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Early Self-Regulation in Infant Siblings

Specific and Shared Associations to Emerging Autism and Co-ocurring ADHD

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Abstract
Andersson Konke, L. 2023. Early Self-Regulation in Infant Siblings. Specific and Shared Associations to Emerging Autism and Co-ocurring ADHD. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Social Sciences* 217. 83 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-1919-3.

The overall aim of this thesis was to examine aspects of self-regulation and the emergence of co-occurring autism and ADHD traits early in life, to enhance our understanding of specific and shared mechanisms underlying these conditions. Previous studies have shown that vulnerabilities in temperament and executive functions (EF) are closely related to both conditions, with overlapping as well as specific features associated to each phenotype. However, most previous studies focus on older children, and it is unclear if specific and shared markers are evident already before symptoms of autism and ADHD emerge. By using an infant-sibling design we were able to follow infants with a family history of autism and/or ADHD, before clinical symptoms emerge. Study I and II focused on infant temperament as either predictors of later autistic and/or ADHD traits or as being predicted by familial quantitative traits, to understand specific and shared associations to autistic and ADHD traits. In Study I, we examined if temperament traits in 1.5-year olds predict autism and ADHD traits at 3 years. Parent-rated temperament showed specific associations to autistic or ADHD traits, respectively. We found some overlap in regulation difficulties across both trait domains. In Study II, we explored the possibility to use probands' autistic and ADHD traits to predict temperament traits in their 10-month old infant siblings (a between-individual design). We found that higher levels of probands' autistic symptoms were specifically associated to lower levels of infant sibling's approach, whereas higher levels of proband's ADHD symptoms were specifically associated to increased activity levels in the infant siblings. Proband autism and ADHD traits thus provide unique information about the infant siblings' temperament. Study III focused on specific and shared links between executive functions and deferred gratification and concurrent associations to autistic traits, ADHD traits, and adaptive behaviors in 3-year-olds. We found that deferred gratification may function as a protective factor, moderating autistic traits and adaptive behaviors and thus act as a buffer for adaptive behaviors Together, these studies contribute to our understanding of specific and shared early aspects of self-regulation and their associations to autistic and/or ADHD traits.

Keywords: Self-Regulation, Autism, ADHD, Temperament, Executive Functions

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To my children Astor, Ingrid & Bodil

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. Konke, L. A., Forslund, T., Nilsson-Jobs, E., Nyström, P., Falck-Ytter, T., & Brocki, K. (2022). How does temperament in toddlers at elevated likelihood for autism relate to symptoms of autism and ADHD at three years of age?. *Journal of autism and developmental disorders*, 1-12.

II. Konke, L. A., Falck-Ytter, T., Jones, E. J., Goodwin, A., & Brocki, K. (2023). Using the Infant Sibling-Design to Explore Associations Between Autism and ADHD Traits in Probands and Temperament in the Younger Siblings. *Journal of autism and developmental disorders*.

III. Konke, L. A., Falck-Ytter, T., Shragge I., Brocki, K., (*in preparation*). To take or wait? Strong Ability to Defer Gratification as a Protective Factor for Adaptive Behaviors.

Linn Andersson Konke contributed in the following way to the three studies included in this thesis: Collected part of the data, specified hypotheses and planned analyses (including analysis plans), pre-processed data and performed data analyses, had a major role in interpreting the results, and wrote the manuscripts in Study I, II and III. This work was done in collaboration with supervisors and co-authors with progressing independence. In Study III Linn Andersson Konke also co-designed and conceived the idea for the study.

Contents

Abbreviations

AB	Adaptive Behaviors
ADHD	Attention-Deficit/Hyperactivity Disorder
ADI-R	Autism Diagnostic Interview – Revised
ADOS-2	Autism Diagnostic Observation Sale, Second Edition
APA	American Psychological Association
ASD	Autism Spectrum Disorder
BASIS	British Autism Infant Sibling Study
CBCL	Child Behavior Checklist
CRS-3	Conners Rating Scale – Third Edition
CSS	Calibrated Severity Scores
C-TRF	Caregiver-Teacher Report Form
DSM-5	Diagnostic Statistical Manual – Fifth Edition
EASE	Early Autism ADHD Sweden
ECBQ	Early Childhood Behavior Questionnaire
EF	Executive Functions
EL	Elevated Likelihood
FH-ASD	Family History of Autism
FH-ASD/ADHD	Family History of Autism and ADHD
FH-TL	Family History of Typical Likelihood
IBQ-R	Infant Behavior Questionnaire – Revised
MSEL	Mullen Scales of Early Learning
NIHM	National Institute of Mental Health
PDP	Pervasive Developmental Problems
RDOC	The Research Domain Criteria
SCQ	Social Communication Questionnaire
TL	Typical Likelihood

Introduction

It's a busy family gathering, baby Naoh is 10-month-old and sits in a baby chair. Overwhelmed by the unfamiliar faces, loud voices, and bright lights, Sam becomes distressed. However, instead of using self-soothing techniques to calm down, such as orienting away from the distressing environment or attending to a caregiver, Noah's distress escalates rapidly. Sam starts to cry inconsolably, and no attempts by caregivers to comfort or soothe him seems to work. The situation becomes overwhelming for both Sam and his caregivers. Fast forward to Noah's 3rd birthday when he is playing with a group of friends. The children are engaged in a fun game when suddenly another child accidentally knocks down the tower of blocks Noah had been building. Noah reacts impulsively and pushes the other child, expressing anger and difficulties regulating his emotions. At a later point in time, during a visit to the supermarket, Noah spots a colourful box of cookies and immediately becomes fixated on having them. Unable to control his impulses, Noha becomes so overwhelmed that he has a temper tantrum. He lies on the floor, crying and screaming, too upset to listen to his parents' reasoning.

In these situations, both at 10 months and at 3 years of age, Noah demonstrates self-regulation difficulties. At 10 months, Noah is overwhelmed by sensory input which cause him distress at a level of which he is uncapable of regulating on his own, affecting his ability to use self-soothing techniques, leading to an escalating emotional response. At 3 years, Noah exhibits difficulties in emotion regulation and impulse control, resulting in frustration and an inability to cope with disappointment and delayed gratification. These examples of self-regulation highlight the challenges that can arise when a child's ability to regulate emotions and behaviors is unmatched with requirements of the social environment or the child's affective state. This underscores the importance of providing support and assistance to children in developing and improving self-regulation skills in positive and constructive ways. These examples are not rare for children this young, and many of us have experienced a similar situation with a child who perhaps was only too tired for going to the grocery store or not ready to be left too far from his or her safe haven, i.e., the caregiver. However, for some children their highly reactive temperament and difficulties in regulating emotions and behaviors might become an escalating problem.

As Noah progress in preschool, his highly reactive traits and reduced self-regulation skills become evident. He encounters challenges such as sharing toys, waiting for a turn, and following classroom rules, often responding with temper tantrums, outbursts, or disruptive behaviors. These behaviors might impact his social interactions and learning environment and inevitably his development. Consequently, peers may hesitate to interact with him due to unpredictable reactions, leading to feelings of loneliness and even more frustration, and potentially cascading developmental effects. Noah may face long-term consequences such as a negative self-image, reduced self-esteem, and increased risk of behavioral and emotional difficulties. However, early identification and recognition of these challenges, an accepting environment and appropriate support may push Noah in a more positive direction, promoting adaptive coping strategies and supporting a positive developmental path.

The motivation behind the research presented in this thesis arises from the various ways in which children's self-regulation abilities differ, and the links to neurodevelopmental conditions, such as autism and ADHD. Self-regulation, including aspects of temperament and executive functions, have been proposed as early antecedents, risk markers, endophenotypes, and even as synonymous with the conditions – autism and ADHD – themselves. The executive dysfunction hypothesis was explicitly proposed as a core deficit in autism (Hill, 2004; Hughes et al., 1994; Pennington & Ozonoff, 1996) and ADHD (Barkley, 1997). Additionally, ADHD has been suggested to be defined as a self-regulation deficit disorder (SRDD; Barkley, 2021) and, as the extreme end of the temperament continuum (Nigg et al., 2004). I will come back to these hypotheses in a later section. Understanding the role of early self-regulation in the etiology of autism and ADHD is one important part of this work, whereas another important part is to understand how variations in self-regulation might impact emerging symptoms and adaptive outcomes. Indeed, increased awareness and improved identification of early emerging symptoms of autism and ADHD, including related difficulties, are much needed in order to support children, since timely identification and intervention promotes long-term well-being.

Autism

Autism Spectrum Disorder (ASD), hereafter referred to as 'autism', is a neurodevelopmental condition with onset in early childhood. Autism is defined by challenges in social communication, patterns of restricted and repetitive behavior, and sensory differences. The Diagnostic and Statistical Manual of Mental Disorders (DSM–5; American Psychiatric Association, 2013 [APA], 2013) outlines two key symptom domains for an autism diagnosis: persistent deficits in social communication and restricted, repetitive patterns of behaviors and interests. Alternatively, autism can be defined as an intrinsic aspect of an individual's identity, encompassing both strengths and weaknesses, and representing a valuable element within the spectrum of human neurodiversity (Kapp, 2020). Alongside the key components, many autistic children have difficulties in self-regulation, motor abilities, sensory sensitivities, and sleep. These challenges can have further impact on daily functioning, social interactions, and learning. Autism is typically diagnosed in early childhood, often before school start, and symptoms might manifest as early as between 2 and 3 years of age (Lord et al., 2018). However, in some cases a diagnosis can be made from already 18 months, depending on the child's developmental progress, symptom severity and availability of community services. Additionally, co-occurring conditions such as anxiety, ADHD, and intellectual disability are frequent. In particular, traits of autism and ADHD commonly co-occur (Simonoff et al., 2008), and share some overlapping features, such as temperamental differences, e.g., higher levels of negative affect and lower levels of regulation, and difficulties with executive functions (Rommelse et al., 2011). This adds complexity to our understanding of whether these co-existing conditions share developmental origins.

Historical background

The term "autism" derives from the Greek word autos i.e., "self", and was first used by the Swiss psychiatrist Eugen Bleuler in 1911 to describe the social withdrawal observed in patients with schizophrenia (Bleuler, 1911). In 1943, Leo Kanner published a seminal paper describing 11 children who showed a marked lack of interest in other people, but an unusual interest in the non-human environment (Kanner, 1943). Kanner termed the condition "early

infantile autism" and suggested that it may have biological origins. Unfortunately, there have been some severe misconceptions about the causes of autism through history, particularly the theory blaming unemotional “refrigerator mothers” for their children’s condition (Bettelheim, 1967). Another such, now debunked, causal theory was the suggested link between the measles-mumps-rubella (MMR) vaccine and autism (Wakefield et al., 1998). The paper was retracted due to fraud, and several epidemiological studies have since evaluated this association, but each found no increased risk of autism (DeStefano & Shimabukuro, 2019). The DSM-III was introduced in 1980 and marked a significant shift from the previously assumed descriptions and believes about autism. One of the major changes was moving away from psychoanalytic ideas towards cognitive accounts and empirically-based theories (Vivanti & Messinger, 2021). The theory of mind hypothesis suggested that the primary deficit in autism applied to difficulties in mentalizing and understanding other’s intentions or feelings. While this hypothesis was able to explain some of the behaviors characteristic of autism in the domain of social reciprocity and communication, it fell short in explaining other domains, such as repetitive behaviors and sensory sensitivities. The weak central coherence model was formed as a response to the theory of mind hypothesis proposing instead that the core cognitive deficit was a narrow focus on details rather than integrating parts to a whole which explained the preference on details instead of a focus on the overall meaning from a set of information or repetitive and restricted behaviors (Frith & Happé, 1994). Another cognitive account intending to explain autism was the executive dysfunction hypothesis (Pennington & Ozonoff, 1996), suggesting that the challenges in tasks requiring EF, such as planning and flexibility, was central to autism.

There is support for enhanced visual local processing in autistic individuals (Happé & Frith, 2006), but mixed findings regarding reduced global visual processing in autistic children (Nilsson Jobs et al., 2018). Similarly, theory of mind is indeed found to be difficult for some autistic individuals, but more recent studies indicate that these difficulties are exacerbated when two individuals with very different ways of experiencing the world interact with one another. Finally, the EF dysfunction hypothesis sparked an interest in EF processes with major development of sensitive tasks for measuring these higher order processes (Ozonoff et al., 1991). However, not all autistic children have difficulties in tasks that require EF indicating that these processes might not be the core cause of autistic cognition. The increasing recognition of the heterogeneity of autism led to an understanding that no single cognitive or neural deficit accounted for all its manifestations (Happé et al., 2006). These cognitive and perceptual differences may be best understood as some of several cognitive and neural disruptions or differences related to autism. Contemporary views of what causes autism are now discussed within a broader context

of multiple interacting factors, with both genetic, biological and environmental etiological factors.

Neurodiversity and the concept of autism

> Neurotypical syndrome is a neurobiological disorder characterized by preoccupation with social concerns, delusions of superiority, and obsession with conformity. Neurotypical individuals (NT) often assume that their experience of the world is either the only one, or the only correct one. NTs find it difficult to be alone. NTs are often intolerant of seemingly minor differences in others. When in groups NTs are socially and behaviorally rigid, and frequently insist upon the performance of dysfunctional, destructive, and even impossible rituals as a way of maintaining group identity. NTs find it difficult to communicate directly, and have a much higher incidence of lying as compared to persons on the autistic spectrum.
>
> *Institute for the Study of the Neurologically Typical*

This institute appeared on a website made up by Laura Tsonic in 1998 as a reaction to the negatively and one-sided description of autism. According to the neurodiversity movement, disability is not a constant within the individual, rather disability is caused by the environment by failing to provide appropriate support and access. The neurodiversity perspective contrasts with the traditional medical model, which views autism as a disorder in need of a cure. Instead, neurodiversity sees autism as a natural variation of human neurology, valuing differences over normalization (Kapp et al., 2013). The medical model aims at treatment, while neurodiversity advocates for societal understanding and acceptance. The debate around language use has been at the forefront of these discussions. Person-first (e.g., "a person with autism") and identity-first (e.g., "an autistic person") languages are terminologies used for individuals on the autism spectrum. Preferences vary both within and outside of the autistic community, although identity-first has been very much called for due to a history of ableism (Dunn & Andrews, 2015; Doe et al., 2020). This debate is far from only a question about semantics but it has practical implications; how we label and discuss autism can form public opinion, shape policy decisions, determine clinical strategies, and influence the course of research (Vivanti, 2020). Although these different perspectives aim to alleviate impairments for neurodiverse individuals, their approaches differ (Sonuga-Barke & Thapar, 2021). However, many scholars have now adopted a more neurodiverse-friendly approach aiming at incorporating a person's physical and social environment, and a focus on strengths and talents, including ethical considerations of interventions, that encourage and facilitate authenticity and aptitudes. Recently, there has been major efforts in trying to bridge these two, seemingly incompatible, models of autism – the biomedical and the neurodiverse – into research and clinical practice (Bölte et al., 2021; Green, 2022). For example,

the International Classification of Functioning Disability and Health (ICF) recommended by the World Health Organization (2001) proposes a dynamic perspective on functioning accounting for the environmental influences. This framework provides a comprehensive and holistic approach to investigate, assess and provide support for individuals on the spectrum (Bölte et al., 2021;Sonuga-Barke & Thapar, 2021).

