity of exposure at which Fergusson et al. (1998), Mick et al. (2002) and Brennan et al. (1999) found links with offspring behaviour problems. Stroud et al. (2009b) also found particular effects between mothers smoking 20 or more cigarettes a day during pregnancy and increased offspring irritability. Replication of the current study using a larger sample size, with a resulting increase in heavy smokers, will increase power and help clarify our findings.

Timing of the assessments. Clearly one of the major limitations of this thesis is that the final assessment was at 12 months of age, which is before a diagnosis of ADHD can be made. A diagnosis of ADHD is commonly made between 4 and 8 years of age (Applegate et al., 1997; Sonuga-Barke et al., 2005), with symptoms present before the child reaches 7 years (Connor, 2002). However, there is evidence that a reliable and valid diagnosis of ADHD can be made in children as young as 2 years of age (Egger et al., 2006) and indeed some researchers report that children as young as 2 years have been prescribed stimulant medication (Zito et al., 2000). Therefore, before firm conclusions can be drawn about whether there is an association between prenatal smoke exposure and ADHD the sample needs to be followed up during preschool years and into early school years so that an assessment of ADHD symptoms can be made. The prevalence rate of ADHD in preschool children has been found to be between 2% and 7.9% (Egger et al., 2006) and so we would expect a diagnosis of ADHD to be made in only a few cases in

the current sample. Therefore, it will be important to consider the spectrum of ADHD symptoms and to consider symptoms on a continuum.

In a review of the effects of prenatal nicotine exposure, Ernst et al. (2001) concluded that in children under the age of 2 results have been less consistent compared with findings in older children. Ernst et al. (2001) suggest two possible reasons for this finding; the first is that the measurements used to study infants and young children may be less sensitive and the second is that deficits are only detectable when a certain level of brain maturation has taken place. Previous researchers have used similar measures to those used in this thesis, in a similar age group and have found differences between infants at risk of ADHD compared with normal controls (e.g. Auerbach et al., 2004; 2005; 2008). Therefore, it is possible that the inconsistencies found in data presented in this thesis are the result of the level of brain maturation and the interaction between brain development and the effect of nicotine exposure, rather than a lack of measurement sensitivity. As discussed above (section 6.2), there is evidence that pathways in the brain associated with attention are not fully developed during the first year of life and therefore, it is possible that neural networks associated with other aspects of development are also not fully developed and hence the adverse effects of in utero nicotine exposure are not fully apparent during the first year of life.

However, there is evidence that some aspects of infant development are affected by prenatal smoke exposure during early infancy. Law, Stroud, LaGasse, Niaura, Liu and Lester (2003) tested infant neurological state within 48 hours of birth and found that infants exposed to prenatal smoke were more highly aroused and reactive than non-exposed infants. This was shown by their higher excitability and handling scores, and

greater muscle rigidity. A dose-response relationship was found and infants with smoke exposure showed greater signs of stress, which may indicate neonatal withdrawal from nicotine. Another study examined infants between 10 and 27 days of age, which is well past the half-life of nicotine and hence the effects of nicotine withdrawal were unlikely to be a factor in the results obtained (Stroud et al., 2009a). In this study it was again found that infants exposed to prenatal smoke showed an increased need for handling and external intervention to be soothed and calmed down, and were more easily aroused and excitable. The authors suggest that these results indicate it may be possible to identify infants at risk of developing adverse neurobehavioural outcomes during the first month of life. In a large community sample a similar result was found (Stroud et al., 2009b). After controlling for significant covariates it was found that there was a significant influence of prenatal smoke exposure on irritability and hypertonicity in the newborn infant. Post hoc tests revealed particular effects of heavy smoking (i.e. 20 or more cigarettes per day) on infant irritability. Replication of the studies carried out in this thesis with an assessment during the neonatal period would provide evidence about whether changes in cardiac and motor activity and deficits in attention, as a result of prenatal smoke exposure, are present during this period and would provide clarification about whether a certain level of brain maturation is required to observe deficits, as a result of in utero nicotine exposure, in these areas.

