

The investigation of Chronic and Severe Irritability in a clinical sample of youths with Attention Deficit Hyperactivity Disorder

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With the hope that this life and professional privilege, culminated in this thesis, will be accessible to many other immigrants to come, regardless of their nationality, ethnicity, or status.

Thesis summary

Chronic and severe irritability is an impairing condition associated with poor clinical and functional outcome. However, little is known about its nature, pathophysiological markers, and risk factors, which are essential to develop effective interventions. These knowledge gaps could be best addressed in youths with Attention Deficit Hyperactivity Disorder (ADHD). Chronic and severe irritability is highly prevalent in this population, leading to greater impairment than those with ADHD alone. Additionally, cognitive deficits seen in severely irritable youths greatly overlap with those observed in individuals with ADHD. Thus, investigating chronic and severe irritability in this population might also help understand the problematic heterogeneity of ADHD, which is observed at clinical, cognitive, and aetiological levels, that impact upon both clinical and research practice.

This thesis had three main aims. The first aim was to explore the possible bi-dimensional nature of chronic and severe irritability, composed of phasic and tonic dimensions, in a clinical sample of children with ADHD. This was achieved by comparing the extent to which phasic and tonic irritability were associated with cross-sectional and longitudinal correlates of ADHD. Findings failed to support a clear distinction between these two dimensions, due to their similar pattern of associations, the strength of which did not differ between irritability dimensions. Chronic and severe irritability was thus considered unidimensional in the following studies of this PhD project. Nonetheless, both phasic and tonic irritability were associated with a poor clinical functioning, supporting the clinical relevance of this phenotype in those with ADHD. The second aim of this thesis was then to explore pathophysiological markers of chronic and severe irritability, possibly leading to impairments in this population. The hypothesis was that chronic and severe irritability measured at baseline predicted poor Hot (as opposed to Cool) cognitive functioning at follow-up; however, this was

not supported by the results obtained. The third and final aim of this thesis was to look at common genetic risk associated with irritability in relation to chronic and severe irritability symptom severity (measured at baseline) and Hot cognitive functioning (measured at follow-up). Investigating pathophysiological markers of chronic and severe irritability at a different level of analysis (i.e., biological underpinnings) led however to similar conclusions. Although common genetic risk for irritability seemed to influence the symptom presentation of this phenotype, it was not associated with Hot cognitive functioning.

Taken together these results seem to suggest that chronic and severe irritability is a marker of severity in those with ADHD, and that future interventions should not target Cool or Hot cognitive functioning. However, considering the pioneering nature of these studies, more research is needed to draw stronger conclusions, possibly using a comprehensive measure of irritability, and addressing other cognitive markers; this might yield different results.

Role and responsibilities

My responsibilities as a PhD student included deciding the area of research to focus on, developing the rationale of this thesis, all the study aims and hypothesis, and deciding the data to use and analysis to perform. More specifically, I chose to conduct my PhD project on the clinical sample of youths with Attention Deficit Hyperactivity Disorder (ADHD) from SAGE (the Study of ADHD Genes and Environment) and to focus on irritability. Children in the SAGE sample were recruited from 2007 to 2011 and were followed up 2 and a half years later, on average (data collection completed in 2016). Both baseline and follow-up data was collected prior to the start of my PhD. Nonetheless, I contributed significantly to data checking, data managing, and data cleaning. More precisely, for the baseline data, I selected the individuals and variables needed to conduct the studies included in this thesis; I studied the scoring procedure, which was essential to understand the meaning of this data and ensure its good quality, that I also checked. For the follow-up data, I created comprehensive databases combining demographic, clinical and cognitive information together. Considering datasets of demographic and clinical variables, I also cross-checked participant' IDs and information with the data included in the paper copies of participant's questionnaires to ensure data was properly entered and when it wasn't, I took responsibility for data entry too. For the cognitive dataset, I gathered raw cognitive data from the different tasks used in the follow-up protocol and I scored it, both creating and using available templates. I then wrote a script in R to automatically combine the derived scores from these templates into a single database. Finally, I extracted from this database the variables of interest for this thesis and ensured the good quality of this data.

For the genetic data, I downloaded the publicly available database from the Neale lab website (Neale lab, 2018) and I created an R script to filter this genetic information, based on parameters set up to ensure the production of robust results. I was

responsible for the choice of these parameters following previous research and advice from a more senior Cardiff University staff member (Dr Joanna Martin). Notably, I was not directly responsible for the filtering, quality control and scoring of the genetic data from the SAGE study; this was done by Dr Joanna Martin as part of an ongoing study. However, I was responsible for double checking that individuals without a Caucasian ethnicity were excluded and for matching genetic data with the relevant participant's IDs. Additionally, I was involved in the dissemination of the findings of this thesis, especially the first two experimental chapters, to Cardiff University internal meetings and national conferences. I will contribute further with publications of the main project aims. Finally, I was responsible for the data analysis process, result interpretation, discussion and writing up.

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List of the recurrent acronyms used across the chapters of this thesis.

ADHD = Attention Deficit Hyperactivity Disorder

AIC = Akaike's Information Criterion

ASQ = Autism Screening Questionnaire

AUC = Area Under the Curve

BD = Bipolar Disorder

BF = Bayes Factor

BIC = Bayesian Information Criterion

BLRT = Bootstrapped Likelihood Ratio Test

CAPA = Child and Adolescent Psychiatric Assessment

CD = Conduct Disorder

CNVs = Copy Number Variants

CPT = Card Playing Task

CxR = Choice per Risk Task

DAWBA = Development and Well-being Assessment

DL-PFC = Dorsolateral Prefrontal Cortex

DMDD = Disruptive Mood Dysregulation Disorder

DSM = Diagnostic and Statistical Manual of Mental Disorders

EFs = Executive Functions

EV = Expected Value

FNR = Frustrative Non-reward

GnG = Go no Go

GWAS = Genome-Wide Association Studies

H_0 = null hypothesis

H_1 = alternative hypothesis

HADS = Hospital Anxiety and Depression Scale

IC = Information Criteria

ICD = International Classification of Diseases

ICU = Inventory of Callous-Unemotional Traits

IL = Instrumental Learning

INFO = Imputation quality probability

IQ = Intelligence Quotient

LMR = Lo-Mendell-Rubin

LPA = Latent Profile Analysis

MAF = Minor Allele Frequency

MDD = Major Depressive Disorder

NICE = National Institute for Health and Care Excellence

NIMH = National Institute of Mental Health

ODD = Oppositional Defiant Disorder

OFC = Orbitofrontal Cortex

PC = Principal Component

PFC = Prefrontal Cortex

QC = Quality Control

RDoC = Research Domain Criteria

RT = Reaction Time

SAGE = Study of ADHD, Genes and Environment

SDQ = Strengths and Difficulties Questionnaire

SES = Social Economic Status

SMD = Severe Mood Dysregulation

SNP = Single-Nucleotide Polymorphism

TDT = Temporal Discounting Task

UG = Ultimatum Game

WASI = Wechsler Abbreviated Scale of Intelligence

WCST = Wisconsin Card Sorting Test

Chapter 1

General Introduction

1.1 Irritability

Irritability is a cross-diagnostic symptom included in both internalising and externalising conditions. In particular, it is included within the DSM (Diagnostic and Statistical Manual of Mental Disorders) diagnostic criteria for Oppositional Defiant Disorder (ODD), Antisocial Personality Disorder (APD) (externalising conditions), Generalised Anxiety Disorder, Major Depressive Disorder (MDD), and Bipolar Disorder (BD) (internalising conditions) (American Psychiatric Association, 2013). Chronic and severe irritability is also the core symptom of Disruptive Mood Dysregulation Disorder (DMDD), a recent diagnostic category introduced in the DSM-5 (American Psychiatric Association, 2013) as a reflection of the increasing interest in this phenotype. This section of the thesis aims to illustrate the current state of research on irritability, suggesting the importance of addressing this phenotype, defined as chronic and severe and conceived dimensionally, in psychiatric research. The clinical relevance of this phenotype stems from being one of the most common reasons children are referred to psychiatric care and its impairing clinical correlates and outcomes (Brotman, Kircanski, & Leibenluft, 2017; Stringaris, Vidal-Ribas, Brotman, & Leibenluft, 2018; Vidal-Ribas, Brotman, Valdivieso, Leibenluft, & Stringaris, 2016) as illustrated in the following sections.

1.1.1 Definition

Irritability is defined as a propensity to react with intense anger under a minor provocation, and this reacting is disproportionate compared to peers at the same developmental stage (Buss & Durkee, 1957; Caprara et al., 1985; Snaith & Taylor,

1985; Stringaris et al., 2018). Despite this seemingly clear definition, irritability in the literature is operationalised in a variety of ways: in its facets (i.e., anger and aggression), as a dimensional construct (i.e., Emotional Lability/Emotional Dysregulation), as part of ODD and as a syndrome (i.e., Severe Mood Dysregulation); whilst these different terminologies are often used interchangeably to refer to irritability.

Anger is the core emotion accompanying irritability, and this emotional state can be expressed as aggressive behaviours, such as temper outbursts, although, grumpiness, grouchiness, and easy annoyance are also behavioural manifestations of irritability that do not involve aggression (Brotman, Kircanski, & Leibenluft, 2017; Leibenluft, Blair, Charney, & Pine, 2003; Vidal-Ribas et al., 2016). Thus, despite anger and aggression being interrelated constructs with irritability, it appears clear that they are just facets of this phenotype. Additionally, severe irritability is also included within the broader constructs of “Emotional Lability” and “Emotional Dysregulation”. Emotional Lability refers to sudden and rapid swings across different negative emotional states, and includes irritable symptoms such as anger, temper outbursts and hot temper, as well as sadness; these symptoms are disproportionate to the situation and inconsistent with the developmental level (Liu et al., 2019; Sobanski et al., 2010). Similarly, Emotional Dysregulation refers to an individual’s inability to change an emotional state that thus interferes in goal directed activities, hindering the possibility to achieve a goal (Shaw, Stringaris, Nigg, & Leibenluft, 2014). Emotional Dysregulation includes irritability alongside intense, context-inappropriate and poorly controlled emotionality. It also includes Emotional Lability and symptoms of anxiety and depression (Shaw et al., 2014; Stringaris et al., 2018). Thus, Emotional Lability and Dysregulation are more complex dimensional constructs that include irritability within a broad range of emotional symptoms.

Oppositional Defiant Disorder is a condition mostly characterised by argumentative, vindictive and defiant behaviours, as well as irritable symptoms (American Psychiatric Association, 2013; Stringaris & Goodman, 2009b). It is also in developmental continuity with Conduct Disorder (CD) which can be conceptualised as a severe disruptive behaviour disorder characterised by violent and antisocial behaviours (American Psychiatric Association, 2013). ODD is consistently shown to have two dimensions: a defiant and argumentative dimension and an irritable dimension, composed of symptoms of feelings of anger, touchiness and temper outbursts (Evans et al., 2017; Stringaris & Goodman, 2009b). The irritable dimension of ODD has been consistently investigated in the literature to understand its developmental trajectories and outcomes (Evans et al., 2017). However, irritability within ODD is composed of only three symptoms and it is part of a specific diagnostic category, which fails to recognise its cross-diagnostic prevalence (American Psychiatric Association, 2013; Leibenluft, 2011). Thus, ODD cannot be used interchangeably to refer to severe irritability, suggesting that this phenotype should be considered separately (Burke et al., 2014; Stringaris & Goodman, 2009b, 2009a).

In an attempt to target a clinically relevant phenotype of irritability, Severe Mood Dysregulation (SMD) syndrome was created including clinical cut-offs related to frequency, pervasiveness and temporal stability (Leibenluft, 2011). In addition to the severe and abnormal irritable mood and behaviours, such as temper tantrums, verbal rages or physical aggression, SMD is also characterised by angry or sad mood and hyperarousal, composed of symptoms of insomnia, agitation and inattention (Leibenluft, 2011).

Thus, whilst several constructs are used synonymously with irritability, none of these constructs or features target irritability specifically. This is particularly relevant as with the release of the DSM-5 (2013), a narrow phenotype of irritability (i.e., DMDD),

operationalised as chronic and severe, has acquired a greater clinical and public health interest. However, findings obtained looking at previously discussed related constructs to irritability are inappropriately used to infer underpinnings of this chronic and severe phenotype (e.g., Brotman, Kircanski, & Leibenluft, 2017; Brotman, Kircanski, Stringaris, Pine, & Leibenluft, 2017). This lack of consistency in the terminology ultimately hinders the ability to comprehensively study and gather generalisable empirical evidence on the nature of chronic and severe irritability and its related features. This lack of empirical evidence led the Developmental Translational Research Division of the National Institute of Mental Health (NIMH, USA) to organise a workshop (2014) aimed at collecting the current knowledge specifically on chronic and severe irritability in youth. Among all the aspects thought to be overlooked, this panel stressed the need to investigate specifically the nature, pathophysiological markers and genetic underpinnings of chronic and severe irritability (Leibenluft & Avenevoli, 2014). These investigations are the focus of this thesis.

