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NEW LIGHT ON NEUROCOGNITIVE PROCESSES LINKED TO AUTISM AND ATTENTION DEFICIT AND HYPERACTIVITY DISORDER IN CHILDHOOD: STUDIES OF EYE MOVEMENTS IN TWINS

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To my family

ABSTRACT

Visual attention and oculomotor response inhibition have been associated with Autism Spectrum Disorder (ASD) and Attention Deficit and Hyperactivity Disorder (ADHD) respectively. The aim of this thesis was to increase our knowledge about these cognitive functions relevant to ASD and ADHD in early infancy and childhood using eye tracking and twin modelling.

Study 1 assessed the relative contribution of genetic and environmental influences to attentional networks and visual disengagement (using the gap overlap task) in a sample of twins from the general population, aged 9-14 years. It also assessed whether visual disengagement was associated with autistic traits. Gaze shift latencies across conditions were driven by shared genetic factors. Additionally, there were unique genetic influences to gaze shift latencies in the gap condition. In line with previous work, autistic traits were found to be heritable. There was no association between visual disengagement and autistic traits.

Study 2 investigated the relative contribution of genetic and environmental factors to oculomotor response inhibition (using the antisaccade task) and the degree to which oculomotor response inhibition was associated with ADHD traits in the same twin sample. Oculomotor response inhibition in the form of premature anticipatory eye movements was heritable and associated to parent rated inattentive traits. This association was partially due to shared genetic factors.

Study 3 investigated how visual disengagement relates to other cognitive developmental processes and behaviors, socioeconomic status and biological sex in early infancy. Gaze shift latencies in the overlap, baseline and gap conditions, of the Gap Overlap task, differed as a function of socioeconomic status and sex. No other associations between visual attention and developmental measures were observed.

Thus, in summary, while these findings do not support neither a phenotypic nor a genetic link between visual disengagement and ASD, they support such association between oculomotor response inhibition and inattention (a core component of ADHD). Finally, these findings highlight the influence of sociodemographic factors on individual differences in visual attention in early infancy, thus underscoring the importance of understanding all sources of variation in attentional functions in childhood.

LIST OF SCIENTIFIC PAPERS

I Siqueiros Sanchez M., Pettersson, E., Kennedy, D. P., Bölte, S., Lichtenstein, P., D'Onofrio, B. M., & Falck-Ytter, T. (2019). Visual Disengagement: Genetic Architecture and Relation to Autistic Traits in the General Population. Journal of Autism and Developmental Disorders. Advance online publication. https://doi.org/10.1007/s10803-019-03974-6

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III Siqueiros Sanchez, M., Ronald, A., Mason, L., Bölte, S., Jones, E. & Falck-Ytter, T. Visual disengagement in young infants in relation to age sex, SES, developmental level and adaptive functioning. In manuscript.

CONTENTS

LIST OF ABBREVIATIONS

-2LL	Minus two log likelihood
ADI-R	Autism Diagnostic Interview-Revised
ADOS	Autism Diagnostic Observation Schedule
ADHD	Attention Deficit and Hyperactivity Disorder
AIC	Akaike's Information Criteria
ANOVA	Analysis of variance
AOI	Area of interest
APA	American Psychological Association
ASD	Autism Spectrum Disorder
BIC	Bayesian Information Criteria
CAADID	Conners Adult ADHD Diagnostic Interview for DSM-IV
CARS-2	Childhood Autism Rating Scale 2nd Edition
CATSS	Child and Adolescent Twin Study Sweden
CI	Confidence intervals
CNV	Copy Number Variant
CS	Central stimulus
DF	DeFries & Fulker extreme analysis method
DISC-IV	Diagnostic Interview for ADHD in Adults
DIVA	Diagnostic Interview Schedule for Children, 4th Edition
DNA	Deoxyribonucleic acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Ed
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Ed
DZ	Dizygotic

EF	Executive Function
FEF	Frontal Eye Fields
GABA	Gamma-Aminobutyric acid
GEE	General Estimation Equation Models
GWAS	Genomewide Association Study
ICC	Intra-class correlation
ICD-10	International Statistical Classification of Diseases 10th Rev
IQ	Intelligence Quotient
LRT	Likelihood ratio test
MLM	Maximum Likelihood Models
MSEL	The Mullen Scales of Early Learning
MZ	Monozygotic
NE	Norepinephrine
PRS	Polygenic risk scores
PS	Peripheral stimulus
RDOC	Research Domain Criteria Initiative
SD	Standard Deviation
SE	Standard Error
SES	Socioeconomic status
SRS	Social Responsiveness Scale
VABS-II	The Vineland Adaptive Behavior Scales 2nd Edition
WISC-IV	Wechsler Intelligence Scale for Children-IV
WM	Working memory

1 INTRODUCTION

This thesis is about attentional functions in children, their etiology, and their link to traits of ASD and ADHD. I will start by briefly introducing the constructs of attention and inhibition as well as the clinical conditions ASD and ADHD, before moving on to eye tracking and experimental oculomotor paradigms in visual attention and response inhibition, their links to ASD and ADHD, and why we can use twin studies to further our understanding of these associations in community samples.

1.1 Attention

Although several definitions of attention exist, we can roughly define it as a selection process that renders certain aspects of the world focused while filtering others out (Desimone & Duncan, 1995; Raz & Buhle, 2006). How, to what, and when we allocate our attention has, therefore, an impact on the way we experience the world around us, and on how we act in it. According to the influential model of attention by Posner and Petersen (1990), attention is a system akin to other sensory systems, with interacting yet relatively autonomous functionality. Posner's attentional system model proposes three distinct attentional networks: alerting, orienting and executive, which differ from each other at functional, anatomical, physiological, and neuromodulator levels. The alerting network is concerned with preparing and sustaining attention in order to detect a prioritized signal (Posner & Petersen, 1990). An active alerting state is thought to lead to a faster response yet at a cost in its execution (higher error rates). Data from imaging, vigilance tasks, and animal studies suggest that the main areas implicated in this network are located in fronto-parietal cortical regions, the right temporal parietal junction, the thalamus, and the superior colliculus (in visual tasks) (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Fan, McCandliss, Sommer, Raz, & Posner, 2002; Posner & Petersen, 1990). This network is physiologically underpinned by the norepinephrine (NE) system, and thus appears to closely follow its cortical layout, with experimental modulations of the NE system resulting in impaired performance in alerting paradigms through the dampening/abolition of warning cues (Coull, Nobre, & Frith, 2001). The second network addressed by Posner's model is orienting. This model defines orienting as the act of overtly or covertly attending to a particular stimulus and thus the selection of information. Overt attention refers to when an attention shift is accompanied by a gaze shift, meanwhile, covert attention refers to when an attention shift is done without an accompanying gaze shift (de Haan, Morgan, & Rorden, 2008; Posner & Petersen, 1990). Thus, overt orienting, which is the focus of this thesis, involves the use of eye movements and foveating on a stimulus, meanwhile covert orienting refers to attending without any eye or head movements. Areas implicated in the orienting network are mainly parietal and frontal areas. Neural activity associated to the

orienting network has been consistently observed in the posterior parietal lobe, the temporal-parietal junction, the lateral pulvinar nucleus of the posterolateral thalamus and the superior colliculus (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Fan et al., 2002; Posner & Petersen, 1990). Finally, we have the executive network. This network is thought to be implicated in conflict resolution and is thus captured/activated by tasks that elicit conflicting responses. Activation in the anterior cingulate, frontal areas, and the midline frontal areas are associated with this network and with conflict resolution tasks in general (Fan et al., 2005; Fan et al., 2002). The idea of independent attentional networks has been supported by a lack of meaningful correlations between these networks (Fan et al., 2002) and differential activation patterns of the networks in imaging studies (Fan et al., 2005; Posner, 2016; Raz & Buhle, 2006). However, it appears that independence may be partial and not absolute since evidence suggests there are interactions between the networks, where modifications in one influence performance on the others (Callejas, Lupiàñez, Funes, & Tudela, 2005; Callejas, Lupiáñez, & Tudela, 2004; Fan et al., 2009).

1.2 Inhibition

Although attention and inhibition are inherently intertwined (as per Posner's model attention has an executive network in which inhibition plays a part), in this thesis we place a special focus on this subdomain of the executive system for its key role in ADHD. Inhibition is typically referred to as an executive type of function that, together with other executive functions (EFs), allow an individual to successfully carry out goal-oriented behavior every day (Barkley, 1997; Nigg, 2001). More specifically, inhibition is the deliberate suppression of a response in favor of another in order to achieve a goal-directed outcome (Miyake & Friedman, 2012). Much like other EFs, the neural underpinnings of inhibition are widespread and encompass brain regions including the prefrontal cortex, the parietal cortex, the anterior cingulate cortex, and the basal ganglia among others. Inhibition, can be manifested in different ways. According to Nigg (2000), inhibitory processes can be classified into: Behavioral inhibition, which refers to the inhibition of an ongoing response (to stop pressing a button when a signal appears); Oculomotor inhibition, such as looking toward the opposite direction of an appearing stimulus; Cognitive inhibition, inhibiting distractors when performing a task (for example to keep performing despite distractors); and interference control which is applied to managing the interference elicited by competing stimuli or competition for resources. These types of inhibition are conceptually distinct according to Nigg, but also partially represent different inhibitory abilities (Miyake et al., 2000). Typical prepotent response inhibition tasks are: the antisaccade task, the stop-signal paradigm and the go/no-go task. It is thanks to research done with these tasks that we know the implications that the lateral prefrontal cortex, the dorsolateral pre-

frontal cortex and the right posterior ventrolateral frontal cortex have in response inhibition (Purves et al., 2013). In this thesis the focus is on response inhibition of a prepotent response or oculomotor inhibition.

1.3 Autism Spectrum Disorders

Autism Spectrum Disorder (ASD) is an early onset neurodevelopmental condition that is hallmarked by social communication and interaction difficulties, and insistence on sameness/resistance to change behaviors. Specifically, and according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5). ASD is defined by two main symptom domains (1) Socio-communication and interaction impairments, co-occurring with (2) Restricted, repetitive patterns of behavior and/or interests (American Psychiatric Association, 2013). While previous classification systems (e.g. DSM-IV) listed "multiple autisms" (e.g. Autism, Asperger's Syndrome), DSM-5 features a dimensional perspective where they all fall under the autism spectrum (Volkmar & Reichow, 2013). ASD is common (Baio et al., 2018; Baird et al., 2006; Baxter et al., 2015; Dawson, 2008), with most prevalence estimates ranging between 0.6-1.4%, or around 1 in ~100 (59-150), and a 3:1 male-female diagnosis ratio (Loomes, Hull, & Mandy, 2017). ASD is no longer considered a rare disorder. It is considered the primary cause of disability among mental disorders in children under five and in the top five for children between 5 and 14 (Baxter et al., 2015). Furthermore, as a life-long condition, ASD children will go on into adulthood and the services required from the community will go beyond pediatric and educational with long-term care goals both in healthcare and quality of life.

In ASD, comorbidity is rather the rule than the exception. An ASD diagnosis is rarely the sole diagnosis an individual receives. Among the most usual comorbidities we find anxiety and mood disorders (Kim, Szatmari, Bryson, Streiner, & Wilson, 2000; White, Oswald, Ollendick, & Scahill, 2009), seizures and epilepsy (Jeste & Geschwind, 2014; Volkmar & Nelson, 1990), gastrointestinal symptoms (McElhanon, McCracken, Karpen, & Sharp, 2014), and motor coordination problems (Fournier, Hass, Naik, Lodha, & Cauraugh, 2010). Overlap with other neurodevelopmental disorders such as Intellectual Disability (Matson & Sturmey, 2011) and ADHD is also common. Needless to say, this high level of comorbidity elevates the complexity of an already complex disorder.

Despite being a lifelong condition, the earliest an ASD diagnosis can be made is around 2 years of age (Charman & Baird, 2002). The gold standards for diagnosing ASD are the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000) and the Autism Diagnostic Interview – Revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994), although using both is considered a better approach (Zander,

Sturm, & Bölte, 2015). In addition, dimensional instruments that focus on severity of ASD symptoms and traits, rather than on diagnosis *per se,* are also available such as the Childhood Autism Rating Scale 2nd Edition (CARS-2) (Schopler, Van Bourgondien, Wellman, & Love, 2010) and the Social Responsiveness Scale (SRS) (Constantino et al., 2003; Constantino & Gruber, 2005). However, for young infants and toddlers diagnosis tools remain limited. Thus, the gold standard in infancy is a clinical diagnosis made by an experienced professional (Volkmar, Chawarska, & Klin, 2005). Although early infancy may not seem too late for diagnosis, the postnatal brain structure and architecture continues to develop, specialize and grow at a rapid pace during the first year of life. Overall brain and cortical plasticity are also high during this time, with sensory and external input playing an important role (Dawson, 2008; Johnson & De Haan, 2015). Furthermore, it is during this period that low-level functions and basic skills, which serve as building blocks for later pivotal skills, are unfolding in a constant interplay with the environment. Thus, a diagnosis after 2 or more years is considered not early enough and great efforts are being taken to reduce time up to diagnosis.

Can we detect ASD any earlier than at 2 years of age? According to an influential developmental ASD model (Dawson, 2008), genetic, environmental and phenotypic risk factors that signal ASD vulnerability exist and are identifiable already in early infancy. Albeit not symptoms *per se,* these early factors contribute to atypical brain development that later on manifest as the altered social behaviors/interactions characteristic of the disorder. In addition, mediating risk processes and altered interactions with the environment, enhance these early vulnerabilities and consequently lead to the autistic phenotype. These risk processes in turn hinder typical pivotal social input that, under typical circumstances, would naturally lead to adequate social brain development, thus acting as mediators between risk factors and outcome behavior (Keehn, Müller, & Townsend, 2013). Early social behaviors which constitute the building blocks of later complex interactions, such as joint attention, imitation and volitional communication, tend to be altered in autism. These theoretical frameworks of ASD etiology in the context of the development, provide an intuitive account of how atypical behaviors may come to happen. Where an interactive chain of altered mechanisms in specialized perceptual, motor and reward neural structures and systems, can lead to an atypical development of the social brain circuitry. The potential different levels of impairment put forward by these accounts also set the stage for one of the main focuses of this thesis, endophenotypes. One of the earliest manifestations of ASD reported by parents is reduced or atypical eye contact (Volkmar et al., 2005) – which make atypical visual patterns a suitable candidate area for early marker and endophenotype research in ASD.

1.4 Attention Deficit and Hyperactivity Disorder

The American Psychiatric Association (2013) defines Attention Deficit and Hyperactivity Disorder as a lifelong condition characterized by pervasive (1) Inattention and/or (2) Hyperactivity/impulsivity. Attention difficulties refer to problems with sustained attention and mental effort, following instructions, organization of tasks and activities, distractibility (often distracted), and keeping track of things. The hyperactivity and impulsivity domain is characterized by behaviors such as fidgeting, being unable to stand still and/or restlessness, and interrupting others. Childhood and adolescent ADHD prevalence rates are about 3-5% (Demontis et al., 2019; Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015).

ADHD is associated with other everyday-life impairments. Academic underachievement and failure, work-related impairments (e.g. low performance reports, higher termination rates), peer rejection, difficulties in emotion regulation and low self-esteem, among others (Nigg, 2013). Poor health outcomes seem to also co-occur with ADHD, with a higher risk of substance use, smoking, drug-use, sleep problems, physical injuries, traffic accidents, riskier sexual activity and obesity (Nigg, 2013). Other developmental disabilities, such as learning disabilities, language disorder and ASD, as well as anxiety and mood disorders, are often comorbid with ADHD, with about 33% of children diagnosed with ADHD also having at least 1 other psychiatric disorder (Antshel, Zhang-James, & Faraone, 2013; Antshel, Zhang-James, Wagner, Ledesma, & Faraone, 2016; Larson, Russ, Kahn, & Halfon, 2011). This high comorbidity only adds to the already high financial healthcare costs and care burden associated with ADHD (Matza, Paramore, & Prasad, 2005; Renhorn, Nytell, Backman, Ekstrand, & Hirvikoski, 2019).

Despite its high prevalence and societal costs, there is no real gold standard measure for ADHD and a multimodal assessment is the most common approach in the clinic. Many instruments are available, including interviews like the Diagnostic Interview Schedule for Children (DISC-IV) (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000), Conners Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (Epstein & Johnson, 2001) and the Diagnostic Interview for ADHD in Adults (DIVA), as well as rating scales like the Conners-3 (Conners, 2008a) which are used for measuring ADHD traits. Several reports suggest that executive and cognitive function deficits are often observed in ADHD individuals – for a review see Willcutt, Doyle, Nigg, Faraone, and Pennington (2005). Thus, it is not uncommon for a battery of common cognitive tasks (e.g. Stroop task, go/no-go, Tower of London/Hanoi, etc.) and general intelligence tests, like the Wechsler Intelligence Scale for Children 4th edition (WISC-IV) (Wechsler, 2003), to accompany an ADHD clinical assessment. More alarmingly so is that the earliest a reliable ADHD diagnosis can be made is between preschool and early childhood (~4-7 years) (Spencer, Biederman, & Mick, 2007). Thus, much like in the case of ASD, efforts are constantly being made to identify at risk individuals for ADHD as early as possible (Sonuga-Barke & Halperin, 2010).