The work by Stroud and colleagues (Law et al., 2003; Stroud et al., 2009a; 2009b) provides strong evidence that the effects of prenatal smoke exposure are evident in neonatal behaviour and even in the first 3 days of life infants exposed to nicotine in utero can be differentiated, based on neonatal examinations, from infants with no prenatal

smoke exposure. High levels of infant fussing and crying may indicate more global and persistent difficulties with behavioural control and self-regulation and the combination of a fussy and difficult infant with a mother under pressure with few resources may lead to strained mother-infant interactions during a critical period for bonding (Stroud et al., 2009b). This could result in a negative cycle of mother-child interaction, which in turn could lead to an increase in behavioural dysregulation in the infant and thus, place the child at greater risk of developing behaviour problems, including ADHD, later in life. This proposal is in line with findings by Wolke et al. (2002), who found persistent crying during infancy was related with increased hyperactivity and conduct problems during childhood. Therefore, Stroud et al. (2009b) propose that although irritability and hypertonicity in the neonatal period may indicate nicotine withdrawal, when these behaviours occur in combination with parenting deficits, they may also represent early endophenotypic markers of risk for the development of behaviour problems later in life.

Thus, it is possible that if an infant receives in utero nicotine exposure but is born into an optimal postnatal environment (e.g. the mother has high levels of social support), then the initial negative effects of prenatal smoke exposure such as high levels of irritability present during the neonatal period may dissipate. This is in line with the suggestion by Fried (2002) that as children get older it is likely that the environment influences the variables of interest to a greater extent and that the effects of prenatal smoke exposure may become less apparent and/or less easy to distinguish from other factors. This also fits in with the fact that prenatal smoke exposure does not result in adverse outcomes in all exposed offspring (Huizink & Mulder, 2006). Further research is needed to examine whether the environment in which the exposed infant is raised affects

the phenotype displayed. Thus, an infant who received in utero nicotine exposure but is raised in an optimum environment may display a milder phenotype compared with a prenatally exposed infant raised in a less optimal environment. Kosofsky and Hyman (2001) suggest it may then be possible to identify specific factors which promote resilience. Therefore, we suggest that in the current study the timing of the assessments may have meant that we missed the peak of adverse effects that occur as a result of prenatal smoke exposure and thus, future studies should begin earlier in development. We also suggest that replication of the current study in 'at risk' populations may clarify and confirm potential mechanisms through which the environment may interact with the effects of prenatal smoke exposure and influence offspring outcomes.

Maternal characteristics and the postnatal environment. There is evidence that women who smoke during pregnancy differ from women who do not smoke during pregnancy on a number of social and behavioural factors. Women who smoke during pregnancy have been shown to be younger, to have lower levels of education, to be more likely to be antisocial and to have children with antisocial men, to have a lower socioeconomic status and an adverse home environment and to be more likely to have had depression than women who do not smoke during pregnancy (Button et al., 2007; Gilman, Breslau, Subramanian, Hitsman & Koenen, 2008a; Huizink & Mulder, 2006; Kleinman & Madans, 1985; Maughan et al., 2004; Raatikainen, Huurinainen & Heinonen, 2007). Thus, it is conceivable that these characteristics are associated with adverse outcomes in infants rather than prenatal smoke exposure per se.

Maughan et al. (2004) controlled for antisocial behaviour in both parents, for depression in mothers and for family disadvantage and genetic influence and found that

estimates of the effects of prenatal smoking on offspring conduct problems were reduced by between 75% and the entire initial effects. Gilman, Gardener and Buka (2008b) found that associations between maternal smoking during pregnancy and offspring conduct problems and academic achievement at 7 years of age was removed after adjustment for measured and unmeasured confounding variables, using a design which compared siblings exposed to prenatal smoke with those with no prenatal smoke exposure. However, the cohort was recruited in 1959 and a limited range of measures was used, for example, there were no measures of motor activity or attention and no assessments of physiological parameters were made. Also, both the studies by Maughan et al. (2004) and Gilman et al. (2008b) focused on symptoms of CD and so it is not clear whether these results generalise to ADHD.

In a study by Robinson et al. (2008) it was found that prenatal smoke exposure was a significant risk factor for child behavioural problems at 2 and 5 years of age, even when controlling for confounding variables, which is in line with a number of studies examining the relationship between prenatal smoke exposure and ADHD (e.g. Kotimaa et al., 2003; Langley et al., 2007; Linnet et al., 2005). Robinson et al. (2008) suggest their results concur with the suggestion by Button et al. (2007) that there is a direct influence of maternal smoking in pregnancy on offspring behavioural problems, including ADHD, and it is not simply a proxy variable.