1.1.2 Historical context & surrounding debate

Historically, the increased interest in irritability started in the late 1990s when psychiatrists reported the challenge of formulating a diagnosis of Bipolar Disorder in childhood (Biederman, Klein, Pine, & Klein, 1998). Clinicians observed an increase in a noncanonical presentation of BD with affected children showing chronic and severe irritability, dysphoria and agitation, as opposed to the classic presentation of episodic related mood and mania (Biederman et al., 1998). This led to a consistent increase in the US diagnostic rates of paediatric Bipolar Disorder in children and adolescents over an eight year period (1996-2004), with an overall stable rate of BD diagnoses in adults (Blader & Carlson, 2007). To ascertain the validity of this subtype of childhood BD, this condition was operationalised as Severe Mood Dysregulation (described in section 1.1.1); a clinical phenotype characterised by chronic and severe irritability in

the form of temper outbursts and negative mood (i.e., anger or sadness) between such outbursts, with a hyperarousal component expressed for instance as agitation, distractibility or racing thoughts (Leibenluft, Charney, Towbin, Bhangoo, & Pine, 2003). SMD and classic BD were then compared on family correlates, longitudinal outcomes and pathophysiological markers; results revealed consistent differences between these two phenotypes on all these external validators (Leibenluft, 2011). In particular, in youths with SMD long terms outcomes were an increased risk of developing depression and anxiety disorders (Leibenluft, 2011). These trajectories are in contrast to youth with classic BD who more likely developed manic episodes over time, the core symptom of BD (Leibenluft, 2011). Family history for individuals with SMD revealed only a small proportion of cases with BD, unlike the high familial rates of BD in the classic BD group (Leibenluft, 2011). Finally, neurocognitive markers showed different patterns of impairment across the two phenotypes (Leibenluft, 2011). Taken together, these results suggested that SMD is consistently different, and not an atypical presentation of Bipolar Disorder in childhood. Thus, a revised version of SMD was included in the DSM-5 as Disruptive Mood Dysregulation Disorder, within the Mood Disorder category, conferring chronic and severe irritability a unique diagnostic status (American Psychiatric Association, 2013). The core feature of DMDD is chronic and severe irritability in the form of intense, frequent and impairing temper outbursts, that are inconsistent with developmental level, as well as severe irritable mood that persists between these outbursts (American Psychiatric Association, 2013). The hyperarousal component included in SMD was dropped, due to the overlap with Attention Deficit Hyperactivity Disorder core symptoms that complicated the differential diagnosis between ADHD and SMD (Brotman, Kircanski, & Leibenluft, 2017). The introduction of DMDD within the DSM-5 was subject to some criticism over whether or not it has diagnostic validity over and above psychiatric disorders already included in the DSM (Evans et al., 2017; Frances & Nardo, 2013; Frances & Widiger, 2012; Wakefield, 2016). Notably, it is not included in the eleventh

and most recent version of the International Classification of Diseases (ICD) (2018). Individuals with DMDD very often receive diagnoses of disruptive behaviours (e.g., ADHD, ODD, CD) and depression, and there is only a small number of individuals endorsing DMDD alone (Evans et al., 2017; Frances & Nardo, 2013; Frances & Widiger, 2012; Wakefield, 2016). An alternative way to adequately describe those with chronic and severe irritability was suggested by Evans and colleagues (2017) and simply requires adding a specifier to the ODD diagnosis to include those who show severe irritability. ODD widely overlaps with DMDD and it has a heterogeneous presentation with symptoms crossing either an irritable or a defiant domain, with a less consistent evidence for a hurtful domain (Evans et al., 2017; Stringaris & Goodman, 2009b). However, it should be considered that there are individuals with DMDD without ODD, albeit a small number (Axelson et al., 2012; Evans et al., 2017; Mayes, Waxmonsky, Calhoun, & Bixler, 2016), and that DMDD also includes irritable mood symptoms that are not well captured by ODD, which is purely considered as a behavioural disorder. In light of the reported clinical relevance of chronic and severe irritability but the questionable utility of a diagnostic category, a continuous conceptualisation of this phenotype may be more promising to study the nature, pathophysiological markers and genetic underpinnings of chronic and severe irritability. This dimensional approach was encouraged by the 2014 workshop conceptualising irritability (Leibenluft & Avenevoli, 2014) and is an approach utilised in this thesis.

1.1.3 Epidemiology and developmental course of irritability

Symptoms of irritability are quite common in clinical samples and among pre-schoolers, with a greater endorsement of temper tantrums compared to other irritable symptoms, such as irritable mood (Axelson et al., 2012; Carlson, Danzig, Dougherty, Bufferd, & Klein, 2016; Copeland, Angold, Costello, & Egger, 2013; Margulies, Weintraub, Basile, Grover, & Carlson, 2012). Irritable symptoms are also very

prevalent in children and adolescents from the general population, with up to 91% reporting some irritable symptoms at some point over the course of development (Carlson et al., 2016; Copeland, Brotman, & Costello, 2015; Wakschlag et al., 2012); temper tantrums also appear to be the most common symptom of irritability in community samples (Copeland et al., 2013, 2015; Dougherty et al., 2014). This almost universal experience of irritability in the general population is not surprising as irritability, in particular anger, could also be an adaptive behaviour; anger is considered to be an approach behaviour, thus it helps maintaining the motivational focus on a goal, increasing the effort to achieve that goal (Carver & Harmon-Jones, 2009; Leibenluft & Stoddard, 2013). Therefore, it is important to identify pathological parameters of irritability to identify a more clinically relevant phenotype and avoid pathologizing a normative reaction, especially in children and adolescents. This has been done with SMD/DMDD which require features of severity, pervasiveness and chronicity; in fact, among other criteria, irritable symptoms need to be present almost every day, in different life settings and be enduring for a period of at least one year (American Psychiatric Association, 2013; Leibenluft, 2011). Applying these clinical cut-offs reduces the prevalence, as chronic and severe irritability, in the form of SMD/DMDD, affects 0.1% to 8.2% of children and adolescents in community samples (Althoff et al., 2016; Brotman et al., 2006; Dougherty et al., 2014, 2016). In clinical samples SMD/DMDD is more common with prevalence rates ranging from 16% to 31% of children and adolescents (Axelson et al., 2012; Freeman, Youngstrom, Youngstrom, & Findling, 2016; Margulies et al., 2012).

Empirical evidence for the stability of irritability, conceptualised either as symptoms or within diagnostic labels, is mixed. Irritable symptoms tend to decrease with age and both their prevalence and trajectories do not seem to vary based on sex (Copeland et al., 2015; Mayes et al., 2015; Wakschlag et al., 2012; Wiggins, Mitchell, Stringaris, & Leibenluft, 2014). This decreasing trend is also observed for diagnostic rates in the general population as DMDD seems to be more prevalent in late childhood as

opposed to young adulthood (Althoff et al., 2016; Copeland et al., 2013). In clinical samples however, SMD/DMDD seems to be more stable with a consistent proportion of individuals with a persistent diagnosis at different time points across childhood and adolescence; there is also an even a greater proportion of individuals with subthreshold SMD/DMDD who still show severe and impairing irritable symptoms in at least one functional domain (Axelson et al., 2012; Deveney et al., 2015). Overall the stability of DMDD is, nevertheless lower compared to other psychiatric disorders (e.g., ADHD) (Axelson et al., 2012; Mayes et al., 2015). It should however be noted that the interest in chronic and severe irritability is recent, and specific measures to assess this phenotype are scarce. In these previous studies, SMD/DMDD diagnosis was assigned post hoc, extracting items from the different clinical interviews administered in the samples analysed. Similarly, irritable symptoms were assessed using different questionnaires and interviews. Additionally, the use of different raters (e.g., parents vs. clinicians), as well as different clinical cut-offs, have been shown to affect the prevalence estimates of both irritable symptoms and SMD/DMDD diagnosis (Eyre et al., 2017; Margulies et al., 2012; Mayes et al., 2015, 2016). Finally, even among clinicians there are inconsistencies in diagnostic agreement for SMD/DMDD (Regier et al., 2013). All these factors may explain the variability in prevalence estimates, and the questionable stability of chronic and severe irritability diagnosis over time.

1.1.4 Clinical correlates and outcomes of childhood irritability

Severe irritability is associated with a wide range of internalising and externalising conditions, both within time and longitudinally, and is associated with persisting impairments.

Cross-sectionally, the most common psychiatric conditions associated with severe irritability are disruptive behaviours, mostly ADHD, where severe irritability is found to co-occur in 65-86% of individuals and ODD, where a 78-96% co-occurrence rate has

been reported (Axelson et al., 2012; Deveney et al., 2015; Freeman et al., 2016; Leibenluft, 2011; Margulies et al., 2012; Mayes et al., 2015, 2016). Depressive disorders (e.g., MDD and Dysthymia) and anxiety disorders (e.g., separation, social and generalised anxiety disorder) are also frequently comorbid with severe irritability with rates ranging from 20%-37.3% and 20%-58.2%, respectively (Axelson et al., 2012; Deveney et al., 2015; Freeman et al., 2016; Leibenluft, 2011; Margulies et al., 2012; Mayes et al., 2015, 2016). These within time associations of severe irritability with both internalising and externalising disorders are consistent both in clinical (e.g., Cornacchio, Crum, Coxe, Pincus, & Comer, 2016; Eyre et al., 2017) and community samples (Mayes et al., 2015, 2016).

Longitudinal associations between severe irritability and a wide variety of psychiatric conditions have also been observed across the life span, from early childhood to adulthood. Severe irritability in the general population predicts several internalising conditions, most commonly depressive disorders (e.g., MDD and Dysthymia) and anxiety disorders (e.g., generalised and social anxiety disorders) over and above psychiatric symptoms and conditions at baseline (Brotman et al., 2006; Copeland, Shanahan, Egger, Angold, & Costello, 2014; Dougherty et al., 2015; Stringaris, Cohen, Pine, & Leibenluft, 2009; Vidal-Ribas et al., 2016). Severe irritability has also been shown to be a significant predictor of externalising conditions, especially ODD (Dougherty et al., 2015; Stringaris et al., 2009; Vidal-Ribas et al., 2016), whereas its longitudinal association with ADHD and Substance Use Disorder (SUD) is less consistent (Leibenluft, Cohen, Gorrindo, Brook, & Pine, 2006; Vidal-Ribas et al., 2016). Research on clinical outcomes of severe irritability in clinical cohorts is scarce. The research to date seems to confirm that severe irritability predicts both depressive and anxiety disorders in clinical samples with a number of different disorders (Deveney et al., 2015; Eyre et al., 2019). Clinical outcomes linked to severe irritability in youths with ADHD are particularly relevant for this thesis and they are discussed in detail in the second section of this general introduction (section 1.2, paragraph 1.2.3).

In children and adolescents from the general population, severe irritability is also associated with negative outcomes in multiple areas of functioning, such as impaired relationships with peers and adults, school impairments with high rates of school suspensions and low academic achievement and substance abuse (Althoff et al., 2016; Copeland et al., 2013; Dougherty et al., 2014, 2015). These irritable youths also show greater health and school service use, they are more likely to come from disadvantaged backgrounds and are twice as likely to have learning disability compared to those with mental health conditions without irritability (Althoff et al., 2016; Copeland et al., 2013). Finally, adults with a history of childhood irritability also have poorer health outcomes, increased rates of antisocial behaviours and poor financial functioning compared to both healthy controls and those with other psychiatric conditions (Copeland et al., 2014; Stringaris et al., 2009). In terms of social relationships those with severe irritability are more likely to have strained and violent relationships and fewer friends compared to healthy controls (Copeland et al., 2014). Another important outcome associated with severe irritability is suicidality, which comprises both suicidal ideations, plans and attempts. Adolescents with DMDD have up to a fourfold risk of suicidality compared to those with other psychiatric disorders without DMDD (Althoff et al., 2016); co-occurring symptoms of severe irritability have also been linked to suicidal ideation in adolescents and adults (Conner, Meldrum, Wieczorek, Duberstein, & Welte, 2004; Pickles et al., 2010). Overall, these clinical and functional impairments, including suicidality, seem to be independent of other comorbid symptoms and conditions (Althoff et al., 2016; Conner et al., 2004; Copeland et al., 2013; Dougherty et al., 2014; Eyre et al., 2019; Stringaris et al., 2009). A number of conclusions can be drawn from these findings. First, these results suggest that despite the variable and debated clinical validity and stability of chronic and severe irritability, severe irritability is consistently associated with both clinical and functional impairments over and above the effect of comorbidity. This supports the clinical and public health relevance of this phenotype and addressing severe irritability

in future research and interventions might thus be useful to prevent the broad range of impairments specifically associated with it. Second, the associations of severe irritability with both internalising and externalising conditions further support the difficulty of studying irritability as a separate diagnostic entity, as it might be differently characterised across psychiatric conditions. Third, although under-researched, results on clinical outcomes of severe irritability in clinical cohorts offer preliminary evidence of this phenotype as a possible source of heterogeneity, leading to different psychiatric conditions and comorbidities. However, it should be considered that in this section the term “severe irritability” is used to indicate both chronic and severe irritability, as per SMD/DMDD diagnoses, and severe irritable symptoms, measured with different assessment instruments across studies. More studies are therefore needed to explore these cross-sectional and longitudinal associations with a more stringent and clinically relevant phenotype of chronic and severe irritability, especially in clinical samples.

1.1.5 Risk factors

The aetiology of irritability is yet to be understood and studies investigating genetic and environmental contributions to the construct are scarce. The few twin studies show both genetic and environmental influences in the aetiology of irritability (Coccaro, Bergeman, Kavoussi, & Seroczynski, 1997; Roberson-Nay et al., 2015; Stringaris, Zavos, Leibenluft, Maughan, & Eley, 2012). In particular, genetic factors seem to play a consistent role in irritability with a heritability (i.e., the proportion of phenotypic variance explained by genes) around 37% in adult twins (Coccaro et al., 1997) and 31% in adolescents (Stringaris, Zavos, et al., 2012). Whether these genetic influences are additive or non-additive in nature is yet to be understood, whilst some studies observe dominance effects, other studies provide evidence for additive genetic effects only (Coccaro et al., 1997; Roberson-Nay et al., 2015). There is also a significant contribution of unique environment that explains 63% and 69% of

irritability phenotypic variance in twin adults and adolescents, respectively; counter to this, the role of shared environment appears to be negligible (Coccaro et al., 1997; Stringaris, Zavos, et al., 2012). Notably, “unique” and “shared” environment refer respectively to the environment experienced by each individual separately, which contributes to individual differences (e.g., individual experiences) and to the one shared by twin pairs (e.g., family setting), contributing to individual similarities instead. Recent work looked at genetic and environmental influences on irritability over time, showing an opposite trend in males and females (Roberson-Nay et al., 2015); the heritability of irritability in males is robust, increasing from 36% up to 89% from childhood to young adulthood with stable genetic influences over time; however, new sets of genes also emerged during adolescence with an influence in late adolescence and young adulthood (Roberson-Nay et al., 2015). Counter to this, in females, genetic liability declines over the course of development from 66% to 46%; similarly to males, both stable and new genetic factors in early adolescence contribute to heritability estimates of irritability in females (Roberson-Nay et al., 2015). Shared environment seems to play a negligible part for both males and females as opposed to a consistent contribution of unique environment in both sexes, characterised by both stable and new factors emerging over time with a decreasing longitudinal contribution (Roberson-Nay et al., 2015). The role of environmental influences are also observed in intervention studies where parent training is shown to effectively reduce severe irritability especially in children (Brotman, Kircanski, Stringaris, et al., 2017; Leibenluft, 2017b). Furthermore, preliminary findings seem to suggest a gene-environment correlation by which genetically driven aggressive behaviours in youths evoke parental negative reactions (O'Connor, Deater-Deckard, Fulker, Rutter, & Plomin, 1998), although more research is needed to identify environmental risk factors and their possible interplay with genetic liability.

