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INDIVIDUAL DIFFERENCES IN INFANT VISUAL ATTENTION: LINKS TO CHILD TEMPERAMENT, BEHAVIOUR AND GENETIC VARIATION

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A Thesis submitted for the Degree of Doctor of Philosophy

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ORIGINALITY STATEMENT

'I, Kostas A. Papageorgiou declare that the work in this thesis is my own.'

Exception: Dr. Rachel Wu collected the eye tracking data (UK sample) during her PhD under the supervision of Dr. Natasha Kirkham; Dr. Teresa Farroni performed the visual data collection and coding (Italian sample) during the past ten years.

All other data collection including the DNA and questionnaire data in the UK and Italy and the analysis of all the datasets (including the previously collected eye tracking and visual data) was performed by the thesis' author.

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September 4th 2014

ABSTRACT

Individual differences in infants' visual attention have been associated with individual variation in cognition in childhood. However, it has not been explored the degree to which individual variation in newborn and infant visual attention relates to individual differences in some forms of temperament and behaviour in childhood. Furthermore, little is known about the genetic causes of individual differences on newborn and infant visual attention. Chapter 1 will review studies on individual differences in infant visual attention. Chapter 2 will review all genetic studies on infant attention, temperament and behaviour. Chapter 3 will present results of a study that explored the degree to which individual differences in infant mean fixation duration (mean age = 7.69 months) are associated with some forms of temperament and behaviour in childhood (sample mean age = 41.59 months). It was found that infant mean fixation duration predicted positively child effortful control and negatively surgency and hyperactivity-inattention. Chapter 4 will present a study that explored whether individual differences in newborn average dwell time (mean age = 2.20 days) are associated with some forms of temperament and behaviour in childhood (mean age = 90.00 months). Newborn mean dwell time predicted negatively child surgency and behavioural difficulties. Chapters 5 will present analyses that explore the degree to which genome-wide variants previously found to increase the liability for ADHD and schizophrenia are associated with infant mean fixation duration and newborn average dwell time. The findings suggest that individual differences in infant visual attention are linked to attentional and behavioural control in childhood. Results are presented on the genetic mechanisms underlying individual differences in infant attention. Chapter 6 will evaluate critically the findings and will present limitations of this work to inform future studies.

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List of Publications & Conferences' Presentation relevant to this Thesis

Publications and Manuscripts:

1) **Papageorgiou, K. A.** & Ronald, A. (2013). "He who sees things grow from the beginning will have the finest view of them" A Systematic Review of Genetic Studies On Psychological Traits In Infancy. *Neuroscience and Biobehavioral Reviews, 37* (8). http://dx.doi.org/10.1016/j.neubiorev.2013.04.013

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1) **Kostas A. Papageorgiou,** Tim J. Smith, Rachel Wu, Natasha Z. Kirkham, Mark H. Johnson, Angelica Ronald. (August 2013). An investigation into the relationship between individual differences in infant fixation durations and later temperament and behaviour in childhood. *Poster presentation* at the 13th European Conference on Eye-Movement in Lund, Sweden.

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4) **Kostas A. Papageorgiou,** Tim J. Smith, Rachel Wu, Natasha Z. Kirkham, Mark H. Johnson & Angelica Ronald. (July 2014). Individual Differences in Infants Fixation Duration Relate to Temperament and Behaviour in Childhood. *Poster* at the International Society of Infant Studies, Berlin, Germany.

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LIST OF ABBREVIATIONS

ADHD – Attention Deficit Hyperactivity Disorder

ANOVA – Analysis of Variance

ASD – Autism Spectrum Disorder

CBQ – Childhood Behavior Questionnaire

CHRNA4 – Cholinergic receptor, nicotinic alpha 4

COMT – Catechol-O-methyltransferase

DAT1 – Dopamine transporter, also known as solute carrier family 6, member 3

DNA – Deoxyribonucleic Acid

DRD2 – Dopamine Receptor D2

DRD4 – Dopamine Receptor D4

ECBQ – Early Childhood Behavior Questionnaire

EOG – Electrooculography

ERPs – Event-Related Potentials

FTII – Fagan's Test of Infant Intelligence

G x E – Gene by Environment interaction

GWAS – Genome-Wide Association Studies

HTR1A – 5-hydroxytryptamine (serotonin) receptor 1A, G protein-coupled

5-HTTLPR – Serotonin transporter linked polymorphic region, also known as solute carrier family 6, member 4

IBQ-R – Infant Behavior Questionnaire-Revised

IQ – Intelligence

LAB-TAB – Laboratory Temperament Assessment Battery

LD – Linkage Disequilibrium

LHC – Life History Calendar

LL – Long Lookers

MAF – Minor Allele Frequency

MAOA – Monoamine Oxidase A

MHC – Major Histocompatibility Complex

NBAS – Neonatal Brazelton Assessment Scale

NS – Novelty Seeking

PGC – Psychiatric Genomics Consortium

PPC – Pairwise Population Concordance

PRS – Polygenic Risk Score

p_T – p-value Threshold

RRPSPC – Revised Rutter Parent Scale for Preschool Children

SDQ – Strengths and Difficulties Questionnaire

SL – Short Lookers

SNAP25 – Synaptosomal-associated protein, 25KDa

SNPs – Single-Nucleotide Polymorphisms

SPEQ – Specific Psychotic Experiences Questionnaire

TEDS – Twins Early Development Study

TMCQ – Temperament in Middle Childhood Questionnaire

TPH2 – Tryptophan hydroxylase 2

THESIS AIMS

The specific aims of this work were:

1. To investigate the degree to which individual differences in infant mean fixation duration are associated with individual differences in childhood effortful control, surgency and hyperactivity-inattention (*First PhD study presented in Chapter 3*).
2. To investigate the degree to which individual differences in newborn average dwell time are associated with individual differences in childhood effortful control, surgency, hyperactivity-inattention and total behavioural difficulties (*Second PhD study presented in Chapter 4*).
3. To explore the degree to which genome-wide variants previously found to increase the liability for ADHD and schizophrenia are associated with newborn average dwell time and infant mean fixation duration. (*Third PhD study presented in Chapter 5*).

INTRODUCTION

1 Visual Attention in Infancy (0-12 months)

Investigating human visual attention has been one of the oldest research pursuits in the field of psychology. William James was probably the first to notice that attention consists of several systems; in his book Principles of Psychology, he wrote: "*Everyone knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible*

objects or trains of thoughts. Focalizations, concentration, of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others, and is a condition which has real opposite in the confused, dazed, scatter-brained state which in French is called distraction, and Zerstreutheit in German" (James, 1891, p. 403-404).

In today's terms, attention is thought to be a cognitive process that has limited capacity, which regards to the limited amount of information or stimuli that can be simultaneously attended to and actively maintained and processed (Corbetta & Shulman, 2002). Attention is constituted from a number of highly associated but distinguishable processes (e.g. alerting, orienting and executive attention) and has both an endogenous (attention is driven by internal representations of task goals) and an exogenous component (attention is captured by events in the environment; Posner, 2012; Scerif, 2010).

In this chapter, a brief description of the development of attentional networks in the first year of postnatal life is presented. Subsequently, the results of a systematic literature review of all studies from 1990 to 2014 that have investigated individual differences in visual attention and their concurrent association with individual variation in cognition, temperament and behaviour in infancy are presented. The review has focused on the past 24 years of research to provide a clear picture on the topic of individual differences in infant visual attention; a systematic description of all studies on this topic could have resulted in presenting some outdated findings and in overloading the reader with information. Selectivefindings prior to 1990 on this topic is also given. Subsequently, findings regarding the reliability of attentional measures in infancy and the first direct evidence to demonstrate continuity of attention from infancy to

childhood to pre-adolescence are presented. Furthermore a systematic review of all studies from 1990 to 2014 that associated individual differences on attention in infancy with individual differences in cognitive abilities later in life are presented. Finally, a systematic literature review on studies that linked individual differences in infant attention with later individual variation in child temperament and behaviour are presented.

To conduct the reviews, PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), Google Scholar (http://scholar.google.co.uk/schhp?hl=en&tab=ws) and PsychINFO (http://www.apa.org/pubs/databases/psycinfo/index.aspx) databases were used. The terms "infants", "infancy", "newborns", "attention", "individual differences" "cognitive ability", "temperament", "behaviour", and "childhood" were used to search for relevant literature. Moreover, the reference lists of the selected articles were explored for relevant publications. Recently published books, which have reviewed findings on individual differences in infant attention and its links with later cognition, temperament and behavioural traits (e.g. Colombo, Kapa, Curtindale, 2010, p. 3-27, in Oakes, Cashon, Casasola and Rakison, 2010) were also searched. The last literature search was performed in July 2014.

The following criteria were used to select studies for inclusion in the literature review: 1) The participants' age, when visual attention was assessed did not exceed 12-months; 2) visual attention was assessed using data derived from video camera or eye tracking; 3) all studies from 1990 to 2014 that explored individual differences in infant visual attention are reviewed; 4) all longitudinal studies from 1990 to 2014 that have associated infant's visual attention with later cognitive traits are reviewed. Example studies prior to 1990 are briefly reviewed;

5) all longitudinal studies that have associated infant's visual attention with temperament and behavioural traits in childhood are reviewed; 6) Studies had to investigate individual differences in attention in non at-risk infants; Recent selective findings on visual attention in at risk infants are reviewed briefly. The results are presented in chronological order, from the oldest to the newest published study.

Finally, a brief summary on the current state of knowledge on individual differences in visual attention in infancy and how they predict individual variation in cognitive, temperament and behavioural traits in childhood is given.

1.1 The Development of Attention in Infancy

One of the most influential neuropsychological models of attentional development, which covers the entire lifespan, was introduced by Posner and Petersen (1990). The authors identified three interconnected attention networks in the brain, including the *orienting system* or *posterior attention network*, the *alerting* or *arousal system*, and the *executive control system* or *anterior attention network* (Petersen & Posner, 2012). This section will briefly describe the development of attentional networks in the first year of postnatal life.

1.1.1 The alerting system.

The alerting attention system involves parts of the brainstem (and later in development the right frontal lobe) and is associated with the ability to maintain a state of alert arousal in order to process effortfully visual information (Posner & Petersen, 1990). Alertness has been studied using long (in duration) tasks to assess sustained vigilance and through various techniques including assessments of the circadian rhythms, reaction times to stimuli, body temperature, and cortisol secretion (Petersen & Posner, 2012).

While infants prior to 3-months of age spend less that 20% of the day in alert states, by 4-months of age, periods of alertness have been consolidated, the dark-light cycle has been well entrained and infants are able to attain longer periods of alertness (Colombo, 2001). From around 7-months of age (and throughout childhood) infants are better able to process relevant visual information from the environment and exhibit an increased ability to sustain or focus their attention, which is indicative of the maturation of the orienting attention system (van de Weijer-Bergsma, Wijnroks, Jongmans, 2008).

1.1.2 The orienting system.

The orienting network is responsible for the ability to prioritize sensory input by selecting a modality or location (Posner & Petersen, 1990). It constitutes from a spatial orienting network in the parietal cortex and an object recognition pathway in the temporal cortex and involves several behavioural processes, including disengagement, shifting, inhibition of return and anticipatory eye movements (Johnson &Tucker, 1996; van de Weijer-Bergsma et al., 2008).

Even at birth, there are early signs of the newborns' ability to orient to environmental events (Posner & Rothbart, 2013). From the first day of life, newborns are selective in their attention and they show consistent preference for some visual information than others (Ruff & Rothbart, 1996). For example, newborns exhibit a consistent preference to faces with direct rather than averted gaze (Farroni et al., 2006).

As the infant becomes older, the degree of maturation of the orienting network has an effect on infants' look duration. For example, 1- to 2-month-old infants exhibit a series of very long look durations, when viewing static stimuli and they have limited capacity to orient to single targets (Johnson, Posner &

Rothbart, 1991).

By the age of 3-, to 4-months, infants exhibit a greater proportion of shorter look durations; this change is thought to reflect a reduction in the early difficulties that infants encounter with disengaging their attention – known as "sticky fixation" or "obligatory attention" (Johnson, Posner & Rothbart, 1991). By 4 months, problems with disengaging from static stimuli have largely disappeared (Johnson, et al., 1991). The orienting system becomes fully functional by the sixth month of life (van de Weijer-Bergsma et al., 2008).

It has been shown that from early infancy (3 months) to early childhood (up to 18 to 24 months) the orienting system serves as the cognitive and emotional control system with the executive system to start exercising cognitive and emotional control from around 18 to 24-months of age (Posner, Rothbart, Sheese & Voelker, 2012).

1.1.3 The executive control system.

The executive attention network is thought to involve two separate brain networks; that is, the frontoparietal and the cingulo-opercular brain network (Petersen & Posner, 2012). Executive attention refers to the ability to regulate responses to conflict situations where several responses are possible and it is a crucial parameter for one's ability to process and encode efficiently visual information (Holmboe & Johnson, 2005).

Although the executive attention system develops in early childhood (18 to 24 months) a study has shown that one element of the executive system – namely, the ability to detect errors, emerges in infancy at around 7-months of age (Posner & Rothbart, 2013). Specifically, infants between 6 and 9 months of age were shown a puppet that was then hidden behind a screen. Subsequently, they

observed a second puppet being hidden behind the screen. Infants looked longer when the screen was lifted to reveal only one puppet (incorrect trial) than when both puppets were revealed (correct trial). Looking times were systematically longer for incorrect trials. In addition, the same frontal electrode sites known to be active for error detection in adults showed activation in the infants (Berger, Tzur & Posner, 2006; Rothbart, Sheese & Posner, 2007). As such, it has been suggested that the frontal anatomy responsible for error detection in adults could be observed at 7 months, which is consistent with the view that some aspects of the executive attention system may be in place as early as in infancy (Gao et al., 2009; Posner et al., 2012).

1.2 Individual Differences in Attention in Infancy

In this section, the results of a literature review of all studies from 1990 to 2014 which have investigated individual differences on attention in infancy and their link to individual variation in infant cognition, temperament and behaviour, are presented. Most of the work in this area has used the visual habituation/dishabituation paradigm. Visual habituation is defined as a decrement of attention to a repeatedly or continuously presented stimulus. According to the cognitive model, this response decrement is a function of the gradual construction of a memory trace of the visual stimulus, the recall of information about the stimulus from memory, and the process of comparing the memory trace with the visual input (Kavsek, 2004). Visual dishabituation refers to the reactivation of attention towards a novel stimulus following habituation. Strength of dishabituation or recovery of attention can be measured by comparing looking time towards the habituation stimulus at the end of the habituation phase with looking time towards the novel stimulus (Kavsek, 2004). When using those

paradigms, researchers have focused mainly on individual differences on the measures of look duration and change of attentional focus (i.e. shifts of gaze between paired targets; van de Weijer-Bergsma et al., 2008). The measure of look duration on those paradigms is used usually to classify participants into long-lookers (LL) or short-lookers (SL) depending on whether their peak look duration is above or below the group's median, respectively (Colombo et al., 2010).

1.2.1 Why study individual differences in infant visual attention?

It has been noticed that within the area of developmental psychology, the interest in infant's development (0-12 months) and in particular, the interest in the development of attention in infancy has increased massively in the past decades (Colombo, Kapa, Curtindale, 2010; Colombo, 2001). This increment on the interest of early attentional processes was driven to some extent from research findings that demonstrated that individual differences in infant's attention could predict both concurrent and future indices of cognitive status (Colombo et al., 2010; Colombo, 2001).

Studying individual differences in infant visual attention is important to the field of psychology for two main reasons: firstly, individual differences in visual attention have long been proposed to reflect individual differences in infant cognitive ability (Colombo et al., 2010). As such, understanding the mechanisms that contribute to individual variation in attention in infancy can shed light into the mechanisms that contribute to individual differences in those later traits with which attention is linked (Colombo & Mitchell, 1990). Secondly, given that individual differences in infants' attention relate to individual differences in cognitive performance during infancy (Colombo et al., 2010) and that there is some evidence for continuity of attention from infancy throughout childhood to

pre-adolescence (Rose et al., 2012), studying individual variation in infant attention could predict individual differences in cognitive development later in life (Colombo & Mitchell, 1990). For example, given that diverse psychological traits (e.g. the temperament trait of effortful control) do not manifest in the first few months of postnatal life, studying individual differences in early infant's attention might constitute a window into the developmental mechanisms that contribute to individual differences in psychological traits--like attentional and behavioural control-- throughout the lifespan.

Furthermore, investigating the causes of individual differences in visual attention as early as in the first days or months of postnatal life might inform early intervention practices that will aim to improve aspects of attention, a cornerstone of human cognition. Finally, such investigation should in theory facilitate the early identification of individuals at risk for developing certain behavioural problems connected to attention difficulties, such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD).

1.2.2 Recent findings on visual attention in infants at risk

Most of the work on at risk population has used infants who are at risk to develop ASD. Some recent key findings on this area are given below to provide an example of how studying individual differences in infant attention can facilitate the identification of individuals at risk for developing certain neurodevelopmental disorders.

The first prospective longitudinal study to describe the development of components of visual attention in infants at high-risk of developing ASD (each with an older sibling with ASD) filmed controls and high-risk infants at 6, 9, 12, 15, 18, 24, and 36 months of age as they played with toys (Sacrey, Bryson &

Zwaigenbaum, 2013). Engaging attention (the duration of time between an overt eye movement toward a target and first movement of the hand toward the target), disengaging attention (the duration of time between grasp of the target and an overt eye movement away from the target) and sustaining attention (look duration on the target throughout the reach and grasp) were recorded using a video camera and were coded offline (Sacrey et al., 2013). The results revealed that infants who were diagnosed with ASD at 36 months of age exhibited longer look duration at the target following grasp, whereas controls began to disengage from the target as it was grasped. In addition, infants that developed ASD at 36 months were characterized by longer latency to disengage (sticky attention) at 12, 15, 18, and 24 months of age in comparison to controls (Sacrey et al., 2013). These findings suggest that the development of visual attention shows different patterns in infants, who later receive a diagnosis of ASD.

Another study assessed longitudinally the efficiency of infants with and without familial risk for autism to disengage from a central visual stimulus to orient to a peripheral one in the gap-overlap task at 6 to 10 months and at 12 to 15 months of age (Elsabbagh et al., 2013). Subsequently, 52 of those at risk for autism were seen for assessment around their second and third birthday. During the 36-month visit, a battery of clinical research measures was administered including the Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview (Elsabbagh et al., 2013). The study showed that while at 7 months of age, disengagement was not associated with later diagnostic outcomes; by 14 months longer latencies to disengage in the risk group--later diagnosed with autism--was observed relative to other infants at risk without a diagnosis and to the low-risk control group. Finally, between 7 months and 14 months, infants who

were diagnosed with autism at 36 months showed no consistent increase in the speed and flexibility of visual orienting (Elsabbagh et al., 2013).

To summarise, recent results on visual attention in infants at risk have shown that distinct developmental profiles indexing the control of visual attention may characterize subgroups of infants at risk. Those two example studies demonstrated that studying the development of visual attention as early as in infancy may offer potential to identify individuals at risk for developing certain neurodevelopmental disorders.

1.2.3 Individual variation in attention is linked with individual differences in infant cognition.

Since 1990, eleven studies have tested whether individual differences in look duration in infancy associate with individual variation in infant information processing (Colombo et al., 2010). This section presents a systematic review of studies from 1990 to 2014 that investigated the degree to which individual variation in infant attention is linked with individual differences in cognitive performance during the first 12 months of life. Example studies on this topic that were conducted prior to 1990 are reviewed briefly.

1.2.3.1 – Example studies prior to 1990. The first study to explore individual differences in infant's attention was conducted by McCall and Kagan (1970). The authors showed to seventy-two, 4-month old infants a standard stimulus and a set of change stimuli (with varying amounts of discrepancy from the standard stimulus) and explored whether infants who were classified as short-lookers (SL) during habituation to the standard stimulus would show differentially longer look durations and more smiling to the several presentations of the change stimuli as compared to those who were classified as long-lookers (LL). Indeed,

individuals who rapidly habituated to the standard stimulus exhibited increasing look duration to increasing amounts of stimulus change. In contrast, LL infants failed to respond differentially to the change stimuli (McCall & Kagan, 1970). This study provided the first evidence to support that attention increases with increases in stimulus novelty but only for individuals who were classified as SL during the initial standard stimulus presentation (McCall & Kagan, 1970).

Given the suggestive link between infant attention and cognition, a study explored whether slow habituators are incapable of storing stimulus information or they are only slower to do so (DeLoache, 1976). The study investigated thirty-six 4-month old infant's responses to discrepancy as a function of the rate of habituation. The study demonstrated that individuals who were classified as slow habituators did not differ significantly in their ability to process and store visual information from individuals that were classified as fast habituators. Instead, there was only a significant difference in the time they needed to form an accurate model of the visual stimulus (DeLoache, 1976).

Since then several studies have investigated the link between individual differences in infant attention with individual variation in infant cognition. The following two sections present a systematic review of those studies from 1990 to 2014.

1.2.3.2 – 1990 to 2000. In a series of experiments, Colombo et al. (1991) attempted to examine whether individual differences in infant visual attention is due to individual differences in strategies for extracting visual information rather than simply processing speed or efficiency of visual processing. To do that, they used a set of stimuli (dots placed in various arrangements) to represent a "global" discrimination and another set of stimuli (alphabetic letters that varied in a single

feature) to represent a “featural discrimination”. The performance of LL and SL 4-month old infants was examined on those discrimination tasks that could be only processed either globally or locally (Colombo et al., 1991). The results indicated that SL infants solved all visual discriminations at the minimum amount of time, while LL infants solved all visual discriminations only when the amount of familiarization time was increased (Colombo et al., 1991). This suggests that individual differences in look duration during habituation are linked with individual variation in information processing in infancy. Specifically, SL infants are faster/more efficient than LL infants in processing visual stimuli (Colombo et al., 1991).

To account for a methodological limitation (in Colombo et al., 1991), that is the use of one set of visual stimuli to assess global processing and another set of visual stimuli to assess local processing, a study used a single stimulus set in a discrimination task. The study aimed to determine whether LL and SL infants differ in the sequence or temporal limits of global and local visual information processing (Freeseman, Colombo &Coldren, 1993). The results demonstrated that both discrimination and generalization occurred after briefer familiarization times for SL infants as compared to LL infants. As such, the evidence do not support the hypothesis that SL and LL infants are differentially sensitive to global versus local visual information at 4 months of age (Freeseman et al., 1993). Instead, the results indicated that longer look duration within ages might reflect less efficient visual processing skills (Colombo et al., 1995).

Despite this evidence it is likely that, under conditions where subjects are sensitive to particular perceptual properties (global versus local property of a stimulus), one such property will be preferred over the other and this preference

will depend upon the individual's attention style (whether an infant has been classified as LL or SL infant; Colombo et al., 1995). This hypothesis was investigated in 4-month-old infants as a function of individual differences in look duration. Preference for global versus local properties was assessed through paired-comparison discrimination tasks in which global and local visual properties were placed in competition with one another for infants' attention (Colombo et al., 1995). The results demonstrated that SL infants showed preference for global properties of the stimuli after shorter familiarization times and preference for local features at longer familiarization times. Importantly, infants with longer look durations never displayed a global preference irrespective of the length of familiarization (Colombo et al., 1995; Colombo et al., 2010). This was the first study to show that individual differences in look duration in infancy are linked with individual variation in the processing of global versus local stimulus properties (Colombo et al., 1995; Colombo et al., 2010).

Another study has tested 4-month-old infants' ability to recognize degraded visual targets as a function of individual differences in look duration. The visual targets were degraded by removing 10% of the total contour either from vertices (vertex-absent) or from midsegments (vertex-present) (Frick & Colombo, 1996). SL infants were able to recognize degrade forms in both vertex-absent and vertex-present conditions. LL infants needed longer familiarization times before exhibiting recognition in the vertex-present condition and were unable to recognize targets in which contour was removed at vertices (Frick & Colombo, 1996).

This set of studies demonstrated that SL infants exhibit a more mature attentional profile in comparison to LL infants. This is also indicative of their

ability to distribute their attention more efficiently across the entire stimulus (Colombo et al., 2010).

This was shown in a study that hand-coded the location of 5-, 7-, and 9-month-old infants' looks during visual tasks and found that the distribution of looking across stimuli varied as a function of look duration (Jankowski & Rose, 1997). Specifically, infants who were classified as SL exhibited wider distribution of looks, more looks (to the stimuli) and shifts (between the stimuli), inspection of more stimulus areas and greater novelty preference in comparison to infants who were classified as LL at all ages (Jankowski & Rose, 1997).

Similar results derived from another study that tested whether SL infants would process symmetrical stimuli faster than asymmetrical stimuli (given that symmetrical forms are amenable to a global visual encoding strategy; Stoecker & Colombo, Frick & Allen, 1998). As hypothesized, SL infants in comparison to LL infants processed symmetrical stimuli more quickly than asymmetrical forms. LL infants did not exhibit differential pattern of processing for symmetrical and asymmetrical stimuli. This suggests that individual variation in look duration may reflect different modes of visual encoding (Stoecker & Colombo, Frick & Allen, 1998).

Evidence regarding the correlation between individual differences in look duration and individual differences in the latency of infants to disengage from a visual stimulus came from a study that investigated 3- and 4-month-olds infants' ocular reaction time to shift fixation from a central target to a peripheral target under conditions in which a central target either remained present or was removed from the display (Frick, Colombo & Saxon, 1999). The evidence demonstrated that SL infants were faster that LL infants to shift attention to the periphery in the

overlap condition, which requires disengagement but the two groups did not differ in the gap condition (Frick et al., 1999). Furthermore, the correlations between look duration and disengagement latency were strikingly large for infant work with the Pearson correlations ranging from $r = .41$ to $r = .55$ ($p < .01$). The results suggest that individual differences in look duration are associated with individual differences in the development of the neural attentional systems that control the ability to disengage, or inhibit visual attention (Frick et al., 1999; Colombo et al., 2010).

1.2.3.3 – 2000 to 2014. This section presents a systematic review of studies from 2000 to 2014, that explored the link between individual differences in infant attention with individual variation in infant cognition.

The difference between LL and SL infants in the ability to disengage attention efficiently has been also demonstrated by Jankowski, Rose, and Feldman (2001). First the authors replicated the results by Jankowski and Rose (1997), showing that 5-, 7-, and 9-month-old infants who were classified as SL exhibited a wider distribution of looks, more looks (to the stimuli) and shifts (between the stimuli), inspection of more stimulus areas and greater novelty preference in comparison to infants who were classified as LL, at all ages (Jankowski & Rose, 1997 and Jankowski, Rose, & Feldman, 2001). Furthermore they showed that when quadrants of the stimuli were sequentially illuminated to capture and guide infants' attention to a larger proportion of the presented stimuli, infants who were previously classified as SL did not differ significantly to infants who were previously classified as LL on either the distribution of attention or on recognition performance and look duration (Jankowski, Rose, & Feldman, 2001).

The same year another study examined individual differences in retention

of dynamic visual stimuli after 1-min, 1-day, and 1-month delays on 3.5-month-old infants' (Courage & Howe, 2001). Given that the direction of an infant's attentional preference following the familiarization phase (i.e. to novel or familiar stimuli, or to both equally) depends on the strength of the familiar information in memory at the time of the retention test, better retention over time would suggest higher memory capacity (Courage & Howe, 2001). The results demonstrated that SL infants showed better retention over time as demonstrated by higher novelty preference scores across familiarization groups in comparison to their LL peers (Courage & Howe, 2001). This suggests that individual differences in peak look duration are linked positively with superior performance on memory test in infancy (Courage & Howe, 2001).

Given that differences between LL and SL infants in disengaging fixation were well established, a study used event-related potentials (ERPs) to examine possible neural mechanisms associated with individual differences in visual attention and recognition memory for 6- and 7.5-month-old infants (Reynolds, Guy & Zhang, 2011). SL infants showed a late slow wave at temporal and frontal electrodes that was significantly greater in amplitude in response to novel stimulus presentations as compared to familiar stimulus presentations; this effect was not observed for the LL infants (Reynolds et al., 2011).

Similar results were obtained by another study that used ERPs to explore individual differences in 6-month-olds' processing of global and local properties of visual stimuli. SL infants demonstrated a late slow wave at central and midline frontal electrodes that was significantly greater in amplitude in response to novel-global stimulus as compared to familiar or novel-local stimuli presentations. LL infants showed the opposite effect--a late slow wave at parietal electrodes that

was significantly greater in amplitude in response to novel-local stimuli as compared to familiar or novel-global stimuli presentations (Guy, Reynolds & Zhang, 2013). As such, the results of the study were in line with the hypothesis that SL and LL lookers utilize different visual processing strategies (see Colombo et al., 1991).

To summarise, individual differences in look duration during habituation are linked with individual variation in information processing in infancy. Specifically, SL infants are faster than LL infants in processing visual information and they distribute their attention more efficiently across the entire visual stimulus (Colombo et al., 2010).

1.2.4 – Individual variation in attention is linked with individual differences in temperament and behaviour in infancy.

Whilst there are several studies that investigated the link between individual differences in infant visual attention with cognitive abilities in infancy, there are only five studies that have tested the degree to which individual differences in infant attention predict individual variation in some forms of temperament and behaviour during the first twelve months of postnatal life (Axia, Bonichini & Benini, 1999; Rose, Frutterwelt & Jankowski, 1999; Sheese, Rothbart, Posner, White & Fraundorf, 2008; Diaz & Bell, 2011; Morasch & Bell, 2012).

A study aimed to test whether infants who exhibit pain and distress for a shorter amount of time after pediatric vaccinations would have shorter look duration at stimuli (Axia, Bonichini & Benini, 1999). The infants' facial expression of pain and distress were videorecorded after pediatric vaccinations and were coded using the Izard's (1979) Maximally Discriminative Facial

Movement Coding System. The infants' duration of attention at schematic faces was tested a week later. The results demonstrated that infants who exhibited pain or distress after vaccinations for a shorter time period exhibited shorter look durations at stimuli (Axia, et al., 1999). The findings support the view that SL infants regulate their negative emotionality more efficiently in comparison to LL infants (Axia, et al., 1999).

Another study examined the association of the temperament trait of positive affect with attention at 5, 7, and 9 months of age. Infants were given an infant photograph (the photograph of the infant had a neutral expression) to observe and they were classified as LL or SL based on their peak look duration at the photograph. Their affect was coded as either positive or neutral. Rate of infant learning was also assessed on a task in which infants learned to distinguish a familiar face from a series of novel faces (Rose, Futterweit & Jankowski, 1999). LL infants showed higher positive affect and slower learning in comparison to SL infants at all ages. Learning was at an optimum level for infants classified as SL and having neutral affect. The finding suggest that whilst look duration might be associated negatively with information processing it could also be linked positively with positive affect in infancy (Rose et al., 1999).

Sheese and collegues (2008) investigated the relationship between infant anticipatory looking and self-regulation in infancy. Specifically, the authors tested whether 6 to 7-month old infants would demonstrate more attempts to regulate negative emotion in response to distress provoking stimuli. The results showed that anticipatory looking was positively related to cautious behavioural approach in response to non-threatening novel objects in 6-, and 7-month-old infants (Sheese et al., 2008). The authors suggested that the executive attention system is

active already at 6-months of age and that anticipatory looking could be used as a measure of individual differences in early executive attention in infancy (Sheese et al., 2008).

A study tested whether 5-month old SL infants would have greater frontal EEG power values than LL infant during baseline and during attentional and regulation tasks; and whether SL infants would demonstrate higher regulatory behaviour than LL infants while in distress (Diaz & Bell, 2011). The infants were presented with a glove puppet and look duration was assessed; during a toy removal task, mothers and infants played with an infant toy for 45 seconds and then the mothers removed the toy from their infants reach. Mothers were also asked to restrain their infants arm movements. Infants regulatory behaviour was measured during toy removal and arm restrain (Diaz & Bell, 2011). SL exhibited greater EEG power that LL across multiple scalp locations; this effect was particularly prominent during restriction of the arm movement (Diaz & Bell, 2011). In addition, SL infants as opposed to LL infants employed a regulatory strategy, where they focused on something other than the source of their distress during the arm restraint task. As such, the results suggested that the lower levels of distraction showed by the LL infants did not help them in refocusing to other aspects of the situation in order to better regulate their distress (Diaz & Bell, 2011).

Finally a longitudinal study that assessed 5-, and 10-month olds infants in the distress tasks described above (see Diaz & Bell, 2011) found that LL infants who were looking longer at a video clip that was presented after the distress tasks exhibited more parent report negative affectivity in the Infant-Behavior Questionnaire-Revised in comparison to SL infants (IBQ-R; Gartstein &

Rothbart, 2003; Morasch & Bell, 2011).

To summarise, the finding indicate that LL infants are at a disadvantage to SL infant in terms of regulating their emotionality. However, Rose and collegues (1999) observed that LL infants displayed higher positive affect as compared to SL infants. As such more research is needed in order to shed light on how individual differences in infant visual attention are linked with individual variation in infant temperament and behaviour.

1.3 Continuity of Individual Differences in Attention from Infancy through Childhood to Preadolescence

There is evidence to support that there is continuity of attention during the first year of life (Colombo et al., 2010) as well as continuity of attention from infancy through toddlerhood to pre-adolescence (Rose, Feldman, Jankowski, & Van Rossem, 2012). The term "*continuity*" of attention here refers to the question: Will scores of an individual on a certain attentional measure be correlated with his or her scores on the same attentional measure at different ages during infancy and from infancy through toddlerhood to pre-adolescence?

Furthermore, several studies have shown that duration-based measures (e.g. mean fixation duration) are reliable measures of individual differences in infant attention (Colombo et al., 2010; Wass & Smith, 2014). The term "*reliability*" of attentional measures in infancy refers here to the question: Can stable individual differences be identified for a certain attentional measure assessed in the same or different experimental conditions at short test-retest intervals (e.g. in sessions that are fifteen days apart)?

In this section, both studies that assessed *reliability* of duration-based (e.g. fixation duration) attentional measures in infancy and studies that assessed the

continuity of attention during infancy and from infancy through toddlerhood to pre-adolescence are reported.

1.3.1 Reliability and continuity of attentional measures in infancy.

One of the first studies to assess systematically (using consistent procedural and stimulus condition), short-term reliability (2 within-age sessions) of visual attention in infancy was conducted by Colombo, Mitchell, O'Brien and Horowitz (1987). Specifically, 186 infants at 3-, 4-, 7-, and 9-months of age were assessed on two within-age sessions on a habituation/dishabituation paradigm that involved eight colour slides of individuals' faces (Colombo et al., 1987). The measures obtained were: peak look duration (the length of the longest look observed during the habituation sequence), the duration of the first look at a stimulus, the average look duration (calculated by dividing total looking time by numbers of looks to habituation stimulus), total looking time (the sum of the duration of all looks to the habituation stimulus) and the total interlook interval (time that the infants spent "off" the stimulus between looks; Colombo et al., 1987).

The results demonstrated that the measures of peak look duration, first look duration, average and total look duration exhibited highly significant ($p < .001$) moderate in size correlations (the r correlation-coefficient across all ages was between .36 to .47) between the two sessions at 4-, 7-, and 9-months of age. At 3-months of age, only the measure of first look duration at stimuli showed a significant correlation between the two sessions. The authors concluded that duration-based measures are a reliable index of individual differences in attention in infancy from 4 months up (Colombo et al., 1987).

Subsequently, a longitudinal sample of 69 infants was assessed on the

same paradigm (as the one mentioned before) within a week of the third-, fourth-, seventh-, and ninth-month birthdays. The results suggested that longest look duration at 3 months was correlated moderately with longest look duration at 4-, 7-, and 9-months of age (Colombo et al., 1987). In addition, average look duration at 3 months was correlated moderately with average look duration at 4-, and 9-months of age but not at 7 months (Colombo et al., 1987). First look duration at 4-months were associated with first look duration at 9-months (but not at other ages); total look duration at 3-months were associated with total look duration at 9-months (but not at other ages); total interlook interval at 7-months were associated with total interlook interval at 9-months (but not at other ages; Colombo et al., 1987). The direction of the correlations was always positive.

The authors concluded that although some measures of infant's visual attention (e.g. total interlook interval) showed weak continuity over the long term the measures of *peak look duration* and *mean look duration* exhibited the highest continuity during infancy. Specifically, the scores of an individual on peak look duration and mean duration of looking were associated moderately (R^2 = 13% and 15%, respectively) with his or her scores on peak look duration and mean duration of looking, respectively at 9-months of age (Colombo et al., 1987). Given the high reliability of duration-based measures, look duration has been since then; the best studied attentional parameter in infancy (Colombo, Kapa, Curtindale, 2010).

1.3.2 Long versus short lookers in infancy.

The measure of look duration is used usually to classify participants into long-lookers (LL) or short-lookers (SL) depending on whether their peak look duration is above or below the group's median, respectively in visual habituation tasks (Colombo et al., 2010). Long-lookers have found to be less efficient at

disengagement and shifting of attention and slower at information processing (Colombo et al., 2010; van de Weijer-Bergsma et al., 2008). Look duration is measured typically using video cameras. It refers to participant's longest time to habituate to a certain stimulus, which in turn is defined as a decrement of attention to a repeatedly or continuously presented stimulus (Kavsek, 2004). A study has shown that individuals who exhibited different habituation patterns tended to differ in both the total look duration at the stimulus and in the total number of orientations at stimulus. Furthermore the results revealed that both habituation patterns and quantitative indices of habituation (e.g. look duration) were reliable indicators of individual differences in visual attention across sessions. The authors concluded that there is high individual variation in 5-month old infant visual attention (e.g. look duration) with both habituation patterns and their indices (e.g. look duration) being highly idiosyncratic (Bornstein & Benasich, 1986).

1.3.3 Eye tracking measures of attention in infancy.

Recent advances in the area of visual attention have enabled researchers to analyze in detail how attention is allocated through individual fixations and saccades. Specifically the development and use of eye tracking, a device that offers much higher spatial (~1° of visual angle) and temporal resolution (typically between 50-300 Hz) in comparison to video coding has enabled assessing the attentional measure of fixation duration as early as in infancy (Wass, Smith & Johnson, 2013). Fixation duration generally refers to the time between saccadic eye movements when the eyes are relatively stable (although fixations can also be bracketed by blinks, smooth pursuit and other less common forms of ocular movement). During a fixation, several cognitive processes may occur: foveal visual information is processed and encoded in working memory, the next saccade

target is selected from peripheral visual stimuli and the oculomotor program required to bring the target into foveal vision is prepared (Rayner, 1998). Fixation duration is made up of the conflict between demands for keeping the eyes stationary (in order to encode foveal visual information) and disengaging attention to shift to peripheral targets (Findlay & Walker, 1999).

Whilst look duration has proven to be a reliable measure of individual differences in infancy (Colombo et al., 2010), fixation duration was found to be a reliable measure of individual differences in adults (Castelhano & Henderson, 2008; Rayner, Li, Williams, Cave, & Well, 2007). There in only one study today that used eye tracking to investigate whether there are stable individual differences in infants' mean fixation duration during the viewing of complex naturalistic scenes; and how do individual differences in spontaneous fixation behaviour during unconstrained orienting relate to performance on other experimental assessments of infant attention (Wass & Smith, 2014). The study assessed the fixation duration of twenty-one typically developing 11-month-old infants across five separate laboratory visits over 15 days, while infants viewed a 90-min battery ranging from complex dynamic to noncomplex static materials. In order to assess how stable are individual differences in mean fixation duration, the authors calculated test-retest reliability, when an identical battery of mixed static and dynamic viewing material was administered twice to the same participants at 15 days' viewing interval (Wass & Smith, 2014). The correlation reported between visits was $r = .78$ ($p < .001$) suggesting for the first time that mean fixation duration in infancy is a stable measure of individual differences in infant attention across short-term assessments (Wass & Smith, 2014).

Subsequently, the authors examined the stability of individual differences

in mean fixation duration across different types of visual stimulus, averaging across visits. The relationship between mean fixation duration for all static and mean fixation duration for all dynamic stimuli was $r = .60$, ($p = .007$). As such, the results suggested that individual variation in mean fixation duration is to a moderate extent independent of the type of stimuli used in a study (Wass & Smith, 2014).

To summarise, the studies reviewed above have shown that duration-based measures (e.g. mean fixation duration) are reliable measures of individual differences in infant visual attention. The following section presents the results of a study that provided the first direct evidence regarding the continuity of attentional style from infancy to childhood.

1.3.4 The link between infant attention with child and adolescent attention.

Rose, Feldman, Jankowski and Van Rossem, (2012) provided the first direct evidence that attention exhibits continuity from infancy (7 and 12 months of age) throughout childhood (24 and 36 months of age) to pre-adolescence (11 years of age). Specifically, the same measures, in the same formats, were used in the infant and toddler years to assess performance in four domains: Processing speed, attention, memory and representational competence; at 11 years, those domains were evaluated again but the tasks were those that are typically used with adolescents and adults (Rose et al, 2012).