1.5 Endophenotypes

Characterizing casual pathways between behavioral symptoms of complex neurodevelopmental disorders as ASD and ADHD is essential to understanding their phenotypes. Since both disorders are currently only diagnosable via behavioral symptoms, it is key to take a step further and understand the underlying neurocognitive functions leading to these atypical behavioral manifestations (Kylliäinen, Jones, Gomot, Warreyn, & Falck-Ytter, 2014).

Linking complex human behavior to its genetic roots is a highly complex task and although great progress has been made, it remains challenging (Geschwind & Flint, 2015). In an effort (in line with that of cognitive theories) to make this task a more manageable undertake, the study of simpler units of complex disorders known as endophenotypes with, ideally, a simpler genetic architecture has been put forward to bridge this gap (Pinto, Asherson, Ilott, Cheung, & Kuntsi, 2016). An endophenotype is a heritable trait that provides a causal link between the underlying genes of a disorder and its phenotype (symptomatology) (Gottesman & Gould, 2003) – but see Kendler and Neale (2010) for a discussion on why/how an endophenotype can provide an equally valid approach for identifying environmental risk factors (not only genetic). An endophenotype can be found at many levels (e.g. biochemical, neurophysiological, even cognitive), but it must fulfill the following criteria: have been linked to the disorder, proved heritability (have a genetic etiology), be state independent, be familial, and be present at a higher rate in the relatives of those with the disorder compared to in the typical population. However, as Kendler and Neale (2010) point out, the relation between a mediating endophenotype – where the causal pathway from genes to the phenotype passes through the endophenotype – is likely far more complex than we like to think. Among the complexities the authors discuss, not all genetic influences on the endophenotype may have an effect on the phenotype, and not all genetic influences on the phenotype may go through the causal pathway that includes the endophenotype (and hence not affect it directly). Although this may seem daunting, the authors are not damning the endophenotype approach but rather encouraging caution by taking these complexities into account.

1.6 Cognitive theories of ASD and ADHD

Many of the potential endophenotypes in the ASD and ADHD literature find their theoretical origins (and homes) among the disorders most prominent theories. ASD theoretical frameworks have contributed enormously to our understanding of the disorder and while they have proven key for understanding symptom dimensions individually, have fallen short from explaining all ASD impairments. This theoretical mismatch is further strengthened by evidence of partially etiological

independence of ASD symptom dimensions, and has prompted researchers to pursue a "fractionable" account of ASD (Happé & Ronald, 2008; Happé, Ronald, & Plomin, 2006). In this thesis, however, we only address those relevant to visual attention. Much like ASD, ADHD is a complex disorder. In fact, it was not until recent decades, that knowledge about its causes and underlying mechanisms was scarce. Several theoretical accounts have attempted to explain ADHD symptomatology. Earlier accounts took a "single deficit" approach but none of them were able to provide a full explanation of the disorder. "Newer" accounts seem to take these previous theories contributions to understanding the disorders symptomatology, and instead take multi-pathway approaches that seem to suit ADHD complexities better. However, as before with ASD, we cover only a subset of them, limited to those relevant to response inhibition.

1.6.1 The Executive Dysfunction theory

This theory's main thesis rests on deficits in frontal-lobe supported high order cognitive functions, like set-shifting/flexibility, planning, working memory, inhibition, and action initiation/monitoring, being behind ASD symptoms (Hill, 2004). Although many individuals underperform in tasks that tap into these functions, not all of them do, with some performing similar to controls or even better (Pellicano, Maybery, Durkin, & Maley, 2006; Rajendran & Mitchell, 2007). This, combined with the fact that other disorders also present deficits in some measures of EFs (e.g. ADHD), and that EF deficits are not consistently found in young children, are some of the challenges this theory faces.

1.6.2 Weak Central Coherence

The Weak Central Coherence theory (Happé & Frith, 2006) proposes that individuals with ASD lack (or are impaired in) the ability to see the whole instead of only the parts. According to this theory this impairment results from a bias towards local processing over global processing in ASD. The theory has gone on to be described as a spectrum of coherence (rather than a deficit *per se*), ranging from a local ("parts") to a more global preference ("whole"), with ASD being towards the local end. Despite that this theory can explain behaviors such as focusing on object parts and some perceptual issues of ASD, much like other theories, this perceptual bias is not consistently found across individuals with ASD, its proposed deficit/bias may not be specific to ASD (versus other disorders), and it has difficulty explaining the whole phenotype (Matson & Sturmey, 2011).

1.6.3 Barkley's Model

The most longstanding cognitive accounts of ADHD have posited an executive function deficit at the source of the condition. Of these, the most prominent is likely Barkley's Model which largely focuses on an inhibitory deficit (Barkley, 1997). According to Barkley, inhibition underlies all other EF impairments (working memory, self-regulation, internalization of speech - or verbal working memory-, and reconstitution). In accordance to this account, an impairment in inhibition will lead to the characteristic behavioral symptomatology of ADHD. This model has been highly influential in the field of ADHD with many studies documenting deficits in these dimensions (Karatekin, 2006; Willcutt et al., 2005). Studies have shown that EF deficits are independent processes that underpin certain aspects of ADHD (Sonuga-Barke, Dalen, & Remington, 2003; Thorell, 2007). However, on their own they are not enough to correctly identify children with ADHD (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006). Barkley's account also faces challenges such as the non-specificity of EF impairments to ADHD and the non-universal prevalence of these deficits in ADHD individuals, in addition to the difficulty of explaining the whole phenotype (Willcutt et al., 2005).

1.6.4 Other views of ADHD

In response to the incomplete picture painted by single deficit explanations, alternative ADHD theories propose a combined approach. Among the ones with most traction are the dual and triple-pathway models, the hot/cold framework and the Cognitive Energetic model. The dual pathway model proposes two separate subtypes of ADHD that differ on cognitive/motivational profiles, symptomatology, etiologies, and conceptual framework (Sonuga-Barke, 2002). The first "ADHD path" is underpinned by an inhibition deficit and the meso-cortical dopaminergic network, and the frontal and pre-frontal areas of the brain. The second path is motivationally driven, with an underlying delay of reward impairment (shortened delayed gradient that leads to an aversion of delay) underpinned by the reward stream of the dopamine network, that is the meso-limbic areas, especially the ventral-striatal network including the nucleus accumbens.

The triple pathway model (Sonuga-Barke, Bitsakou, & Thompson, 2010), although similar to the dual pathway model, characterizes ADHD along three, rather than two, dissociable dimensions of impairment: inhibition, motivational and timing. Despite this ambitious explanation, later accounts have taken it further, to multiple pathways models since individuals with ADHD show differential impairments in up to six distinct neuropsychological functions (Coghill, Seth, & Matthews, 2013).

The hot/cold framework (Castellanos et al., 2006) integrates inhibitory dysfunction (EF dysfunction– "cold") and emotional regulation/delay aversion impairments ("hot" – motivational style). The "cold", is more cognitively oriented and associated

with the dorsolateral prefrontal cortex, while the "hot" is associated to affective regulation and the orbital and medial prefrontal cortices. This framework is one of the few theoretical accounts of ADHD that have posited emotional dysregulation (the "hot") issues as an independent deficit, rather than as a consequence of an EF-associated ("cold") impairment (Van Cauwenberge, Sonuga-Barke, Hoppenbrouwers, Van Leeuwen, & Wiersema, 2015).

Another ADHD framework featuring a non-cognitive (emotional) dimension is the cognitive energetic model (Sergeant, 2000, 2005). This model postulates three levels of ADHD deficits: (1) cognitive processes, (2) energetic pools, and (3) executive function management. According to this framework, the deficits observed in cognitive processes are limited to motor response organization (and not to encoding nor to central processing). The non-cognitive dimension, energetic pools, is comprised by arousal, activation, and effort, with deficits primarily linked to the activation pool and to a lesser extent to the effort pool. The executive function management dimension is mainly driven by an inhibition impairment – similar to Barkley's account. However, according to the cognitive energetic model, the inhibitory deficits observed in ADHD are dependent upon the energetic state of the individual. The main strength of all the aforementioned multiple pathway models is that they address the within disorder heterogeneity of ADHD as, more often than not, ADHD individuals display impairments in only one of the assessed neuropsychological domains (Coghill et al., 2013; Sonuga-Barke, 2002; Sonuga-Barke et al., 2010).

1.7 Eye tracking as a tool to measure attention and inhibition

One of the main reasons why eye tracking has become so common in developmental research is the introduction of corneal-reflection eye-tracking which allows for remote eye tracking (Hunnius, 2007). Modern eye tracking technology such as corneal reflecting remote eye tracking is able to map eye movements in a 3D space. The eye tracker consists of a set of beam near infrared light micro projectors, a camera to capture images of the eyes and the beam infrared light reflected on the eyes, and image processing algorithms to triangulate, and thus determine, the gaze location on the screen (Holmqvist et al., 2011).

We move our eyes because visual acuity substantially drops as a function of eccentricity, that is, the further the object is from the line of sight the less well we see it. This drop in acuity is a result of different distributions of photoreceptors in the retina, with high acuity vision being exclusive to the fovea, anything beyond this part of the retina is less well perceived. When it comes to distance measures in vision, we use visual degrees (°) rather than cm/in. A visual degree is $1/360^{th}$ of an

imaginary circle around the head (Purves et al., 2013). Vision beyond the width of 1° is exceedingly reduced, which is why we must move our eyes constantly and rapidly to explore the world visually. These abrupt, ballistic gaze shifts are called saccades, and the typical adult executes about 3-4 per second. While there are other type of eye movements (e.g. smooth pursuit) for the purpose of the studies in this thesis, the focus will be solely on gaze shifts, of which saccadic eye movements are part of. Gaze shifts are one of the earliest behavioral indices of visual attention that can be studied. Exogenously driven saccades or reactive gaze shifts (triggered by an external stimulus) are present almost since birth (Colombo, 2001). Thus, despite the fact that saccades early in life tend to be less accurate (and thus require more catch-up saccades), slower and require more effort, they are an attractive tool for measuring cognitive functions in infancy when little is available.

1.7.1 Eye movements to measure attention

As a higher order function, attention is complex to measure, but there are ways. One of these ways is using eye movements (Posner & Petersen, 1990). Eye movements are a useful tool to study the underlying neurophysiology of higher order functions, mainly due to the substantial existing knowledge about the visual system (Karatekin, 2007). Eye movements are controlled by six extraocular muscles which are innervated by a series of different motor neurons, a large number of which are located in the brainstem reticular formation. Nonetheless, plenty of neural structures are part of the visual circuitry. Non-cortical areas, such as the thalamus, the superior colliculus, the cerebellum, and the caudate nucleus, as well as several cortical areas, for instance the visual cortex, the dorsolateral prefrontal cortex, the lateral intraparietal area in the parietal cortex, and the frontal eye fields (FEF), are part of the eye movement generating circuitry (Munoz, 2002). Furthermore, research has shown that the functional and anatomical neural networks characteristic of visual attention and execution of eye movements are extensively overlapping (Corbetta et al., 1998; de Haan et al., 2008). More specifically, activation in specific parietal and temporal cortical regions as well as in the human homolog of the macaque's FEF and supplementary eye fields have been found to be common to both eye movements and attention (Corbetta et al., 1998; de Haan et al., 2008); but see (Corbetta, 1998) and Posner, 2016, for a discussion), thus making eye movements an effective tool to study attention.

1.7.1.1 The gap-overlap paradigm

The gap task (as it is also often referred as) is a task commonly used to assess visual attention disengagement. At a general level, the gap task is a prosaccade task. Prosaccade tasks, like other eye movement tasks, focus on studying gaze shifts and its different metrics. Saccades are rapid ballistic eye movements (reaction time of ~200ms; Fischer & Breitmeyer, 1987). In this thesis we use "saccade" loosely, as

in practice we measure gaze shifts inferred from fixation-detection algorithms. However, we make this equivalence on the basis that in these paradigms (and in general) both saccades and gaze shifts' aim is to direct the gaze towards a particular location or stimulus, typically with the purpose of aligning the fovea (the area of the retina with the highest resolution) with the stimulus (Munoz, 2002). Prosaccades or gaze shifts in these tasks are usually considered to be exogenously driven or elicited by a stimulus in the environment (Fischer & Breitmeyer, 1987; McDowell, Dyckman, Austin, & Clementz, 2008), unlike volitional saccades.

This task is composed of three conditions: the gap, the baseline and the overlap (although some studies only use the conditions gap and overlap). In this task, a central stimulus (CS) appears on a screen and is followed by a new stimulus that appears on the periphery. The conditions differ in regards to when the CS disappears in relation to when the peripheral stimulus (PS) appears. In the "gap condition" the CS disappears before the PS appears. This condition is also characterized by eliciting the shortest gaze reaction times (~150ms). In the "baseline condition" the CS disappears simultaneously as the PS appears. The baseline has commonly been considered a neutral condition and is often used to calculate additional measures (e.g. disengagement and facilitation indices). However, recent accounts suggest that this condition may be more complex, and less straight forward to interpret, than it was initially thought to be and thus caution it's use as a neutral reference point (Siqueiros Sanchez et al., 2019; Van der Stigchel, Hessels, van Elst, & Kemner, 2017). Finally, in the "overlap condition" the CS remains displayed when the PS appears and is characterized by the longest latencies (~250ms) to begin a gaze shift. The overlap condition is thought to capture attention disengagement since in both the gap and baseline conditions attention is released by the disappearance of the central stimuli. These different conditions differ not only in the length of the latencies to execute an eye movement, but also at a neural activation level, thus supporting the idea of distinct attention processes underpinned by different networks (Csibra, Johnson, & Tucker, 1997; Fischer & Breitmeyer, 1987; Fischer et al., 1993; Posner & Petersen, 1990).

1.7.1.2 Visual attention and ASD

Atypicalities in attention are often found in ASD as well as in infants at risk for this disorders. According to Posner's influential model of attention (Hood & Atkinson, 1993; Posner & Petersen, 1990), the attention allocation process can be partitioned into different stages, where disengagement of attention is the first step (1). Disengagement is followed by re-direction (orienting) of attention towards a new target (2), and concludes with engagement (fixating) of attention on the new target (3). It is the first step where ASD individuals seem to have difficulties. Thanks in part to eye tracking technology, visual atypicalities in infancy and toddlerhood have been detected in children with autism (Chawarska & Shic, 2009; Elsabbagh

et al., 2013) in a similar fashion to in older ASD individuals. Non-invasive remote eye tracking has made these type of paradigms feasible with very young children, without sacrificing the precision of more invasive eye trackers, which would be the case when using only manually coded data from video recordings. Studies of infants at risk of ASD constitute an invaluable aid in identifying early phenotypic markers of the disorder. One of the earliest of these studies (Zwaigenbaum, 2005), reported several ASD predictive behavioral risk markers using the Autism Observation Scale for Infants, both social and non-social, at 12 months of age. One of these risk markers was visual disengagement. They observed a decline in visual attention - impaired visual disengagement from one stimuli to a subsequent stimuli – from 6 months to 12 months. On the contrary, infants whose performance was improved or remained stable did not go on to develop ASD.

The ability to shift gaze from one stimuli to the other, "visual disengagement", is observed early on (at around 2 months of age), with a rapid development between 2 and 4 months of age (Frick, Colombo, & Saxon, 1999; Johnson, Posner, & Rothbart, 1991). Infants characteristically go through a period where they struggle to shift their gaze from one target to another and experience periods of prolonged visual fixation known as "sticky fixation" (Johnson & De Haan, 2015). This period, however, takes place from birth till the 2nd month. Visual disengagement times tend to decrease with age and this decrease is typically considered an improvement in performance of this function. Which is why this slower visual disengagement is referred to as a decline in visual attention progression and flagged as atypical. However, the Zwaigenbaum study (2005) was not an isolated account, as other studies of infants at risk, and on individuals with the disorder, have since reported slowed visual disengagement (Elison et al., 2013; Elsabbagh et al., 2013;). Theoretically, these atypicalities would have cascading effects on development, including social and non-social aspects, and on how individuals experience the world in general (Keehn et al., 2013), ultimately leading the impaired social skills characteristic of ASD. Thus, atypicalities in low-level attentional processes could be an endophenotype for autism.

However, despite the seeming association between ASD and visual disengagement, there are no studies to date that have studied if there are any shared genetic factors between the two. Moreover, whether visual disengagement is in fact a heritable trait is yet to be explored. In addition, even though there appears to be a link between early visual disengagement and later social skills, whether visual disengagement is associated to social skills and other developmentally relevant behaviors in infancy is still unknown. Therefore, although an interesting possibility, there are still some unknowns that go beyond visual disengagement being effectively linked to ASD in the path to considering it as an intermediate psychophysiological phenotype for the disorder.

1.7.2 Inhibition at the level of eye movements

Plenty of inhibitory probing paradigms exist, however, inhibition is a broad concept and thus different inhibitory paradigms assess different types of inhibition (Friedman & Miyake, 2004). Experimental response inhibition paradigms are designed to elicit a prepotent response that per instructions must be overcome in favor of another response. Plenty of paradigms following this general principal exist in varied forms and fall under the response-inhibition category. For instance, some experimental paradigms address oculomotor response inhibition and instruct participants to look to the opposite direction of an appearing stimulus (e.g. Antisaccade task). Others create a response to later suppress it - stop pressing a button when a signal appears (e.g. Stop-Signal paradigm). While others require controlling external interference when performing a task, for example to keep performing despite distractors (e.g. Stroop Color Word Interference Test).