Additionally, in the attempt to identify specific genes associated with this phenotype, several Genome-Wide Association Studies (GWAS) have been conducted. GWAS approach aims to identify Single-Nucleotide Polymorphism (SNP); SNPs are common genetic variants present with a frequency of 5% or more in the general population across the entire genome that are involved in the genesis of the clinical phenotype considered. No GWAS study to date has investigated common genetic variants associated specifically with chronic and severe irritability. Most of the empirical evidence comes from previous GWASs investigating related traits and constructs to irritability, such as Emotional Lability, Emotional Dysregulation and antisocial behaviours (including aggression). As shown in section 1.1.1, these terminologies do not specifically identify severe irritability, therefore it is not entirely possible to generalise findings obtained with such operationalisations. A recent GWAS identified several loci across the genome associated with Emotional Lability with SNPs explaining 9% of phenotypic variance (Ward et al., 2019). These common genetic variants were expressed in the brain tissue and enriched in genes involved in brain development and neuron differentiation (Ward et al., 2019). Additionally, they were associated with different psychiatric traits such as MDD, anxiety, Post Traumatic Stress Disorder, schizophrenia and BD (Ward et al., 2019). Previous work on Emotional Dysregulation obtained more modest results, revealing only one SNP (i.e., common genetic variant) associated with this phenotype, and in males as opposed to females; this SNP was located on a gene regulating inflammatory responses (Powers et al., 2016). However, this study was underpowered, mostly due to the small sample size used to conduct a GWAS analysis, which might also explain the identification of only one SNP. Additionally, this study was conducted on an adult sample, largely females and with small income, making it difficult to generalise these findings to different populations, such as children and adolescents (Powers et al., 2016). Previous work was also conducted on antisocial behaviours, although it failed to identify genome-wide significant genetic variants (Tielbeek et al., 2017). Promising

SNPs with p-values close to significance were identified, and they showed sex-specific differences as males and females had different enriched loci on different chromosomes across the genome; the proportion of phenotypic variance explained was however negligible (Tielbeek et al., 2017). Common genetic contributions to irritability have also been investigated in the context of other psychiatric disorders, such as Bipolar Disorder. GWAS results on irritable temperament in a sample of individuals with BD provide evidence for two common genetic variants located in genes on chromosome 1. These genes seem to be involved in DNA damage control and replication, and in RNA processing and transcription (Greenwood, Akiskal, Akiskal, & Kelsoe, 2012). Finally, GWAS findings in a sample of adults with BD identified promising loci on chromosome 13 uniquely associated with irritable mood in BD as opposed to elated mania BD or controls (Greenwood et al., 2013). The peak of common genetic variants identified in this region does not seem to be within any known gene, although neighbouring genes associated to neurite outgrowth may influence its genetic expression (Greenwood et al., 2013). These promising results failed however to be replicated in a clinically diverse sample of individuals with BP (Greenwood et al., 2013). Taken together these findings suggest that irritability is a heritable trait and that both genetic and environmental factors play a role across development; however, more research is needed to identify specific genetic variants, especially those associated with a narrower and more clinically relevant definition of chronic and severe irritability as opposed to irritability-related constructs and facets (e.g., Emotion Dysregulation/Lability, temperament, antisocial behaviours, or episodic irritable mood).

1.1.6 Treatments and interventions for chronic and severe irritability

As the heightened interest in chronic and severe irritability is relatively recent, interventions studies are limited; the findings gathered so far suggest promising effects for pharmacological, cognitive and psychosocial treatments (Stringaris et al.,

2018). It should however be noted that intervention studies have been conducted on facets of irritability (e.g., aggression) or related constructs, such as ODD; these represent the vast majority of empirical evidence on treatments related to this phenotype. In particular, in clinically diverse youths, pharmacological treatments based on antidepressant drugs seem to be associated with a reduction of aggression and disruptive behaviours (Kim & Boylan, 2016). Similarly, behavioural interventions developed to help parents reinforce adaptive, instead of maladaptive, behaviours in youths also yield significant improvements in antisocial and disruptive behaviours, emotion dysregulation, and aggression (Brotman, Kircanski, & Leibenluft, 2017).

There are, however, few studies looking at severe irritability in the form of SMD and only one addressing chronic and severe irritability diagnosis (i.e., DMDD). In particular, only two pharmacological studies have been conducted in severely irritable youths (i.e., individuals with SMD) (Dickstein et al., 2009; Krieger et al., 2011). One study found a significant improvement of irritable symptoms, comorbid psychiatric symptoms (i.e., ADHD, anxiety and depression) and associated impairments using antipsychotic medications; these benefits seemed to persist over time with an adequate degree of drug tolerability (Krieger et al., 2011). It should however be noted that this study did not include any placebo, thus results might be biased. The only other published study was a Randomised Control Trial (Dickstein et al., 2009) and was the first well-controlled study to date that investigated the efficacy of pharmacological treatment in those with SMD. The aim was to look at the efficacy of lithium treatment in reducing symptoms of irritability and associated functional and clinical outcomes, and overall it yielded non-significant results (Dickstein et al., 2009). A pilot study of cognitive training targeting hostile interpretation bias was also conducted in those with chronic and severe irritability (i.e., DMDD) in the attempt to reduce these impairing symptoms (Stoddard et al., 2016). This study had promising findings associated with a reduction of severe irritability manifestation and related impairment which was persistent over time; although more research is needed to

understand the role of comorbid conditions and relevant psychiatric symptoms (Stoddard et al., 2016). There is also preliminary anecdotal evidence from clinical cases on the effectiveness of Cognitive-Behavioural Therapy targeting symptoms related to DMDD such as irritability and aggression (Tudor, Ibrahim, Bertschinger, Piasecka, & Sukhodolsky, 2016), although well-controlled research on psychotherapeutic interventions on chronic and severe irritability is lacking.

Taken together these findings suggest that there is a paucity of interventions studies targeting chronic and severe irritability specifically. However, it should be considered that pharmacological, therapeutic, cognitive or behavioural interventions should be developed in accordance with robust knowledge of aetiological and neurocognitive underpinnings, and with the nature of chronic and severe irritability, that are currently lacking. Additionally, due to the different terminologies associated with this severe phenotype and their interchangeable use, evidence obtained focusing on aspects of severe irritability cannot be generalised to the phenotype as currently conceptualised.

In conclusion, chronic and severe irritability has become increasingly prominent for research, clinical practice, children with ADHD and their families, especially with the introduction of DMDD in the DSM-5. The clinical usefulness of this diagnostic label is however questioned due to the high comorbidity rates and mixed evidence on its prevalence and longitudinal stability, possibly suggesting that a dimensional conceptualisation of this phenotype might be more promising. Nonetheless, the clinical importance of severe irritability is well documented, being associated with a wide range of internalising and externalising disorders and being a predictor of consistent functional and clinical impairments. Thus, this phenotype is worth investigating further, as a potential source of comorbidity and in the public health interest, especially since the empirical knowledge gathered so far has proven to be insufficient due to the interchangeable use of different terms. Digging into the wide knowledge gaps related to chronic and severe irritability, priority should be given to

clarify the nature, cognitive markers and aetiological factors specifically associated with this phenotype, as recommended by the 2014 workshop of the NIMH (Leibenluft & Avenevoli, 2014). Indeed, further knowledge of these aspects can inform the development of better tailored interventions targeting specifically chronic and severe irritability.

1.2 Attention Deficit Hyperactivity Disorder

Attention Deficit Hyperactivity Disorder is a neurodevelopmental disorder characterised by impairing symptoms in the dimensions of inattention, hyperactivity and impulsivity (Cortese & Coghill, 2018). ADHD is a very heterogeneous condition; this heterogeneity affects core symptom presentation, developmental trajectories, co-occurring conditions, functional impairments, neurocognitive functioning and relevant risk factors (Thapar & Cooper, 2016). This great variability ultimately represents a barrier to both clinical practice and research, as it impacts upon the possibility of identifying well-established aetiological pathways, pathophysiological mechanisms, and developing effective treatments (Agid et al., 2013; Feczko et al., 2019; Hayman, 2007; Sonuga-Barke & Coghill, 2014; Sonuga-Barke & Halperin, 2010). This section of the introduction aims to explain the clinical relevance of ADHD, stressing the importance of addressing its great heterogeneity to both gain a deeper understanding of its pathological underpinnings and improve clinical practice. The important role of irritability in achieving this aim is also illustrated.

1.2.1 ADHD diagnostic criteria

ADHD diagnosis formulation is informed by national practice guidelines that find consensus across different countries, to ensure diagnostic reliability and improve evidence-based clinical practice (Seixas, Weiss, & Müller, 2012). A diagnosis of ADHD in children is ascertained by asking adult informants, most commonly parents and teachers, about children's behaviours in the domains of inattention and hyperactivity-impulsivity, often using standardised clinical interviews. These measures are normally designed based on two complementary diagnostic systems: The Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) or the International Classification of Diseases (World Health Organization, 2018). Prior to the third version of the DSM, intense emotionality,

characterised in particular by anger, was considered a pivotal feature of ADHD and included in the diagnostic criteria for the disorder. However, after the publication of the DSM-III these symptoms were removed and considered as marginal, focusing the diagnosis of ADHD mostly on inattentive and hyperactive-impulsive symptoms (Faraone et al., 2019). According to the fifth and most recent version of the DSM (2013), a diagnosis of ADHD is given to children endorsing six or more inattentive and/or hyperactive-impulsive symptoms, such as “often does not seem to listen when spoken directly”, “often runs about” and “often has difficulty waiting his/her turn”; for individuals aged 17 or older endorsing five symptoms of either domains suffice (American Psychiatric Association, 2013). To be diagnosed with ADHD, these symptoms must be present prior to the age of 12 and be significantly impairing in multiple everyday life settings, such as in an academic/occupational or social setting (American Psychiatric Association, 2013). The DSM-5 accounts for the heterogeneity of ADHD core symptom presentation by using diagnostic descriptors based on the predominant symptoms endorsed; thus an individual with ADHD could have a predominantly inattentive, hyperactive-impulsive or combined presentation of core symptoms, where a combined ADHD presentation includes symptoms of both inattentive and hyperactive-impulsive domains (American Psychiatric Association, 2013). It should be noted that this thesis includes measures that investigate ADHD clinical symptoms and diagnosis using the fourth edition of the DSM criteria (American Psychiatric Association, 2000), as data was collected prior to the publication of DSM-5. The DSM-IV and DSM-5 criteria for ADHD however did not differ dramatically; there are only three main changes in the DSM-5: 1) the age of onset for ADHD increased from 7 to 12 years of age, to facilitate the formulation of ADHD diagnosis in adults (Cortese & Coghill, 2018); 2) total symptoms required to diagnose ADHD in those aged 17 or older decreased from six to five, to acknowledge the persistence of ADHD symptoms whilst accounting for developmental decreases overtime (Cortese & Coghill, 2018); 3) ADHD “subtypes” have been replaced by ADHD “presentation”, to

account for the heterotypic continuity of ADHD symptoms within the core domains; “subtype” is in fact a more static concept (American Psychiatric Association, 2000, 2013; Cortese & Coghill, 2018). The International Classification of Diseases is developed by the World Health Organization (WHO) that has recently published the eleventh edition of the ICD (World Health Organization, 2018). The ICD diagnostic criteria for ADHD greatly overlap with those included in the DSM (American Psychiatric Association, 2013; World Health Organization, 2018). ICD-11 however seems to identify a more severe form of ADHD diagnosis, symptoms from all three domain of inattention, impulsivity and hyperactivity need to be endorsed which is akin to the combined symptom presentation in the DSM-5. Similarly to the DSM, the ICD accounts for the heterogeneous presentation of ADHD using diagnostic descriptors to describe the most prevalent symptoms endorsed by those with this condition (World Health Organization, 2018).

Both DSM and ICD diagnostic systems follow a categorical approach to diseases, thus the ADHD diagnosis is reliant on arbitrary clinical cut-offs. ADHD symptoms are however normally distributed in the population, with those in the extreme end of the distribution having a greater severity of symptoms and being more likely to receive a diagnosis (Larsson, Anckarsater, Råstam, Chang, & Lichtenstein, 2012). A dimensional approach is noted to be difficult to utilise in clinical practice and categorical approaches are considered to be the best option to decide on access to treatment and resource allocation, in the absence of more objective, biologically-based and robust parameters (Thapar & Cooper, 2016). It should finally be noted that in this thesis ADHD as conceptualised by the most recent versions of the DSM (DSM-IV and DSM-5) would be considered. This is due to the worldwide use of the DSM diagnostic system, especially in research practice, although ICD is in fact more commonly used in clinical practice and mostly in European countries (Thapar & Cooper, 2016).

1.2.2 Prevalence of ADHD

The diagnostic prevalence of ADHD had been a matter of debate in some circles for many years, mainly due to the variability in prevalence estimates across studies and across countries, and to the increase in diagnostic prevalence over time (Cortese & Coghill, 2018). Findings from the most comprehensive meta-analyses address this great variability showing that it mainly reflects methodological differences related to the inclusion of an impairment requirement to formulate a diagnosis, to different diagnostic system used (DSM vs. ICD) and to clinical information gathered using different informants (parents and/or teachers) (Polanczyk, De Lima, Horta, Biederman, & Rohde, 2007; Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014; Willcutt, 2012). Once these methodological differences are accounted for, prevalence estimates are similar worldwide and ADHD appears to be the most common neurodevelopmental disorder with a worldwide pooled prevalence around 5.3% (95%CI= 5.01 - 5.56) in children and adolescents up to 18 years of age (Polanczyk et al., 2007, 2014; Willcutt, 2012).

ADHD seems to affect predominantly males with a ratio of 4:1 compared to females in the general population that reaches 7-8:1 in clinical samples (Thapar & Cooper, 2016), although these differences seem to disappear in adulthood (Matte et al., 2015). Previous work suggested that these discrepancies could be due to referral bias of females with ADHD as, compared to males, they display fewer problematic externalising behaviours that are likely to drive clinical referrals (Abikoff et al., 2002; Biederman et al., 2002; Gershon, 2002). This is also supported by the comparable levels of social, educational and psychological impairments across males and females with ADHD (Biederman et al., 2005), suggesting that ADHD might be simply underdiagnosed in females. This referral bias in youths could also explain the near 1:1 ratio of male and female adults diagnosed with ADHD as adults can self-refer themselves, thus reducing the referral bias (Faraone et al., 2000). Counter to this, it is also possible that females with ADHD show a greater burden of genetic risk for this

condition, compared to males, that could lead to the diagnosis of only the most severe female cases; this is consistent with the “female protective effect” model that seems to characterise neurodevelopmental disorders and according to which females require a greater exposure to risk factors to fully develop a clinically relevant condition, compared to males (Taylor et al., 2016). This model seems to be supported by behavioural findings as evidence from population based twin studies suggest that cotwins of females with ADHD had greater ADHD symptom severity than cotwin of males with ADHD (Taylor et al., 2016). Despite these possible insights on sex differences in ADHD, evidence is mixed and more research is needed to explore the nature and underpinnings of female ADHD (Biederman et al., 2005; Greven, Richards, & Buitelaar, 2018; Martin et al., 2018).