Although a full discussion about this topic is beyond the scope of this thesis, I think that it is important to raise some of these fundamental questions. In particular since the paradigm of infant sibling studies has been involved in these debates, concerning early identification and intervention. Importantly, the goal is not to prevent or mitigate autism or ADHD (as in the traditional medical model lenses), but to embrace different ways of functioning while supporting children with their difficulties, which often is not the autistic traits per se but rather concerns aspects of co-occurring mental health issues and self-regulation. One way to do interventions in a neurodiverse-friendly way has been through the use of parent-mediated interventions focusing on child-led play and interaction (Green et al., 2022). A recent meta-analysis comparing different types of interventions found that naturalistic behavioral interventions and developmental intervention approaches, such as in parent-led interventions, seemed promising for supporting children with autism in achieving certain developmental outcomes, such as improved communication (Sandbank et al., 2020). Parent perspectives on participating in early intervention studies with their pre-schoolers have also been overall positive (Bent et al., 2022).

An alternative framework to approach mental health issues and psychiatric conditions that were constrained by a categorical diagnostic perspective was done by The Research Domain Criteria (RDoC; Insel, 2013). This research framework was introduced by the National Institute of Mental Health (NIMH) to foster a better understanding of mental disorders. The RDoC represents a shift away from traditional diagnostic categories, like those in the Diagnostic and Statistical Manual of Mental Disorders (DSM), and towards a more dimensionally-based, biologically-informed approach to understanding and classifying mental health disorders. In practice this means studying dimensions of functioning rather than being tied to categorical diagnoses. RDoC was not developed to be used as a diagnostic manual or to replace the current diagnostic systems. Instead, "the aim is to understand the nature of mental health and illness in terms of varying degrees of dysfunction in fundamental psychological/biological systems" (Insel et al., 2010). This approach was not specifically developed for neurodevelopmental conditions but have since its formulation been applied to developmental psychology (Conradt et al., 2021), to neurodevelopmental conditions more generally (Pacheco et al., 2022), and more specifically to autism (Mandy, 2018) and ADHD (Musser & Raiker,

2019). The RDoC framework is organized around five domains: i) Negative valence systems: involve negative emotions, such as fear, sadness, and anger, ii) Positive valence systems: involve experience of positive emotions, such as joy, pleasure, and interest, iii) Cognitive systems, such as attention, learning, memory, and decision-making, iv) Affective systems, which involve regulation of emotions, v) Motivational systems, such as pursuit of goals and rewards. Each of these domains contain specific units of analysis, i.e., constructs or processes, proposed to be linked to mental disorders. For instance, in the negative valence systems domain, a key unit is fear conditioning, where a neutral stimulus becomes associated with negative results. These biological systems overlap well with the aim of this thesis, namely to understand if early self-regulation is specifically or commonly linked to the development of autism and/or ADHD.

The RDoC framework is still under development, but offers a framework beyond the categorical view of a diagnosis. The clinical utility of categorically defined ASD and ADHD are well established (Biederman, 2005), and there is strong evidence supporting the notion of ADHD as the extremes of a continuous trait. However, although there is much support for a dimensional view of autism (Constantino & Charman, 2016; Volkmar & McPartland, 2016), a recent meta-analysis indicates otherwise (Frazier et al., 2023). Despite finding support for a categorical model, Frazier and colleagues (2023), emphasise the importance of using quantitative scores since they are often more strongly correlated with other measures. In population-based samples, symptom scores for autism and ADHD manifest as continuous traits without a definitive cut-off threshold linked to negative outcomes (Rutter, 2011). It's worth noting that autism and ADHD not only frequently co-occur but also often co-exist with other mental health issues, such as anxiety, tics, and intellectual disability. Therefore, by emphasizing underlying biological and psychological processes, we might learn more about different states, independent of label. Early self-regulation, looking at temperament (including positive and negative valence systems and affective systems), and executive functions (related to cognitive systems and motivational systems) might offer a first step to better understand co-occurrence of conditions. I will discuss this more in detail in the following sections.

Etiology

Autism is a heterogeneous condition both with regards to variations in symptom severity and co-occurrence with other conditions (Thapar et al., 2017). This results in a particular mix of causal influences that varies from child to child (Hobson, 2013). Autism and ADHD diagnoses are defined on the basis of practical and clinical purposes (Thapar & Cooper, 2016). Traits from each

domain are continuously distributed in the general population (Rutter, 2011) and are linked to similar environmental and genetic risk factors as their corresponding clinical diagnoses (Lichtenstein et al., 2010; Mandy & Lai, 2016; Constantino & Todd, 2003; Thapar & Cooper, 2016). The prevalence rate of autism is estimated to about 1 % worldwide (Zeidan et al., 2020), with generally higher estimates in countries with established health care practices and increased autism awareness (Delobel-Ayoub et al., 2020). However, since autism is a heritable condition (Sandin et al., 2017) meaning that having a family member with autism elevates the likelihood of receiving an autism diagnosis, or having autistic traits (Hansen et al., 2019). Around 20 % of infant siblings to an older diagnosed sibling also meet diagnostic criteria for autism, with an increased likelihood by having several autistic family members (Sandin et al., 2014). In these inherited variants of autism, more than 100 genes seem to be implicated in increased likelihood for autism and for related conditions (Betancur, 2011; Jiang et al, 2013; Yuen et al., 2017). In turn, genetic predisposition interacts with pre- and postnatal environmental factors which alters the likelihood for autism. Symptoms may therefore reflect vulnerabilities related to these factors, or emerge as secondary effects, also called cascading effects, due to atypical interactions with the environment (Johnson, Jones, & Gliga, 2015). Furthermore, siblings of individuals with ADHD are four times more likely to receive an autism diagnosis compared to the general population (Jokiranta-Olkoniemi et al. 2016; Miller et al., 2019). This have led to the proposal that some of the etiological factors contributing to autism are specific and some non-specific, and can be found also in the general population (Constantino, Charman, & Jones, 2021). Due to the difficulty in findings genes that are specifically linked to the autistic phenotype, intermediate phenotypes, which are commonly called endophenotypes, have been proposed as feasible and possible contributors to these conditions (Constantino, 2019). A *phenotype* refers to the observable characteristics or traits, that can relate both to physical appearance, such as eye color, and to behavioral characteristics, such as autism, which is a collection of traits. While a phenotype results from the interaction between genotype (i.e., the genetic makeup) and, importantly the environment, the *endophenotype* is a heritable trait or character believed to be an intermediate expression between the genetic expression and the clinical phenotype. Endophenotypes can be seen as biological markers and are typically less complex than clinical phenotypes in that they often are more closely linked to particular genes (Gottesman & Gould, 2003). I will also use the term *antecedent*, which can be defined as "an event or stimulus that precedes some other event or stimulus and often elicits, signals, or sets the occasion for a particular behavior or response" (APA, 2013), indicating a causal relationship. And lastly, *potential marker* differentiates between groups in the development of children with later autism or ADHD (Johnson et al., 2015).

ADHD

Attention-Deficit/Hyperactivity Disorder (ADHD) is characterized by a persistent pattern of inattention and hyperactivity/impulsivity, reaching a degree that impacts adaptive functioning and deviates from the expected developmental level (American Psychiatric Association [APA], 2000). Today it is the most common neuropsychiatric condition among children, with a prevalence rate of around 5 % globally (Polanzcyk et al., 2019). Prevalence rates vary and traits become apparent early in life, but ADHD is rarely diagnosed before reaching school-age (Holland & Sayal, 2019) when the demands of attention and self-regulation get more pronounced. ADHD persists throughout life and is increasingly recognized as dimensions that should be evaluated in a multifaceted manner (Castellanos, 2009; Haslam et al., 2006). Indeed, there is a broad range of behavioral variations observed among individuals with ADHD. This variability extends not only to the expression of symptoms, but also to levels of adaptive functioning, coexisting conditions, and the occurrence of behavioral and emotional challenges (Wilens, Biederman, & Spencer, 2002).

Co-occurring Autism and ADHD

The introduction of DSM-5 in 2013 marked a significant departure from previous editions (APA, 2013). Prior to this revision, the diagnostic criteria for autism and ADHD did not allow a simultaneous diagnosis, despite significant co-occurrence. The revised edition was also made more inclusive with regards to diagnostic criteria. Autism can now be diagnosed based on current symptomatology or by history, which opens up for opportunities for adults to be diagnosed later in life. Similarly, the current criteria for ADHD now allows for the presence of symptoms prior to the age of 12, instead of the previous threshold of age 7. A recent meta-analysis estimates that 28 % of individuals with autism have co-occurring ADHD (Lai et al., 2019). However, prevalence rates are highly varied, with estimates as high as 50–70% of children diagnosed with autism meeting criteria for ADHD, whereas 15–25% of youth with ADHD have a co-existing autism diagnosis. In recent decades there has been increases in the prevalence rates of autism and ADHD diagnoses. This rise can be attributed to a combination of factors including changes in diagnostic criteria, but also to shifts in policies for special education, increasing awareness, and improved access to medical services.

Autism is frequently diagnosed in boys more often than girls, with a male to female ratio of 3:1 (Loomes et al., 2017). ADHD tends to have a slightly higher prevalence in boys than girls, with a ratio of approximately 2:1 (APA, 2013). Important to note is that these ratios can vary based on factors such as diagnostic criteria, population studied, and research methodologies. The

reason to these gender disparities are not clear. However, various theories have been proposed, including differences in brain development, hormonal influences, genetic susceptibility, and social and cultural factors (Quinn & Madhoo, 2014). Girls might also be better at hiding or masking their symptoms, and they are often diagnosed with other mental health conditions, such as anxiety or depression, which may overshadow autistic or ADHD traits.

Models to explain the overlap between autism and ADHD

Autism and ADHD are likely the results of a complex interplay between emerging neurodevelopmental vulnerabilities and influences from the child's prenatal and postnatal environment (Johnson et al., 2015). Some symptoms may stem from genetic or environmental risk factors, while others might manifest as compensatory mechanisms or secondary effects due to unique interactions with the environment (Gliga et al., 2014). Once symptoms of a condition have emerged, it becomes much more difficult to untangle preceding or antecedent markers from the symptoms or the effects of the symptoms. One way of limiting these difficulties is to use prospective longitudinal studies to explore the earliest development of behaviors, such as intermediate phenotypes, that might elucidate whether autism and ADHD share similar features early in development.

The identification of early signs *uniquely* associated with the development of autism and/or ADHD is of importance for enhancing accurate early detection efforts and determining optimal targets for intervention strategies. At the same time, it is crucial to recognize the potential impact of early interventions by identifying transdiagnostic factors—namely, processes *shared* across both conditions—that underlie the development of symptoms. This approach is well-suited for autism and ADHD due to the presence of some shared biological and behavioral atypicalities. As a result, it is reasonable to expect that certain early behavioral signs may overlap, serving as general indicators of atypical development. Such shared indicators can serve as valuable resources for designing effective transdiagnostic interventions and support strategies that aim at reaching children beyond diagnostic criteria.

Dimensional or overarching category?

How can we explain and understand the co-occurrence between autism and ADHD? Are they two distinct phenotypes that exists on the same continuum or are they best viewed as separate conditions that share the same risk pathways and are associated with shared vulnerabilities? The idea that autism and

ADHD might be different expressions of an overarching condition has been proposed (van der Meer et al., 2012) given the frequent co-occurrence, overlapping genetic factors and cognitive functions – intermediate phenotypes, linked to a familial vulnerability for autism and ADHD, such as in executive functioning, motor activity level and emotion recognition to name a few. Indeed, there are some suggested shared etiological pathways for autism and ADHD. Although the question of whether autism and ADHD are one or two separate condition(s), is a question beyond the scope of this thesis, we may provide some valuable information regarding the early development of these conditions and if they share or show specificity in certain aspects of early self-regulation. By using an infant sibling design, we are able to examine possible markers before the emergence of the clinical symptoms or traits, which provides, although not a definite answer, but at least some clues, to the overlap between autism and ADHD.

Equifinality and multifinality are two concepts commonly used in the developmental psychopathology literature to understand the complex ways in which genes and environment interacts and results in a particular outcome (Cicchetti & Rogosch, 1996). Assuming that all individuals in a diagnostic category have experienced the same developmental journey is indeed an oversimplified perspective (Hinshaw, 2015). Equifinality means that there can be multiple ways leading to a particular developmental outcome. Multifinality, on the other hand, refers to a specific risk factor (e.g., family history of autism) that may lead to various different outcomes (e.g., autism, ADHD or language disorder), depending on various intervening factors.

One fruitful way to understand the relationship between autism and ADHD and overlapping traits is to explore the early development of children with elevated likelihood of autism by having a family member (often an older sibling or a parent) with ASD. This way we are able to investigate the early development before core characteristics of these conditions emerge. This early investigation increases the possibility to find early developmental features, e.g., endophenotypes that can be useful both for theory, and for clinical purposes.

Specific and shared pathways

Why is it important to study specific and common behaviors early in development? Cross-etiology comparisons are essential to determine whether certain patterns of strengths and weaknesses are characteristic of and unique to a specific phenotype. Such comparisons are helpful in refining our understanding of autism and ADHD, given their overlap. Additionally, these comparisons facilitate the identification of potential markers, which can provide insights

into the early development of these conditions. This understanding may: i) shed light on the etiology of these conditions, ii) highlight early differences which, when combined with other developmental markers, may indicate increased likelihood for autism and/or ADHD, and iii) lead to potential vulnerabilities that can be addressed in interventions. These interventions can be individually tailored – potentially used as stratification markers, for instance, if certain temperament traits are predominantly associated with either autism *or* ADHD. Conversely, they can be approached from a transdiagnostic perspective, e.g., if differences are shared across both conditions, and finally iv) using a dimensional approach (based on symptoms instead of a categorical diagnosis), findings may extend to children with vulnerabilities independent of diagnosis. In essence, an early focus on behavioral patterns can not only refine our understanding of how conditions like autism and ADHD manifest but also guide the development of timely and more effective interventions.

Prospective Longitudinal Studies

The prospective longitudinal design of so-called 'infant sibling studies' follow infants with a first degree relative with ASD, often an older diagnosed sibling (so called 'proband') from infancy and onwards. This research design allow us to study autism symptoms as they emerge (Jones, Gliga, Bedford, Charman, & Johnson, 2014; Szatmari et al., 2016) and importantly both behavioral (Ozonoff et al., 2011) and neurocognitive mechanisms (Jones et al., 2019) associated to the autism phenotype. Autism is a highly heritable condition, with genetic contributions explaining between 64–91% of the phenotypic variation (Tick, Bolton, Happé, Rutter, & Rijsdijk, 2016). Given the high heritability of the condition, about 20% of the infant siblings are found to develop the condition (Ozonoff et al., 2011). Additionally, another 20% of infant siblings may show subthreshold symptoms or have other developmental concerns, such as ADHD (Charman et al., 2017; Messinger et al., 2013). Similarly, ADHD has been shown to have a strong familial component. Heritability estimates for ADHD, derived from twin and family studies, are consistently high, often around 70–80% (Faraone & Larsson, 2019). Interestingly, growing evidence indicate that autism and ADHD not only co-occur frequently within individuals but also within families (Ghirardi et al., 2017). Studies have suggested a shared familial etiology between autism and ADHD (Rommelse et al., 2010). This implies that siblings of an individual with autism have a higher likelihood of ADHD and vice versa, pointing to shared genetic factors between the two conditions. Notably, I will use the term 'likelihood' or 'family history' throughout this thesis to avoid the negative connotations of the term 'risk', in line with the preferences of the autistic community (Fletcher-Watson et al., 2017). The prospective design has been found to be a valuable method to track the development of infants and identify early signs of autism, as well as ADHD (Johnson et al., 2015; Visser et al., 206). Indeed, given the familial

aggregation of autism and ADHD, an increasing number of studies have shown that studying ADHD symptoms in infant siblings of probands with a family history of autism provide information about ADHD outcome (Miller et al., 2018) and specific and shared pathways to symptoms of both conditions (Shephard et al., 2019). As stated previously, examining the early-life associations to autistic traits and ADHD traits by using a dimensional approach to the emergence of shared features may help determine if the onset of one condition contributes to the other or if autism and ADHD arise from shared early risk factors.