It is worth restating that in this thesis, our focus is on oculomotor response inhibition solely. Suppressing a reflexive eye movement and executing a volitional, endogenously driven, one instead, involves a top-down mechanism that will require the engagement of higher order processes like inhibition (McDowell et al., 2008). But why use eye movements to measure response inhibition skills? Neuropsychological and lesion studies have been crucial in establishing the link between inhibition skills/deficits in eye movements and top-down inhibition in general (Munoz & Everling, 2004). Key neural structures involved in the generation of voluntary saccades are the FEFs, the supplementary eye fields, and the dorsolateral prefrontal cortex, with a key role of GABAergic neurons in the inhibitory pathways implicated (Munoz & Everling, 2004). The use of oculomotor paradigms for probing inhibition is further strengthened by the precision they offer in terms of timing accuracy in comparison to other methods, such as functional magnetic resonance imaging (Mahone, Mostofsky, Lasker, Zee, & Denckla, 2009), and by their simplicity.

Inhibition tasks can be classified as simple and complex tasks (Garon, Bryson, & Smith, 2008). The simpler the tasks the lower, if not minimal, degree of participation of other EF components/abilities recruited. Eye movement tracking paradigms tend to be on the simpler side and are among the earliest tasks that children are able to perform (Garon et al., 2008). Performance on some of these oculomotor paradigms has been correlated with measures on other, more complex, inhibitory probing tasks, such as shifting in the Wisconsin Card Sorting Task (Malone & Iacono, 2002), which strengthens its validity. Thus eye movement inhibitory probing paradigms are not perfect but are among the simplest and easiest of paradigms that can be used, which is advantageous when working with children and atypical populations.

1.7.2.1 The antisaccade task and ADHD

The antisaccade is a top-down inhibition task where participants are instructed to look at the opposite side (mirror-position) of an appearing visual stimulus, thus inhibiting the natural tendency to generate a prosaccade towards the appearing stimulus (stimulus-driven, or bottom-up) and generating a voluntary saccade instead. Antisaccades are longer than prosaccades (exogenously driven saccades) due to this added cognitive component of withholding a saccade and executing one in an opposite direction (Munoz & Everling, 2004). This task is sensitive to the top-down inhibitory mechanism needed to perform a volitional gaze shift instead of a reflexive one (Hutton & Ettinger, 2006). The inability to suppress prosaccades towards the stimulus and perform the task correctly is thought to be a reflection of poor executive control (Munoz, Armstrong, Hampton, & Moore, 2003; Munoz & Everling, 2004), and to reflect impairments in the frontal lobes and in the basal ganglia (Hutton & Ettinger, 2006; Munoz & Everling, 2004).

The measures where ADHD individuals have shown impairments when compared to controls are slower reaction times, higher direction errors and higher intra-individual variability in reaction times (Castellanos & Tannock, 2002; Epstein et al., 2011; Kofler et al., 2013; Munoz et al., 2003). However, intra-individual variability seems to actually mediate the association between slower reaction times and ADHD (Hervey et al., 2006). One potential caveat of this task is that it likely depends on working memory (Malone & Iacono, 2002). However, the anti-saccade task is among the simplest and earliest tasks that children are able to resolve (Garon et al., 2008). Already at 4 months, infants are able to inhibit a prosaccade (albeit with training) (Johnson, 1995). Being able to produce an antisaccade (also with training) comes shortly after, at around 12 to 18 months of age (Scerif et al., 2005).

The heritability of individual differences in response inhibition via antisaccade error has only been investigated in a few studies. Heritability estimates appear to be moderate to high (~50%) in young adults (Malone & Iacono, 2002; Vaidyanathan et al., 2014) and in female pre-adolescents (Malone & Iacono, 2002). However, whether genetic factors influence individual differences in response inhibition, as assessed by the antisaccade task, in childhood is still unknown. Furthermore, whether there are shared genetic influences between ADHD traits and oculomotor response inhibition, as is the case of other types of response inhibition (Kuntsi et al., 2014), also remains unexplored. Thus, despite oculomotor response inhibition (in the antisaccade task) seeming as a promising endophenotype for ADHD, important questions are yet to be answered.

1.8 Etiology of ASD and ADHD

Both ASD and ADHD are highly heritable and tend to run in families. Heritability is defined as the amount of variation in a trait that can be explained by genetic factors (Van Dongen, Slagboom, Draisma, Martin, & Boomsma, 2012). The first reports of ASD having a genetic underpinning came from twin studies (Folstein & Rutter, 1977a, 1977b). At that time, ASD was attributed to cold parenting, the "refrigerator mothers" theory. However, thanks to these twin studies, which compared the degree of ASD concordance between monozygotic twins (MZ) with the degree of ASD concordance between dizygotic twins (DZ) and found a higher concordance rate in MZ twins, it became apparent that the condition was largely due to genetic factors (Ronald & Hoekstra, 2011). These results and studies were crucial in changing the focus from maternal deprivation to biological factors in ASD etiology.

Big steps have been taken since, with the advances of molecular genetics and bioinformatics, to better gain an understanding of the genetic underpinnings of ASD. In recent years, it has become clear that ASD is both genetically and phenotypically heterogeneous, with several genes having been linked to the disorder (de la Torre-Ubieta, Won, Stein, & Geschwind, 2016), with the exception of a small fraction which result from single gene abnormalities (e.g. fragile-X syndrome, tuberous sclerosis complex, neurofibromatosis, Rett syndrome) (Jeste & Geschwind, 2014). Many ASD associated gene variants are implicated in pathways of cortical development, synaptic function, synaptogenesis, microglia activity, neuronal morphology, and neurogenesis, all of which have been reported to be disrupted in ASD (de la Torre-Ubieta et al., 2016; De Rubeis et al., 2014). This implies that a large part of ASD etiology resides in common variants, meaning that a large portion of the genetic sources of ASD are also present in the typical population. Unsurprisingly, ASD also runs in families. Relatives of individuals with ASD often present subthreshold manifestations of autism symptomatology, that is, milder non-clinical traits at a higher degree than relatives of unaffected individuals. This wider dimension composed of subthreshold ASD traits is known as the broad autism phenotype. This account falls under the theoretical framework of polygenic risk models, which argue that many inherited variants with small effects are responsible for the disorder (de la Torre-Ubieta et al., 2016; Gaugler et al., 2014; Geschwind & Flint, 2015; Sanders et al., 2012).

However, the genetic liability of autism is also due to rare genetic variants. This view corresponds to that of major gene models. Major gene models argue that one or a few rare genetic variants (e.g. de novo mutations), with moderate-to-high penetrance, are responsible for the disorder (de la Torre-Ubieta et al., 2016; Gaugler et al., 2014; Geschwind & Flint, 2015; Sanders et al., 2012). Polygenic and major gene models are, however, not mutually exclusive. The current perspective is that

common genetic variants of additive risk make the largest contribution to genetic risk for ASD, but that an important, albeit smaller, contribution comes from rare and de novo genetic variations (de la Torre-Ubieta et al., 2016). Nonetheless, environmental factors also play a role in ASD etiology. Environmental factors such as elevated maternal and paternal age, maternal ingestions, exposures and disease (valproate, toxic chemicals, diabetes), and metal uptakes among others, increase the risk for autism (Arora et al., 2017; Bölte, Girdler, & Marschik, 2019).

Evidence from multiple twin studies suggests that ADHD is highly heritable (Faraone & Larsson, 2018). Research on the genetic etiology of ADHD suggests is mostly polygenic, with no single gene causing the disorder in most cases. Thus, the disorder is the result of the sum of the small effects of many genes, with both common genetic variants and rare genetic variants adding to the disorder's genetic risk (Neale et al., 2010; Thapar, Cooper, Eyre, & Langley, 2013; Williams et al., 2012; Yang et al., 2013). Initial research on candidate genes association studies points at genes involved in the dopamine and serotonin pathways (Hawi et al., 2015). However, it was not until recently that the first common genetic variants for ADHD, that surpassed critical significance thresholds, were identified (Demontis et al., 2019). Nonetheless, the number of studies is still small and the search continues with the addition of rare gene variants and a notable focus on large rare structural and copy number variants (CNVs) (Faraone & Larsson, 2018). However, not all ADHD causal factors are genetic, many are actually environmental factors (Sciberras, Mulraney, Silva, & Coghill, 2017). For example low birth weight (Hultman et al., 2007), premature birth (Silva, Colvin, Hagemann, & Bower, 2014) and maternal smoking during pregnancy (Dong et al., 2018). Although, some of these associations between environmental factors and ADHD appear to have been due to confounding factors not properly addressed in the past (Sciberras et al., 2017), for example maternal antidepressant consumption during pregnancy (Sujan, Öberg, Quinn, & D'Onofrio, 2019).

The diagnosable phenotypes are also likely the result of a complex interaction between genetic predispositions and environmental factors, rather than the unfolding of a genetic code where the environment has no influence on biological factors, such as gene expression (Dawson, 2008; Johnson, Gliga, Jones, & Charman, 2015). How different factors interact at different time points in development can help our understanding of these disorders and of how and when to optimally intervene.

1.8.1 ASD and ADHD traits in the typical population

In the past (and sometimes still in the present), many have inquired if ASD and ADHD traits are etiologically different than clinically diagnosed ASD and ADHD. For the most part, they are quantitatively different but not qualitatively so. That is, the genetic influences to ASD and ADHD traits are, to a large extent, shared

between clinically diagnosed ASD and ADHD and the subthreshold variation in ASD and ADHD traits found in the typical population. Thus, the diagnostic forms can be understood as the phenotypic extremes of normally distributed traits in the population. Supporting evidence of this view of ASD and ADHD comes from similar study designs dedicated to each disorder/traits.

Some of the earliest findings to suggest this dimensional view of both neurodevelopmental disorders come from twin studies using the DeFries & Fulker (DF) extremes analysis method (DeFries & Fulker, 1985) and liability threshold models. On DF analysis, the focus is on the mean standardized quantitative trait score of the co-twin of an ascertained (or extreme) proband of the trait in question, and the extent to which this departs from the population mean and approaches the proband's mean standardized score (Kovas, Malykh, & Petrill, 2013). The main estimate of this analysis is group heritability. Group heritability reflects the degree of shared genetic influences between variation in clinically diagnosed cases and normal subthreshold trait variation. Complete independence of genetic influences between clinical cases and normal trait variation would be reflected by a group heritability of zero. It is worth pointing out that to find group heritability, both forms (clinical and subthreshold trait variation) must be heritable and share genetic etiology. Studies using this method were among the earliest to demonstrate a genetic link between clinical ASD and ADHD and ASD and ADHD traits respectively (Levy, Hay, McStephen, Wood, & Waldman, 1997; Robinson et al., 2011). These earlier studies reported similar heritability in clinical disorder forms and heritability in the subthreshold trait variation, which were largely due to additive genetics. Subsequent studies using this method have replicated these earlier findings but have also expanded their scope (Frazier et al., 2014; Greven et al., 2016; Larsson, Anckarsater, Råstam, Chang, & Lichtenstein, 2012; Lundstrom et al., 2012). For example, by suggesting a non-linear influence of shared environmental factors across the ADHD spectrum, with a larger influence at the low end (Greven et al., 2016). Or a more nuanced view of ASD, by observing higher heritability in the extreme high end that likely represents the strong effect of rare genetic factors (Frazier et al., 2014) - which was, however, not replicated by a later meta-analysis whose results are in line with earlier ASD twin studies (Tick, Bolton, Happé, Rutter, & Rijsdijk, 2016).

Liability threshold models are another twin approach that supports the shared etiology between trait and clinically diagnosed disorder. Liability threshold models allow to estimate relative genetic and environmental contributions to categorical data (e.g. categorical disorders). They assume that categories are imprecise measurements of an underlying distribution of liability to the disorder and that this liability distribution has at least one threshold that separates categories (typically known disorder prevalence estimates). Studies incorporating these models in their

analyses could assess genetic correlations between diagnostic ASD (categorical) and ASD traits and observe a substantial overlap of the underlying genetic underpinnings of the two (Colvert, Tick, McEwen, & et al., 2015).

Studies employing molecular genetic methods have also supported a dimensional view of ASD and of ADHD. Genetic correlations between genetic influences on social communication difficulties (a measure of autistic traits) in the typical population and genetic influences (common variants and de novo) on ASD risk in ASD diagnostic cases, showed evidence of an etiological overlap (shared genetic risk) between the two (Robinson et al., 2016). This suggests that at least some of the ASD risk genes in diagnostic cases are the same as those underlying social autistic traits in the general population. ASD polygenic risk scores studies (PRS) report, however, somewhat mixed results. One study (Bralten et al., 2018) showed evidence of etiological genetic overlap between PRS from both social and non-social ASD traits and clinical ASD. Similarly, associations between ASD risk and common polygenic ASD influences support the ASD dimensional view, with rare variants influencing only a subset of cases, and common variants having a more pervasive influence on ASD cases (Weiner et al., 2017). However, others find associations between clinical ASD scores and socio-communicative ASD traits only in childhood but not in adolescence (St Pourcain et al., 2018), or no associations at all (Krapohl et al., 2016). Furthermore, a recent meta-analysis identified the first common risk variants associated with ASD, of which five common loci were linked exclusively to ASD (Grove et al., 2019). This last study (Grove et al., 2019) observed that common variants appear more pervasive in high-functioning ASD (e.g. Asperger), and also replicated previous results where rare variants have been linked to ASD cases with intellectual disability.

In the case of ADHD, similar approaches have yielded similar results. Molecular genetic studies appear to also support that clinically diagnosed ADHD represents the extreme end of a continuous distribution (Martin, Taylor, & Lichtenstein, 2018). Polygenic risk scores studies in ADHD show that population scores of risk alleles of ADHD traits significantly distinguish between ADHD cases and controls (Stergiakouli et al., 2015) and vice versa - where polygenic risk for ADHD strongly predicted ADHD traits in large population samples (Brikell et al., 2018; Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2014). Moreover, a recent meta-analysis (Demontis et al., 2019) reported the first common genetic risk variants to be associated with clinical ADHD, as well as high concordance rates between their ADHD genomewide association study (GWAS) and previous GWAS of ADHD traits. All in all, research in both ASD and ADHD seems to support a dimensional view of these disorders. That is, where clinical ASD and ADHD represent the extreme end of normal trait variation spectrums, underpinned by partially, yet substantially, shared genetic etiologies. Thus, understanding variation of these traits in typical development is of value for understanding them at the "full-blown" level of the disorder.

1.9 Research Domain Criteria Initiative (RDoC) framework

The studies in this thesis try to follow the approach put forward by the Research Domain Criteria Initiative (RDoC) framework of the U.S. National Institute of Mental Health (Insel et al., 2010). One of the principles of RDoC is to design research hypotheses that build on what is known in terms of the neural basis of typical function and behavior. The studies in this thesis attempt to do exactly that by studying cognitive functions as potential endophenotypes via the well-documented visual system. Additionally, RDoC encourages research to assume a dimensional view of neurobehavioral processes. As discussed in the previous section, this thesis capitalizes on a dimensional approach to ASD and ADHD symptoms, where both disorders are the extreme ends of continuously distributed traits that extend to the subthreshold population.

1.10 Knowledge gaps

When looking at the literature reviewed above, we can see that although these attentional functions are of relevance for the understanding of ASD and ADHD, there are in fact some remaining questions. For instance, despite the reported links between early visual disengagement and ASD, to the best of the author's knowledge, there are no studies that have studied whether visual disengagement is associated to social skills and other developmentally relevant behaviors in early infancy. Additionally, if there is indeed a link between visual disengagement and ASD, there is no evidence of the etiology of this link. Furthermore, whether individual differences in visual disengagement are due to genetic or environmental factors is still unknown. Thus, although positing visual disengagement as an ASD early marker or endophenotype is sensible given current evidence, there are gaps that need to be addressed.

Similar gaps can also be encountered when considering response inhibition as an intermediate cognitive endophenotype for ADHD. Although genetic factors have been reported as important to individual differences in response inhibition, whether this extends to oculomotor response inhibition is still unknown. Similarly, whether the associations between response inhibition and ADHD are driven by genetic or environmental factors and if so, if these factors are shared between the two or not, has seldom been explored. Additionally, while oculomotor response inhibition seems to be negatively associated with ADHD and ADHD traits, most of the literature on the topic comes from case control studies rather than from studies exploring the possibility of trait/dimension specific deficits.

2 PURPOSE AND AIMS

The overarching aim of the thesis was to increase our knowledge about selected attentional functions thought to be important for ASD and ADHD in infancy and childhood using eye tracking and twin modelling. The specific aims of the three studies were the following:

2.1 Study 1

1. To investigate the relative contribution of genetic and environmental influences to attentional functions relevant to ASD. Specifically, to visual disengagement as assessed with the gap overlap task.

2. To examine whether visual disengagement was associated with parent-rated autistic traits, and to estimate the contribution of genetic and environmental factors to this putative association.