Finally, the prevalence ADHD diagnoses tends to decrease in adulthood and the overall prevalence of adults with this condition is 2.5% (95%CI= 2.1 - 3.1) (Simon, Czobor, Bálint, Mészáros, & Bitter, 2009). However, in line with the heterogeneous presentation of its core symptoms, ADHD trajectories show great variability. In fact, some evidence suggests that only ~10% of youths with ADHD fully grow out of this condition as adults, whereas ~15% keeps endorsing full diagnostic criteria; the majority of those with ADHD shows however a partial remission (~40-60%), they don't meet all the diagnostic criteria but still show consistent impairments (Biederman, Mick, & Faraone, 2000; Faraone, Biederman, & Mick, 2006). Furthermore, this decline is particularly evident for hyperactive-impulsive symptoms, whereas inattentive symptoms tend to persist (Biederman, 2000).

In conclusion, ADHD is a neurodevelopmental condition seen in around 5% of children, making it one of the most prevalent mental health disorders in childhood. Despite the natural decrease of its core symptoms and the variability of developmental trajectories, individuals with ADHD show consistent impairments over-time, which also highlight the lifelong clinical relevance of this condition.

1.2.3 Clinical correlates and functional outcomes of childhood ADHD

Clinical correlates

Large population studies show that the vast majority (67%-87%) of those with ADHD have at least one comorbid psychiatric condition, whereas 16%-67% of youths with ADHD are affected by more than one co-morbid disorder and 18%-33% have three or more co-morbid conditions (Kadesjo & Gillberg, 2001; Larson, Russ, Kahn, & Halfon, 2011). Similar rates of comorbidity are also observed in those with subthreshold ADHD (whereby individuals demonstrate some subthreshold symptoms and impairment, which do not meet diagnostic criteria) (Kadesjo & Gillberg, 2001). The great variability of these estimates is striking, although it could mainly be due to the methodological differences across studies, such as the time frame considered to define comorbidity, the diagnostic criteria used and variability across informants (Jensen & Steinhausen, 2015; Jensen, Martin, & Cantwell, 1997). Even using more stringent parameters to define the comorbidity and to diagnose ADHD (i.e., ICD-10 diagnosed disorders), estimates still suggest that 50% of youths with ADHD have at least one comorbid disorder, whilst 26% have two or more (Jensen & Steinhausen, 2015). These rates of comorbidity seem to be consistent also in clinical samples of children with ADHD (Reale et al., 2017). More specifically, ADHD in children and adolescents shows a complex pattern of comorbidity encompassing both externalising and internalising disorders. The most prevalent comorbidities within the externalising domain are Oppositional Defiant Disorder and Conduct Disorder (Biederman et al., 2002; Jensen & Steinhausen, 2015; Kadesjo & Gillberg, 2001; Larson et al., 2011; Reale et al., 2017). These behavioural disorders can affect up to 66% and 21% of male youths with ADHD in clinical samples, respectively (Biederman et al., 2002). ADHD is also comorbid with internalising disorders, for example, studies have shown that 18% of youths with ADHD endorse an anxiety disorder and 14% have depression in large population cohorts (Larson et al., 2011).

Neurodevelopmental disorders also co-occur frequently with ADHD, especially autism (12.4%) and learning disability (46.1%) (Jensen & Steinhausen, 2015; Larson et al., 2011). Finally, ADHD is also comorbid with disorders such as tics, epilepsy and Tourette syndrome, although to a lesser extent than both internalising and externalising disorders (Larson et al., 2011). Notably, ADHD comorbidity with internalising and externalising conditions is observed both within and across time (Chronis-Tuscano et al., 2010; Franke et al., 2018; Langley et al., 2010). This great variability is problematic for both clinical and research practice. The comorbid heterogeneity of ADHD represents a barrier to psychiatric care as this great overlap of psychiatric conditions is an obstacle to the diagnostic process. In particular, symptoms overlap across different psychiatric diagnoses, leading to a lack of clear criteria to define the presence or absence of a diagnosis, especially in the presence of co-occurring disorders (Feczko et al., 2019); for instance, lack of concentration and restlessness pertain both to ADHD and anxiety disorders (American Psychiatric Association, 2013). Similarly, the wide heterogeneity of ADHD clinical correlates impacts upon the possibility to identify reliable and robust pathophysiological markers specifically associated with this neurodevelopmental disorder (Agid et al., 2013; Feczko et al., 2019; Hayman, 2007; Uddin, Dajani, Voorhies, Bednarz, & Kana, 2017). More precisely, a pathophysiological marker leading to ADHD might also contribute to the presence of either internalising or externalising conditions, being possibly relevant only for a proportion of individuals with this neurodevelopmental disorder (Feczko et al., 2019). Addressing this heterogeneity by identifying sources of comorbidity is therefore important to possibly provide a comprehensive characterisation of ADHD, especially in terms of pathophysiological markers. This might then lead to the development of personalised interventions, based on different clinical profiles (Agid et al., 2013; Feczko et al., 2019; Hayman, 2007; Sonuga-Barke & Coghill, 2014; Sonuga-Barke & Halperin, 2010).

Functional Outcomes

ADHD is associated with poor outcomes in multiple everyday-life settings (e.g., at school, at home) representing a burden to the individuals with the condition as well as to their families. Poor academic performance is frequently observed in children and adolescents with ADHD and it is a common reason for which children with ADHD receive clinical attention (Loe & Feldman, 2007). This poor performance can be observed in various ways; youths with ADHD show poorer reading and maths skills (Frazier, Youngstrom, Glutting, & Watkins, 2007; Kadesjo & Gillberg, 2001; Scheffler et al., 2009), more adverse school experiences (e.g., low grades, frequent school drop-out, low attendance and school suspension/expulsion) (Bussing et al., 2010; Kent et al., 2011; Klein et al., 2012; Loe & Feldman, 2007), and they make greater use of special education services (Barkley, Fischer, Smallish, & Fletcher, 2006; Loe & Feldman, 2007; Murray et al., 2014), compared to typically developing controls. This impaired academic functioning seems to affect also individuals with subthreshold ADHD (Kadesjo & Gillberg, 2001; Loe & Feldman, 2007). Additionally, youths with ADHD show poor social functioning with both peers and family members. Family relationships seem often characterised by greater levels of conflict and hostility, ultimately being more stressful than relationships of control families (Klassen, Miller, & Fine, 2004; Nijmeijer et al., 2008; Wehmeier, Schacht, & Barkley, 2010). Similarly, peer relationships could be problematic due to difficulties of those with ADHD in establishing and maintaining social relationships, often leading to peer rejection. These strained relationships seem characterised by inability to take turns in conversations, oppositionality, intrusiveness and negative and intense emotionality (Gardner & Gerdes, 2015; Nijmeijer et al., 2008; Wehmeier et al., 2010). Educational and social impairments negatively affect self-esteem and quality of life of youth with ADHD and their families in comparison to typically developing controls (Klassen et al., 2004; Varni & Burwinkle, 2006; Wehmeier et al., 2010). These impairments are enduring and persists into adulthood, (Barkley et al., 2006; Bussing et al., 2010;

Galéra, Melchior, Chastang, Bouvard, & Fombonne, 2009; Klein et al., 2012) even in those who no longer meet criteria for a full ADHD diagnosis (Kadesjo & Gillberg, 2001; Klein et al., 2012). In particular, adults with childhood ADHD show poorer occupational outcomes, resulting in a lower socio-economic status (Barkley et al., 2006; Hechtman et al., 2016; Klein et al., 2012), and less stable relationships leading to greater number of divorces compared to controls (Barkley et al., 2006; Klein et al., 2012; Rokeach & Wiener, 2018). Those with ADHD as children also have greater occurrence of legal problems in adulthood, as they seem to have a greater history of incarceration than peers without this neurodevelopmental condition (Klein et al., 2012; Lichtenstein et al., 2012; Young, Moss, Sedgwick, Fridman, & Hodgkins, 2015). Finally, adult life of those with childhood ADHD also appears to be characterised by greater mortality rates, mainly related to unnatural accidents; in particular they have twice the risk of premature death compared to those without this condition as children (Dalsgaard, Ostergaard, Leckman, Mortensen, & Pedersen, 2015; Sun et al., 2019). This empirical evidence draws a concerning picture for individuals with ADHD and it should be noted that the risk of such negative outcomes increases in those with comorbid conditions. Coexisting psychiatric symptoms and diagnoses in individuals with ADHD are associated with greater school problems, such as poorer performance on academic standardised tests compared to individuals with ADHD alone (Larson et al., 2011; Loe & Feldman, 2007). The co-occurrence of ADHD and comorbid conditions also has a negative impact on perceived quality of life (Klassen et al., 2004). Additionally, those with ADHD and other psychiatric disorders show poorer family and social relationships than those with ADHD alone (Hurtig et al., 2007; Larson et al., 2011; Wehmeier et al., 2010). The risk of these impairments seems to be greater as the number of comorbid conditions increases (Larson et al., 2011), and especially in the presence of comorbid ODD/CD (Wehmeier et al., 2010). Similarly, the presence of ODD/CD negatively impacts on health and social outcomes, as individuals with ADHD and comorbid disruptive disorders (i.e., ODD/CD) are more likely to show substance

abuse (especially alcohol and cigarettes) and criminal behaviours, such as stealing and use of violence (Langley et al., 2010). Early antisocial behaviours in ADHD are also potential predictors of criminal behaviours as observed in incarcerated populations (Jensen & Steinhausen, 2015). Additionally, the presence of both ODD/CD and SUD is associated with greater mortality rates (Dalsgaard et al., 2015). Even the presence of internalising comorbidity is associated with a worse prognosis; previous work has shown that children and adolescents with ADHD and comorbid anxiety disorders are at increased risk for strained family relationships and more school and peer problems compared to those with ADHD alone (Bowen, Chavira, Bailey, Stein, & Stein, 2008). Taken together these findings suggest that although ADHD functional outcomes are heterogeneous, for some cases an ADHD diagnosis increases the risk of negative functional impairments over the course of development. The presence of comorbid psychiatric symptoms and conditions is associated with a worse prognosis, which remarks the need of addressing the clinical heterogeneity of ADHD in the attempt to prevent such broad impairments that are matter of public health concern.

Severe irritability in those with ADHD

Severe irritability is common in individuals with ADHD. More precisely, although irritability is not uniquely associated with ADHD, 25% to 50% of children with this condition show irritability when comprised in the broader phenotype of Emotional Dysregulation (Faraone et al., 2019; Shaw et al., 2014). As briefly noted in section 1.1.4 of this chapter, ADHD is also the most common condition associated to chronic and severe irritability in the form of SMD and DMDD with rates up to 86% (Leibenluft, 2011). Additionally, a previous study using the same clinical ADHD sample as the one considered in this PhD found that 92% of children with ADHD endorsed irritable symptoms, especially losing temper and temper tantrums (Eyre et al., 2017). Severe irritability is also associated with poor clinical and functional outcomes in those with

ADHD. More precisely, the presence of severe irritability in this clinical group is linked to the high cross-sectional and longitudinal prevalence of comorbid internalising and externalising conditions, such as ODD/CD, Substance Abuse Disorder, and mood disorders (Biederman, Petty, et al., 2012; Biederman, Spencer, et al., 2012; Eyre et al., 2017, 2019; Sobanski et al., 2010). Further evidence has shown that severe irritability could predispose children and adolescents with ADHD to this wide range of psychiatric conditions. More specifically, compared to controls, in this clinical population severe irritability seems to increase and mediate risk for both internalising (Anastopoulos et al., 2011; Karalunas et al., 2014; Seymour et al., 2012; Seymour, Chronis-Tuscano, Iwamoto, Kurdziel, & MacPherson, 2014) and externalising conditions (Anastopoulos et al., 2011; Karalunas et al., 2014; Rosen, Walerius, Fogleman, & Factor, 2015). This predisposition seems to be independent of comorbid psychiatric disorders (Karalunas et al., 2014; Seymour et al., 2012, 2014). In terms of functional outcomes severe irritability in those with ADHD seems associated with ADHD symptom severity, behavioural, emotional, school and social problems (Biederman, Petty, et al., 2012; Biederman, Spencer, et al., 2012; Bunford, Evans, & Langberg, 2014; Mulraney, Zendarski, Mensah, Hiscock, & Sciberras, 2017; Sobanski et al., 2010). Similar functional impairments linked to severe irritability in those with ADHD are shown across time from childhood to adolescence and they are observed both when comparing individuals with ADHD and severe irritability against typically developing controls and most importantly, against those with ADHD alone (Biederman, Petty, et al., 2012; Biederman, Spencer, et al., 2012). Additionally in youths with ADHD, severe irritability shows associations with sleep problems (e.g., reduced sleep duration), high rates of hospitalisation, and poor parental mental health (Biederman, Petty, et al., 2012; Graziano, McNamara, Geffken, & Reid, 2011; Mulraney et al., 2017; Nixon et al., 2008). Finally, severe irritability in children with ADHD is also associated with self-perceived low self-esteem especially in terms of poor quality of social relationship with peers and parents, poor well-being and less

confidence in physical appearance (Ek, Westerlund, Holmberg, & Fernell, 2008). Symptoms of irritability are also common in adults with ADHD (44%-73%) or those with a past history of childhood ADHD (~36%), and they contribute significantly to impairments in social, familial and romantic relationships, as well as to poor financial/occupational outcome, quality of life, unsafe driving and criminal behaviours (Barkley & Fischer, 2010; Barkley, Murphy, & Epstein, 2010; Skirrow & Asherson, 2013; Surman et al., 2013). It should be noted that the influence of additional comorbid conditions in explaining poorer functional outcomes associated with severe irritability in those with ADHD is yet to be understood. Despite being under-researched in children and adolescents with ADHD, preliminary evidence seems to suggest that the association between severe irritability and functional impairments is independent of the presence of comorbid symptoms and conditions (Bunford et al., 2014; Skirrow & Asherson, 2013; Sobanski et al., 2010; Surman et al., 2013), although there are some findings to the contrary (Bunford et al., 2014; Mick, Spencer, Wozniak, & Biederman, 2005) and the different operationalisations of severe irritability used, such as defining irritability within Emotion Dysregulation/Lability, limit the conclusions that can be drawn.