In this thesis the effect of potentially confounding variables was not examined, which is clearly a limitation and an important direction for future research. Identifying, measuring and providing adequate statistical control for all potential confounding variables is a challenge faced by all researchers in this field. Some researchers have

attempted to overcome these challenges with new and innovative methodologies (e.g. Gilman et al., 2008b; Rice et al., 2009; Thapar et al., in press) but even these designs come with problems, such as small sample sizes and reduced power. Thus, the future success of this area of research depends on well-designed prospective, longitudinal human studies considered in conjunction with animal research. Animal research is important because confounding factors can be controlled in a way which they cannot in human studies. Animal models have also provided biological plausibility for an association between prenatal smoke exposure and adverse effects in offspring (e.g. Miao et al., 1998; Roy et al., 1998; Slotkin, 1998; Van de Kamp & Collins, 1994). However, caution needs to be used when generalizing findings from animal studies to humans because of methodological limitations and differences between species.

Smoking cessation during pregnancy. There is evidence that infants born to women who stop smoking during pregnancy have better outcomes than infants whose mothers do not stop smoking. Given that relapse rates after the birth of the baby are high, the decision to stop smoking during pregnancy seems to reflect a woman's desire to protect her baby as opposed to her intention to permanently stop smoking (DiClemente, Dolan-Mullen & Windsor, 2000). In a study by Pickett et al. (2008) it was found that infants born to women who gave up smoking whilst pregnant received the highest scores of easy temperament and were at a decreased risk of showing distress to novelty and irregularity compared with infants in the non-smoking and heavy smoking groups. Pickett et al. (2008) suggest that the ability to defer smoking for the duration of the pregnancy probably reflects maternal personality characteristics and as a result smoking cessation during pregnancy does not simply reflect the absence of smoke exposure. Pickett et al.

(2008) suggest the design of their study helps further knowledge about whether prenatal smoking has an aetiological role in the pathways to problem behaviours and/or whether it is a marker for intergenerational transmission processes and the results suggest that both maternal characteristics and teratological effects are in operation. Pickett et al. (2008) call for further studies which examine differences between women who quit smoking and women who continue to smoke heavily throughout their pregnancy and to investigate how these differences contribute to the emergence of early precursors and the development of problem behaviour in offspring. This will be an important step for clarifying pathways from prenatal smoke exposure to the occurrence of behaviour disorders, such as ADHD.

The '1st trimester' smoking group created in this thesis may be a comparable group to the 'quit smoking' group used in the study by Pickett et al. (2008). In the variables examined in this thesis, we found no significant evidence of the '1st trimester' group performing better than both the 'non-smoking' and the 'all trimester' smoking groups, which would be in line with the findings by Pickett et al. (2008). However, during the attention task at 6 months the '1st trimester' group did receive significantly higher scores than the 'non-smoking' group and there was a non-significant trend for the '1st trimester' smoking group to receive better scores than the 'all trimester' group. Power analyses suggest increasing the sample size to over 20 infants in the '1st trimester' group would increase power sufficiently (Faul et al., 2007). Pickett et al. (2008) collected retrospective information about maternal smoking status during pregnancy and mothers were asked simply to report whether they quit smoking during pregnancy, with no information given about the time period during which smoking stopped, making it

difficult to directly compare the studies. Also, the sample size used by Pickett et al. (2008) was much larger than that presented in this thesis; in Pickett et al.'s (2008) 'quit smoking' group there were over 2300 infants compared with only 15 infants in the '1st trimester' group in the current thesis. Replication of the studies carried out in this thesis, using a larger sample size and consideration of the role of maternal characteristics involved with the decision to stop smoking during pregnancy would be an important step for future research.

Environmental smoke exposure. Environmental tobacco smoke (ETS) has been shown to be associated with a number of adverse health outcomes in children, such as respiratory disease (Mannino, Moorman, Kingsley, Rose & Repace, 2001), low birth weight (Eskenazi, Prehn & Christianson, 1995) and SIDS (McMartin et al., 2002). There is evidence ETS may affect the neurobehavioural functioning of young infants (Eskenazi & Castorina, 1999; Schuetze & Eiden, 2006) and Machaalani, Waters and Tinworth (2005) carried out a study on piglets which indicated that ETS exposure may be responsible for some adverse neurological changes observed in infants who die from SIDS. There are two types of ETS; the first is maternal exposure to ETS during pregnancy and the second is postnatal ETS exposure of the child. Prenatal exposure to ETS has been shown to result in an upregulation of nicotinic acetylcholine receptors and a dysregulation of serotonin (5HT) receptors (Slotkin et al., 2002; 2006b) in animals and postnatal ETS exposure results in the infant being exposed to high concentrations of toxins which readily enter the infant's bloodstream (Gillies, Kristmundsdottir, Wilcox & Pearson, 1986).