To assess attention in infancy and toddlerhood the measures of look duration and shift rate were used. Look duration was assessed using a number of different tasks, including familiarization and test phases of visual recognition memory tasks (the “Rose” and the “Fagan” tasks) and test phase of cross-modal transfer and trials from the continuous familiarization task. Scores on each task

were standardized and then averaged (Rose et al., 2004a; Rose, Feldam & Jankowski, 2005b). The final measure represented the average of six standardized look duration scores (Rose et al., 2012). The measure of shift rate was derived from the same tasks used to calculate look duration. Only the scores from the Fagan test were not available. As such, the final measure represented the average of five standardized shift rate scores (Rose et al., 2012). Shorter look duration and higher shift rates were indicative of better attention.

To assess sustained attention at 11 years of age the rapid visual information-processing task was used. The measures that were assessed in this task include number of false alarms and number of hits (Rose et al., 2012). To measure selective attention the span of apprehension task was used that assesses the accuracy with which a target can be apprehended when distracters are present (Rose et al., 2012).

The results demonstrated that attention in infancy (indexed by look duration and shift rates assessed at 7 and 12 months) was positively associated with attention in toddlerhood (indexed by look duration and shift rates assessed at 24 and 36 months; $r = .43$, $p < .01$); attention in toddlerhood was positively associated with attention at 11 years (indexed by span of apprehension, false alarms and hit rate; $r = .28$, $p < .01$). Attention in infancy though was not predictive of attention at 11 years of age ($r = .12$, $p > .05$; Rose et al., 2012). Those results revealed for the first time that individual differences in visual attention as early as in infancy are predictive of individual differences in attention in early childhood (Rose et al., 2012).

1.4 Infants' Attention and its Link with Cognition, Temperament and Behaviour Later in Life

Individual differences in visual attention in infancy have been used extensively to predict variation in cognition later in life (Colombo et al., 2010). McCall (1981) was one of the first to suggest that infant visual attention indexed by individual differences in visual habituation and dishabituation could be used--instead of traditional tests of infant intelligence (IQ)--to predict IQ later in life (McCall, 1981). This suggestion was based on the cognitive model which posits that both visual habituation and dishabituation reflect basic information processing skills; therefore individual differences in infant habituation and dishabituation could predict individual variation in IQ (Kavsek, 2004).

Whilst many studies have tested whether individual differences in infant visual habituation and dishabituation predict later IQ, only few studies to date have investigated the degree to which individual differences in infants' visual attention relate to temperament and behaviour in childhood. Specifically, only three studies have tested longitudinally whether parameters of infant visual attention associate with later temperament and behaviour.

Sections 1.4.1 and 1.4.2 below will review all studies from 1990 to 2014 that associated infant attention with child and adolescent cognitive abilities; and all studies that explored longitudinally whether parameters of infant visual attention associate with later temperament and behaviour, respectively.

1.4.1 Infant Attention and its Link with Child Cognitive Abilities.

1.4.1.1 – 1990 to 2004. A study used same sex twin pairs and their parents to investigate the degree to which infant attention at 7- and 9-months of age would predict IQ at 1-, 2-, and, 3-years of age as well as the twins' parents' IQ (DiLalla et al., 1990). The participants were assessed on several measures including the Fagan's Test of Infant Intelligence (FTII; DiLalla et al., 1990). In the

FTII the experimenter watched the infant's eyes through a peephole centred between the stimuli, then observed the corneal reflection of the stimulus over the pupils of the infant's eyes and recorded infants' look duration. The FTII final score represented the average percentage of time spent looking at the novel stimulus across the 10 trials (DiLalla et al., 1990). It is noted here that the measure of average look duration reflects infants' novelty preference and it is not similar to the measure of peak (or longest) look duration that has been used traditionally to discriminate betweeen SL and LL infants. Average look duration at 7 and 9 months was predictive of IQ scores at 1- and, 3- years of age but not at 2 years. Infants' average look duration at 9 months (but not at 7 months) was predictive of their parents' IQ. The direction of the correlations was always positive suggesting that longer average look duration at stimuli (indicating higher novelty preference) in infancy was associated with higher IQ scores in childhood and adulthood (DiLalla et al., 1990).

Another study used the Fagan Test of Infant Intelligence to assess the degree to which look duration at novel stimuli at 5-, and 7-months of age will predict IQ scores at 12-, 24-, and, 36-months of age (Thompson, Fagan, & Fulker, 1991). The results indicated that novelty preference in infancy indexed by longer average look duration at novel stimuli was positively associated with IQ at 24-and 36-months of age but not at 12 months (Thompson et al., 1991). Furthermore novelty preference in infancy was predictive of language and memory skills at 36-months of age (Thompson et al., 1991).

Rose and Feldman (1995) examined the relationship between 7- and 12-month old infant information processing with perceptual speed, memory, spatial and verbal ability and IQ (Rose & Feldman, 1995). In infancy the percentage of

time spent attending to the novel stimulus (compared with the familiar one) was computed on a total of nine paired-comparison problems assessing visual recognition memory for abstract patterns, faces, and three-dimensional geometric forms. Furthermore visual attention was measured indirectly by exposure-time that reflect the time that the stimulus is on display during familiarization before the infant actually accumulates the required amount of looking (Rose & Feldman, 1995). The results demonstrated that individual differences in visual recognition memory and visual exposure time at 7-months were positively associated with individual variation in memory and perceptual speed at 11-years. In addition, individual differences in visual recognition memory at 12-months were positively associated with spatial ability and verbal ability at 11-years. Finally, individual variation in visual recognition memory at 7-months were predictive of individual differences in IQ at 11 years. The authors concluded that infant visual attention predict IQ in childhood (Rose & Feldman, 1995).

In 2004, Kavsek published the most comprehensive meta-analysis of studies on the predictive validity of infant (0-12 months of age) visual habituation and dishabituation ensuring that each sample was considered only once in order not to overweight a sample's contribution to the overall statistical values (Kavsek, 2004). The correlation coefficients reported in the meta-analysis were always positive. The positive direction of the correlations suggests that individuals who were faster to habituate on visual task scored higher on standardized tests (such as of intelligence) as children (Kavsek & Bornstein, 2010; Kavsek, 2004). As such, the positive direction of the correlations indicated that SL infants score higher on IQ as children. In fact, Kavsek and Bornstein (2010) claimed that "…*we know of no correlations that report findings in the opposite direction.*" (Kavsek &

Bornstein, 2010, p. 957).

The results indicated that the mean correlation between infant visual habituation and child IQ was .40 and the mean correlation between infant visual dishabituation and child IQ was .32 (Kavsek, 2004). The average correlation values were derived by transforming the correlation between visual attention style and later outcome returned by each individual study into Fisher z-values that were subsequently weighted to produce a weighted and normalized average correlation (Kavsek, 2004). Furthermore the findings showed that the relationship between infant visual habituation and dishabituation and child IQ was not affected by the infant age and that the prediction was strongest for samples that were older than 6 years of age (Kavsek, 2004). The author concluded that individual differences in infant visual attention predicts moderately individual differences in child IQ and that habituation and dishabituation scores reflect both encoding speed and recognition memory performance (Kavsek, 2004).

1.4.1.2 – 2004 to 2014. Since 2004, four studies have tested whether individual differences in infant attention predict cognition later in life. A study assessed the academic achievement and IQ of sixty-one 21-year-old adults on the Peabody Picture Vocabulary Test-Revised (PPVT-R; Dunn & Dunn, 1981). The adults were assessed originally when they were 7-12 months of age on their ability to selectively attend to novel visual targets (Fagan, Holland & Wheeler, 2007). For each novelty problem, the infant was exposed to a picture, such as the face of a baby, until the infant was looked at it for a standard period of time. The coder recorded infant look duration at each picture (Fagan et al., 2007). The results demonstrated that look duration in infancy was correlated with adult IQ and academic achievement (r = .34 and .32 respectively) (Fagan et al., 2007).

Another longitudinal study assessed look duration in infancy (7 and 12 months of age) and childhood (24 and 36 months of age) and shifting and working memory at 11 years of age (four computerized tasks that were drawn from the Cambridge Neuropsychological Testing Automated Battery (CANTAB; Sahakian, et al., 1988): spatial span, spatial working memory, rapid visual information processing, and intradimensional-extradimensional shift (Rose, Feldman & Jankowski, 2012). The findings were not significant, although infants' attention indexed by look duration and shift rate (see Rose, Feldman, Jankowski & Van Rossem, 2012 above for details) was related to cognitive abilities at 11 years of age (Rose et al., 2012).

A longitudinal study assessed 3- and 6-month old infants on a variety of visual measures including look duration during visual habituation/dishabituation paradigms and novelty preference tasks; in addition, participants were assessed at 24 and 32 months on the Bayley scales of infant development II (Bayley, 1993) and the German versions of the speech test (SETK-2; Grimm, 2000) and the K-ABC test (Kaufman & Kaufman, 1983), which assesses aspects of child IQ and language ability. The results revealed that at all ages look duration during habituation and dishabituation was negatively associated with measures of child IQ and language abilities. As such, shorter look durations were indicative of better developmental outcomes with the magnitudes of the significant correlations being in line with Kavsek's (2004) meta-analysis (Domsch, Lohaus, & Thomas, 2009).

Finally, a recent longitudinal study has found that SL infants exhibited significantly higher executive function scores throughout early childhood (24-, 36-, and 48-months of age) as compared to LL infants (Cuevas & Bell, 2014). Specifically, 211 infants were presented with a glove puppet until they accrued

four looks; median peak look duration to the glove puppet was used to classify infants as SL or LL (Cuevas & Bell, 2014). A composite score of executive function measures were used that included the A-not-B looking procedure (Morasch & Bell, 2011); the tongue task (Kochanska, Murray & Harlan, 2000); the day-night task (Gerstadt, Hong & Diamond, 1994); the Simon says task (Wolfe & Bell, 2007); the Dimensional Change Card Sort (Zelazo, Frye & Rapus, 1996); and the visual search task (Espy & Bull, 2005).

To summarise, the results of the studies that were reviewed above suggest that individual differences in attention style between SL and LL are linked to the efficiency and speed of information processing in childhood with SL infants scoring higher than LL infants in a variety of later cognitive abilities including executive functions.

1.4.2 Infant attention and its link with child temperament and behaviour.

Only three studies to date have investigated the degree to which individual differences in infants' visual attention relate to some forms of child temperament and behaviour. A fourth study is also reviewed (Nakagawa & Sukigara, 2013) here; whilst this study did not investigate longitudinally whether individual differences in attention in infancy would predict individual differences in temperament in childhood (due to the small sample size, N = 23) it provided evidence regarding the link between visual attention and temperament that is relevant to the current PhD work (hence reviewed here).

A study investigated the relationship between individual differences in infant (9-month-old) sustained attention assessed using video camera with the trait of behavioural inhibition at 14 months, 24 months, 4 years and 7 years (Perez-Edgar et al., 2010). Given that behavioural reactivity is a precursor of behavioural

inhibition (Fox, Henderson, Pérez-Edgar, & White, 2008) and it has been associated with less sustained attention in children (Pérez-Edgar & Fox, 2005) the authors hypothesised that infants with low levels of sustained attention will show increased behavioural inhibition throughout childhood.

Infants were shown a fixation stimulus for 3 seconds; the distracter stimulus was subsequently presented with the fixation stimulus still present. The experimenters coded the total time that the infant attended to the fixation stimulus and the distracter stimulus (Perez-Edgar et al., 2010). Sustained attention was calculated by subtracting the time spent attending to the distracter stimulus from the time spent attending to the fixation stimulus (Perez-Edgar et al., 2010). At 14 and 24 months, the children's reactions to unfamiliar stimuli in the laboratory were coded to provide an index of behavioural inhibition; at 4 and 7 years, children participated in a group play session with three unfamiliar, same sex, same-age peers. Scores at each age were derived for each child's two 15-min free play session; finally, participants returned to the laboratory in adolescence and completed a social scenarios task with a same-age, same-sex, unfamiliar peer (Perez-Edgar et al., 2010).

The results showed that infants with low levels of sustained attention exhibited increasing behavioural inhibition throughout early childhood as compared to infants with high levels of sustained attention. While sustained attention in infancy did not predict directly adolescent social difficulties, the initial levels of inhibition at 14 months associated positively with later adolescent social difficulties but only for participants who showed low levels of sustained attention in infancy (Perez-Edgar et al., 2010). This was the first evidence to show that individual differences in sustained attention in infancy are associated with

individual differences in behaviour throughout early childhood.

A recent longitudinal study assessed look duration in infancy (7 and 12 months of age) and childhood (24 and 36 months of age) and inhibition at 11 years and demonstrated that infants' attention indexed by look duration and shift rate (see Rose, Feldman, Jankowski & Van Rossem, 2012 above for details) showed a non-significant trend towards a positive association with the temperament trait of inhibition at 11 years of age (Rose, Feldman, & Jankowski, 2012).

Another study tested whether individual differences in 12-month-old infants' ability to disengage attention from fearful expressions in the facial expression overlap paradigm would predict individual differences in negative affectivity assessed using the Japanese versions of the Infant Behavior Questionnaire-Revised (Nakagawa & Sukigra, 2005) at 12-months of age and the Early Childhood Behavior Questionnaire (Sukigara, Nakagawa, & Mizuno, 2007) at 18-, 24-, and 36-months of age (Nakagawa & Sukigara, 2012). Videotapes of the eye movements were coded off-line by two independent coders. The index for attentional bias to threat was calculated by dividing the number of fixed responses on fearful faces by the total number of remaining fixed responses on faces (Nakagawa & Sukigara, 2012). The results indicated that 12-month-old infants with greater difficulty in disengaging attention from fearful faces exhibited higher parent report negative affectivity at 12-months. No significant association between infants' ability to disengage attention from fearful faces and later childhood negative affectivity was found (Nakagawa & Sukigara, 2012). The results suggest that attention disengagement is influenced by fearful faces; hence there is a link between attention and temperament in infancy that seems to be

preserved in childhood (the association between infant attention disengagement and negative affectivity was not significant although it was to the expected direction).

Finally, a cross-sectional study examined how individual differences in the duration of saccadic latencies in infancy relate to the infant temperament trait of orienting/regulation at 12-month as well as how individual differences in child attention would associate with individual differences in child effortful control at 18-, 24-, and 36-months of age. The small sample size (N =26) did not allow investigating longitudinally how individual differences in infant attention predict individual differences in effortful control later in life.

To assess saccadic latencies the authors used the gap-overlap task; to assess orienting/regulation and effortful control the authors used the Japanese versions of the Infant Behavior Questionnaire-Revised (Nakagawa & Sukigra, 2005) at 12-months of age and the Early Childhood Behavior Questionnaire (Sukigara, Nakagawa, & Mizuno, 2007) at 18-, 24-, and, 36-months of age. In addition, two delay-of-gratification tasks from the Inhibitory Control Battery (Kochanska, Murray, Jacques, Koenig, & Vandegeest, 1996) were used at 36 months to assess inhibitory control (Nakagawa & Sukigara, 2013). The authors hypothesised that longer saccadic latencies in infancy assessed using eye tracking would associate with lower orienting/regulation scores in infancy. However longer saccadic latencies in childhood would associate with higher effortful control in childhood since children are more flexible in inhibiting responses to distracters; this is due to the development of the executive attention system (Nakagawa & Sukigara, 2013). Longer saccadic latencies are indicative of higher sustained attention and longer look duration at stimuli (Nakagawa & Sukigara,

2013).

The results revealed that at 12-months longer saccadic latencies to the peripheral stimuli in the overlap condition were associated with lower orienting/regulation scores. However at 18 and 24 months, longer saccadic latencies to the peripheral stimuli were indicative of higher effortful control. No significant associations between child attention and effortful control in childhood were reported at 36 months (Nakagawa & Sukigara, 2013).

The findings suggest that in infancy--when mainly the orienting network regulates attention--longer saccadic latencies may be indicative of less efficient attentional control. However the time to initiate a saccade to the peripheral stimuli in childhood may depend upon the executive attention system. Those with high effortful control may process the central stimuli deeper and thus rather slowly initiate saccades to the periphery (Nakagawa & Sukigara, 2013). As such, the findings suggest that in childhood longer look duration at stimuli (as indicated by the duration of saccadic latencies) might be indicative of higher scores on the temperament trait of effortful control (Nakagawa & Sukigara, 2013).

The authors suggest that future research could examine how individual differences in the early orienting network would predict later temperamental traits because such investigation may provide valuable information that can be used in the fields of parenting, early education, and child psychiatry (Nakagawa & Sukigara, 2013).

In sum, there is evidence to support the link between individual differences in infant attention with individual variation in infant temperament; and the link between individual differences in attention in childhood with individual variation in temperament in childhood.

However there is currently limited evidence to support that there is an association between individual differences in attention in infancy with temperament and behaviour in childhood. As such, more longitudinal research is necessary to understand how individual differences in infant attention predict individual variation in children temperament and behaviour. In addition, future research could use younger participants (for example newborns) to explore whether the link between early attention and later temperament and behaviour is present already at birth.

1.5 Summary

Attention is defined as a cognitive process that is constituted from a number of highly associated but distinguishable processes and that has both an endogenous and an exogenous component (Scerif, 2010).The interest in the development of attention in infancy has increased massively in the past several years because individual differences in infant's attention could predict both concurrent and future indices of cognitive status (Colombo, Kapa, Curtindale, 2010). There is evidence to support that there is continuity of attentional style during the first year of life (Colombo et al., 2010) as well as continuity of attention from infancy through toddlerhood to pre-adolescence (Rose, Feldman, Jankowski, & Van Rossem, 2012). Furthermore, several studies have shown that duration-based measures (e.g. mean fixation duration) are reliable measures of individual differences in infant attention (Colombo et al., 2010; Wass & Smith, 2014). Colombo, Mitchell, Coldren and Freeseman (1991) proposed that the most useful manner of characterizing such individual differences is by classifying infants into long lookers (LL) or short lookers (SL).

The most consistent and replicated set of findings in infant's visual

attention studies is that SL infants are processing information more efficiently that LL infants and that the measure of longest look duration in infancy can predict negatively cognitive abilities (e.g. IQ) in childhood, adolescence and adulthood (Colombo et al., 2010; Kavsek & Bornstein, 2010). Such investigations may provide valuable information that can be used in the fields of parenting, early education, and child psychiatry (Nakagawa & Sukigara, 2013).

However only a handful of studies have investigated whether SL and LL infants differ in temperament and behavioural traits and how infant's attention can predict temperament and behavioural traits later in life. For example, a study has shown that infants with high levels of sustained attention--hence longer look duration to central stimuli--exhibited increasing behavioural inhibition throughout early childhood as compared to infants with shorter look duration (Perez-Edgar et al., 2010).

The results of the literature review presented above demonstrated that infant attention research is in need of newer techniques of assessing attention that could provide with "fine-grained" attentional measures. Indeed, recent advances in the area of visual attention have enabled researchers to analyze in detail how attention is allocated through individual fixations and saccades. Specifically the development and use of eye tracking, a device that offers much higher spatial (~1° of visual angle) and temporal resolution (typically between 50-300 Hz) in comparison to video coding, has enabled assessing the attentional measure of fixation duration as early as in infancy (Wass, Smith & Johnson, 2013). However, eye tracking has not yet been implemented in a longitudinal design to investigate how infant's attention predicts later temperament and behaviour. In addition, the categorical distinction between SL and LL infants results in loss of valuable data

and limits the ability to investigate in depth individual variation in visual attention; quantitative measure of infant visual attention could be used instead, to explore how infant looking behaviour predicts variation in temperament in childhood.

Finally, a striking result of the literature review is that there are currently no studies that assessed attention in the first days of postnatal life in order to test whether individual differences in newborn's attention would also predict individual differences in temperament and behavioural traits later in life. Given that newborns have not been exposed to many environmental influences outside the womb, studying neonatal visual attention may facilitate our understanding of causal factors (e.g. prenatal factors and genetic factors) operating at birth to contribute to individual variation in attention, temperament and behaviour later in life. Investigating the causes of individual differences in visual attention as early as in the first hours after birth might inform early intervention practices that will aim to improve aspects of attention, a cornerstone of human cognition.

2 Genetic Association Studies in Infancy

2.1 Chapter's Summary

In comparison to genetic research in childhood and adulthood, only few studies, to date have investigated the link between genes and psychological phenotypes in infancy. Most of these have studied how individual differences in common genetic variation are linked with individual differences in visual attention, temperament and behaviour.

The aim of this chapter is to present the results of a systematic review of the literature on studies that have aimed to discover genes that influence attention, temperament and behaviour in infancy (from birth to age 12 months). The age range from birth to age 12 months is considered being the typical definition of infancy (Mallina et al., 2004). Beyond 12 months, when there are some major normative shifts in behaviour, such as learning to walk and to speak, is generally defined as the start of childhood (Mallina et al., 2004).

The review was focused on attention, temperament and behaviour, as these are the phenotypes of interest in the current PhD work. Those traits are considered complex with largely unknown genetic aetiology. Longitudinal studies are also reviewed that have aimed to identify genes that associate with attention, temperament and behaviour in older ages but which included data on infants. This chapter also addresses what genetic approaches such as genome-wide association studies (GWAS) and polygenic risk score analysis (PRS) could offer infant genetics.

Chapter 2 is based on the following published article: Papageorgiou, K. A. & Ronald, A. (2013). "He who sees things grow from the beginning will have

the finest view of them" A Systematic Review of Genetic Studies On Psychological Traits In Infancy. *Neuroscience and Biobehavioral Reviews, 37* (8). http://dx.doi.org/10.1016/j.neubiorev.2013.04.013

A literature review was performed again in July 2014 to ensure that any study that was published after 2013 will be included in the thesis.

2.2 Genetic Research in Infancy

Genetic research in infancy should be considered important because, first, it forms part of a larger goal of understanding the causes of individual differences in human behaviour. It can test for genetic variants that might be specific to influencing infant behavioural development, as well as test whether genetic variants associated with psychological traits in later development are also associated with related phenotypes in infancy. That is, infant genetic research can be informative about genetic continuity and change across the lifespan (Ronald, 2011). Knowledge about which genes play a role in psychological development in infancy would contribute to the broader field of developmental cognitive neuroscience by providing clues about the mechanisms involved in early brain development (Johnson, 2011). Finally, because most psychological disorders appear to have their onset after infancy, knowledge about genetic risk that can be applied to infant samples has considerable potential for the identification of populations at risk of atypical development, based on genetic propensity, and thus for informing early prevention and intervention approaches (Papageorgiou & Ronald, 2013).

Furthermore in genetics, the search for genes associated with complex traits in children and adults has been notoriously difficult (Manolio et al., 2009; Plomin, 2013). A hypothesis is that finding genes associated with infant

psychological traits might be easier than finding genes associated with psychological traits in older age groups. The reason behind this hypothesis is that across development, multifactorial gene x environment (G x E) interactions are taking place which could make 'main effect' associations between genes and behaviour more difficult to identify (Johnson & Fearon, 2011). The hypothesis is that there will be fewer cumulative gene-environment interaction effects on infant psychological phenotypes, and, as such, main effects of genetic influences will be easier to find (Papageorgiou & Ronald, 2013).

2.3 Method

PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), Google Scholar (http://scholar.google.co.uk/schhp?hl=en&tab=ws) and PsychINFO (http://www.apa.org/pubs/databases/psycinfo/index.aspx) databases were used to conduct a systematic search on genetic studies in infancy. The terms "genetic study", "candidate genes", "polygenic risk score", "Genome-wide association study", "DNA sequencing study" "infants", and "infancy" were used. The reference lists of the selected literature for relevant publications were searched. The last literature search was performed in July 2014. The following criteria were used to select studies for inclusion in the literature review: 1) The participants' age did not exceed 12-months of age; 2) Longitudinal studies that have aimed to identify genes that influence attention, temperament and behaviour in older ages are also reviewed, if they included data on infants; 3) Studies had to include psychological phenotypes and specifically, attention, temperament and behavioural traits. Research on biological or physical phenotypes were not included here; 4) Research on known genetic syndromes was not reviewed (e.g., Williams Syndrome) because these represent a different genetic model where the

genes associated with the phenotype have been identified.

Twenty-one genetic studies on attention, temperament and behaviour in infancy were identified. Two studies (out of twenty-one) attempted to associate genetic variation with both temperament and electrophysiological markers. Sample sizes ranged from N = 48-1136 (Mean N = 212; Median N = 90). Table 2.1, provides a quick look summary of the twenty-one studies. It includes the phenotypes and the genetic markers and outlines, for each study, whether the association between the genetic marker and the phenotype was significant or non-significant based on the authors' criteria. All studies have employed a candidate gene association design.

Table 2.1 *Quick look summary of the 21 genetic association studies on attention, temperament and behaviour in infancy (presented chronologically within phenotype domain).*

STUDY	SAMPLE (N & AGE)	PHENOTYPE	GENES	ASSOCIATION (YES✔) (NO ✗)
Auerbach, J. et al., 2001a	64 participants at 12-months of age	ATTENTION	DRD4	✔
			5-HTTLPR	✗
Laucht, M. et al., 2006	232 3-months-old infants (longitudinal study of early risk factors which followed participants from birth to adolescence)	ATTENTION	DRD4	✔
Sheese, B.E. et al., 2009	Longitudinal study of infants at age 6-7 (50 participants) and 18-20-months (37 participants) of age	ATTENTION	COMT	✗
			SNAP25	✗
			CHRNA4	✔
Holmboe, K. et al., 2010	102 infants at 9-months of age	ATTENTION	DRD4	✗
			DRD2	✗
			DAT1	✔
			COMT	✔
Leppanen, J. K. et al., 2011	66 infants at 7-months of age	ATTENTION	TPH2	✔
Forssman et al., 2013	139 infants at 5-and-7-months of age	ATTENTION	TPH2	✔
			HTR1A	✗
Markant et al., 2014	88 infants at 7-months of age	ATTENTION	CHRNA4	✗
			DAT1	✗
			COMT	✔
Ebstein, R. P. et al., 1998	81 participants at 2-weeks of age	TEMPERAMENT	DRD4	✔
			5-HTTLPR	✗
Auerbach, J. et al., 1999	76 participants at 2-months of age	TEMPERAMENT	DRD4	✔
			5-HTTLPR	✔

Jorm, A. F. et al., 2000	660 participants, assessed for temperament from 4–8 -months to 15–16-years, and for behaviour problems from 3–4-years to15–16-years	TEMPERAMENT	5-HTTLPR	✗ 13-14 years of age ✔
Jorm, A. F. et al., 2001	The same as Jorm, AF et al., 2000	TEMPERAMENT	DAT1	✗
De Luca, A. et al., 2001	122 participants at 1 and 5-months of age	TEMPERAMENT	DRD4	1-month of age ✔ 5-months of age ✗
Auerbach, J. G. et al., 2001	61 participants at 12-months of age	TEMPERAMENT	DRD4 5-HTTLPR	✔ ✔
Lakatos, K. et al., 2003	90 participants at 12-months of age	TEMPERAMENT	DRD4 5-HTTLPR	✔ ✔
Sheese, B. E. et al., 2009	Longitudinal study of infants at age 6-7 (50 participants) and 18-20-months (37 participants) of age	TEMPERAMENT	COMT SNAP25 CHRNA4	✔ ✔ ✔
Becker, K. et al., 2010	384 participants - assessments were conducted at 3-months and 2, 4.5, 8, 11, and 15-years of age	TEMPERAMENT	DRD4	✔
Holmboe, K. et al., 2011	90 participants at 4 and 9-months of age	TEMPERAMENT	DRD4 5-HTTLPR	✔ ✔
Pluess, M. et al., 2011	1136 participants at 6-months of age	TEMPERAMENT	5-HTTLPR	✗
Zhang, M. et al., 2011	331 participants at 6-months of age and their mothers	TEMPERAMENT	MAOA	✔
Hill, J. et al., 2013	209 participants at 5-weeks of age	TEMPERAMENT	MAOA	✔

	and their mothers			
Pickles et al., 2013	193 infants at 14-months of age	TEMPERAMENT	MAOA	✔
Markant et al., 2014	97 infants at 7-months of age	TEMPERAMENT	MAOA	✔
Schmidt, L. A. et al., 2009	88 participants followed since infancy - the results reviewed here are based on the EEG data collected at 9-months and gene and temperament measures collected at 48-months of age	EEG MEASURES-TEMPERAMENT AND ATTENTION MEASURES	DRD4	✔
Grossmann, T. et al., 2011	48 infants at 7-months of age	ELECTROCORTICAL AND TEMPERAMENT MEASURES	COMT	✔
			5-HTTLPR	✔

Note. Reported significant or nonsignificant association based on authors' criteria.

2.4 The Candidate Gene Association Design

Candidate gene association studies seek to draw linear association between genetic markers and continuous traits using linear regression analysis. This assumes a linear relationship between mean value of the trait and genotype (Balding, 2006). The standard choice in genetic association studies involves exploring main linear effects of individual alleles on the trait of interest. The alleles derive from genes that may code for the synthesis of a protein, which is hypothesized to contribute to the phenotype's causal pathway (Ronald, 2011).

For psychological traits, examples of such hypotheses relate to the neurotransmitters dopamine and serotonin. The dopamine receptor D4 (DRD4)

gene has been selected as a dopamine system gene that might affect frontal cortex functioning in infancy, since it is expressed in the retina and the prefrontal cortex; its polymorphisms have been associated with several phenotypes, including an increase risk of attention deficit hyperactivity disorder (ADHD), impulsivity, lower levels of response inhibition and sensation seeking in toddlers, when combined with poor parenting (Holmboe et al., 2010). Empirical data has demonstrated that the dopaminergic system mainly influences the frontal lobe and basal ganglia and acts as a strong regulator of several aspects of cognition and attention (Nieoullon, 2002). Serotoninergic neurons in mammals form the most extensive axonal arborizations of all neuronal systems and their innervations appear early in development. Converging evidence supports the hypothesis that serotonin is a neurotransmitter that plays a major role in a variety of cognitive functions (Turlejski, 1996).

As such, genes that directly or indirectly influence the serotoninergic or dopaminergic systems are often included in candidate gene association studies of psychological traits. Specifically to the current work, investigating the association between dopamine-related genes with attention, temperament and behaviour was the main focus of the majority of genetic research that is reviewed here. For example, given that the dopaminergic pathways are a core factor in many aspects of attention (Sheese et al., 2009), genes related to dopamine have been hypothesized to be associated with several attentional parameters. In Table 2.2, the candidate genes that have been assessed in genetic research in infancy are presented.

Table 2.2. *Genes that have been associated with attention, temperament and behaviour in infancy and longitudinally*

Gene & Chromosome	Approved name	N of studies that used the gene	Function
CHRNA4 20 (20q13.2–20q13.3)	Cholinergic receptor, nicotinic alpha 4	2 out of 21	"This gene encodes a nicotinic acetylcholine receptor, which belongs to a superfamily of ligand-gated ion channels that play a role in fast signal transmission at synapses…. Mutations in this gene cause nocturnal frontal lobe epilepsy type 1..." **NCBI's article on CHRNA4 gene retrieved from:** (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene&cmd=Retrieve&dopt=full_report&list_uids=1137)
COMT 22 (22q11.21-q11.23)	Catechol-O-methyltransferase	4 out of 21	"Catechol-O-methyltransferase catalyzes the transfer of a methyl group from S-adenosylmethionine to catecholamines, including the neurotransmitters dopamine, epinephrine, and norepinephrine. This O-methylation results in one of the major degradative pathways of the catecholamine transmitters…" **NCBI's article on COMT gene retrieved from**: http://www.ncbi.nlm.nih.gov/gene/1312
DAT1 (also known as SLC6A3) 5 (5p15.3)	Dopamine transporter, also known as solute carrier family 6, member 3	3 out of 21	"This gene encodes a dopamine transporter which is a member of the sodium- and chloride-dependent neurotransmitter transporter family. The 3' UTR of this gene contains a 40 bp tandem repeat…. Variation in the number of repeats is associated with idiopathic epilepsy, attention-deficit hyperactivity disorder, dependence on alcohol and cocaine, susceptibility to Parkinson disease and protection against nicotine dependence." **NCBI's article on DAT1 gene retrieved from:** (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene&cmd=Retrieve&dopt=full_report&list_uids=6531)
DRD2	Dopamine Receptor D2 11 (11q22-q23)	1 out of 21	"This gene encodes the D2 subtype of the dopamine receptor… A missense mutation in this gene causes myoclonus dystonia; other mutations have been associated with schizophrenia…" **NCBI's article on DRD2 gene retrieved from:** (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene&cmd=Retrieve&dopt=full_report&list_uids=1813)
DRD4	Dopamine	9 out of 21	"This gene encodes the D4 subtype of the dopamine

	Receptor D4 11 (11p15.5)		receptor. The D4 subtype is a G-protein coupled receptor which inhibits adenylyl cyclase…" **NCBI's article on DRD4 gene retrieved from:** (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene&cmd=Retrieve&dopt=full_report&list_uids=1815)
5-HTTLPR (also known as SLC6A4) 17 (17q11.2)	Serotonin transporter linked polymorphic region, also known as solute carrier family 6, member 4	9 out of 21	"This gene encodes an integral membrane protein that transports the neurotransmitter serotonin from synaptic spaces into presynaptic neurons…. A repeat length polymorphism in the promoter of this gene has been shown to affect the rate of serotonin uptake and may play a role in sudden infant death syndrome, aggressive behavior in Alzheimer disease patients, and depression-susceptibility in people experiencing emotional trauma." **NCBI's article on 5-HTTLPR gene retrieved from:** (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene&cmd=Retrieve&dopt=full_report&list_uids=6532)
HTR1A 5 (5q11.2-q13)	5-hydroxytryptamine (serotonin) receptor 1A, G protein-coupled	1 out of 21	"This gene encodes a G protein-coupled receptor for 5-hydroxytryptamine (serotonin), and belongs to the 5-hydroxytryptamine receptor subfamily… Inactivation of this gene in mice results in behavior consistent with an increased anxiety and stress response. Mutation in the promoter of this gene has been associated with menstrual cycle-dependent periodic fevers." **NCBI's article on HTR1A gene retrieved from:** (http://www.ncbi.nlm.nih.gov/gene/3350)
MAOA X (Xp11.4 – p11.3)	Monoamine Oxidase A	4 out of 21	"This genes encodes monoamine oxidase A, an enzyme that degrades amine neurotransmitters, such as dopamine, norepinephrine, and serotonin…. The gene is adjacent to a related gene on the opposite strand of chromosome X. Mutation in this gene results in monoamine oxidase deficiency, or Brunner syndrome." **NCBI's article MAOA gene retrieved from:** (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene&cmd=Retrieve&dopt=full_report&list_uids=4128)

SNAP25 20 (20p12–20p11.2)	Synaptosomal-associated protein, 25KDa	1 out of 21	"Synaptic vesicle membrane docking and fusion is mediated by SNAREs (soluble N-ethylmaleimide-sensitive factor attachment protein receptors) located on the vesicle membrane (v-SNAREs) and the target membrane (t-SNAREs)…. this gene product is a presynaptic plasma membrane protein involved in the regulation of neurotransmitter release…" **NCBI's article on SNAP25 gene retrieved from:** (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene&cmd=Retrieve&dopt=full_report&list_uids=6616)
TPH2 12 (12q21)	Tryptophan hydroxylase 2	2 out of 21	"This genes encodes a member of the pterin-dependent aromatic acid hydroxylase family. The encoded protein catalyzes the first and rate-limiting step in the biosynthesis of serotonin, an important hormone and neurotransmitter…. This gene is expressed predominantly in the brain stem. Mutations in this gene may be associated with psychiatric diseases such as bipolar affective disorder and major depression." **NCBI's article on TPH2 gene retrieved from:** (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene&cmd=Retrieve&dopt=full_report&list_uids=121278)

2.5 Associations between Common Genetic Variants and Visual Attention

In this section, the findings from seven studies that have linked attentional parameters with candidate genes in infancy are presented. Tables 2.3 presents in chronological order further information about the candidate gene studies that associated genetic markers with attention.

Table 2.3. Seven studies that associated candidate genes with attention in infancy

STUDY	SAMPLE (N & AGE)	MEASURES	POSITIVE RESULTS	NEGATIVE RESULTS
Auerbach, J. et al., 2001a	64 participants at 12-months of age	The laboratory observation of temperament, which uses a task orientation episode to measure sustained attention _____ The Fagan test of Infant Intelligence, which uses a novelty preference paradigm to measure information processing	L-DRD4 carriers exhibited less sustained attention and novelty preference than infants without the L-DRD4 _____ L-DRD4 and s/s 5-HTTLPR carriers displayed the shortest duration of looking	5-HTTLPR did not have a main effect on infants sustained attention and information processing
Laucht, M. et al., 2006	232 3-months-old infants (longitudinal study of early risk factors which followed participants from birth to adolescence)	Visual exploratory behaviour at 3-months of age was assessed in a habituation-dishabituation paradigm _____ The Junior Temperament and Character Inventory (JTCI/12–18) was used to measure novelty seeking in adolescence	L-DRD4 was associated with greater attention decrement (more rapid habituation) in infancy and higher scores on novelty seeking in adolescence in males	No association between DRD4, attention and novelty seeking has been observed in girls

Sheese, B.E. et al., 2009	Longitudinal study of infants at age 6-7 and 18-20-months of age	Temperament measures– parent reports: The Infant Behavior Questionnaire Revised (IBQ-R; 14 subscales) _____ The Early Childhood Behaviour Questionnaire (ECBQ; 18 subscales) at 6-7 and 18-20-months respectively	6-7-months old infants with the T/T allele of the CHRNA4 displayed better performance to anticipatory looking _____ At 18-months of age C/C CHRNA4 homozygotes displayed the highest effortful control scores	6-7-months old infants with the C/C allele of the CHRNA4 displayed lower performance to anticipatory looking _____ At 18-months of age T/T CHRNA homozygotes had lower effortful control
Holmboe, K. et al., 2010	102 infants at 9-months of age	The Freeze-Frame task (please see Holmboe et al., 2008 for details)	Infants carrying the COMT Met/Met genotype exhibited lower distractibility levels in comparison to infants with the Val/Val genotype; this effect was present only to those participants that did not carry two copies of the DAT1 10-repeat allele	Both the L-DRD4 and the DRD2 did not associate with infants' performance in the Freeze-Frame task
Leppanen, J.K. et al., 2011	66 infants at 7-months of age	Attention disengagement and shifting has been measured in the context of neutral and affectively salient stimuli (please see Leppanen et al., 2011 for details)	Infants with the T-carrier genotype of the TPH2 displayed significantly increased missing attention shifts in comparison to infants with the G/G TPH2 genotype	No direct effect of the TPH2 to infants' temperament

		Mother filled the Infant Behavior Questionnaire	TPH2 gene regulated indirectly the infants' soothability via its effect on attention disengagement	
Forssman et al., 2013	139 infants at 5-and-7-months of age	Attention disengagement and shifting has been measured in the context of neutral and affectively salient stimuli (please see Forssman et al., 2013 for details) Mothers' stressful life events have been assessed using the recent life events questionnaire that consists of 18 yes or no questions about recent (last 12-months) life events; to assess maternal postnatal depressive symptoms, mothers filled out the 10-item Edinburgh Postnatal Depression Scale. Mother filled	Both G/G homozygotes and T-carriers show the typical patterns of increased number of missing attentions shifts in the context of fearful facial expressions but the typical pattern of increased number of missing shifts for fear is significantly larger in the T-carriers. T-carriers with mothers, who scored relatively higher on postnatal depression exhibited the highest levels of missing attention shifts for fearful facial expression	No significant main effect of the TPH2 and the HTR1A on the number of missing attention shifts were observed between infants with the T-carrier genotype and infants with the G/G TPH2 genotype and infants with the G-carrier genotype and infants with the C/C HTR1A genotype. No direct effect of the TPH2 or HTR1A to infants' temperament

		the Infant Behavior Questionnaire		
Markant et al., 2014 (see also Markant et al., 2014 on Table 4 below)	88 infants at 7-months of age	Facilitation of orienting and inhibition of return were assessed using a spatial cueing task that included a central fixation target, a peripheral cue and a target shape; the experimenter monitored the infant's eye movements and indicated when the infant was looking central, left, right or away from the screen.	COMT Val carriers showed better inhibition of return relative to infants with the Met/Met genotype.	COMT genotype was unrelated to infants' facilitation of orienting, and there were no effects of CHRNA4 or DAT1 on either facilitation of orienting or inhibition of return

2.5.1 DRD4 & 5-HTTLPR and infant attention

The first candidate gene study that investigated attention in infancy genotyped 12-month-old infants on the DRD4 and 5-HTTLPR gene variants and assessed their sustained attention and information processing (*Table 2.3*). Sustained attention was measured using the laboratory observation of temperament (Goldsmith & Rothbart, 1996), while information processing was measured using the Fagan test of infant intelligence (Fagan & Shepherd, 1991). The laboratory observation of temperament assesses sustained attention using a task orientation episode; the infant is seated at a table and four brightly coloured

blocks of different shapes are placed in front of the infant. The coded variables were: 1) latency to first look away; 2) duration of looking; 3) toy manipulation and 4) intensity of facial interest (Auerbach, Benjamin, Faroy, Geller & Ebstein, 2001a). The Fagan test of infant intelligence assesses information processing using a novelty preference paradigm that consists of ten trials in which the infant is presented with one picture or two identical pictures of faces. After the infant has looked at the pictures, the familiar picture is then paired with a novel picture and the time spend looking at each picture is recorded. Novelty preference refers to the percentage of looking time over the ten trials that the infant prefers the novel facial stimuli to the familiar facial stimuli (Auerbach, et al., 2001a).