Overall, these findings suggest that the negative clinical and functional impact of severe irritability in youths with ADHD does not seem to be a mere epiphenomenon of other comorbid psychiatric conditions. Most importantly, this severe phenotype appears to be a source of variation, which may be related to the broad patterns of comorbidity of ADHD with both internalising and externalising clinical correlates. Understanding the pathological mechanisms of severe irritability in those with ADHD by might therefore contribute to explain the problematic heterogeneity associated with this neurodevelopmental disorder, enabling a better understanding of ADHD and the development of tailored interventions that might possibly reduce the broad functional impairments too.

1.2.4 Risk factors for ADHD: genes and environment

Considering the wide phenotypic heterogeneity of ADHD, it is not surprising that there is not a single cause of the disorder. The aetiology of ADHD has a complex architecture involving both genetic and environmental risk factors. ADHD risk is shown to be continuously distributed across the population, thus the same genetic and environmental risk factors are involved in ADHD and differences between affected and non-affected individuals are quantitative rather than qualitative (Chen et al., 2008; Demontis et al., 2018; Larsson et al., 2012). According to this dimensional model of disease, ADHD is just the extreme end of this distribution of risk that operates across the inattentive and hyperactive-impulsive symptoms (Chen et al., 2008; Larsson et al., 2012). A very large twin study has confirmed this dimensional nature of ADHD in both males and females (Larsson et al., 2012).

Genetic Risk Factors

ADHD is known to run in families; the estimated heritability ranges from 60% to 80% with a 5 to 9-fold increased risk in proband's siblings of developing the condition (Biederman et al., 1992; Biederman, Faraone, Keenan, Knee, & Tsuang, 1990; Chen et al., 2008; Faraone & Larsson, 2018); these high heritability estimates seem to persist across the life span (Larsson, Chang, D'Onofrio, & Lichtenstein, 2014). Different genetic study designs have tried to investigate more specifically the genetic architecture of ADHD to identify underlying aetiological and pathophysiological pathways leading to this condition. Initially, within molecular genetic research, candidate gene studies dominated this field, looking at specific genes in the aetiology of ADHD. These candidate genes, thought to be involved in ADHD, were selected aprioristically and their choice was mostly informed by pharmacological treatments that flagged the importance of monoamine neurotransmitter systems, namely dopamine, serotonin and noradrenaline (Banaschewski, Becker, Scherag, Franke, & Coghill, 2010; Gizer, Ficks, & Waldman, 2009; Hawi et al., 2015). Other promising

genetic candidates possibly involved in ADHD affect neuronal transmission, outgrowth and plasticity; however overall these polymorphisms only accounted for a negligible proportion of ADHD heritability (Cortese & Coghill, 2018; Gizer et al., 2009; Hawi et al., 2015). Technological advances enabled a paradigm shift moving from candidate genes to more promising and powerful hypothesis-free design: The GWAS, aiming to identify Single-Nucleotide Polymorphisms across the entire genome. A recent population-wide GWAS has identified 12 regions (i.e., loci) involved in the aetiology of ADHD (Demontis et al., 2018). SNPs on these loci encompass genes involved in neurodevelopmental processes, such as synapse formation, neuronal development and plasticity; they explained overall 22% of ADHD heritability and each individually has a modest odds ratios (OR= 1.08 to 1.98) (Demontis et al., 2018). Interestingly, the genes identified do not overlap with previous candidate genes of molecular genetic studies (Demontis et al., 2018; Hawi et al., 2015). Evidence from the study of common genetic variants also shows a consistent genetic risk overlap between ADHD and comorbid psychiatric symptoms and diagnosis, in particular depression, Bipolar Disorder, autism spectrum disorder, schizophrenia and anxiety (Anttila et al., 2018; Demontis et al., 2018; Du Rietz et al., 2018; Hamshere, Stergiakouli, et al., 2013; Schork et al., 2019). This suggests a pleiotropic effect of these common genetic variants that could also act through shared intermediate phenotype, such as cognitive functioning; this might be particularly relevant especially considering the negative correlation between ADHD and cognitive ability, also shared by other psychiatric conditions (e.g., schizophrenia) (Anttila et al., 2018; Du Rietz et al., 2018). Finally, common genetic risk also links ADHD with increased risk-taking behaviours that have negative health outcomes, such as smoking, obesity, alcohol use and substance abuse (Anttila et al., 2018; Demontis et al., 2018; Du Rietz et al., 2018). Recent evidence suggests that these common genetic variants shared across psychiatric conditions could affect genes involved in foetal neurodevelopment of the brain (Schork et al., 2019). Common genetic variants specifically associated with

ADHD also seem to contribute to the persistence of ADHD over time, as well as to the ADHD diagnostic status and symptom severity; notably, persistent trajectories of ADHD symptoms were linked to a greater burden of ADHD common genetic variants (Riglin et al., 2016; Stergiakouli et al., 2015). Additionally, this common genetic risk obtained from clinical samples contributes to subclinical level of ADHD symptoms in the general population (Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2014) and viceversa, ADHD common genetic variants obtained in population samples is also associated with ADHD diagnostic status and symptom severity in ADHD clinical samples (Stergiakouli et al., 2015). This further confirms the pivotal role of genetic risk factors in the pathophysiology of ADHD (Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2014).

Genetic research on ADHD has also focused on rare mutations that affect less than 1% of individuals in the general population; these are called Copy Number Variants (CNVs) and consist of duplications or deletions of sections of the genome (e.g. >100kb in length) (Faraone & Larsson, 2018). Previous research has shown that CNVs are consistently present in ADHD, with a prevalence around 15% compared to the 7% of controls, representing a 2.09 increased risk of having a large, rare CNVs (Williams et al., 2010). These estimates increase dramatically in those with ADHD and comorbid learning disability, where CNVs have been found in 42% of individuals (Williams et al., 2010). These CNVs seem to be linked to genes involved in learning, central nervous system development and in neuronal signalling (Elia et al., 2010). Similarly to common genetic variants, CNVs have also been found to be enriched in loci reported to be involved in schizophrenia and autism, further supporting the genetic overlap across psychiatric conditions (Elia et al., 2010; Thapar et al., 2016; Williams et al., 2010). However CNVs only explain 0.2% of ADHD heritability (Cortese & Coghill, 2018) and as they are rare, genetic studies investigating CNVs require a very large sample. Taken together this evidence suggests that ADHD has a strong genetic component with a complex architecture, composed of common and rare genetic

variants, with some specific genes involved identified, but many more to be discovered. Investigating both common and rare genetic risk is therefore needed, and this is further supported by both additive and multiplicative effects of these types of genetic variants found to contribute to ADHD disease risk (Martin, O'Donovan, Thapar, Langley, & Williams, 2015). However, common genetic risk explains only the 22% of the large ADHD heritability; this low estimate might be due to the relationships between genetic risk factors and environmental risk factors, possibly leading to ADHD.

Environmental Risk Factors

Twin studies show a negligible contribution of shared environment as opposed to a greater importance of unique environment in the aetiology of ADHD (Nikolas & Burt, 2010). Environmental factors potentially conveying risk for ADHD have been identified both prenatally and postnatally; some environmental risks are represented by early exposure to maternal smoking, alcohol, and toxic chemicals (e.g., organophosphate pesticides), as well as low birth weight and premature birth (Cortese & Coghill, 2018; Faraone et al., 2015). The association of these environmental risks with ADHD is however weak and further investigations revealed that the increased risk for ADHD associated with some of these environmental factors might be due to the confounding effect of genetic factors (Cortese & Coghill, 2018; Langley, Heron, Smith, & Thapar, 2012). Preterm birth and severe deprivation are risk factors that do not seem to be accounted for by genetic factors, however these risks are not specific to ADHD but rather are risk factors for a broad range of psychiatric conditions (Cortese & Coghill, 2018; Faraone et al., 2015). Severe maternal deprivation is also more specifically associated with ADHD-like symptoms rather than ADHD diagnosis (Stevens et al., 2008). Additionally, a mechanism that can account for the difference between high heritability estimates and the small variance explained by the common and rare genetic risk variants identified is the interplay between genes and environment.

Investigation into gene-environment interactions are therefore worth exploring, although overall so far it yielded inconclusive results; possibly this is due to the low power of previous studies to detect an effect as very big samples are needed to address this matter properly (Faraone et al., 2015). Nonetheless, despite the most studies being underpowered and the complexity of studying environmental risk factors and gene-environment interaction, studies in this area revealed a modest and non-specific role of the environment in the aetiology of ADHD.

In conclusion, the genetic, environmental, and gene-environment risk factors identified so far do not account for the whole ADHD heritability and its high estimates reported by twin studies. This suggests that more research in this area is needed to identify more robust factors involved in the aetiology of this condition. An alternative explanation considers the role played by heterogeneous clinical correlates of ADHD. As mentioned previously, ADHD is comorbid with a variety of psychiatric symptoms and diagnosis which is also observed at genetic risk level. Genes involved in the aetiology of ADHD overlap with genetic risk for a variety of psychiatric conditions; in other words, the same risk factors increase the risk for several psychiatric conditions, being therefore a-specifically associated with ADHD. In GWAS, this heterogeneity is found to reduce both the power to find significant genetic associations and the effect sizes associated with the common genetic variants contributing to disease risk (Manchia et al., 2013). Additionally, this variability suggests that the genetic risk variants identified might be relevant for distinct subgroups of individuals with ADHD with specific clinical profiles, and thus underly different aetiological pathways leading to this condition (Agid et al., 2013; Hayman, 2007). The high degree of comorbidity with ADHD might therefore be problematic for the identification of robust risk factors with big effect sizes, ultimately preventing both a deeper understanding of the aetiology of ADHD, and the possibility to delineate preventing strategies, effective and relevant for all cases of ADHD.

1.2.5 Neuro-functioning

ADHD is also associated with consistent structural and functional brain abnormalities. In terms of structure, recent mega-analyses reveal that the ADHD brain is characterised by a smaller volume in many regions, such as the frontal, temporal and cingulate areas, although strongest effect sizes are found for the total brain volume (Greven et al., 2015; Hoogman et al., 2017, 2019). Some regions in the brain of those with ADHD also differ from those of controls based on cortical thickness as individuals with ADHD show thinner temporal and fusiform gyrus areas (Hoogman et al., 2019). These results seem to be independent of the effect of sex, IQ (Intelligence Quotient) and comorbidity although there is an effect of age; differences in cortical volume and thickness are seen in children but not in adolescents and adults with ADHD (Hoogman et al., 2019). This seems to support the idea that those with ADHD are characterised by a cortical maturation delay compared to typically developing controls (Shaw et al., 2007). Similar volume abnormalities have been found also in relatives of probands confirming the familiarity of ADHD (Greven et al., 2015; Hoogman et al., 2019); a set of these areas with different volume also correlate with attention symptoms in the general population, providing further evidence in favour of a dimensional distribution of ADHD traits and risk in the general population (Hoogman et al., 2019). Meta-analytic findings from the field of functional neuroscience found both hypo- and hyper-activation of several brain networks, such as the frontoparietal and the attention networks involved respectively in goal-directed activities and decision-making, and attention orientation to relevant stimuli (Cortese et al., 2012). Abnormal functioning of the sensorimotor network has also been detected, possibly underpinning motor hyperactivity (Cortese et al., 2012). Finally, the default network, involved in lower cognitive processes and suppressed during cognitive performance, is characterised by hyperactivity in those with ADHD compared to controls, possibly suggesting interference in goal-directed activities (Cortese et al., 2012). Other findings show consistent hypoactivation of the ventral striatum, an area important for reward

processing and connected with the limbic system, highly involved in emotion processing (Plichta & Scheres, 2014). It should be noted that these functional and structural brain abnormalities are associated with small effect sizes and, despite the robustness of these findings, there are studies that fail to show brain differences comparing those with ADHD to controls (e.g., emotional and motivational network differences in Cortese et al., 2012). Once again, the heterogeneity of ADHD might play a role in these inconsistencies and small effect sizes, as the great degree of comorbidity in those with ADHD is shown to possibly mask the identification of brain differences comparing cases to controls (Adisetiyo et al., 2014).

It might also be worth considering that these differences in the activity and structure of the brain between youths with ADHD and controls might reflect ADHD impairments at the cognitive level. These impaired brain areas are indeed implicated in cognitive, motivational and emotional functioning, such as memory and response inhibition, reward processing, and emotion processing and regulation (Greven et al., 2015; Hoogman et al., 2017, 2019). Thus, these structural and functional differences in the brain could lead to ADHD symptoms by affecting cognitive functioning.

It should however be noted that ADHD is heterogeneous also in terms of cognitive functioning impairments (for more discussion see section 1.3.4 of this chapter).

In conclusion, there are several functional and structural differences in brain regions comparing ADHD to typically developing controls, although the role of the heterogeneity in terms of ADHD clinical correlates needs to be understood as possibly linked to the small effect sizes and inconsistencies found across studies. This appears to be highly relevant for the discovery of brain-related underpinnings of ADHD.

1.2.6 Treatment of ADHD

Pharmacological, behavioural, cognitive or, more often, combined interventions could all be used for those with ADHD. These are all recommended by the UK National Institute for Health and Care Excellence (NICE) guidelines (National Institute for

Health and Care Excellence, 2018) that indicate first-line treatments for ADHD, based on age and severity of this condition.

Pharmacological treatment is recommended for adults with ADHD and for school children or young persons with severe and consistently impairing ADHD symptoms who did not respond to non-pharmacological treatments (National Institute for Health and Care Excellence, 2018). The most common pharmacological treatments are psychostimulants, in particular methylphenidate and amphetamines, especially lisdexamfetamine and dexamfetamine, that are associated with a significant reduction of ADHD core symptoms as endorsed by multiple raters (Cortese et al., 2018; Faraone et al., 2015; National Institute for Health and Care Excellence, 2018). Methylphenidate is mostly used in children as proven to be effective as well as well tolerated and accepted by those with ADHD and their family (Cortese et al., 2018). Similarly, amphetamines are the preferential choice for the treatment of ADHD in adults achieving good standards in terms of effectiveness, tolerability and acceptability (Cortese et al., 2018). The efficacy of these treatments in reducing inattentive and hyperactive-impulsive symptoms seems independent of comorbidities, IQ and dose used (Cortese et al., 2018). It should be noted however that medications are a short-term option for the treatment of ADHD, as long-term effectiveness over a number of years is less well understood and there seem to be an adaptation to psychostimulants over-time (Rutter & Pickles, 2016). Furthermore, despite the efficacy of psychostimulants in reducing core symptoms of ADHD and comorbid disruptive behaviours (e.g., ODD and CD), impairing symptoms, such as Emotional Dysregulation, still persist (Shaw et al., 2014). This suggests that severe irritability and related constructs might still represent an adverse outcome, warranting tailored interventions; although one previous study seems to show promising effects combining stimulants and psychosocial treatment in reducing symptoms of severe irritability in this population (Blader et al., 2016).