Self-Regulation

Self-regulation is implicated in most neurodevelopmental conditions and can be defined as the organization or modulation of affective, cognitive, and behavioral responses (Blair & Diamond, 2008; Fuster, 1997; Kopp, 1989; Posner & Rothbart, 2007). Self-regulation is a multidimensional and broad construct, extensively studied across various domains of psychology, from cognition by the concept of executive functions (Diamond, 2013) and from personality as means of temperament (Rothbart & Bates, 2006). Top-down and bottom-up processes are involved to a varying degree in self-regulation. Top-down processes are deliberate, volitional and slow, responding to a mental representation. They are activated when engaging in novel problems, resolving conflicts, or preparing for upcoming goals. In contrast, bottom-up processes are automatic and rapid processes driven by sensory stimuli. Referring back to baby Sam, the loud voices and bright lights are examples of such external stimuli that elicit a reactive, bottom-up response e.g., anxiety, fear and avoidance, and these are often the behaviors that are being regulated by top-down processes, but can also be regulating per se. In psychology in general, processes seldom exist in isolation or as distinct categories. Similarly, this holds true for top-down and bottom-up processes, which are intricately linked and lie on a continuum (Nigg, 2000, 2017). Self-regulatory skills involve processes of inhibition and excitation, that is, the ability to actively supress or delay behaviors in certain situations, whereas in others, initiating or activating behaviors. In addition, it involves control and allocation of attention (Posner & Rothbart, 2007). This allows individuals to focus on the relevant information, filter out distractions, and direct cognitive resources toward achieving a goal. As children develops, self-regulation becomes essential for social adaptation and for adjusting behaviors with the expectations of others and in accordance to societal norms (Eisenberg, Smith, & Spinrad, 2016; Kochanska, Murray, & Harlan, 2000).

From infancy to adolescence, the development of self-regulation undergoes a profound shift, transitioning from being predominantly externally influenced to gradually becoming more internalized. In infancy, regulatory mechanisms are largely extrinsic; infants rely on caregivers or another significant individual to soothe, regulate arousal, or guide behaviors (Bernier, Carlson & Berner, 2010). As children grow, they begin to internalize these regulatory processes,

relying less on external cues and more on intrinsic abilities to modulate emotions, behaviors, and cognitive responses. However, although children develop more intrinsic regulation, i.e., *self*-regulation, this regulation is still shaped and mediated by social contexts, family and peer interactions, and societal norms. This dynamic reflects the interplay between growing autonomy and the omnipresent influence of the social world in shaping behaviors (Vygotsky, 1978).

This thesis focuses on identification of shared and distinct early indicators of self-regulation and relations to autistic traits and ADHD traits. We use temperament and executive functions as measures of early aspects of self-regulation to better understand early developmental trajectories that may lead to autistic and ADHD traits.

Temperament

The study of temperament has a long history originating from the Greek physician Hippocrates and later by Galen in the 2nd century AD. The idea was that four basic cardinal fluids: blood, phlegm, black bile and yellow bile, applied to different temperaments or *humours* (from Latin "liquid" or "fluid") depending on the relative balance of these body fluids (West, 2014). The different temperaments were divided into sanguine (warm, pleasant), phlegmatic (slow-moving, apathetic), melancholic (depressed, sad), and choleric (quick to react, hot tempered). Despite the evolution of our understanding of temperament, some aspects have endured from the historical perception of temperament. The view that temperament refers to different type of moods, e.g., being hot-tempered when describing an individual who becomes angry easily, is still used in everyday language. Contemporary theories have moved away from describing mood to describing distinct traits that encompasses biological predispositions in emotional, behavioral and attentional responses from early infancy and throughout the lifespan with genetic underpinnings manifested as a consistent pattern of reactivity and regulation (Derryberry & Rothbart, 1997; Rothbart, 1981). Much of the biological underpinnings of temperament derives from Gray (1991) and studies based on animal research (Réale et al., 2007). Gray (1991) introduced the behavioral activation system (BAS) tied to reward sensitivity (Corr, 2004), and the behavioral inhibition system (BIS), a subsystem that resolves conflicts among competing goals, such as approach-withdrawal conflicts. BAS has been linked to sensitivity to punishment, lack of reward, novelty, and innate fear stimuli. These systems counterbalance each other, shaping extraversion-introversion traits (Blair, 2003). Gray also proposed a fight-flight system regulating unconditioned (i.e., not learnt by prior experience) punishment (Gray, 1991). According to Gray's BAS model, reward-related projections from the amygdala to the nucleus accumbens activate

motoric processing that increases proximity to the desired stimulus and facilitates goal-oriented behavior (Gray & McNaughton, 1996).

During a pivotal roundtable discussion and subsequent publication, Goldsmith et al (1987) gathered distinguished researchers representing four prominent temperament theories. The four approaches that were represented have since contributed in important ways: Rothbart's focus on the structure of temperament and the importance of self-regulation (Rothbart, 1981; Rothbart et al., 2008), Tomas and Chess' proposal of temperament dimensions, *goodness of fit* and the practical applications of temperament (Chess & Thomas, 1977), Buss and Plomin's investigation of the interplay between genetic and environmental factors in development (Buss & Plomin, 1975, 2008), and Goldsmith's attention to the importance of the emotional nature of temperament (Goldsmith et al., 1997; Goldsmith & Campos, 1982). A follow-up on the roundtable was organized 25 years later by Shiner and colleagues (2012) where they defined temperament as "early emerging basic dispositions in the domains of activity, affectivity, attention, and self-regulation, and these dispositions are the product of complex interactions among genetic, biological, and environmental factors across time." (Shiner et al., 2012).

Prior to focusing on Rothbart's neurobiological approach, it is relevant to briefly acknowledge the pioneering work of Tomas and Chess (1968) that emerged from the New York Longitudinal Study which started in 1953. This study was the first ever to follow individuals from infancy to adulthood, with the attempt to observe behavioral patterns over time. The study resulted in nine identified temperament dimensions, including activity, approach-withdrawal, rhythmicity (of biological functions), mood (positive/negative), distractibility (ease of soothing), threshold (to respond), intensity (of response), persistence and adaptability. From parent-ratings of their child, the infants were classified as easy, difficult or slow-to-warm-up. These classifications, in turn, were related to different clinical profiles. However, this typology received critique for being judgemental and today we rarely use the classification of a "difficult" child but instead use the more specific descriptions of traits and behavioral tendencies. Nevertheless, many important findings came from the study, such as the emphasis on transactional dynamics between the child's temperament and the environment which was explained in the conceptual framework of *goodness of fit*. Within this model, developmental outcomes are dependent not on the interactional fit between a child's temperament and the specific features of the surrounding environment. Chess and Tomas (1991) proposed that: "demands, stresses, and conflicts, when in keeping with the person's developmental potentials and capacities for mastery, may be constructive in their consequences and should not be considered as an inevitable cause of behavioral disturbance. The issue involved in disturbed behavioral functioning is rather one of excessive stress resulting from poorness of fit

between environmental expectations and demands and the capacities of the individual at a particular level of development." (Chess & Thomas, 1991). The *godness of fit* paradigm is still highly relevant today, particularly with the neurodiversity movement that urge a change for more neurodiverse-friendly environments and awareness to meet the capacities of the individual.

Rothbart's three-factor model of temperament (Rothbart, 1981; Putnam et al., 2001) is arguably the most extensively used contemporary model of childhood temperament (De Pauw & Mervielde, 2010; Zentner & Bates, 2008). This model approach temperament from a neurobiological and developmental perspective and is a comprehensive framework that categorizes and explains individual differences in reactivity and regulation. The model comprises three overarching factors; negative affect, extraversion/surgency and effortful control (Rothbart, 1981), these in turn are composites of more specific dimensions (Rothbart et al., 2007). Negative affect includes aspects such as fear, sadness, discomfort, and frustration. Extraversion/surgency encompasses traits like impulsivity, activity level, and positive anticipation. Meanwhile, effortful control refers to the ability to inhibit a dominant response and self-regulation capacities, such as soothability, or orienting/regulation in early infancy.

Temperament in Autism and ADHD

While increased negative affectivity and low effortful control are generally associated with both autism and ADHD, specific early temperament differences have also been found between the two (Johnson et al., 2015; Visser et al., 2016). Toddlers who later received a diagnosis with autism often show lower approach and adaptability, coupled with greater negative affect and perceptual sensitivity (Clifford et al., 2013; Del Rosario et al., 2014; Zwaigenbaum et al., 2005). In contrast, toddlers with ADHD exhibit higher levels of activity and approach and show reduced levels of effortful control (Kostyrka-Allchorne et al., 2020; Nigg et al., 2020). Low infant positive affect and infant attentiveness to parent at 12-months during an episode of parent–child interaction was shown to predict autism in 3 year olds (Wan et al., 2013). No such relationship was found when the infants were 6-month old suggesting that this difference may unfold only later in development. Importantly, Nigg (2004) proposed different temperamental pathways to ADHD, one by high levels of negative affectivity, and one pathway defined by increased levels of exuberance/surgency and approach (Nigg et al., 2020). However, whereas these proposed pathways are shared with autism or specific to ADHD is unclear.

While there are only a handful of studies examining autism and ADHD together, even fewer have done so prospectively. From the limited studies available, increased activity level seem to be the most common finding related to

ADHD traits in a cohort of infants with elevated likelihood for autism (Shephard et al., 2019) and ADHD (Miller et al., 2020; Reetzke et al., 2022). However, this pattern is unclear in infants (Johnson, 2015; Visser et al., 2016). Investigating potential specific and common developmental traits in infants with elevated likelihood may help us clarify how inherited factors influence early development. Early shared features across autism and ADHD in infants indicate the potential of transdiagnostic intervention efforts. Given that temperament traits might constitute intermediate phenotypes, temperament traits that are common in autism and ADHD may be more closely linked to the shared genetics underlying these conditions, whereas temperament traits that seem to be specifically linked to *either* condition might be considered as targets for individualized interventions particularly targeting more specific aspects of a phenotype.

Executive Functions

The concept of 'EF' emerged in the mid-20th century, mainly referring to functions linked to the frontal cortex. This concept owes much to the now widely-cited case of Phineas Gage, a railroad worker who survived a horrific accident by getting an iron bar through his skull, more specifically through his frontal lobes. Despite surviving the accident with largely preserved general intelligence, his personality was changed, including self-regulation and EF abilities such as planning and organization. Cases such as Phineas Gage emphasised the more specific role of the frontal lobes in higher-order cognitive processes, but have since been a subject of high interest due to its relevance in solving everyday life tasks.

Executive functions are a set of cognitive processes that facilitate decision-making, planning, problem-solving, delay of gratification, and other higher-order tasks (Friedman & Miyake, 2008; Jurado & Roselli, 2007). As such, EFs correspond to the top-down processes of self-regulation (Nigg, 2017) and are integral for the ability to engage in goal-directed behaviors and to adapt to changing environments. Executive functions can be broken down into three main components: shifting, working memory, and inhibition (Friedman & Miyake, 2000). These components are interrelated but distinct and load on a common EF factor (Miyake & Friedman, 2012). However, in childhood EF seem to be less differentiated and there are suggestions for a unitary factor (Wiebe, Espy, & Charak, 2008) as well as a two-factor model (Garon, Smith, & Bryson, 2014). Garon et al. (2008) emphasized the development of executive functions in early childhood, proposing that these functions undergo substantial maturation during the preschool years and lay the foundation for cognitive and social-emotional development. The development of EF follows a hierarchical progression from simpler to more complex cognitive processes

(Garon et al., 2008). Early in life, foundational skills such as inhibition and attentional control lay the groundwork for the emergence of more complex abilities including flexibility, updating and integration of conflict resolution (Diamond, 2013). In order to perform more complex EF tasks, children must be able to integrate simpler EF skills, such as holding in mind and inhibiting a response (Garon et al., 2017), emphasizing the integrative and building-block nature of EF (Miyake & Friedman, 2012; Zelazo & Carlson, 2012). Importantly, rapid improvements in more complex EFs occur during the preschool and early school years (Carlson & Moses, 2001; Zelazo, Muller, Frye, & Marcovitch, 2003).

Another way to understand EF is by using the "hot/cool" framework (Metcalfe & Mischel, 1999), which emphasize the contextual framing of a task and associated brain-network involved (Zelazo & Carlson, 2012). For example, in adults the orbitofrontal region has been linked to challenges in utilizing emotionally-induced experiences to make decisions that require integration of future rewards and negative consequences (Bechara, 2004), suggesting different involvement of brain-networks than in performance of cooler cognitive tasks. Within this framework "cool" EFs apply to cognitive and task-based activities, while "hot" EFs are triggered in situations that elicits emotions, motivation, or create a conflict between seeking instant satisfaction and pursuing long-term gains, such as delay of gratification (Zelazo & Muller, 2002). This framework was built upon the question of drives, incentives and motivation. Daily deliberate actions and choices are shaped by an interplay of both these hot and cool executive functions (Perone et al., 2018). Although the division of hot versus cool has been debated regarding the overlap and specificity of the cognitive and motivational processes involved and their interplay, a strength of this approach has been the emphasis on how emotionally-loaded versus more neutral situations or tasks affect and elicit cognitive processes. In the realm of developmental psychology, before the concept of "hot EF" became popular, the now popular Delay of Gratification paradigm was introduced by Mischel (1989). This task requires ´children to resist the temptation of an immediate reward (such as a treat placed within their view and reach) in favor of a larger reward later on. Since Mischel's foundational research, numerous longitudinal studies have underscored the significance of performance in this paradigm, suggesting it plays a crucial role in cognitive and emotional development (Mischel & Ayduk, 2011).