Studies have found that postnatal ETS exposure is associated with cognitive deficits in young children (Eskenazi & Trupin, 1995) and academic failure in teenagers (Collins, Wileyto, Murphy & Munafò, 2007), even when prenatal smoke exposure is controlled. In a study by Maughan et al. (2001) it was found that persistent maternal smoking, both during and after pregnancy, was associated with early-onset conduct problems. Several studies have shown an association between maternal ETS exposure during pregnancy and adverse offspring outcomes, such as reduced foetal growth (e.g. Cornelius & Day, 2000). Given that the Welsh Health Survey found that ETS exposure occurs in 43% of homes with children, this is clearly an important factor to consider when studying child outcomes (Dolman, Gibbon & Roberts, 2007).

Prenatal smoking and postnatal ETS are highly associated since women who smoke during pregnancy are likely to continue smoking after the birth of the child (Eskenazi & Castorina, 1999). Thus, when studies find an association between prenatal smoke exposure and infant outcomes it is unclear whether this association is the result of maternal smoking during pregnancy or of prenatal and/or postnatal exposure to ETS (Schuetze & Eiden, 2006). However, Schuetze and Eiden (2006) found that there were significant differences in infant autonomic functioning between the ETS and prenatal exposure groups and as a result suggest that it can be assumed prenatal smoke exposure is responsible for at least a part of the observed effects. To fully examine the effects of maternal smoking during pregnancy compared with prenatal and postnatal ETS exposure, large sample sizes are required, which include women who only smoke during pregnancy and women who only smoke during the postnatal period. Given the relatively small numbers of women likely to fall into these groups, non-human animal studies should also

be utilized. In this thesis it was not possible to measure postnatal smoking and thus the effect of prenatal and postnatal ETS was not considered. Therefore, the next step following on from this thesis, will be to consider the role of prenatal and postnatal ETS exposure on infant outcomes and the association between maternal smoking during pregnancy and ETS exposure on offspring development.

Gene-environment interactions. Smoking during pregnancy may be a marker of behavioural problems in the mother (Button et al., 2007). For example, research has shown that adults with ADHD smoke significantly more than adults without ADHD (Kollins et al., 2005). ADHD has a heritable component (Payton et al., 2001) and so it is possible that a woman smokes during pregnancy because of a genetic predisposition and it is this predisposition that is inherited by the child and thus, maternal smoking during pregnancy is a proxy of this association (Button et al., 2007). However, if it was the case that the genetic components of behavioural disorders were linked autosomally to smoking, then they should be passed equally from mother and father to child (Weitzman et al., 2002). Whilst there is some evidence that paternal smoking is as strongly associated with an increased risk for ADHD as maternal smoking during pregnancy (Altink et al., 2009; Eskenazi & Castorina, 1999), the majority of research suggests that it is maternal smoking, which has the stronger association (Bastra et al., 2003; Trasti et al., 1999; Weitzman et al., 2002).

Evidence from twin studies suggests that shared and unique environmental factors account for between 12% and 40% of the variance in twin ADHD scores (Thapar et al., 2005). A study by Thapar et al. (2003) found that prenatal smoke exposure was significantly associated with ADHD symptoms, in addition to genetic factors and non-

shared environmental influences. Maughan et al. (2004) also found that maternal smoking during pregnancy continued to be associated with offspring behaviour problems, even when controlling for genetic factors. Two studies utilising a novel research design have found that the association between prenatal smoking and antisocial behaviour (Rice et al., 2009) and ADHD (Thapar et al., in press) was dependent on inherited factors and thus the associations reported between maternal smoking and antisocial behaviour and ADHD may represent an inherited effect. However, the studies by Rice et al. (2009) and Thapar et al. (in press) have several limitations. For example, the rates of smoking were very low which meant that the power to detect the effect of environmental influences was low. Hence the studies can not rule out the possibility of prenatal environmental influences and only show that inherited factors are involved. There is also evidence that IVF samples differ epigenetically from samples in which normal conception took place (Gosden, Trasler, Lucifero & Faddy, 2003).

There is evidence that both environmental and genetic factors may contribute to the phenotypic heterogeneity of ADHD. For example, Langley et al. (2007) found that maternal smoking during pregnancy was a significant predictor of hyperactive-impulsive symptoms in children diagnosed with ADHD, but no association was found between prenatal smoke exposure and severity of inattentive symptoms. Although this was a clinical sample of children between 6 and 16 years of age and it is unclear whether the results generalise to younger, non-clinical populations. This finding, together with a similar finding by Kahn et al. (2003), may go some way to explaining our finding that there was no relationship between prenatal smoke exposure and attention problems.