According to NICE, pharmacological treatments are however not recommended for preschool children, school aged children and young people with mild ADHD. In this case, behavioural interventions, often addressed to parents but can involve children and adolescents as well, are recommended, such as parent-training, educational programmes and Cognitive-Behavioural Therapy (National Institute for Health and Care Excellence, 2018). Meta-analyses show evidence of behavioural treatments in reducing comorbid symptoms of ADHD (e.g., ODD/CD), as well as improving parenting skills, family functioning, and social and academic skills, with however only limited support in reducing ADHD core symptoms (Daley et al., 2014; Rimestad, Lambek, Zacher Christiansen, & Hougaard, 2019; Sonuga-Barke et al., 2013). It should be noted that the results are discrepant considering unblinded or blinded assessments, with the latter producing less empirical evidence on the efficacy of behavioural interventions (Daley et al., 2014; Rimestad et al., 2019; Sonuga-Barke et al., 2013).

Finally, other non-pharmacological treatments have been developed in the attempt to reduce ADHD core and comorbid symptoms and improve impairment, although these are not included in NICE. For instance, cognitive interventions and neurofeedback are also available and stem from the idea that neurocognitive impairments seen in ADHD mediate the pathophysiology and phenotypic expression of this condition (Cortese et al., 2015, 2016). Whilst cognitive training targets mostly working memory, inhibition and attention; neurofeedback aims to restore the aberrant pattern of brain activity seen in ADHD (Cortese et al., 2015, 2016). In meta-analyses, both cognitive training and neurofeedback yielded similar results of those obtained with behavioural interventions whereby when considering only well-controlled interventions with blinded raters, significant improvements were not robustly observed in either ADHD core symptoms or in cognitive impairments (Cortese et al., 2015, 2016; Sonuga-Barke et al., 2013; Van Doren et al., 2019). However, conclusions on the effectiveness of neurofeedback and cognitive training interventions should be made with caution due

to the recent development of these interventions, warranting further investigation. Additionally, systematic meta-analyses have been conducted only on EEG neurofeedback (Cortese et al., 2016; Sonuga-Barke et al., 2013; Van Doren et al., 2019), whereas neurofeedback can also rely on other techniques (e.g., Functional Magnetic Resonance Imaging) (Alegria et al., 2017; Marx et al., 2015), possibly yielding different results, but those have not been robustly investigated yet. Considering the high heterogeneity in clinical correlates, neurocognitive and biological underpinnings of ADHD, inconsistent results on ADHD treatment is not surprising (Feczko et al., 2019; Franke et al., 2018). Addressing the high variability of this neurodevelopmental condition is therefore a priority to develop more effective pharmacological, behavioural, and neurocognitive interventions.

To conclude, ADHD is the most common psychiatric condition in children and adolescence (Cortese & Coghill, 2018; Polanczyk et al., 2007). Despite the decrease in some symptoms and remittance for some over time, the associated impairments are very broad and enduring. ADHD however is very heterogeneous, especially in its clinical correlates, which makes it difficult to gain a complete understanding of risk factors, biological underpinnings and neurocognitive markers of this condition; this also has a negative impact on the development of preventative strategies and on the efficacy of treatments. Future research should therefore aim to understand this variability, considering in particular the public health relevance of this neurodevelopmental condition. In this section the potential role of irritability in explaining the clinical heterogeneity of ADHD is also illustrated, being a cross-diagnostic symptom and a possible source of heterogeneity.

1.3 Executive functions

This section covers a main aspect of this thesis that is cognitive functioning, describing its operationalisation in terms of Executive Functions (EFs) and showing its relevance for both irritability and ADHD.

1.3.1 Origin and definition

The term “Executive Functions” describe a variety of high order and top-down cognitive processes involved in goal directed activities and supported by the frontal lobes (Zelazo & Carlson, 2012). Historically, the conceptualisation of EFs developed from clinical studies investigating the variety of cognitive deficits displayed by patients with damages in the Prefrontal Cortex (PFC), a brain region anterior to the premotor and motor areas (Zelazo & Carlson, 2012; Zelazo & Muller, 2002). Based on these clinical observations, several cognitive processes have been identified that are grouped into Cool and Hot Executive Functions (Zelazo & Muller, 2002). Cool EFs refer to cognitive processes that take place during abstract and decontextualized scenarios, such as perception, attention, and memory. Counter to this, Hot EFs are involved in motivational and emotional contexts and are thought to require different cognitive processes than Cool EFs, such as reward-related and emotion regulation strategies (Zelazo & Carlson, 2012; Zelazo & Muller, 2002).

Cool and Hot EFs have been found to be independent in many aspects and using different methodological approaches. More precisely, individuals with brain lesions can show impairments in Hot but not Cool EFs and vice-versa (Zelazo & Carlson, 2012); this distinction is also supported at the brain level. In particular, Cool EFs are underpinned by the Dorsolateral Prefrontal Cortex (DL-PFC) whereas Hot EFs are associated with the activity of the Orbitofrontal Cortex (OFC) whose impairments often produce non-adaptive social and emotional behaviours. These brain regions show connections with distinct parts of the brain as well; the DL-PFC is associated with the

thalamus, part of the basal ganglia, the hippocampus and primary and secondary association areas that altogether enable the integration of both sensory and mnemonic information, and they also regulate the intellectual functions and actions (Zelazo & Muller, 2002). OFC shows connections with brain areas in the limbic system, such as the amygdala and it is important for the regulation of motivation, reward and emotion (Zelazo & Carlson, 2012; Zelazo & Muller, 2002). Finally, studies looking at overarching factors of different EFs have consistently shown a distinction between Hot and Cool EFs, as tasks measuring motivation and emotion tend to group together, and Cool tasks appear to load on separate factors to Hot EFs in factor analysis (Brock, Rimm-Kaufman, Nathanson, & Grimm, 2009; Kim, Nordling, Yoon, Boldt, & Kochanska, 2013; Willoughby, Kupersmidt, Voegler-Lee, & Bryant, 2011). This distinction between Cool and Hot EFs is also confirmed by factor analyses in clinical samples, especially in those with ADHD (Coghill, Seth, & Matthews, 2014; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Sonuga-Barke, Bitsakou, & Thompson, 2010; Sonuga-Barke, Dalen, & Remington, 2003). It is also important to note that, although Cool and Hot EFs are overall distinct at the phenotypical and neuroanatomical level, there are also shared neural connections and brain regions between DL-PFC and OFC (Zelazo & Carlson, 2012). This is also reflected by the functional overlap between Cool and Hot EFs as goal-directed activities normally take place in emotional or motivational settings but they also require Cool cognitive processes, such as information processing and planning, to be accomplished; nonetheless Cool and Hot EFs put emphasis of distinct processes underpinned by largely distinct brain regions (Zelazo & Carlson, 2012).

There are several Cool and Hot EFs, although the most relevant for this thesis are: behavioural inhibition and cognitive flexibility for Cool EFs, and temporal discounting, decision-making and reward processing for Hot EFs. *Behavioural inhibition* is a component of inhibitory control which is the ability to control cognitive processes, such as attention and behaviour, against an intense predisposition to respond to internal or

external circumstances (Diamond, 2013; Jurado & Rosselli, 2007). Behavioural inhibition refers specifically to the ability to successfully suppress preponderant motor responses to maintain goal-directed activities (Diamond, 2013). *Cognitive flexibility*, also known as set-shifting, is the ability to flexibly adjust one's behaviours to ever-changing environmental circumstances and demands to adaptively respond to them (Diamond, 2013; Jurado & Rosselli, 2007). Considering Hot EFs, *temporal discounting* is the tendency to devalue a reward as a function of time, the more the delay the lesser the value (Richards, Zhang, Mitchell, & de Wit, 1999). Similarly, *decision-making* is a complex cognitive function that enables individuals to make optimal decisions in emotional circumstances (i.e., those that involve rewards or losses) (Kerr & Zelazo, 2004). Finally, *reward processing* refers to several cognitive processes that enables to learn, predict, and respond to environmental contingencies, to achieve a goal (i.e., reward) (Brotman, Kircanski, & Leibenluft, 2017).

1.3.2 Developmental trajectories and impairments in EFs

EFs emerge early in life, around the end of the first year, when young children seem to use these skills as a reaction to environmental demands (e.g., avoid touching an attractive toy in response to a parental request); as they get older, they learn how to effectively process environmental stimuli, planning a more adaptive response (e.g., I should stop watching tv now, so I can watch more later) (Diamond, 2013; Garon, Bryson, & Smith, 2008; Jurado & Rosselli, 2007; Zelazo & Muller, 2002). EF skills seem to decrease in late adulthood as older adults tend to meet environmental demands with a decreased planning ability. Thus EFs developmental trajectories seem to follow a U-shape over the course of development (Diamond, 2013; Jurado & Rosselli, 2007; Zelazo & Muller, 2002). However, Cool and Hot EFs seem to follow slightly different developmental trends across childhood; they both develop at the end of the first year, but while Cool EFs seem to improve rapidly with age, to the point that 12-year olds perform as well as adults on many tasks (e.g., Wisconsin Card Sorting

Test – a measure of cognitive flexibility) (Zelazo & Muller, 2002), Hot EFs seem to develop at a slower rate (Zelazo & Carlson, 2012). These developmental differences seems to be present also at the anatomical level (Jurado & Rosselli, 2007; Zelazo & Carlson, 2012; Zelazo & Muller, 2002), suggesting a maturational delay of the OFC as opposed to the DL-PFC. A typical development of EFs is particularly important as it enables an individual to properly respond and to adapt to environmental demands. In fact, EF skills show associations with intellectual functioning (Brock et al., 2009; Hongwanishkul, Happaney, Lee, & Zelazo, 2005), academic functioning and achievement (Allan, Hume, Allan, Farrington, & Lonigan, 2014; Brock et al., 2009; Willoughby et al., 2011), suggesting that they are particularly relevant for school success. Additionally, EF skills seem to be important for physical health (Riggs, Spruijt-Metz, Sakuma, Chou, & Pentz, 2010) and they are also associated with a better quality of life (Davis, Marra, Najafzadeh, & Liu-Ambrose, 2010) in youths and adults. Counter to this, impaired cognitive functioning is associated with a variety of psychiatric symptoms and conditions (Diamond, 2013; Jurado & Rosselli, 2007), especially within the externalising domain (Granvald & Marciszko, 2016; Schoemaker, Mulder, Deković, & Matthys, 2013; Woltering, Lishak, Hodgson, Granic, & Zelazo, 2016). Taken together these findings suggest that Cool and Hot EFs appear to be distinct even in their developmental trajectories, and that both are important for a range of functional outcomes across development. This is further supported by the frequently observed EF impairments in clinical populations; this thesis focuses in particular on cognitive impairments in chronic and severe irritability and ADHD, outlined in the sections below.

1.3.3 Executive Functions and chronic and severe irritability

Executive Functions are relevant to research on severe irritability and this phenotype is particularly intertwined with the concept of reward, included in the Hot EF domain. The neuroscientific paradigm of irritability relies on the concept of “Frustrative Non-

Reward” (FNR), proposed by the NIMH and included within the Research Domain Criteria (RDoC) framework (Brotman, Kircanski, & Leibenluft, 2017; Lilienfeld, 2014). The RDoC is an alternative dimensional approach to mental illness developed by the NIMH that stems from dissatisfaction with the current diagnostic nosology (Lilienfeld, 2014). It is complementary to the DSM, which has been considered too reductionist and unable to capture the neurobiological underpinnings leading to the development and maintenance of psychiatric conditions (Garvey, Avenevoli, & Anderson, 2016). Within the RDoC, FNR is defined as an emotional state, characterised mostly by anger, induced by frustrating circumstances, for example in scenarios where the attainment of a previously available reward is blocked (e.g., a child who must stop playing a videogame to do other duties) (Leibenluft, Blair, et al., 2003). This conceptualisation of irritability seems to have biological foundations as previous work using animal models showed that mice react with aggressive behaviours and increased activity when facing frustrating circumstances (Amsel, 1958; Burokas, Gutiérrez-Cuesta, Martín-García, & Maldonado, 2012); similar behaviours have been observed in primates (Davenport & Thompson, 1965) as well as children (Deveney et al., 2013; Perlman, Luna, Hein, & Huppert, 2014; Ryan & Watson, 1968). As mentioned previously (Chapter 1, section 1.1.3), the discomforting emotion of anger that follows frustration is a normative and possibly adaptive reaction, however compared to typically developing peers, severely irritable youths seem to respond differently to this FNR paradigm. In particular, they seem to display both a lower tolerance of frustration, and a more intense and dramatic emotional response, with a greater duration (Deveney et al., 2013; Leibenluft, Blair, et al., 2003; Perlman et al., 2015; Rich et al., 2011, 2007). In other words, severely irritable individuals react with dramatic and intense emotions to frustrating circumstances to which typically developing individuals react only mildly; this emotional response is also more enduring compared to peers.