2.2 Study 2.

1. To investigate the relative contribution of genetic and environmental influences to oculomotor response inhibition as assessed with the antisaccade task.

2. To examine whether oculomotor response inhibition was associated with parent-rated ADHD traits, and to estimate the contribution of genetic and environmental factors to the association.

2.3 Study 3.

To investigate how visual disengagement relates to other cognitive developmental processes and behaviors, such as motor, language, social, and adaptive behaviors, socioeconomic status and sex in early infancy.

3 MATERIALS AND METHODS

3.1 Data Sources

3.1.1. iTWIN

Participants from *Studies 1 and 2* were recruited from The Child and Adolescent Twin Study in Sweden (CATSS) (Anckarsater et al., 2011). CATSS is an ongoing nation-wide population longitudinal twin study with a 70% inclusion rate. The study targets all twins born in Sweden since July 1st 1992 and it started in 2004. The aim of CATSS is to understand the relative genetic and environmental influences on behavior and health in childhood and adolescence. CATSS collects information on mental and physical health through a telephone interview with the twins' parents when the twins are nine years old. Twins from CATSS were invited to take part in additional in person experimental and cognitive assessments and if they accepted they were included in the iTwin cohort. The iTwin cohort consists of 723 individuals (twins), between the ages of 9-14 years old. The cohort was phenotyped for ASD and ADHD traits as well as other functioning data. Participants took part in an eye-tracking task battery including a series of paradigms tapping into different cognitive functions and sub-functions, including the gap-overlap task and the antisaccade task.

3.1.2 Babytwins

Babytwins is a population based longitudinal infant twin study with a 29% inclusion rate of same-sex twins in the larger Stockholm area and central Uppsala. The purpose of Babytwins as a project is to understand the relative contribution of genetic and environmental influences to early cognitive functions and behaviors. Babytwins focuses on functions underpinning pivotal developmental skills, particularly those hypothesized to potentially contribute to behavioral atypicalities later in life. The study entails one lab visit at 5 months of age and subsequent questionnaire data collection at later ages.

3.2 iTWIN measures

3.2.1 Eye tracking

Eye movements in *Studies 1 and 2* were recorded with remote infrared eye tracking using a Tobii T120 (120 Hz sampling rate). The stimuli for these studies were displayed as full-screen on a 23" monitor with a 1024 x 1280 pixel resolution using Tobii Studio. Prior to the start of both eye tracking paradigms (Gap-Overlap and Antisaccade) in these studies, a 9-point calibration image was used to determine the positions of the eyes. The task only begun after a calibration was deemed successful, and thus achieved, by the experimenter and was repeated if necessary.

Visual disengagement was assessed in *Studies 1 and 3,* using the Gap Overlap task, which has three conditions: the gap, the baseline and the overlap (although some studies only use the conditions gap and overlap). However, due to the different age groups taking part in study 1 versus in study 3, the task varies slightly to accommodate these differences. Thus the paradigm used in study 1 that belongs to iTWIN will be described in this section, while the paradigm used in study 3 that is part of Babytwins will be described in its own section.

3.2.1.1 The iTwin Gap-Overlap task

In the task a central stimulus (CS) (a black cross) appears on a screen with a grey background and is followed by a new stimulus that appears in the periphery (a yellow dot). The three experimental conditions differ with regards to when the CS disappears in relation to when the peripheral stimulus (PS) appears. Different gaze shift latencies are obtained in the conditions. In the "gap condition" the CS disappears (200 ms) before the PS appears. Hence, in this condition, there is no stimulus to disengage from, and the disappearance of the central object may function as a (spatially non-predictive) preparatory cue. Gaze shift latencies in this condition are the shortest (150 ms). In the "baseline condition" the CS disappears simultaneously as the PS appears; hence in this condition, no preparatory cues are given, but there is also nothing to disengage from at the moment the PS appears. Finally, in the "overlap condition" the CS remains displayed when the PS appears. Gaze shift latencies are the longest during this condition (250 ms), which is thought to reflect the active disengagement process, by deliberately swapping their fixation focus from the CS towards the PS (Fischer & Breitmeyer, 1987). The main outcome measure was visual disengagement defined as the median average of gaze shift latencies in milliseconds (e.g. time taken to move away one's gaze from the CS to the PS) from all conditions, and is also referred to as the leaving latency.

3.2.1.2 The Antisaccade task.

As introduced above, the antisaccade is a response inhibition eye tracking paradigm where a CS appears on a screen and is followed by a new stimulus that appears in the periphery. This task was the inhibition paradigm used in *Study 2.* The participants are typically instructed to look as fast as they can to the mirror location of the PS once it appears. The stimuli used for this task is the same employed in the Gap-Overlap task, minus the Baseline condition. Therefore, only the Gap (the CS disappears before the PS appears) and the Overlap (the CS remains displayed when the PS appears) conditions where part of the Antisaccade stimuli. In the Antisaccade task, a CS appeared on a gray background and was followed by a new stimulus that appeared on the periphery. The CS consisted of a black cross and the PS of a yellow circle, both were 1.5° visual degrees wide. In all conditions, the CS appeared in the center of the screen and was followed by the PS. In

the Gap, the CS disappeared 200ms before the PS appeared. In the Overlap the CS remained on the screen when the PS appeared. Trial duration and presentation were randomized, the side where the PS appeared was counterbalanced, and a set of test trials to assess comprehension of the task was included (with repetition of instructions when deemed necessary). The main response inhibition (outcome) measures were the proportion of direction errors in respect to total number of valid trials, and the proportion of anticipatory eye movements in respect to total number of valid trials. A direction error was recorded whenever a gaze shift was made toward the peripheral target instead of toward its mirror location. An anticipatory eye movement error was recorded whenever 50% or more of the gaze samples in the 200ms time-window prior to the peripheral target onset were recorded outside the CS. Both variables were used to operationalize a deficit in oculomotor response inhibition, with a higher number of errors/anticipatory eye movements reflecting a more severe deficit.

3.2.1.3 Fixation and gaze shift detection in Studies 1 and 2

How were eye movements detected/coded? There are different approaches for fixation and eye movement detection, and of eye tracking metrics in general. However, there isn't a one size fits all approach. The choice of algorithm (along with its accompanying features such as data smoothing/filtering and missing data handling procedures) relies on several factors: the type of eye movement to be recorded, the eye movement metrics relevant to the research question (e.g. time to initiate an eye movement), the type of eye tracker and its sampling rate (120, 300, 1000 Hz), and the population of study (infants, adults) (Holmqvist et al., 2011; Salvucci & Goldberg, 2000). All algorithms have pros and cons but the idea is to try to balance those in a way that suits the data better. Among the most commonly used algorithms for fixation parsing are: area-based algorithms, also known as Area of Interest (AOI) identification algorithms, and velocity-based algorithms (Salvucci & Goldberg, 2000). In *Study 1* an AOI based algorithm was used. AOI based algorithms are typically employed when the measures of interests are fixations and/or looking times, however they can also be used to detect gaze shifts and other gaze related metrics. In short, AOI based algorithms are focused on identifying eye metrics within pre-specified areas of interest (Salvucci & Goldberg, 2000). In the case of *Study 1,* the main interest were eye movement reaction times (or latencies). Thus, in this study, rectangular AOIs encapsulated the stimuli in the paradigm (the Gap-Overlap task). Fixations within the AOI were identified as consecutive data points located in close proximity of each other spanning a minimum duration threshold. Special attention was placed on the last fixation within the central AOI, for the last data point of said fixation within the AOI was marked as the start of a gaze shift. Gaze shifts within the AOI were ignored, and only those that landed outside the AOI were selected for subsequent processing. In *Study 2,*

a combined algorithm was used (AOI and velocity detection). A velocity based algorithm differentiates saccades (in this case gaze shifts) from fixations on the basis of different point-to-point velocities, as saccades tend to have much higher velocity distributions than fixations (Salvucci & Goldberg, 2000). Typically the point-to-point velocity is calculated using the distance between two consecutive points – the moment one of these computed velocities exceeds a certain velocity threshold (°/ms) a saccade is flagged. In order to calculate velocities in *Study 2,* the median of two 67 ms-long sliding windows of sampled gaze positions averaged from both eyes was compared. If the velocity threshold of 39°/s was exceeded it was considered as a gaze shift. This velocity threshold was selected after visually inspecting the data and based on the task's sparse stimulus, prior to the main analysis. A set of criteria had to be met for a directional gaze shift to be deemed as such: (1) the gaze shift had to begin within the Central AOI (width 7°3′ and height 10°4′) and terminate outside this AOI subsequently to the peripheral stimuli onset. (2) Latencies to initiate a gaze shift needed to be at least 60ms and last no more than 800ms.

The criteria for trials to be considered valid was the same for both studies: (a) Gaze data was registered inside the central AOI for at least 50% of the samples during the last 200 ms prior to when the gaze first exited it (following the PS appearance). In case of *Study 2,* this time window was parsed to identify anticipatory eye movements in order to record them as such. (b) At least 50% of the time the fixation cross was displayed prior to the PS onset, gaze data had to be recorded within the central AOI. (c) Gaze samples subsequent to a gaze shift being flagged had to be part of a fixation (at least 50% of the gaze data in the following 200ms had to be either within the PS's AOI (*Study* 1) or on either side of the central AOI (*Study2*). These steps ensured that latencies were not based on spurious data and excluded trials with substantial data loss.

3.2.2 The Wechsler Intelligence Scale for Children IV (WISC-IV)

Cognitive ability was assessed using scores from the vocabulary, digit span, coding, and matrix reasoning subscales of The Wechsler Intelligence Scale for Children IV (Wechsler, 2003). The WISC-IV is a valid and widely used assessment for intelligence ability, providing both an overall score of intelligence as well as functioning scores for its subscales (Wechsler, 2003). The aforementioned subscales were selected as proxies from their WISC-IV subtest areas (Vocabulary, Perceptual reasoning, Working memory and Processing speed) which are considered potential confounders due to the negative association found between IQ and ADHD traits (Rommelse et al., 2018) and the common genetic underpinnings of this association (Kuntsi et al., 2004; Polderman et al., 2006). Despite being able to use a composite measure of IQ there is a clear interest on independently con-

trolling for performance on the working memory (WM) subscale because of the role it plays on the performance on the antisaccade task (Unsworth, Schrock, & Engle, 2004) and the reported WM deficits in ADHD (Klingberg, Forssberg, & Westerberg, 2002).

3.2.3 The Social Responsiveness Scale (SRS)

Autistic-like traits were assessed using the Social Responsiveness Scale (Constantino & Gruber, 2005). The SRS is a valid 65-item parental rating scale assessing autistic-like traits (stable elements of autism spectrum disorder) sensitive to a continuum of social impairment severity including subthreshold variation levels (Constantino et al., 2003). The SRS raw total score from the Swedish adaptation of this scale (Zander & Bölte, 2019) was the overall measure of autistic-like traits.

3.2.4 Conners 3-P

ADHD behaviors were assessed via parent report using the Inattention and Hyperactivity subscales from the long version of the Conners 3-P (Conners, 2008b). The Conners 3-P is a valid, reliable and consistent assessment of ADHD traits and its most common comorbidities (Conners, 2008b; Thorell et al., 2018). Since the interest was in ADHD core traits, the only scores used were the raw total of the Inattention and Hyperactivity/Impulsivity subscales. These subscales (with a combined total of 24 items) independently address inattentive behaviors as well as hyperactive and impulsive behavior during the last month. The Inattention scale consists of 10 items with statements addressing inattentive behaviors (e.g. “has problems focusing”, “has difficulties concentrating”). The Hyperactivity scale consists of 14 items with statements regarding hyperactive and impulsive behavior (e.g. “behaves as if driven by a motor”, “cannot sit still or fidgets”). Parents are instructed to assess how well each statement describes their child or how often they have taken place in the last month, on a 4-point Likert scale. The Swedish version of these scales also shows good psychometric properties with excellent internal consistency and test-retest reliability ($r_{\alpha} \geq .90$) (Thorell et al., 2018).

3.2.5 Additional measures

In addition to the aforementioned measures, the study included parental ratings of various aspects of child behavior beyond the ones mentioned above. These measures were not part of the studies in this thesis and thus were not included.

3.3 Babytwins measures

3.3.1 Eye tracking

Eye movements in *Study 3* were recorded with remote infrared eye tracking using a Tobii TX-300 (300 Hz sampling rate) eye tracker. Stimuli were displayed on a 23" monitor with a 1920 x 1080 pixel resolution. The task was preceded by a 5-point infant-friendly, manually controlled calibration sequence. The stimuli in the calibration was a set of colorful dynamic spirals that contracted to a single point. These spirals had an onset diameter of ~6° and gradually shrunk to a 0.5° diameter once gaze measurement was completed. The task begun only when this calibration was deemed successful by the experimenter (repeated if necessary). In addition to the initial calibration, subsequent calibration stimuli were presented at randomized positions throughout the task battery to which the Gap Overlap task pertained.

3.3.1.1 The Babytwins Gap Overlap task.

As aforementioned, the Gap Overlap task, or for simplicity the Gap task, is a visual attention shifting paradigm to operationalize and measure visual disengagement. Although in principle it is the same task used in *Study 1*, in this section the infant friendly version of the task adapted from previous studies with infants (Elsabbagh et al., 2013; Johnson et al., 1991) and used in *Study 3* is described. In contrast to the "iTWIN version", this adaptation featured attractive and dynamic stimuli against a pink background and a gaze-contingent modality for the peripheral stimulus. The central stimuli (a constricting-expanding cartoon clock) ranged between 2.1° x 2.1° and 3.3° x 3.3°, while the peripheral stimuli (sun, cloud, ball, star, and dog) had a 2.5° x 2.5° size and appeared at a 19° eccentricity from the center. The conditions in the task were the same as in the iTWIN version (Gap, Baseline and Overlap). However, in this gaze-contingent version of the task, the central stimulus remains displayed until the infant fixates on it. Inter-stimulus intervals (600/700ms) and screen side (right/left) for peripheral stimuli onset were randomized. The main outcome variables for this study were: gaze shift latencies in ms in the (1) Gap condition and in the (2) Overlap condition, and (3) visual disengagement score. Gaze shift latencies were defined as the time it takes the gaze to shift from the central stimulus to the peripheral stimulus upon the onset of the latter. The visual disengagement was computed as a difference score between gaze shift latencies in the Baseline and Overlap conditions (Jones et al., 2019). While infants were performing the task, their behavior was monitored "online" by the experimenters through a camera placed on top of the eye tracker's monitor. Experimenters were hidden from the infant's view behind a curtain. Auditory attention grabbers were embedded in the script and could be triggered with a simple key press, these aids were built in with the purpose of redirecting the gaze of the infant back to the screen in the instance that they looked away during the task.

3.3.2 The Mullen Scales of Early Learning (MSEL)

The MSEL (Mullen, 1995) were created to assess cognitive skills in infancy and childhood, from birth up to 68 months and were used to assess developmental level in *Study 3*. The MSEL consists of five subscales: Gross motor, Visual perception, Fine motor, Receptive language and Expressive language. For *Study 3,* raw scores for each subscale were calculated manually on each participant's MSEL scoring sheet. Age adjustments for prematurity and both younger/older twins (4-6 months) were made in line with MSEL guidelines. Each twin was assessed by a different member of the experimental team on a majority of cases. Special care was taken on this measure as to ensure a blind assessment of each child in the twin pair. A total raw score consisting of the sum of the raw scores of these scales was used as proxy of developmental attainment at 5 months.

3.3.3 The Vineland Adaptive Behavior Scales 2nd Edition (VABS-II)

In *Study 3,* current adaptive level was assessed via parental report using the translated questionnaire format of the VABS-II (Sparrow, Balla, & Cicchetti, 2005). The scales and respective items completed by the parents were the following: Listening and comprehension (items 1-5), Speaking and communicating (items 1-6), Self-care (items 1-5), Relationship skills (items 1-9), Play and free time (items 1-3), Gross motor (items 1-7), and Fine motor (items 1-5). A total raw score consisting of the sum of the raw scores of these VABS-II subscales was used as a proxy of overall adaptive level.

3.4 Behavioral genetic analyses – Twin studies

The most common method in quantitative behavioral genetics is the twin method. The basic principle of the twin design is that it takes advantage of the existing differences in genetic relatedness between identical twins (monozygotic (MZ) – sharing 100% of their genes) and non-identical twins (dizygotic (DZ) – fraternal twins sharing approximately 50% of their segregating genes) (Eaves, Last, Young, & Martin, 1978). The studies in this thesis are population based twin studies. This kind of twin study design typically focuses on continuously distributed common traits, where twins are normally drafted from registers and similarity is assessed by comparing intra-class correlations (ICCs) of twin types (Eaves et al., 1978; Rijsdijk & Sham, 2002).