Executive Functions in Autism and ADHD

EF has been implicated in etiological models of both autism and ADHD and is a suggested endophenotype (Rommelse et al., 2010), and seen as a protective factor (Johnson, 2012). Autism and ADHD are associated with

differences in EF in comparison to neurotypical peers (Demetriou et al., 2018; Willcutt, 2005), with relative stability across development. However, research is mixed regarding the specificity and overlap of these differences (Johnson et al., 2015). This depend, in part, on the assessment methods used (e.g., rating scales or behavioral tasks). In addition, relatively few studies have examined autism and ADHD simultaneously which makes it difficult to assess the impact of potentially overlapping symptoms. A recent systematic review on 4-year-olds indicated both overlap and specificity in EF in relation to autism and ADHD (Christoforou, Jones, White, & Charman, 2023). In a review with children between 3 to 18 years, shifting and planning deficits were more common in autism, while inhibition deficits were more apparent in ADHD (Craig et al., 2016). However, when considering the overlap and co-occurrence of the two disorders, discerning specific EF deficits becomes more complex. The heterogeneity within each condition, as well as differences in study designs, populations, and measurement tools, contribute to the mixed findings. The most pronounced impairments related to response inhibition are found in children with ADHD, both at clinical levels and subclinical (Visser et al., 2016), while shifting seemed more pronounced in relation to autistic traits. Although most psychiatric conditions are associated with EF dysfunction, the largest effect size observed is for response inhibition in individuals with ADHD (Willcut, 2005). For individuals with autism, it is often challenging when tasks require flexibility and planning, which may manifest as difficulties adapting to changes or transitioning between activities (Visser et al., 2016). Whereas inhibitory control is strongly associated with ADHD, studies on working memory indicate mixed results (Brocki et al., 2007). Interestingly, there is an overlap in the EF deficits seen in both autism and ADHD, leading to question whether EF might be a shared difficulty, or a shared potential protective factor (Johnson, 2012).

Adaptive Behavior

Adaptive behavior encompasses the skills required for an individual to achieve age-appropriate independence (Sparrow et al., 1984; Tasse et al., 2012). These skills emerge from the bi-directional interplay between an individual's physical and cognitive functions and the societal norms regarding everyday functioning (Bölte et al., 2019). This encompasses the skills to navigate daily life activities, such as usual home living skills and self-care, using public transportation, engaging in conversations, comprehending others, and participating in group or community activities. The extent of adaptive functioning directly impacts level of independence, success in school or work, and engagement within the community, which in turn has major effect on overall well-being and mental health (Farley et al., 2009; Paul et al., 2004). Deficiencies in these abilities can manifest early in a child’s life (Szatmari et al., 2015; Sacrey et

al., 2018; Ventola, Saulnier, Steinberg, Chawarska, & Klin, 2014), and children with autism demonstrate slower age-related progression in these domains compared to their neurotypical peers (Kanne et al., 2011; Klin et al., 2007; McGovern & Sigman, 2005). Despite heterogeneous presentation of adaptive behaviors in autistic individuals, lower levels of cognition and language, including increased autistic symptoms are associated with reduced adaptive behavior (Bal, Kim, Cheong, & Lord, 2015; Sacrey et al., 2018; Szatmari et al., 2015). Indeed, deficits in adaptive behavior limits the potential of individuals with autism, over and above the impacts of autism-specific symptoms and cognitive challenges (Knapp, Romeo, & Beecham, 2009). In addition, children with autism and co-occurring ADHD seem to be seem to exhibit even more impairments in adaptive functioning (Liu et al., 2021). However, it is suggested that social-communicative symptoms in particular predicts lower adaptive behaviors, over and above ADHD symptoms (Tillmann et al., 2019).

Aims of the thesis

The overarching aim of this thesis is to examine aspects of self-regulation and the emergence of co-occurring autism and ADHD traits with an infant-sibling design, aiming to enhance our understanding of specific and shared mechanisms underlying these conditions. This, in turn, was divided into two specific aims:

1. To examine if infant temperament traits were specifically associated to later autistic traits and/or ADHD traits (Study I) and if older probands' autistic traits and/or ADHD traits predicted specific and shared temperament traits in their younger infant siblings (Study II).

2. To examine if executive functions were associated to familial likelihood of autism and ADHD, and autistic traits and ADHD traits, and if executive functions moderated the association between autistic versus ADHD traits and adaptive functioning (Study III).

Study I and II focused on infant temperament as either predictors of later autistic and/or ADHD traits or as being predicted by familial quantitative traits to understand specific and shared associations to autistic and ADHD traits. First, we examined if temperament traits in 1.5-year olds predict autism and ADHD traits at 3 years. Secondly, we explored the possibility to use probands' autistic and ADHD traits to predict temperament traits in their 10-month old infant siblings (a between-individual design).

Study III focused on executive functions in 3-year olds and concurrent associations to autistic traits, ADHD traits, and adaptive behaviors to understand how these EFs differ between children with a family history of autism, or autism and ADHD, or no FH of these conditions, and finally if EF could function as a protective factor in the associations between autism versus ADHD traits and adaptive behaviors.

Methods

Participants

The participants in the three studies of this thesis were part of two longitudinal studies: The Early Autism Sweden (EASE; Study I, II, and III) and the British Autism Study of Infant Siblings (BASIS; Study II). The EASE study was approved by the Regional Ethical Board in Stockholm, Sweden. The BASIS was approved by the National Research Ethics Service (London, UK). Both studies were conducted in accordance with the 1964 Declaration of Helsinki and its later amendments and the American Psychological Association. Informed consent was collected from all parents.

Participants in the EASE were recruited from the greater Stockholm area and participants from the BASIS were recruited from the greater London area and surrounding areas. They comprised mainly of middle-class families with a relatively high parental educational level (see Table 1 for sample characteristics). Exclusion criteria for both studies were premature birth (prior to week 36 for both samples), any known genetic syndrome associated to ASD, diagnosis of epilepsy or history of convolutions, any known condition likely to affect brain development, or any known hearing or visual impairments.

The EASE sample

The EASE study was a longitudinal autism sibling study including children with first-degree family members with an ASD diagnosis that were followed from infancy (5 months age) to early childhood (6 years age). These children had an older sibling or parent with an autism diagnosis, which was confirmed through clinical interviews and medical records. At the time of enrolment, none of the infants had been diagnosed with any medical or developmental condition. Due to the heredity of autism, the infant siblings had a familial elevated likelihood of developing autism themselves (EL). The EL children were recruited via the EASE project's website, advertisements, and clinical units. As a comparison group, infants with no first-degree family members with an autism diagnosis were recruited via the Uppsala Child and Babylab's recruitment data base, based on birth records of children born in the Uppsala County. These typically developing children formed the typical likelihood group (TL). The inclusion criteria for the typical likelihood infants were as

follows: being born full-term, having a normal birth weight, and no history of ASD among first-degree family members. These criteria were determined through parent interviews and the family's medical history. Additionally, all infants in the TL group had at least one older sibling.

The BASIS sample

The BASIS is a longitudinal infant sibling study following infants with elevated likelihood of autism (EL). The study protocol is very similar to the EASE protocol and criteria described above. At the time of enrolment, none of the infants had been diagnosed with any medical or developmental condition. The EL group comprises infants who have at least one older sibling (referred to as the proband) diagnosed with ASD through community clinical evaluation. The proband's diagnosis was confirmed by a specialized clinician, relying on information obtained from the Development and Well-Being Assessment (DAWBA) and the parent-reported Social Communication Questionnaire (SCQ). Parent-reported family medical histories were included, encompassing significant medical conditions within the proband and extended family members, without any exclusions based on medical history. Infants in the typical likelihood (TL) control group were recruited from a volunteer database at the Birkbeck Centre for Brain and Cognitive Development. Inclusion criteria for the TL-group required infants to have been born full-term, with a normal birth weight, and having no history of ASD among first-degree family members. These criteria were ascertained through parent interviews focusing on the family's medical history. All TL-participants also had at least one older sibling. To ensure the absence of possible ASD in these older siblings, a screening process was conducted using the SCQ, whereby no child scored above the instrument cut-off for ASD.

The three studies of this thesis include partly different participants. This is due to different focus of the studies (i.e., age and measures) and that recruitment and data collection was ongoing during the cause of the three studies. For Study I and II, children were included from the inception of the EASE study in 2011, including data from the BASIS (Study II). Study III included children who had completed the EF-battery, which was introduced in 2016 and became a part of the data collection process at that point and onwards.

General procedures of Study I-III

The Eurosibs consortium is a European multisite neurocognitive study of infants with an older sibling with ASD conducted across nine sites in five European countries with a common standardised experimental protocol (Jones et

al., 2019). The Eurosibs involve investigators in the UK (Birkbeck College, London; King's College London, University of Cambridge), Sweden (Karolinska Institute, Uppsala University), Belgium (Ghent University), Poland (University of Warsaw), and the Netherlands (Radboud University Nijmegen, Utrecht University). For the studies included in this thesis, data from Sweden (EASE, Study I-III) and UK (BASIS, Study II) was used.

Procedures of the EASE study

Study I and III were part of the EASE study and thus followed a similar protocol. The EASE protocol comprises six lab visits scheduled at 5, 10, 14, 18, 24, and 36 months. Upon reaching the 36-month visit, a comprehensive diagnostic assessment of the child was administered by a team of experienced psychologists using gold-standard instruments and procedures. The infant and the caregiver(s) visited the Uppsala Child and Babylab at the age of 10, 14, and 18 months. The families visited the Center of Neurodevelopmental Disorders at Karolinska Institutet (KIND) at the age of 5, 24 and 36-months. Generally, families spent approximately 4-5 hours at the lab, participating in a variety of assessments. These assessments included play observations, developmental assessments, parent-child interaction, eye tracking, motion tracking, electroencephalography (EEG) and magnetic resonance imaging (MRI). The caregiver(s) participated in parent-interviews and were also requested to complete several online questionnaires about their child before each of the visit. The testing day commenced in the morning, with scheduled breaks for lunch and a nap, and continued with an afternoon session. Throughout all the assessments, the caregiver remained present alongside the infant. The tasks were adapted to be fun and engaging for the infants.

Procedures of the BASIS study

Study II included data from the BASIS, which has a comparable study protocol to of the EASE protocol. At each age point, the preferred testing window was +/-1 month from the relevant birthday; if this was not possible testing up to +2 months was occasionally approved to minimise data loss. This means that the age at enrolment differed somewhat between the two study sites (Sweden versus UK). The data that was used from the BASIS included caregiver reported data of their infant at 10 month of age, and ratings of the older sibling from the time of enrolment in the study. Both caregiver reports consisted of online questionnaires completed from home. Developmental level of the infant was collected at the 10-month visit to the lab.

Measures included in Study I-III

Autistic and ADHD traits rating scales

CBCL and C-TRF

The Child Behavior Checklist (CBCL) 1½–5 and the Caregiver-Teacher Report Form (C-TRF) are similarly constructed to evaluate behavioral, emotional and social function problems (Achenbach & Rescorla, 2000). The CBCL was rated by parents and the C-TRF was rated by teachers and equivalent pre-school staff. Both forms comprise 99 items that are rated on a scale between 0 (not true), 1 (somewhat or sometimes true), and 2 (very or often true). The DSM-related scales of Pervasive Developmental Problems (PDP) was used as a proxy for autistic traits, and the ADHD problem scale as a proxy for ADHD traits. An aggregated mean score between teachers and parents for PDP and ADHD problem scale respectively were used as outcome measures (Study I).

CRS-3

Conners Rating Scale 3rd version (CRS-3; Conners, 1989; 2008) is a parent-rated questionnaire used to assess challenging behaviour in their child during the last month rated on a four-point scale (0 = "not true at all", to 4 = "very frequent"). Scales include an ADHD index based on hyperactivity/impulsivity and inattention traits, and related challenges such as oppositional behaviors, anxiety and social problems. The ADHD index was used as a proxy for dimensional ADHD traits in the older siblings (Study II).

SCQ

The Social Communication Questionnaire (SCQ; Rutter, Baily, & Lord, 2003) is a parent questionnaire which asks parents about their child's communication skills and social functioning by 40 "yes"/"no" (1,0?) questions. Total score was used as a proxy for autistic traits in the older siblings (Study II).

ADOS-2

The Autism Diagnostic Observation Schedule (ADOS) Toddler module 1 and 2 was used as a measure of autistic traits (Study III). These assessments were always run by an experienced clinical psychologist. Tasks include imaginary play, social communication, joint attention and turn-taking games. Two different modules were used (depending on the child's language ability). The calibrated severity score (CSS) was used as dimensional measure of traits and symptoms.

DSM-5 ADHD Symptom Ratings

Based on DSM-V symptoms, a clinical psychologist observed and rated the 18 criteria included in the DSM-5 for ADHD during a full day visit to the lab. The scores range between 0-2 scale (0 = "unlikely", "no definite", or "unknown", 1 = "probable", 2 = "yes, definite"). The total score was used as a measure of ADHD traits (Study III).

Temperament

IBQ-R

The Infant Behavior Questionnaire Revised (IBQ-R; Gartstein & Rothbart, 2003) is a parent-report measure for assessing temperament in infancy (< 12 months). Parents rate their child's behaviour from the last 2 weeks on a 0-7 scale (0 = "never", to 7 = "always", or, "does not apply"). Parents are asked questions about the frequency of certain behaviors, such as: "When put into the bath water, how often did the baby splash or kick?" (example from activity level scale). A total of 14 temperament scales cluster onto three broad scales; surgency, negative affectivity, and orienting/regulation. Mean scores for respective temperament scale were used as independent variables (Study II).

ECBQ

The Early Childhood Behavior Questionnaire (ECBQ; Putnam et al, 2006) is parent-report questionnaire used to assess temperament in toddlers between 18 and 36 months of age. The ECBQ contains 18 dimensions based on 201 items. Parents rate their infants' behavior over the past 2 weeks on a 1–7 scale reflecting frequency. We used the low-level dimensions at 18 months (Study I).

Activity Level

Accelerometer activity level

Physiological activity level was measured using wearable accelerometers (Q-Sensors, Affectiva, Inc.; Waltham, MA) which recorded the 3D acceleration of the arm. The Q-sensors are worn on the wrist and records arm movements by accelerometers along the x, y and z axis of the device in gravity units (i.e. a completely still sensor records 1 G). Movement activity level was calculated by transforming these axes to a three-dimensional space and computing the root mean square (RMS) of all samples in the 3D acceleration profile (Study I).

Observed activity level

Observed activity level was assessed from the bubbles task in the ADOS-2 Toddler (Lord, Rutter, DiLavore, Risi, Gotham, & Bishop, 2012). Activity

level was coded on a 1–5 scale, with 1 being the lowest score and 5 being the highest score. The global score was a total score based on the total 2.5-min task and used as a proxy for activity level (Study I).

Exuberance

The global coding of the 2.5 min sequence from the bubbles task in the ADOS-2 was used as a means to elicit joy and excitement, and to assess exuberant behaviors. The three scales Activity level, Positive affect and Sociability were highly correlated (r = 0.67–0.78) and a mean estimate was used as a composite score of exuberance (Study I).

Executive Functions (Study III)

Inhibition/Deferred Gratification

Delay of Gratification

A simplified version of the Delay of Gratification (Mischel et al., 1989) was used to assess deferred gratification. Children chose between raisins or smarties, a big or small amount, and received their preference placed in front of the child. The experimenter briefly stepped out, instructing the child not to eat until returning. The parent was present but occupied. The task was video-coded, and the score was the time until eating (0-90 sec range).

Prohibition Task

The prohibition task (Friedman et al. 2011) involved reframing from touching an attractive toy placed before the child. The experimenter placed the toy on the table and said "[child's name] don't touch". The trial ended after 45 seconds. The latency to touch was measured, with latencies ≥ 45 sec indicating a full wait (range: 0-45 sec).