The results revealed a significant DRD4 main effect in the laboratory observation of temperament; the effect was significant only for the measures of duration of looking and latency to the first look away (Auerbach, et al., 2001a). Infants with the L-DRD4 genotype exhibited significantly lower scores on duration of looking (indicating shorter looking time) and significantly shorter latencies to the first look away in comparison to infants without this variant, which suggest that having the L-DRD4 genotype in infancy is indicative of less sustained attention (Auerbach, et al., 2001a). There was also a significant interaction between the DRD4 and 5-HTTLPR; infants with the L-DRD4 and the s/s 5-HTTLPR genotypes exhibited the lowest scores (indicating shorter looking time) on duration of looking (Auerbach, et al., 2001a). The L-DRD4 genotype showed also a significant main effect on the Fagan test of infants' intelligent; infants with the L-DRD4 genotype scored lower than infants without this genotype on the Fagan test, which indicates less preference for novel stimuli (Auerbach, et al., 2001a).

A recent study (*Table 2.3*) did not find an association between the L-DRD4 and performance of 9-month-old infants on the 'Freeze Frame' task (Holmboe, Nemoda, Fearon, Csibra, Sasvari-Szekely & Johnson, 2010). The Freeze Frame task has been proposed to assess attention and frontal cortex functioning in 9-month-old infants, by evaluating the ability of infants to inhibit looks to peripheral distractors (Holmboe Fearon, Csibra, Tucker & Johnson, 2008). In this task, infants are presented with animations (the trials are separated into "interesting" and "boring"; the dynamic and colourful animations were considered to be the interesting trials, while a rotating orange star was considered to be the boring trials), while white squares (distractors) are flashed on the right or left side of the screen. If the infants look at the distractor the animation is stopped for 3,000 milliseconds (ms); distractor duration is calibrated individually for each infant by increasing it by 40 ms on every trial where the infant did not look to the distractor. For the purposes of the analysis the proportion of looks to the distractors per individual is calculated, separately for interesting and boring trials within the three phases (beginning, middle and end) of the experiment (Holmboe et al., 2010; Holmboe et al., 2008). As mentioned above, infants with the L-DRD4 genotype did not differ significantly to infants without the L-DRD4 genotype, on the proportion of looks to the distractors, as assessed by the Freeze-Frame task (Holmboe et al., 2010).

2.5.2 Other candidate genes and infant attention.

Holmboe et al., (2010) have also tested for association between the catechol-O-methyltransferase gene (COMT), the dopamine D2 receptor gene (DRD2) and the dopamine transporter gene (DAT1), with performance of 9-month-old infants on the Freeze-Frame task. The genes have been selected

because they are linked to the dopaminergic system and importantly, while COMT gene is mainly expressed in the frontal cortex, the DRD2 and DAT1 genes are mainly expressed in subcortical areas and in particular the striatum (Holmboe et al., 2010). They found a significant effect of the COMT Valine^{158}Methionine (Val^{158}Met) polymorphism; infants carrying the Met/Met genotype exhibited lower distractibility levels in comparison to infants with the Val/Val genotype, a finding that provides additional evidence for the association of variation in COMT gene and frontal cortex functioning (Holmboe et al., 2010). It also highlights the importance of having biological theory behind the selection of genes in candidate gene association methodology. In addition, they found that the effect was present only in those participants that did not carry two copies of the DAT1 10-repeat allele (Holmboe et al., 2010). This finding suggests the existence of epistasis (Gene by Gene interaction), a phenomenon that could partially account for the unreplicated findings in candidate gene studies. Finally, DRD2 TaqIA (and DRD4, as noted above) did not associate with performance on the Freeze-Frame task at 9-months of age (Holmboe et al., 2010).

A study (*Table 2.3*) examined the association of the tryptophan hydroxylase 2 gene (TPH2) with attention and temperament in 7-month-old infants. TPH2 was selected as a candidate gene in this study because recent work has shown that the G allele is associated with lower serotonin concentration, which could have functional consequences on brain function and behaviour (Leppänen et al., 2011). The authors reported that infants with the T-carrier genotype displayed significantly increased missing attention shifts (they assessed attention using a paradigm which measures disengagement and shifting of attention in the context of neutral and affectively salient stimuli), in comparison to

infants with the G/G TPH2 genotype. According to the authors disengaging attention away from an aversive stimulus is a key factor on infant's attempt to regulate their negative emotionality (Leppänen et al., 2011). They claimed that, because the increased missing attention shifts (that were displayed by infants with the T-carrier genotype) were associated with less effective regulation of negative affect (soothability), the TPH2 gene can regulate indirectly the infants' soothability (they measured infants' temperament by asking the mother to complete the Infant Behavior Questionnaire) via its direct effect on attention disengagement (Leppänen et al., 2011). As such, the results suggest a possible relationship between common genetic factors, attention and temperament in infancy.

Recently, another study (*Table 2.3*) assessed the main effect of the TPH2 and HTR1A genes, as well as the interactive effect of those genes with early life stress, in contributing to variation in attention to social signals of fear in 5-and-7-month-old infants (Forssman et al., 2013). The authors assessed infants' attention and temperament using the same protocol as Leppänen et al., (2011), described above. In addition, they assessed maternal stress and depressive symptoms using the recent life events questionnaire (based on Brugha, Babington, Tennant & Hurry, 1985) and the 10-item Edinburgh Postnatal Depression Scale (Cox, Holden, & Sagovsky, 1987). The recent life events questionnaire consists of one open-response item and 18 "yes" or "no" items that ask about the presence of diverse stressful life events that might have taken place in the past 12 months. The sum score of the 10-item Edinburgh Postnatal Depression Scale indexes depressive symptoms with higher total score to indicate higher levels of depressive symptoms (Forssman et al., 2013). The results showed that the

increase in missing attention shifts for happy expressions in TPH2 T-carriers (presented for the first time by Leppanen et al., 2011) did not replicate in this sample; despite that, there was a significant difference between the TPH2 T-carriers and carriers of the G/G genotype in the number of missing saccades for fearful facial expression with the former showing more missing saccades than the latter. There was no main effect of the HTR1A genotype on attention disengagement (Forssman et al., 2013). Finally, TPH2 T-carriers with mothers who scored higher on postnatal depression, exhibited the highest levels of missing attention shifts for fearful facial expression (Forssman et al., 2013).

The most recent study (*Table 2.3*) to date that explored the association between genetic markers and attention in infancy examined the relationship between CHRNA4, DAT1 and COMT genes to spatial attention in eighty-eight 7-month-old infants (Markant, Cicchetti, Hetzel & Thomas, 2014). The infants took part in a spatial cueing task that included a central fixation, a peripheral cue and a target shape stimuli; the fixation stimuli remained visible through the cue presentation and subsequent delay and disappeared at target onset (Markant et al., 2014). The targets remained visible up to 1,500 ms or until the infant looked away for longer than 500 milliseconds. The experimenter monitored the infant's eye movements and indicated when the infant looked at the centre, left, right, or away from the screen, while the computer calculated the cumulative duration of looking during each trial (Markant et al., 2014). The results showed that DAT1 and CHRNA4 genotypes did not associate with attention in infancy. Carriers of the COMT-Val genotype showed faster overall response times to cued location in comparison to COMT-Met carriers and their inhibition of return to the cued location was above chance (Markant et al., 2014). The finding of the study

suggest that normative differences in COMT gene, which impacts dopaminergic signalling in prefrontal cortex (see Holmboe et al., 2010 and 2011) relate to individual differences in attention orienting among 7-month-old infants (Markant et al., 2014).

2.5.3 Longitudinal studies of infant attention.

A longitudinal study (*Table 2.3*) examined the association of DRD4 with visual exploratory behaviour in 3-month-old infants. The main hypothesis was that both visual exploratory behaviour in infancy and novelty seeking (NS) in adolescence (which was previously associated with L-DRD4; Benjamin, Li, Patterson, Greenberg, Murphy & Hammer, 1996) could be viewed as developmentally specific phenotypes of the DRD4 gene. While male infants who were habituating faster showed higher scores of NS as adolescents, females did not show a significant correlation between infants' habituation measures and NS in adolescents. Male infants carrying the L-DRD4 exhibited more rapid habituation (they shifted their attention away from a standard stimulus more quickly) during repeated stimulation in a habituation-dishabituation paradigm than males without L-DRD4. These same individuals with L-DRD4 showed higher scores of NS (measured using the Junior Temperament and Character Inventory) in adolescence. In females, L-DRD4 did not show a significant association with either attention or adolescent NS (Laucht, Becker & Schmidt, 2006).

Finally, a longitudinal study (*Table 2.3*) conducted by Sheese et al., (2009) found that the T/T genotype of the CHRNA4 was associated with a higher percentage of looks that were considered correct anticipations in 6-7-months old infants (Sheese et al., 2009; Voelker, Sheese, Rothbart & Posner, 2009). Recent

work suggests that in infancy, self-regulation depends upon orienting attention (which is linked to anticipatory looking) and that the cholinergic systems arising in the basal forebrain appear to play an important role in orienting attention (Petersen & Posner, 2012). At 18-months of age participants homozygous for the T allele were found to have less effortful control, in comparison to both heterozygous and homozygous for the C allele infants (Sheese et al., 2009). Since being homozygous for the T allele of the CHRNA4 was associated with higher percentage of looks that were correct anticipations in 6-7-months of age, one could expect that being homozygous for the T allele of the CHRNA4 will be associated with better effortful control at 18-months of age (since effortful control, anticipatory looking and orienting attention are linked). This puzzling finding could be explained by findings that suggest that, while in infancy self-regulation depends primarily upon a brain network involved in orienting to sensory events that includes areas of the parietal lobe and frontal eye-field, self-regulation in childhood and adulthood depends on the executive attention system that involves the anterior cingulate, the insula and areas of the basal ganglia (Petersen & Posner, 2012; Posner, Rothbart, Sheese, & Voelker, 2012). It is therefore possible that the advantage of being homozygous for the T allele of the CHRNA4 in infancy on anticipatory looking (hence self-regulation) did not hold later in development because the control of self-regulation is passed from the orienting attention system (which is linked to anticipatory looking in infancy) to the executive attention system (Voelker, Sheese, Rothbart & Posner, 2009).

To summarise, genes related to dopamine (e.g. DRD4) have been hypothesized to be associated with several attentional parameters. L-DRD4 was the most well studied genotype and it was found to be associated with shorter

looking duration, shorter latencies to the first look away, less sustained attention, less novelty preference in infancy and higher novelty seeking in adolescent. The inconclusive findings in genetics of infant attention could be explained partially by the existence of epistasis (see Holmboe et al., 2010) or by "true" changes in the genetic architecture on a particular attentional domain across infant development (see Sheese et al., 2009).

2.6 Associations between Common Genetic Variants and Temperament and Behaviour

From the twenty-one published candidate gene studies, fourteen attempted to associate a particular genetic marker with temperament and behaviour in infancy. Those studies are presented in the following order: studies that associated the DRD4 and 5-HTTLPR genes with infant temperament and behaviour; studies that associated other genes (other than the DRD4 and 5-HTTLPR) with infant temperament and behaviour; longitudinal studies that associated the DRD4 and 5-HTTLPR genes with infant temperament and childhood/adolescent behaviour; longitudinal studies that associated other genes (other than the DRD4 and 5-HTTLPR genes) with infant temperament and childhood/adolescent behaviour. Tables 2.4, presents in chronological order further information about the candidate gene studies that associated genetic markers with temperament and behaviour in infancy.

Table 2.4. Fourteen genetic studies that associated genes with temperament and behaviour in infancy

STUDY	SAMPLE (N & AGE)	MEASURES	POSITIVE RESULTS	NEGATIVE RESULTS
Ebstein, R. P. et al., 1998	81 participants at 2-weeks of age	The Brazelton Neonatal Behavioral Assessment Scale (NBAS). Trained examiners assess the infants in 28 behavioral items and 18 neonatal reflexes items. The items are summarized in seven clusters: "*orientation, motor organization, range of state, state regulation, autonomic stability, habituation and reflexes*".	L-DRD4 was associated with higher scores in infants' orientation, motor organization, range of state and regulation of state _____ The presence of the s/s 5-HTTLPR in combination with the absence of the L-DRD4 reduced the scores in the orientation scale	No direct effect of the 5-HTTLPR on any of the four temperamental clusters (orientation, motor organization, range of state and regulation of state) of the NBAS.
Auerbach, J. et al., 1999	76 participants at 2-months of age	The Rothbart's Infant Bahavior Questionnaire (IBQ). 94-items parent report that consists of six behavioural scales: activity, smiling and laughter, distress to sudden or novel stimuli, distress to limitations, soothability, and duration of	L-DRD4 was associated with lower negative emotionality and distress to limitations scores _____ The s/s 5-HTTLPR was associated with higher negative emotionality and distress to limitations scores _____ Lack of the L-	No associations observed between the DRD4 and the 5-HTTLPR and infants' activity, smiling, distress to novel stimuli, soothability, orientation and positive emotionality

		orienting. _____ The Brazelton Neonatal Behavioral Assessment Scale (NBAS) (please see above).	DRD4 combined with the s/s 5-HTTLPR resulted in the highest negative emotionality and distress to limitations scores	
Jorm, A. F. et al., 2000 and Jorm, A. F. et al., 2001	660 participants, assessed for temperament from 4–8 -months to 15–16-years, and for behavior problems from 3–4-years to15–16-years	*Parental reports for temperament:* The Short Temperament Scale for Infant (STSI) at 4–8 months _____ The Short Temperament Scale for Toddler (STST) at 1–2 and 2–3-years of age _____ The Short Temperament Scale for Child (STSC) at 3–4 through to 7–8 years of age _____ The EAS Temperament Questionnaire at 9–10-years of age _____ The School Aged Temperament Inventory (SATI) at 11–12 through to 15–16-years of age	The l/l 5-HTTLPR genotype associated with higher anxiety at 13-14-years of age (Jorm et al., 2000) _____ No significant results reported (Jorm et al., 2001)	No significant association of the 5-HTTLPR with all the measures at most ages (Jorm et al., 2000) _____ The DAT1 VNTR polymorphism did not associate with any measure at all ages (Jorm et al., 2001)

		——————— *Parental reports for Behavioral problems:* The Behar Pre-school Behavior Questionnaire at 3–4-years of age ——————— The Rutter Problem Behaviour Questionnaire at 5–6 through to 12–13-years of age ——————— The Revised Behaviour Problem Checklist (RBPC) at 13–14 and 15–16-years of age		
De Luca, A. et al., 2001	122 participants at 1 and 5-months of age	Parent Report: The Italian version of the Early (EITQ-78 items) and the Revised Infancy Temperament Questionnaires (RITQ-87 items); both instruments measure: activity level, rhythmicity, approach, adaptability, threshold of responsiveness, intensity of reaction, quality	The L-DRD4 associated only with higher adaptability at 1-month of age	No association of the L-DRD4 with any of the temperamental measures at 5-months of age

		of mood, distractibility, attention span/persistence		
Auerbach, J. G. et al., 2001b	61 participants at 12-months of age	The Laboratory Temperament Assessment Battery **(**Lab-TAB Locomotor version) - Observational assessment	L-DRD4 was positively associated with the temperamental domains of interest and activity while the s/s 5-HTTLPR was negatively associated only with the temperamental domains of fear and pleasure	No significant association between the DRD4 and infants' fear, pleasure and anger _____ No significant association between the 5-HTTLPR and infants' anger, activity and interest
Lakatos, K. et al., 2003	90 participants at 12-months of age	The 94 items Rothbart's Infant Behavior Questionnaire – Mother Report _____ The 12-to-13-months-old infants and their mothers were videotaped in the Ainsworth Strange Situation	Infants with the combination of L-DRD4 and l/l 5-HTTLPR showed less anxiety, while Infants with the combination of L-DRD4 and s/s 5-HTTLPR showed more anxiety	No genotype effect on any of the Rothbart's temperamental dimensions
Sheese, B. E. et al., 2009	Longitudinal study of infants at age 6-7-months of age (50 participants) and 18-20-months of age (37participants)	Temperament measures: The Infant Behavior Questionnaire Revised (IBQ-R; 14 subscales) and the Early Childhood Behavior Questionnaire	Carriers of COMT heterozygotes exhibited higher positive affect at 6-months of age compared to those who are homozygotes for either valine or	No significant association between COMT, negative affect and orienting at 6-months of age _____ No significant association between COMT, negative and positive affect and

		(ECBQ; 18 subscales) at 6-7 and 18-20-months respectively – parent reports	methionine _____ Carriers of one or two copies of the SNAP25 C allele exhibited higher negative affect at 6-and 18-months of age _____ Carriers of the CHRNA4 T/T alleles exhibited higher effortful control (anticipatory looking) at 18-months of age	effortful control at 18-months of age _____ No significant association between SNAP25 with negative and positive affect and orienting at 6-months of age _____ No significant association between SNAP25 positive affect and effortful control at 18-months of age _____ No association between CHRNA4 with positive affect, negative affect and orienting at 6 and 18-months of age
Becker, K. et al., 2010	384 participants - assessments were conducted at 3-months and 2, 4.5, 8, 11, and 15-years of age	Temperamental characteristics and behaviour problems at age 3-months was based on observations of behaviour and structured parent interview data _____ Parent interviews were conducted to assess any difficulties in their infant's eating and sleeping behaviour and digestive problems 4	The combination of the L-DRD4 with regulatory problems in infancy associated with higher ADHD risk in childhood. No main effects were observed	Regulatory problems in infancy did not associate with higher ADHD risk in childhood in the absence of the L-DRD4. No main effects were observed

		weeks previously to the assessment _____ The Mannheim Parent Interview (MEI) was used to assess attentional, hyperkinetic, and impulsive problems in the 2-to 11-year-old children _____ The German version of the KIDDIE-SADS PL was used to assess attentional, hyperkinetic, and impulsive problems in the 15-year-old children		
Holmboe, K. et al., 2011	90 participants at 4 and 9-months of age	When the infants were 4 and 9-months old their parents filled in the Revised Infant behavior Questionnaire (IBQ-R)	L-DRD4 associated with higher negative affectt at 4 and 9-months of age; infants with both the L-DRD4 and l/l 5-HTTLPR had the highest negative affect	No main effects or interactions involving the L-DRD4 or the 5-HTTLPR reached significance for Surgency/Extraversion and Orientation/ Regulation
Pluess, M. et al., 2011	1136 participants at 6-months of age	Maternal Prenatal and Postnatal Psychopathology measured using the Brief Symptom Inventory, a	Higher levels of maternal anxiety during pregnancy was correlated with higher levels of negative emotionality in infancy; this	5-HTTLPR did not associate with infants' negative emotionality or maternal prenatal anxiety

		validated 53 items self report questionnaire _____ Infant Negative Emotionality measured using a 6 subscale version (out of the original 14 subscales) of the Infant Behavior Questionnaire—Revised (IBQ-R)	relationship was strongest for infants carrying the s/s 5-HTTLPR genotype	
Zhang, M. et al., 2011	331 participants at 6-months of age and their mothers	They measured the infants self-regulatory behaviour by coding the duration of looking to other places when the examiner was displaying a chimpanzee to the infants	Females with the MAOA 4/4 exhibited higher regulation than females with 3/3 and 3/4 genotypes	No association has been found between the MAOA and the male infants' self-regulatory behavior
Hill, J. et al., 2013	209 participants at 5-weeks of age and their mothers	Negative emotionality at 5-weeks of age was measured with the Brazelton Behavioral Assessment Scale (NBAS) (please see above) _____ Mothers' life events during pregnancy was assessed with the Life History	MAOA-LPR low activity variant interacted with total number of life events during pregnancy and deprivation to be associated with higher negative emotionality in 5-week-old infants	MAOA-LPR variants did not produce main effects in any of the assessed variables _____ No sex differences were observed

		Calendar, which is administered as a structured interview and assesses the total number of life events during pregnancy _____ Maternal anxiety at 32 weeks gestation was assessed using the State Anxiety scale _____ Maternal depression was assessed using the Edinburgh Postnatal Depression Scale		
Pickles, A. et al., 2013	193 participants at 14-months of age and their mothers	Temperament was assessed at 29-weeks and 14-months of age with the Infant Behavioral Questionnaire-Revised (IBQ-R). _____ Maternal Sensitivity at 20 weeks postnatal was assessed with a 15-min standard laboratory-based procedure; the mothers' sensitivity was rated from video recordings on a	MAOA-HH low activity variant interacted with maternal sensitivity in predicting high anger proneness in 14-months old infants	MAOA variants did not produce main effect in the temperament domain of anger proneness

		global 5-point scale reflecting mothers' appropriate, supportive, warm responses to infant communications, playful bids or distress.		
Markant, J. et al., 2014	97 participants at 7-months of age	A motor approach task was used to assess infants' latencies to grasp a toy presented to them for the first time _____ A Habituation-Dishabituation Task was used to assess total cumulative look duration and looking times _____ The revised version of the infant behavior questionnaire was used to assess infant's temperament domains of Surgency, Negative Affect and Orientation/Regulation	COMT-Val carriers showed a significant approach bias for the novel versus the typical toys and faster responses to approach the novel toys as compared with the COMT-Met carriers _____ COMT-Val carriers received lower scores on Orientation/Regulation factor as compared to COMT-Met carriers	COMT-Val carriers did not show differences in approach latencies to the toy as compared to COMT-Met carriers _____ COMT-Met carriers did not show a significant approach bias for the novel versus the typical toys _____ There were no statistically significant differences between COMT-Val and COMT-Met carriers on the total or average cumulative looking time and duration of looking in the habituation/dishabituation tasks _____ There were no statistically significant differences between COMT-Val and COMT-Met carriers on the temperament traits of Surgency or Negative Affect

2.6.1. DRD4 & 5-HTTLPR and infant temperament and behaviour

The DRD4 and the 5-HTTLPR have been included in seven and seven studies respectively, out of the fourteen studies that linked a candidate gene with temperament in infancy.

2.6.1.1. Birth to 4-months of age. A longitudinal study (*Table 2.4*; Ebstein et al., 1998; Auerbach et al., 1999 and Auerbach et al., 2001b) has found that 2-week-old infants with long DRD4 alleles (L-DRD4) had higher scores on four temperament scales (orientation, motor organization, range and regulation of state) of the Neonatal Brazelton Assessment Scale (NBAS; Brazelton & Nugent, 1995), in comparison to infants with the short DRD4 alleles (S-DRD4; Ebstein et al., 1998). Moreover, they found that infants homozygous for the short allele (s/s) of the 5-HTTLPR gene and lacking L-DRD4 exhibited significantly lower performance on the orientation cluster. No direct effect of the 5-HTTLPR was found on any of the temperamental clusters (Ebstein et al., 1998).

At 2-months of age, participants, who were carrying the L-DRD4 were reported by their mothers on the Rothbart's Infant behavior questionnaire (Rothbart, 1981) to be less distressed to limitations and to display less negative emotionality, in comparison to those with the S-DRD4 genotype. Infants who were carrying the s/s 5-HTTLPR genotype exhibited the highest scores on distress to limitations and negative emotionality in comparison to both l/s and l/l genotypes (*Table 2.4*; Auerbach, Geller, Lezer, Shinwell, Belmaker, Levine & Ebstein, 1999). Interestingly, infants with the s/s 5-HTTLPR genotype, who were also lacking the L-DRD4, were reported to display higher negative emotionality and distress to limitations (Auerbach et al., 1999).

The effect of the L-DRD4 on infants' temperament has been replicated by

another longitudinal study, which found that 1-month-olds with L-DRD4 showed significantly lower scores on the adaptability scale of the Italian version of the Early Infancy Temperament Questionnaire (Medoff-Cooper, Carey, McDevitt, 1993) in comparison to infants lacking the long allele. According to the authors, the lower adaptability scores were indicative of better responses to novel situations. This study failed to replicate the results in the same sample at 5-months of age (De Luca et al., 2001).

2.6.1.2. 4-to-9-months of age. Contrary to the above findings from the longitudinal study by Auerbach et al., (1999) and Ebstein et al., (1998), a recent longitudinal study (*Table 2.4*), which employed parental reports of the Revised Infant Behavior Questionnaire (IBQ-R; Gartstein & Rothbart, 2003), found that L-DRD4 was consistently associated with higher levels of negative affect in 4-and-9-month-old infants; in addition, participants carrying both L-DRD4 and the highest expressing l/l 5-HTTLPR genotype displayed the highest level of negative affect (Holmboe, Nemoda, Fearon, Savari-Szekely & Johnson, 2011). A recent study *(Table 2.4)* that used the Infant Behavior Questionnaire-Revised (Gartstein & Rothbart, 2003) and the Brief Symptom Inventory (Derogatis & Melisaratos, 1983) tested for an association between prenatal maternal anxiety and 5-HTTLPR, in a sample of 6-month-old infants. Consistent with the results of Ebstein et al., (1998) and Auerbach et al., (1999), they found that infants with the s/s 5-HTTLPR genotype, had higher negative emotionality scores (in comparison to those carrying the l/l 5-HTTLPR), but only under the condition that their mothers had reported high anxiety levels during pregnancy (Pluess et al., 2011).

2.6.1.3. 12-months of age. The third study *(Table 2.4)* of the longitudinal series of studies presented above (Ebstein et al., 1998; Auerbach et al., 1999),

reported that infants with L-DRD4 showed less negative emotionality and higher activity level scores at 12-months of age (Auerbach, Faroy, Ebstein, Kahana & Levine, 2001b). Infants with the s/s 5-HTTLPR genotype showed lower scores (as compared to both l/l and l/s 5-HTTLPR genotypes) on the fearful distress composite and significantly longer latency to the first fear expression, but they scored lower on a positive emotionality composite (Auerbach, Faroy, Ebstein, Kahana & Levine, 2001b). The 12-month-old participants were assessed using the Laboratory Temperament Assessment Battery (Lab-TAB-Locomotor version; Goldsmiths & Rothbart, 1996), which measures the temperamental domains of interest, fear, pleasure, anger and activity level (Auerbach et al., 2001b). Finally a study *(Table 2.4)* that used the Rothbart's Infant Behavior Questionnaire (Rothbart, 1981) and the Ainsworth's Strange Situation procedure (Ainsworth, Blehar, Waters & Walls, 1978) tested the effect of the DRD4 and 5-HTTLPR on infants' temperament and found that 12-month-old infants, who carried both L-DRD4 and s/s 5-HTTLPR genotype exhibited higher anxiety and were uninterested in interacting with a stranger, while participants with both L-DRD4 and l/l 5-HTTLPR genotype were calmer and interacted smoothly with an unfamiliar person (Lakatos et al., 2003).

2.6.2 Other candidate genes and infant temperament and behaviour.

A study *(Table 2.4)* tested for an association between Monoamine oxidase-A gene (MAOA) and 6-months-old infants' self-regulatory behaviour. In order to measure the self-regulatory behavior, the researchers showed the infants a picture of a chimpanzee (aversive event) and measured how long the infants looked away from the chimpanzee. The authors reported that a common functional MAOA variable number tandem repeat (MAOA-uVNTR), was associated with the self-

regulatory behaviour of the female infants. More specifically, the more active 4/4 genotype was associated with better regulatory behavior, but this effect was present only in girls (Zhang, et al., 2011).

Finally, a study *(Table 2.4)* tested for an association between COMT gene and 7-month-old infants' cognitive stability and flexibility (Markant, Cicchetti, Hetzel &Thomas, 2014). Cognitive stability and flexibility was assessed using: a motor approach task, which measures the infants' latencies to grasp a toy that was presented to them for the first time; a habituation-dishabituation task that assesses the total cumulative look duration and looking times at stimuli; and the revised version of the Infant Behavioral Questionnaire that measures the infant's large temperament domains of surgency, negative affect and orientation/regulation (Markant et al., 2014). The results indicated that COMT-Val carriers were faster to reach for novel toys during the motor approach task and received higher scores on the temperament trait of approach to novelty; COMT-Met carriers showed enhanced dishabituation to the novel stimulus during the habituation task and received higher scores on the temperament measures of sustained attention and behavioural regulation (Markant et al., 2014). The authors concluded that the COMT-Met and COMT-Val alleles are associated with increased cognitive stability and flexibility, respectively; the suggest that the COMT genotype could affect cognitive functions in the first year of life (Markant et al., 2014).

2.6.3 Longitudinal studies of infant temperament and childhood/adolescent behaviour.

2.6.3.1. DRD4 & 5-HTTLPR. A study *(Table 2.4)* investigated longitudinally the association of the 5-HTTLPR genotype with the temperamental parameter of approach-withdrawal (from 4-8 months to 15-16 years), anxiety

(from 3-4 to 15-16 years) and of depression (11-12 to 15-16 years; Jorm, Prior, Sanson, Smart, Zhang & Easteal, 2000). The results revealed a non-significant association at all ages between the 5-HTTLPR and all of the temperamental domains measured in that study; however at 13-14 years and 15-16 years the l/l alleles of the 5-HTTLPR were associated with higher anxiety. This study has also tested for gender difference, but it failed to report any significant result (Jorm, et al., 2000).

Another longitudinal study *(Table 2.4)*, which assessed temperamental characteristics and regulatory problems based on observations of infants' behaviour and structured parent interview data at age 3-months found that individuals with the L-DRD4 genotype and classified as having regulatory problems at 3-months of age had higher risk of developing ADHD symptoms in childhood; individuals who were not carrying the L-DRD4 but with a history of regulatory problems in infancy were not at elevated risk for ADHD (Becker, Blomeyer, El-Faddagh, Esser, Schmidt, Banaschewski & Laucht, 2010).

2.6.3.2. Other candidate genes. Apart from the DRD4 and the 5-HTTLPR genes, two studies have examined longitudinally the role of other dopamine-related genes. The first study (*Table 2.4)* tested for an association between the dopamine transporter gene (DAT1) and both temperamental traits (from 4–8 months to 15–16 years) and behaviour problems (from 3–4 years to 15–16 years), but failed to report any significant association at any age (Jorm, Prior, Sanson, Smart, Zhang & Easteal, 2001). The second study *(Table 2.4)* measured temperament in 6-7-month-olds infants and 18-month-olds respectively, and tested for association with the Catechol-O-methyl transferase (COMT), the Cholinergic receptor nicotinic alpha 4 (CHRNA4) and the Synaptosomal-

associated protein, 25KDa (SNAP25). They found that infants heterozygous for the COMT alleles exhibited higher positive affect at 6-7-months-old, in comparison to infants with the G/G or A/A COMT alleles. No significant association was found between COMT and temperament at 18-months of age (Sheese et al., 2009). Finally 6-month-old infants with one or two copies of the SNAP25 C allele exhibited lower negative affect, as compared to those that were homozygous for the T allele; the same effect was also present at 18-months of age (Sheese et al., 2009).

Recently, a longitudinal G x E interaction study *(Table 2.4)*, examined whether genetic variation in the MAOA gene interacts with environmental factors during pregnancy to predict negative emotionality in a sample of 209 5-week-old infants. The MAOA gene is expressed in the brain during fetal development and the MAOA-LPR low activity variant (as opposed to the high activity variant), has been found in several studies to interact with childhood maltreatment to be associated with child and adult antisocial outcomes (Hill, Breen, Quinn, Tibu, Sharp, Pickles, 2013). Infants' negative emotionality was assessed with the Brazelton Neonatal Behavioral Assessment scale (NBAS; Brazelton & Nugent, 1995); infants' birth weight and one minute Apgar scores were obtained from hospital birth records (Hill et al., 2013). Mothers completed the Life History Calendar (LHC; Caspi et al., 1996) at 32 weeks gestation, which assesses the total number of life events during pregnancy. The results revealed that MAOA-LPR low activity variant showed an interaction with total number of life events leading to significantly higher levels of negative emotionality in 5-week-old infants. Specifically, there was a 3-times increase in the likelihood of infants to react with fussing or crying, if they were carrying the low activity MAOA-LPR and if their

mothers were reporting 4 or more life events during pregnancy or they were scoring high in neighborhood deprivation on the LHC. On the contrary, infants with the MAOA-LPR high activity variant and with mothers who were reporting 4 or more life events during pregnancy or neighborhood deprivation were either unaffected (life events) or they were exhibiting less negative emotionality (deprivation; Hill et al., 2013).

Finally, a longitudinal G x E interaction study (*Table 2.4)* explored the main effect of MAOA genotype as well as the interactive effect of the MAOA genotype with maternal sensitivity on infant temperament (Pickles et al., 2013). The authors assessed infant temperament at 29 weeks and 14 months of age using the Infant Behavioral Questionnaire – Revised (Gartstein & Rothbart, 2003) and maternal sensitivity at 29 weeks postnatal with a 15-min laboratory-based procedure (NICHD Early Child Care Research Network, 1999). The mothers' sensitivity was rated from video recordings on a global 5-point scale reflecting mothers' appropriate, supportive, warm responding to infant communications, playful bids or distress (Pickles et al., 2013). There were no significant associations between MAOA status and infant temperament at 29 weeks and at 14 months of age. There was a significant interaction between MAOA status and maternal sensitivity at 29 weeks of age; Participants carrying the low expression genotype (MAOA-L carriers versus MAOA-H carriers) and with mothers, who were exhibiting low sensitivity showed the highest scores on proneness to anger at 14 months of age (Pickles et al., 2013).

To summarise, the most coherent set of results in genetics of infant temperament were on the L-DRD4 genotype. This genotype was significantly associated with several "positive" infant psychological phenotypes, namely

orientation, motor organization, range of state and regulation of state at 2-weeks of age, better responses to novel situation at 1-month of age, less negative emotionality and less distress to limitations at 2- and 12-months of age and higher activity levels at 12-months of age.

2.7 Studies that Associated Genes with Temperament and Electrophysiological Measures

Two studies have associated genetic markers with both temperament and electrophysiological measures in infancy. Table 2.5 presents, in chronological order, further information about the candidate gene studies that associated genetic markers with both temperament and electrophysiological markers in infancy.

Table 2.5. Two studies that associated candidate genes with temperament and electrophysiological measures in infancy

STUDY	SAMPLE (N & AGE)	MEASURES	POSITIVE RESULTS	NEGATIVE RESULTS
Schmidt, L. A. et al., 2009	88 participants followed since infancy - the results reported by Schmidt et al., (2009) are based on the EEG data collected at 9-months and gene and temperament measures collected at 48-months of age	At 9-months of age resting EEG data was recorded for 3 min _____ At 48-months of age the 30 items Colorado Childhood Temperament Inventory (CCTI) - Parent report	Participants with the L-DRD4 and left frontal EEG asymmetry at 9-months of age, were more soothable at 48-months of age _____ Infants carrying the L-DRD4 and with right frontal EEG asymmetry at 9-months of age, had the lowest scores in soothability and they had difficulties in focusing and sustaining attention at 48-months of age	Resting frontal EEG asymmetry did not influence temperament in the absence of the L-DRD4
Grossmann, T. et al., 2011	48 infants at 7-months of age	The neutral, happy and fearful stimuli were color portrait photographs of two actors taken from the Nimstim stimulus set _____ The EEG was recorded with Ag–AgCl electrodes from 19 scalp locations of the10–20 system; for analysis of	COMT met/met and met/val genotype was associated with increased negativity to fearful expression at central and parietal electrodes from 200 to 400ms _____ COMT met/met and met/val genotype was associated with increased negativity to fearful expression at central and parietal electrodes from 400 to 600ms _____ l/l and l/s 5-HTTLPR genotype	COMT val/val genotype was associated with increased positivity to fearful expression at central and parietal electrodes from 200 to 400ms _____ No effect of COMT over frontal, temporal and occipital regions _____ COMT val/val genotype was associated with increased positivity to fearful expression at central and parietal electrodes from 400 to 600ms _____

		mean amplitude effects, time windows of 0–200 ms, 200–400ms and 400–600ms were selected _____ Parents completed the Infant Behavior Questionnaire (IBQ-R), which consists of 14 subscales: approach, vocal reactivity, high intensity pleasure, smile and laughter, activity level, perceptual sensitivity, sadness, distress to limitations, fear, rate of recovery from distress, low intensity pleasure, cuddliness, duration of orienting, soothbility	was associated with higher negativity in response to happy expressions over frontal and temporal electrodes from 200 to 400 ms., while the s/s 5-HTTLPR genotype was associated with a positivity in response to happy expressions over frontal and temporal electrodes from 200 to 400 ms. _____ l/l and s/l 5-HTTLPR genotype was associated with higher negativity in response to happy expressions from 400 to 600ms over temporal electrodes, while the s/s 5-HTTLPR genotype was associated with higher positivity in response to happy expressions from 400 to 600ms over temporal electrodes _____	The processing of happy expressions did not associate with COMT over central and parietal electrodes from 400 to 600ms _____ COMT did not associate with responses over frontal, temporal and occipital regions from 400 to 600ms, while COMT did not associate with ERP responses from 0-200ms. _____ 5-HTTLPR did not associate with responses to fearful expressions over frontal and temporal electrodes from 200 to 400ms. _____ The 5-HTTLPR did not associate with ERP responses over central, parietal and occipital regions and with ERP responses from 0-200ms. _____ The ERP responses for the neutral face were unaffected by the COMT and 5-HTTLPR genotype _____

				Infants carrying the s/s 5-HTTLPR were reported as smiling less and as being less able to sustain their attention to an object in comparison to infants with the s/l and l/l genotype _____ No significant interaction between genes on the brain and temperament measures

The first study *(Table 2.5)* tested for a G x E interaction, between the DRD4 gene and endoenvironmental factors (endoenvironment is defined by the authors as the environment inside the organism – in this case resting frontal electroencephalogram, EEG, asymmetry; Schmidt, Fox, Perez-Edgar and Hamer, 2009). The main hypothesis was that genetic variation in the DRD4 gene and endoenvironmental factors at 9-months of age would predict individual differences in temperament and attention at 48-months of age. The results revealed an interaction of the L-DRD4 with right frontal EEG asymmetry; infants carrying the L-DRD4 and with right frontal EEG asymmetry at 9-months of age had the lowest scores in soothability as compared to those with the S-DRD4 and right frontal EEG asymmetry (Schmidt, Fox, Perez-Edgar & Hamer, 2009). A second interaction was observed between the L-DRD4 variant and left frontal EEG asymmetry; participants carrying the L-DRD4 variant and with left frontal EEG asymmetry at 9-months of age, were more soothable at 48-months of age as compared to those with the L-DRD4 and right frontal EEG asymmetry (Schmidt et al., 2009). Moreover infants carrying the L-DRD4 genotype and with right

frontal EEG asymmetry at 9-months of age had difficulties in focusing and sustaining attention at 48-months of age (Schmidt et al., 2009). This evidence suggests that both the L-DRD4 and the s/s 5-HTTLPR genotype can have different roles in different environmental (or endoenvironmental) conditions and further that their role in infants' temperament might be highly dependent upon their interaction (e.g. whether someone will carry the s/s 5-HTTLPR and will lack the L-DRD4). Despite the fact that this study tested for the G x E interaction it should be mentioned here that the endoenviromental parameters included in this study could be better seen as specific endophenotypes instead of endoenvironmental factors, since variation in brain activity is itself likely to be associated by genes as well as environment.

The second study *(Table 2.5)* tested if variation in the COMT and 5-HTTLPR genes is associated with electrocortical responses to facial expressions and temperamental domains in 7-month-old infants. They reported that carriers of the COMT met alleles exhibited an increased negativity to fearful expression, while carriers of the COMT Val/Val genotype displayed enhanced positivity to fearful expressions (Grossmann, et al., 2011). Furthermore, the l/l 5-HTTLPR carriers displayed higher negativity in response to happy expressions, while s/s 5-HTTLPR carriers exhibited higher positivity to happy expressions (Grossmann et al., 2011). In respect to infants' temperament the met COMT alleles were associated with better recovery from distress while carriers of the s/s 5-HTTLPR genotype were reported as laughing less in comparison to infants carrying the l/l 5-HTTLPR genotype (Grossmann et al., 2011).

2.8 Summary

Twenty-one genetic studies in infancy on attention, temperament and behaviour have been identified from the literature search. These studies all employed the candidate gene association design. Moreover infant genetic research is beginning to investigate the possibility of gene x gene interactions, gene x environment interactions and gene-brain relationships. While most studies examined just one candidate gene in association with one phenotype, some studies investigated two or more candidate genes in association with two or more phenotypes. None of the significant associations have consistently replicated across studies. DRD4 and 5-HTTLPR genes were the most frequently used candidate genes.