The variance in a trait can be partitioned into genetic and environmental influences. These, and thus total phenotypic variance, can be further decomposed into additive (A) and dominance (D) genetic effects as well as shared (C) and non-shared or unique (E) environmental effects, in the form that:

$$V = A + D + C + E \quad or \quad V_P = V_A + V_D + V_C + V_E$$

In behavioral genetics, additive genetics is the sum of all allelic effects across multiple loci and is commonly referred to as A. Non-additive genetic effects are due to interactions between alleles either at the same locus (Dominance or D) or a different locus (epistasis). MZ twins share all additive and dominant genes. Meanwhile, DZ twins only share approximately half of additive genes and a quarter of dominant genes. The degree to which genetic factors influence individual differences of a particular trait is known as heritability (h^2). A distinction can be made between broad and narrow heritability. Broad heritability includes all genetic effects that are relevant to said trait:

$$h^2_B = (V_A + V_D)/ V_P$$

While narrow heritability corresponds to additive or homozygous genetic effects:

$$h^2_n = V_A / V_P$$

Environmental influences can be split into shared (C) and unique (E). Shared environmental influences (C), refer to the aspects both twins will be equally exposed to when raised together, such as shared home/household, neighborhood and socioeconomic status (to name a few). Thus, twins are expected to have a correlation of 1 on C regardless of their zygosity (MZ or DZ) as long as they have been reared together. This, however, does not mean that twins do not have unique experiences of their own that might also matter for the trait. This is known as the non-shared environment or E. E encompasses the individual experiences of each twin such as illness, individual experiences and/or perceptions of said experiences, differential treatment by caregivers, peers and teachers, accidents, and virtually any environment that is experienced differently from their co-twin (Verweij et al. 2012). The non-shared environment variance also captures measurement error, which is why in twin modelling the E parameter cannot be dropped from models. There is zero correlation of E between twins in a pair.

3.4.1 Univariate analyses

Univariate analyses partition the variance in a single trait into genetic and environmental influences ($V = A + D + C + E$). In the classic twin design, genetic and environmental sources of a trait are considered latent components which one can estimate by combining existing biometrical theory with structural equations based

on actual observable variables. Thus, genetic and environmental influences to variance in a phenotype or trait are not directly measured but rather inferred from the pattern of observed correlations of MZ and DZ twins. Observed twin phenotypic correlations are the first pieces of information one can extract from twin data that provide an idea of the relative contribution of genetic and environmental factors. One can visualize twin correlations partitioned into variance components as well:

$$r\text{MZ} = \text{A} + \text{D} + \text{C}$$

$$r\text{DZ} = \tfrac{1}{2}\text{A} + \tfrac{1}{4}\text{D} + \text{C}$$

Under the equal environments assumption, which refers to twins experiencing the same environment (regardless of their zygosity), one can infer that if trait similarity is greater in MZ twins than in DZ twins, genetic factors are likely at play. However, if the similarity between MZ and DZ twins is roughly the same, then shared environmental factors are assumed to be of importance for the trait. Actual contributions of genetic (h^2) and environmental effects (c^2 and e^2) can be estimated without modelling (by hand) using Falconer's formula (Plomin, DeFries, & McClearn, 2008). Falconer's formula uses the MZ and DZ correlations to calculate genetic and environmental influences:

$$h^2 = 2(r\text{MZ} - r\text{DZ})$$

$$c^2 = r\text{MZ} - h^2 \text{ OR } 2r\text{DZ} - r\text{MZ}$$

$$e^2 = 1 - (h^2 + c^2)$$

However, in the case of the classic twin design, due to the amount of information available (only the twins) one cannot decompose into more than three sources of variance. In twin and family studies one can estimate the contributions of different parameters to a trait depending on the amount of information one has. The more family relations included in the design, the more parameters one will be able to estimate because the number of "knowns" (informative statistics) should be larger than the number of "unknowns" (parameters to be estimated). If there is only information from the twins (MZ and DZ) then the effects of A, C, D and E cannot be estimated simultaneously since, without any additional information (e.g. adoptive siblings) there would be more unknowns than knowns, leading to C and D being confounded in a typical twin study of twins reared together. Thus, one must opt for a narrow heritability and broad environmental sources model (A, C and E), or for a broad heritability but narrower environmental sources model (A, D and E). When doing twin modelling, the choice of fitting an ACE or an ADE model can be guided by looking at the pattern of MZ and DZ twin correlations. If the DZ correlation is more than half of the MZ correlation it suggests a role of

common environment and thus an ACE model is likely a better fit. However if the DZ correlation is less than half of the MZ correlation, it suggests the presence of dominance genetic effects or contrast effects thus an ADE model would be a better fit for the data (Knopik, DeFries, Plomin, & Neiderheiser, 2013). In line with the assumptions of the classic twin design, in both ACE (Figure 1) and ADE models, the additive genetics (A) and the shared environment (C) latent variables are fixed to correlate 1 for MZ twins, as MZ are assumed to shared 100% of their genes and their environments. Meanwhile, for DZ twins, although the shared environment (C) latent variable will also be fixed to 1 in the ACE model (since reared together DZ twins are assumed to share their environment to the same extent than reared together MZ twins do), the additive genetics (A) latent variable is instead fixed to correlate 0.5 in both models (as additive genetics are on average 50% shared between DZ twins) and in the ADE model, which includes dominant genetic effects, this latent variable (D) will be fixed to 0.25. The latent variable for non-shared environmental effects is always fixed to 0 for both types of twins (Neale & Cardon, 1992).

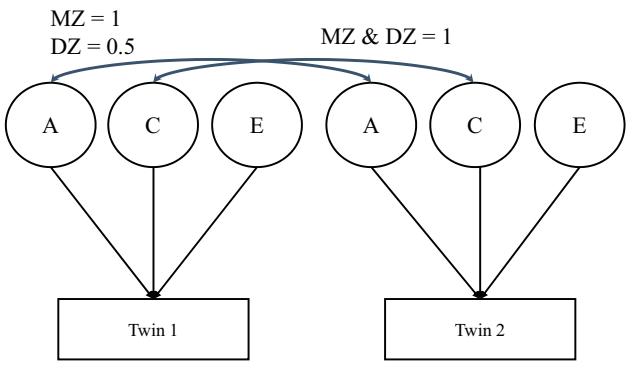

Figure 1. Example of an ACE univariate twin model. Latent variables are represented by circles and observed variables by rectangles. Single headed arrows represent paths. A stands for additive genetics, C for shared genetic environment, and E for non-shared environment. Additive genetic correlations in MZ twins are set to 1 since MZ twins share 100% of their genes. DZ correlation are set to 0.5 since DZ twins share about 50% of their segregating genes. Shared environmental correlations of both MZ and DZ twins are set to 1 in the classic twin design since they are twins reared together.

3.4.2 Multivariate analyses

Traits often covary and this covariation can also be explained in terms of genetic and environmental influences. So unlike in univariate analyses, where the focus is on one variable and decomposing its sources, multivariate analyses focus on decomposing the covariation of two (or more) variables into genetic and environmental sources of covariation (Knopik et al., 2013), thus explaining the etiologic

sources of the phenotypic correlation observed between variables. While in univariate analyses we compare twin scores on a trait to their co-twin's score on said trait, in multivariate analyses – where two or more traits are involved –we use cross-trait cross-twin correlations. That is, the score of a twin on one trait is compared to the score of the co-twin on the other trait (Kovas et al., 2013). Similarly to in univariate analyses, genetic overlap between traits in multivariate analyses can be inferred from the degree that MZ cross-twin cross-trait correlations surpass DZ cross-twin cross-trait correlations. In addition, in multivariate analyses the shared and non-shared influences on the covariation can be converted into either bivariate heritability or to a genetic/shared/non-shared correlation. Bivariate heritability is the degree of genetic influence to the covariance between variables (phenotypic correlation), and thus it takes into account each variable's heritability. Genetic correlation refers to the degree to which the genetic effects influencing individual differences on one variable correlate with the genetic effects on the other, thus are shared between variables (Knopik et al., 2013). So, it could be that the bivariate heritability is low, meaning that the role played by genetics to the phenotypic correlation between variables is not that important, even though the genetic correlation could still be high if all the genetic influences are shared between variables. An example of this is when genetic correlations based on molecular data are quite high, but molecular genetic heritability is still quite low in comparison to heritability from twin studies.

Three types of models were fitted in order of decreasing complexity in this thesis: the correlated factors model, the independent pathway model, and the common pathway model (Rijsdijk and Sham 2002).

3.4.2.1 Cholesky Model

Although technically not a model (because it estimates as many parameters as degrees of freedom) and not used in this form in this thesis, the Cholesky decomposition (Figure 2) or triangular factorization (triangular decomposition), is the most widely used multivariate model in twin research (Ronald, Larsson, Anckarsäter, & Lichtenstein, 2011). The Cholesky has been likened to hierarchical multiple regression outside of the genetic studies arena in the sense that it allows to estimate the independent contribution of a variable in addition to the shared contribution made with other variables (Kovas et al., 2013). This is often misinterpreted as a decomposition into common and specific factors, though the Cholesky decomposition requires prioritizing or a theoretically supported ordering of variables, for example in a case where there is a time sequence ordering it may be naturally suitable (Loehlin, 1996). However, if the order of the variables is arbitrary and the sole aim is to partition variance into common and specific components, the Cholesky is easily transformed into more appropriate solutions.

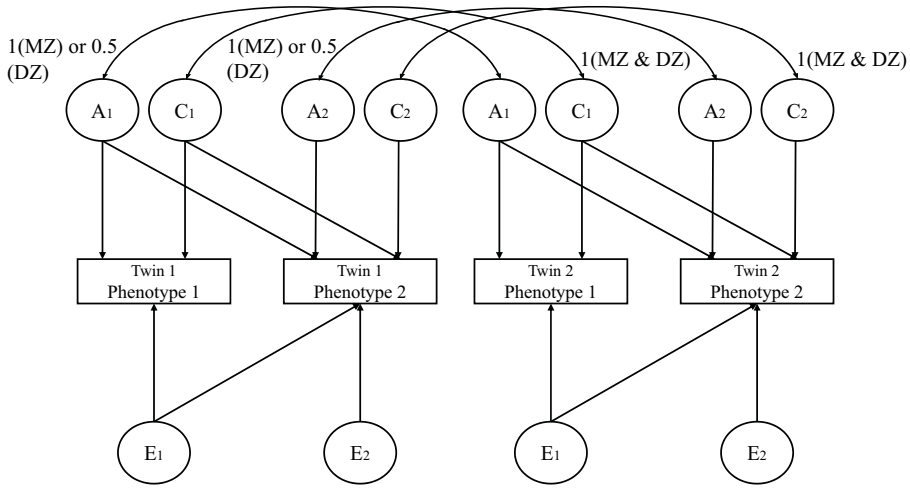

Figure 2. Example of a bivariate Cholesky triangular decomposition. Latent variables are represented by circles and observed variables by rectangles. Single headed arrows represent paths. A stands for additive genetics, C for shared genetic environment, and E for non-shared environment.

3.4.2.2 Correlated Factors Model

One of these transformations is the correlated factors model (Figure 3). In the correlated factors model, the sources of variance (genetic and environmental in behavior genetics approaches) are allowed to correlate between phenotypes, these correlations (r) typically range from zero (no overlap) to 1 (complete overlap).

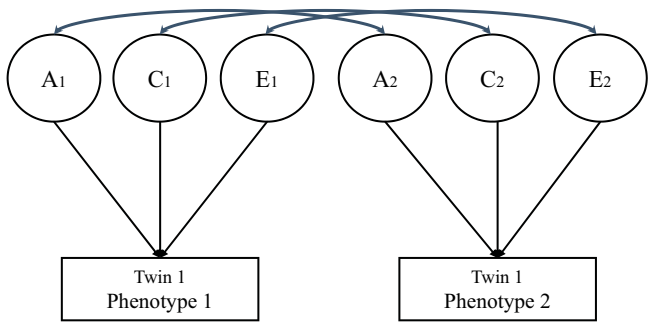

Figure 3. Example of a bivariate correlated factors model. Latent variables are represented by circles and observed variables by rectangles. Single headed arrows represent paths. Double-headed arrows represent correlations. A stands for additive genetics, C for shared genetic environment, and E for non-shared environment.

3.4.2.3 Independent pathway model

Another model in multivariate twin research is the independent pathway model. This model is a more restricted model than the correlated factors model. In this decomposition, shared genetic and environmental factors influence the response variables separately but also includes residual sources of variance to each variable (Figure 4) (Rijsdijk & Sham, 2002; Ronald et al., 2011).

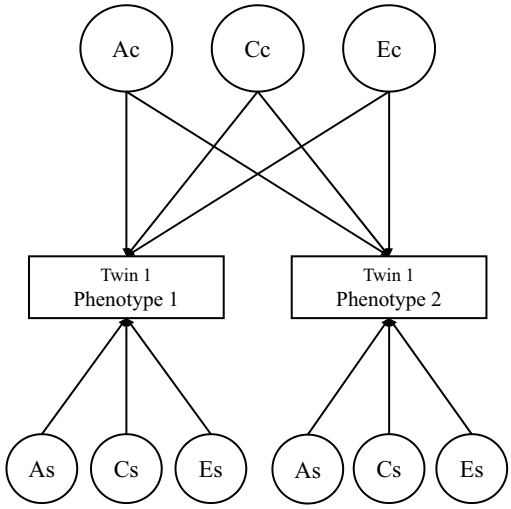

Figure 4. Example of a bivariate independent pathway model. Latent variables are represented by circles and observed variables by rectangles. Single headed arrows represent paths. A stands for additive genetics, C for shared genetic environment, and E for non-shared environment. Subscripts c and s stand for common and specific respectively.

3.4.2.4 Common pathway model

The common pathway model is another way of partitioning variance in twin studies that include three or more variables per twin. In this model, which is the most constrained model of the ones in this thesis, it is assumed that a single latent factor is the source of the common variation between outcome variables, and this single latent factor is in turn influenced by genetic and environmental factors (Figure 5) (Rijsdijk & Sham, 2002; Ronald et al., 2011). In addition, the model also includes specific etiological (genetic and environmental) influences on the outcome variables.

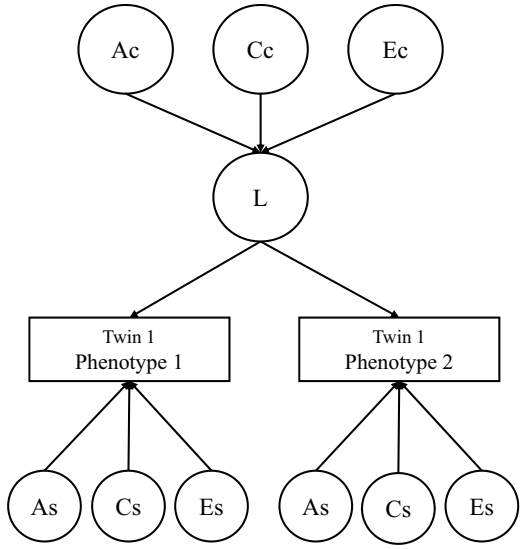

Figure 5. Example of a bivariate common pathway model. Latent variables are represented by circles and observed variables by rectangles. Single headed arrows represent paths. A stands for additive genetics, C for shared genetic environment, E for non-shared environment and L for a common latent factor onto which common shared genetic and environmental influences to both phenotypes load on. Subscripts c and s stand for common and specific respectively.

3.4.3 Model selection

In twin studies, and behavioral genetics studies in general, model fitting involves selecting the model that best describes the data. There are different tools to accomplish this, however, the choice of correct statistic will depend on the characteristics of the data set as well as the complexity of the models being compared. Although there are many, an exhaustive review of all is beyond the scope of this thesis, therefore only the three used in this thesis will be described.

3.4.3.1 Likelihood ratio testing

The likelihood framework (MLM -2LL x^2 – Maximum likelihood models) allows to calculate parameter estimates in twin modelling and to choose the most likely parameter estimates given the observed data. Additionally, it allows to test model fit (e.g. comparing the model to a saturated model) by using a likelihood ratio test (LRT). Beyond assisting in the choice of the parameter estimates with the highest probability of observing the present data and overall model fit, LRT can also help to test the significance of a parameter in the model (e.g. is shared environment, "C" parameter, making a significant contribution to the model) or test a specific value for a specific model parameter. LRT is a chi-square distribution

statistic of the change of the minus two log likelihood (-2LL) where significance is also influenced by the degrees of freedom between models. A non-significant chi-square means that the model doesn't significantly differ from the data and thus explains the data well.

3.4.3.2 Information Theoretic Criteria

In information theoretic model selection, the fundamental principle is to choose the most parsimonious model that offers the simplest, and thus most efficient, description of the data. Although information based inference shares similarities to likelihood inference, namely minimizing information, they offer some advantages over likelihood methods. Most notably, information-theoretic methods can also be applied to non-nested models (Markon & Krueger, 2004). Several information criteria have been put forward with two of the most common being Aikaike's Information Criteria (AIC) and the Bayesian Information Criteria (BIC).

3.4.3.2.1 The Bayesian Information Criteria (BIC)

The BIC goodness of fit statistic identifies the most parsimonious model by weighing both how well the models fit the data, and how many parameters they use. This index is designed this way because a model that uses more parameters always fits the data better, but such a model might not be the most parsimonious. Lower BIC values indicate a better fit of the model to the data (Raftery 1995). BIC is also explained as an estimate of the Bayes factor; when used to compare against the saturated model, BIC will be negative when an alternative model fits the data best.

3.4.3.2.2 Akaike's Information Criterion (AIC)

Another widely used information criteria for model selection in behavioral genetics, is Akaike's Information Criterion. Very simply put, AIC is a statistic that measures how inefficient the model is at describing the data. Thus, smaller AIC values reflect more efficient models that more closely resemble the unknown but true model (Markon & Krueger, 2004).