Common EF

Reversed Categorization

The Reversed Categorization (Carlsson et al., 2004) was used to assess switching and consisted of sorting big/small horses into the correct bucket with an image of that particular horse. In the second phase, the children were instructed to reverse sorting. The score was total correct post-switch placements (0-12 range).

Beads Task

The Beads task (Stanford-Binet Intelligence Scales 4th ed., Thorndike et al., 1986) was used to measure nonverbal short-term memory. Children were

shown a picture of beads in different forms and shapes and were instructed to identify the bead that had been shown to them. After a practice trial, nine trials followed: three with one bead (2 seconds each), three with two beads (2 seconds each), and three with three beads (3 seconds each). Performance was total number of correct trials (0-18 range).

Spin the Pots

The spinning pots task (Hughes & Ensor, 2005) was used as a measure of working memory. The experimenter and the child hide 6 "jewels" under a total of 8 boxes, and is instructed to retrieve them one by one. Prior to starting the game, the experimenter shows the two empty boxes. The child is instructed to search for the jewels by choosing one pot at the time. The score is total lifted boxes minus errors made.

Day/Night Stroop

The Day/Night Stroop task (Gerstadt et al., 1994) was used to assess interference control. The child must remember a rule while inhibiting their natural response tendency. The child is instructed to say "moon" for the image of a sun and "sun" for an image of the moon. The total correct switch-trial response is used as interference control (ranging from 0-12).

Empirical Studies

Study I

How Does Temperament in Toddlers at Elevated Likelihood for Autism relate to Symptoms of Autism and ADHD at Three Years of Age?

Background and Aims

Temperament, according to Rothbarts model, comprises a triad of overarching factors: Effortful Control, Negative Affectivity and Surgency (Gartstein & Rothbart, 2003). These factors in turn, consists of lower-level temperament traits. Autism and ADHD have been linked to a general pattern of low Effortful Control and increased levels of Negative affectivity. However, the associations to Surgency indicate mixed findings. A few studies have found that autistic children show lower levels of surgency only during the second year of life (del Rosario et al., 2014; Garon et al., 2009) while high levels of surgent and exuberant behaviors have been linked to school-aged externalizing behaviors (Forslund et al., 2016; Rydell et al., 2003) and ADHD traits (Brocki et al., 2019). However, only a limited number of studies have examined autistic and ADHD traits simultaneously which is important for understanding shared versus specific pathways. Research examining temperament have commonly relied on indirect measures such as parent questionnaires. While this information is highly useful, adding other measures can provide a more comprehensive view of the child´s temperament (Karp et al., 2004). The aim of Study I was to explore specific and shared associations between temperament traits at 18 months and autistic and ADHD traits at 36 months in toddlers at elevated likelihood for autism. We were interested in testing if there was specificity in surgent behaviors, such as lower sociability and lower positive anticipation, but higher negative affectivity in terms of increased levels of fear and sadness in relation to autistic traits. Consequently, if increased surgent behaviors, such as increased sociability, impulsivity, exuberance and activity level and negative affectivity in terms of frustration would be related to ADHD traits. We posed mostly shared hypotheses regarding the effortful control dimensions, such as lower attention shifting and attention focus associated to both autistic and ADHD traits due to mixed findings.

Method

Temperament at 18 months was assessed by parent-ratings, observations and triaxial accelerometers. Parent-rated temperament was assessed by the Early Childhood Behavior Questionnaire (ECBQ; Putnam et al., 2006) which consists of 18 dimensions (low-level temperament scales). Observed temperamental exuberance and activity level was assessed by the bubble task from the ADOS-2, modified from Lab-Tab (Goldsmith & Rothbart, 1991). Physiological activity level was assessed by accelerometers which recorded 3D acceleration of the arm. The outcome measures, autistic and ADHD traits, were assessed by ratings from parents (CBCL) and preschool teachers (C-TRF). Both questionnaires are similarly constructed to assess behavioral, emotional and social problems (Achenbach & Rescorla, 2000). The DSM-related scales of Pervasive Developmental Problems (PDP) was used as a proxy for autistic traits and the ADHD problem scale as a proxy for ADHD traits. The parent-rating and the teacher-ratings were moderately correlated ($r = 0.55$, $p = .001$ for the ADHD-scales, and $r = 0.43$, $p = .008$ for the PDP-scales) and were collapsed into a mean score and used in the following analyses.

Results

Concurrent correlations at 18-months between the predictor variables showed significant correlations between all activity variables ($r = 0.34$, $p < .04$). Increased accelerometer activity level correlated with decreased parent-rated infant attentional focus ($r = 0.32$, $p = .03$). Higher levels of exuberance (in the bubble task) was related to lower fear-ratings by the parent ($r = 0.29$, $p = .04$). At 36-months, autistic and ADHD traits were positively correlated ($r = 0.55$, $p < .001$).

For the pre-specified hypotheses, we found support for the following hypotheses. Regarding the parent-rated temperament dimensions, longitudinal correlations showed that poor inhibitory control ($r = - 0.49$, $p = .001$), and increased activity level ($r = 0.42$, $p = .003$) was associated with ADHD traits at 36-months after controlling for autistic traits. Higher levels of frustration correlated with ADHD traits ($r = 0.34$, $p = .01$), but did not hold after accounting for autistic traits ($r = 0.27$, $p = .05$). Lower rates of attention shifting ($r = - 0.31$, $p = .01$), sociability ($r = -0.43$, $p = .002$) and higher levels of fear ($r = 0.33$, $p = .01$) was associated with increased autistic traits at 36-months after controlling for ADHD.

In exploratory analyses (without pre-specified hypotheses) we found that lower levels of parent-rated fear was specifically associated with increased ADHD-traits ($r = - 0.33$, $p = .01$), after controlling for autistic traits. Higher levels of discomfort was negatively correlated with autistic traits ($r = 0.43$, p

= .001), after partialling ADHD traits. Higher activity level was associated with increased autistic traits, but when controlling for ADHD traits, this association became non-significant. Finally, lower levels of soothability was associated with autistic traits (r = - 0.33, p = .01) and ADHD traits (r = - 0.36, p = .01), but not when controlling for the respective trait domain.

As for the observed temperamental exuberance and activity level, we found only marginal trends. Bivariate correlation showed that higher levels of exuberance was related to ADHD traits (r = 0.31, p = .05), but only marginally when controlling for overlapping autistic traits (r = 0.27, p = .09). Autistic traits were not associated to activity level after controlling for ADHD traits (r = 0.06, p = .70. Observed activity level was marginally associated to autistic traits but not to ADHD traits in partial correlations (r = 0.26, p = .09 for autistic traits, r = 0.16, p = .24 for ADHD traits). Finally, increased accelerometer activity level was associated with ADHD traits (r = 0.38, p = .01), but this association did not hold after controlling for autistic traits (r = 0.26, p = .10).

Discussion

The main aim of Study I was to investigate specific and shared associations between temperament traits at 18-months and autistic and/or ADHD traits at 3 years of age.

Lower levels of sociability, increased levels of fear and discomfort and lower attention shifting was specifically associated to autistic traits, after controlling for ADHD traits. Interestingly, fear was not associated to autistic traits in bivariate correlations, but when controlling for overlapping ADHD traits this association became significant. Similarly, lower rates of impulsivity were only associated with autistic traits in partial correlations. Increased levels of impulsivity were only marginally associated to ADHD traits. Lower levels of fear, inhibitory control and parent-rated activity level were associated to ADHD traits. However, all the three measures of activity level did not point at clear specific associations to ADHD, and autistic traits seem to somewhat influence this association. Lower soothability was associated, in the same direction, to both autistic and ADHD traits. Soothability concerns the rate of recovery from peak distress, excitement, or general arousal (Putnam et al., 2006) and is an important indicator of regulation. Our findings point toward a shared connection between this difficulty in regulation and later traits. However, the mechanisms behind these difficulties remains an open question.

We did not find support for the following hypotheses on specificity: lower positive anticipation and autistic traits, and higher rates of sociability, impulsivity, exuberance, lower cuddliness and ADHD traits in comparison to

autistic traits. We predicted that lower levels of inhibitory control would be associated to both autistic and ADHD traits. Here we found that lower inhibitory control was associated to ADHD traits, and not autistic traits. This might indicate that difficulties in inhibitory control is a specific early marker of ADHD traits, or, that inhibitory control difficulties in relation to autism emerge only later, or that in many cases, are explained by ADHD traits. Lower attentional focus has also been shown to be associated to both autistic and ADHD traits in recent studies (Visser et al., 2016), but we were unable to find any association between parent-rated attention focus and traits. In summary, our findings indicate specificity along with overlap in soothability in the associations between temperament and autistic traits and ADHD traits.

Study II

Using the Infant Sibling-Design to Explore Associations Between Autism and ADHD Traits in Probands and Temperament in the Younger Siblings

Background and Aims

The purpose of the current study was to use the infant sibling design to explore whether proband traits of autism and ADHD would provide information about the infant sibling's temperament. Phenotypic congruence between biological siblings with autism seem to be evident in domains such as language and adaptive functioning (Goin-Kochel et al., 2008). More recent work found that proband's autistic traits predicted diagnostic outcome in younger siblings at 24 months (Girault et al., 2020) and brain phenotypes related to the visual circuitry in infant siblings (Girault et al., 2022). Applying a familial trait approach, we were interested in exploring whether probands autistic and ADHD traits would be associated with the infant sibling's temperament at 9 months of age.

Method

A total of 216 infant siblings (n = 115 from BASIS and n = 101 from EASE) and their respective proband were included in the study. The IBQ-R (Gartstein & Rothbart, 2003) was used to assess infant temperament. Autistic traits were assessed by the SCQ (Rutter et al., 2003) and ADHD traits were measured by the CRS-3 (Conners, 2008). Age and sex of the siblings, infant developmental level and site were included and used as control variables in the analyses.

Results

Zero-order correlations indicated that autistic traits in the probands were associated with lower levels of approach, falling reactivity, cuddliness and soothability, and higher levels of fear in the infant siblings. Proband's ADHD traits were associated with higher activity levels in the infant sibling. Separate regression models were conducted with autistic traits and ADHD traits as predictors and infant temperament as dependent variable, and control variables. Proband's autistic traits were associated to lower levels of approach, and proband ADHD traits were associated to increased activity levels in the infant sibling (see Figure 1). Infant developmental level provided unique variance in the model with infant approach and site explained variance in the model with infant activity (b = -0.26).

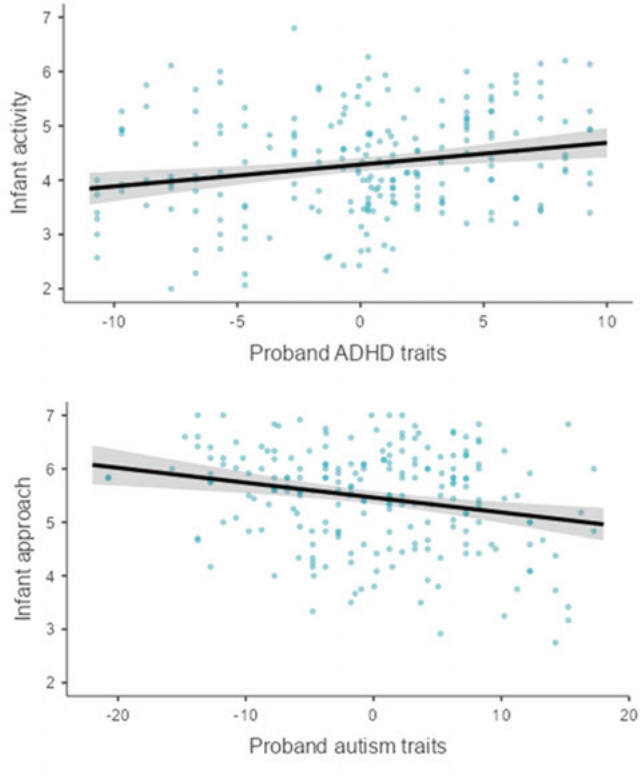

Figure 1. Associations between probands' ADHD traits and infant activity level, and between proband's autistic traits and infant approach, respectively.

Discussion

Proband autism and ADHD traits provided unique information about the infant sibling's temperament. Proband's autism traits were associated with

lower levels of approach while proband's ADHD traits were associated to higher activity levels in the infant siblings. Although the effects were small, we reason that these particular associations between siblings reflect shared familial effects, e.g., additive genetic effects. These findings add to the few, but accumulating, studies using quantitative proband traits as a proxy for accumulative liability. These findings support the hypothesis that temperament constitute an important aspect in early development, with both specific and shared aspect related to autism and ADHD traits respectively.

Study III

Deferred Gratification as a protective factor in the relation between autistic traits and adaptive skills

Background and Aims

Deferred gratification involves inhibiting a response in situations that evoke emotions or appetitive impulses. This self-regulation ability is used in many everyday tasks for children in pre-school age, such as waiting for your peers before eating or to take turns during play. Deferred gratification can be seen as part of executive functioning, but is often considered as a more emotionally, bottom-up driven process than other types of EFs (Metcalfe, 1999). Deferred gratification and EF are both key components of self-regulation (Diamond, 2013; Nigg, 2000) and predicts later positive outcomes, such as academic skills and pro-social behaviors. Children with autism and ADHD often struggle with deferred gratification, executive functioning and adaptive behaviour skills. Less is known about the specificity of these domains in relation to autistic traits and ADHD traits early in life and whether deferred gratification and strong EF skills might function as protective factors in the trait-adaptive behaviour association. The aim of this study was threefold. First, we examined group differences depending on type of family history, using three groups; FH-ASD, FH-ASD+ADHD, and FH-typical likelihood (TL), in EF performance, deferred gratification skills and adaptive behaviors. Second, by adopting a dimensional trait approach we studied whether associations between EF, deferred gratification and adaptive behaviors was specific to, or shared between, autistic and ADHD traits. And third, we examined if EF performance and deferred gratification skills moderated the potential associations between autistic and/or ADHD traits and adaptive functioning.

Method

Children with a family history of autism, a family history of co-occurring autism and ADHD, and a typical likelihood comparison group were participated

in the study at the age of 3 years (total $N = 77$). The children visited the lab during a full-day and took part in a 45-minute long session of behavioral tasks. The measures assessed in the lab consisted of 4 tasks used as a composite score to assess common EF and two tasks to assess deferred gratification. Adaptive behaviour was assessed by the VABS, and observed traits using the ADOS-2 and ADHD DSM-5 Rating Scale. MSEL was used to control for developmental level in FH-group comparisons.