Possibly the most coherent set of results were on the L-DRD4 genotype. This genotype was significantly associated with several "positive" infant psychological phenotypes, namely orientation, motor organization, range of state and regulation of state at 2-weeks of age, better responses to novel situation at 1-month of age, less negative emotionality and less distress to limitations at 2- and 12-months of age, higher activity levels at 12-months of age and more rapid habituation at 3-months of age. However, L-DRD4 was also associated with higher levels of negative affect at 4- and 9-months of age, shorter looking duration, shorter latencies to the first look away, less sustained attention, less novelty preference and poor performance on the Fagan test of infant intelligence at 12-months of age. Finally, other studies found no significant main effect of the L-DRD4 on infants' activity, smiling, distress to novel stimuli, soothability, positive emotionality at 2-months of age; surgency, extraversion and orientation at 4- and 9-months of age; adaptability at 5-months of age; infants' performance in

the Freeze-Frame task at 9-months of age.

Based on the above brief overview the most promising result to date appears to be an association between the L-DRD4 polymorphism and several "positive" temperamental characteristics in infants from birth to 4-months of age and at 12-months of age.

2.8.1 How can the mixed evidence be interpreted?

Studies tended to place importance on obtaining a sample that had a similar chronological age in order to capture a specific developmental stage. The inconsistent findings across different infant ages may reflect "true" changes in the genetic architecture on a particular domain across infant development. Alternatively, lack of replication across ages could be due to other more prosaic reasons such as measurement issues, genotyping errors, lack of power, or other problems with a study design.

In terms of the measurement explanation, infant genetic research on psychological phenotypes has the demanding task of developing age-appropriate measures that pick up on reliable individual differences. Distinct domains within a trait might involve different measures. If longitudinal studies on infancy are conducted then researchers need to be sure their measures are tapping the same underlying constructs at different ages.

The statistical power of each study reviewed here has not been discussed explicitly; several reviews exist which outline the power issues present in candidate gene studies and genetic research on complex traits (e.g. Eichler, et al., 2010; Hirschhorn, Lohmueller, Byrne & Hirschhorn, 2002). Several authors have claimed that one of the limitations of candidate gene studies is that researchers do not correctly adjust the significance level in light of the numbers of tests that they

performed. Not reducing the significance level to below 5% in the presence of multiple related statistical tests can lead to false positive results (Van Gestel & Van Broekhoven, 2003).

Recent theoretical ideas can provide other viewpoints on the inconclusive findings. A theory-based perspective for considering why the same trait might show mixed findings in terms of genetic associations across infant development and later ages is to question whether there are different underlying mechanisms involved on the same trait domains at different ages. For example, being homozygous for the T allele of the CHRNA4 might be advantageous for orienting attention (and hence self-regulation) only in infancy and not later in development. Looking at the cognitive level and the development of different systems of attention provides with an interesting interpretation: it is possible that the advantage of being homozygous for the T allele of the CHRNA4 in infancy for orienting attention might not hold later in development, when the control of self-regulation is passed from the orienting attention system to the executive attention system (Petersen & Posner, 2012; Posner, Rothbart, Sheese, & Voelker, 2012). Looking at the genetic level, failure to replicate direct effects of candidate vulnerability genes on specific traits suggests that genes might not influence phenotypes directly (Belsky, et al., 2009); instead genes may moderate effects of the environment on human complex traits and as such inconclusive findings might come about if there were different environmental modifiers in the studies and the developmental stage of the sample was different (Belsky & Pluess, 2009).

A different proposed explanation for the lack of replicable findings in candidate genes studies, though not specific to this age group, is a weak a priori hypothesis. Plomin (2013) suggests that: "*One problem with the candidate gene*

approach is that we often do not have strong hypotheses as to which genes are candidate genes. Indeed, the general rule of pleiotropy (each gene has many effects) suggests that most of the thousands of genes expressed in the brain could be considered as candidates." (Plomin, 2013, p. 107).

2.8.2 Other genetic approaches for investigating how genes operate in infancy

2.8.2.1 GWAS. Genome-wide association studies (GWAS) aim to identify common genetic variation across the entire human genome (Manolio & Collins 2009). GWAS are more systematic than candidate gene studies because instead of focusing just on one gene, they capture most of the common variation in the genome (and thus both inside and outside of the coding regions), which enables the researcher to identify different sources of genetic variation at different developmental stages (Plomin, 2013). Based on the findings of this review the inconsistent results of the genetic association studies across infancy may reflect 'true' changes in the genetic architecture across infant development. A candidate gene association design would not be very informative with respect to these changes as by default it is limited to a priori hypotheses about the genes that are potentially involved in a particular phenotype in infancy. The advantage of the GWAS is that it is a hypothesis-free design, which allows associating genes that have not been previously considered as important in relation to a particular phenotype. As such, GWAS has the potential to reveal changes in the genetic architecture of infant development, which would not be otherwise detected.

At the present time there are no GWA studies on attention, temperament and behaviour in infancy. GWAS require large sample sizes to secure sufficient power to detect effects. Assessing visual attention, for example, from thousands of infants longitudinally is extremely time consuming. There are also many

practical difficulties, which are related to the age of the sample. For example, special facilities are required to test infant visual attention; while adults can be persuaded to behave in line with the demands of the task, infants are less compliant and more likely to move and blink during the experimental session (Wass, Smith, & Johnson, 2013). Newborns and infants below the age of 1-2 months spend most of their time sleeping, which makes it difficult to retain them awake to complete the task; furthermore the fact that their visual system is immature in comparison to older infants places several constraints (Farroni & Menon, 2008). Genotyping infants is also challenging because infants cannot be asked to discharge sufficient amount of saliva to extract the DNA or to retain their mouth open so that cheek cells could be obtained; furthermore caregivers are usually reluctant in giving ethical approval to collect DNA samples from their infant offspring. As such, a constructive move forward would be to establish consortia across infant research labs and aim at data sharing using equivalent paradigms and age groups in order to increase the sample sizes.

2.8.2.2. Sequencing. DNA sequencing methodology involves identifying the entire sequence of DNA code in an individual's genome. Recent developments in genetic technology have dramatically reduced the time and cost of DNA sequencing (from $1,000 per megabase down to ten cents per megabase) enabling researchers to conduct studies that involve many millions of sequencing reads (Shendure & Aiden 2012). Plomin (2013) suggested that sequencing would influence developmental research in two ways. First, it will provide information about the entire genome, including rare variants, mutations (both rare variants and mutations are not detected by microarrays used for the purposes of GWAS) and non-coding genes, which might be contributing to the heritability of complex trait

and disorders. Second, when sequencing data becomes available, conducting genetically sensitive studies will become much easier because there will be no need for DNA to be collected more than once or for genotyping to be conducted (Plomin, 2013).

2.8.2.3 Implications. New genetic methodologies can address some of the limitations of this literature but will also bring new challenges. Succeeding in this task will help to better understand human development and, specifically, the common genetic variation that influence the development of attention, temperament and behaviour from the very earliest stages of life. Finally, it is hoped that a better understanding of the genes that influence those traits in infancy and throughout development will be informative in the area of developmental psychopathology for predicting risk, instead of diagnosing and, as a result, preventing instead of curing developmental psychopathology.

2.8.3 Polygenic risk score analytic approach

An analytic approach that could be informative towards predicting risk for developmental psychopathology is the Polygenic Risk Score analysis (PRS). Its main characteristics and a selective review of recent studies that used PRS analysis are outlined below.

For behavioural traits, the largest effect sizes in the first GWA studies of cognitive abilities in children are less than 0.5% of the variance (Butcher, Davis, Craig, & Plomin, 2008; Docherty, Davis, et al., 2010; Meaburn, Harlaar, Craig, Schalkwyk, & Plomin, 2008; Plomin, 2013). Although individually significant genetic markers in GWAS account for a small proportion of the heritability of complex traits, it is possible that a moderate proportion of variation in complex traits could be accounted by the ensemble of common genetic markers not

achieving significance individually due to the study's sample size (Dudbridge, 2013).

In order to construct the PRS and to assess the contribution of an ensemble of markers on a particular trait, a GWAS is conducted on a training sample and the markers are ranked based on the level of statistical significance (p-values) that they have returned. Subsequently, a PRS is constructed on an independent replication sample using the weighted sum of its trait-associated alleles; the polygenic risk score for each individual is expressed as the mean score per SNP in the set (Dudbridge, 2013). The PRS could then be used to predict individual's trait values or risk of disease or to establish a common polygenic basis between two disorders or quantitative measures. PRS analysis has the potential to provide a predictor with better discrimination properties in comparison to one based on individual genetic markers and to maximize the study's statistical power to detect an association (Wray, Goddard, & Visscher, 2007; Wray et al., 2014).

Given that the main target of the PRS analytic protocol is to predict risk of disorder or individual's trait values, polygenic risk score analysis could be particularly informative when used in samples at the earliest stage of development (e.g. infancy) or at a prodromal stage of a disorder (e.g. in adolescence for adult-onset disorders).

To date there are no studies that have used PRS approach with infant samples. The work that is reported in this thesis is the first application of this analytic protocol in newborn and infant samples. As such, a selective review of PRS studies with psychological traits will be presented. It consists of: the first successful application of the PRS methodology (Purcell, Wray, Stone, Visscher, Donovan et al., 2009); the two studies that have used PRS analysis in adolescent

samples (Zammit et al., 2013; Sieradzska et al., 2014) to explore whether schizophrenia PRS are associated with psychotic experiences; and a study that reported a shared genetic component between childhood attention-deficit hyperactivity disorder (ADHD) and adult schizophrenia. This selective review will demonstrate the applications of the PRS methodology in human complex traits and the implications of the PhD work, which will be presented later on (chapter 5).

The first successful application of the PRS analysis to GWAS data was in schizophrenia. The study used 3,322 European individuals with schizophrenia and 3,587 controls to explore the extent to which common genetic variation underlies risk of schizophrenia using GWAS data (Purcell, et al., 2009). While the GWAS analysis did not find a large number of strongly associated SNPs, the polygenic risk score created by combining the individual effect of 37,655 single nucleotide polymorphisms (SNPs) was highly correlated with schizophrenia ($p = 9.4 \times 10^{-19}$), explaining approximately 3% of the variance (Purcell et al, 2009). Furthermore, the study reported a substantial shared genetic component between schizophrenia and bipolar disorder using independent GWAS samples (Purcell et al., 2009).

Recently, a study explored the extent to which a PRS representing common genetic risk variants for schizophrenia predict psychotic experiences in a sample of 3,483 children assessed longitudinally at ages 12 and 18 (Zammit et al., 2013). The PRS were created using the Schizophrenia Psychiatric Genome-Wide Association Study Consortium dataset (Ripke, Sanders, Kendler et al., 2011) as discovery sample to identify alleles with which to produce PRS in the test sample (Avon Longitudinal Study of Parents and Children; *Boyd* et al., 2013). The study did not find evidence that individuals who had higher polygenic scores were at an

increase risk of psychotic experiences during adolescence (Zammit et al., 2013).

Another example study tested whether schizophrenia and bipolar disorder PRS were associated with adolescent dimension-specific psychotic experiences in a sample of 2,152 16-year old derived by the Twins Early Development Study (TEDS; Haworth, Davis & Plomin, 2013). The study provided the first evidence of whether schizophrenia and bipolar disorder PRS are predictive of dimension-specific psychotic experiences in adolescence (Sieradzka et al., 2014). Psychotic experiences were assessed using the Specific Psychotic Experiences Questionnaire (SPEQ; Ronald et al., 2014) that includes five self-report subscales: Paranoia, Hallucinations, Cognitive Disorganization, Grandiosity and Anhedonia and one parent-rated negative symptoms subscale (Sieradzka et al., 2014). The PRS were created using the Psychiatric Genomics Consortium schizophrenia (Ripke et al., 2011) and bipolar disorder (Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011) stage-1 GWAS mega-analysis datasets. The polygenic risk score yielded no significant associations with the SPEQ measures (Sieradzka et al., 2014).

Finally, a study tested whether there is overlap between common alleles conferring risk of schizophrenia and bipolar disorder in adults with those that do so for ADHD in children (Hamshere et al., 2013). Specifically, the study used Psychiatric Genomics Consortium schizophrenia (Ripke et al., 2011) and bipolar disorder (Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011) stage-1 GWAS mega-analysis datasets to test whether alleles that were over-represented in adults with schizophrenia and bipolar will also be over-represented in 727 children with ADHD as compared to 2,067 controls.

Comparisons between ADHD cases and controls demonstrated that

schizophrenia PRS alone were significantly different in the two groups; interestingly, the strongest discrimination between cases and controls was given by alleles that were risk alleles for both adult schizophrenia and adult bipolar disorder. Adult bipolar PRS alone did not discriminate significantly between ADHD cases and controls. The authors concluded that there is a small but significant shared genetic susceptibility between adult schizophrenia and childhood ADHD stressing the importance of conducting research across traditional diagnostic categories (Hamshere et al., 2013).

2.9 Thesis Rationale

The introduction has reviewed studies on individual differences in infant visual attention and how individual variation in attention in infancy is linked with individual differences in cognition, temperament and behaviour in childhood. Findings regarding the reliability of duration-based attentional measures and the continuity of visual attention from infancy to preadolescence have also been presented. Furthermore the introduction has reviewed all genetic studies on infant visual attention, temperament and behaviour. The results of the reviews demonstrated that:

1) Longitudinal research could explore further the link between individual differences in infant visual attention and child traits, to phenotypes other than general cognitive ability; such traits could be temperament and behaviour.

2) Longitudinal work that aims to investigate the extent to which individual differences in infant visual attention predict individual variation in temperament and behaviour in childhood could be benefitted from newer techniques (e.g. eye tracking) that will provide with more “fine-grained” measures of infant visual attention.

3) A gap in the literature was observed; there are currently no studies that have explored the degree to which individual variation in newborn visual attention (first 5 days of postnatal life) relates to individual differences in child psychological traits.

4) Candidate gene studies have provided with limited and mixed findings regarding the possible association of genes with visual attention in infancy. Newer genetic approaches--such as Polygenic Risk Score analysis—might prove to be more informative in the field's attempt to shed light on the genetic mechanisms underlying individual differences in infant visual attention.

METHODOLOGY & RESULTS

3 Infant Attention & Child Temperament & Behaviour

3.1 Chapter's Summary

Currently there are no studies that have used eye tracking and a longitudinal design to examine the degree to which individual differences in infants' mean fixation duration relate to individual differences in temperament and behavioural problems in childhood.

One hundred and twenty infants (mean age in months = 7.69, SD = 1.90) participated in three eye-tracking studies that were conducted by Dr. Rachel Wu (under the supervision of Dr. Natasha Kirkham) at Birkbeck's Babylab from March 2008 to December 2010 (Wu & Kirkham, 2010; Wu, Gopnik, Richardson, & Kirkham, 2011; Wu, Tummeltshammer, Gliga, & Kirkham, 2014). Novel analysis was applied by the thesis' author to the previously collected raw eye tracking data in order to extract the attentional measure of mean fixation duration in infancy. The parents of the children (mean age of children = 41.59, SD = 9.83) were invited to participate in the current work by the thesis' author. Depending on their child's age (preschool group; N=29: 19-36 months of age; school group; N=91: 36-54 months of age) they completed either the short forms of the Early Childhood Behaviour Questionnaire (ECBQ; Putnam, Jakobs, Gartstein & Rothbart, 2010) and the Revised Rutter Parent Scale for Preschool Children questionnaire (RRPSPC; Hogg et al., 1997); or the Childhood Behaviour Questionnaire (CBQ; Putnam & Rothbart, 2006) and the Strengths and Difficulties Questionnaire (Goodman, 1997). The findings suggest that individual

differences in fixation duration in infancy are linked to attentional and behavioural control in childhood.

This chapter is based on the following published article: Papageorgiou, K.A., Smith, T.J., Wu, R., Johnson, M.H., Kirkham, N.Z., & Ronald, A. (2014). Individual Differences in Infant Fixation Duration relate to Attention and Behavioral Control in Childhood. *Psychological Science*. Doi:10.1177/0956797614531295

3.2 Introduction

Some of the information that is presented here has been reviewed in Chapter 1. This brief introduction focuses on the most relevant concepts and findings to this first study in order to make explicit to the reader the rationale behind the hypotheses that were tested in the present work.

Fixation duration refers to the time between saccadic eye movements when the eyes are relatively stable. During a fixation several cognitive processes may occur: foveal visual information is processed and encoded in working memory, the next saccade target is selected from peripheral visual stimuli, and the oculomotor program required to bring the target into foveal vision is prepared (Rayner, 1998).

In infancy, fixation duration exhibits a robust developmental change (Colombo, Mitchell, Coldren &Freeseman, 1991). For example, while 1- to 2-month-old infants exhibit a series of long fixations when viewing static stimuli, 3 to 4-month-old infants exhibit a greater proportion of shorter fixations (Johnson, Posner & Rothbart, 1991). This change is thought to reflect a reduction in the early difficulties that infants encounter with disengaging their attention – known as “sticky fixation” or “obligatory attention”. By 4 months, problems with

disengaging from static stimuli have largely disappeared (Johnson et al., 1991).

There is only one study to suggest that mean fixation duration in infancy assessed using eye tracking is a stable measure of individual differences in infants' attention (Wass & Smith, 2014). The study assessed twenty-one typically developing 11-month-old infants on fixation duration across five separate laboratory visits over fifteen days, while infants viewed a 90-minute battery ranging from complex dynamic to noncomplex static materials. In order to assess how stable are individual differences in mean fixation duration, the authors calculated test-retest reliability, when an identical battery of mixed static and dynamic viewing material was administered twice to the same participants at 15 days viewing interval (Wass & Smith, 2014). The correlation reported between visits was $r = .78$ ($p < .001$) suggesting, that mean fixation duration in infancy is a stable measure of individual differences across short-term assessments (Wass & Smith, 2014).

Subsequently, the authors examined the stability of individual differences in mean fixation duration across different types of visual stimulus, averaging across visits. The relationship between mean fixation duration for all static and mean fixation duration for all dynamic stimuli was $r = .60$, ($p = .007$); as such, the results suggested that individual variation in mean fixation duration is to a moderate extent, independent of the type of stimuli used in a study (Wass & Smith, 2014).

Based on the fact that a fixation is made up of the conflict between demands for keeping the eyes stationary in order to encode foveal information and disengaging attention to shift to peripheral targets (Findlay & Walker, 1999) it is hypothesised to be linked with executive attention – the ability to regulate

responses to conflict situations where several responses are possible (Holmboe & Johnson, 2005).

3.2.1 Executive attention and effortful control

While the executive attention system develops in early childhood (18 to 24 months) a study has shown that one element of the executive system – namely, the ability to detect errors, emerges in infancy at around 7-months of age (Posner & Rothbart, 2013). This finding is in line with the view that some aspects of the executive attention system may be in place as early as in infancy (Gao et al., 2009; Posner et al., 2012).

Findings from neuroimaging studies have shown that brain areas that form part of the limbic system, like the anterior cingulate cortex, play a role in self-regulation and exhibit higher activation in tasks that include conflict including the colour-word Stroop task, the numerical Stroop task and the use of congruent and incongruent flankers task (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Bush, Luu & Posner, 2000; Petersen & Posner 2012; Rothbart, Ellis, Rueda & Posner, 2003). Behavioural data indicate that the time that children spend to resolve conflict (in the tasks mentioned above) is correlated with scores in parental report measures of *effortful control* (Rothbart, Sheese, Rueda & Posner, 2011).

The trait of effortful control refers to the child's volitional use of executive attentional abilities that include inhibitory control, detection of errors and planfulness (Bell &Calkins, 2012). Effortful control emerges around the second year of postnatal life with significant improvement taking place between 3 and 4 years of age and up until age 7 (Bell & Calkins, 2012). Furthermore stable individual differences in effortful control have been observed with around 25% of

the variance in attention regulation (a parameter of effortful control) in middle childhood explained by variation in attention regulation in early childhood (Deater-Deckard, Petrill & Thompson, 2007).

Given the aforementioned findings and the fact that effortful control in childhood correlates negatively with the temperament traits of anger, fear and discomfort (Rothbart, Ellis &Posner, 2004), Bell and Calkins (2012) suggested that the development of executive attention underlies the development of effortful control and emotion regulation (Bell & Calkins, 2012). Effortful control has been found also to correlate negatively with *surgency* (Rothbart, Ahadi, & Evans, 2000).

3.2.2 Surgency

Surgency is the trait aspect of temperament in which a child tends toward high activity and impulsivity, low shyness and enjoyment of highly intense activities. In observational studies, surgency can be seen by the age of two to three months, in a cluster of behaviours involving vocal activity, motor movement, and positive affect (Kistiakovskaia, 1965; Rothbart, Derryberry & Hershey, 2000; Rothbart & Putnam, 2002 in Pulkkinen & Caspi, 2002).

In terms of stability of individual differences in surgency, it has been shown that individuals that score high on aspects of surgency (for example approach to low-intensity toys) in infancy also score high on the temperament trait of impulsivity at seven years (Rothbart, Derryberry et al., 2000). Individual differences in surgency are manifested in terms of individual variation in orientation to and exploration of novelty as well as expressions of positive affect; however when rewards are blocked, high levels of surgency may also lead to high levels of aggression to overcome obstacles—as such, in line with other

temperament traits (for example fear) high surgency may result in both costs and benefits for an individual (Rothbart & Putnam, 2002).

Some studies have examined the relationship between surgency and behaviour. For example, Berdan, Keane and Calkins (2008) examined the degree to which individual differences in surgency predict externalising behavioural problems in early childhood. The results demonstrated that surgency in pre-kindergarten children explained approximately 11% of the variance in hyperactivity in kindergarten years; importantly individual differences in surgency were stable with pre-kindergarden and kindergarten surgency correlating significantly ($r = .81$, $p < .001$; Berdan et al., 2008).

3.2.3 Effortful Control, executive attention and the behavioural traits of hyperactivity and inattention

This section will show the connection between the executive attention system with attention deficit hyperactivity disorder (ADHD) and the behavioural traits of hyperactivity and inattention.

Effortful control has been found to correlate negatively with impulsivity (Eisenberg et al., 2005) and hyperactivity (Gusdorf, Karreman, van Aken, Dekovic &Tuijl, 2011) and to differentiate reliably between typically developing children and children with Attention Deficit Hyperactivity Disorder (ADHD), with the latter scoring significantly lower on measures of effortful control (Samyn, Roeyers & Bijttebier, 2011).

Attention deficit hyperactivity disorder (ADHD) is a condition characterized by symptoms of *hyperactivity* and *inattention*; these behaviours are thought to lie on a continuum with normal variation in attention and activity level in the general population (Larsson et al, 2012). Executive attention is impaired in

children with ADHD (Dovis, Oord, Wiers & Prins, 2013). A meta-analysis of 83 studies that administered executive functioning measures to a group with ADHD reported that individuals with ADHD showed significant deficits on all executive functioning measures with one of the most prominent and consistent effects observed on measures of response inhibition and planning (Willcutt, Doyle, Nigg, Faraone & Pennington, 2005).

During visual tasks, children with ADHD have difficulties inhibiting responses to salient stimuli and sustaining attention on task-relevant stimuli (Karatekin & Asarnow, 1999). In a video-based eye monitor study, children with ADHD exhibited a trend towards shorter fixations (Karatekin & Asarnow, 1999). Their reduced ability to sustain attention was demonstrated in a study that required children with ADHD to view two televised stories either in the presence of toys in the room or without toys, and to answer causal relations questions regarding the stories. The direction of the child's gaze was recorded with a video camera. In the toy-presence condition, children with ADHD answered significantly fewer questions in comparison to typically developing children indicating the group's reduced ability to spend time in long looks in order to follow the continuity of the story (Lorsch et al., 2004). Finally an electrooculography (EOG) study found that, in comparison to typically developing individuals, individuals with ADHD exhibited difficulties suppressing intrusive saccades in a task that required them to maintain steady fixation (Munoz, Armstrong, Hampton &Moore, 2003).

If these findings extend to the continuous traits of hyperactivity and inattention in the general population, it would predict that hyperactivity and inattention would negatively correlate with mean fixation duration.

3.2.4 The current study

The current study is the first to use eye-tracking combined with a longitudinal design to investigate the degree to which individual differences in infants' attention relates to individual differences in parent report measures of effortful control, surgency and hyperactivity-inattention in childhood.

Based on the evidence from the aforementioned studies, it was hypothesised that mean fixation duration in infancy would be: 1) positively associated with effortful control in childhood; 2) negatively associated with surgency in childhood and 3) negatively associated with hyperactivity-inattention in childhood.

3.3 Methodology

3.3.1 Sample and procedure

The participant pool comprised of 271 children (141 males, 130 females), born between March 2008 and December 2010, who took part in three eye-tracking studies, when they were between 4- and 10-months of age (mean age in months = 7.69, SD = 1.90). The eye tracking studies were conducted by Dr. Rachel Wu under the supervision of Dr. Natasha Kirkham at Birkbeck's Babylab. Eye tracking offers the opportunity to study infants' attention; it is a non-invasive technique that has much higher spatial (~1° of visual angle) and temporal resolution (50 Hz for the Tobii 1750 used in this study) in comparison to video coding. Most eye-tracking setups are non-invasive and simple to use with infant participants. Especially with table-mounted setups, eye-trackers are infant friendly because they tolerate head and body movements and, in most cases, do not involve attaching anything to the infant. These characteristics open the possibility of analysing in detail how infant attention is allocated through individual fixations

(Wass et al., 2013).

The questionnaire data that were collected at follow up and the novel analysis of the eye tracking data reported here has been conducted by the thesis' author.

The contact details of the parents of the infants were found from the existing database at Birkbeck's Babylab. The parents were invited to participate in the present study by e-mail, telephone, and post between February 2012 and May 2012. Prior to participation infants were assigned a unique identification number and their names did not appear on either the questionnaire booklet or the file containing their eye tracking data. One hundred and seventy two participants accepted the invitation (response rate = 63.5%). Following the acceptance of the invitation, they were posted an information sheet, which provided them with details regarding the study's aims, two copies of a consent form and a questionnaire booklet (*genetic data was also collected; please see relevant section in Chapter 5*). Parents posted back the questionnaire booklet and a signed copy of the consent form using a prepaid envelope. Fifty-one participants did not return questionnaires. One participant was excluded from the analysis because of insufficient eye tracking data.

One hundred and twenty participants (55 males, 65 females; mean age of the children in months when the parents competed the questionnaire = 41.59, SD = 9.83) took part in the present study. The project was granted ethical approval by the Department of Psychological Sciences, Birkbeck University of London's departmental ethics committee.

3.3.2 Eye tracking studies apparatus

The thesis' author did not contribute to the eyetracking studies; the studies

were conducted by Dr Rachel Wu under the supervision of Dr Natasha Kirkham. A description of the eye tracking studies and apparatus used by Wu and collegues, is given here in order for the reader to have a clear understanding of the eye tracking data that were subsequently analysed by the thesis' author.

The eye tracking studies' apparatus was common across all three studies. Specifically, the experimental room was 18 ft x 8 ft, with a curtain partitioning the control area and the infant area. The control area was located in the back half of the room, while the infant area was in the front half. Overhead light levels were constant throughout the experiment to reduce tracking errors based on changes in pupil size due to changes in overhead lighting. Infants were seated 50 cm away from the monitor attached to the eye-tracker; they were either strapped in a car seat or sat on their caregiver's lap depending on what the caregiver reported was the infant's preference (Wu, 2011).

Across all three studies, the infants' looks were monitored with a Tobii 1750 eye-tracker (Tobii Technology, Danderyd, Sweden, 2003). The Tobbii 1750 table-mounted unit uses a common corneal-reflection procedure to track eye movements. A corneal reflection eye-tracking unit requires a near-infrared light source, a camera with image sensors, and image processing hardware. When the near-infrared light shines into the eyes, it creates visible reflections on the eyes that can be recorded with the camera. Although the eyes can reflect the light in many ways, two key reflections are obtained: One from the surface of the cornea (referred to as the first Purkinje image) and the other from the pupil. The reflection from the surface of the cornea is smaller than the pupil reflection and located below the pupil. The relationship between the corneal reflection and pupil reflection can indicate the specific direction and location of the gaze. The Tobii

1750 eye-tracker unit contained one camera and near-infrared light-emitting-diodes to record movements from both eyes. Data samples were recorded at 50Hz (50 samples per second; Wu, 2011).

Infants were calibrated with the standard 5-point Tobii infant calibration procedure in the four corners and centre of the screen (Senju & Csibra, 2008). The vast majority of infants were properly calibrated after two or three attempts. The calibration procedure ranged from one to three minutes (Wu, 2011).

All stimuli were presented on a 17-inch monitor (resolution was set to 600 x 800 pixels) attached to the eye-tracker. Infants were shown dynamic stimuli (i.e., Bert and Ernie from Sesame Street, bouncing rattle, dragon, or keys) that moved within a 10 cm x 8.25 cm area in the four corners and centre of the screen until they fixated each location. Each block consisted of six familiarization trials and two test trials. Each trial was played to the end (not infant-controlled). Presentation of all trials was spliced with attention-getters, which were movies displaying stationary kaleidoscopic shapes on a black background with salient ring sounds that were meant to attract the infants' attention back to the screen. Attention-getters were set to loop until a key press by the experimenter. When the participants looked at the centre for approximately 1.5 seconds, the attention getter was turned off and the next trial was presented (Wu, 2011).

3.3.3 Eye tracking studies

Collectively, the studies investigated which cues are most useful for infants' learning about the structure of the environment. Infants learned from different attention cues or no attention cues about multimodal objects (Wu & Kirkham, 2010; Wu, Tummeltshammer, Gliga, & Kirkham, 2014) and about statistically coherent shapes (Wu, Gopnik, Richardson, & Kirkham, 2011).

3.3.3.1 Wu and Kirkham (2010). Fifty-six participants in the current study derived from the Wu and Kirkham (2010) study. The study aimed to investigate how infants learned from different attention cues or no attention cues about multimodal objects. Four- and 8-month-olds were eye-tracked in the face cue condition, which showed a social cue (a young Caucasian woman) that turned to one of two identical multimodal events. The simultaneously presented multimodal events served as the noisy environment within which infants needed to choose where to focus their attention. Infants saw pairs of audiovisual events (two orange toy cats or two blue toy dogs), contained within white frames on a black background and moving in synchrony to associate sounds in diagonally opposite corners. Prior to these multimodal objects the social cue (only the woman's neck and head were presented) looked at infants and said "*Hi baby, look at this*!" and then turned to look down at either the lower left or lower right corner of the screen. The woman's turned smiling face remained on the screen while the multimodal events appeared and played for 6 seconds (Wu & Kirkham, 2010). In the second and third condition the social cue (woman) was either substituted by a flashing square wrapped around the target frame, or there was no cue, respectively. During intermittent test trials, the infants were presented with four blank frames and a sound previously paired with an object to measure whether they could anticipate (hence learn) the associated object's appearance (Wu & Kirkham, 2010).

3.3.3.2 Wu et al. (2011). Thirty participants in the current study derived from Wu, Gopnik, Richardson, and Kirkham, (2011). In this study infants saw sequences of looming statistically coherent shapes appearing in one of two white frames in the bottom corners of the screen. In two conditions, the social cue

(Caucasian woman) identical to that from Wu and Kirkham (2010) directed infants' attention to a particular frame in the bottom corner of the screen with or without (depending on the condition) the presence of a distractor. In two other conditions, the shapes were presented to a particular frame in the bottom corner of the screen with or without (depending on the condition) the presence of a distractor but there was not a social cue (Caucasian woman) to guide infants' attention (Wu, et al, 2011).

3.3.3.3 Wu et al. (2014). Thirty-four participants in the current study derived from Wu, Tummeltshammer, Gliga, & Kirkham, (2014). This study presented similar stimuli to those from Wu and Kirkham (2010). In one condition, the social cue (Caucasian woman) did not turn to a particular corner to guide infants' attention – it froze with a smile looking at the infant after it spoke. In another condition, a different central stimulus was presented immediately before the audio-visual events and the red flashing squares: Instead of the social cue (Caucasian woman) providing ostensive signals, a new group of infants saw a video of two Sesame Street puppets interacting with each other. And, in a third condition, there were no social cues; infants were presented with identical stimuli as in the first condition, with one critical difference—the absence of ostensive signals during the training phase. In all three conditions, infants also were exposed to a second set of trials (doubling the length of the experimental session compared to Wu & Kirkham, 2010) with only the multimodal events and flashing squares (Wu et al., 2014).

3.3.4 Eye tracking derived measure

Fixation duration was extracted from the infants' raw eye tracking data that included information on periods during which the infants' eyes were stable,

periods during which the velocity of the gaze was high and periods when gaze was lost due to blinks. All stages of the analysis that is presented below were carried out by the thesis' author.

At the initial stage of the analysis a standard dispersal based algorithm designed for processing adult eye tracking data was applied to the infant data. This algorithm is the fixation detection algorithm supplied with Clearview 2.7 (Tobii Eye Tracker User Manual, 2006) at the default settings (dispersal threshold of 30 pixels [corresponding to 0.9°] and a minimum temporal duration of 100 ms; Wass et al., 2013).

It has been shown that there are several issues when using standard dispersal based algorithms to identify fixations in infants' eye tracking data (Wass et al., 2013). Specifically, most of those algorithms treat an instance in which contact with the eye-tracker was lost during a fixation as signalling the end of that fixation. Flickery data may, therefore, lead to the storing of multiple separate fixations, whereas in fact they are part of one long fixation (Wass et al., 2013). In addition, most algorithms operate via a velocity threshold, according to which a fixation is treated as ending following an increase in velocity above a certain velocity threshold. Noisy infants' eye tracking data can result in an increase in the velocity that exceeds the saccade detection threshold, which leads to multiple incomplete fixations to be stored, instead of one long fixation (Wass et al., 2013). These issues reflect potentially serious confounds that reduce the accurate detection of fixation duration in infants' eye tracking data that are characterized by both flicker contact with the eye-tracker and lower precision in the reported point of gaze (Wass et al., 2013).

3.3.4.1 Dealing with low quality infants' eye tracking data. In order to

deal with such issues, fixation detection was performed using a two-stage approach. First, Matlab scripts (The MathWorks, Natick, MA) designed by Wass and collegues (2013) specifically to cope with low quality infant data were used to detect fixations. Briefly, the scripts use a bilateral filtering algorithm written by Ed Vul (Frank, Vul, & Johnson, 2009; based on those by Durand & Dorsey, 2002) to smooth the data; they interpolate the data in order to fill periods of data loss up to 150ms; they perform velocity thresholding by using a velocity threshold of 35˚/sec; they only keep as "real" fixations, those that meet the following criteria: a) fixation is a complete fixation. Complete fixations are those that are begun and ended by a saccade, rather than a smooth pursuit, or blink; incomplete fixations were excluded from any further analysis); b) displacement since previous fixation is >0.25˚; c) average velocity during previous fixation is < 12˚/sec; d) velocity in the three samples immediately preceding the saccade is < 12˚/sec; e) binocular disparity is not above 3.6˚; f) the fixation identified has a minimum temporal duration of 100ms (Wass et al., 2013). Only 33% of the fixations detected by the standard-dispersal algorithms passed the stringent quality control of Wass et al., (2013) algorithms (mean N of fixations per individual = 147; SD = 103).

Subsequently, in order to further improve the quality of the data and to correct for the limitation of the algorithms, which is that they are not able to distinguish efficiently between fixations and sections of smooth pursuit, a "supervised" approach was applied to the data derived by the algorithms. This approach consisted of hand moderating the data returned by the algorithms and correcting for sections of smooth pursuit, which have been identified as fixations.

To do that, an in-house fixation detection tool, GraFIX was used (Saez de Urabain, Johnson & Smith, 2014). GraFIX allows variable quality of gaze data to

be accounted for across several stages of both automated and hand moderated processing. In the current analysis GraFIX was used only to hand-moderate the data derived by Wass et al., (2013) algorithms; hand-moderation was performed via inclusion, exclusion or modification of artificial fixations. Using automatic algorithms in combination with GraFIX has been shown to be the most efficient and accurate method for identifying fixations in noisy gaze data like that encountered in infants (Saez de Urabain, Johnson, & Smith, 2014).

On average, sixty-four additional fixations per participant were identified in the hand moderation analysis (mean N of fixations = 211; SD N of fixations = 125). The amount of fixations detected per participant was used as a covariate in the regression analysis. The hand-moderated data were significantly correlated ($r = .54$, $p < .01$) with the data derived by the algorithms (Wass et al., 2013) and were the data used in the regression analysis (*see table 3 for details*).

The reliability of the algorithms used in the analysis has been shown on multiple infants' datasets (see Wass et al., 2013 for details). The significant correlation between the hand-moderated data and the data derived by the algorithms suggests that, while potential errors of the automatic algorithms were corrected (hence why the correlation between the hand moderated data and the data derived by the algorithms was not at unity), the data derived by the hand moderation analysis using GraFIX were not deviating majorly from the original pre-hand-moderated data.

3.3.5 Questionnaires

Eight subscales of the short form of the Early Childhood Behaviour Questionnaire parent report (ECBQ; Putnam, Jakobs, Gartstein & Rothbart, 2010) that load onto two factors, namely effortful control and surgency, were employed

to assess temperament in preschool age children (19-36 months of age). The scores on the ECBQ scale of effortful control represented the average score of the ECBQ subscales of attentional focusing (6 items), inhibitory control (6 items), low-intensity pleasure (6 items) and perceptual sensitivity (5 items). The scores on the ECBQ scale of surgency represented the average score of the ECBQ subscales of activity level (8 items), high-intensity pleasure (6 items), impulsivity (4 items) and shyness (5 items reversed)). The rater reported the frequency of a particular behaviour (example question for effortful control: "Your child can wait before entering into new activities if s/he is asked to; example question for surgency: "Your child likes to play so wild and recklessly that he/she might get hurt."), on a seven-point scale (ranging from "never" to "always") and the subscales scores represented the mean score of all items applicable to the child. The ECBQ scales of effortful control and surgency showed excellent internal consistency (Cronbach's alphas = .86 and .85, respectively).

The equivalent eight subscales of the short form of the Childhood Behaviour Questionnaire parent report (CBQ; Putnam & Rothbart, 2006) were employed to assess effortful control and surgency in school age children (36-58 months of age). The scores on the CBQ scales of effortful control and surgency represented the average score of the same subscales as for the ECBQ. The CBQ scales of effortful control and surgency showed excellent internal consistency (Cronbach's alphas = .81 and .89, respectively).

The mean instead of the sum score of the items was used to ensure that missing data (ECBQ missing data = 3.34%; CBQ missing data = 3.76%) would not affect the scales' final score.

To assess hyperactivity-inattention in preschool children the Revised

Rutter Parent Scale for Preschool Children parent report (RRPSPC; Hogg et al., 1997) was used. The RRPSPC hyperactivity-inattention scale consisted of 4 items and the rater reported on the frequency of a particular behaviour (e.g. "Restless; runs about or jumps up and down, doesn't keep still") on a three-point scale ("not true"; "sometimes true"; "certainly true").

To assess hyperactivity-inattention in school age children the SDQ hyperactivity-inattention scale parent report version of the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) was employed. The SDQ hyperactivity-inattention scale consisted on 5 items that are of identical format to the RRPSPC and it is a reliable and valid measure of hyperactivity-inattention of children age 3 to 16 year olds (Goodman, 1997).

The SDQ and RRPSPC scales of hyperactivity-inattention showed good and moderate internal consistency respectively (Cronbach's alphas = .76 and .54, respectively; RRPSPC missing data = 2.22%; SDQ missing data = 2.63%).

3.3.6 Statistical analyses

3.3.6.1 Descriptive statistics. Mean fixation duration and the questionnaire data were explored using descriptive statistics in SPSS version 18.0. Due to skewness of the data, Van der Waerden's transformation (Lehmann, 1975) was used to normalise the data before further statistical analyses were undertaken. Analysis of Variance (ANOVA) was performed to test for significant mean sex differences (at $p < .01$).

3.3.6.2 Correlations. Partial correlations were performed to test for significant correlations (at $p < .05$) between the questionnaire scales of effortful control, surgency and hyperactivity-inattention. Sex and age of the child when the parents completed the questionnaires were used as covariates. In addition,

whether the preschool or school age versions of the questionnaires were used was included as a covariate in the analysis.

3.3.6.3 Regressions. Multiple linear regression was performed to test for significant associations (at $p < .05$) between mean fixation duration in infancy with effortful control, surgency and hyperactivity-inattention in childhood. The effects of age when the child took part in the eye tracking study and the age of the child when the parents completed the questionnaire, the type of the questionnaire booklet, sex, total number of trials (completed by participants in the eye-tracking studies) and total number of fixations detected were treated as covariates in the regression analysis in order to investigate to what degree variation in fixation duration in infancy accounted for variation in scores on effortful control, surgency and hyperactivity-inattention in childhood. The current analyses disregarded the stimulus differences and the location of fixations on the screen (in line with Wass et al., 2014). While the stimuli across all experimental conditions were very similar, the particular condition that each individual took part in the eye tracking studies was treated as covariate in the regression analysis to address any differences based on stimulus presentation.

Finally, the multiplicative effect of infant fixation duration and age of the infant (interaction effect between fixation duration and age of the infant) on explaining variation in effortful control, surgency and hyperactivity-inattention was explored using a moderated multiple regression model (Baron & Kenny, 1986). All variables (covariates and main variables) were added to the model. Fixation duration and age were centered (subtract the mean from all scores) before calculating their product to avoid collinearity issues (i.e. avoid strong correlation between the interaction term and the variables from which it is

calculated).