Both model selection statistics have their pros and cons, and the selection of one over the other depends on various factors such as sample size, number of variables and distributional specification. For example AIC, when compared to BIC, has shown higher selection power for the correct model in smaller samples, and more stability in power as sample size increases, but to perform poorer when a skewed distribution is falsely specified as normally distributed (Markon & Krueger, 2004). On the contrary, BIC performance is more robust against distribution misspecification but selection power is greatly affected by sample size, which improves as a function of sample size (Markon & Krueger, 2004). In *Studies 1 and 2* of this thesis we selected best fitting models in accordance to the BIC statistic.

3.4.4 Assumptions of twin studies

As with other statistical methods, twin analyses are built on a series of assumptions that need to be met in order to provide unbiased information. Violations of these assumptions will lead to misestimating both heritability and common environmental contributions (Rijsdijk & Sham, 2002).

3.4.4.1 Twins are not a different population

This assumption addresses generalizability of results from twin studies to the non-twin population, meaning that twins are representative of the target general population and not systematically/significantly different. In most cases this is a fair assumption, however twins tend to be considered higher risk pregnancies and often have more obstetric and pediatric complications early in life (Rijsdijk & Sham, 2002). Therefore, if the trait in question is not related to complications more prevalent in twins, it is fair to assume representativeness, otherwise it needs to be addressed and implications for results need to be disclosed and discussed.

3.4.4.2 Equal environments between MZ and DZ twins

In short, this assumption refers to MZ and DZ twins sharing environments to the same extent. That is, that the environment shared by MZ twins is not more similar than the environment shared by DZ twins. A violation of this assumption (for instance if MZ twins have a more similar environments due to their parents treating them more alike than parents of DZ twins) would inflate MZ correlations and misleadingly overestimate heritability (Rijsdijk & Sham, 2002). This assumption has been mainly challenged by the arguments that (1) MZ twins "are" treated more similarly by their parents than DZ twins and, (2) that later in life MZ twins are closer to each other than DZ twins. However, support for the equal environments assumption comes from different sources. First, studies looking at mislabeled twins (DZ erroneously labelled as MZ) have showed no evidence of more equal treatment of mislabeled DZ twins (Kendler, Neale, Kessler, Heath, & Eaves, 1993). Second, studies of MZ twins reared apart have showed similar heritability estimates to those from MZ twins reared together on multiple measures, for example IQ (Bouchard, Lykken, McGue, Segal, & Tellegen, 1990). And third, more contact between twins in a pair does not appear to increase behavioral similarity (Rijsdijk & Sham, 2002).

3.4.4.3 There is no presence of assortative mating

Assortative mating refers to when partner selection is driven by phenotypic correlation, which in certain phenotypes can lead to genetic similarity between partners (Rijsdijk & Sham, 2002). If assortative mating is present, the effects of common environment will likely be overestimated because DZ correlations will

be artificially inflated and result in genetic influences (additive and non-additive) being underestimated. However, assortative mating will not increase MZ twin correlations because they are already perfectly genetically matched. Interaction between partners can also increase phenotypic similarity. If there are reasons to believe non-assortative mating, as it is the case with certain traits (ASD and ADHD included), some precautions should be taken (for example, assortative mating can be assessed by studying the similarity of a trait in the spouses of twins).

3.4.4.4 Absence of gene-environment correlations

Gene-environment correlations refer to when the genotype can influence the selection of the environment, as a function of the individual's genotype (active) or when the genotype is exposed to an enhancing environment due to parental genotype (passive). That is, the exposure of genotypes to different environments is not random (Rijsdijk & Sham, 2002). Active correlations between genetic and unique environmental factors (GxE) when positive will increase heritability estimates and when negative will decrease them. Meanwhile passive correlations between genetic and shared environmental factors (GxC) when positive will increase environmental shared effects. Disentangling these kind of effects is challenging and it requires tailored research designs, such as longitudinal designs for active correlations and adoption designs for passive correlations.

3.4.4.5 Absence of gene-environment interactions

Gene-environment interactions refer to the different liabilities and/or susceptibilities different genotypes have to different environments (Rijsdijk & Sham, 2002). Interactions also present challenges as gene-shared environment interactions will be captured as additive genetic effects, and gene-unique environment interactions will be captured under non-shared environmental effects. Both types of interactions are notoriously difficult to detect and special methods are required to do so.

3.5 General Estimating Equations

General Estimating Equation (GEE) models are typically regarded as extensions of the standard general linear model. General linear models within the GEE framework are, however, able to handle correlated and clustered data as well as a variety of data types (Hardin & Hilbe, 2002; Homish, Edwards, Eiden, & Leonard, 2010). When working with twin data, one must take into account that the data points are not independent. Assuming independence when there is in fact correlation between the data, will result in inference errors since although the estimates will be the same, the standard errors (SE), and thus the CIs and the hypothesis testing, will be wrong. Therefore, GEE models are suitable for testing associations in twin data since GEEs are able to account for the non-independence of the data (twin pairs)

by computing cluster-robust SEs using the Sandwich Estimator. The Sandwich estimator allows for heteroscedasticity, meaning each cluster (twin pair) is allowed to have its own variance as residuals are not required to be homogeneous. Thus, associations were estimated using general linear regression models within the GEE framework using the drgee package from R (Zetterqvist & Sjölander, 2015).

4 STUDY SUMMARIES AND RESULTS

4.1 Visual Disengagement: Genetic Architecture and Relation to Autistic Traits in the General Population (Study 1)

4.1.1 Rationale

Visual disengagement has been posited as a potential endophenotype of ASD. According to widely used endophenotype criteria, the endophenotype in question should be heritable and associated to the disorder (Gottesman & Gould, 2003). However, there are no reports about the heritability of visual disengagement. Furthermore, results from studies examining the link between ASD and slowed visual disengagement are mixed. Therefore, this study's aim was twofold:

(1) Estimate the relative role of genetics in basic measures of visual disengagement (operationalized as gaze shift latency).

(2) Assess their putative association to parent reported ASD traits in the general population.

4.1.2 Methods

A total of 492 twins (50% MZ) recruited from the Child and Adolescent Twin Study in Sweden (CATSS) from the larger Stockholm area, took part in the Gap Overlap eye tracking task to assess basic measures of visual disengagement (gaze shift latencies) and gaze shift amplitude. Additionally, parent-reported ASD traits and ADHD traits in the twins were measured with the Social Responsiveness Scale (SRS) and the Conners-3P, respectively. IQ was assessed onsite with the Wechsler Intelligence Scale for Children IV (WISC-IV).

Mean gaze shift latencies and amplitudes from the Gap Overlap task were computed using custom-made scripts on MATLAB (for details on the calculation of eye tracking metrics see subsection 3.2.1 of the Methods). The heritability of trait and eye tracking variables was estimated using ICCs and univariate twin modelling. The relative contributions of genetic and environmental effects (shared and non-shared) to the covariation of gaze shift latencies across experimental task condition was estimated using multivariate twin modelling. IQ, sex and age at testing time were regressed out of all of twin analyses Additionally, phenotypic associations between eye tracking variables (visual disengagement and gaze shift amplitude) and parent-reported ASD traits and ADHD traits, as well as IQ, were computed using Pearson correlations with the sandwich estimator for unbiased standard errors (as observations were nested within twin pairs).

4.1.3 Results

4.1.3.1 Heritability of eye tracking variables (ICCs and Univariate analyses)

Intra-class correlations (Table 1) suggested an influence of genetic effects on both visual disengagement and saccade amplitude. ACE univariate twin modelling (Table 2) confirmed moderate heritability of both visual disengagement and gaze shift amplitude as elicited by all the experimental conditions in the task were heritable. In the case of ASD traits, the pattern of twin correlations (monozygotic correlations being more than twice the magnitude of dizygotic correlations) suggested dominance effects, thus an ADE model was fitted. ASD traits appeared influenced mainly by dominance genetic effects (D = 0.62; 95% CI 0.45, 0.79). Additive genetic effects (A = 0.14; 95% CI − 0.30, 0.58) and non-shared environment (E = 0.24; 95% CI − 0.17, 0.65) were non-significant.

Table 1. Intra-class correlations between MZ and DZ twins for arriving latencies and gaze shift amplitude on the three conditions

	Gap	**Baseline**	**Overlap**
Leaving latencies			
MZ	.62 (.50 , .74)*	.54 (.40 , .68)*	.42 (.26 , .58)*
DZ	.28 (.12 , .44)*	.10 (-.08 , .28)	.15 (-.03 , .33)
Gaze shift amplitude			
MZ	.67 (.57 , .77)*	.59 (.47 , .71)*	.41 (.25 , .57)*
DZ	.24 (.08 , .39)*	.01 (-.17 , .19)	.16 (-.02 , .34)

95% confidence intervals (CI) estimates are given in parentheses. *$p < .05$

Table 2. Univariate estimates of genetic and environmental contributions to the leaving latency and gaze shift amplitude.

	Genetic h^2	**Environment Shared** c^2	**Non-Shared** e^2
Leaving latency			
Gap	.55 (.33 , .76)*	.05 (-.13 , .23)	.40 (.30 , .50)*
Baseline	.48 (.34 , .62)*	0 (-.04 , .04)	.52 (.38 , .66)*
Overlap	.38 (.22 , .54)*	.02 (-.06 , .10)	.61 (.47 , .75)*
Gaze shift amplitude			
Gap	.68 (.58 , .78)*	0 (0 , 0)	.32 (.22 , .42)*
Baseline	.47 (.33 , .61)*	0 (0 , 0)	.53 (.39 , .67)*
Overlap	.46 (.36 , .56)*	0 (0 , 0)	.54 (.44 , .64)*

95% confidence intervals (CI) estimates are given in parentheses. *$p < .05$

4.1.3.2 Covariation of relative genetic and environmental influences in eye tracking variables (multivariate analyses)

For multivariate analyses, three different models were fitted to describe the data. The goodness of fit BIC statistic indicated the common pathway model fit the data best for both leaving latency and gaze shift amplitude. BIC statistics for the leaving latencies were: Independent pathway model (11153.048) > Correlated factors model (11152.858) > Common pathway model (11137.967). For gaze shift amplitude, BIC statistics were: Independent pathway model (11056.071) > Correlated factors model (11054.498) > Common pathway model (11039.023). The common pathway multivariate model showed that most of the covariance among eye movement latencies across conditions of the Gap Overlap task was shared and primarily genetic (Table 3). Further, there were unique genetic contributions to individual differences in gaze shift latencies in the Gap condition, but not to the Overlap condition—i.e. the one theorized to capture visual disengagement (Table 3).

Table 3. Common and unique parameter estimates of genetic and environmental to the common underlying factor and the unique measured variance in leaving latency and gaze shift amplitude according to the fitted Common Pathway model

	Common variance			**Unique variance**		
	h^2	**c²**	**e²**	h^2	**c²**	**e²**
Leaving latency						
Shared	.66 (.52 , .80)*	0	.34(.20 , .48)*	-	-	-
RG	-	-	-	.21(.11 , .31)*	0	.29 (.21 , .37)
RB	-	-	-	.09(-.01 , .19)	0	.29 (.19 , .39)*
RO	-	-	-	0	0	.33 (.25 , .41)*
Gaze shift amplitude						
Shared	.82 (.72 , .92)*	0	.18(.08 , .28)*	-	-	-
RG	-	-	-	.07(-.00 , .15)	0	.23 (.15 , .31)*
RB	-	-	-	.09(-.00 , .19)	0	.43 (.31 , .55)*
RO	-	-	-	0	0	.37 (.29 , .45)*

RG=Residual Gap; RB=Residual Baseline; RO=Residual Overlap; Shared=Shared covariance; h^2= additive genetics; c^2=shared environment; e^2=non-shared environment. Confidence intervals estimates at 95% are given in parentheses. *$p < .05$.

4.1.3.3 Phenotypic associations between trait and eye tracking variables

Pearson correlations testing putative associations between ASD traits and visual disengagement were non-significant (Table 4). Thus, these results did not support the hypothesis of visual disengagement as an endophenotype for ASD traits (Table 4).

Table 4. Phenotypic correlations between the dependent variables and autistic traits, age and IQ

		SRS	Age	IQ
Leaving latency	Gap	-.01 (-.07 , .05)	-.05 (-.16 , .05)	.07 (.02 , .12)*
	Baseline	-.03 (-.03 , .09)	-.11 (-.21 , -.01)*	.03 (-.02 , .08)
	Overlap	-.03 (-.09 , .04)	-.04 (-.14 , .06)	.05 (-0 , 0.11)
Gaze shift amplitude average (all conditions)		-.00 (-.05 , .05)	.09 (-.01 , .20)	.07 (.03 , .12)*

SRS: Social Responsiveness Scale. 95% confidence intervals (CI) estimates are given in parentheses. *$p < .05$

4.2 Volitional eye movement control and ADHD traits: a twin study (Study 2)

4.2.1 Rationale

A deficit in response inhibition has been proposed as an underlying casual factor of ADHD symptomatology. Similarly, it has been suggested that response inhibition impairments could represent an endophenotype of ADHD. Top-down volitional command of eye movements as operationalized by inhibiting a prepotent eye movement response in the Antisaccade Task could represent a candidate endophenotype of ADHD and aid the mechanistic understanding of the condition. The aim of this study was to evaluate the suitability of response inhibition in the context of eye movements as an ADHD endophenotype. Thus, the following were examined: (1) the relation between performance on the antisaccade task (oculomotor response inhibition) and parent-rated ADHD traits, as well as (2) the relative contributions of genetic and environmental factors to this putative association in a population based twin sample.

4.2.2 Methods

A total of 640 twins (320 pairs, 50% monozygotic, aged 9–14 years) from CATSS participated. Twins took part in the antisaccade task which operationalized inhibitory alterations as either direction errors or premature anticipatory eye movements (failure to wait for cues). ADHD inattentive and hyperactivity/impulsivity traits were assessed via parent report using the Conners 3P and cognitive ability using scores from The Wechsler Intelligence Scale for Children 4th Edition (WISC-IV) (subscales: vocabulary, digit span, coding, and matrix reasoning). Associations between eye movement control and parent reported ADHD traits were assessed using linear regression mixed-effects models (to account for the non-independence within twin pairs) with bootstrapped asymmetric standard errors (to account for the skewness of the dependent variables). Multivariate twin modelling was used to calculate the heritability of individual differences in ADHD traits and response inhibition variables, as well as to estimate the relative genetic and environmental influences to putative associations between ADHD traits and eye movement control.

4.2.3 Results

4.1.2.1 Group comparisons

Group comparisons of average response inhibition measures and ADHD traits between ADHD diagnosed participants and those without a diagnosis showed higher values among those with a clinical diagnosis (Table 5). In the case of response inhibition measures, analyses showed moderate effect sizes for direction errors gHedges = 0.61 (95% CI: 0.06, 1.16) and for anticipatory eye movements, gHedges = 0.80 (95% CI: 0.27, 1.33).

Table 5. Means and standard deviations of response inhibition and ADHD traits for participants with and without an ADHD diagnosis

		N	**Mean (SD)**	**Range**
Direction errors (*n*=628)	No diagnosis	615	.36 (.24)	0-1
	ADHD diagnosis	13	.51 (.32)	.06-1
Anticipatory eye movements(*n*=636)	No diagnosis	622	.14 (.21)	0-1
	ADHD diagnosis	14	.31 (.29)	0-1
Inattentive traits (*n*=616)	No diagnosis	604	4.02 (4.45)	0-26
	ADHD diagnosis	12	14.58 (6.98)	7-25
Hyperactive/Impulsive traits (*n*=616)	No diagnosis	604	3.96 (5.39)	0-35
	ADHD diagnosis	12	17.17 (11.67)	1-35

4.2.3.2 Phenotypic associations between ADHD traits and eye movement response inhibition measures

Associations between response inhibition measures and ADHD traits were specific to one response inhibition variable and to inattentive traits. Premature anticipatory eye movements were positively associated with total ADHD traits (β=0.11, 95% CI: 0.04, 0.19). However, this association was mostly driven by inattentive traits which were positively associated with anticipatory eye movements (β=0.19, 95% CI: 0.09, 0.29), while hyperactivity/impulsivity traits were not (β=-0.01, 95% CI: -0.09, 0.07). The association between premature anticipatory eye movements and inattentive traits remained even after covariate inclusion (age, sex, hyperactivity and IQ*;* β = 0.15, 95% CI: 0.02, 0.28). However, this was not the case between direction errors and ADHD traits - despite the observed differences in direction errors between individuals with and without an ADHD diagnosis. Neither total ADHD traits (β = -.01; 95% CI: -.07, .04), inattention (β = .03; 95% CI: -.09, .16), nor hyperactivity/impulsivity (β = -.08; 95% CI: -.23, .07) predicted direction errors in this sample. Due to this lack of association, no further analyses with this variable were conducted.