Results

In contrast to children with FH-TL, children with FH-ASD and FH-ASD+ADHD had lower common EF and adaptive skills generally. Developmental level explained the differences in in adaptive behaviors but not in common EF. Deferred gratification did not differ between the groups. Related to our second question, after adjusting for ADHD traits, the correlation between autistic traits and common EF was small (*rho* = -.25), and did not reach statistical significance ($p = .06$). Similarly, the correlation between autistic traits and deferred gratification did not remain significant after controlling for ADHD traits, although there was a negative trend (*rho* = -.30, $p = .03$). Associations between autistic traits and the adaptive behaviour scale and subscales withstood control for ADHD traits (range between *rho* = -.39 to -.51, all ps < .003). ADHD traits and common EF remained significantly associated with a moderate effect (*rho* = -.37, $p = .004$), and similarly communication (*rho* = -.31, $p = .02$), but deferred gratification, adaptive behaviour total score, and socialization were not significant when autistic traits were partialled out. In relation to our third question we found that deferred gratification, but not common EF, played a moderating role in the association between autistic traits and adaptive behaviour, with a significant association at low, and moderate levels, but not at high levels of deferred gratification (see Figure 2 for simple slopes of these effects).

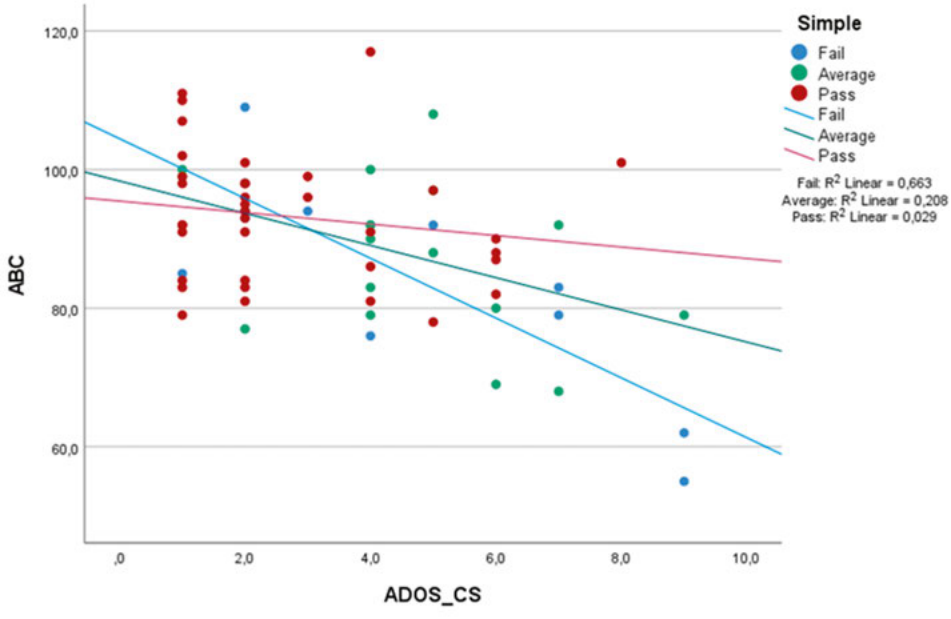

Figure 2. Moderation effect of deferred gratification in the association between autistic traits (ADOS CSS) and adaptive behaviors (Vineland ABC).

Discussion

These results suggest that children with FH-ASD or FH-ASD+ADHD have more difficulties in the cognitive and complex EF task in comparison to children with FH-TL. However, these groups did not differentiate on deferred gratification. This might suggest that, at a group level, more complex, cognitive tasks are more affected than the ability to defer a gratification. Indeed, there are two commonly used paradigms – choice and maintenance – to assess delay or deferred gratification. The choice paradigms involve choosing a smaller reward immediately, or wait to have a bigger reward (Mischel, 2011), and the maintenance paradigms involve a single trial measuring how long children wait for a reward. Here, we used the maintenance design due to the age of the children and to not complicate the task instructions. However, independent of group there seemed to be variation in performance of this task. Although we found a link between autistic traits and lower deferred gratification, this link did not seem to be specific to autistic traits but shared with overlapping ADHD traits. Lower levels of common EF were specifically associated to ADHD traits. Because strong ability to defer gratification attenuated the association between autistic traits and adaptive behaviors it may serve as a potential protective function for adaptive behavior challenges. As a result, improving the ability to defer gratification and self-regulation, could potentially improve adaptive functioning.

General Discussion

The overarching goal of this thesis was to examine the relation between early aspects of self-regulation and the emergence of co-occurring autism and ADHD traits, aiming to enhance our understanding of specific and shared mechanisms underlying these conditions. Autism and ADHD, like many neurodevelopmental conditions, emerge from multiple gene and environment interactions that influence the neurobiological systems even before birth (Rutter, 2011; Sounga-Barke & Halperin, 2010). Studying the early mechanisms contributing to the unfolding of these conditions is important for two reasons, i) from a basic science perspective, and ii) from a clinical perspective. These perspectives will guide this discussion. From a basic science perspective, it's important to untangle the early developmental mechanisms before autistic and ADHD traits emerge in order to increase our knowledge of their developmental roots. Research following children with a diagnosis of autism and/or ADHD have identified self-regulation difficulties, some which overlap across conditions and some of which seem more specific to either phenotype. However, our understanding of the etiology behind the phenotypic overlap between autism and ADHD is limited. This makes infant sibling studies invaluable as they provide an opportunity to study behaviors early in life in individuals that have a genetic predisposition towards later elevated traits of both autism and ADHD. From a clinical perspective, early identification may pave the way for improved care and support for these individuals and their families in need.

In the subsequent sections I will discuss theoretical implications of the findings from Study I-III. The discussion will center on two themes: 1) specificity and overlap in relation to temperament, and 2) EF and deferred gratification. The following sections will include a discussion on measurement, followed by clinical implications, limitations, and future directions. A summary of the main results from the studies are shown in Figure 3.

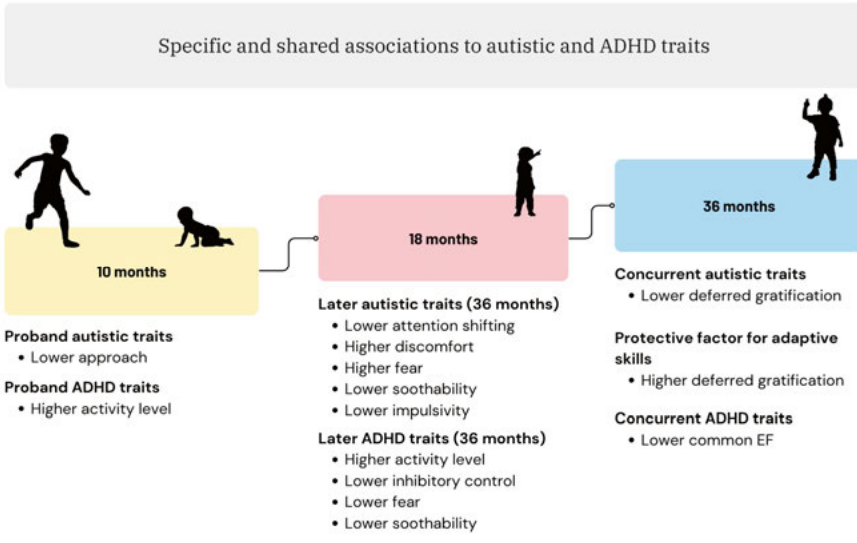

Figure 3. A brief summary of the findings.

In Study I, we found associations between temperament at 18 months and 3-years autistic and ADHD traits, with specific associations to each phenotype, but also some overlap. The temperamental aspects; lower level of attention shifting, increased discomfort, increased fear, lower impulsivity and lower sociability were specifically associated to subsequent autistic traits. In contrast, lower levels of inhibitory control, increased activity level, and decreased level of fear were specifically related to subsequent ADHD traits. Difficulty with soothability was found as a common temperamental feature for both autistic- and ADHD traits. In relation to our hypotheses that increased surgency/exuberance and activity level would be specifically related to ADHD traits, this was only partially supported. Out of the parent-rated temperamental surgency scales, activity level was the only scale that was significantly related to subsequent ADHD traits. Impulsivity, and high-intensity pleasure, were elevated in relation to later increased ADHD traits, although not significant. Observed exuberance and observed activity level based on the bubbles-task did not seem to explain any of the variance in later ADHD traits, or autistic traits. Interestingly, the accelerometer activity level predicted ADHD traits at 3 years, but not after controlling for autistic traits. This finding is interesting since this is one of the first few studies that have used accelerometer activity level as a predictor of later autistic and ADHD traits. Indeed, we found an association to later ADHD traits in bivariate correlations, but this did not hold after controlling for autistic traits, which might indicate that activity level is not specific to ADHD, a finding that is not in line with parent-rated activity level, which indicate specific associations to ADHD traits, and not to autistic traits.

In Study II, we found several specific correlations across siblings, particularly between proband's autistic traits and infant temperament traits. However, in regression analyses, while accounting for overlapping ADHD traits and other control variables, only a few and modest associations remained. Proband's autistic traits were related to lower levels of infant sibling's approach behavior, whereas proband' s ADHD traits were related to increased activity level in their 10-month-old infant siblings. We proposed that these particular associations reflect shared familial effects, which include both genetic predispositions and environmental influences within the family. While proband's autistic traits were associated with infant approach, infant's developmental level significantly contributed to levels of approach, suggesting that infants who are more developmentally mature or advanced seem to approach new situations at a higher speed.

Finally, in Study III, we found that performance on common EF differed between family history groups. Children with FH-TL performed at a higher level compared to the other two groups, but with no difference between children with FH-ASD or FH-ASD+ADHD. Performance on deferred gratification did not differ between any of the FH-groups. Autistic traits were associated with lower performance on deferred gratification, but this association did not hold after controlling for overlapping ADHD traits. Autistic traits were associated with lower levels of adaptive behaviors across subscales, but, unexpectedly not with the communication scale. ADHD traits were associated with lower levels of communication and socialization, but not with daily living skills. We found a strong association between ADHD-traits and lower EF performance, but not with deferred gratification. Interestingly, deferred gratification moderated the association between autistic traits and adaptive behaviors, such that lower scores on deferred gratification increased the association whereas high scores on deferred gratification decreased this association. This suggests that strong ability to defer gratification seem to act as a protective factor for adaptive behaviors given autistic traits.

Specificity and overlap in the associations between temperament and ASD and ADHD traits

Approach and activity level

Study I and II demonstrate specific associations between temperament and each of the two phenotypes, but also some overlap. A consistent finding across both studies was that approach at 18 months uniquely predicted 36-month autistic traits (Study I), and at 10 months, infant approach was specifically

associated with probands' autistic traits (Study II). Although we found that parent -rated activity level at 18-months was specifically linked to 36-month ADHD traits (Study I), and parent-rated 10-month activity level was uniquely associated with probands' ADHD traits (Study II), the correlation at 10-months was low, and activity level as assessed by accelerometers was not associated to ADHD traits after controlling for overlapping autistic traits. These findings raise questions regarding the specificity of activity level to ADHD traits. One possible explanation for the low correlations observed at 10 months could be attributed to the across-sibling design. Despite siblings sharing approximately 50% of inherited gene variants (Visscher et al., 2006), environmental factors and additive genetic effects also contribute to variations in siblings' traits. This suggests that the design itself does not allow for finding strong correlations, and at the same time indicates that caution needs to be taken in drawing strong conclusions about this finding. A question related to the accelerometer-measured activity level at 18-months is if we also capture stimming behaviors which is common in autistic children. In conclusion, activity level seems to be more closely linked to ADHD traits but seem to also be somewhat explained by autistic traits, at least in the population of infant siblings.

A large body of research (Visser et al., 2016) suggest a low behavioral approach profile in autistic children from around the age of 2. Considering the large overlap between Autistic and ADHD traits, our findings add to this literature, showing that this profile is specific to autism, and not to ADHD, and additionally, that lower approach is apparent at an earlier age, and can be predicted by probands' autistic traits, from around 10 months of age. Differences in temperament traits might represent different developmental mechanisms underlying autism and ADHD, respectively. For instance, we found that not only probands autistic traits, but lower developmental level, was related to lower infant approach (Study II). In addition, different mechanisms may be at work, e.g., lower cuddliness and lower soothability in relation to autistic traits might stem from differences in sensory perception (Baranek et al., 2013). Whereas the soothability-scale at 10 months involve the caregiver's ability to calm down the infant, this scale at 18 months involve questions about the rate of the infant's own ability to recover from peak distress and excitement. Lower soothability at 18 months were associated to both autistic traits and ADHD traits respectively, explaining unique variance. This suggests that different underlying processes may contribute to why children with either symptom cluster experience difficulties in soothing.

Attention shifting, focusing and orienting

Low levels of attention shifting at 18 months were associated with autistic traits at 3 years of age, in line with the hypothesis in Study I. However, in

contrast to what we expected, we did not find a link between lower attentional focus and later traits of autism or ADHD. A large body of research indicate disrupted attentional processing, including top-down attentional control, in relation to both autism at a behavioral (Murray et al., 2005) and neural level (Fan, 2013), and as a predictor of subsequent ADHD traits (Frick et., 2019). However, attentional focusing seem to be fluctuating over development and we might need to map developmental pathways to properly capture the heterogeneity coupled with attentional focusing in relation to autism and/or ADHD. Hendry et al., (2020) applied a data-driven approach using Latent Class Analysis (LCA) to examine the developmental trajectories of attentional control in infant siblings at several time-points (10, 15 and 24 months) and autistic traits, ADHD traits, and adaptive behaviour at 36 months of age. Most children ended up in a normative developmental class, showing increased ability to focus over time. Unlike the normative class, a small percentage (< 10 %) exhibited attenuated attentional control between 10 and 25 months. This plateaued growth in attentional control was linked to higher traits of autism and ADHD, as well as decreased adaptive functioning at 3 years of age. This study points to the importance of using a developmental approach to the study of attention to better understand the heterogeneity, timing and onset of these processes. Based on Hendry et al., (2020), atypical attentional control may serve as a shared feature for both autism and ADHD. However, they also found a group with a consistently low attention focus profile that was associated to elevated ADHD traits. Thus, ADHD traits were found to be linked to the plateaued growth class and to the early disruption class. Hendry and colleagues suggested that this might depend on differences in the two scales used at the early versus late assessments.

In Study I, we found relations between decreased attention shifting, but not attention focus, and subsequent autistic traits, but not with ADHD traits. In Study II, we did not find any association between proband's traits and the infant sibling's attention (as measured by the scale "duration of orienting"). Taking a closer look at the scales used to assess attentional shifting and focus (18 months) might give some clues to differences in results. The attentional focus scale asks about duration of playing with a favourite toy, or playing alone, or playing with e.g., blocks, that require focused attention. On the other hand, the attention shifting scale include e.g., "When playing outdoors, how often did your child look immediately when you pointed at something?", another question concerns the ability to pay attention to the parent when called at, and "while talking with someone else, how often did your child easily switch attention from speaker to speaker?". Although these examples from both scales illustrate the ability to shift attention from one activity/task to another, there might be qualitative differences, or motives, for why a child might not do so. For example, a joint attention difficulty has been pointed out as a fundamental feature of the early social communication differences seen in autistic children

(Mundy, 1986; 2003), and other's gaze have a reduced influence on object processing in autistic children compared to typically developing children (Falck-Ytter et al., 2015; Thorup et al., 2017). The attention shifting scale seem to reflect some of these basic joint attention skills that might be lagging behind in infants with later autistic traits, which might explain part of the differences in findings.

Lastly, duration of orienting at 10 months, which has been associated with later autistic and ADHD traits in conventional within-individual designs, was not observed in Study II. This discrepancy might be due to the between-sibling design that employed proband traits and infant sibling temperament. If that depends on differences in the Gene X Environment interactions related to the within-individual design or differences in shared familial factors warrants further examination.