3.4 Results

3.4.1 Descriptive statistics

Descriptive statistics for mean fixation duration and for the scales of effortful control, surgency and hyperactivity-inattention are shown in Table 3.1. Table 3.2 presents the descriptive statistics for the ECBQ and CBQ scales of effortful control and surgency and the RRPSPC and SDQ scales of hyperactivity-inattention.

Table 3.1. Descriptive statistics for mean fixation duration, effortful control, surgency and hyperactivity-inattention for all participants

	N = 120 (19-58 months of age)			
	Mean Fixation Duration	Effortful Control	Surgency	Hyperactivity-Inattention
N	120	120	120	120
Mean	.70	5.34	4.59	2.76
SD	.12	.64	.78	2.01
Median	.69	5.35	4.55	2.00
Mode	.48	5.42	4.52	2.00
Minimum	.48	3.90	2.64	0.00
Maximum	1.16	6.59	6.72	10.00
Kurtosis	2.54	-.50	.36	1.56
Skewness	1.19	-.03	-.05	1.08

Table 3.2. Descriptive statistics for CBQ and ECBQ scales of effortful control and surgency and SDQ and RRPSPC scales of hyperactivity-inattention

	CBQ and SDQ scales (N = 91) 36-58 months of age			**ECBQ and RRPSPC scales (N = 29) 19-36 months of age**		
	Effortful Control	Surgency	Hyperactivity-Inattention	Effortful Control	Surgency	Hyperactivity-Inattention
N	91	91	91	29	29	29
Mean	5.51	4.54	2.67	4.80	4.76	3.06
SD	.58	.84	2.15	.51	.49	1.48
Median	5.51	4.52	2.00	4.86	4.73	3.00
Mode	5.42	4.52	2.00	5.33	4.00	2.00
Minimum	4.11	2.64	.00	4.03	2.92	.00
Maximum	6.59	6.72	10.00	6.59	6.22	9.00
Kurtosis	-.43	-.09	1.75	-.98	-.44	-1.16
Skewness	-.06	.04	1,26	.02	.39	-0.05
Cronbach's alpha	.81	.89	.76	.86	.85	.54

Figures 3.1 display the histogram for infant mean fixation duration; Figures 3.2 to 3.4 display the histograms for child effortful control, surgency and hyperactivity-inattention, respectively.

Figure 3.1. Histogram for mean fixation duration (N=120; 4-10 months)

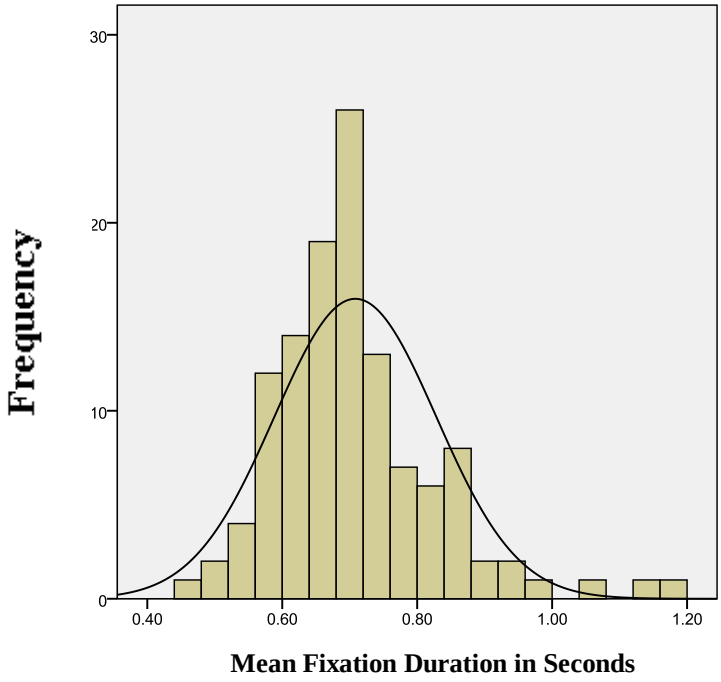


Figure 3.2. Histogram for effortful control (N=120; 19-58 months)

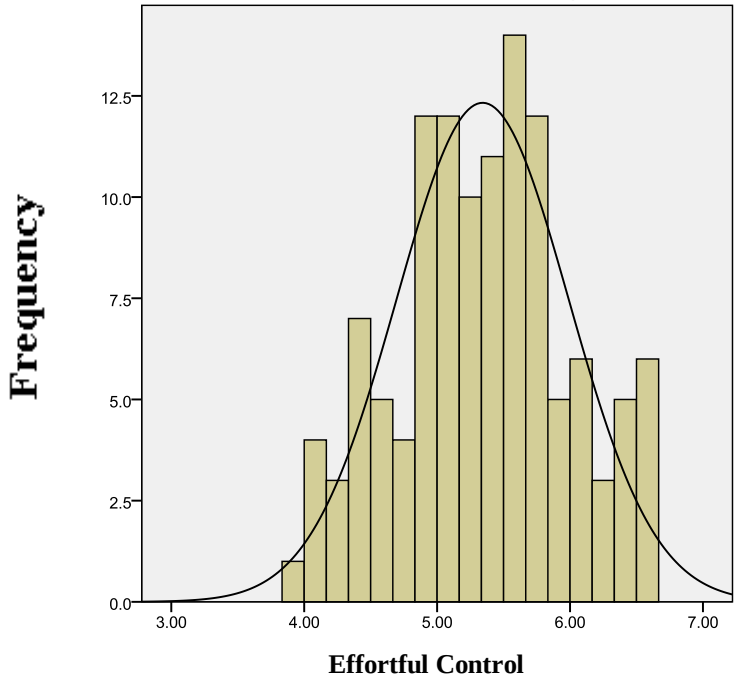


Figure 3.3. Histogram for surgency (N=120; 19-58 months)

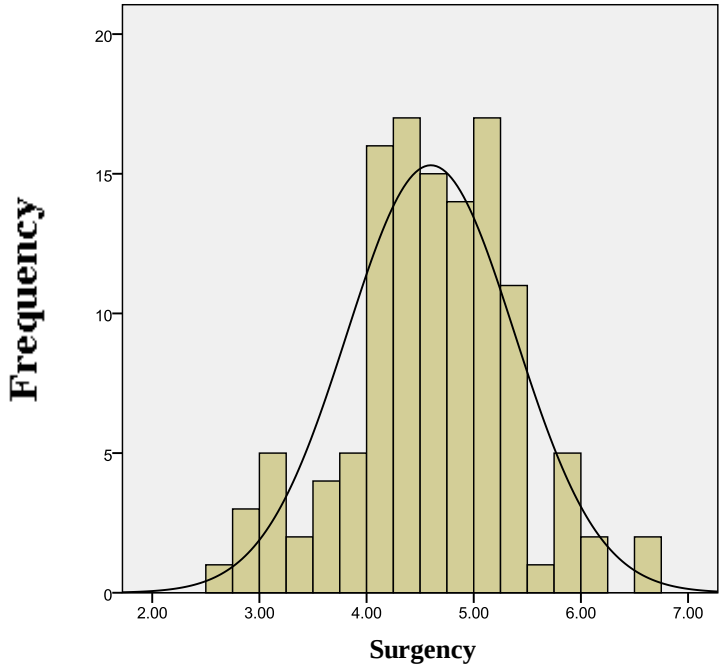


Figure 3.4. Histogram for hyperactivity-inattention (N=120; 19-58 months)

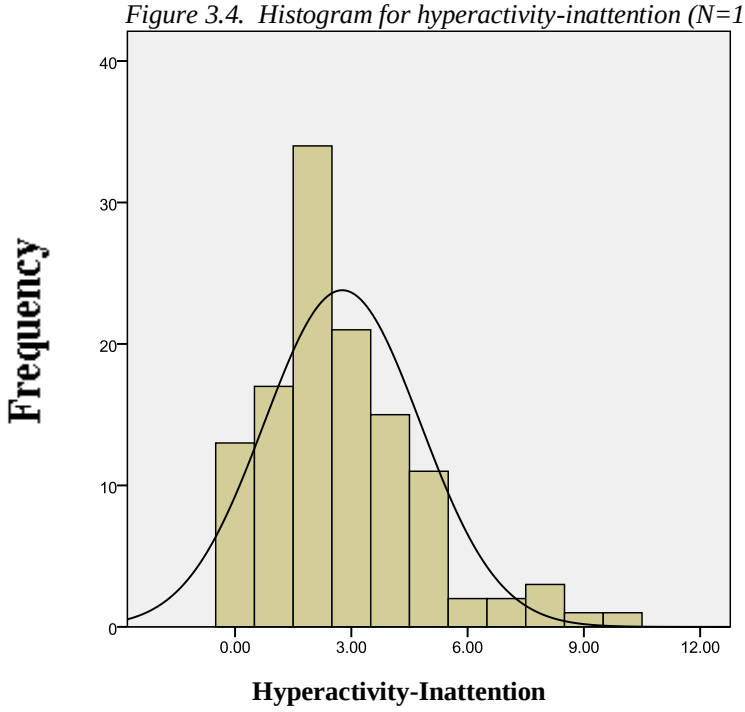


Figure 3.5 presents the distribution of fixations for all participants after running standard dispersal based algorithms to detect fixations; Figure 3.6 presents the distribution of fixations for all participants once the two stage quality control was applied (Wass et al., 2013 algorithms and hand-moderation using

GraFIX; Saez de Urabain et al., 2014). Figures 3.5 and 3.6 differ from Figure 3.1 in that they represent the distribution of all individual fixations that were detected per participant. Figure 3.1 represents the distribution of mean fixation duration.

Fig 3.5 Distribution of fixations after running standard dispersal based algorithms

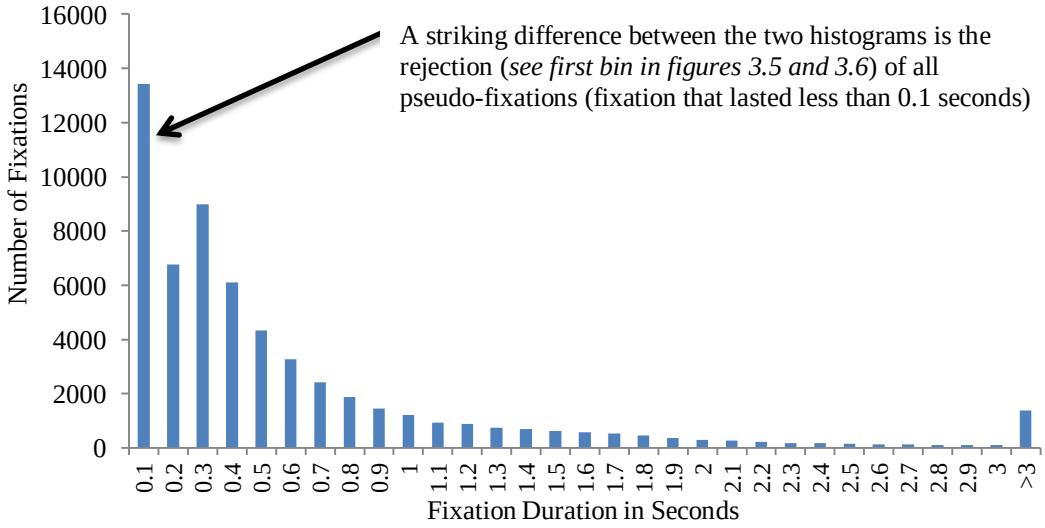


Fig 3.6. Distribution of fixations after first and second stage of quality control (Wass et al., 2013 algorithms and Hand-Moderation usign GraFix)

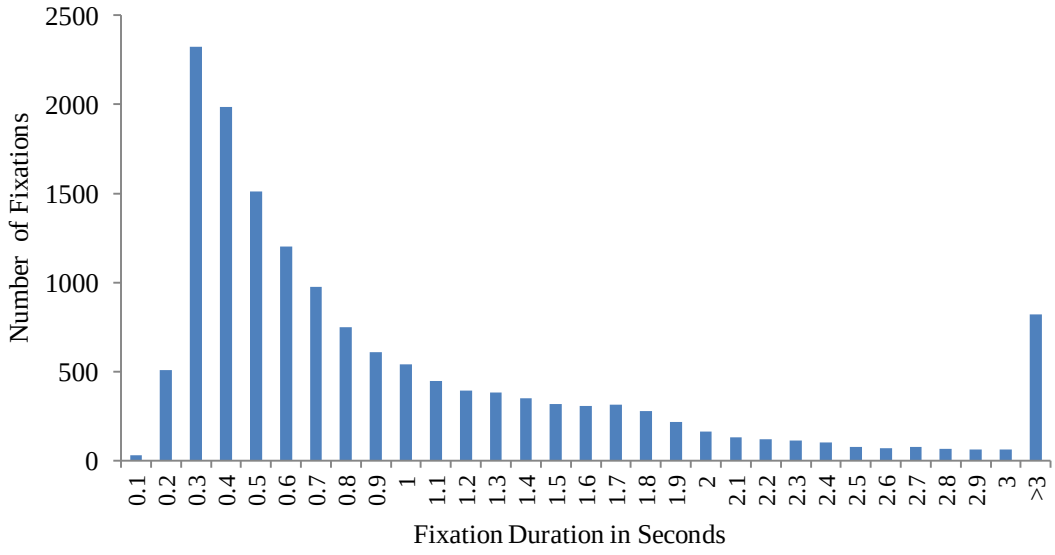


Table 3.3 presents the correlations between mean fixation duration prior to quality control, mean fixation duration detected using Wass et al., (2013) algorithms and mean fixation duration after the second stage of quality control (hand moderation of the data derived by Wass et al., 2013 using GraFIX; Saez de Urabain et al., 2014).

Table 3.3 Correlation between mean fixation duration derived from different stages of the analysis

	N = 120 (4 to 10 months of age)		
	Standard dispersal based algorithms	**Wass et al., 2013 Algorithms (1st stage)**	**Hand-Moderated data using GraFix (2nd stage)**
Standard dispersal based algorithms	-	.36**	.005*
Wass et al., 2013 Algorithms (1st stage)	.36**	-	.54**
Hand-Moderated data using GraFix (2nd stage)	.005*	.54**	-

‘ *p < 0.01, * p < 0.05*

3.4.2 Sex differences

No statistically significant sex differences were observed for mean fixation duration, effortful control, surgency and hyperactivity-inattention. Table 3.4 presents the mean sex differences analyses.

Table 3.4. Mean sex differences on mean fixation duration, effortful control, surgency and hyperactivity-inattention

N=120 (19-58 months)	**Male (N = 55)**		**Female (N = 65)**					
	M	**SD**	**M**	**SD**	**F**	**df**	**p-value**	**Partial η^2**
Mean Fixation Duration	.70	.13	.71	.10	.01	1, 113	.90	.000
Effortful Control	5.25	.59	5.41	.68	3.30	1, 116	.07	.02
Surgency	4.60	.87	4.59	.69	.02	1, 116	.87	.000
Hyperactivity-Inattention	2.80	1.81	2.73	2.17	.04	1, 116	.83	.000

3.4.3 Infant age and mean fixation duration

To explore the effect of infant age on infant fixation duration, a regression analysis was performed with infants' age (continuous variable measured in months) as an independent variable and infants' mean fixation duration as dependent variable. The condition in which each participant took part in the eye tracking study, sex, number of fixations detected and number of trials that participants took part in the eye tracking study were treated as covariates. Age of the infant did not significantly associate (at $p < .05$) with mean fixation duration ($\beta = .23$, $R^2 = .01$, $p = .07$).

3.4.4 Correlations between effortful control, surgency and hyperactivity-inattention in childhood

Correlations between effortful control, surgency and hyperactivity-inattention are shown in Table 3.5 for all groups. As expected effortful control was correlated negatively (at $p < .05$) with surgency ($r = -.17$, $p = .05$) and hyperactivity-inattention ($r = -.52$, $p < .001$). Surgency was correlated positively with hyperactivity-inattention ($r = .26$, $p < .001$).

Table 3.5. Correlations between effortful control, surgency and hyperactivity-inattention in childhood

	N = 120 (19-58 months of age)		
	Effortful Control	Surgency	Hyperactivity-Inattention
Effortful Control	1.00	-.17*	-.52**
Surgency	-.17*	1.00	.26**
Hyperactivity-Inattention	-.52**	.26**	1.00

‘ *p < 0.01, * p < 0.05*

3.4.5 Multiple linear regression between mean fixation duration in infancy and effortful control, surgency and hyperactivity-inattention in childhood

The results of the multiple linear regression for mean fixation duration in infancy (independent variable) with effortful control, surgency and hyperactivity-inattention in later childhood (dependent variables) are shown in Table 3.6. In line with the hypotheses, mean fixation duration was associated positively (at $p < .05$ given that each hypothesis was tested separately) with effortful control ($\beta = .20$, $R^2 = .02$, $p = .04$) and negatively with surgency ($\beta = -.37$, $R^2 = .07$, $p = .003$) and hyperactivity-inattention ($\beta = -.35$, $R^2 = .06$, $p = .005$).

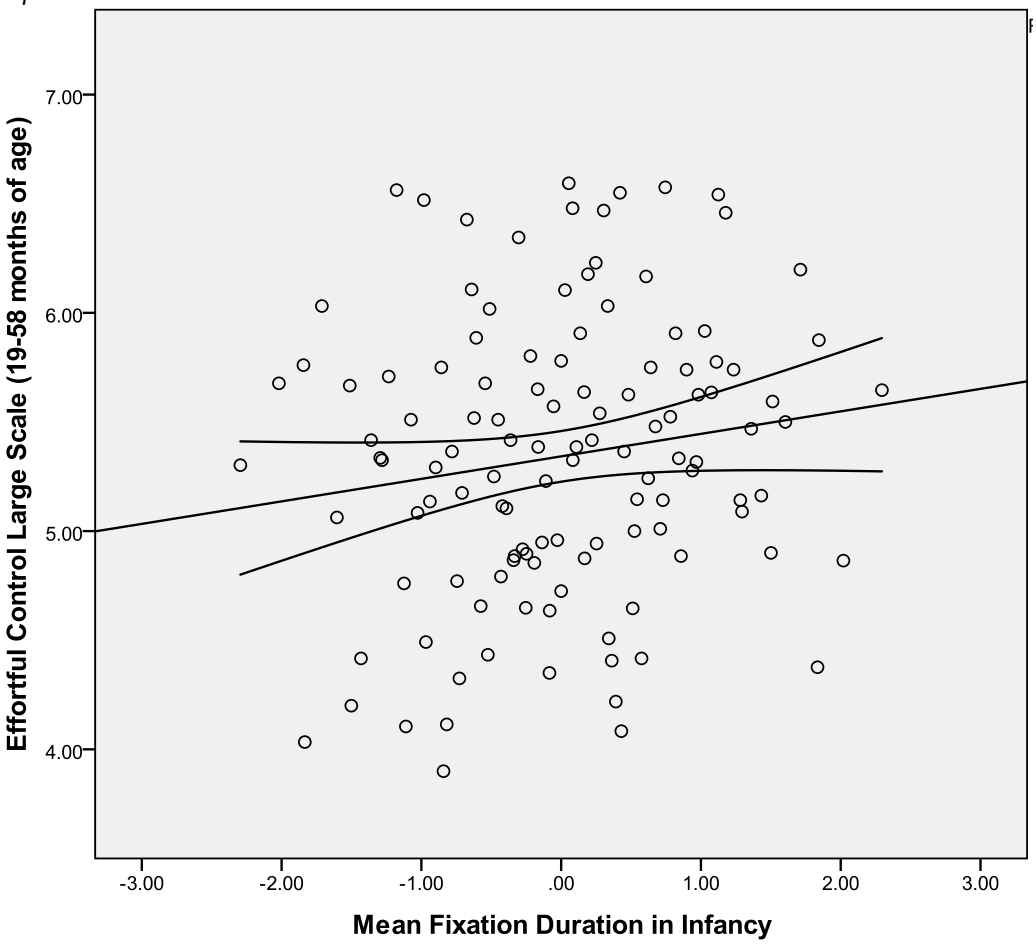
Table 3.6. Linear regressions between mean fixation duration in infancy and effortful control, surgency and hyperactivity-inattention

N=120							
Independent Variable: Mean Fixation Duration							
Dependent Variable	B	β	t	95% CI for β Lower Bound	95% CI for β Upper Bound	R^2	p-value
Effortful Control	.14	.20	2.00	.001	.28	.02	.04
Surgency	-.30	-.37	-3.05	-.51	-.10	.07	.003
Hyperactivity-Inattention	-.76	-.35	-2.90	-1.28	-.24	.06	.005

Note: The "B" and "β" refer to the unstandardised and standardized regression coefficients respectively followed by the "t-statistic". The "R^2" represents the variance explained by the independent variable on the dependent variables after regressing out the effect of the covariates; finally, the p-value represents the value of statistical significance of the effect of the independent variable on the dependent variables, while keeping constant the effect of the covariates.

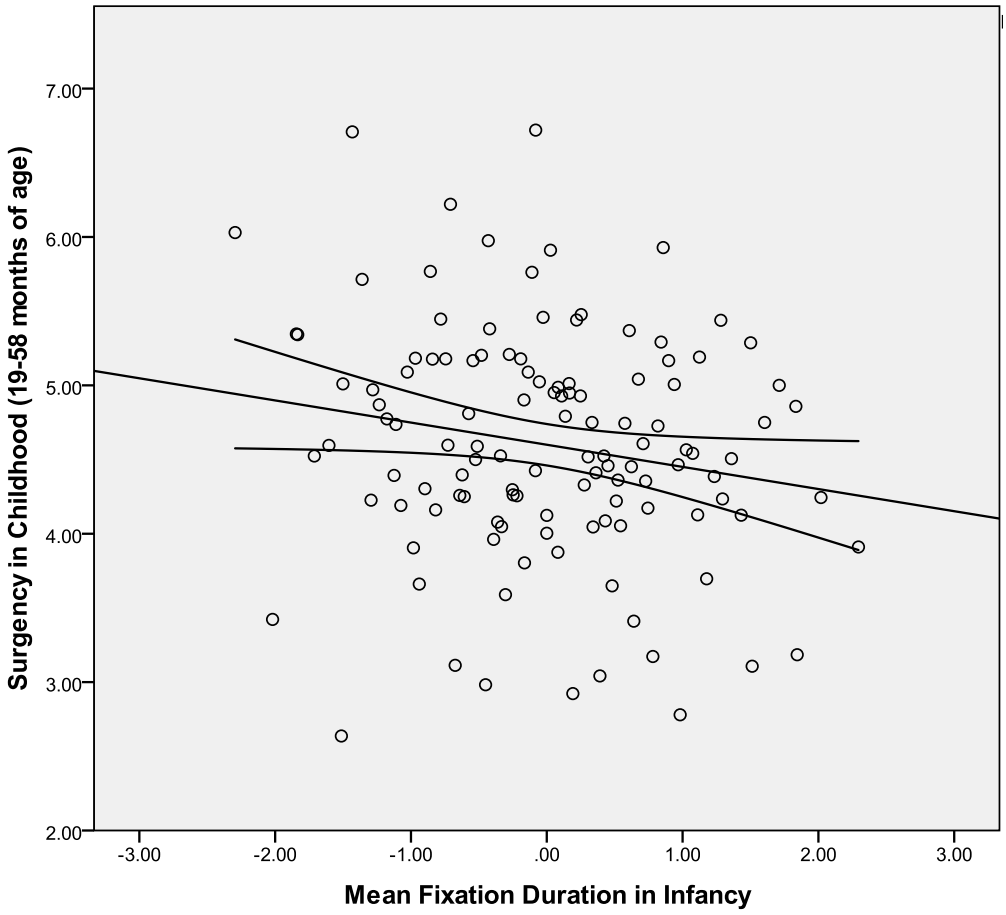
Scatter plots for the reported associations are shown in Figures 3.7, Figure 3.8 and Figure 3.9 for effortful control, surgency and hyperactivity-inattention, respectively.

Figure 3.7. Scatter plot showing the relationship between mean fixation duration in infancy and effortful control in childhood. The x-axis represents the normalised scores of individual mean fixation duration.



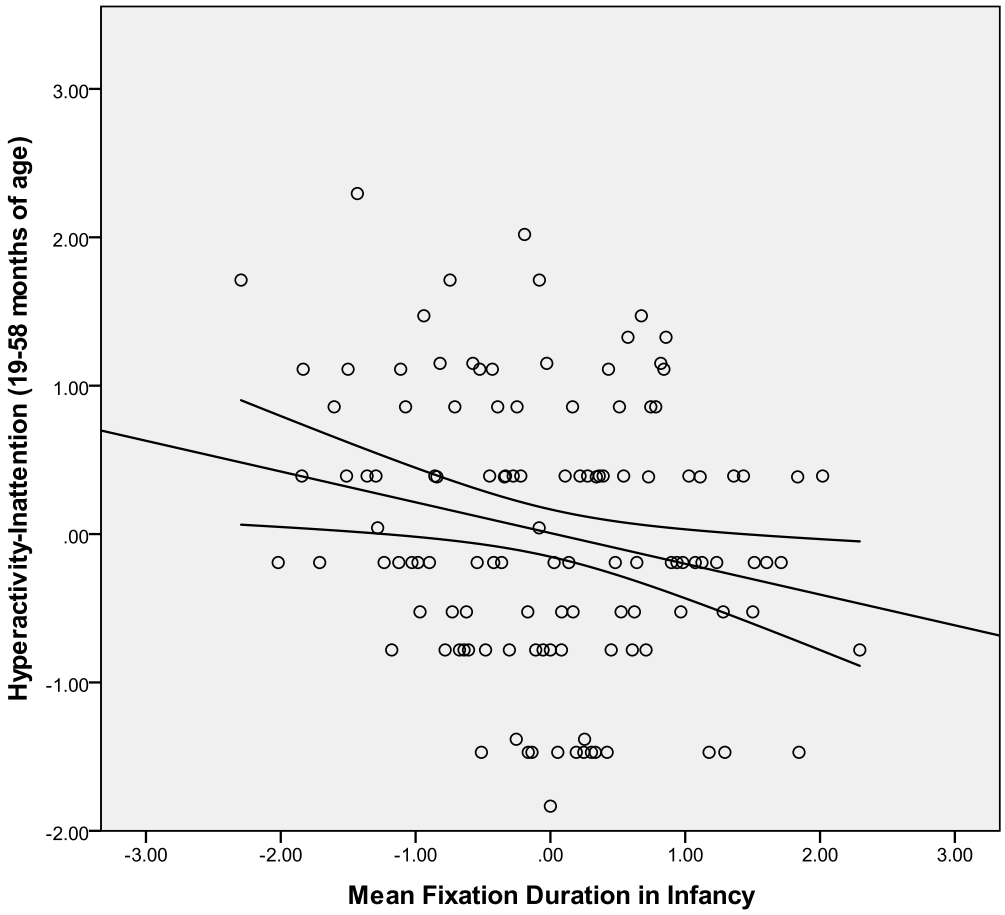
The line represents the best fit line of the model and the confidence bands surrounding the line represent the confidence intervals of the best fit line

Figure 3.8. Scatter plot showing the relationship between mean fixation duration in infancy and surgency in childhood. The x-axis represents the normalised scores of individual mean fixation duration.



The line represents the best fit line of the model and the confidence bands surrounding the line represent the confidence intervals of the best fit line

Figure 3.9. Scatter plot showing the relationship between mean fixation duration in infancy and hyperactivity-inattention in childhood. The x-axis represents the normalised scores of individual mean fixation duration.



The line represents the best fit line of the model and the confidence bands surrounding the line represent the confidence intervals of the best fit line

3.4.6 Multiple linear regression between mean fixation duration x infant age on effortful control, surgency and hyperactivity-inattention in childhood

To shed light on the developmental mechanisms that link attention in infancy to temperament and behaviour in childhood, the interactive effect of infant fixation duration and age of the infant (fixation duration x infant age) on explaining variation in effortful control, surgency and hyperactivity-inattention was explored.

Table 3.7 presents the results of the regression model. A significant interaction effect between mean fixation duration and infant's age on childhood surgency was observed. Fixation duration x infant age interaction was significantly associated with surgency in childhood (β = -.20, R^2 = .03, p = .05). The result suggests that the direction of the association between mean fixation duration and surgency remains the same (negative), irrespective of the age of the infant; the fact that the association is significant suggests that the variance of childhood surgency accounted for by variation in infant fixation duration increases as the age of the infant increases.

Table 3.7. Multiple regression model presenting the multiplicative effect of fixation duration x infant age on effortful control, surgency and hyperactivity-inattention

N=120 (19-58 months of age)							
Independent Variable: Mean Fixation Duration x Infant Age							
Dependent Variable	B	β	t	95% CI for β Lower Bound	95% CI for β Upper Bound	R^2	p-value
Effortful Control	.05	.07	.90	-.06	.18	.005	.36
Surgency	-.17	-.20	-1.92	-.35	.006	.03	.05
Hyperactivity-Inattention	-.07	-.07	-.73	-.29	.13	.004	.46

3.5 Discussion

The aim of this study was to investigate the degree to which individual differences in fixation duration in infancy relate to the temperament domains of effortful control and surgency and the behavioural trait of hyperactivity-inattention in childhood.

As hypothesised, longer mean fixation duration was associated with higher levels of effortful control and lower levels of surgency and hyperactivity-inattention. These findings show for the first time a longitudinal association between infant mean fixation duration (derived from eye-tracking data) and child effortful control, surgency, and hyperactivity-inattention. The reported associations were of moderate magnitude, with the proportion of variance to be explained by mean fixation duration in infancy being 2%, 7% and 6% for child effortful control, surgency and hyperactivity-inattention, respectively. Moderate effects are to be expected given that many factors within a dynamic developmental framework operate to produce individual variability on high-level behaviours (e.g. hyperactivity-inattention; Nigg, 2009).

These findings should be considered in light of some limitations. The Cronbach's alpha reported for the RRPSPC hyperactivity-inattention scale was moderate. There was attrition in the sample due to the longitudinal nature of the study. Nevertheless, the final sample was powered to detect moderate effects and was considerably larger than the sample size of most studies in infant eye tracking research (typically 10-20). Furthermore, there was unavoidable loss of in usable eye tracking data within participants. This was due to fact that infant eye tracking data are generally of poorer quality (less precise and with more lost samples) compared to adult data (Wass et al., 2013).

Because of this, considerable attention was given to ensure that the observed variation per participant reflected individual variation in fixation duration and not noise produced by extraneous components (e.g. data quality). Fixation parsing algorithms, designed specifically to detect fixations in low quality infants' data were employed; and hand moderation was performed to improve the quality of the data used in the regression analysis. This two-stage approach has significant advantages over using fixation detection algorithms or hand coding alone. More specifically, this approach provides stability in the criteria used to detect fixations (in the first stage) and with the flexibility to address limitations of the automatic fixation parsing algorithms in the second stage (hand-moderation). Finally, a limitation of the study was the reliance on parent report of children's behaviour and temperament. While parents are typically most familiar with their children's behaviour, all types of raters include some bias. Future research should consider collecting data from multiple raters or employing additional objective measurements of behaviour.

The findings of the current study demonstrate that mean fixation duration in infancy is linked to some forms of attentional and behavioural control in early childhood. This is of importance considering that, while the temperament trait of surgency emerges in the first year of life, effortful control--the temperament trait that refers to the child's volitional use of executive attentional abilities (Bell & Calkins, 2012) develops in the second and third year of life and beyond, making it difficult to find appropriate measures to assess it in infancy (Rothbart, Sheese & Posner, 2007). As such, studying fixation duration in infancy could have significant implications for understanding the mechanisms through which effortful control--as well as other aspects of executive attention--develop.

Investigating the causes of individual differences in voluntarily control of attention as early as in infancy might inform early intervention practices that will aim to improve aspects of executive attention. Executive attention is an important network for the acquisition of a wide variety of skills (Rothbart et al., 2007). Finally, given the role of effortful control in differentiating typically developing children from children with ADHD (Samyn et al., 2011) and the association between fixation duration in infancy with later effortful control and hyperactivity-inattention, reported here, a tentative idea for future research would be to explore whether fixation duration in infancy could be used to indicate individuals at risk for developing ADHD.

3.5.1 Brief summary and next chapter

The current work has shown that individual differences in infant attention at 4- to 10-months old significantly predicts some forms of temperament and behavioural traits in childhood: the ability to hold fixations for a longer period of time as an infant was predictive of better effortful control, and less surgency and hyperactivity-inattention in later childhood. Although the relationship that was observed between mean fixation duration and temperament was linear (the longer the mean fixation duration the higher the effortful control) it might be possible that having too long fixations might be disadvantageous. Future research could explore whether having significantly longer fixation duration (for example 3 standard deviations above the mean) is associated with lower effortful control.

Finally, an open question is to what degree these individual differences in infant visual attention, which predict individual variation in later temperament and behaviour, develop in the first months of life, perhaps as a result of caregiver and other environmental stimulation, and to what degree they are present at birth.

Chapter 4 will present a study that aimed to answer this question by investigating the degree to which individual differences in newborns' visual attention is predictive of individual variation in effortful control, surgency, hyperactivity-inattention and total behavioural difficulties in childhood.

4 Newborn Attention & Child Temperament & Behaviour

4.1 Chapter's Summary

The previous study has shown that individual differences in infants' mean fixation duration at 4- to 10-months old significantly predicts effortful control, surgency and hyperactivity-inattention in childhood. This second study investigated whether effortful control, surgency and hyperactivity-inattention in childhood can be predicted even earlier, from individual differences in newborns' average duration of gaze to stimuli. Given that in the first study those forms of temperament and behaviour in childhood were associated significantly with attention in infancy, in this second study the link between individual variation in newborns' average dwell time with individual differences in total behavioural difficulties was also explored.

Eighty newborns participated in visual preference and habituation studies. The studies were conducted by Dr. Farroni and her lab in Monfalcone hospital in Italy during the past ten years. Novel analysis was applied by the thesis' author to the previously collected visual data in order to create the attentional measure of newborn's average dwell time at stimuli. The parents of the newborns were invited to participate in the current work by the thesis' author; they completed age appropriate questionnaires at follow up (mean age = 7.5 years, SD = 1.0 year) that assessed their children's effortful control, surgency, hyperactivity-inattention and total behavioural difficulties. The results suggested that individual differences in newborn visual attention significantly associated with individual variation in child surgency and total behavioural difficulties, showing that some of the factors

responsible for this variation are present at birth.

4.2 Introduction

Given that newborns have been exposed to few environmental influences outside the womb, studying neonatal visual attention may facilitate our understanding of causal factors (e.g. prenatal factors and genetic factors) operating at birth to contribute to individual variation in some forms of attention, temperament and behavioural traits later in life. Investigating the causes of individual differences in visual attention as early as in the first hours after birth might inform early intervention practices that will aim to improve aspects of attention, a cornerstone of human cognition. Furthermore such investigation should in theory facilitate the early identification of individuals at risk for developing certain behavioural problems connected to attention difficulties, such as attention deficit hyperactivity disorder (ADHD).

4.2.1 Parameters of newborn and infant attention

As described in detail in chapter 1, the most well studied attentional parameter in infancy (0-12 months) is the measure of look duration. The measure of look duration is usually measured using video cameras. It refers typically to participant's longest time to habituate to a certain stimulus (Colombo et al., 2010). Shorter look duration is associated with better cognition, in theory because it shows that it takes a child less time to process and encode a new stimulus in working memory (Colombo et al., 2010). A different type of parameter that can be measured is the duration of individual eye fixations (typically the periods of relative oculomotor stability between saccadic eye movements) that take place during the 'look' at a stimulus. These individual fixations or saccades can be measured in several ways. Eye tracking offers the highest spatial and temporal

resolution to capture fixation duration, the time between saccadic eye movements (Rayner, 1998).

How are look duration and fixation duration related? Recent evidence suggests that mean fixation duration shows a trend towards a negative association with infants' peak look duration, although this association did not reach statistical significance (Wass & Smith, 2014). As such, the attentional style that is associated with better later cognition appears to be taking less time overall before habituating to a stimulus (i.e. having a shorter peak look duration) and having relatively longer mean fixation duration.

When studying newborns, collecting video coded data presents fewer practical challenges than eye tracking. It is possible from videos to derive a measure of average dwell time. Dwell time is best described as the duration that gaze remains upon individual stimuli (Becker, 2011). In order to process a scene normally, adult viewers needed to foveate the scene for at least 150 milliseconds during each eye fixation (Rayner, Smith, Malcolm & Henderson, 2009). In addition, the duration of fixations can be controlled on-line in an attempt to delay a saccade until encoding has completed (Henderson & Smith, 2009). As such, not all fixations succeed in delaying until encoding is finished. Taken together, these findings indicate that mean fixation duration and average dwell time are linked.

A hypothesis is that, based on the proposed link between fixation duration and dwell time in adults, it may also be the case that fixation duration and dwell time may be also linked in infancy. However, it is noted that there is a developmental change in look duration in the context of a habituation paradigm over the first year of life, with different types of cognitive processing influencing looking durations at different ages (see Colombo et al., 2004). As such, it is

difficult to establish continuity in the relationship between average dwell time and mean fixation duration from infancy to childhood; and there are currently no studies that explored the degree to which those measures are linked across development.

The current work has used dwell time as the best available proxy for fixation duration in a sample of newborns. A proxy measure for fixation duration was selected because the target of this study was to explore how a similar (to the previous study) attentional parameter at birth would link to the same traits in childhood.

4.2.2 Studying newborns' attention

Empirical assessement of newborns' attention in the first days after birth is challenging. There are issues involving the accessibility of the sample; for example mothers typically leave the clinic within two days after they give birth. In addition, the fact that newborns spend most of their time sleeping makes it difficult to assess them when awake to complete the task. Finally newborns' visual system is immature in comparison to older infants; this places several constraints with regard to the tasks to use. Furthermore, there is the challenge of determining the degree to which individual differences in attention are due to differences in the maturation of peripheral structures (for example the eye, the lens and muscles) or to differences in the maturation in the brain.

For example newborns at birth cannot dilate fully their pupils and the curvature of their lenses is spherical. Also their retina is not fully developed, they have some degree of astigmatism, they have poor fixation ability and they have very limited ability to discriminate colours. Finally, they have restricted visual fields and an estimated acuity of somewhere between 20/200 and 20/400. Because

their ability to orient depends upon subcortical rather that cortical brain areas, there is limited orienting to single targets up until the age of 3 months (Farroni & Menon, 2008).

Despite those challenges, investigating individual differences in newborn visual attention is of value considering that the study of a previous developmental stage can shed light on the underlying mechanisms of a later development stage (Papageorgiou & Ronald, 2013). As such, research at birth--the first stage of life when attention can be measured--may be informative for understanding the development of attention as well as the development of the later traits to which attention is linked.

4.2.3 Hypotheses

The current study is the first to evaluate the link between neonatal visual attention and individual differences in effortful control, surgency, hyperactivity-inattention and behavioural difficulties in childhood. The study aimed to test the same hypotheses that were investigated in the study presented in chapter 3. Given that mean fixation duration in infancy is associated with effortful control, surgency and hyperactivity-inattention in childhood (see results of Chapter 3), it was hypothesised that newborns' average dwell time would be positively associated with effortful control in childhood; and negatively associated with surgency and hyperactivity-inattention in childhood. Finally given that surgency, the trait aspect of temperament in which a person tends toward high levels of extraversion, motor activity and impulsivity has been found to predict aggression and externalising behavioural problems in early childhood (Berdan, Keane and Calkins, 2009), it was hypothesised that newborns' average dwell time would be negatively associated with behavioural difficulties in childhood. It was expected

also that the magnitude of the reported associations would be lower than in the previous study since independent and dependent variables were further apart in developmental time (in comparison to the study described in Chapter 3).

4.3 Methodology

4.3.1 Sample and procedure

The participant pool comprised of 151 children, born between 2004 and 2010, who took part in four visual preference and habituation studies carried out in the maternity ward of the Pediatric Unit of Monfalcone hospital in Italy. The newborns' visual data collection and coding was performed by Dr. Farroni and her lab. The common aim of these visual studies was to investigate newborns' visual attention. The newborns were between 1-to-4 days of age (mean age in days = 2.20, SD = 1.20), when they took part in the studies. Findings of the studies from which the visual data used in the current study were retrieved are presented in detail in the following published articles: Rigato, Johnson, Faraguna, & Farroni, (2011); Farroni, Menon, Rigato & Johnson, (2007); Farroni, Menon, & Johnson, (2006); Farroni, Johnson, Menon, Zulian, Faraguna & Csibra, (2005).

The families were invited to participate by the thesis author by telephone and post between August 2013 and October 2013. One hundred and two participants accepted the invitation (response rate = 67.5%). Following the acceptance of the invitation, they were given the option to either visit the lab in Monfalcone hospital or for the thesis author to visit them at their homes to collect the questionnaire data. All participants returned fully completed questionnaires and signed consent forms.