4.2.3.3 Heritability of eye tracking variables (ICCs and univariate analyses)

Intra-class twin correlations were more than twice as large in monozygotic than in dizygotic twins for inattentive traits (*r*MZ= .27, 95% CI: .13, .41; *r*DZ=.06, 95% CI: .001, .12) and for premature anticipatory eye movements (*r*MZ= .39 95% CI: .17, .61; *r*DZ= .02, 95% CI: -.11, .15). This twin correlation patterns suggested the influence of genetic effects on both variables. Given the twin correlations (MZ ICCs being more than twice as large as DZ ICCs), a correlated factors ADE model was fitted, as well as nested AE and DE (which models dominant instead of additive genetic effects) models for comparison. The AE model was identified as a reasonable compromise between model fit and previous theoretical conceptions

and research findings, which have favored an ACE model as a starting point (Table 6). Heritability unadjusted estimates from the selected AE models (Figure 6) are high for inattention (h^2=.70; 95% CI: .60, .79) and moderate for anticipatory eye movements (h^2=.49; 95% CI: .35, .62). Both inattention heritability estimates (h^2=.57; 95% CI: .44, .67) and anticipatory eye movements heritability estimates (h^2= .40, 95% CI: .21, .56) remained significant after adjusting for covariates.

Table 6. Model fitting results for inattention and anticipatory eye movements' bivariate model

Model	Model fit	
	AIC	BIC
ADE	3395.93	3444.92
AE	3399.72	3437.41
DE	3389.96	3427.65

AIC= Akaike Information Criteria; BIC= Bayesian Information Criteria

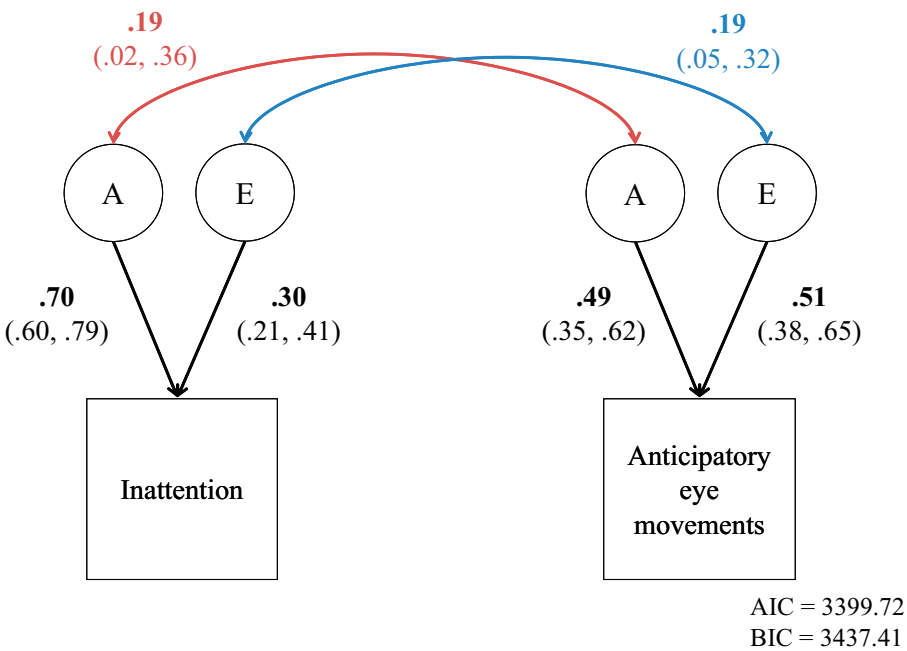

Figure 6. Path diagram of the AE bivariate model correlated factors solution for inattentionand anticipatory eye movements. Path coefficients and 95% confidence intervals for additive genetic influences (A) and non-shared environmental (E) effects are standardized (black arrows). Genetic correlations (red arrows) and non-shared environmental correlations (blue arrows) are displayed in the upper part of the figure.

4.2.3.4 Relative genetic and environmental influences to covariation between response inhibition variables and ADHD traits (multivariate analyses)

We found a moderate genetic correlation (Figure 6) between inattention and proportion of anticipatory eye movements ($r = 0.19$; 95% CI: .02, .36) – however confidence intervals were wide. After adjusting for covariates in our bivariate model, the aforementioned genetic correlation was no longer significant (r_a=.09; 95% CI: -.16, .36). Nonetheless, it is worth pointing out that the confidence intervals between the unadjusted and adjusted bivariate models were relatively similar. We found similar results from a bivariate model where we adjusted for all covariates minus hyperactivity/impulsivity.

4.3 Visual disengagement in young infants in relation to age sex, SES, developmental level and adaptive functioning (Study 3)

4.3.1 Rationale

Visual attention has been linked (concurrently and prospectively) with motor, social and language skills, and adaptive behaviors in early and late childhood. However, there is a lack of knowledge on how elements of visual attention such as visual disengagement relate to other cognitive developmental processes and behaviors in early infancy. Therefore, it is the aim of this study to assess the associations between individual differences in visual disengagement in infants and concurrent developmental behaviors in the context of socioeconomic status and sex.

4.3.2 Methods

A total of 436 infant five month old same-sex twins were recruited for the longitudinal Babytwins study and took part in the eye tracking Gap Overlap task to assess gaze shift latencies and visual disengagement. In addition, infants took part in a developmental assessment, the MSEL, to assess current developmental level in motor, language and perception domains. Adaptive behaviours (such as social skills: listening, comprehension, communicating and relationship skills; self-care skills, motor skills, and behavior during play and free time) were also recorded via parent report through the VABS-II. Socioeconomic status (SES) was operationalized as highest level of maternal education.

Eye tracking data from the Gap Overlap task, meaning gaze shift latencies in each condition as well as the visual disengagement index (average Overlap latency minus average Gap latency), were calculated with custom made MATLAB scripts. Condition-elicited differences in gaze shift latencies were assessed with a repeated measures ANOVA on a subsample of the data (n=237), comprised of only one twin

from each pair. To calculate the phenotypic associations between visual attention measures (latencies in the Gap Overlap task conditions and visual disengagement) and concurrent correlates (developmental cognitive processes and behaviours in early infancy, SES and sex, with age as covariate), we used general linear regression models within the generalized equation (GEE) framework, using the drgee package from R (Zetterqvist & Sjölander, 2015). GEE analyses were done on the whole sample (n=436) since these models account for the non-independence of the data (twin pairs).

4.3.3 Results

4.3.3.1 Condition effect in the Gap Overlap Task

The repeated measures ANOVA showed significant mean differences in latencies as an effect of condition ($F(2, 708) = 449.77$, $p < 0.0001$, $eta^2[g] = 0.56$). Latencies followed the expected pattern where those in the Gap condition are the shortest (m=306.27), followed by the Baseline (m=355), and lastly by the Overlap (m=501.34) (Figure 7). Planned comparisons with the Bonferroni correction confirmed mean latencies were significantly different between all conditions at an individual level (p<.001).

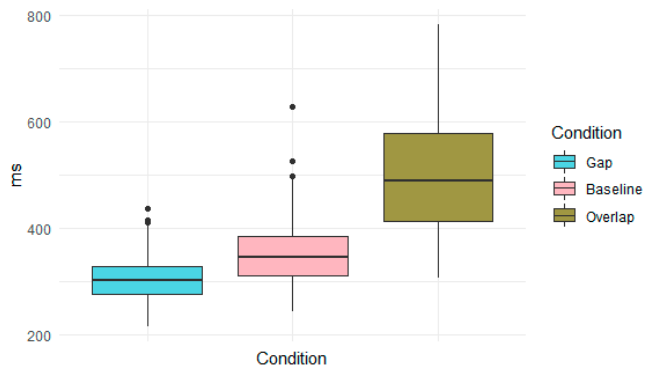

Figure 7. Gap task latencies displayed by condition.

4.3.3.2 Phenotypic associations between visual attention measures and concurrent developmental and sociodemographic correlates

GEE models showed statistically significant associations between gaze shift latencies in the Gap and sex (p=.004), between gaze shift latencies in the Overlap and SES (p=.031), and of gaze shift latencies in the Baseline with both sex (p=.009) and SES (p=.01). Specifically, females were significantly faster than their male

peers in the Gap and Baseline conditions (Figure 8), and infants from higher SES displayed slower gaze shift latencies in the Overlap and Baseline conditions compared to low SES infants. However, there was no evidence of associations between visual attention measures with any of the concurrent behavioural and developmental correlates (MSEL and VABS-II total scores) (see Table 7). Age, which although relatively similar across participants (~5m), was included as a covariate but had no impact on any of the visual attention variables.

Table 7. GEE models of Gap Task conditions (Gap and Overlap) and Visual Disengagement. MSEL= Mullen Scales of Early Learning Raw total score; VABS-II= Vineland Adaptive Behavior Scales 2nd Ed.; SES=Socioeconomic Status.

	Gap		**Overlap**		**Visual Disengagement**	
	Estimate	*P*	**Estimate**	*P*	**Estimate**	*P*
MSEL	-1.2 (-2.8 , 0.3)	0.125	-2.9 (-6.7 , 0.9)	0.123	-1.36 (-4.4 , 1.7)	0.39
VABS-II	0.3 (-0.3 , 0.9)	0.299	0.1 (-01.4 , 1.6)	0.887	-0.57 (-2 , 0.7)	0.391
Sex	**6.2 (1.9,3.8)**	**0.004**	6.3 (-5.1, 17.1)	0.315	-2.22 (-12.1, 7.7)	0.66
SES	-0.9 (-6.5 , 4.7)	0.744	**-14.9 (-28.5, -1.4)**	**0.031**	-6.9 (-18.5, 4.8)	0.248
Age	0.1 (-0.4 , 0.5)	0.817	-0.6 (-2 , 0.7)	0.410	-0.8 (-1.9 , 0.4)	0.19

Confidence intervals estimates at 95% are given in parentheses

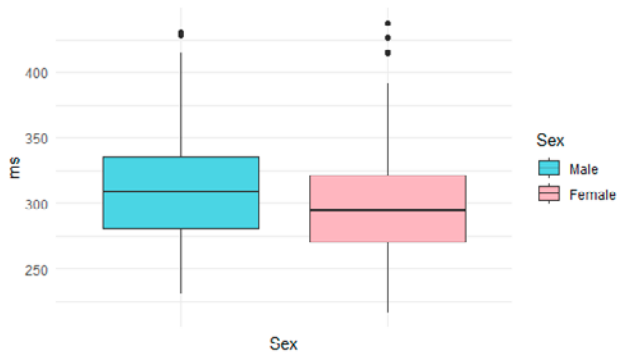

Figure 8. Comparison of males and females' mean latencies in the Gap condition

5 DISCUSSION

The overarching aim of this thesis was to increase our knowledge about selected attentional functions in infancy and childhood thought to be important for ASD and ADHD using eye tracking and twin modelling. We tried to address the following questions*:* (1) Are cognitive functions (attention/response inhibition) operationalized as eye movements, heritable - of key importance for potential endophenotypes (Gottesman & Gould, 2003) (*Studies 1 and 2*)? (2) What are the relative contribution of genetic and environmental influences to individual differences in the attentional networks tapped by the Gap Overlap Task (*Study 1*)? (3) Are there any shared genetic influences between a cognitive function and a core trait of a neurodevelopmental disorder, which are trait and disorder specific (*Study 2*)? (4) Can we expand what we know about attentional subfunctions (visual disengagement) and attentional networks (measured through eye movements) in terms of their relationships to other aspects of development in early infancy (*Study 3*)*?*

The studies in this thesis try to follow the approach put forward by the RDoC framework (Insel et al., 2010). For all studies, we build on the well-established knowledge of the neural basis of the visual system (execution and control of eye movements) and its links to cognitive functions (Corbetta, 1998; Corbetta et al., 1998; Munoz & Everling, 2004) on well researched cognition-probing oculomotor paradigms. Studies like the ones included in this thesis, where a cognitive experimental paradigm is embedded in a twin/family design to assess heritability and shared genetic influences with a psychopathological trait are not unprecedented. Similar approaches with community samples have been used to study ADHD and ASD traits, albeit with cognitive tasks (Pinto, Asherson, et al., 2016) rather than eye tracking, and family studies instead (Crosbie et al., 2013; Pinto, Rijsdijk, Ronald, Asherson, & Kuntsi, 2016). However, they are rare. Specially so featuring eye tracking, although they do exist but with broader scopes (Vaidyanathan et al., 2014).

In *Studies 1 and 2* we provided evidence of the heritability of attentional functions, however we did not consistently find support for their association to the psychopathological traits of interest. In *Study 1* we did not observe an association between visual disengagement, nor gaze shifts in general (in the Gap Overlap task), and ASD traits. On the contrary, in *Study 2* we found evidence suggesting an association between oculomotor response inhibition and inattention traits. However, this association was small. This small effect should not come entirely as a surprise as oculomotor behavior likely represents a very basic manifestation of the cognitive function the task taps into. However, albeit small, these findings of genetic correlations between cognitive process and trait remain encouraging of the potential that cognitive, eye tracking-based, endophenotypes have for understanding the underlying mechanisms and etiology of complex traits and disorders.

Large multi-method experimental twin studies in infancy, are also scarce, with only a few to date (Constantino et al., 2017; Hawks, Marrus, Glowinski, & Constantino, 2019), but with smaller samples and in toddlers (21 months) rather than infants. Thus *Study 3* adds to this scarce literature and expands on the visual attention literature in early infancy and its developmental correlates. Furthermore, *Study 3* sets the stage for future infancy twin studies where the aim is to assess the relative contribution of genes and environment to cognitive functions, operationalized as eye movements, relevant to ASD and ADHD.

5.1 Visual disengagement as an endophenotype for autism

Visual disengagement has been linked to later development of autism (Elsabbagh et al., 2013). This finding has propelled the idea of visual disengagement as a potential endophenotype for ASD, especially since it would aid in identifying individuals who would later develop the condition much earlier than is currently possible (~24-36 months). Visual disengagement as a potential autism "endophenotype" makes sense, theoretically – but does the available evidence so far support this hypothesis? As eloquently put by Keehn et al. (2013), atypicalities in how we are able to move our eyes (e.g. switch our gaze from one stimuli to another) and thus how we explore and sample our environment will shape our interaction with our surroundings much like typical eye movements do. Albeit, with atypical interactions with the environment as a result. The skill to shift our gaze is so elementary that it likely affects the sampling of our surrounding indiscriminately, affecting how one learns social and non-social skills, and in case of atypicalities being present, leads to atypical skill learning that could manifest as the behaviors characteristic of autism. However, our findings from *Study 1* do *not* support the link between visual disengagement and autism, at least in late childhood. Additionally, we find a lack of genetic specificity to latencies in the overlap condition which is the condition characterized by competing visual stimuli and thus meant to challenge visual disengagement abilities. The lack of genetic specificity to this condition questions its value at capturing disengagement as a dissociable construct in the context of the Gap Overlap Task.

Nonetheless, these findings do not preclude visual disengagement as an ASD endophenotype or as a useful autism marker before the onset of symptoms. It may be that slowed or atypical visual disengagement is only observable during a short time window (after 5 months and before 24 months) but not later - as other studies in toddlerhood and childhood also fail to replicate a link to autism (Fischer et al., 2013; Fischer et al., 2015). Another potential explanation for the observed lack of association between visual disengagement and ASD in *Study 1* could be that the Gap Overlap task stimuli in late childhood do not probe visual disengagement in

a challenging enough way that atypicalities would be observed. There is evidence of social and semantic biases in individuals with ASD (Behrmann, Thomas, & Humphreys, 2006; Chawarska & Shic, 2009; Wang et al., 2015), where these individuals look *less* at semantic level based properties (relevant to the context, e.g. emotion, touch, third party gaze) when viewing natural scenes and social stimuli (e.g. faces) in comparison to non-social stimuli. Thus, it could be that the non-social stimuli in the version of the Gap Overlap task in *Study 1* was too, and that with more complex, perhaps socially charged (as in the real world), stimuli we would observe atypicalities linked to autistic traits.

In terms of the classic theories of autism etiology, the hypothetical line of questioning taken by *Studies 1, 2* and *3* would have provided support to both the executive function and the weak central coherence if results had confirmed them. Alas this was not the case. For instance, if visual disengagement had been significantly associated to autistic traits, it would have suggested that slower switching could be linked to the autistic traits and in turn symptoms, thus providing support for the executive function theory (Hill, 2004). Whether visual disengagement would have been sufficient to explain non-social and/or social symptoms would have been dependent on the pattern of associations observed - in this case neither was observed. Similarly, the executive functioning account of autism is meant to explain the attentional deficits found in autism as a result of neocortical circuitry dysfunction (e.g. reduced connectivity between dorsal anterior cingulate cortex and FEF) (Agam, Joseph, Barton, & Manoach, 2010; Minshew, Luna, & Sweeney, 1999). Existing evidence appears to support this explanation, as there are reports of higher number of errors in the antisaccade task in adolescents and young adults with autism than in controls (Agam et al., 2010; Minshew et al., 1999). However, in *Study 2,* we found no links between number of errors in the antisaccade task and autistic traits – although not included in the published version of the study (we initially included autistic traits in our models assessing phenotypic associations but removed them at the request of the reviewers/editor). Thus, our results from *Study 2* do not support the explanation proposed by executive function theory either. In case of *Study 3,* had we observed any associations between visual disengagement and either non-social (e.g. motor) or social (e.g. language, socio-interaction) developmental skills, these would have also provided sensible support to an interaction between the two dimensions that could result in later autistic like symptoms akin to the cascading effects course of action discussed by Keehn et al. (2013). Thus, *Study 1*, conjointly with the other studies included in this thesis, does not support the executive function theory of Autism.