Irritability from a cognitive perspective is also associated with other important Hot EFs related to reward processing. Frustrating circumstances are often precipitants of irritability as modelled by the FNR paradigm, however the increased efforts to achieve the withheld reward can induce Instrumental Learning (IL), that is the ability to learn and adjust to reward and punishment contingencies (Brotman, Kircanski, Stringaris, et al., 2017). Optimal IL is essential to adapt to the environment, as it would increase the chance of gaining a reward and avoid punishment in a variety of contexts (Brotman, Kircanski, Stringaris, et al., 2017). This is done by retaining behaviours that lead to reward and dropping those that lead to punishment, thus Instrumental Learning could reduce the probability of an individual incurring in frustrating circumstances. IL is a complex ability that contributes to more basic reward processing skills, such as the ability to value a reward, the ability to predict the instances when a reward is given, as well as the ability to learn from reward contingencies (Brotman, Kircanski, Stringaris, et al., 2017). Conversely, individuals with chronic and severe irritability seem to be characterised by impaired IL and related reward processing. In particular, impairments in this population are observed in reward prediction, reward learning and reward sensitivity (Brotman, Kircanski, & Leibenluft, 2017; Brotman, Kircanski, Stringaris, et al., 2017; Leibenluft, 2017b). Expected value representation, meaning the anticipated value attributed to a reward, is also impaired in those with severe irritability both at the neural and behavioural level, leading to suboptimal decision-making choices and failure to learn from environmental contingencies (White et al., 2014, 2013, 2016). Similar cognitive impairments are likely to increase the probability of individuals with chronic and severe irritability encountering frustrating circumstances, as they would struggle to value, learn, predict, and respond to reward contingencies, failing to attain the desired reward. This would in turn elicit the aberrant and enduring emotional response observed during FNR paradigms, compared to peers (Brotman, Kircanski, & Leibenluft, 2017). Empirical evidence on reward processing impairments in youths

with chronic and severe irritability is covered more in detail in Chapter 4. At this point in this thesis, it should however be remembered that the current conceptualisation of chronic and severe irritability is a recent construct and research on neurocognitive markers of this phenotypes is at its early stages, therefore more empirical evidence is necessary to validate reward processing as neurocognitive markers of irritability. This would be beneficial to both gain a deeper understanding of underpinnings of chronic and severe irritability as well as develop tailored interventions.

1.3.4 Executive Functions in ADHD

As mentioned previously, ADHD is a heterogeneous condition, and its heterogeneity also lies in neuropsychological impairments (Thapar & Cooper, 2016). Neuropsychological deficits in ADHD may overlap in an individual but there is no specific cognitive profile that identifies children with this neurodevelopmental disorder (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Thapar & Cooper, 2016). Consistent with the heterogeneous nature of ADHD, different neuropsychological models have been developed in the attempt to understand the origin and the extent of cognitive impairments in ADHD, possibly identifying pathways leading to this neurodevelopmental condition. For instance, the default-mode network model has acquired a great importance in the ADHD literature as failure to regulate this network seems to lead to lapses of attention, performance variability and impulsive behaviour. All these impairments are frequently observed in individuals with ADHD and they also interfere with goal directed activities (Sonuga-Barke & Castellanos, 2007). Counter to this, according to the state-regulation model, those with ADHD have consistent problems in regulating effort, arousal and activation, which refers to the physiological readiness to respond (Sergeant, 2000, 2005; Wahlstedt, Thorell, & Bohlin, 2009). These regulatory impairments are thought to disrupt cognitive processes and underpin the Reaction Time (RT) variability frequently observed in this condition (Sergeant, 2005; Wahlstedt et al., 2009). However, over the past decades the

dominant and more extensively studied model conceived ADHD as having impaired Executive Functions. The EF model (Barkley, 1997; Castellanos et al., 2006; Sonuga-Barke, 2002; Zelazo & Muller, 2002) also has a biological foundation as the PFC (the anatomical underpinning of EFs) is strictly intertwined with the dopamine system, the main target of ADHD pharmacological treatment (Fusar-Poli, Rubia, Rossi, Sartori, & Balottin, 2012). Additionally, ADHD core symptoms and executive functioning seem to be normally distributed in the general population, and these symptom severity and cognitive performance seem to be associated with one another (Petrovic & Castellanos, 2016). Historically, ADHD was thought to be characterised by a core inhibitory control deficit, disrupting Cool EFs in a cascade effect (Barkley, 1997), although this paradigm failed to explain the totality of ADHD cases. This failure to account for all ADHD cases determined a shift in the study of cognitive impairments in ADHD, suggesting that there are multiple aberrant pathways leading to this condition; the idea being that the heterogeneity of ADHD would be better accounted for by multiple deficits, as opposed to a single deficit in inhibitory control. In particular, empirical work stresses the importance of studying motivational and emotional aspects in ADHD. Impairments in Hot EFs are in fact shown to be robust in this clinical population, although less thoroughly studied compared to Cool EFs (Castellanos et al., 2006). Thus, ADHD is now more comprehensively conceptualised as having both Cool and Hot Executive Function impairments, which is also supported by neuroanatomical findings (Petrovic & Castellanos, 2016). More precisely, the most consistent Cool deficits in youths with ADHD appear to be poor inhibitory control, attention, working memory and vigilance. Working memory refers to withholding and updating task-relevant information for either further processing or for recall, within a span of a few seconds (Castellanos & Tannock, 2002; Diamond, 2013); whereas vigilance (i.e. sustained attention) is the ability to maintain a conscious focus and to keep processing stimuli with repetitive and dull features (McAvinue et al., 2015; Thapar & Cooper, 2016). Considering Hot EFs, meta-analyses show consistent

impairment in reward processing and decision-making, characterised by impulsivity and poor evaluation of consequences in individuals with ADHD, compared to typically developing controls (Dekkers, Popma, Agelink van Rentergem, Bexkens, & Huizenga, 2016; Jackson & MacKillop, 2016; Mowinckel, Pedersen, Eilertsen, & Biele, 2015; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Despite this established model, ADHD still shows a consistent amount of heterogeneity related to EF impairments. There is in fact a substantial proportion (7% to 29%) of those with ADHD who do not have any cognitive impairment, and among those who do show similar deficits, youths with ADHD can display impairments in Cool EFs (working memory, behavioural inhibition, set-shifting) and/or Hot EFs (e.g., delay aversion - the preference for smaller-immediate over larger-delayed rewards - and emotion processing) (Sjöwall, Roth, Lindqvist, & Thorell, 2013; Sjöwall & Thorell, 2018). Additionally, those with ADHD can fail multiple tasks tapping EFs, although generally individuals show impairments in one or two tasks more commonly than they fail multiple tasks (Nigg et al., 2005; Sjöwall et al., 2013; Sjöwall & Thorell, 2018). This seems to be consistent even when Cool and Hot EFs were rearranged into overarching factors, as empirical evidence reports cognitive impairment variability to a similar extent (Coghill et al., 2014; Nigg et al., 2005; Sonuga-Barke et al., 2010; Sonuga-Barke et al., 2003).

Overall, these findings show the relevance as well as the wide heterogeneity of executive functioning impairments in ADHD that neither looking at “single” EFs nor using factor solutions is able to reduce. This also suggests that these deficits are not required nor sufficient to formulate a diagnosis, nonetheless they appear to be relevant pathophysiological mechanisms at least for a subset of individuals with ADHD. More research is therefore needed in order to account for this cognitive heterogeneity, looking at possible sources of variability that can explain some of these cognitive impairments in ADHD. Considering the cognitive overlap in Hot EF deficits between chronic and severe irritability and ADHD, this phenotype might be a good candidate to serve this purpose.

In conclusion of this general introduction, chronic and severe irritability appears to be understudied, despite being a clinically relevant phenotype (see section 1.1). In particular, the NIMH task force highlighted the investigation of the nature, pathophysiological markers and aetiological factors of this phenotype as research priorities (Leibenluft & Avenevoli, 2014). Addressing these priorities in youths with ADHD might be particularly beneficial. This is due to chronic and severe irritability being highly prevalent in this population and associated with worse clinical and functional outcomes than ADHD alone (see section 1.2.3). The investigation of this phenotype in ADHD might additionally be beneficial in helping to understand the heterogeneity of ADHD, observed at the clinical, cognitive and aetiological levels, that ultimately impacts on clinical practice (see section 1.2.3). Considering that chronic and severe irritability is associated with a wide range of internalising and externalising conditions, and its Hot cognitive impairments overlap with those observed in ADHD, this phenotype appears to be a possible source of heterogeneity in this population. However, no study to date has investigated chronic and severe irritability as a source of heterogeneity in a sample of youths with ADHD. Thus, addressing the nature, pathophysiological markers, and aetiological factors of chronic and severe irritability in those with ADHD might enhance the understanding of both this phenotype, increasingly important to research and clinical practice, and the heterogeneity of ADHD. This would ultimately enable the development of tailored and more effective interventions. This thesis addresses these knowledge gaps and research priorities as follows.

1.3.5 Thesis Aims

The main aim of this thesis is to explore the characterisation of chronic and severe irritability in a sample of children with ADHD and it is split into three specific aims, covered in Chapter 3, Chapter 4, Chapter 5.

- 1) The first aim, addressed in Chapter 3, is to investigate the nature of chronic and severe irritability. In particular, the validity of a bi-dimensional construct of this phenotype, exploring patterns of co-occurrent associations with clinical correlates of ADHD and further validate these, looking at longitudinal clinical associations and maternal psychopathology. This will inform how irritability will be conceptualised in subsequent chapters.
- 2) The second aim, addressed in Chapter 4, looks at Hot EFs (as opposed to Cool EFs) as a possible pathophysiological marker of chronic and severe irritability, using both a variable-driven and a data-driven approach. More precisely, this is a longitudinal study where chronic and severe irritability is measured in childhood and EFs in adolescence. This will inform of chronic and severe irritability as a possible source of cognitive heterogeneity and its impact on cognitive functioning in adolescents with ADHD.
- 3) The third aim, addressed in Chapter 5, explores the common genetic risk associated with childhood chronic and severe irritability and investigate possible associations with cognitive performance. This will inform of the genetic underpinnings of chronic and severe irritability that could be useful to understand biological mechanisms that impact on adolescents with ADHD.

Taken together these investigations will increase the understanding of chronic and severe irritability in terms of its nature, pathophysiological markers, and risk factors, ultimately answering to the research priorities in this field as outlined by the 2014 workshop (Leibenluft & Avenevoli, 2014). Additionally, considering the relevance of this phenotype in ADHD, addressing these aims could help identifying and eventually explain the heterogeneity of ADHD at the behavioural, cognitive, and genetic level.

The following chapter (Chapter 2) describes the methods used across all the studies that are part of this thesis; whereas Chapter 6 discusses the overall findings from the three main aims of this thesis, especially in terms of clinical implication, strengths and limitations, and future directions.

Chapter 2

Methods

Chapter description

In this thesis a clinical sample of children with ADHD was used across the different studies. Longitudinal data was also collected on a subsample of these children. In particular, Chapter 3 uses both the baseline data from this clinical ADHD sample, as well as follow-up data from those available, whereas Chapter 4 and Chapter 5 only focus on participants for whom follow-up data was available. This chapter describes the recruitment, assessment procedures and methods related to this sample within and across time.

2.1 Sample

2.1.1 Baseline

This clinical ADHD sample is composed of children who participated in the SAGE study at Cardiff University. The study took place between 2007 and 2011. Participants were recruited from child psychiatry and paediatric clinics across the UK, where clinicians asked families of children aged 6-18 years, and with either a suspected or ascertained ADHD diagnosis, if they would be interested in taking part in research. Contact details of families who assented were then passed on to the research team who contacted them by phone, conducting a brief screening interview. This interview aimed to check the inclusion and exclusion criteria to determine the eligibility and willingness of the family to participate in the study. Children were considered eligible if they had a clinical diagnosis of ADHD or if they were going through diagnostic assessment for ADHD when they were first contacted. Only British Caucasian children were taken forward in the study, as relevant for the genetic analyses. Finally, children had to be living with at least one biological parent. Exclusion criteria related to the child having a common neurological, neuropsychiatric, or genetic disorder, namely fragile X syndrome, tuberous sclerosis, epilepsy, and psychosis. Children with any Tourette syndrome, autism, or pervasive developmental disorder, as specified by the DMS-IV and ICD-10 guidelines, were also excluded. Notably, a low IQ (conventionally < 70) was not considered an exclusion criterion to account for the heterogeneity of clinical samples commonly seen in psychiatric clinics. Once children were screened, the research team scheduled home visits with eligible participants to proceed with the assessment protocol. An invitation letter was also sent out to family homes, together with details of the study, consent forms, questionnaires to complete ahead of the visit, and a reminder of the date and time of the appointment. Research visits were conducted by a pair of trained psychologists, one conducting the parent assessment

and the other the child assessment. For the purpose of genetic analyses, a venous blood or saliva sample was also collected from the child and both parents, where possible. Following the home assessment that was overall 2-3 hours long, a research report summarising the main clinical and neuropsychological findings was written for all participants and sent to the referring clinician. Finally, a £15 voucher was given to the families to thank them for their participation in the study, whilst regular newsletters were sent to keep these families updated on relevant aspects of the study, such as the results.

Before taking part in the study, parents had to sign a consent form as did those participants aged 16 years or older. For participants 15 years of age or younger, a written assent form was collected. Ethical approval was obtained from the Wales Multicentre Research Ethics Committee (reference number: 06/MRE08/75). This study was funded by the Wellcome Trust (Grant No: 079711).

2.1.2 Follow-up

Families who took part in the SAGE study, and who consented to be contacted for future research, were asked if they were interested in taking part in a follow-up study that ran at Cardiff University from 2011 until 2016. Initially, only boys aged 10-17 years and with an IQ > 70 were considered eligible, and they were followed up two to five years after their original participation (two and a half years later, on average). These inclusion criteria were then broadened to be inclusive of females and younger children with a broader range of IQ. Families who agreed to take part were sent clinical questionnaires through post and then invited to Cardiff University for further assessment. Diagnostic interviews, clinical questionnaires, and questionnaires about the young person were administered to parents, whilst adolescents completed research diagnostic interviews and neuropsychological tasks. The research protocol was delivered by two trained psychologists.

The assessment took approximately 4-5 hours, after which families received £25 as a thank you for their participation, in addition to their food and travel expenses.

The UK Medical Research Council fund this research (grant number: G1000632) and ethical approval was obtained from the Wales Multicentre Research Ethics Committee (reference number: 11/WA/0050). Parents (and adolescents over the age of 16) gave written informed consent, whilst children gave written informed assent.

2.2 Assessment Measures

This section describes the assessment measures used to collect both baseline and follow-up data, a summary of these methods are shown in Figure 2.1. It should be noted that both the baseline and follow-up data collection preceded the publication of DSM-5, released in 2013 (American Psychiatric Association, 2013) and/or used clinical measures based on previous versions of the DSM. Therefore, ADHD research diagnosis was formulated following DSM-IV or DSM-III-R criteria (American Psychiatric Association, 1987, 2000). Following the publication of DSM-5 and considering the changes to ADHD diagnostic criteria, data for all participants was reassessed for DSM-5 ADHD diagnosis by two child and adolescent psychiatrists.