Temperament – antecedent, endophenotype, or a consequence?

Relating back to the theoretical models of temperament and developmental psychopathology (Nigg, 2006; Martel et al., 2014) proposing that temperament and neurodevelopmental conditions lie on the same spectrum (spectrum/common cause), or represent an early vulnerability factor in the development of these conditions (vulnerability model). According to the spectrum model, temperament can be seen as a subclinical manifestation of psychopathology. That is, temperament at extreme levels of the normal distribution is synonymous to psychopathology (Egger & Arnold, 2006). The vulnerability model on the other hand also suggest strong concurrent correlations between the two domains but suggest that temperament contributes to the heterogeneity in psychopathology (Nigg et al., 2004), influencing the course of pathology (Martel et al., 2016). Importantly, these two models are not mutually exclusive, suggesting that the truth may not lie in one or the other. Although both of these models have gained some support, the spectrum model, as opposed to predisposition/vulnerability model seem to more closely explain the temperament-psychopathology association (De Bolle et al., 2012, 2016; Martel et al., 2014). In addition, twin studies show that a substantial proportion of the genetic influences underlying temperament are shared with psychopathology (Gjone & Stevenson, 1997). While our studies did not directly evaluate the vulnerability model, our findings do align with the spectrum model as reflected in the strong associations between approach and activity level, and autism and ADHD traits at a very early age.

Nigg's hypothesis (2004; 2006) states that the temperamental aspects of effortful control and surgency, represent two separate pathways leading to ADHD. This idea has been supported in several studies (Frick et al., 2019;

Brocki et al., 2019; Rydell et al., 2003). Thus, motivated by theory and empirical findings, in Study III we wished to examine if exuberance was uniquely linked to subsequent ADHD traits, and not to autistic traits. However, our findings did not support the hypothesis. Several potential explanations could account for this. First, the aforementioned studies used samples of older children, suggesting that our 18-month-olds might not yet exhibit pronounced exuberance. Another possibility is that our "bubble task" may not have been sensitive in capturing exuberant behaviors. Further, ADHD traits potentially manifests differently in children with a family history of autism in comparison to children with a primary diagnosis of ADHD. Finally, there is a difference in showing increased levels of surgency/exuberance in situations where it "fits", than showing the same behaviour in other types of situations where it might be inappropriate. As suggested by Rydell et al (2003) the problem might lie in the regulation of these strong positive emotions, and this particular task was not coded for regulation.

An interesting question raised by Lahey (2004) was: "if temperament is related to almost all forms pf psychopathology why does not all end up in the same domain or display the same symptoms?". This is a relevant question, and the answer may partly lie in the complex developmental and bi-directional interactions between predisposition and environmental influences, with some predisposed individuals being more susceptible to certain environmental influences. While temperament provides a foundational understanding of an individual's predisposition towards various forms of psychopathology, it represents just one potential piece of the puzzle. The dynamic interplay of genes, temperament, environment, and individual experiences creates a myriad of possible outcomes, which can explain the diverse manifestations of conditions from similar temperamental vulnerabilities, such as difficulty in soothing and regulation as found in Study I and II. Whether these traits in turn, represents primary or secondary effects is another question to ask when it comes to temperament and the interplay with the key features of autism and ADHD. For instance, are certain temperament traits isomorphic to the symptoms of a condition (primary effect) or are they a consequence of symptoms or a condition (secondary effects). When it comes to infant sibling studies we are hoping to be able to assess even earlier effects, such as antecedents of a later symptom cluster. Indeed, temperament can both be seen as an antecedent marker, due to the early appearance but also as primary (e.g., Nigg, 2006) and as a secondary effect. For example, regulatory soothing difficulties (Study I and II) precedes the condition at an early stage, but may be exacerbated by the unfolding of autistic or ADHD traits, which then would represent a consequence, resulting in bi-directional cascading effects. These effects do not only concern the ability to regulate, but any temperament deviance. Child temperament has a reciprocal influence on parenting behaviors, and similarly with siblings and peers. For instance, certain temperamental traits have been linked to specific

types of parental responses during mother-infant interactions (McClowry et al., 2008).

Although temperament may be a key player in explaining heterogeneity in developmental psychopathology, only a few children with extreme temperament result in a diagnosis (Kagan & Snidman, 2004). A recent study tested whether temperament could predict, at an individual level, the likelihood of receiving a later autism diagnosis in infants with elevated likelihood of autism (Pijl, et al., 2019). However, temperament had poor predictive power and the authors suggested that temperament was not a valid specifier for who go on to receive a diagnosis of autism. Yet, EL-ASD could not be identified accurately, whereas EL infants without autism could. This underscores the multiple pathways hypothesis and the necessity to identify moderating factors during development.

Taken together, temperament might be viewed as a set of characteristics that both precedes and is sometimes the same as autism and ADHD, and may act as a consequence of cascading effects, creating either possibilities for learning, or limiting some of those learning opportunities. Despite this complex path of interactions, the studies in this thesis suggest that temperamental traits are both differentially linked to either autistic or ADHD traits, particularly in reactive components, and with some overlap, particularly in regulation. This suggests the potential for both specific and shared biological origins for these trait domains. While we found shared difficulties in soothability, the mechanisms driving this vulnerability in autism and ADHD might differ. Hence, outwardly manifested behaviours might appear similar, yet have different biological underpinnings.

Heterogeneity in Executive Functions and Delaying Gratifications

In Study III we found a difference between the FH-ASD/ADHD and FH-TL in complex EF tasks but not on deferred gratification. We suggested that children with a family history of both autism and ADHD may, on a group level, exhibit a developmental delay in tasks that necessitate more advanced executive function skills. This is in contrast to tasks that required a simpler (in the sense of a one demand task) inhibiting or postponing an action as in the deferred gratification composite. Although theoretical accounts have incorporated EF and delay of gratification as core components in both autism (Pennington & Ozonoff et al., 1996) and ADHD (Barkley, 1997; Sonuga-Barke, 2002), empirical studies have not yielded a clear picture of the specificity in EF and delay deficits in relation to autism and ADHD. Some of these mixed findings depend on differences in measurement, with parent-reports indicating

more EF difficulties in real-world settings than behavioral assessments in autistic children. However, we also proposed that a potential interpretation of these findings may be linked to the conceptual distinction between "hot" and "cool" EF. "Hot" EF tasks, like deferred gratification, are suggested to engage motivational processes that are predominantly bottom-up. On the contrary, "cool" EF tasks, as represented in our common EF composite, primarily involve top-down processes. In experimental tasks, inhibitory control (as measured by the stop/signal task) and delay of gratification are shown to independently contribute to ADHD traits (Sonuga-Barke et al., 2003), indicating that they depend on different underlying processes. Nevertheless, the differentiation between hot and cool EF is not so clear-cut, but is better viewed as existing on a continuum. The differentiation between what is more cognitive and emotional-eliciting may depend on individual differences and contexts (Welsh & Peterson, 2014). For example, a child who has recently had a snack may not be as tempted by the smarties in our delay task. Likewise, a school-aged child may perceive a math problem as more cognitive or anxiety-inducing. Notably, lower scores on complex EF was specifically associated to ADHD traits. While our initial hypothesis was based on the literature suggesting that inhibition is a core difficulty specifically related to ADHD (Sonuga-Barke, 2002) would play out in lower deferred gratification. Instead, we found that lower common EF was specifically associated to ADHD traits.

Central to Study III was the idea that executive functioning skills could function as a protective factor in relation to adaptive behaviors. Corroborating this idea, our findings showed that deferred gratification moderated the association between autistic traits and adaptive behaviors. We suggested that this finding points towards a possible protective effect of higher levels of deferred gratification in children with pronounced autistic traits, concerning adaptive behavior. Johnson (2012) proposed that children with a genetic predisposition or a family history of autism, with robust EF skills, may demonstrate better neural adaptability, consequently reducing the likelihood of a subsequent diagnosis. The emphasis of our study on adaptive behaviors, instead of autistic traits, as an outcome measure provides a slightly different perspective to the proposal of Johnson (2012). However, given that adaptive skills provide a more functional perspective of everyday living than a diagnosis or symptoms, our findings may be more closely related to practical use and clinical implications. Finally, the moderation was not explaining any difference in the ADHD trait-adaptive behaviour association. This can be interpreted in at least two ways. First, it might be caused by the relatively low correlations between ADHD traits and the adaptive behaviour scales, and second, ADHD is rarely diagnosed until later and we might be difficult to detect these interactions in this particular sample.

In sum, EF and deferred gratification seem to show different associations to concurrent autistic and ADHD traits in 3-year olds, and in particular the ability to defer gratification might constitute a buffering factor for adaptive behaviors, but these findings need to be further replicated and corroborated.

Methodological implications

Measuring behaviors is a complicated matter and most measures only capture some, or a particular aspect of behavior. Study I included both parent- and teacher-ratings, observations and accelerometers. In Study II we relied on parent-ratings to assess behaviors, whereas Study III used different types of measures such as clinical assessments and ratings, interview-data with caregivers and experimental behavioral measures assessed in the lab. While each of these measures have a potential in capturing certain aspect of a child's behavior there are also limitations with each. Parent-ratings are a valuable source of information of young children's traits across different situations and contexts, due to the parent's in-depth knowledge of their child. However, all types of ratings are filtered through subjective evaluations and can depend on mood, ability, memory, comparisons to other children in the family and so forth. Complementing ratings with what is often called "objective" measures, can offer a more comprehensive view of the child's behavior. In Study I we used accelerometers to assess activity level during a full day at the lab. We measured the 3-D acceleration of the child's arms, which is a very rough measure of overall activity level, and limited to the movement of the arms. Self-stimulating behaviour, known as "stimming", is common in autistic children and includes arm or hand-flapping, rocking, jumping, spinning or twirling. We were not able to identify the type of activity of the child wearing the accelerometers. Reetzke et al. (2022) identified increased accelerometer activity levels in autistic children and children with ADHD concerns, proposing activity level as a transdiagnostic marker. However, it is still early to make any strong claims about this type of rough measure and more research is needed to answer the more detailed questions, such as disentangling different types of movement and motor activity.

Clinical Implication

It is important to note that when interventions or support is mentioned throughout this thesis it's not about removing symptoms or changing the autistic individual to appear more "typical" or "normal" (which unfortunately has been the case in some earlier therapies or prevention efforts), but about helping children to flourish and to strive, and importantly to find strategies for coping with difficult situations. What is distressing for a specific child is

highly individual, but early identification and early support help children to get on the right track. Self-regulation interventions involve giving children tools to navigate and manage situations that becomes overwhelming. The more specific clinical implications of the findings from the three studies included in this thesis are primarily indirect and must be taken into consideration with other findings on early behavioral indicators of autism and ADHD, and most importantly in combination with intervention studies that directly tests the effects of targeted interventions.

Studies of infant siblings offer some important perspectives for developing early intervention programs. First, by identifying and understanding early developmental delays or deviances, we can tailor interventions to address specific early-onset challenges in self-regulation. Another, perhaps more important factor, is to explore factors that promote resilience or promotes well-being and a high quality of life. This could mean enhancing the quality of interactions between infants and their caregivers, as discussed by Wan, Green, & Scott (2019), which is a key aspect for developing self-regulation. EF and deferred gratification, when strengthened, can potentially alter early neurodevelopmental paths, as outlined by Johnson et al. (2021), and adaptive behaviors as proposed by the findings in Study III. By reinforcing these adaptable traits, interventions could act as buffering or protective factors, guiding a child's growth towards the best possible outcome (Sonuga-Barke 2021). Intervening in development also serve a theoretical purpose since it, finally, is the only way in which *causal* developmental theories of autism can be validated (Gliga, Jones et al., 2014).

Limitations

There are several limitations that merit consideration. One central question in psychology in general and also central to this thesis, is what we are genuinely capturing with our measurements. Parent- and teacher-ratings of behaviors, observations, clinical assessments, interviews, accelerometer activity, and behavioral assessments in the lab each bring advantages, but also drawbacks and potential biases. Parents who rate their children's behaviour provide information based on various situations across different contexts, but these ratings are influenced by reliance on memory, and biases which cause both over- and under-report of a child's behavior. Although we used different types of measures for predictors and outcomes in Study I and Study III, in Study II we used parent-ratings for both siblings. These ratings were done at different time-points, and in some cases by different caregivers, which might have reduced some of this shared methods bias. Thus, while parent ratings are invaluable source of infant behaviors, they should ideally be used in combination with other data sources to ensure a more comprehensive and accurate

understanding of particular behaviors. In addition, more detailed behaviors, particularly attentional processes, might be better captured with methods such as eye-tracking.

A particular limitation in Study III is its reliance on concurrent data. For a more accurate assessment of the associations and the moderation effects, longitudinal analyses would be more suitable. Additionally, the evaluation of ADHD traits at the age of 3 might not be entirely reliable and a follow-up at a later age would yield information of the stability and longitudinal associations.

Anyone who has spent time with a 3-year-old may be well familiar with their rapid mood swings between bursts of joy and sudden tantrums, and between being high motivation and an unexpected loss of interest. Thus, selecting suitable tasks for young children requires careful considerations including several challenges. Given the diversity in attention spans, language skills, and general knowledge among children, the tasks need to be easy to understand and intuitive. This means minimizing verbal instructions and complicated actions. The tasks should tap into foundational concepts that are universally recognized by children of this age group with diverse backgrounds and developmental levels (Carlson, 2005). Although we intended to choose developmentally sensitive and primarily nonverbal tasks, suited for 3-year olds, many studies indicate a discrepancy between EF as measured in the lab (as in Study III) and EF as assessed by parent-ratings. In addition, using EF processes in a laboratory setting might be very different from using EF in real life.

Understanding the development of a behavioral repertoire, which results from interactions with the environment and interpersonal transactions, necessitates a comprehensive approach. This approach is essential for capturing the processes of developmental change and the factors driving these changes. In Study I and II, follow-up outcome data and a typical likelihood comparison group was lacking which limits generalizability. Self-regulation is heavily dependent on social interaction. Although associations emerged between certain temperament ratings and autistic and ADHD traits, moderating factors that might influence behaviour over time, including the parent-child interaction or other important social interactions over time remains unanswered.

Finally, a limitation that needs to be highlighted is the need to consider the findings in Study I-III in the context of the infant sibling population. Although this design offers a way to examine early markers before symptoms emerge, we have only included children with heritable autism, and ADHD. This means that we are examining so called multiplex families (with multiple affected children), but not simplex autism (one affected child). There are some differences between multiplex and simplex in terms of genetics, with simplex autism more associated to de novo mutations and generally lower developmental

level than in multiplex autism (Dissanayake et al., 2019). Recruiting participants based on familial likelihood may introduce bias, as parents with prior experience of autism in the older child may enrol younger infants more actively in research studies (Herlihy et al., 2015; Zwaigenbaum et al., 2007) but may also be more familiar with the early signs of the condition and awareness of early support. Growing up in a family where one child has autism might also benefit the younger sibling, potentially leading to more positive outcomes (Zwaigenbaum et al., 2007) since parents may already be familiar with early interventions, influencing their parenting styles and interactions—resources that may not be as readily available in simplex families.