For twenty-two (of the remaining one hundred and two) participants, the relevant visual data that were collected previously by Dr. Farroni could not be

retrieved from the datasets. The final sample in the analyses thus consisted of eighty participants (44 males, 36 females; mean age of the children in months when the parents competed the questionnaire = 90.00, SD = 11.80). The majority of the participants (93.75%) were Italians and residents of Gorizia province; 5 families (6.25%) originated from Slovenia but they were also residents of Gorizia province and they could speak and write Italian.

The thesis author obtained ethical approval for this study by the Department of Psychological Sciences, Birkbeck University of London's departmental ethics committee and the ethics committee of the University of Padua in Italy. Dr. Farroni obtained ethical approval for all the visual studies during the past several years.

4.3.2 Visual studies

The newborn visual studies were conducted by Dr. Farroni and her lab during the past ten years; the thesis author has not contributed to conducting those studies. The newborn visual studies had several important parameters in common: the stimuli that were used in the studies were always faces (human faces and schematic face-like configurations) with two stimuli presented at the same time side-by-side on the screen. All the experiments were run in the maternity ward of the Pediatric Unit of Monfalcone hospital in Italy and the equipment that was used to conduct the experiments was the same across all the visual studies. The analytic protocol for coding the visual data was the same across all studies. Each individual that took part in the current study participated in only one of the experiments. Finally, all participants were born full-term, they were not older than 4-days of age and had an Apgar score of above 8, at five minutes after birth.

The studies followed either the visual preference (49% of the studies from

which our data come) or the visual habituation procedure (51% of the studies from which our data come). A brief description of these procedures and of the apparatus and stimuli is given below.

4.3.3 Visual preference

In the visual preference studies (49% of the studies from which our data come), the newborns sat on the experimenter's lap, 35cm distant from a translucent screen. The newborn holder was not actively involved in the experiment. As soon as the newborn started looking at the centre of the screen, the experimenter, who was watching the newborn's eyes via a video monitor system, initiated a trial and presented the stimuli on the screen. In accordance with the infant-control procedure, the stimuli remained on display for as long as the newborn looked at one or more of them (Slater, Morison, Town, & Rose, 1985).

Newborns were presented with two trials in which the position of the stimuli was reversed. The initial side of the two stimuli, left or right was counterbalanced across the subjects. When they shifted their gaze from the display for more than 10 seconds, the experimenter turned off the stimuli. Two coders, who were blind to the location of the stimuli, analysed videotapes of the newborns' eye movements throughout the experiment. The coders recorded, separately for each stimulus and each trial, the number of orientations (how many times the newborn fixated on the stimuli) and the total fixation time at each stimulus.

To help establish the position of the newborn looks, the coders could see the corneal reflection of the stimulus, but they were blind to the type of stimuli at display. The Cohen's kappa inter-rater reliability for 10% of the data was calculated for both the number of orientations and the total looking time at

stimuli. The Cohen's Kappa was above .80 for both measures across all the visual studies (Rigato, Johnson, Faraguna & Farroni, 2011; Farroni, Menon, Rigato & Johnson, 2007; Farroni, Menon & Johnson, 2006; Farroni, Johnson, Menon, Zulian, Faraguna & Csibra, 2005).

4.3.4 Visual habituation

In the visual habituation studies (51% of the studies from which our data come), the newborns sat on the experimenter's lap, 35cm distant from a translucent screen. The experiments were carried out using a visual habituation technique with infant control procedure (Slater, Earle, Morison, & Rose, 1985).

The infant-controlled procedure is the most widely used technique in the study of infant visual habituation (Colombo et al., 2010). Unlike the fixed-trials procedure (Fantz, 1964), where the number, duration, and interval between stimulus exposures are determined by the experimenter often independent of the infant's visual attention (Bornstein & Benasich, 1986), the infant-controlled procedure guarantees that the participant is looking in the spatial location of the stimulus at the time of stimulus onset. The infant-controlled procedure fixes stimulus offset to be when the infant stops looking, it permits individual differences assessment by proportional transformation of infants' absolute levels of looking and it reveals individual patterns of habituation (Bornstein & Benasich, 1986). The greater sensitivity of the infant-controlled procedure in testing individual differences in infant visual attention was demonstrated in a study conducted by McCall (1979). Using the infant-controlled procedure the author showed that nearly half of the participants at 5-months and 90% of the participants at 10-months manifested their peak look duration on a trial other than the first (McCall, 1979). Indeed, some of the participants habituated rapidly,

others first increased looking and then habituated, whereas still others showed highly idiosyncratic patterns of looking (Bornstein & Benasich, 1986; McCall, 1979). As such, McCall concluded that the accuracy of simple indices of habituation that are based on the difference between the response to the first and last familiarization trial is limited and does not necessarily reflect individuals' rate of information processing, as has often assumed (McCall, 1979).

In the visual habituation studies used here the newborn was judged to have habituated when, from the fourth look on, the sum of the durations of any three consecutive looks was 50% or less than the total of the first three looks. When the habituation criterion was reached, the stimulus was automatically turned off and a preference test phase started. The initial side of the two stimuli, left or right, was counterbalanced across subjects. In accordance with the infant-control procedure, the coding of the visual measures (total fixation time and number of orientations) in the habituation studies was performed online (Slater, et al., 1985). The beginning and the end of a trial were dependent upon the newborns' time to reach the habituation criterion. During the post-habituation phase two identical stimuli were presented.

Once the newborns looked at the centre of the screen, the experimenters pressed a button to indicate the start of the trial. The habituation was followed by a preference test (post-habituation) in which a preference could be expressed between the familiar stimulus and a novel one. The two test stimuli were shown in both left and right positions, the positions being reversed from the first to the second presentation. Each presentation lasted at least 20 seconds. A video camera recorded the newborn's eye movement to monitor their looking behaviour and to allow off-line coding of their looks.

Subsequently, two coders, who were unaware of the stimuli presented, analyzed videotapes of the baby's eye movements throughout the trials. The coders recorded, separately for each stimulus and each trial, the number of orientations (how many times the newborn fixated on the stimuli) and the total looking time to stimuli. The experimenter coded an orientation when newborns were looking at one of the two stimuli without turning their gaze away for more than 2 seconds. The Cohen's Kappa was above .80 for both orientation and looking time across all the habituation studies.

The number of orientations was coded in an identical way for both the visual habituation and visual preference studies. Specifically, the coders recorded, separately for each stimulus how many times the newborn looked at the stimuli (i.e. total number of orientations to the stimuli). (Rigato, Johnson, Faraguna & Farroni, 2011; Farroni, Menon, Rigato & Johnson, 2007; Farroni, Menon, Johnson & 2006; Farroni, Johnson, Menon, Zulian, Faraguna & Csibra, 2005).

4.3.5 Visual studies apparatus and stimuli

The common aim of the visual studies that were conducted by Dr. Farroni was to investigate newborns' visual attention. The studies are described in chronological order from the newest to the oldest.

The study by Rigato, Johnson, Faraguna and Farroni, (2011) involved four experimental conditions (33.75% of the participants in the current study came from this study):

In the first two experiments (1a and 1b), the visual habituation procedure was used to investigate whether gaze direction modulates identity recognition from birth. Experiment 1a tested whether eye contact attracts newborns' attention and induces identity recognition from birth. Newborns were shown a face with

direct gaze, and subsequently given a preference test involving the same face and a novel one, both of them with direct gaze. In Experiment 1b, the same procedure and face stimuli were used, in order to test identity recognition, when faces displayed an averted gaze. Therefore, newborns were presented with a face accompanied with averted gaze, and subsequently given a preference test involving the same face and a novel one, both of them with averted gaze (Rigato et al., 2011).

In Experiment 2a and 2b, a visual preference paradigm was followed using the same stimuli (as in experiments 1a and 1b) accompanied with direct and averted gaze, respectively. The aim was to test whether newborns show a visual preference for one of the two faces. The apparatus was the same used in Experiment 1. The stimuli were the same face identities used in the previous experiments, and faces displayed direct gaze in Experiment 2a and averted gaze in Experiment 2b. The stimuli remained on the screen as long as the infants fixated one of them. When they shifted their gaze from the display for more than 10 seconds, the experimenter turned off the stimuli (Rigato et al., 2011).

The study by Farroni, Menon, Rigato and Johnson (2007) involved three experiments (8.75% of the participants in the current study came from this study).

Experiment 1 aimed to establish if newborns have a spontaneous preference for fearful versus neutral facial expressions. Newborns were shown two pictures of the same person's face, one on the right and one on the left of the centre of the screen. One of the faces had a neutral face (no emotion) and the other had a fearful expression; both faces had a straight head and direct gaze. Two different identity faces were used, but each newborn saw only one of them (randomly assigned; Farroni et al., 2007).

Experiment 2 aimed to determine whether newborns could discriminate between the two stimuli presented in Experiment 1 using a visual habituation and discrimination method. The apparatus and the stimuli were the same as these used in Experiment 1. During the habituation phase the newborns viewed pairs of identical face stimuli (same identity, same expression, one on the right and one on the left of the screen) with either a neutral expression or a fearful expression. During the test phase the two different expressions of the same identity face were presented bilaterally (Farroni et al., 2007).

Experiment 3 aimed to determine whether newborns could discriminate between stimuli with a fearful expression and stimuli with a happy facial expression. The apparatus was the same as that used in Experiment 1. Newborns were shown two pictures of the same person's face, one on the right and one on the left of the centre of the screen. One of the faces had a happy expression and the other had a fearful expression, both with a straight head and direct gaze (Farroni et al., 2007).

The study by Farroni, Menon and Johnson, (2006) involved three experiments (21.25% of the participants in the current study came from this study):

Experiment 1 aimed to establish whether newborns prefer to look significantly more at a face with direct gaze than at one with averted gaze. Newborns were shown two pictures of the same face: one on the right and one on the left of the centre of the screen. One of the faces had direct gaze, whereas in the other face the eyes were averted randomly to the right or left. The inner edges of the images were 8.5 cm from the centre (Farroni, Menon and Johnson, 2006).

Experiment 2 aimed to establish whether inverting faces affects gaze

perception in newborns. The apparatus was the same as in Experiment 1 only this time the faces were inverted, with one face having direct gaze and the other face having a left or right averted gaze. The faces were presented at life size and 8.5 cm apart (Farroni, et al., 2006).

Experiment 3 followed procedures similar to those in Experiments 1 and 2 except that the faces used as stimuli were upright faces with the heads turned 45° to the left or right. As before, preferences for direct and averted gaze were compared. The faces were presented at life size and 8.5 cm apart (Farroni et al., 2006).

The study by Farroni, Johnson, Menon, Zulian, Faraguna and Csibra, (2005) involved two experiments (22.5% of the participants in the current study came from this study):

Experiment 1 included three parts (1a, 1b, 1c) and aimed to establish whether newborn's preference for upright schematic face-like configurations would disappear if they were composed of light elements on a dark background. The stimuli that were used in Experiment 1a were two head-shaped, head-sized, dimensional images with three-square features inside. One of the stimuli had the squares in the appropriate locations for eyes and mouth (i.e., an upright face-like configuration), whereas in the other stimulus the position of the squares was vertically reversed, with two squares located below one square (i.e., an inverted face-like configuration). In Experiment 1a the stimuli presented differed only in contrast polarity: in the positive polarity condition the head-shape was white against a black background and the internal squares were black; in the negative polarity condition the head-shape was black against a white background and the internal squares were white. Experiment 1b used the same stimuli as in the

negative polarity condition of Experiment 1a with the exception that the stimuli appeared on a mid grey (50 %) background. In Experiment 1c the stimuli used in Experiment 1b were changed slightly by inserting small black squares into the white ones (Farroni et al., 2005).

Experiment 2 included two parts (2a and 2b) and aimed to establish whether the contrast polarity sensitivity of newborns' preference extended to real faces and across different lighting conditions. In Experiment 2a newborns were presented with two high-quality black-and-white photographs of a woman's face digitally modified to create an upright and an inverted version of it. The two stimuli were identical except for the inner region of the face, which was preserved in its canonical orientation in the upright face, but was rotated by 180° in the inverted face. Experiment 2a essentially replicated the findings of Experiment 1a. Experiment 2b tested directly whether newborns could discriminate between, and are biased towards one of, two faces, which are illuminated either from above or from below. The newborns were shown the same female face photographed with two different directions of illumination: from above and from below. The average luminance of the two stimuli was the same, while the distribution of the darker and lighter patches was markedly different. The face showed a neutral expression (Farroni et al., 2005).

Finally, eleven participants (13.75% of the participants) came from the following unpublished study: Di Gangi, V., Menon, E., De Pangher Manzini, E., and Farroni, T. (2008). La Costruzione dell'intenzionalità: uno studio sui neonati. Presentation at the XXII. Congresso Nazionale della Sezione di Psicologia dello Sviluppo. The study included two experiments (1: biological agent; 2: not biological agent) and aimed to evaluate whether there is evidence of goal-directed

actions from birth. The stimuli were static scenes representing an agent touching one of two possible objects (two yellow bowling pins marked by a central red shape: a cross or a triangle). The participants were 31 full term newborns (20 for Exp. 1 and 11 for Exp.2).

4.3.6 Visual measures-Calculating average dwell time

The measure of total looking time on the stimuli was divided by the measure of total number of orientations at stimuli for each participant separately. This calculation that was performed by the thesis author produced a measure of the average dwell time: the time spent looking at stimuli during the experiment per participant.

Average Dwell Time = Total Looking Time / Total Number of Orientations

Average dwell time did not differ significantly as a function of whether the newborn took part in a visual preference or visual habituation study (please refer to result section below). Nevertheless, the particular experiment that an individual took part in the visual study was treated as a covariate in the regression analysis.

4.3.7 Questionnaires

Eight subscales of the short form of the Italian version of the Childhood Behaviour Questionnaire parent report (CBQ-sf; Putnam & Rothbart, 2006; translated by Giada Matricardi) that have been shown to load onto two factors, namely effortful control and surgency, were employed to assess temperament in 36-84-month-old children.

The scores on the Italian short form version of the CBQ scale of effortful control represented the average score of the CBQ subscales of inhibitory control (12 items), attentional focusing (12 items), low-intensity pleasure (13 items) and perceptual sensitivity (12 items). The scores on the Italian short form version of the CBQ scale of surgency represented the average score of the CBQ subscales of activity level (7 items), high-intensity pleasure (6 items), impulsivity (4 items) and shyness (6 items reversed). The rater reported the frequency of a particular behaviour (example question for effortful control: "Your child prepares for trips and outings by planning things s/he will need; Si prepara per gite o uscite pianificando le cose di cui avrà bisogno". Example question for surgency: "Your child likes to play so wild and recklessly that he/she might get hurt; Gli/Le piace giocare in modo così vivace e spericolato che si potrebbe far male", on a seven-point scale (ranging from "never/assolutamente falso" to "always/assolutamente vero").

The Italian version of the CBQ short form scales of effortful control and surgency showed excellent internal consistency (Cronbach's alphas = .75 and .91, respectively) in the sample used in this study.

The equivalent eight subscales of the Italian version of the Temperament in Middle Childhood Questionnaire parent report (TMCQ; Simonds & Rothbart,

2004; translated by Lavinia Barone) were employed to assess effortful control and surgency in 84-120 month old children. The scores on the Italian version of the TMCQ scales of effortful control and surgency represented the average score of the same subscales as for the Italian version of the CBQ short form. The rater reported the frequency of a particular behaviour (example question for effortful control: "Your child can stop himself/herself when s/he is told to; Si ferma quando gli/le viene detto di farlo. Example question for surgency: "Your child likes rough and rowdy games; Gli/le piacciono i giochi scalmanati e chiassosi"), on a five-point scale (ranging from "almost always untrue; quasi sempre falso" to "almost always true; quasi sempre vero"). The TMCQ scales of effortful control and surgency showed excellent internal consistency (Cronbach's alphas = .90 and .89, respectively) in the sample used in this study.

The two age groups were merged to increase the statistical power to detect significant associations; given that the parents rated the frequency of a particular behaviour on a seven point scale on the CBQ and on a five point scale on the TMCQ the two scales (effortful control and surgency) were z-scored separately before merging the datasets.

To assess hyperactivity-inattention and total behavioural difficulties the scales of hyperactivity-inattention and total behavioural difficulties of the parent report Italian version of the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997; translated by Andrea De Giacomo, Paola Dazzan and Loreta Bernardi) were employed. The SDQ hyperactivity-inattention scale consisted of 5 items. The SDQ total behavioural difficulties scale represents the total score of 20 items (that include the 5 items used to assess hyperactivity-inattention) that load on four scales, namely: Hyperactivity-inattention, conduct problems, emotional

symptoms and peer problems. The rater reported on the frequency of a particular behaviour (e.g. “Restless, runs about or jumps up and down, doesn’t keep still; Irrequieto, iperattivo, incapace di stare fermo per molto tempo”) on a three-point scale (“not true (non vero)”; “sometimes true (parzialmente vero)”; “certainly true (assolutamene vero)”). The SDQ is a reliable and valid measure of total behavioural difficulties and hyperactivity-inattention of children age 3 to 16 year olds (Goodman, 1997). The SDQ scale of hyperactivity-inattention and total behavioural difficulties showed excellent internal consistency (Cronbach’s alphas = .76 and .80, respectively).

4.3.8 Statistical analysis

4.3.8.1 Descriptive statistics. Average dwell time and the questionnaire data were explored using descriptive statistics in SPSS version 18.0. Due to skewness of the data, Van der Waerden’s transformation (Lehmann, 1975) was used to normalize the data before further statistical analyses were undertaken. Analysis of Variance (ANOVA) was performed to test for significant mean sex differences (corrected for multiple comparisons at $p < .05/5 = .01$; five represents the number of comparisons that were performed). Similar analysis was performed to test for significant mean differences on average dwell time between the group of participants that took part in visual preference studies and those that took part in visual habituation studies.

4.3.8.2 Correlations. Partial correlations were performed to test for significant correlations (corrected for multiple comparisons at $p < .05/5 = .01$; five represents the number of correlations that were performed) between the questionnaire scales of effortful control, surgency, hyperactivity-inattention and total behavioural difficulties. Sex and age of the child when the parents completed

the questionnaires were used as covariates. In addition, whether the CBQ or TMCQ questionnaires were used was included as a covariate in the analysis. Given that the parents rated the frequency of a particular behaviour on a seven point scale on the CBQ and on a five point scale on the TMCQ the two scales (effortful control and surgency) were z-scored separately before merging the datasets.

4.3.8.3 Regressions. Multiple linear regression was performed to test for significant associations (at $p < .05$ as each of the hypothesis was tested separately) between newborns' average dwell time with effortful control, surgency, hyperactivity-inattention and total behavioural difficulties in childhood. The effects of age when the child took part in the visual study and the age of the child when the parents completed the questionnaire, the type of questionnaire that was completed by the parents (CBQ or TMCQ) and newborns' total time to complete the visual experiment were treated as covariates in the regression analysis. Finally, the particular study (specifically the particular experiment within each study) that each newborn took part in was treated as covariate in the regression analysis.

4.4 Results

4.4.1 Descriptive statistics

Descriptive statistics for average dwell time and for the scales of effortful control (z-score), surgency (z-score), hyperactivity-inattention and total behavioural difficulties for the whole sample are shown in Table 4.1. Table 4.2 presents the descriptive statistics for the CBQ and TMCQ scales of effortful control and surgency. Table 4.3 presents the descriptive statistics for the SDQ scales of hyperactivity-inattention and total behavioural difficulties for two

different groups of participants (that were combined in the main analysis to form the total sample): the younger group of participants, age 5 to 7 years and the older group of participants, age 7 to 9. The raw (instead of the normalised data) are presented on all tables below for all measures. The normalised scores that were used in the analysis meet the assumptions of normality.

Table 4.1. Descriptive statistics for average dwell time, effortful control (z-score), surgency (z-score) and SDQ hyperactivity-inattention and total behavioural difficulties for all participants

	N = 80 (5-9 years of age)				
	Average Dwell Time (in ms)	Effortful Control (z-score)	Surgency (z-score)	SDQ Hyperactivity-Inattention	SDQ Total Behavioural Difficulties Score
N	80	80	80	80	80
Mean	3,808	.00	.00	1.10	7.60
SD	1,963	.99	.99	1.26	5.46
Median	3,319	-.02	.00	1.00	7.00
Mode	559	-.01	-2.23	.00	2.00
Minimum	559	-2.75	-2.23	.00	.00
Maximum	12,389	2.31	2.47	4.00	27.00
Kurtosis	4.16	-.17	.20	-.42	1.58
Skewness	1.60	-.03	.16	.83	1.09

Table 4.2. Descriptive statistics for CBQ and TMCQ scales of effortful control and surgency

	CBQ (5-7 years of age)		**TMCQ (7-9 years of age)**	
	Effortful Control	**Surgency**	**Effortful Control**	**Surgency**
N	13	13	67	67
Mean	5.69	5.01	3.47	3.45
SD	.44	1.02	.47	.42
Median	5.65	5.07	3.46	3.45
Mode	4.99	2.71	3.47	2.60
Minimum	4.99	2.71	2.17	2.60
Maximum	6.59	6.59	4.57	4.50
Kurtosis	.27	1.18	-.15	.17
Skewness	.52	-.75	-.12	.31
Cronbach's Alpha	.75	.91	.90	.89

Table 4.3. Descriptive statistics for the SDQ scales of hyperactivity-inattention and total behavioural difficulties

	SDQ (5-7 years of age)	**SDQ (5-7 years of age)**	**SDQ (7-9 years of age)**	**SDQ (7-9 years of age)**
	Hyperactivity-inattention	**SDQ Total Behavioural Difficulties**	**Hyperactivity-inattention**	**SDQ Total Behavioural Difficulties**
N	13	13	67	67
Mean	1.30	6.53	1.05	7.80
SD	1.54	4.27	1.21	5.66
Median	1.00	6.00	1.00	7.00
Mode	.00	3.00	.00	2.00
Minimum	.00	.00	.00	0.00
Maximum	4.00	15	4.00	27.00
Kurtosis	-.77	-.29	-.40	1.47
Skewness	.82	.55	.81	1.09
Cronbach's Alpha	.71	.76	.76	.83

The two age groups were merged in order to increase the statistical power to detect significant associations. Given that the parents rated the frequency of a particular behaviour on a seven point scale on the CBQ and on a five point scale on the TMCQ the two scales (effortful control and surgency) were z-scored separately before merging the datasets. No such transformation was necessary for the SDQ scales.

No statistically significant mean differences between the two age groups were observed for the scales of effortful control (z-score), surgency (z-score), hyperactivity-inattention and total behavioural difficulties, respectively ($F(1, 79) = .09$, $p = .76$; $F(1, 79) = .009$, $p = .92$; $F(1, 79) = .13$, $p = .71$; $F(1, 79) = .31$, $p = .57$).

Figures 4.1 to 4.5 display the histograms for newborn average dwell time, and child effortful control (z-score), surgency (z-score), hyperactivity-inattention and total behavioural difficulties, respectively.

Figure 4.1. Histogram for average dwell time (N=80; 1-4 days old)

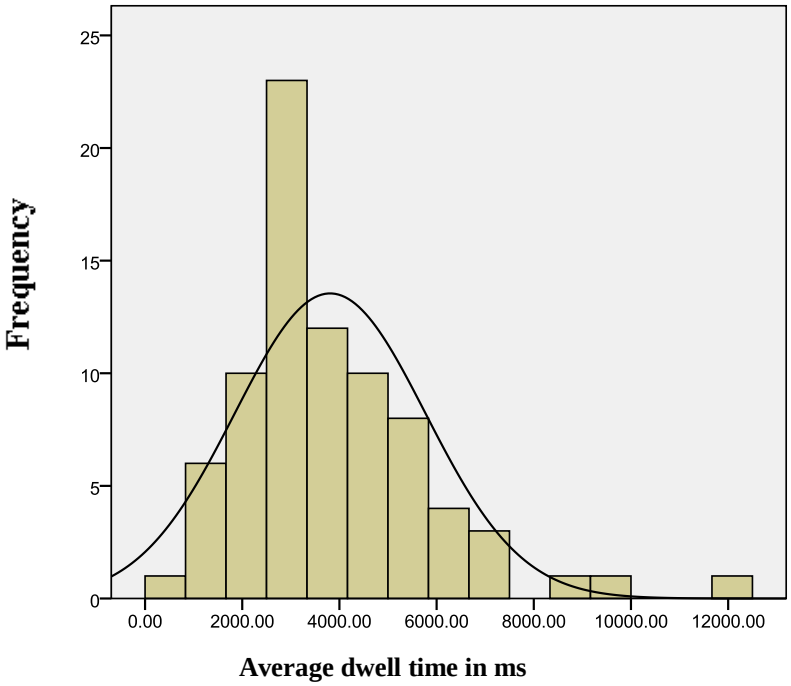


Figure 4.2. Histogram for z-score effortful control (N=80; 5-9 years of age)

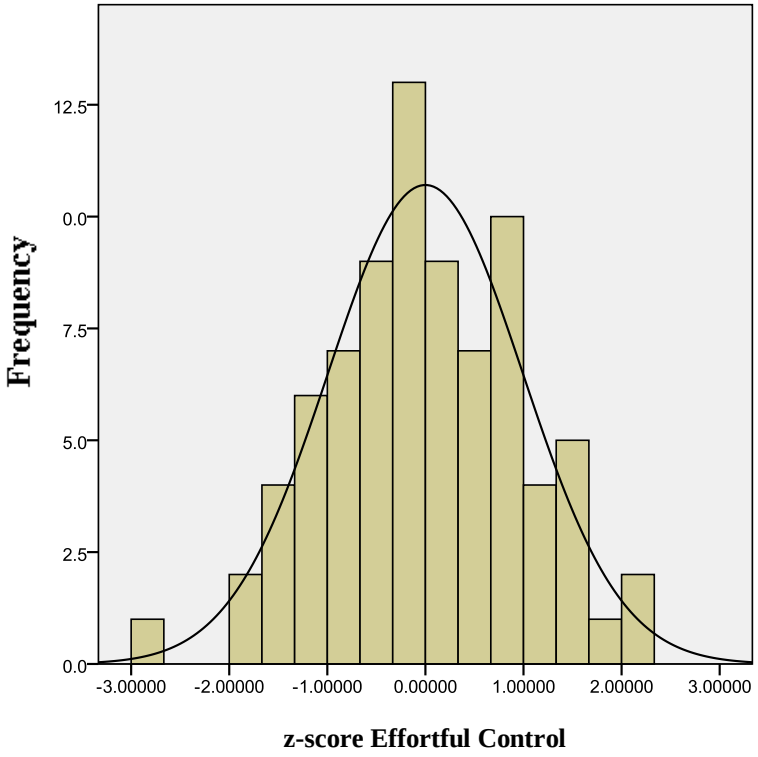


Figure 4.3. Histogram for z-score surgency (N=80; 5-9 years of age)

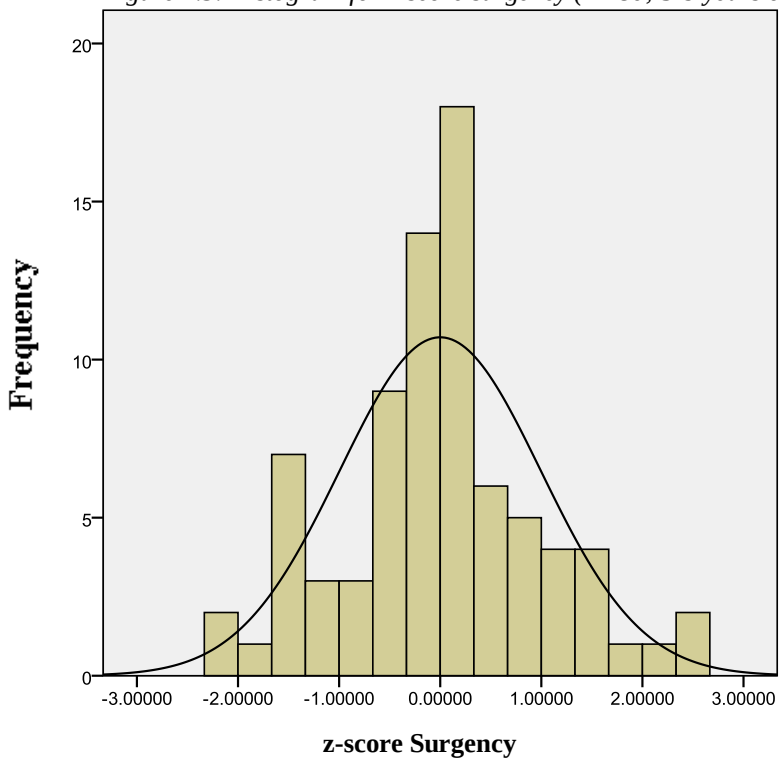


Figure 4.4. Histogram for hyperactivity-inattention (N=80; 5-9 years of age)

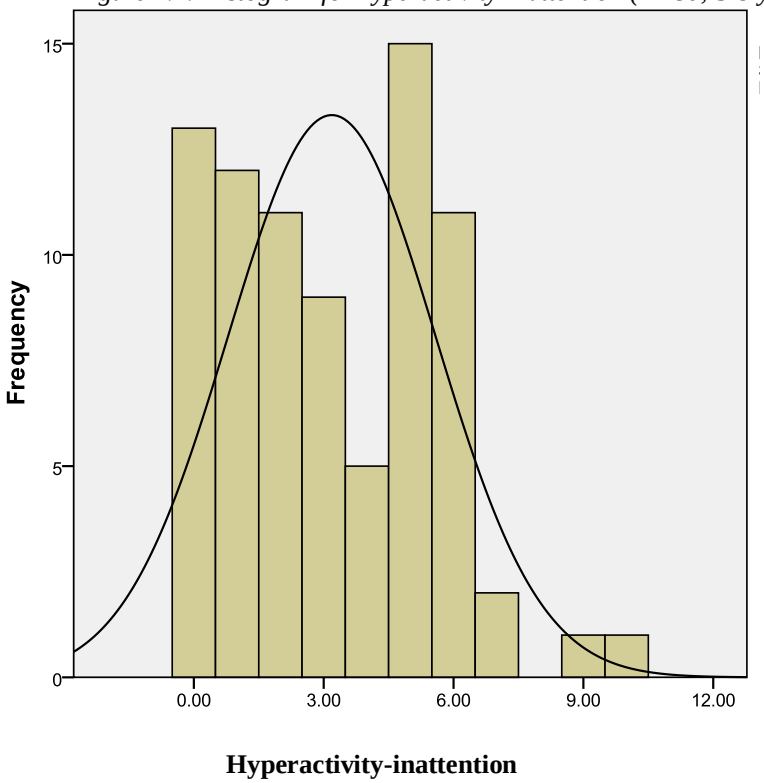
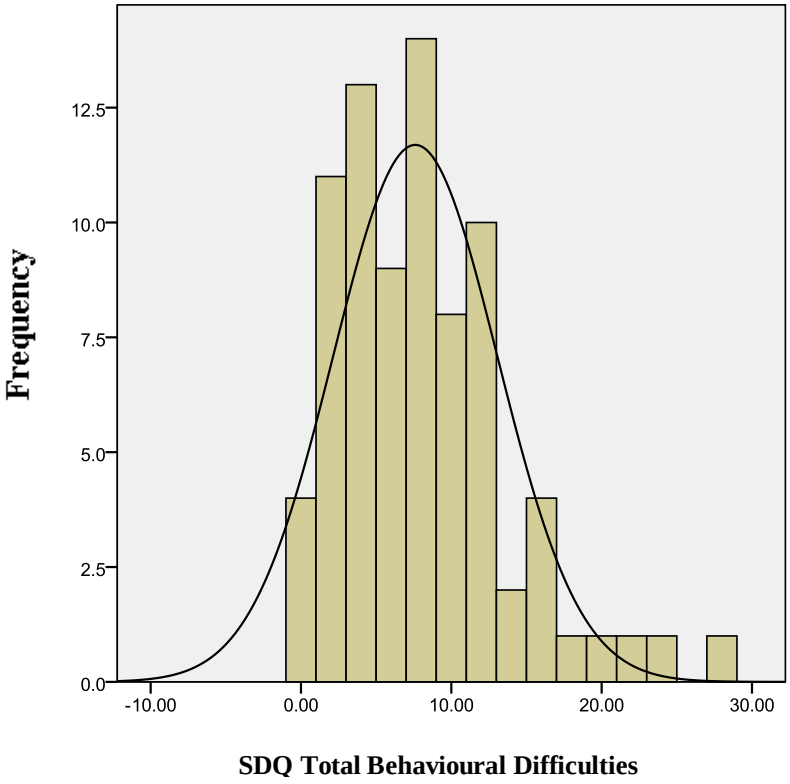


Figure 4.5. Histogram for SDQ total behavioural difficulties (N=80; 5-9 years of age)



4.4.2 Sex differences

Females showed higher means than males in effortful control (F (1, 79) = 5.92, p = .01). No other statistically significant mean sex difference was observed (see Table 4.4).

Table 4.4. Mean sex differences on average dwell time (in milliseconds), effortful control (z-score), surgency (z-score), hyperactivity-inattention and total behavioural difficulties

N=80 (5-9 years of age)	**Male (N = 44)**		**Female (N = 36)**					
	M	**SD**	**M**	**SD**	**F**	**df**	**p-value**	**Partial η^2**
Average Dwell Time in milliseconds	3,583	1,592	4,083	2,333	.04	1, 61	.84	.07
Effortful Control (z-score)	-.24	.87	.30	1.06	5.92	1, 76	.01	.05
Surgency (z-score)	.07	1.02	-.09	.95	.57	1, 76	.45	.008
Hyperactivity-inattention	3.36	2.50	2.97	2.27	.52	1, 76	.47	.007
Total Behavioural Difficulties	7.50	4.92	7.72	6.12	.03	1, 76	.86	.000

4.4.3 Mean group differences on visual measures between visual preference and visual habituation studies

There were statistically significant mean differences (at $p < .01$; corrected for multiple comparisons: $p < .05/3 = .016$; three is the number of comparisons between the two groups of participants for the three variables) for the variables total looking time at stimuli and number of orientations between participants that took part in a visual preference study and those that took part in a visual habituation study. Individuals who participated in visual preference studies exhibited longer total looking time ($F (1, 79) = .41.92$, $p < .001$ and greater number of orientations ($F (1, 79) = .35.46$, $p < .001$). Importantly though, no statistically significant differences (at $p < .01$) between the two groups were observed for the measure of average dwell time at stimuli ($F (1, 79) = .005$, $p = .94$; see Table 4.5). Despite the fact that there were no differences in the measure of average dwell time at stimuli, the type of study that an individual took part in was treated as covariate in the regression analysis.

Table 4.5. Mean group differences on total looking time at stimuli, total number of orientations and average dwell time between participants that took part in visual preferences and visual habituation studies

N=80 (5-9 years of age)	**Preferences Studies**		**Habituation Studies**					
	M	**SD**	**M**	**SD**	**F**	**df**	**p-value**	**Partial η^2**
Total Looking Time at Stimuli in milliseconds	97,465	3.81	49,203	1.58	41.92	1, 79	.000	.36
Total Number of Orientations	29.44	11.19	15.19	6.13	35.46	1, 79	.000	.31
Average Dwell Time in milliseconds	3,735	1,651	3,960	2,523	.005	1, 79	.94	.000

4.4.4 Correlations between effortful control, surgency, hyperactivity-inattention and total behavioural difficulties in childhood

Correlations between effortful control, surgency, hyperactivity-inattention and total behavioural difficulties are shown in Table 4.6, for all participants. Effortful control was correlated negatively at $p < .01$ (corrected for multiple comparisons) with surgency ($r = -.37$, $p < .001$), hyperactivity-inattention ($r = -.69$, $p < .001$) and total behavioural difficulties score ($r = -.60$, $p < .001$). As expected surgency was correlated positively with hyperactivity-inattention ($r = .45$, $p < .001$) and total behavioural difficulties ($r = .28$, $p = .01$).

Table 4.6. Correlations between effortful control, surgency, hyperactivity-inattention and total behavioural difficulties in childhood

	N = 80 (5-9 years of age)			
	Effortful Control	Surgency	Hyperactivity-inattention	Total Behavioural Difficulties
Effortful Control		-.37**	-.69**	-.60**
Surgency	-.37**		.45**	.28**
Hyperactivity-inattention	-.69**	.45**		.79**
Total Behavioural Difficulties	-.60**	.28**	.79**	

*** p < 0.01, * p < 0.05*

4.4.5 Multiple linear regression between newborns' average dwell time on stimuli and effortful control, surgency, hyperactivity-inattention and total behavioural difficulties in childhood

The results of the multiple linear regression for newborn's average dwell time on stimuli (independent variable) with effortful control, surgency, hyperactivity-inattention and total behavioural difficulties in later childhood (dependent variables) are shown in Table 4.7. Average dwell time was associated significantly (at $p < .05$) with surgency ($\beta = -.25$, $R^2 = .04$, $p = .02$) and total behavioural difficulties score ($\beta = -.28$, $R^2 = .05$, $p = .04$) but not with effortful control ($\beta = .03$, $R^2 = .001$, $p = .54$) and hyperactivity-inattention ($\beta = -.19$, $R^2 = .02$, $p = .16$).

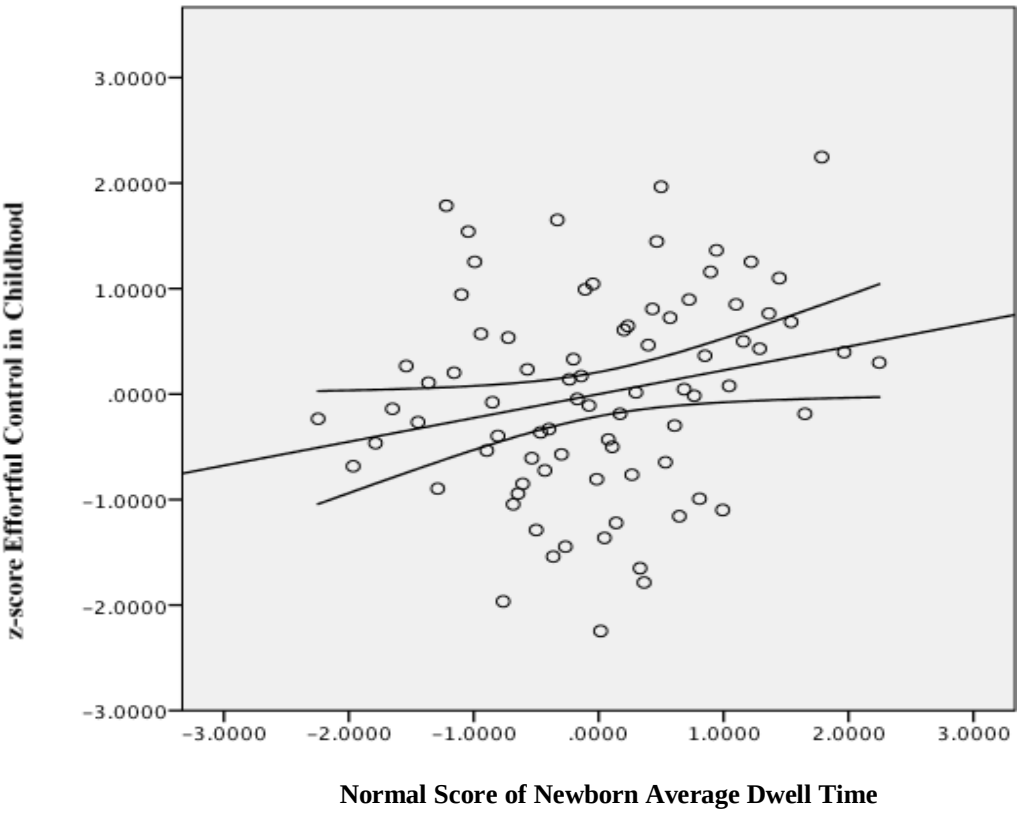
Table 4.7. Linear regressions between newborns' average dwell time and effortful control, surgency, hyperactivity-inattention and total behavioural difficulties score in childhood.

N=80							
Independent Variable: Average Dwell Time							
Dependent Variable	B	β	t	95% CI for β Lower Bound	95% CI for β Upper Bound	R^2	p-value
Z-Score Effortful Control	.03	.03	.30	-.17	.23	.001	.54
Z-Score Surgency	-.25	-.25	-2.24	-.49	-.02	.04	.02
Hyperactivity-inattention	-.18	-.19	-1.41	-.43	.07	.02	.16
Total Behavioural Difficulties	-.28	-.28	-2.09	-.55	-.01	.05	.04

Note: The "B" and "β" refer to the unstandardised and standardized regression coefficients respectively followed by the "t-statistic". The "R^2" represents the variance explained by the independent variable on the dependent variables after regressing out the effect of the covariates; finally, the p-value represents the value of statistical significance of the effect of the independent variable on the dependent variables, while keeping constant the effect of the covariates.