The results also have indirect relevance to the weak central coherence (Happé & Frith, 2006). Since the focal bias described by the weak central coherence theory has been compared to a deficit in the allocation of the attentional window

(Behrmann et al., 2006), one could speculate that perhaps atypical disengagement could be an early manifestation of this perceptual pattern or even play a role in its etiology. The studies in this thesis do not test directly focal vs global perception styles, or social vs non-social stimuli, however the null results from correlations between visual disengagement and autistic traits/socio-communicative skills do not suggest visual disengagement as one of the perceptual impairments that could underpin the perceptual pattern observed in autism.

Another influential theory of autism that is indirectly, and quite honestly unintentionally, tested by *Study 1* is cerebellar abnormalities underlying attention shifting atypicalities reported in ASD (Courchesne et al., 1994). Evidence for this theory seems mixed (Nowinski, Minshew, Luna, Takarae, & Sweeney, 2005; Takarae, Minshew, Luna, & Sweeney, 2004), and results from our study do not support it either. Foremost by the lack of association between slowed attentional/gaze shifting and ASD traits. But also by the lack of association between gaze shift amplitude (accuracy) and ASD traits in our sample which would be the case if the cerebellar vermal lobules VI and VII were in fact impaired as hypothesized by the cerebellar impairments theory of ASD (Minshew et al., 1999).

5.2 Unique genetic influences on latencies in the Gap condition suggest unique genetic contributions to the alerting network

Study 1 provides support for the independence of the alerting network in Posner's attentional model. By looking into the relative contributions of genetic and environmental influences to the different networks thought to be differentially probed by the conditions in the Gap Overlap task, *Study 1* provides evidence of unique genetic influences underpinning the alerting network which is tapped by the Gap condition. This study adds to the existing literature on heritability of eye movements in the context of an experimental task and highlights genetic specificity to alerting beyond common oculomotor processing. Thus, *Study 1* provides further knowledge about the underlying physiological mechanisms of the alerting network. Given the known sensory modulation impairments characteristic of ASD (Orekhova & Stroganova, 2014), phasic alerting could be a potential ASD endophenotype. However, we, as others, did not observe an association between the alerting network and ASD traits which does not encourage a link between arousal and ASD (Kleberg, Thorup, & Falck-Ytter, 2017), at least in this context. Whether we indeed observe a lack of true effect or rather the result of the sensory heterogeneity of ASD (Schoen, Miller, Brett-Green, & Hepburn, 2008) in our sample is unclear.

5.3 Response inhibition as an endophenotype for ADHD

Study 2 highlights the merit of cognitive functions as ADHD endophenotypes and how twin studies can aid in this endeavor. Findings from this study illustrate how eye movements are informative of higher order cognitive functions likely implicated in ADHD pathophysiology thanks to shared genetic influences between psychological trait (inattention) and cognitive function (response inhibition in the form of premature anticipatory eye movements). By identifying the genetic correlation between inattentive traits and oculomotor response inhibition, *Study 2* contributes to the understanding of inhibition and inattention by shedding light on their shared genetic etiology. From the RDoC framework perspective, these results contribute to understanding the cross-domain interaction between cognitive constructs (attention), cognitive subconstructs (cognitive control: inhibition) and sensorimotor constructs (response inhibition). In *Study 2* we observe that premature anticipatory eye movements were specifically, and partially genetically, associated to inattentive traits and not to hyperactivity/impulsivity traits. This finding addresses and highlights the within-disorder heterogeneity of ADHD and illustrates how deep phenotyping (further subdividing the disorder based on more specific commonalities such as the presence of specific executive function deficits) can aid our understanding of this heterogeneity (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). Although "deep phenotyping" is usually reserved for smaller studies, since there is an increased interest in big data approaches, it seems reasonable to provide a compromise between the two as we do in this study (especially since with bigger samples we are likely to mitigate power-related complications). The same finding, also offers indirect support to ongoing clinical initiatives advocating for further delineated disorder subgroups based on neuropsychological functions, both for designing interventions and/or as potential treatment moderators (Cortese et al., 2015; Karatekin, 2006; Powell, Wass, Erichsen, & Leekam, 2016; Sonuga-Barke et al., 2010). It is, however, worth remembering to be cautious about this genetic correlation as it was weak.

It is also relevant to note that the link between inattentive traits and oculomotor response inhibition (premature anticipatory eye movements) in *Study 2* was not universal to response inhibition processes, as it did not extend to *direction errors* (failing to inhibit a responsive gaze toward the appearing sitmulus instead of looking at the mirror location as instructed). These findings are in line with ADHD theoretical accounts that posit multiple causal pathways for the disorder. Multiple pathways models emphasize that EF (or "cold") deficits, as response inhibition, are not present in all individuals, with some evidence suggesting that even when present, they are not consistently observed (Kuntsi, Wood, Van Der Meere, & Asherson, 2009). Several explanations for this pattern exist. For instance, there are genetic influences that are unique to each ADHD domain, although a

large part of the underpinning genetic factors are shared between inattentive and hyperactivity/impulsivity traits (McLoughlin, Ronald, Kuntsi, Asherson, & Plomin, 2007). Furthermore, a prior study has also shown differential etiological associations between ADHD trait domains and cognitive functions (reaction time and direction errors, albeit in non-eye tracking paradigms), as well as small genetic correlations between the two, with reaction time representing bottom up arousal and direction errors top-down inhibition control (Kuntsi et al., 2014). Interestingly, Kuntsi et al. (2014) reported that additive genetic correlations of reaction time (bottom-up arousal) with inattention were large, and moderate with hyperactivity/impulsivity. Meanwhile, the additive genetic correlation of direction errors (top-down inhibition) with both ADHD domains was low. This pattern is similar to what we observed in *Study 2's* additive genetic correlations, with our energetically influenced response inhibition measure (anticipatory eye movements) linked solely to inattention and our top-down response inhibition measure (direction errors) linked to neither. By having a smaller sample in *Study 2* than Kuntsi et al. (2014) did, we may have lacked the power to detect smaller, yet meaningful, associations. Alternatively, there is the possibility that the additive genetic links are lower when cognitive measures are operationalized as eye movements, in which case we could also be affected by lack of power. The findings from *Study 2* can also be explained by Sergeant's cognitive-energetic model (Sergeant, 2000, 2005), specifically that the observed inhibition deficit may be a consequence of the participants' energetic state. In this study, we observed that an anticipatory control deficit (premature anticipatory eye movements) was linked to inattentive traits. These "oculomotor anticipations" have been physiologically associated to an altered electrophysiological contingent negative variation, underpinned by the dopaminergic network (primarily the basal ganglia), theorized as a consequence of the overall energetic state of the individual (Barry, Johnstone, & Clarke, 2003; Linssen et al., 2011; Perchet, Revol, Fourneret, Mauguière, & Garcia-Larrea, 2001; Sergeant, 2000, 2005), and observed among inattentive children in comparison to controls (Grünewald-Zuberbier, Grünewald, Rasche, & Netz, 1978).

Finally, *Study 2* addresses the comorbidity issue among neurodevelopmental disorders, by exploring the specificity of response inhibition to ADHD. Comorbidity between ASD and ADHD is often high (Antshel et al., 2016; Matson & Sturmey, 2011; Pinto, Rijsdijk, et al., 2016), and impairments in cognitive functions are rarely exclusive to one disorder as they are often present in many and tend to be polygenic (Kovas & Plomin, 2006; Lukito et al., 2017; Pinto, Rijsdijk, et al., 2016). The lack of phenotypic association observed between autistic traits and premature anticipatory eye movements observed in *Study 2* (albeit not included in the manuscript per peer-review and editor request) is supportive of the value of the latter as a potential endophenotype of inattentive traits that is trait and disorder specific. Thus, overall, *Study 2* is encouraging of the premise that a less complex, trait/disorder specific, with shared genetic etiological underpinnings, cognitive based endophenotype is viable and likely of use for ADHD.

5.4 Visual disengagement and gaze latencies in early infancy

In *Study 3*, we conducted a study of attention (visual disengagement) in 436 five month old infants. Mean latencies in the Gap Overlap Task were in line with those previously reported for the 5 month old age group (Johnson et al., 1991; Jones et al., 2019). Disengagement scores were strikingly similar to those reported in the Gap Overlap Task from a recent multisite infant (5 months) study (Jones et al., 2019). This confluence is of relevance since infant twins have higher rates of being born prematurely (<37 weeks of gestation) in comparison to singletons (Chauhan, Scardo, Hayes, Abuhamad, & Berghella, 2010). Prematurity can be an issue, as it has been reported that twins can be delayed in their development compared to singletons, and that this is mediated by premature birth (Lung, Shu, Chiang, & Lin, 2009). However, the literature is mixed as others have reported no differences between twins and singletons (0-24 months) in attaining motor milestones (Brouwer, van Beijsterveldt, Bartels, Hudziak, & Boomsma, 2012), or in adaptive behaviors before age 9 (Robbers et al., 2012). Premature birth was inevitable in the Babytwins sample. However, twins had to be born at 34 weeks gestation or later to be included in the project – at 34 weeks babies typically go to term nursery and not to the intensive care unit (Garite, Clark, Elliott, Thorp, & the Pediatrix/Obstetrix Perinatal Research, 2004), thus mitigating prematurity effects. More importantly, as mentioned above, gaze shift latencies in the Gap Overlap task did not appear to differ between the 5 month old twins in *Study 3* and those of 5 month old singletons in other studies (Johnson et al., 1991; Jones et al., 2019). This uniformity of results across studies (including our own) speaks to the generalizability of this measure (and of *Study 3's* results), even in infancy, an age group notorious for its difficult-to-manage data (Hessels & Hooge, 2019). Therefore, findings from *Study 3* in terms of gaze latencies and visual disengagement scores can be used as a reference for future studies using this eye tracking task in young infants.

5.5 Visual disengagement and cross-sectional developmental correlates

One of the main findings from *Study 3,* was that visual disengagement was not associated with observational nor parent-reported concurrent socio-communicative behaviors nor to adaptive functioning measures. Similar explanations to those discussed for *Study 1* could be relevant here. It may be that the link to developmental behaviors/milestones in other domains (social, motor) is only observed longitudinally when more complex skills are assessed. Another interesting contribution of this part of the thesis (*Studies 1 and 3*) is the fuller picture of the developmental trajectory of visual disengagement. By asking a similar question in different age

groups it incorporates, to a certain degree, a developmental perspective, which is an important aspect of mental health research that has been sidelined to a large extent. This advantageous picture is, nonetheless, rather precarious since we only address select age groups.

5.6 Socioeconomic status and its implications in the Gap Task

In our sample we found that infants from higher SES families were slower than infants from lower SES families in the overlap condition. Given the age of the infants at the time of our study (5 months) and the generous parental leave offered in Sweden (up to 14 months), children are typically, and in even more so in our sample of twins, always in sole parental care. Hence, the differences are unlikely to be linked to the amount of nursery/day care versus parental care, but rather to factors playing out within the families. One could wonder and speculate of the implications of early parental practices (since SES was measured as a factor of maximum educational attainment in mothers) on efficiency of basic visual skills in infancy, given this uniform, prolonged and high level of parental exposure. However, one must be cautious when using these results as points of comparison as proposed before since, like in our other studies, the level of SES is higher than average in the sample of *Study 3*. An interesting aim of future studies could be to replicate these results in other samples from countries with similarly generous parental leaves and high SES (e.g. Norway). Additionally, future studies could also attempt to replicate these findings in samples with more diverse SES.

5.7 Sex effects in gaze latencies in the Gap Task

Last, but certainly not least, *Study 3* brings to the forefront the relevance of sex effects in cognitive processes, even at the level of eye movements and in early infancy. One of the main findings in this study was that females were faster than males at executing gaze shifts in the Gap condition. As discussed in *Study 3,* one explanation could be that females are more receptive to cueing effects. Studies on cognitive tasks conducted in adults report that there may be in fact sex differences in response to cues (Bayliss, di Pellegrino, & Tipper, 2005; Mezzacappa, 2004; Stoet, 2010). However, contrary to our findings, some of these studies reported that females display slower reaction times than males in response to incompatible cues and to non-informative cues (akin to the gap). Meanwhile, another study reported no sex differences in reaction times in response to neutral cues (like the gap that also gives no information on where the peripheral stimuli will appear – only that it is coming) (Stoet, 2010). Although one of these studies also reported faster reaction times to compatible cues in females than in males, these were not significantly faster and actually suggested that being faster may have been disadvantageous

since females also made more mistakes (Mezzacappa, 2004). Thus, that "readiness" to cues may come at a cost of accuracy in females. Alternatively, since the Gap condition is thought to tap into the alerting network (Posner & Petersen, 1990), it could be that these sex differences are linked to arousal mechanisms differing between males and females (Papageorgiou, Farroni, Johnson, Smith, & Ronald, 2015; Papageorgiou et al., 2014). Since arousal and visual orienting mechanisms appear to be intertwined even from early on (Rothbart, Posner, & Rosicky, 2008), it could be that these latencies in the gap are a result of less efficient arousal management in males. We did not measure the accuracy of the gaze shifts in this study, thus, whether the observed effects were favorable or detrimental remains unclear. In addition, we observed that gaze shift latencies in the Baseline condition were associated with both SES and biological sex. Therefore, it appears that the observed association pattern is not clearly linked to any of the conditions. It may be that the observed effects are rather associated to a shared factor between all conditions such as oculomotor efficiency or function (Elison et al., 2013), rather than the processes selectively captured by each condition.

5.8 Heritability of visual disengagement and attentional networks – future directions

Due to the ongoing data collection, we did not pursue twin modeling in *Study 3*. However, an estimation of relative contributions of genes and environmental factors (akin to the one in *Study 1*) to visual disengagement at 5 months of age, will be initiated in the near future. Heritability estimates, as well as environmental influence estimates, vary across the lifespan, with a common trend being that the influence of genes on a trait tends to increase with age, while environmental influences tend to be highest earlier in life and to decrease with age (Haworth et al., 2010; Jelenkovic et al., 2016; Knopik et al., 2013; Lenroot & Giedd, 2008). This trend is also observed for cognitive ability (Haworth et al., 2010; Plomin & Deary, 2014). Evidence suggests that this may well also be the case for eye movements and cognitive functions operationalized as oculomotor responses, with environmental influences playing a higher role in infancy (Constantino et al., 2017), compared to late childhood and early adolescence (Kennedy et al.; Malone & Iacono, 2002; Siqueiros Sanchez et al., 2020; Siqueiros Sanchez et al., 2019). Thus highlighting the value of exploring heritability estimates in infancy to understand how the genetic influences to individual differences in cognitive functions develop across the lifespan.

5.9 Limitations

One of the limitations of two of the studies in this thesis (*1 and 2*) was that the number of individuals with a clinical diagnosis (ASD or ADHD) was low. However, since iTWIN is a community sample the low rates of these disorders were expected. This being said, while *Study 1*'s percentage of ASD clinical cases was in accordance to average prevalence (~1%), in *Study 2* the overall ADHD prevalence was lower than expected. A potential explanation for the observed below average prevalence in our sample could be a result of differences in diagnostic practices. Recruitment for the iTWIN sample, on which *Study 2* was conducted, took place from 2013 to 2016. Therefore, we can infer that at least some clinical diagnoses were made following the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (World Health, 2004) criteria since it is more commonly used in Europe. However, for children to meet ICD-10 ADHD criteria, they require to have a high degree of symptoms on both domains (akin what is required for combined ADHD diagnosis according to DSM-IV). Thus it could be that some individuals which would fall under inattentive or hyperactive/impulsive subtypes would have subthreshold symptoms in the other ADHD domain, failing to meet ICD-10 ADHD criteria and thus remain undiagnosed. Despite this lower prevalence, we observed group differences in both response inhibition oculomotor measures when comparing diagnosed to undiagnosed participants, with diagnosed individuals showing a higher response inhibition deficit (a higher number of premature anticipatory eye movements and direction errors).

Another potential limitation of this thesis are the sample sizes of *Studies 1* and *2* since, despite not considered at all small for experimental eye tracking studies, are relatively small by behavioral genetics twin studies standards. The main issue of a small sample is that both studies may have lacked power to detect small but significant associations and to estimate parameters. An additional limitation for this thesis (as it applies to all studies) is the perhaps limited generalizability of results in the context of socioeconomic status. While our results may very well be generalizable to Nordic countries and other western countries with high SES (as indexed by maternal highest attained level of education) and low wealth disparity, these may not extend or reflect appropriately the effect of SES in countries were SES is lower and wealth disparity is higher (and for instance widespread poverty or low access to education, particularly for women). Finally, a commonly noted limitation in most ASD and ADHD twin studies is the threat to the "No assortative mating" assumption. The risk comes from assortative mating being typically high in ASD and ADHD - thus relevant for *Studies 1 and 2.* The presence of assortative mating, and thus the problem it can present, is that it would typically lead to an underestimation of heritability. However, all in all it seems unlikely that this was actually an issue in our studies, since our heritability estimates are in line with those previously reported for ASD and ADHD trait in child and adolescent samples.

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