Future Directions

In the three studies included in this thesis, we may draw some conclusions about early aspects of self-regulation, such as how reactive and regulatory skills relates specifically to certain traits of autism and ADHD, and it is reasonable to imagine that these early traits constitute potential markers that push development towards certain trajectories. However, this question needs to be followed-up in future studies, together with many other questions that haven't been answered with the approach taken here. For example, temperament traits do not exist in isolation, but are a result from gene-environment interactions, similar to more higher-level executive functioning skills. Although some of these early self-regulatory behaviors might seem atypical, or different, it is important to note that many behaviors are functional and we should thoroughly investigate the context in which these behaviors appear to evaluate the functionality of certain behaviors. An interesting way to go forward would be to integrate a systemic approach (Bronfenbrenner, 1977) and track the temporal dynamics of the child's changing behaviors in relation to the context, such as the home-environment and the preschool (McClelland et al., 2018). This would provide information not only to how a child acts, but *inter*acts, with the environment. Most studies on self-regulation, including the three studies in this thesis, measure behaviors away from its natural context, such as in a lab, or are filtered by caregivers or teacher reports. However, a child acts and reacts quite differently in different contexts and situations. If we were able to complement the picture of a child's temperament with observations in real-life situations (and not in the lab), we could much better estimate how the child is actually behaving in their natural environment with the typical streams of information and interactive exchange with other individuals. Executive functioning is one such area where the lab-setting and parent-ratings of real-life executive functioning of their child not always match (Doebel, 2022). The highly controlled lab environment with low conflicting stimuli might decrease task demands in comparison to everyday executive functioning whereas ratings might miss detailed information about a child's specific abilities. Thus,

assessing executive functions with observations in different situations in real life would be a way to still gain some control over specific abilities while increasing ecological validity. There have been some recent attempts to increase ecological validity in neurodevelopmental research moving towards a better understanding of underlying mechanisms and multimodal assessments (Wass, 2021) and moving away from the lab to measure more naturalistic behaviors (Wass & Jones, 2022).

Another interesting avenue is how future studies will integrate a neurodiversity approach with regards to thinking about conceptualization, language use, and create new research questions. For example, the theory about double-empathy was a result from insights brought forward by autistic researchers who questioned the assumption that autistic individuals have poor theory of mind, and instead brought forward a hypothesis about double empathy difficulties between individuals who do not share similar perception. Although this theory has not yet been thoroughly tested to draw any firm conclusions, a change in perception of what is an individual difficulty versus a difficulty that stem from social interactions with dyads and groups of individuals may allow for new avenues, and hopefully reduce stigma.

A study by Ros & Graziano (2019) found that different temperamental profiles predicted response to a behavioral intervention, over and above autistic or ADHD symptomatology. Subgrouping by self-regulation profiles (similar to Nigg's approach), instead of traditional diagnostic categories or symptoms seem to be a way forward to better understand heterogeneity and overlap across conditions and finally to improve interventions. Another way would be to incorporating a multiple pathway perspective (e.g., Frick et al., 2019) and a longitudinal perspective of infant siblings, examining how self-regulation abilities evolve over longer time frames and how these changes correlate with the development of autistic and ADHD traits. This would provide insights into when and how interventions might be most effectively applied, but also how early aspects of self-regulation in the early infant and toddler years unfolds over time, up to adolescence.

Given the inherent genetic predispositions of infant siblings, examining environmental factors that interacts with genetic risks is important. This includes studying the impact of different environments, educational settings, or socioeconomic conditions on the development of self-regulation and subsequent autism or ADHD outcomes. Clearly, there is a need to use larger samples and to broaden the perspectives and include populations with other types of psychiatric conditions to further assess specificity and overlap.

The field of self-regulation stem from different research traditions using different terminology which has hindered progress, however there are some good

examples of initiatives intending to converge disparate research traditions (see Nigg, 2016). Future studies may continue to build on the attempts to further unite overlap and divergence in concepts and measures. In the current thesis, I conceptualized temperament, executive functions, and deferred gratification as "aspects of self-regulation", however there are clear differences across these aspects, and the "self" in self-regulation may seem as an overstatement in the first years of life when regulation is most often co-regulated by a parent or caregiver. Reactive and regulatory components of temperament are measured separately in Rothbart's model (Rothbart, 1981), but some reactive components, such as fear which is both regulated and regulating, including the inter-connectedness between reactive and regulatory processes make disentangling these processes at a behavioral level difficult. To be able to fully measure this type of autonomic responses and proposed regulation of arousal using other types of physiological and biological measures is essential. But a parent's response (co-regulation) should be similarly recorded. During a stress-response (e.g., fight or flight), the body reacts by physiological changes affecting heart-rate, pupil dilation, eye gaze (Warnock et al., 2016), and neurological processing (Burgess & Smith-Chant, 2017). Pupil contagion is linked to increased arousal related to both pleasant and unpleasant events and reflects arousal linked to increased sympathetic activity (Bradley et al., 2008). Findings show that even infants dilate their pupils in response to others dilated pupils (Fawcett et al., 2017). Using eye-tracking measures on both caregiver and infant could potentially lead to more insights into the dyadic synchrony, and whether early aspects of self-regulation, such as soothing difficulties, is affected by differences in these types of synchronous, or asynchronous, patterns.

Historically, research on autism and ADHD has been male-centric due to higher male:female ratio. However, recent studies emphasize that females with autism and ADHD present differently than males. For instance, girls often camouflage their symptoms, leading to under-diagnoses or mis-diagnoses. Girls with ADHD are more often diagnosed with a primary inattentive profile than hyperactivity, however it is still unclear why and how these differences emerge. In the studies included in this thesis we were unable to examine differences between girls and boys, but supposedly some temperament traits, e.g., activity level and frustration levels, may appear differently in girls than in boys, similarly the behavioral profiles (EF, deferred gratification) would be interesting to examine further.

Conclusions

In this thesis, I focused on the early aspects of self-regulation by means of temperament and executive functioning to better understand the development

of autism and ADHD. The findings underscore the associations between temperament, EF, and the manifestation of these conditions. Particularly, the studies shed light on how temperament may indicate both specific, but also common, associations to autism and ADHD, whereas the ability to defer gratification may serve as a protective factor in the relation between autistic traits and adaptive behaviors. The findings indicate the complexity and the heterogeneity in, and across autistic and ADHD trait domains. The early associations between temperament and autistic traits, but only weak and few associations to ADHD traits, may be a result of the specific sample, or the more protracted development of ADHD traits. While this exploration has provided some insights into possible specific and overlapping self-regulation features, it also underscores the need for continued research, especially in understanding the distinct and shared biological underpinnings of these conditions. But furthermore, more details about if, and how, temperament may push and potentially affect developmental trajectories. For future research, interesting avenues include incorporating different moderators and mediators in the associations between early temperament and subsequent traits, more properly build on the RDoC framework and using more ecologically-valid and holistic approaches are some suggestions moving forward.

Summary in Swedish

Hur vi reagerar och reglerar våra emotioner, beteende och handling är viktiga aspekter av självreglering. Även om självreglering anses vara top-down styrt och involvera komplexa och viljestyrda processer, utvecklas självreglering tidigt, redan i spädbarnsåldern. Tidiga tecken på självreglering kan vara att barnet suger på fingrar, eller tittar bort, eller kallar på en förälder för att reglera upplevelser. Genom att undersöka temperament, som både består av reaktivitet och reglering, kan vi tidigt mäta barns tendens att reagera på stimuli (både inre och yttre) och att reglera aktivitetsnivå, upprymdhet eller negativa emotioner. Autismspektrumtillstånd (AST; autism) och Attention-Deficit/Hyperactivity Disorder (ADHD) är två av de vanligaste diagnoserna hos barn idag. Autism innebär svårigheter med social kommunikation, och repetitiva och begränsade intressen och beteenden. ADHD har tre kategorier, i) hyperaktivitet som primär svårighet, ii) ouppmärksamhet som primär svårighet, iii) kombinerad typ. Det är två tillstånd med en komplex etiologi, som utvecklas genom interaktion mellan genetisk predisposition och miljömässiga faktorer som börjar redan prenatalt och fortgår över utvecklingen. Autism förekommer hos ca 1 % i den generella populationen, och den höga ärftligheten innebär att yngre syskon till barn med AST har ca 20 % sannolikhet att själva få autism, eller andra relaterade utvecklingssvårigheter. Autism och ADHD samvarierar inom individ, genom att ha drag av både autism och ADHD, och även mellan individ, som innebär att inte bara autism, men även ADHD, är vanligare i en familj med en (eller flera) familjemedlemmar med autism. Svårigheter med självreglering är gemensamt hos barn med autism och ADHD, men det finns även vissa aspekter som skiljer dessa åt. Idag har vi en god forskningsgrund att stå på när det gäller barn med autism och ADHD, men det saknas forskning kring den tidiga utvecklingen av dessa tillstånd. För att veta mer om hur olika drag och symptom utvecklas behöver vi följa barnen från ett tidigare tillfälle, redan innan symptomen är etablerade. Tidiga interventioner och tidigt stöd till barn med funktionsvariation och deras familjer utgör en viktig grund för att främja goda relationer, en positiv utveckling och god livskvalitet. Men för att utveckla effektivt och välgrundat stöd behöver vi kunna identifiera och förstå vilka mekanismer som är gemensamma och vilka som är specifika för autism och ADHD. En ytterligare dimension handlar om hur autism och ADHD är relaterade, är det två separata tillstånd med vissa överlappande utvecklingsvägar, eller ses autism och ADHD bäst som en kategori? För att komma närmare

det svaret behöver vi undersöka specifika och överlappande faktorer i den tidiga utvecklingen, då det är lättare att försöka särskilja vad som föregår symptom och inte är en konsekvens av symptomen i interaktion med omgivande miljö.

I Studie I undersökte vi sambandet mellan yngre barns temperament vid 18 månader och autistiska respektive ADHD symtom vid 3 års ålder. Ett av de vanligaste sätten att mäta barns temperament är genom föräldraskattningar. För att få en mer omfattande bild av barnets beteende adderade vi observationer samt ett fysiologiskt mått på aktivitetsnivå (genom så kallade accelerometrar, som fästes på barnens handleder). Vi kunde urskilja vissa tydligt specifika associationer mellan temperament vid 1,5 års ålder och 3 års symptom. Lägre sociala beteenden och lägre grad av impulsivitet, ökad rädsla och obehag (eng: *discomfort*) samt minskad förmåga att skifta uppmärksamhet, kopplades specifikt till autistiska symtom vid 3 år. Högre impulsivitet var marginellt associerat till ADHD, likaså aktivitetsnivå mätt med accelerometrar. Svårigheter med att reglera sina emotioner och sitt beteende efter en situation av stark stress (eng: *soothability*) relaterade till både autistiska symtom och ADHD symtom vid 3 år, vilket visar på att reglering är en gemensam sårbarhetsfaktor för autism och ADHD. Det finns fortfarande frågetecken kring de bakomliggande mekanismerna för dessa svårigheter och det är troligt att orsakerna bakom gemensamma regleringssvårigheter beror på olika mekanismer hos barn med respektive tillstånd. Vi fann inte stöd för vissa hypoteser om specifika samband, men våra resultat pekar på både särdrag och överlapp mellan temperament och autistiska respektive ADHD symtom.

Syftet med Studie II var att undersöka om det äldre syskonets autistiska och ADHD symtom predicerade småsyskonets temperament vid 10 månader. Tidigare forskning har visat att autistiska syskon ofta delar vissa gemensamma drag inom områden som språk och anpassningsförmåga. Autistiska symtom predicerar diagnos hos det yngre syskonet vid 2 års ålder, samt relaterar till skillnader i hjärnaktivitet som kopplats till visuellt processande vid 6 månader. Det här visar på att ärftlighetsfaktorer inte enbart handlar om symtom-kluster utan även om så kallade endofenotyper, dvs olika beteenden eller drag som är närmare kopplade till specifika gener än diagnosen i sig, såsom särskilda temperamentsdrag. Totalt 216 syskonpar från två olika kohorter (Early Autism ADHD of Sweden; EASE, samt British Autism Infant Sibling Study; BASIS) ingick i studien. Det äldre syskonets autistiska symtom relaterade till en minskad benägenhet av närmande-beteenden hos småsyskonet (eng: *approach*) medan ADHD symtom var associerade med högre aktivitetsnivå hos det yngre syskonet. Vi kontrollerade för syskonens ålder, kön och utvecklingsnivå, samt kohort (vilket kan spegla eventuella kulturella skillnader). Det yngre syskonets utvecklingsnivå förklarade även en del av variansen i närmande-beteenden, med högre utvecklingsnivå relaterat till mer närmande-beteenden. En

rimlig förklaring skulle kunna vara att motorisk förmåga och kommunikation är viktiga för närmande-beteenden. Även om effekterna var små, tänker vi oss att dessa samband mellan syskon återspeglar dels den delade familjemiljön och dels additiva genetiska effekter. Resultaten från Studie II bygger vidare på de få studier som undersökt det äldre syskonets symtom för att uppskatta sannolikheten för vissa egenskaper, t ex endofenotyper, hos det yngre syskonet. Resultaten stödjer hypotesen att temperament är en viktig faktor i den tidiga utvecklingen, med både specifika och gemensamma egenskaper relaterade till autistiska respektive ADHD symtom.

Studie III fokuserade på exekutiva funktioner och särskilt förmågan att skjuta upp belöning (eng*: deferred gratification*), vilket handlar om att kunna vänta och kontrollera sina impulser. Uppskjuten belöning och exekutiva funktioner är centrala för självreglering och är viktiga för skolframgång och kamratrelationer. Autistiska barn och barn med ADHD har ofta svårigheter med dessa färdigheter. Det är dock mindre känt hur dessa egenskaper specifikt relaterar till autism respektive ADHD tidigt i livet, och om god förmåga och exekutiva funktioner kan fungera som skyddsfaktorer för hur väl barn fungerar och anpassar sig i vardagen (eng: *adaptive behavior*), inklusive kommunikation, sociala relationer och vardagliga aktiviteter, som för en 3-åring kan handla om att klä på sig, tvätta händerna eller hjälpa till att duka. Resultaten visade på att barn med familjehistorik av autism och/eller ADHD presterade lägre på det komplexa EF-måttet än jämförelsegruppen, men ingen skillnad gällande förmåga att stoppa impulsen att ta leksaken eller äta godiset. Däremot var autistiska symtom relaterat till sämre förmåga att inhibera i dessa uppgifter, medan ADHD symtom relaterade till mer svårigheter i de mer komplexa EF-uppgifterna. Deferred Gratification påverkade associationen mellan autistiska symtom och adaptivt beteende (AB) genom att god förmåga att vänta eller stoppa en impuls (Deferred Gratification) resulterade i att associationen mellan autistiska symtom och lägre adaptivt beteende blev icke-signifikant. På så sätt verkar förmågan att kunna skjuta upp beteende för en senare belöning fungera som en skyddande faktor.

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In the ocean, there's a mountain
On the mountain, there's a forest
In the forest, there's a garden
In the garden, there's a flower
In the flower, there's a nectar
In the nectar, there's an answer
In that answer, there's another
And another, and another
And another, and another

"Up the mountain" Regina Spector

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