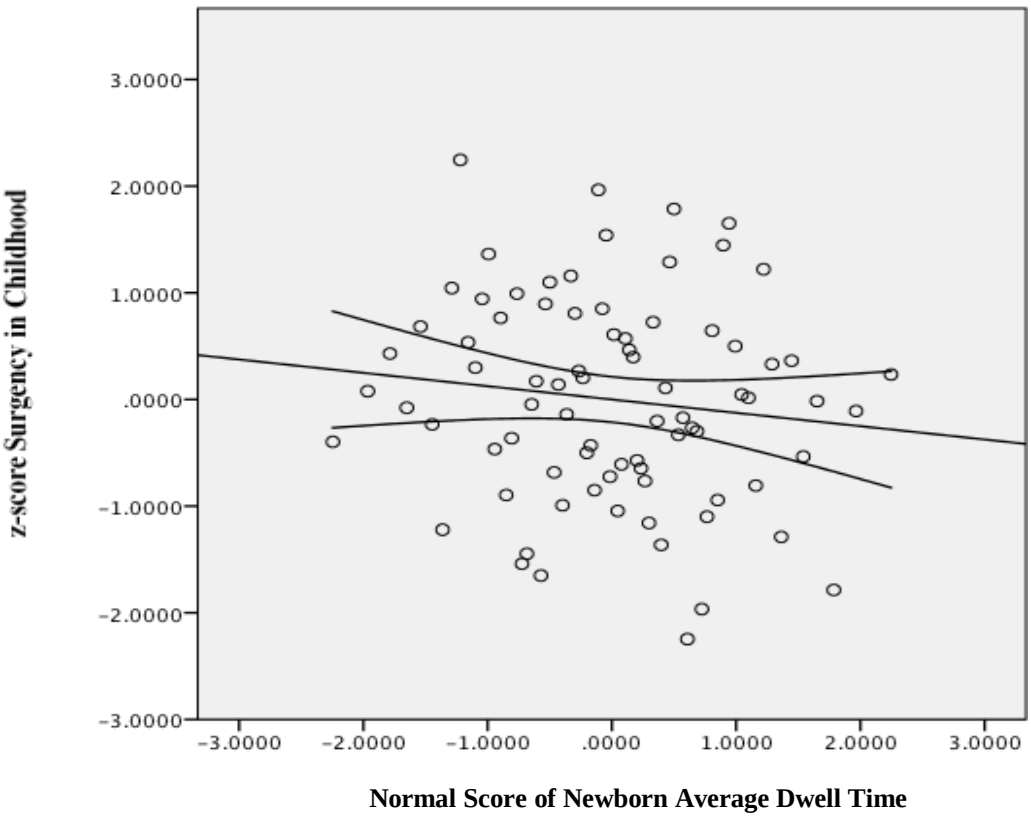
Scatter plots for the reported associations are shown in Figures 4.6, 4.7, 4.8 and 4.9 for effortful control, surgency, hyperactivity-inattention and total behavioural difficulties, respectively.

Figure 4.6. Scatter Plot showing the relationship between newborns' normalised average dwell time and z-score effortful control in childhood.



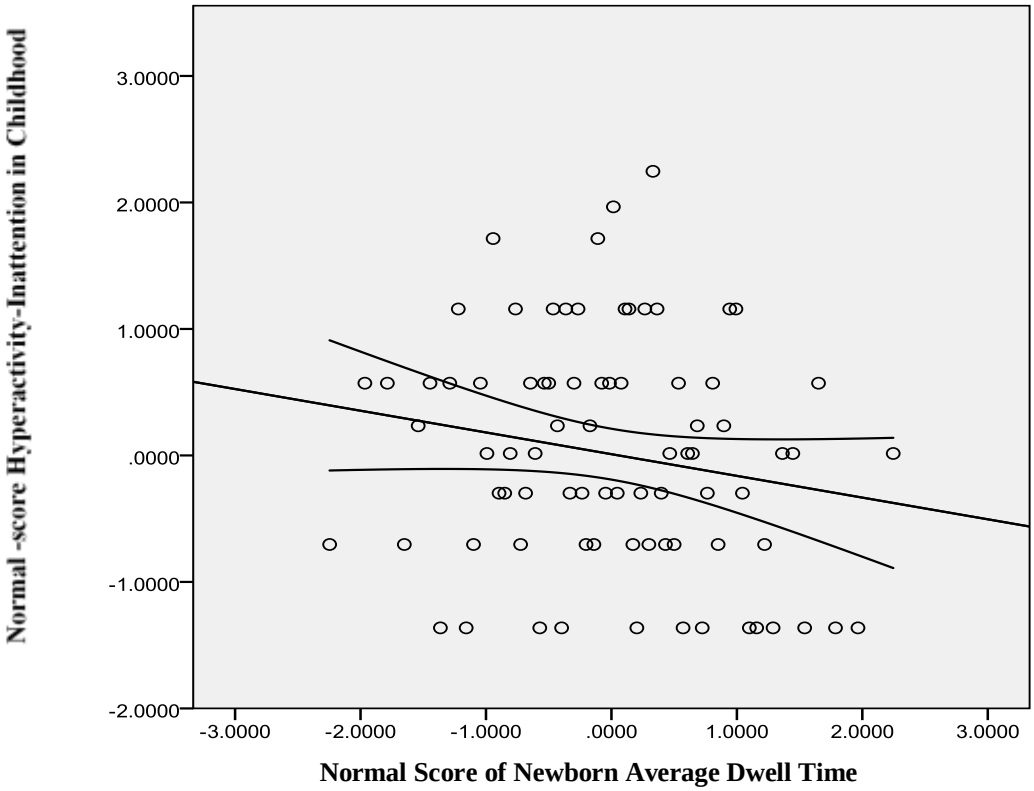
Note. The line represents the best-fit line of the model and the confidence bands surrounding the line represent the 95% confidence intervals of the best-fit line

Figure 4.7. Scatter Plot showing the relationship between newborns' normalised average dwell time and z-score surgency in childhood.



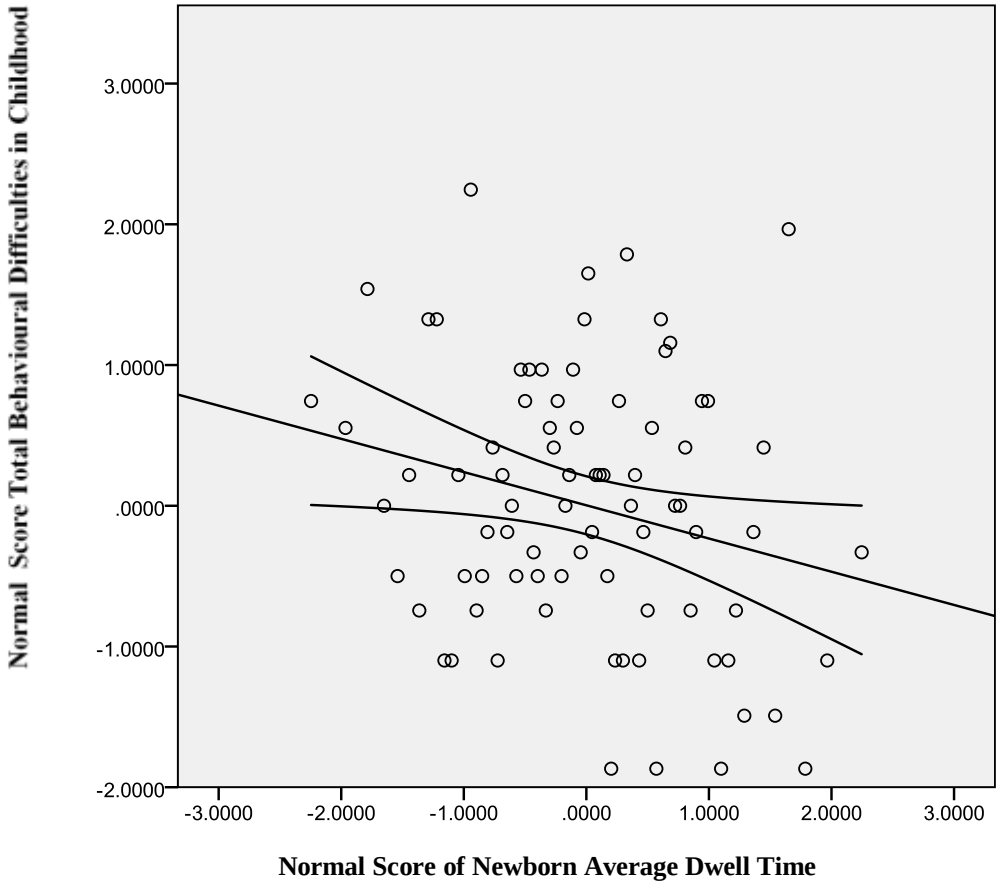
Note. The line represents the best-fit line of the model and the confidence bands surrounding the line represent the 95% confidence intervals of the best-fit line

Figure 4.8. Scatter Plot showing the relationship between newborns' normalised average dwell time and normalized hyperactivity-inattention in childhood.



Note. The line represents the best-fit line of the model and the confidence bands surrounding the line represent the 95% confidence intervals of the best-fit line

Figure 4.9. Scatter Plot showing the relationship between newborns' normalised average dwell time and normalised total behavioural difficulties in childhood.



Note. The line represents the best-fit line of the model and the confidence bands surrounding the line represent the 95% confidence intervals of the best-fit line

4.5 Discussion

The aim of the current study was to explore the degree to which individual differences in newborns' average dwell time associate with effortful control, surgency, hyperactivity-inattention and total behavioural difficulties in childhood. As hypothesised, average dwell time was associated negatively with surgency and total behavioural difficulties in childhood. This is the first study to report an association between individual differences in attention in the first days after birth with temperament and behaviour in childhood. As such, the results of the current study bridge the existing gap in the literature demonstrating that a measure of visual attention at birth is significantly associated with temperament and behavioural traits in childhood.

The significant associations were of moderate magnitude, with the proportion of variance explained by newborns' average dwell time at stimuli being 4% and 5% for surgency and total behavioural difficulties in childhood, respectively. The previous study reported that mean fixation duration in infancy (4-10 months of age) explained 7% of the variation in surgency in early childhood (18-54 months of age) and that this association becomes stronger as the age of the infant increases. The slightly lower proportion of variation in surgency that is explained by newborns' average dwell time reported here could be explained either by the fact that predictor and dependent variable were further apart in developmental time as compared to the previous study; or the differences in the dwell time measure compared to the eye tracking-derived fixation duration previously used.

The non-significant association between newborn average dwell time and child effortful control could be explained from the fact that the association

between infant attention and effortful control in the previous study showed the trend of being the weakest association of the significant findings. In light of the smaller sample size in the present work, the negative result might reflect a lack of power to detect a more modest association between newborn attention and effortful control, or it might reflect a genuine null finding.

The non-significant association between newborn average dwell time and child hyperactivity-inattention could also be explained to some extent by the lack of power to detect a more modest association between newborn attention and hyperactivity-inattention. This was supported from the fact that, when the scale of hyperactivity-inattention was combined with other behavioural traits to form the SDQ scale of total behavioural difficulties the association became significant.

Studying individual differences in newborns' attention constitutes a window into the developmental mechanisms that contribute to individual differences in attentional and behavioural control throughout the lifespan. For example, while attentional and behavioural control in childhood depends mainly upon overlapping cortical brain systems (Petersen & Posner, 2012), at birth (and prior to 3-months of age) attentional control depends upon subcortical brain structures (Farroni & Menon, 2008). The reported associations between newborns' attention with temperament and behaviour in childhood suggests that some of the underlying factors that may contribute to individual differences in the efficiency of young children to control their attention and behaviour are present as early as at birth; that is, before the cortical systems that underlie behavioural and attentional control start to influence behaviour.

These findings should be considered in light of some limitations. The measure of newborns' attention was not derived from eye tracking data, which has

much higher spatial (~1° of visual angle) and temporal resolution (typically between 50-300 Hz) in comparison to video coding (typically around 25Hz). For example, long dwells could be made up of a small number of long fixations or a large number of short fixations (Henderson & Smith, 2009). The significant associations reported in this study support the former view but some of the variance in the dwells might be due to the latter. As such, future research could use simultaneous eye tracking and video coding in young infants to estimate the correlation between average dwell time with fixation duration assessed using eye tracking and to attempt to replicate the findings of this study.

A second limitation of this work is that the measure of average dwell time was only hypothesised to be a proxy for fixation duration. It has been argued that there are at least three critical postnatal periods of attentional development in infancy (see Colombo, 2001): the first involves the period from birth to 2-, 3-months of age, when the development of alert state takes place (Colombo, 2001). The second involves the period from 3 to about 6 months, when the orienting system emerges (Colombo, 2001). The third refers to the period from 6 months to 12 months, when executive attention is starting to practice control (Colombo, 2001). As such, looking measures may represent different underlying constructs at different points during the first year of postnatal life. For example, individual differences in newborn average dwell time may be more closely tied to the development of the alert state rather than to the development of the orienting or executive attention system. The lack of findings on the relationship between average dwell time and mean fixation duration across development and the fact that the current study did not take into account specific developmental stages of attention in infancy do not allow to state with certainty the degree to which the

two measures are linked.

Another limitation of the study was the reliance on parent report of children's behaviour and temperament. While parents are typically most familiar with their children's behaviour, all types of raters include some bias. Future research should consider collecting data from multiple raters or employing additional objective measurements of behaviour.

In terms of how individual differences in children's behaviour and temperament are influenced, these data show that part of the variance is explained by factors already present on the first or second day of life. As such, the origins of individual differences in behaviour are not likely to be wholly due to the postnatal environment. These causal factors could be genetic or stemming from the prenatal environment.

Longitudinal studies could investigate prenatal factors (e.g. prenatal maternal stress) that may contribute to individual differences in attention at birth and in temperament and behaviour in childhood. Finally, neuroimaging could be used to explore individual differences in the development of the brain systems upon which newborns' and infants' attention is based (Henderson, Choi & Luke, in press).

Finally, genetic research could investigate genetic variation that contributes to individual differences in attention at birth and to individual differences in attentional and behavioural control in childhood. This was the main aim of the third study that is presented in the next chapter (Chapter 5).

5 Genetics of Newborn and Infant Visual Attention

5.1 Introduction

The first PhD project that was described in Chapter 3 of this thesis has shown for the first time that longer mean fixation duration was associated with higher levels of effortful control and lower levels of surgency and hyperactivity-inattention. The second PhD project that was described in Chapter 4 of this thesis has shown that average dwell time was associated negatively with surgency and total behavioural difficulties in childhood. As such, the causal factors that contribute to individual differences in visual attention are not likely to be wholly from the postnatal environment. These causal factors could be prenatal or genetic.

5.1.1 Genetic research in infancy

Genetic research in infancy should be considered important because, first, it forms part of a larger goal of understanding the causes of individual differences in human behaviour. It can test for genetic variants that might be specific to influencing infant behavioural development, as well as test whether genetic variants associated with psychological traits in later development are also associated with related phenotypes in infancy. That is, infant genetic research can be informative about genetic continuity and change across the lifespan (Ronald, 2011).

Specifically to the study of infant attention, knowledge about which genes play a role in attentional development in infancy would provide clues about the mechanisms involved in individual variation in early visual attention and brain development (Johnson, 2011). Knowledge about genetic risk that can be applied to infant samples has considerable potential for the identification of populations at

risk of atypical development, and thus for informing early prevention and intervention approaches. This becomes apparent considering that most psychological disorders appear to have their onset after infancy; and because studying individual difference in infant visual attention could facilitate the early identification of individuals at risk for developing certain behavioural problems connected to attention difficulties (for example ASD and ADHD).

5.1.2 Candidate gene studies of infant visual attention

Seven studies have linked attentional parameters with candidate genes in infancy (*Please refer to chapter 2 for details*). All employed the candidate gene association design. Genes related to dopamine (e.g. DRD4) have been hypothesised to be associated with several attentional parameters. L-DRD4 was the most well studied genetic variant and it was found to be associated with shorter look duration, shorter latencies to the first look away, less sustained attention, less novelty preference in infancy and higher novelty seeking in adolescent. However there are currently mixed findings regarding the possible association between genetic variants and visual attention in infancy (see Papageorgiou & Ronald, 2013 for a review).

The present chapter aimed to study GWAS-derived SNPS. L-DRD4 is not a SNP; it belongs to a type of common genetic variation named Variable Number Tandem Repeats (VNTRs). Microarrays do not tag VNTRs. It is possible to use a haplotype based on the combination of two SNP's as a marker of certain VNTRs (for example the 5-HTTLPR) but this technique involves limitations as it provides only with a distant proxy for the original VNTR (Vinkhuyzen, 2011). The aim here was to employ SNP data and to focus on genome-wide significant SNP variants, which have stronger evidence of

association than candidate genes. As such, the L-DRD4 has not been explored as a candidate marker in the current work.

Genetic research in the area of infant visual attention has faced similar challenges to research in the area of infant genetics more broadly. These refer mainly to the inconclusive findings regarding the link between genes and attentional parameters in infancy. The inconclusive findings in genetics of infant attention could be explained by "true" changes in the genetic architecture on a particular attentional domain across infant development (see Sheese et al., 2009). For example, it was reviewed in section 2.5.2 of Chapter 2 that being homozygous for the T allele of the CHRNA4 might be advantageous for orienting attention (and hence self-regulation) only in infancy and not later in development. Looking at the cognitive level and the development of different systems of attention provides with an interesting interpretation: it is possible that the advantage of being homozygous for the T allele of the CHRNA4 in infancy for orienting attention might not hold later in development, when the control of self-regulation is passed from the orienting attention system to the executive attention system (Petersen & Posner, 2012; Posner, Rothbart, Sheese & Voelker, 2012). The inconclusive findings could also be explained from inherited limitations of the candidate gene association methodology, namely a weak a priori hypothesis; or other reasons such us lack of power and genotyping errors (Plomin, 2013).

5.1.3 The current study

The current project represents a preliminary study into the role of genome-wide derived common SNPs previously associated with psychopathology in predicting variation in infant mean fixation duration and newborn average dwell time. Specifically, the aim of the project was to investigate whether genome-wide

derived, common single nucleotide polymorphisms (SNPs) previously associated with psychopathology also explain variation in newborn average dwell time and infant mean fixation duration. This approach brings the potential to decrease the chances of false positive associations—a major limitation in the candidate gene association design. This is due to the fact that associations between genes and psychological phenotypes that were derived by GWAS are more systematic in comparison to associations that were derived by candidate gene studies (see Papageorgiou & Ronald, 2013).

ADHD and schizophrenia polygenic risk score (PRS) were also constructed and tested for association with newborn average dwell time and infant mean fixation duration. PRS analysis has the potential to provide a predictor with better discrimination properties in comparison to one based on individual genetic markers and to maximise the study's statistical power to detect an association (Wray, Goddard, Visscher & 2007). Given that the main target of the PRS analytic protocol is to predict risk of disorder or individual's trait values, polygenic risk score analysis could be particularly informative when used in samples at the earliest stage of development (e.g. infancy). The project is innovative in two key ways:

1) It associates genome-wide derived SNPs--rather than variants derived from a theoretical a priori hypothesis--with infant mean fixation duration and newborn average dwell time. This is the first time that genome-wide derived SNPs are tested for association with infant phenotypes.

2) It constitutes the first attempt to bring together the polygenic risk score methodology (PRS) with psychological phenotypes in infancy and at birth.

5.1.4 Hypotheses

Considering that individual variation in mean fixation duration in infancy and average dwell time at birth is negatively associated with individual variation in surgency, hyperactivity-inattention and total behavioural difficulties in childhood respectively, it was hypothesized that:

1) SNPs that have been found previously to increase the risk for diagnosed ADHD in a large scale meta-analysis of ADHD GWAS studies in childhood (Neale et al., 2010) will be negatively associated with individual variation in infant mean fixation duration and newborn average dwell time. Specifically, SNPs that represented the two most significant hits (*rs1464807* and *rs7463256*) in Neale et al (2010) meta-analysis of ADHD GWAS studies have been selected (please refer to 5.2.5 for detail).

2) ADHD PRS would be negatively associated with both infant mean fixation duration and newborn average dwell time.

Moreover, given that recent evidence suggest that certain SNPs are associated with a range of psychiatric disorders of childhood onset or adult onset (Smoller et al., 2013); and that there is some evidence to show shared genetic susceptibility between adult schizophrenia and childhood ADHD (Hamshere et al., 2013), it was hypothesised that:

3) SNPs that have been found previously to increase the risk for diagnosed schizophrenia in a large scale meta-analysis of schizophrenia GWAS studies (Ripke et al., 2013) will be negatively associated with individual variation in infant mean fixation duration and newborn average dwell time. Specifically, SNPs that represented the two most significant hits (*rs7085104* and *rs6461049*) in Ripke et al. (2013) meta-analysis of schizophrenia GWAS studies have been selected (please refer to 5.2.5 for detail).

4) Schizophrenia PRS would be negatively associated with both infant mean fixation duration and newborn average dwell time. The main reason for this analysis was that Ripke et al. (2013) meta-analysis represents the study with the largest sample size and SNPs out of all studies that are available in the Psychiatric Genomics Consortium (PGC) database. As such, schizophrenia PRS constitutes the best available risk predictor of psychopathology at present.

Given that the predictive accuracy of the PRS depends upon the size of the training sample (that refers to the sample size of the original GWAS meta-analysis; Dudbridge, 2013) and the fact that genome-wide significant SNPs (those that returned a p-value of less than 5×10^{-8}) have been detected only in the schizophrenia meta-analysis (not in the ADHD meta-analysis) it was expected that schizophrenia PRS will return stronger and more systematic associations with newborn and infant visual attention parameters in comparison to ADHD PRS.

Finally, It was expected that the associations between candidate SNPs and PRS with visual attention parameters would not be specific to either mean fixation duration or to average dwell time; instead they would show pleiotropic effects (i.e. be associated with both parameters of visual attention) and the direction of all associations would be negative.

5.2 Method

5.2.1 Sample

5.2.1.1 Validation Samples. The participant pool comprised of 120 children (the UK sample; 55 males, 65 females) and 80 children (the Italian sample; 44 males, 36 females) that took part in the studies that were described in Chapter 3 and 4, respectively. In the UK sample, the parents of the children collected the DNA (using a buccal cheek swab collection kit; see section 5.2.2

below). The thesis author posted the DNA collection kit (please refer to section 5.2.2 for detail) to their home along with detailed instructions as to how to perform the DNA sample collection. The parents returned the DNA samples after collection using a prepaid envelope. In the Italian sample the author of this thesis visited the families in their home to collect the DNA samples using the same (to the UK study) DNA collection kit. Immediately after collection the UK and Italian DNA samples were placed in locked cabinets in typical room temperatures at Birkbeck University of London and at the University of Padua, respectively. Subsequently, they were posted to the Institute of Psychiatry, King's College London to be processed using standard DNA extraction protocols (please refer to section 5.2.2 for detail).

The concentration of DNA in fifteen samples was found to be below 70ng/ul. These samples were excluded from further analysis; ten participants had call rates of below 95% so they have been excluded from any further analysis (please refer to section 5.2.3 for detail). As such, the final sample consisted of 100 children in the UK sample (48 males, 52 females) and 75 children in the Italian sample (44 males, 31 females), respectively.

The project has received ethical approval by the Ethics Committees of the Psychology Departments of both Birkbeck University of London and the University of Padua.

5.2.1.2 The Psychiatric Genomics Consortium (PGC) result datasets. The purpose of the Psychiatric Genomics Consortium (PGC; http://www.med.unc.edu/pgc) is to conduct mega-analyses of genome-wide data for psychiatric disorders. In the current study the PGC ADHD (Neale et al., 2010) and schizophrenia (Ripke et al., 2013) meta-analysis result datasets were used.

The ADHD sample comprised of 2,064 trios, 896 cases, and, 2,455 controls genotyped for 1,206,461 SNPs. The schizophrenia sample comprised of 13,833 cases and 18,310 controls genotyped for 9,898,078 SNPs.

The PGC ADHD (Neale et al., 2010) and Schizophrenia (Ripke et al., 2013) result datasets were used. The result datasets that were used in this study to construct the PRS (see section 5.2.6 for detail) are freely available (http://www.med.unc.edu/pgc/downloads) and include the results of the meta-analyses (Neale et al. 2010; Ripke et al., 2013). Specifically, the files include information on all SNP names and chromosomal positions; the SNP minor and major allele; the odds ratio, standard error and p-value that each SNP returned in the original meta-analysis; and information on the quality of imputation (for imputed SNPs only).

5.2.2 Cheek swab collection, DNA extraction and genotyping

The DNA sample collection was performed either by the participants' parents (UK sample) or by the thesis author (Italian sample). The DNA extraction and quantification was performed at the Institute of Psychiatry, King's College London. The genotyping was performed at the UCL Genomics Lab. All subsequent analysis including quality control was performed by the thesis author. The only stage of the quality control that was first performed at UCL and was redone by the thesis author was checking for genotyping rate per individual.

In the UK study, a standard DNA collection kit was sent to all participants that also contained a prepaid return envelope and detailed instructions on how to perform the DNA collection; 10 cotton wool buds, and a 15-ml tube containing 2.5 ml of a storage/preservative solution. The parents were asked to swab the inside of their child's mouth; each swab was carried out for approximately 20

seconds using a different area of the mouth. The swabs were then immediately placed in the tube with the storage medium and sealed. All 10 swabs were placed into a single storage tube (Freeman et al., 1997). The parents could contact the thesis author via phone, email or post to ask for additional information regarding the procedure. When all the samples were collected, they were returned to the thesis author by post. On receiving the samples, they were stored at room temperature. The method to collect the DNA is described in detail in Freeman et al., (1997).

In the Italian study that was conducted in Trieste, Italy and it was described in Chapter 4 the thesis' author performed the collection of the DNA.

DNA extraction was performed at the Institute of Psychiatry, King's College London by trained lab technicians. DNA from cheek swabs needs to be extracted within a few weeks to prevent degradation. The samples were processed within 3 to 5 weeks after collection. DNA concentration and purity was determined by UV spectrophotometrically and confirmed by gel electrophoresis (Freeman et al., 1997).

The average DNA concentration in the UK sample was 70,00 ng/ul, which is the stated minimum concentration required for the genotyping microarray protocol's. The average DNA concentration in the Italian sample was 444,00 ng/ul. This difference could stem from the fact that the children in the Italian sample were older in comparison to the UK sample hence more cooperative during the DNA collection process. In addition, the DNA collection in the Italian sample was performed by the thesis' author; as such, additional care was given to ensure thorough collection of the DNA samples. However the intergrity and purity of the DNA that was obtained from both samples were high as proven by

the small number of participants that were excluded due to low call rate (13 out of 185 participants). Following DNA extraction and quantification, the samples were stored at -80^{o} C and transferred to UCL Genomics Lab for genome-wide genotyping.

Genotyping was performed on the Illumina HumanOmniExpress v1.0. (http://res.illumina.com/documents/products/datasheets/datasheet_human_omni_express.pdf). The HumanOmniExpress microarray contains >715,000 SNPs and is designed to capture the majority of common SNP variation in human populations. The thesis author was not involved in this process.

Following genotyping, the genotyping call rate per individual was tested at UCL lab. Thirteen individuals were excluded from any further analysis because their genotyping call rate was below 95%. Low genotyping call rate (usually < 95%) for each individual is associated with statistical uncertainty because first, in heterozygous individuals, both alleles may not have been sampled (Nielsen, Korneliussen, Albrechtsen, Li & Wang, 2012); and secondly, high raw error rates may cause a significant amount of homozygous genotypes to be wrongly inferred as heterozygous, if genotype calling is based on just absence/presence of an allele (Nielsen, et al. 2012). The genotyping rate in the remaining 175 individuals in both samples was always above 99%.

5.2.3 Quality control

SNP quality control in the UK and Italian datasets was performed using PLINK version 1.07 (Purcell et al., 2007, http://pngu.mgh.harvard.edu/purcell/plink/). The genotyping rate for the remaining 175 individuals was recalculated to ensure that all individual had a call rate of above 95%. The SNPs in both samples were also required to have a minor

allele frequency (MAF) > .0.02; call rate > .0.90; and Hardy-Weinberg Equilibrium $p > 1 \times 10^{-6}$. SNPs that did not meet those criteria were removed from any further analysis. As a result after quality control the UK dataset had 645,100 SNPs. The Italian dataset had 614,328 SNPs.

From the PGC SNPs' dataset, SNPs with quality imputation information of less than .899 and the Major Histocompatibility Complex (MHC) region were excluded due to complex LD structure.

5.2.4 Population stratification

In case-control genetic association studies, the most important spurious cause of an association is population structure (Balding, 2006). This problem arises when cases disproportionately represent a genetic subgroup, so that any SNP with allele proportions that differ between the subgroup and the general population will be associated with case or control status (Balding, 2006). It has also been shown that population stratification can be a major cause of spurious associations in association analyses of quantitative traits with the rate of false positives to increase with simultaneous increase in differences in the marker allele frequencies in the subpopulations (Haldar & Ghosh, 2012).

To check for the presence of population stratification, population principal components were calculated based on pairwise population concordance (PPC) test for both the UK and the Italian sample in PLINK. This is a simple significance test for whether two individuals belong to the same random-mating population; it creates population clusters that do not contain individuals differing at a certain p-value (.0001 in the present study). Eleven and six principal components were identified in the UK and Italian sample, respectively. The principal components were used as covariates in the regression analysis.

5.2.5 SNP selection

Table 5.1 below presents the SNPs that were selected in the current study to be tested for association with infant and newborn attentional measures. The first two columns present the chromosome and the gene that each SNP resides, respectively. The third and fourth column presents the SNPs and their reference (minor) alleles and the minor alleles' frequencies (in brackets). The last three columns present the p-value that each SNP has returned in the original study, the disorder that has been linked with and the reference of the original study.

In Neale et al. (2010) meta-analysis the top hit was the SNP rs1464807 ($p = 1.10x10^{-6}$), which is in a gene-poor region. The SNP lays 230 kb 5´to SHFM1 gene (Neale et al., 2010). Eight SNPs in the region were among the top 50 hits in Neale et al. (2010), which gives credibility to this association finding (Neale et al., 2010). However according to the authors, the second hit (rs177290098; $p = 1.68 x10^{-6}$) was most likely a false positive, as SNPs in the region, which were in linkage disequilibrium (LD) with this SNP, did not show any association signal (Neale et al., 2010). As such, in the present study the SNP that was the third most significant hit in Neale et al. (2010) meta-analysis has been selected. The third strongest hit (rs7463256; $p=3.17 x10^{-6}$) showed strong regional association, indicating that this was not likely to be a technical artifact. This association signal is close to the 5´end of the CHMP7 gene, with a number of additional SNPs in the top 50 list (see Neale et a., 2010) present located within the gene (Neale et al., 2010).

In Ripke et al. (2013) meta-analysis the second and third top hit were the SNPs rs7085104 ($p = 3.68 x10^{-13}$) and rs6461049 ($p = 5.93 x10^{-13}$), respectively. Those two SNPs were selected in the current study to be tested for association

with infant and newborn attentional measures. The SNP that returned the strongest association in Ripke et al. (2013) meta-analysis was not available in the current dataset; no proxy for this SNP could be identified either using SNAP (Johnson et al. 2008).

Table 5.1. SNPs selected in the current study to be tested for association with infant and newborn mean fixation duration and average dwell time.

CHR	GENE	SNP	A1	p-value	Disorder	Reference
7	-	rs1464807	T(.10)	$1.10x10^{-6}$	ADHD	Neale et al., 2010
8	CHMP7	rs7463256	T(.34)	$3.17x10^{-6}$	ADHD	Neale et al., 2010
10	AS3MT	rs7085104	G(.39)	$3.68x10^{-13}$	Schizophrenia	Ripke et al., 2013
7	MAD1L1	rs6461049	C(.47)	$1.07x10^{-11}$	Schizophrenia	Ripke et al., 2013

5.2.6 Creating the polygenic risk scores

In the current study, Psychiatric Genomics Consortium (PGC) schizophrenia (Ripke et al. 2013) and PGC ADHD (Neale et al. 2010) stage-1 GWAS mega-analysis full results were downloaded and used to create two PRS; one for schizophrenia and one for ADHD. First, linkage disequilibrium (LD) pruning (independent-pairwise approach) at p-value thresholds of 0.01 (p_T1), 0.05 (p_T2), 0.1 (p_T3), 0.2 (p_T4), 0.3 (p_T5), 0.4 (p_T6), 0.5 (p_T7), and 1.00 (p_T8) was performed separately on both datasets in PLINK version 1.07 (Purcell et al. 2007). LD pruning considers a window of 200 SNPs; it calculates LD between each pair of SNPs in the window and removes one SNP per pair if the LD is greater than a certain threshold (0.25 in the current analysis). Subsequently it shifts the window forward by 5 SNPs and repeats the procedure. The PRS for each genotyped individual in the UK and Italian sample represented the sum of risk alleles

weighted by the log of the odds ratio from the PGC samples. The number of SNPs per threshold and the correlations between each p-value threshold for ADHD and schizophrenia PRS are summarised in tables 5.2 and 5.3, respectively.

Table 5.2. Number of SNPs per threshold and the correlations between each p-value threshold for ADHD PRS in the UK and Italian sample

ADHD Polygenic Risk Score Pearson Correlation Coefficients UK sample (N = 100)									
	N of SNPs	PT1	PT2	PT3	PT4	PT5	PT6	PT7	PT8
PT1 (*.00-.01*)	953	-	.66**	.56**	.50**	.41**	.36**	.34**	.32**
PT2 (*.00-.05*)	4,503	.66**	-	.84**	.75**	.73**	.69**	.69**	.67**
PT3 (*.00-.1*)	8,845	.56**	.84**	-	.87**	.80**	.75**	.75**	.73**
PT4 (*.00-.2*)	17,526	.50**	.76**	.87**	-	.92**	.90**	.88**	.86**
PT5 (*.00-.3*)	26,236	.41**	.73**	.80**	.92**	-	.97**	.96**	.93**
PT6 (*.00-.4*)	34,879	.36**	.69**	.76**	.90**	.97**	-	.98**	.96**
PT7 (*.00-.5*)	43,532	.34**	.69**	.75**	.88**	.95**	.98**	-	.98**
PT8 (*.00-1.0*)	86,520	.32**	.67**	.73**	.86**	.93**	.96**	.98**	-
ADHD Polygenic Risk Score Pearson Correlation Coefficients Italian Sample (N = 75)									
	N of SNPs	PT1	PT2	PT3	PT4	PT5	PT6	PT7	PT8
PT1 (*.00-.01*)	865	-	.51**	.43**	.21	.28*	.26*	.25*	.26*
PT2 (*.00-.05*)	4,163	.51**	-	.76**	.52**	.53**	.50**	.52**	.47**
PT3 (*.00-.1*)	8,131	.43**	.76**	-	.79**	.77**	.74**	.74**	.70**
PT4 (*.00-.2*)	16,038	.21	.51**	.79**	-	.93**	.91**	.87**	.84**
PT5 (*.00-.3*)	23,841	.28*	.53**	.77**	.93**	-	.97**	.94**	.91**
PT6 (*.00-.4*)	31,664	.26*	.50**	.74**	.91**	.97**	-	.97**	.94**
PT7 (*.00-.5*)	39,560	.25*	.52**	.74**	.87**	.94**	.97**	-	.97**
PT8 (*.00-1.0*)	78,937	.26*	.47**	.70**	.84**	.91**	.95**	.97**	-

p<.05; p<.001***

Table 5.3. Number of SNPs per threshold and the correlations between each p-value threshold for schizophrenia PRS in the UK and Italian sample

Schizophrenia Polygenic Risk Score Pearson Correlation Coefficients UK sample (N = 100)									
	N of SNPs	PT1	PT2	PT3	PT4	PT5	PT6	PT7	PT8
PT1 (*.00-.01*)	2,107	-	.71**	.62**	.59**	.57**	.57**	.57**	.58**
PT2 (*.00-.05*)	7,792	.71**	-	.93**	.87**	.85**	.83**	.83**	.82**
PT3 (*.00-.1*)	14,025	.62**	.93**	-	.93**	.91**	.89**	.89**	.87**
PT4 (*.00-.2*)	25,610	.59**	.87**	.93**	-	.97**	.94**	.94**	.93**
PT5 (*.00-.3*)	36,647	.57**	.85**	.91**	.97**	-	.97**	.96**	.95**
PT6 (*.00-.4*)	47,262	.57**	.83**	.89**	.94**	.97**	-	.99**	.97**
PT7 (*.00-.5*)	57,661	.57**	.83**	.89**	.94**	.96**	.99**	-	.98**
PT8 (*.00-1.0*)	108,361	.57**	.82**	.87**	.93**	.95**	.97**	.98**	-
Schizophrenia Polygenic Risk Score Pearson Correlation Coefficients Italian Sample (N = 75)									
	N of SNPs	PT1	PT2	PT3	PT4	PT5	PT6	PT7	PT8
PT1 (*.00-.01*)	1,935	-	.64**	.53**	.47**	.45**	.43**	.42**	.40**
PT2 (*.00-.05*)	7,189	.64**	-	.88**	.82**	.78**	.75**	.74**	.70**
PT3 (*.00-.1*)	12,966	.53**	.88**	-	.87**	.85**	.81**	.80**	.75**
PT4 (*.00-.2*)	23,511	.47**	.82**	.87**	-	.95**	.93**	.91**	.86**
PT5 (*.00-.3*)	33,595	.45**	.78**	.85**	.96**	-	.97**	.96**	.93**
PT6 (*.00-.4*)	43,227	.43**	.75**	.81**	.93**	.97**	-	.98**	.95**
PT7 (*.00-.5*)	52,759	.43**	.75**	.80**	.91**	.96**	.98**	-	.97**
PT8 (*.00-1.0*)	98,566	.40**	.70**	.75**	.86**	.93**	.95**	.97**	-

*p<.001***

5.2.7 Phenotypic measures

The phenotypic measures consisted of the visual attentional measures of infant mean fixation duration (N=100; mean age in months = 7.60; SD = 1.84) and newborn average dwell time (N=75; mean age in days = 2.17; SD = 1.17) that were presented in detail in sections 3.3.4 and 4.3.6 in Chapters 3 and 4, respectively.

5.2.8 Statistical analyses

5.2.8.1 Descriptive Statistics. Mean fixation duration and average dwell time were explored using descriptive statistics in SPSS version 18.0. Given that the current datasets involved 100 (instead of 120) and 75 (instead of 80) infants and newborns, respectively descriptive statistics were recalculated for the two measures--although no major changes from the descriptive statistics that were reported before were expected. Due to skewness of the data, Van der Waerden's transformation (Lehmann, 1975) was used to normalise the data before further statistical analyses were undertaken.

5.2.8.2 Genome-wide derived single SNP analyses. Allelic and genotypic association analyses were undertaken between infant mean fixation duration and newborn average dwell time and the four selected SNPs using the linear regression function in PLINK. Allelic association analyses were performed using an additive linear regression model; genotypic association analyses were performed using a two degree of freedom joint test of additivity and dominance deviation. The corrected p-value significance threshold using Bonferroni adjustment was set to $p < .01$ (0.05/(2x2)), where 0.05 represents nominal significance cut-off, 2 represents the number of selected SNPs (tested separately for ADHD and schizophrenia) and 2 represents the types of genetic tests conducted (i.e. allelic and genotypic). However, it is noted that the Bonferroni correction is conservative as it assumes that all tests performed are independent of one another and could therefore result in overcorrection and potential false negatives.

5.2.8.3 Regression analysis between PRS and phenotypic measures. Linear regression analyses were performed in SPSS for Windows (version 18.0) with

ADHD and schizophrenia PRS scores as predictors of infant mean fixation duration and newborn average dwell time. The significance threshold for the polygenic risk analyses was set to $p < 0.05$.

5.2.8.4 Covariates. A number of covariates were used in both set of analysis (candidate SNP and PRS analysis). In the UK sample, the effects of age when the infant took part in the eye tracking study, sex, total number of trials (completed by infants in the eye-tracking studies) and total number of fixations detected were treated as covariates in the regression analysis. In the Italian sample, the effects of age when the newborn took part in the visual study, the newborns' total time to complete the visual experiment and the particular study (specifically the particular experiment within each study) that each newborn took part in were treated as covariates in the regression analysis. Finally, 11 (UK sample) and 6 (Italian sample) population principal components previously identified, were included as covariates in the regression analysis to account for population stratification.

5.3 Results

5.3.1 Descriptive statistics

Descriptive statistics for infant mean fixation duration and newborn average dwell time are shown in Table 5.4. As expected, the descriptive statistics did not deviate majorly from the descriptive statistics that were described in Chapters 3 and 4 for the infant and newborn visual measures, respectively. Tables 5.5 and 5.6 present the descriptive statistics for the ADHD and schizophrenia polygenic risk scores, respectively, across the eight p-value thresholds for the UK and Italian samples. Similarly to previous research, PRS means were close to

zero. Given that most individuals would have low risk to develop a certain disorder and that fact that PRS represent risk scores for a disorder, means around zero are to be expected. Also PRS means reflect a log-additive score in which each risk allele was weighted by the log of the per-allele odds ratio (OR), as previously described (Purcell et al., 2009).