Evidence of an interaction between prenatal smoke exposure and genetic risk in the development of ADHD was provided in a study by Kahn et al. (2003). In this study it was found that a polymorphism in the gene for the dopamine transporter (DAT) was only associated with hyperactivity-impulsivity in children who were also exposed to nicotine in utero. This suggests that infants with a particular genotype may be more vulnerable to the effects of maternal smoking during pregnancy and highlights the need to examine both genetic and environmental factors in studies of the development of ADHD. Animal research provides evidence that the interaction between prenatal smoke exposure and the DAT polymorphism is biologically plausible. In utero exposure to nicotine results in the upregulation of nicotine acetylcholine receptors (Miao et al., 1998; Slotkin, 1998; Slotkin et al., 2002; Van de Kamp & Collins, 1994), which have been found to be present in the foetal brain as early as the eight week of gestation (Ernst et al., 2001; Hellström-Lindahl et al., 2001). Evidence suggests that activation of these receptors increases the release of dopamine from DAT (Drew, Derbez & Werling, 2000). The DAT polymorphism has been linked to a chain of events which results in the increase in transcription of DAT (Michelhaugh, Fiskerstrand, Lovejoy, Bannon & Quinn, 2001; Miller & Madras, 2002). Therefore, in children exposed to nicotine in utero and in possession of the DAT polymorphism, the upregulated nicotine receptors may interact with an increase in availability of DAT (Kahn et al., 2003). In line with these findings, dopaminergic dysregulation has been implicated in the pathophysiology of ADHD (Farone & Biederman, 1999). Support for the finding by Kahn et al. (2003) has recently been provided by Baler, Volkow, Fowler and Benveniste (2008) who suggest a similar

relationship when examining CD in individuals with a polymorphism of the monoamine oxidase A allele (MAO-A).

In conclusion, ADHD is likely to develop as a result of complex interactions between environmental, including prenatal smoke exposure, and genetic factors. Thus, to advance our knowledge of the development of ADHD and potential associations with prenatal smoke exposure, future studies need to examine both genetic and environmental factors and the interactions between these factors (Auerbach et al., 2008; Rutter, 2003; Sonuga-Barke et al., 2005).

6.4. Concluding remarks

The aim of this thesis was to investigate the effects of prenatal smoke exposure on infant temperament, specifically the domains of attention, motor activity and cardiac activity. To further understanding of the relationship between temperament and physiology we also studied VT as an index of infant temperament. Results from our studies revealed that at 6 months infants exposed to prenatal smoke showed more sustained attention, increased rates of motor activity and disrupted patterns of HR. However, at 12 months there was no evidence of an effect of prenatal smoke exposure on infant attention or motor activity but there was evidence of an effect on HR. There were a number of important strengths of the studies carried out in this thesis, for example, the sample was representative of the UK population on a number of key socio-demographic variables, infants were studied twice during the first year of life, physiological measures were used in combination with behavioural observations and parent report and the sample size was large given the measures used. However, our results were not consistent, not

always in line with our hypotheses and difficult to interpret. We suggest that future studies need to begin earlier in infancy, during the neonatal period, to fully capture the effect of prenatal smoke exposure on offspring outcomes and to enhance our knowledge of potential pathways from prenatal smoke exposure to the development of behaviour disorders. Although, results from our study of VT as an index of temperament were ambiguous, the indication is that this is an important direction for future research studying infant temperament and the effects of prenatal smoke exposure on early development. Thus, combining the novel and rigorous designs presented in this thesis to study the effects of prenatal smoke on offspring development at several time points during the first year of life, using physiological measures in combination with parent report and behavioural observations, both at home and in more intensive laboratory settings will be an important task for the future.

Excessive motor activity and problems with attention are key characteristics of children with ADHD and disrupted patterns of cardiac activity are a known correlate of ADHD and other behaviour disorders. Therefore, results from this thesis add to the growing literature examining the pathways from prenatal smoke exposure to the development of ADHD and other behaviour disorders in offspring. Maternal smoking during pregnancy is not the only causal factor in the development of ADHD and ADHD likely results from complex interactions between gene x gene, gene x environment and environment x environment (Rutter, 2003). Future research examining the association between prenatal smoke exposure and ADHD needs to be designed with this in mind. As highlighted by Brook et al. (2000) and Langley et al. (2007) prenatal smoke exposure can be measured relatively easily and so whether or not it is proved to have a direct causal

effect in the development of ADHD, it can be used to help identify children at risk, so that interventions can be implemented when necessary.

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