Table 5.4. Descriptive statistics for infant mean fixation duration and newborn average dwell time

	UK sample	**Italian Sample**
	Infant Mean Fixation Duration (in sec)	Newborn Average Dwell Time (in ms)
N	100	75
Mean	.70	3,731
SD	.11	1,741
Median	.69	3,298
Mode	.47	559
Minimum	.47	559
Maximum	1.16	9,285
Kurtosis	3.11	1,006
Skewness	1.31	.96

Table 5.5 Descriptive statistics for the ADHD polygenic risk scores across the eight p-value thresholds for the UK and Italian samples.

Descriptive statistics for the ADHD PRS across the eight p-value thresholds-UK sample									
		PT1	PT2	PT3	PT4	PT5	PT6	PT7	PT8
N		100	100	100	100	100	100	100	100
Mean		-.04069	.01706	.04769	.04079	.03281	.02537	.02047	.01000
Std. Deviation		.04247	.01691	.01058	.00697	.00529	.00434	.00364	.00188
Range		.26472	.11532	.06278	.04338	.03253	.02750	.02215	.01123
Skewness		-.72	-.36	-.24	-.22	-.69	-.78	-.67	-.65
Percentiles	*25*	-.06856	.00668	.04073	.03616	.02999	.02331	.01846	.00901
	50	-.04038	.01697	.04701	.04099	.03306	.02539	.02057	.00999
	75	-.01075	.02790	.05481	.04458	.03569	.02803	.02272	.01134
Note. PRS, polygenic risk score; PT , p-value threshold.									
Descriptive statistics for the ADHD PRS across the eight p-value thresholds-Italian sample									
		PT1	PT2	PT3	PT4	PT5	PT6	PT7	PT8
N		75	75	75	75	75	75	75	75
Mean		-.04416	-.02253	.00792	.01186	.01617	.01468	.01140	.00601
Std. Deviation		.03662	.01594	.00909	.00640	.00467	.00376	.00310	.00164
Range		.16173	.06590	.03943	.03170	.02129	.01853	.01479	.00761
Skewness		.008	-.15	.39	.18	.39	.43	.49	.40
Percentiles	*25*	-.06849	-.03344	.00143	.00752	.01285	.01186	.00930	.00479
	50	-.04140	-.02182	.00771	.01135	.01591	.01453	.01121	.00583
	75	-.01799	-.00896	.01420	.01662	.01930	.01717	.01347	.00700
Note. PRS, polygenic risk score; PT , p-value threshold.									

Table 5.6 Descriptive statistics for the schizophrenia polygenic risk scores across the eight p-value thresholds for the UK and Italian samples.

Descriptive statistics for the schizophrenia PRS across the eight p-value thresholds-UK sample									
		PT1	PT2	PT3	PT4	PT5	PT6	PT7	PT8
N		100	100	100	100	100	100	100	100
Mean		-.00141	-.00123	-.00096	-.00073	-.00061	-.00054	-.00047	-.00026
Std. Deviation		.00025	.00015	.00011	.00008	.00006	.00005	.00004	.00002
Range		.00141	.00079	.00065	.00045	.00034	.00030	.00026	.00015
Skewness		.37	1.06	1.40	1.18	1.33	1.31	1.28	1.45
Percentiles	*25*	-.00160	-.00133	-.00104	-.00079	-.00066	-.00058	-.00050	-.00027
	50	-.00142	-.00125	-.00098	-.00074	-.00062	-.00055	-.00048	-.00026
	75	-.00125	-.00116	-.00090	-.00070	-.00058	-.00052	-.00045	-.00025
Note. PRS, polygenic risk score; PT , p-value threshold.									
Descriptive statistics for the schizophrenia PRS across the eight p-value thresholds-Italian sample									
		PT1	PT2	PT3	PT4	PT5	PT6	PT7	PT8
N		75	75	75	75	75	75	75	75
Mean		-.00222	-.00107	-.00075	-.00055	-.00046	-.00036	-.00030	-.00016
Std. Deviation		.00027	.00012	.00008	.00006	.00004	.00003	.00003	.00002
Range		.00108	.00062	.00037	.00032	.00023	.00001	.00001	.00008
Skewness		.33	-.01	-.25	-.29	-.01	.08	.06	.02
Percentiles	*25*	-.00241	-.00115	-.00080	-.00058	-.00049	-.00038	-.00031	-.00017
	50	-.00226	-.00107	-.00074	-.00054	-.00046	-.00036	-.00030	-.00016
	75	-.00204	-.0097	-.00069	-.00051	-.00043	-.00034	-.00027	-.00015
Note. PRS, polygenic risk score; PT , p-value threshold.									

5.3.2 Genome-wide derived candidate SNP analysis

Allelic and genotypic association analyses were undertaken between infant mean fixation duration and newborn average dwell time and the four selected SNPs using the linear regression function in PLINK. None of these variants were significant. Table 5.7 presents the results of the allelic and genotypic association analyses between the four SNPs and transformed infant mean fixation duration and newborn average dwell time.

Table 5.7. Full results of allelic & genotypic association analyses for transformed mean fixation duration and average dwell time

				Allelic Association				**Genotypic Association**
	SNP	Chr	Allele	Beta	*t*-Stat	SE	ADD *p*-value	Geno_2DF *p*-value
UK Sample N=100								
	rs1464807	7	A	-.02	-.09	.23	.92	.45
	rs7463256	8	G	-.07	-.53	.14	.59	.79
	rs7085104	10	G	-.10	-.88	.12	.37	.07
	rs6461049	7	G	.01	.10	.14	.91	.13
Italian Sample N=75								
	rs1464807	7	A	.52	1.49	.21	.14	.19
	rs7463256	8	G	-.22	-1.17	.16	.24	.39
	rs7085104	10	G	.02	.12	.15	.89	.93
	rs6461049	7	G	.17	1.07	.15	.28	.12

Note: Chr, chromosome; Allele, risk allele; Beta, regression coefficient; ADD, additive linear regression model; GENO_2DF, two degrees of freedom joint test of additivity and dominance deviation (it does not assume a linear relationship)

5.3.3 Associations between ADHD PRS with infant and newborn visual attention

Neither infant mean fixation duration nor newborn average dwell time showed significant associations with ADHD PRS across all thresholds. However, as hypothesised the direction of the association between ADHD PRS and infant mean fixation duration was negative (although the results were not significant).

The direction of the association between ADHD PRS and newborn average dwell time was positive, which was not expected. The summary of results for the ADHD PRS at all thresholds for the UK and Italian sample is presented in Tables 5.8 and 5.9, respectively.

Table 5.8. Summary of results for ADHD PRS as a predictor of infant mean fixation duration

ADHD Polygenic Risk Score							
Phenotype: Mean Fixation Duration (N = 100)							
p-value thresholds	N of SNPs	β	t	95% CI for β Lower Bound	95% CI for β Upper Bound	R^2	p-value
PT1 (*.00-.01*)	953	-.10	-1.12	-.285	.079	.009	.26
PT2 (*.00-.05*)	4503	-.07	-.87	-.257	.100	.005	.38
PT3 (*.00-.1*)	8845	-.11	-1.19	-.302	.075	.01	.23
PT4 (*.00-.2*)	17526	-.17	-1.80	-.357	.017	.02	.07
PT5 (*.00-.3*)	26236	-.09	-1.01	-.284	.093	.007	.31
PT6 (*.00-.4*)	34879	-.12	-1.34	-.307	.059	.01	.18
PT7 (*.00-.5*)	43532	-.11	-1.25	-.304	.069	.01	.21
PT8 (*.00-1.0*)	86520	-.12	-1.319	-.311	.063	.01	.19

Note: PT , p-value threshold.

Table 5.9 Summary of results for ADHD PRS as a predictor of newborn average dwell time

ADHD Polygenic Risk Score							
Phenotype: Average Dwell Time (N = 75)							
p-value thresholds	N of SNPs	β	t	95% CI for β Lower Bound	95% CI for β Upper Bound	R^2	p-value
PT1 (*.00-.01*)	865	-.07	-.58	-.289	.159	.004	.56
PT2 (*.00-.05*)	4163	.12	.99	-.116	.345	.01	.32
PT3 (*.00-.1*)	8131	.08	.61	-.165	.310	.005	.54
PT4 (*.00-.2*)	16038	.04	.27	-.225	.296	.001	.78
PT5 (*.00-.3*)	23841	.02	.21	-.219	.271	.001	.83
PT6 (*.00-.4*)	31664	.08	.545	-.168	.314	.005	.54
PT7 (*.00-.5*)	39560	.02	.20	-.218	.266	.001	.84
PT8 (*.00-1.0*)	78937	.004	.03	-.240	.247	.000	.97

Note. PT , p-value threshold.

5.3.4 Associations between schizophrenia PRS with infant and newborn visual attention

Infant mean fixation duration showed significant association with schizophrenia PRS across thresholds PT2 to PT8. The most significant association was found at threshold PT5; 36,647 SNPs (that returned p-values between .00 and .30 in Ripke et al., 2013 meta-analysis) explained 7% of the variation in infant mean fixation duration (β = .28, R^2 = .07, p = .001). Although the result was highly significant accounting for a moderate amount of variation in the phenotype, the direction of the association was positive suggesting that higher polygenic risk score for schizophrenia is associated with longer mean fixation duration in infancy.

Only a weak significant association between schizophrenia PRS and newborn average dwell time was observed. Specifically, 12,966 SNPs (that returned p-values between .00 and .10 in Ripke et al., 2013 meta-analysis)

explained 2% of the variation in newborn average dwell time (β = .25, R^2 = .02, p = .04); the direction of the association was again positive.

The summary of results for the schizophrenia PRS for all thresholds for the UK and Italian sample are presented in Tables 5.10 and 5.11, respectively.

Table 5.10. Summary of results for schizophrenia PRS as a predictor of infant mean fixation duration

Schizophrenia Polygenic Risk Score							
Phenotype: Mean Fixation Duration (N = 100)							
p-value thresholds	N of SNPs	β	t	95% CI for β Lower Bound	95% CI for β Upper Bound	R^2	p-value
P_T1 (*.00-.01*)	2,107	.13	1.37	-.06	.32	.01	.17
P_T2 (*.00-.05*)	7,792	.21	2.24	.025	.407	.03	.02
P_T3 (*.00-.1*)	14,025	.28	3.06	.099	.466	.06	.003
P_T4 (*.00-.2*)	25,610	.30	3.19	.114	.489	.06	.002
P_T5 (*.00-.3*)	36,647	.31	3.32	.126	.501	.07	.001
P_T6 (*.00-.4*)	47,262	.27	2.88	.087	.472	.05	.005
P_T7 (*.00-.5*)	57,661	.24	2.55	.055	.442	.04	.01
P_T8 (*.00-1.0*)	108,361	.23	2.35	.036	.426	.03	.02

Note. P_T , p-value threshold.

Table 5.11. Summary of results for schizophrenia PRS as a predictor of newborn average dwell time

Schizophrenia Polygenic Risk Score							
Phenotype: Average Dwell Time (N = 75)							
p-value thresholds	N of SNPs	β	t	95% CI for β Lower Bound	95% CI for β Upper Bound	R^2	p-value
P_T1 (*.00-.01*)	1,935	.09	.71	-.155	.326	.006	.47
P_T2 (*.00-.05*)	7,189	.18	1.40	-.069	.393	.02	.16
P_T3 (*.00-.1*)	12,966	.25	2.07	.007	.452	.02	.04
P_T4 (*.00-.2*)	23,511	.18	1.50	-.055	.384	.02	.13
P_T5 (*.00-.3*)	33,595	.17	1.34	-.076	.382	.02	.18
P_T6 (*.00-.4*)	43,227	.18	1.44	-.065	.398	.02	.15
P_T7 (*.00-.5*)	52,759	.13	1.02	-.113	.349	.01	.31
P_T8 (*.00-1.0*)	98,566	.08	.66	-.169	.321	.005	.51

Note. P_T , p-value threshold.

5.4 Discussion

The aim of the current study was twofold. Firstly it explored the degree to which individual SNPs that have been found previously to increase the risk for diagnosed ADHD and schizophrenia would account for individual differences in infant mean fixation duration and newborn average dwell time. Secondly, it investigates whether a moderate amount of variation in infant mean fixation duration and newborn average dwell time could be accounted by the ensemble of thousands of common genetic markers previously associated with diagnosed ADHD (Neale et al., 2010) and schizophrenia (Ripke et al., 2013). The single SNPs analysis raised no significant associations between the four selected SNPs and infant mean fixation duration and newborn average dwell time. The PRS results revealed that genetic markers previously found to increase the risk for

diagnosed schizophrenia account for up to 7% of the variation in infant mean fixation duration.

This is the first study to explore the role of common genetic variation in visual attention at birth; and the first work to combine the polygenic risk score methodology with an infant psychological phenotype. Although preliminary, the results of the current pilot project bring several theoretical advances in the area of individual differences in infant visual attention.

The selected SNPs had found to increase the risk for diagnosed ADHD and schizophrenia in large meta-analyses of case-control GWAS (Neale et al., 2010; Ripke et al., 2013). As such, it is possible that the selected loci exhibit some degree of specificity contributing significantly to the development of the disorders but not to parameters of visual attention in infancy. In addition, the ADHD related SNPs have failed to reach genome-wide significance in the original study (Neale et al. 2010), which compromises the reliability of the reported associations. Most likely however, the sample size of this study was a limiting factor in detection of the potential positive associations.

PRS analysis has the potential to offer a predictor with better discrimination properties in comparison to one based on individual genetic markers and to maximize the study's statistical power to detect an association (Wray, Goddard &Visscher, 2007). Indeed, schizophrenia PRS were a significant predictor of infant mean fixation duration assessed using eye tracking.

ADHD PRS did not yield any significant associations with newborn average dwell time and infant mean fixation duration. Given that the predictive accuracy of the PRS depends upon the size of the training sample (that refers to the sample of the original GWAS meta-analysis; Dudbridge, 2013); and the fact

that genome-wide significant SNPs (those that returned a p-value of less than 5 x 10^{-8}) have been detected only in the schizophrenia meta-analysis--and not in the ADHD meta-analysis--means that this was somewhat expected.

Schizophrenia PRS return significant associations between newborn average dwell time and infant mean fixation duration. The significant association between schizophrenia PRS and newborn average dwell time was weak with the proportion of variance in newborn average dwell time to be explained by schizophrenia PRS being 2% (PT3). The significant associations between schizophrenia PRS and mean fixation duration were of moderate magnitude, with the proportion of variance in infant mean fixation duration to be explained by schizophrenia PRS being between 4% (PT7) and 7% (PT5). The smaller number of significant associations that were observed between schizophrenia PRS and average dwell time as compared to schizophrenia PRS and mean fixation duration could be due to the smaller sample size in the Italian sample as compared to the UK sample. As mentioned in previous chapters, it is also possible that fixation duration assessed using eye tracking is a more fine grained measure of visual attention in comparison to newborn average dwell time assessed using video camera.

The direction of the significant associations between schizophrenia PRS and newborn average dwell time and infant mean fixation duration were positive. As such the results suggest that genes influencing liability for schizophrenia influence infant development, specifically predicting infants to have longer mean fixation duration and longer average dwell time. Although preliminary, the results could also suggest that similar genetic factors operate to produce variation in those two attentional measures in the first year of postnatal life.

It was hypothesized that higher polygenic risk scores for liability for schizophrenia would be associated with shorter mean fixation duration. This was hypothesised because it was shown in Chapter 3 that shorter mean fixation duration was associated with increased psychopathology (albeit for a different form of psychopathology and in childhood rather than adulthood). It has been reported that common SNPs have pleiotropic effects, being associated with multiple psychiatric disorders of childhood onset and adult onset (Smoller et al., 2013). Furthermore there is some evidence to show shared genetic susceptibility between adult schizophrenia and childhood ADHD (Hamshere et al., 2013), although other studies suggest this is not the case (Lee et al., 2013). As such, the positive direction of the associations between schizophrenia PRS and attentional measures in infancy that were reported in this study were unexpected.

However a recent visual study that investigated eye movement differences during facial emotion recognition between 101 patients with schizophrenia and 101 controls reported that mean fixation duration was significantly longer in patients with schizophrenia in comparison to normal controls (Zhu et al., 2013). Similar results have also derived from an eye tracking study that reported longer mean fixation duration during free exploration of six photos of daily life situations in schizophrenia patients as compared to healthy individuals (Sprenger et al., 2013). Atypical scanpaths in response to broad range of visual stimuli and in different tasks were also reported with schizophrenia patients exhibiting increased mean fixation duration as compared to healthy viewers (see Beedie, Clair & Benson, 2011 for a review). The results of the current research demonstrate for the first time that there is a shared genetic link between newborn average dwell time and infant mean fixation duration with diagnosed schizophrenia in

adulthood. As such, if replicated these findings could have significant implications for the development of early identification of populations at risk of developing schizophrenia.

The findings should be considered in light of some limitations. The most important limitation refers to the sample size. The small (for genetic research) sample size of the current study placed constraints on how many SNPs could be tested for an association with the phenotypic measures. Quantitative traits are polygenic; many genetic markers with tiny effect sizes are contributing to individual differences on those traits. As such, large sample sizes are necessary in order to detect associations between genetic markers and human complex traits (Plomin, 2013). A second limitation of this work is that the 'replication' sample (the sample of newborns) was not an exact match in terms of age or phenotype. Given that many candidate gene studies have reported false positive associations in the past, it is essential to replicate genetic association findings in an independent sample.

The polygenic risk scores have been derived from large meta-analyses of GWAS in childhood (ADHD; Neale et al., 2010) and adulthood (schizophrenia; Ripke et al., 2013). Once large-scale GWAS on infant visual attention have been conducted it would be interesting to test whether individual differences in infant mean fixation duration and newborn average dwell time would be predicted by visual attention PRS that derived from infant samples.

The current pilot study brings together for the first time the polygenic risk score methodology with infant eye tracking data and newborn visual data. The results revealed a significant genetic link between adult schizophrenia PRS and infant mean fixation duration and newborn average dwell time. As such, future

longitudinal studies could investigate whether individual differences in average dwell time and mean fixation duration in infancy would predict individual variation in psychotic experiences in adulthood. Future studies could also explore whether the direction of the association between schizophrenia PRS and mean fixation duration changes across development. Future work could explore developmentally the function and product of the genes that associate with both schizophrenia and infant mean fixation duration in order to understand the biological mechanisms that link the two phenotypes.

DISCUSSION

6 General Discussion

6.1 Overview

Attention is defined as a cognitive process that is constituted from a number of highly associated but distinguishable processes and that has both an endogenous and an exogenous component (Scerif, 2010). Individual differences in infants' visual attention have been associated with individual variation in cognition in infancy and later in life (Colombo et al., 2010). Specifically, the results of the literature review that was presented in Chapter 1 have shown that the most replicated set of findings in infant's visual attention studies is that SL infants are processing information more efficiently that LL infants; and that shorter peak look duration during habituation and dishabituation paradigms in infancy is associated with higher cognitive abilities (e.g. IQ) in childhood, adolescence and adulthood (Colombo et al., 2010; Kavsek & Bornstein, 2010).

The results of the literature review that was presented in Chapter 1 has demonstrated also that longitudinal research could expand the link between individual differences in infant visual attention and child traits, to phenotypes other than general cognitive ability; such traits could be temperament and behaviour. Specifically, given that attentional and behavioural control is based upon overlapping brain systems (Petersen & Posner, 2012) future research could explore the link between individual differences in infant visual attention and traits such as effortful control, surgency and hyperactivity-inattention in childhood (see section 3.2.1 for details). In addition, longitudinal work that aims to investigate the extent to which individual differences in infant visual attention predict individual variation in

some forms of temperament and behaviour in childhood would benefit from newer techniques-such as eye tracking-that will provide with more "fine-grained" measures of infant visual attention. A further gap in the literature was observed; there were no studies that have explored the degree to which individual variation in newborn visual attention (first 5 days of postnatal life) relates to individual differences in child psychological traits. Given that newborns have been exposed to few environmental influences outside the womb, studying neonatal visual attention may facilitate our understanding of causal factors (for example prenatal factors and genetic factors) operating at birth that contribute to individual variation in attention, temperament and behaviour later in life. Investigating the causes of individual differences in visual attention as early as in the first hours after birth might inform the development of early intervention practices that will aim to improve aspects of attention, a cornerstone of human cognition.

The results of the literature review that was presented in Chapter 2 has shown that candidate gene studies have provided with limited and mixed findings regarding the possible association of genes with visual attention in infancy. Newer genetic approaches--such as polygenic risk score analysis (PRS; Purcell et al., 2009)—might prove to be more informative for shedding light on the genetic mechanisms underlying individual differences in infant visual attention.

The work that was presented in this thesis aimed to address these gaps in the literature. Specifically, this PhD thesis that comprised of three studies aimed to:

1. Investigate the degree to which individual differences in infant mean fixation duration are associated with individual differences in childhood effortful control, surgency and hyperactivity-inattention (*First PhD study presented in Chapter 3*).

2. Investigate the degree to which individual differences in newborn average dwell time are associated with individual differences in childhood effortful control, surgency, hyperactivity-inattention and total behavioural problems (*Second PhD study presented in Chapter 4*).
3. To explore the degree to which genome-wide variants previously found to increase the liability for ADHD and schizophrenia are associated with newborn average dwell time and infant mean fixation duration. (*Third PhD study presented in Chapter 5*).

The following section reviews the main findings of the first, second and third PhD study, respectively. The rest of the discussion states the direct contributions of the thesis, it addresses the limitations of the current research and it explores future directions for this line of work.

6.2 Main findings

This thesis included three main studies over three chapters. The first, second and third PhD studies are discussed in sections *6.2.1*, *6.2.2* and *6.2.3*, respectively.

6.2.1 Individual differences in infant fixation duration relate to attention and behavioural control in childhood

The first study (see chapter 3) used eye-tracking combined with a longitudinal design to investigate the degree to which individual differences in infants' mean fixation duration relates to individual variation in parent report measures of effortful control, surgency and hyperactivity-inattention in childhood. One of the study's strengths was that considerable attention was given to ensure that the observed variation per participant reflected individual variation in fixation duration and not noise produced by extraneous components (e.g. data quality). In doing that, two methodological approaches were combined for the first time to

analyse fixation duration in infancy (Saez de Urabain, 2014; Wass et al., 2013). Specifically, fixation parsing algorithms, designed to detect fixations in low quality infants' data and hand moderation using GraFix (Saez de Urabain, 2014) was performed to improve the quality of the data used in the regression analysis. This two-stage approach has significant advantages over using fixation detection algorithms or hand coding alone. More specifically, this approach provides stability in the criteria used to detect fixations (in the first stage) and with the flexibility to address limitations of the automatic fixation parsing algorithms in the second stage (hand-moderation).

In line with the hypotheses, mean fixation duration was associated positively with effortful control and negatively with surgency and hyperactivity-inattention. The reported associations were of moderate magnitude, with the proportion of variance to be explained by mean fixation duration in infancy being 2%, 7% and 6% for child effortful control, surgency and hyperactivity-inattention, respectively. Moderate effects are to be expected given that many factors within a dynamic developmental framework operate to produce individual variability on high-level behaviours (e.g. hyperactivity-inattention; Nigg, 2009).

An open question from these results was to what degree these individual differences in newborn average dwell time and infant mean fixation duration, which predict individual variation in effortful control, surgency and hyperactivity-inattention develop in the first months of life, perhaps as a result of caregiver and other environmental stimulation, and to what degree they are present at birth. The second study (see chapter 4) aimed to answer this question by investigating the degree to which individual differences in newborns' average dwell time is predictive of individual variation in effortful control, surgency, hyperactivity-inattention and

total behavioural difficulties in childhood.

6.2.2 Individual differences in newborn attention relate with temperament and behavioral difficulties in childhood

The second study (see chapter 4) has linked individual variation in newborn average dwell time with individual differences in effortful control, surgency, hyperactivity-inattention and behavioural difficulties in childhood.

It was hypothesised that newborns' average dwell time would be positively associated with effortful control in childhood; and negatively associated with surgency, hyperactivity-inattention and total behavioural difficulties in childhood. It was expected also that the magnitude of the reported associations would be lower than it was in the previous study since independent and dependent variables were further apart in time (in comparison to the study described in chapter 3).

Average dwell time was associated significantly with surgency and total behavioural difficulties but not with effortful control and hyperactivity-inattention. The significant associations were of moderate magnitude, with the proportion of variance explained by newborns' average dwell time at stimuli being 4% and 5% for surgency and total behavioural difficulties in childhood, respectively. The previous study reported that mean fixation duration in infancy (4-10 months of age) explained 7% of the variation in surgency in early childhood (18-54 months of age) and that this association becomes stronger as the age of the infant increases. The slightly lower proportion of variation in surgency that is explained by newborns' average dwell time reported here could be explained either by the fact that predictor and dependent variable were further apart in time as compared to the previous study; or the differences in the dwell time measure compared to the eye tracking-derived fixation duration previously used.

The non-significant association between newborn average dwell time and child effortful control could be explained from the fact that the association between infant attention and effortful control in the previous study showed the trend of being the weakest association of the significant findings. In light of the smaller sample size in the present work, the negative result could be explained by the lack of power to detect a more modest association between newborn average dwell time and effortful control in childhood. The non-significant association between newborn average dwell time and child hyperactivity-inattention could also be explained to some extent by the lack of power to detect a more modest association between newborn attention and hyperactivity-inattention.

This is the first study to report an association between individual differences in attention in the first days after birth with temperament and behaviour in childhood (5-9 years). Given that the origin of the individual variation in visual attention at birth could be due to genetic factors, an open question was how much of the variance in newborn average dwell time and infant mean fixation duration is explained by common genetic variation previously found to increase the risk for diagnosed ADHD (Neale et al., 2010) and schizophrenia (Ripke et al., 2013) in childhood and adulthood, respectively. This was the main aim of the third study that was presented in Chapter 5.

6.2.3 Genetics of newborn and infant visual attention

The aim of the third PhD project (see Chapter 5) was to investigate whether genome-wide derived SNPs previously associated with ADHD and schizophrenia explain variation in newborn average dwell time and infant mean fixation duration. Considering that variation in mean fixation duration in infancy and average dwell time at birth was negatively associated with individual variation in surgency,

hyperactivity-inattention and total behavioural problems in childhood respectively, it was hypothesised that: 1) SNPs that have been found previously to increase the risk for diagnosed ADHD will be associated with shorter infant mean fixation duration and newborn average dwell time; 2) ADHD PRS would be predictive of shorter infant mean fixation duration and newborn average dwell time.

Schizophrenia PRS were also constructed and tested for association with newborn average dwell time and infant mean fixation duration. The main reason for this analysis was that schizophrenia PRS derived from the largest sample size of all studies that are available in the Psychiatric Genomics Consortium database. As such, schizophrenia PRS constitutes the best available genetic risk predictor for psychopathology at present. Moreover, given recent evidence which suggests that some of the same common genetic variation is associated with multiple psychiatric disorders of childhood onset or adult onset (Smoller et al., 2013); and some evidence to show a degree of shared genetic susceptibility between adult schizophrenia and childhood ADHD (Hamshere et al., 2013), it was hypothesised that: 3) SNPs that have been found previously to increase the risk for diagnosed schizophrenia will be negatively associated with individual variation in infant mean fixation duration and newborn average dwell time; 4) Schizophrenia PRS would be predictive of shorter infant mean fixation duration and newborn average dwell time.

Whilst the single SNPs analysis raised no significant associations with infant mean fixation duration or newborn average dwell time, the PRS results revealed that genetic markers previously found to increase the risk for diagnosed schizophrenia account for up to 7% of variation in infant mean fixation duration. The direction of the association was positive, suggesting that higher polygenic risk score for schizophrenia is associated with longer mean fixation duration in infancy. As such,

the results indicated a significant genetic link between liability for schizophrenia in adulthood and mean fixation duration in infancy.

6.3 Implications

In achieving the initial three aims, this thesis provides theoretical and empirical contributions.

6.3.1 Aim 1: To investigate how individual differences in infant mean fixation duration are associated with individual differences in childhood effortful control, surgency and hyperactivity-inattention (First PhD study presented in chapter 3).

In terms of the theoretical implications, the first study reached its aim by demonstrating for the first time that infant mean fixation duration in infancy is linked to some forms of attentional and behavioural control in early childhood. This is of importance considering that, while the temperament trait of surgency emerges in the first year of life, effortful control--the temperament trait that refers to the child's volitional use of executive attentional abilities (Bell & Calkins, 2012) develops in the second and third year of life and beyond, making it difficult to find appropriate measures to assess it in infancy (Rothbart, Sheese & Posner, 2007). As such, studying fixation duration in infancy could have significant implications for understanding the mechanisms through which effortful control--as well as other aspects of executive attention--develop.

The results also suggest that some of the factors that contribute to individual variation in childhood behaviour are already present in infancy. This finding argues against the idea that individual variation in behaviour can be accounted completely by factors in post-infancy (for example, schooling); and demonstrates the importance of early developmental research to shed light on the causes of individual variation in some forms of psychological traits throughout childhood.

In terms of the empirical implications, investigating the causes of individual differences in voluntarily control of attention as early as in infancy might inform the development of early intervention practices that will aim to improve aspects of executive attention (Diamond & Lee, 2011). Executive attention is an important network for the acquisition of a wide variety of skills that draw upon general intelligence (Rothbart et al., 2007). Finally, given the role of effortful control in differentiating typically developing children from children with ADHD (Samyn et al., 2011) and the association between fixation duration in infancy with later effortful control, surgency and hyperactivity-inattention, reported in this study, a tentative idea for future research would be to explore how differences in fixation duration in infancy relates to risk for developing ADHD.

6.3.2 Aim 2: To investigate how individual differences in newborn visual attention are associated with individual differences in childhood effortful control, surgency, hyperactivity-inattention and behavioural difficulties(Second PhD study presented in chapter 4).

The second study was the first to report an association between individual differences in attention in the first days after birth with some forms of temperament and behaviour in childhood (5-9 years). Studying individual differences in newborns' attention constitutes a window into the developmental mechanisms that contribute to individual differences in attentional and behavioural control throughout the lifespan. For example, while attentional and behavioural control in childhood depends mainly upon overlapping cortical brain systems (Petersen & Posner, 2012), at birth (and prior to 3-months of age) attentional control depends upon subcortical brain structures (Farroni & Menon, 2008). The reported associations between newborns' average dwell time with surgency and total

behavioural difficulties in childhood suggests that some of the underlying factors that may contribute to individual differences in the efficiency of children to control their attention and behaviour are present as early as at birth; that is, before the cortical systems that underlie behavioural and attentional control start to influence behaviour.

As such, in achieving its main aim this study provided with theoretical contribution demonstrating that part of the variance in some forms of temperament and behavioural control is explained by factors already present on the first or second day of life. This suggests that the origins of individual differences in behaviour are not wholly due to the postnatal environment. These causal factors could be genetic or stemming from the prenatal environment.

Finally, the measure of average dwell time used in this study has been selected because it was hypothesised to be linked with mean fixation duration (Rayner et al., 2009; Henderson & Smith, 2009). However no studies have tested directly the degree to which the two measures are linked. The fact that both newborn average dwell time and mean fixation duration was associated negatively with surgency in childhood provide tentative support that there are parallels between the two measures.

6.3.3 Aim 3: To explore the degree to which genome-wide derived SNPs previously found to increase the liability for ADHD and schizophrenia are associated with newborn average dwell time and infant mean fixation duration (Third PhD study presented in chapter 5).

Although preliminary, the results of the third study bring some theoretical as well as empirical advances in the area of individual differences in infant visual attention.

In terms of the theoretical implications, the current project provided a suggestive genetic link between individual differences in newborn average dwell time and infant mean fixation duration with diagnosed schizophrenia in adulthood. The results were highly significant with SNPs previously found to increase the liability for diagnosed schizophrenia to be associated with longer mean fixation duration in infancy.

A recent visual study compared eye movement differences during facial emotion recognition between 101 patients with schizophrenia and 101 controls reported that mean fixation duration was significantly longer in patients with schizophrenia in comparison to normal controls (Zhu et al., 2013). Similar results have also derived from an eye tracking study that reported longer mean fixation duration during free exploration of six photos of daily life situations in schizophrenia patients as compared to healthy individuals (Sprenger et al., 2013). Atypical scanpaths in response to broad range of visual stimuli were also reported with schizophrenia patients exhibiting increased mean fixation duration as compared to healthy viewers (see Beedie, Clair & Benson, 2011 for a review). The current research demonstrated for the first time that there is a shared genetic link between mean fixation duration in the first year of postnatal life with liability to diagnosed schizophrenia in adulthood. As such, these findings, if replicated, could have significant implications for the early identification of populations at risk of developing schizophrenia.

Knowledge about which genes contribute to individual differences in attentional development in infancy would provide clues about the mechanisms involved in individual variation in early visual attention and brain development (Johnson, 2011). Finally, knowledge about genetic risk that can be applied to infant

samples has considerable potential for the identification of populations at risk of atypical development, and thus for informing early prevention and intervention approaches.

The single SNP analysis did not return any significant association between previously identified loci for ADHD liability and infant and newborn mean fixation duration and average dwell time, respectively. This could be due to the fact that ADHD related SNPs have failed to reach genome-wide significance in the original study (Neale et al. 2010), which compromises the reliability of the reported associations. ADHD PRS did not yield any significant associations with either newborn average dwell time or infant mean fixation duration. Given that the predictive accuracy of the PRS depends upon the size of the training sample (that refers to the sample of the original GWAS meta-analysis; Dudbridge, 2013) and the fact that genome-wide significant SNPs (those that returned a p-value of less than 5×10^{-8}) have been detected only in the schizophrenia meta-analysis (not in the ADHD meta-analysis) this was somewhat expected.

This study achieved its aim to be the first to explore the role of common genetic variation in visual attention at birth; and the first work to combine the polygenic risk score methodology with eye tracking data in infancy. PRS analysis has the potential to provide a predictor with better discrimination properties in comparison to one based on individual genetic markers and to maximise the study's statistical power to detect an association (Wray, Goddard & Visscher, 2007).

6.4 Limitations and future directions

The findings described above should be considered in light of some limitations. The following section presents the studies' limitations and considers possible directions for future work.

6.4.1 First study (see Chapter 3)

In the first PhD study, the Cronbach's alpha reported for the RRPSPC hyperactivity-inattention scale was moderate. Despite that, this measure was used in the analysis as it is of identical format to the SDQ measure of hyperactivity-inattention. This offered the opportunity to merge the younger and older group of participants in order to increase the sample size and the statistical power to detect an association between infant mean fixation duration and hyperactivity-inattention in childhood. Future research could attempt to replicate the results of the current work using a different measure of hyperactivity-inattention in childhood. Another limitation that was shared between the first and second study (presented in chapter 4) was the reliance on parent report of children's behaviour and temperament. While parents are typically most familiar with their children's behaviour, all types of raters include some bias. Future research should consider collecting data from multiple raters or employing additional objective measurements of behaviour.

There was attrition in the sample due to the longitudinal nature of the study. Nevertheless, the final sample was powered to detect moderate effects and was considerably larger than the sample size of most studies in infant eye tracking research (typically N = 10-20). There was also missing data in usable eye tracking data within participants. This was due to fact that infant eye tracking data are generally of poorer quality (less precise and with more lost samples) compared to adult data (Wass et al., 2013).

There was heterogeneity in participants' age both in infancy (4 to 10 months of age) and in childhood (19 to 58 months of age). Whilst age of the infant was used as a covariate in the regression model the study did not take into account specific developmental stages of attention in infancy. It has been argued that there are at

least three critical postnatal periods of attentional development in infancy (see Colombo, 2001): the first involves the period from birth to 2-, 3-months of age, when the development of alert state takes place (Colombo, 2001). The second involves the period from 3 to about 6 months, when the orienting system emerges (Colombo, 2001). The third refers to the period from 6 months to 12 months, when executive attention is starting to practice control (Colombo, 2001). It is possible that mean fixation duration reflects different parameters of attention at different ages in infancy; therefore future work could explore whether the relationship between mean fixation duration--assessed at different ages across infancy--with effortful control, surgency and hyperactivity-inattention is similar to the one described in the current research.

A related limitation--that is shared between the first and second study--is that the reported associations cannot provide a mechanistic account of the development of attentional control across infancy and which parts of the brain contribute to individual variation in mean fixation duration and later temperament and behaviour.

Moreover, although age appropriate questionnaires have been used and the participants' age and the type of questionnaire that their parents completed have been included as covariates in the regression model, it will be important to test whether the results replicate in a sample that include participants across narrower age ranges.

The eye tracking studies involved several experimental conditions that were designed to assess learning in infancy (Wu et al. 2010; 2011, 2014). Future studies could attempt to collect data on infants' mean fixation duration in a single condition that will be designed to assess aspects of infant executive control (for example, error detection at 7-months of age; see Berger, Tzur & Posner, 2006; Rothbart, Sheese &

Posner, 2007) and to investigate whether the relationship between mean fixation duration with effortful control, surgency and hyperactivity-inattention is similar to the one described in the current research. Future work could collect both infants' behaviour questionnaire data and eye tracking data concurrently and reassess those traits longitudinally to investigate whether the relationship between mean fixation duration with effortful control, surgency and hyperactivity-inattention remains stable across development.

Finally, the relationship between mean fixation duration with effortful control, surgency and hyperactivity-inattention that was described here was linear, with longer mean fixation duration to be associated with more effortful control and less surgency and hyperactivity-inattention. However it might be possible that having too long mean fixation duration is also disadvantageous. As such, future research with larger samples could explore whether having very long mean fixation duration (for example, 3 standard deviations above the mean) is associated with more psychopathology in childhood.

6.4.2 Second study (see Chapter 4)

In the second PhD study that was presented in Chapter 4, the measure of newborns' average dwell time was not derived from eye tracking data. Eye tracking data has much higher spatial (~1° of visual angle) and temporal resolution (typically between 50-300 Hz) in comparison to video coding (typically around 25Hz). Use of video coded data limited the ability to compare directly the results of the first and second study. For example, long dwells could be made up of a small number of long fixations or a large number of short fixations (Henderson & Smith, 2009). The significant associations reported in the second study (see chapter 4) support the former view but some of the variance in the dwells might be due to the latter. As

such, future research could use simultaneous eye tracking and video coding in young infants to estimate the correlation between average dwell time and fixation duration assessed using eye tracking and to attempt to replicate the findings of this study. Similarly to the previous study there was heterogeneity in terms of the children's age at follow up (5 to 9 years of age). Finally, the visual data derived from a number of visual studies that aimed to investigate newborns' visual attention using similar but not identical experimental paradigms (i.e. both habituation and preference paradigm) and conditions. Similarly to the previous study, future research could assess newborns' average dwell time in a single experimental paradigm and condition and to attempt to replicate the results of the current work.

6.4.3 Third study (see Chapter 5)

The most important limitation of the third study (see chapter 5) refers to the sample size. The small sample size (for genetic research) placed constraints as to how many SNPs could be tested for an association with the phenotypic measures. Quantitative traits are polygenic; many genetic markers with small effect sizes are contributing to individual differences on those traits. As such, large sample sizes are necessary in order to detect associations between genetic markers and human complex traits (Plomin, 2013). A second limitation of this work is that the 'replication' sample (the sample of newborns) was not an exact match in terms of age or phenotype. Given that many candidate gene studies have reported false positive associations in the past it is essential to replicate genetic association findings in an independent sample.

The polygenic risk scores have been derived from large meta-analyses of GWAS in childhood (ADHD; Neale et al., 2010) and adulthood (schizophrenia; Ripke et al., 2013). Once large-scale GWAS on infant visual attention have been

conducted it would be interesting to test whether individual differences in infant mean fixation duration and newborn average dwell time would be predicted by visual attention PRS that derived from infant samples.

Another limitation of this work is that it does not explore the degree to which individual differences in gene expression predict variation in the infant attention measures. Future work could explore developmentally the function and product of the genetic variants that associate with both schizophrenia and infant mean fixation duration in order to understand the biological mechanisms that link the two phenotypes.

Given the suggestive genetic link between infant mean fixation duration and adult schizophrenia, future longitudinal studies could investigate whether individual differences in mean fixation duration in infancy predict individual variation in psychotic experiences in adulthood. Finally, future studies could also explore whether the direction of the association between schizophrenia PRS and mean fixation duration is stable across development.

6.5 Concluding Remarks

This thesis investigated the degree to which individual differences in visual attention in the first twelve months of postnatal life predict individual variation in some forms of temperament and behaviour in childhood.

This research is important because it shows for the first time that individual differences in visual attention as early as in the first days of postnatal life can predict individual variation in attentional and behavioural control in childhood. In addition, this work goes beyond describing a link between two psychological phenotypes (for example, infant attention with temperament in childhood) by testing whether genetic variants associated with later psychopathology predict variation in visual attention at

birth and in infancy.

Along with the theoretical implications that were briefly stated above, this work brought several novel approached to the field of developmental psychology, including the use of novel analytic methods to detect fixation duration from infants' eye tracking data, the use of microarrays in infancy and the successful application of the polygenic risk score methodology with infant data.

As such, by combining several areas of developmental psychology and genetics, this research pushes the field further towards describing and understanding the causes of individual differences in early visual attention and attentional and behavioural control throughout childhood.

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