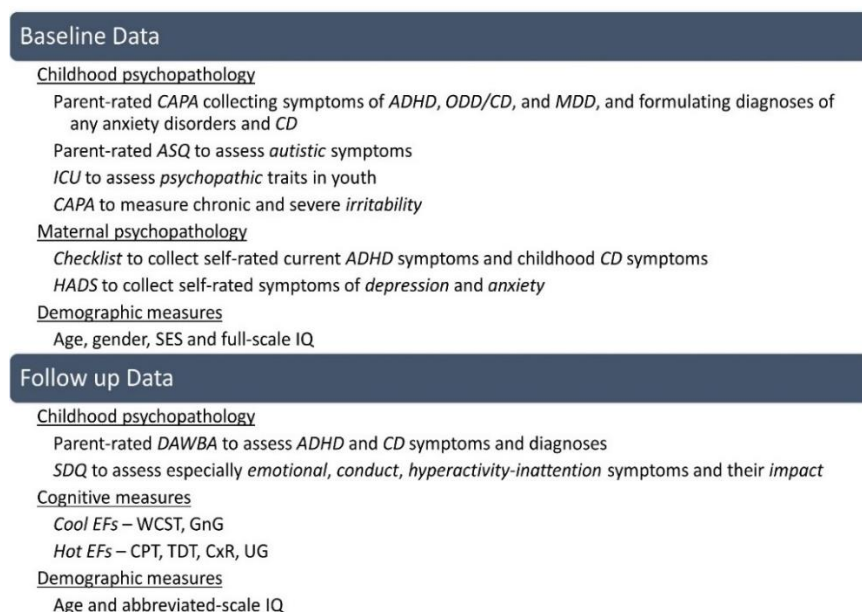


Figure 2.1 Summary of the different baseline and follow-up assessment measures

CAPA = Child and Adolescent Psychiatric Assessment; ADHD = Attention Deficit Hyperactivity Disorder; ODD = Oppositional Defiant Disorder; CD = Conduct Disorder; MDD= Major Depressive Disorder; ASQ = Autism Screening Questionnaire; ICU = Inventory of Callous-Unemotional Traits; HADS = Hospital Anxiety and Depression Scale; SES = Social Economic Status; DAWBA = Development and Well-Being Assessment; SDQ = Strengths and Difficulties Questionnaire; EFs = Executive Functions; WCST = Wisconsin Card Sorting Test; GnG = Go no Go; CPT = Card Playing Task; TDT = Temporal Discounting Task; CxR = Choice per Risk Task; UG = Ultimatum Game.

2.2.1 Baseline Measures

Child Psychopathology

Child psychopathology was assessed using the parent version of the Child and Adolescent Psychiatric Assessment (CAPA), a semi-structured psychiatric interview covering the presentation of a wide range of clinical symptomatology within the preceding 3-months (Angold & Costello, 2000). The CAPA was specifically used to make research diagnoses and to collect symptoms related to ADHD, Oppositional Defiant Disorder / Conduct Disorder, Separation Anxiety Disorder, Generalised Anxiety Disorder, Social Anxiety Disorder and Major Depressive Disorder. Where psychiatric symptoms were endorsed, impairment was also assessed, including for ADHD. In particular, for each area where symptoms were present, parents had to rate their child's impairment in different areas of functioning: home, social interactions, community activities, school, sports / clubs, learning to take care of oneself, play / leisure activities and handling of daily chores / responsibilities. Impairment was rated on a 4-point Likert scale where 0 is 'never', 1 is 'rarely', 2 is 'sometimes' and 3 'often', with scores of 2 and 3 considered indicative of impairment in the relevant area of functioning. Thus it was possible to derive a continuous score of ADHD burden, summing up the impairment rated in different settings, with scores ranging from 0 to 8 consistent with previous research (Agha, Zammit, Thapar, & Langley, 2013). In

addition to impairment, the pervasiveness of symptoms across settings is required to formulate an ADHD diagnosis. This criterion was confirmed by teachers using the Child ADHD Teacher Telephone Interview (ChATTI) (Holmes et al., 2004), a telephone interview investigating ADHD core symptoms and school impairment. Whenever the research team struggled to get in contact with teachers to assess the ADHD impairment, they sent out to schools the Conner's Teacher Rating Scale (Conners, Sitarenios, Parker, & Epstein, 1998) and the DuPaul teacher rating scales (DuPaul, 1991) for teachers to complete. For each measure, the pervasiveness criterion was met if teachers endorsed at least one symptom for each ADHD core domain, plus impairment.

All interviewers undertook comprehensive training and had weekly supervisions with an experienced child and adolescent psychiatrist. They also maintained a high level of inter-rater reliability; the kappa for ADHD diagnosis was 1.00 and parent-rated CD symptoms also showed a very good inter-rater reliability with intra-class correlation of .98.

Parent-rated autistic symptoms were collected using the Autism Screening Questionnaire (ASQ), a 40-item measure assessing symptoms in the domain of social interaction, language and communication, and repetitive and stereotyped behaviours (Berument, Rutter, Lord, Pickles, & Bailey, 1999). ASQ items are scored 0 or 1 to indicate the absence and presence of autistic symptoms, respectively. A 0 to 39 total score is computed summing individual items, except for the first item investigating current language level which is not included in the total score.

The parent-rated version of the Inventory of Callous-Unemotional Traits (ICU) was also included in the clinical assessment. This measure aimed to assess callous and unemotional traits in children and adolescents, as indexed by three subscales: callous, unemotional and uncaring (Kimonis et al., 2008; Moore et al., 2017;

Willoughby, Mills-Koonce, Waschbusch, & Gottfredson, 2015). The ICU is composed of 24 items; responses on each item were made on a scale from 0 to 3, ranging from “not at all true” to “definitely true”. ICU total score was computed summing items, with a maximum obtainable score of 72.

Chronic and Severe Irritability

A measure of chronic a severe irritability was obtained post hoc, extracting items from the ODD and Depression sections of the CAPA (Angold & Costello, 2000), consistent with previous works (Copeland et al., 2015; Eyre et al., 2017). In particular, from the ODD section the items “Losing Temper” and “Temper Tantrums” were considered, whereas from the Depression section the items selected were “Touchy or Easily Annoyed”, “Angry or Resentful” and “Irritability”. Losing Temper refers to discrete episodes of shouting or name calling, whereas Temper Tantrums are similar discrete episodes but also characterised by violent behaviours against people or property. Irritable symptoms from the depression section are respectively manifested with the child being sulky (“Touchy or Easily Annoyed”), prone to resentment and anger under a minor provocation (“Angry or Resentful”), and with irritable mood characterised by enduring feelings of anger that persist between outbursts (“Irritability”).

To identify a more clinically relevant phenotype of irritability and thus, to operationalise irritability in its severity and chronicity, cut-offs based on frequency, pervasiveness and duration were applied. These cut-offs determined the presence and absence of each one of these five symptoms of irritability and they were chosen based on DSM-5 DMDD criteria, consistent with previous research on this sample (Eyre et al., 2017). More specifically, a symptom was considered as present if it was endorsed frequently within a week, for a period longer than 12 months and in more than one setting, details of these thresholds are reported in Table 2.1.

CAPA ITEMS	DESCRIPTION
“LOSING TEMPER” AND “TEMPER TANTRUMS”	Items extracted from the ODD section of the CAPA. CAPA considers the inconsistency with development.
FREQUENCY ≥ 36 (3 TIMES PER WEEK OVER 3 MONTHS)	Items must have a frequency of ≥36, consistent with the average of 3x per week over the 3-month period assessed by the CAPA, to be endorsed.
DURATION >12 MONTHS	Items must be present for more than 12 months at the expected frequency to be endorsed.
PERVASIVENESS IN AT LEAST TWO SETTINGS	Items must be present in at least two settings at the expected frequency to be endorsed.
“TOUCHY/EASILY ANNOYED”; “ANGRY/RESENTFUL”; “IRRITABILITY”	These items are extracted from the Depression section of the CAPA.
FREQUENCY >45 (PER WEEK OVER 3MTHS)	To be endorsed, these symptoms must have a frequency greater than 45, therefore being present more days than not, over the 3-month period of time assessed by the CAPA.
DURATION >12 MONTHS	These symptoms are endorsed if they are present for more than 12 months at the expected frequency.
PERVASIVENESS ACROSS AT LEAST TWO SETTINGS	Implicitly asked in question concerning irritable mood (i.e., “irritability” item).

Table 2.1 Criteria used to assess Chronic and Severe irritability with frequency/severity cut offs

Maternal Psychopathology

Maternal psychopathology was assessed using self-report questionnaires, investigating ADHD, Conduct Disorder, and Anxiety and Depression symptoms.

Current maternal DSM-IV/5 ADHD symptoms were collected using a DSM-based 18 item check-list, assessing the presence of ADHD symptoms in the last 6 months (American Psychiatric Association, 2000, 2013). Symptoms were considered as present if items had a score of at least 2 on a 4-point Likert-scale (0 “not at all”, 1 “just a little”, 2 “pretty much” and 3 “very much”). A 0 to 18 total score for ADHD current symptoms was generated summing individual items. Additionally, Cronbach’s alpha for ADHD measures showed adequate reliability ranging from .91 to .94.

Similarly, mothers completed a self-rated DSM-IV/5 Conduct Disorder symptom checklist, assessing the presence of maternal CD symptoms in childhood, when mothers were 7 to 11 years of age. This checklist was composed of 15 items on scale from 0 to 3, where 0 is “never”, 1 is “rarely”, 2 is “sometimes” and 3 is “often”; symptoms were rated as “present” if mothers scored at least “sometimes”. Maternal childhood CD symptoms total score was computed, ranging from 0 to 15. Finally, it should be noted that ODD symptoms were excluded from this checklist.

Self-rated maternal anxiety and depression symptoms in the past week were collected using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). Anxiety and Depression subscales were composed of seven items each, focusing mostly on cognitive expression of anxiety (e.g., “worry a lot”) and anhedonia (i.e., pleasure no longer gained from previously enjoyable activities), respectively. Symptom severity was measured on a 4-point Likert scale, from “not at all” to “most of the time” and total scores were generated separately for the depression and anxiety scale, ranging from 0 to 21 each. The anxiety and depression symptoms were considered separately in this thesis. Cronbach’s alpha for the HADS depression scale in this study is .83.

Sociodemographic Measures

Demographic information on child sex, age, Social Economic Status (SES) and IQ were also gathered. In particular, SES was determined based on the occupation of the family member who earned the highest, following the guidelines of the UK Standard Occupation Classification (Office for National Statistics, 2000); this is also consistent with previous work (e.g., Agha, Zammit, Thapar, & Langley, 2017b). A dichotomous score of SES (i.e., low or not low) was then computed classifying families as having a low SES, if the main earner was in unskilled employment or unemployed

(Agha et al., 2017b). A full-scale measure of IQ was collected using the Wechsler Intelligence Scale for Children (WISC-IV) and used dimensionally (Wechsler, 2003). This full-scale is composed of 10 subtests measuring four main abilities: Verbal Comprehension, Perceptual Reasoning, Working Memory and Processing Speed. Finally, parents were also asked to provide information on any current ADHD medication used by the child.

2.2.2 Follow-up Measures

Youth Psychopathology

Adolescent psychopathology was measured at follow-up using the parent-rated version of the Development and Well-Being Assessment (DAWBA), a structured clinical interview investigating common emotional and behavioural DSM-IV disorders in the present and recent past (Goodman, Ford, Richards, Gatward, & Meltzer, 2000). Of relevance to this study, at this follow-up, parents were administered the ADHD and CD sections of the DAWBA from which continuous measures of symptom severity for both conditions were generated. Additionally, diagnoses of CD and ADHD were also derived following the DSM-5 diagnostic criteria as the DAWBA provides information on symptoms duration (where required), their burden on adolescent's life and their pervasiveness in family life, learning, social relations and leisure activities. It should however be noted that at this follow-up assessment, teacher-rated symptoms were not assessed, thus pervasiveness across settings was only endorsed by parents. The shorter DAWBA was administered instead of the previously used CAPA to reduce the duration of the assessment families were committed to.

The Strengths and Difficulties Questionnaire (SDQ), including the impact section, was also used to investigate psychological adjustments of youths as rated by parents (Goodman, 1999). In particular, the SDQ is composed of 25 items grouped into five

subscales, representing emotional, conduct, hyperactivity-inattention, peer problems and prosocial behaviours. Each item is rated on a 3-point Likert scale where 0 is "not true", 1 is "somewhat true" and 2 is "certainly true" and subscale scores are generated summing the relevant items (Goodman, 1997). Subscale scores for emotional, conduct, hyperactivity-inattention, and peer problems (excluding the prosocial subscale), are then added together to derive an adolescent's total difficulties score. In addition to these 25 items, the utilised version of the SDQ also investigates the impact of these adjustment problems. More precisely, parents are asked whether they think their children have a problem and if so, to rate how long this problem is lasting, and to what extent this represents a burden to either the parent or the family as a whole. Additionally, parents rate the distress these symptoms cause to their children and in terms of their impact on family life, friendship, learning and leisure. Scores on these items are then combined into a total impact score ranging from 0 to 10.

Finally, it should be noted that all measures were administrated by trained psychologists who undertook weekly supervision meetings with a child psychiatrist and a psychologist.

Cognitive Measures

In this section it is important to note that the cognitive measures described below are taken from a more comprehensive cognitive battery, originally selected as its tasks are widely validated and used in ADHD populations. The Cool and Hot tasks described below are the ones most relevant to this project, as being able to capture cognitive makers associated with chronic and severe irritability (more details are provided in Chapter 4). Cognitive tasks were administered by trained psychologists and participants were asked to suspend their ADHD medication 24h prior the assessment to prevent this affecting their performance on the cognitive battery.

Cool EF tasks

The “*Wisconsin Card Sorting Test*” (WCST) (Figure 2.2) is a measure of set-shifting behaviour, the ability to flexibly adapt one’s response to changes in positive feedback contingencies. The WCST is considered an indicator of prefrontal cortical functioning and it is designed for both children and adults, being sensitive to developmental changes (Chelune & Baer, 1986). During this task, participants need to discern matching criteria to sort a set of cards (Greve, 2001). These matching criteria rely on stimulus features such as colour, form or number and the criteria vary after 10 consecutive and correct trials. Based on received feedback, participants need to detect changes in the matching criteria and flexibly adapt their response to keep sorting the cards properly. The 64-card computerised version was used in this thesis (Greve, 2001). To detect impairments in set-shifting, total number of errors and perseverative errors were considered.

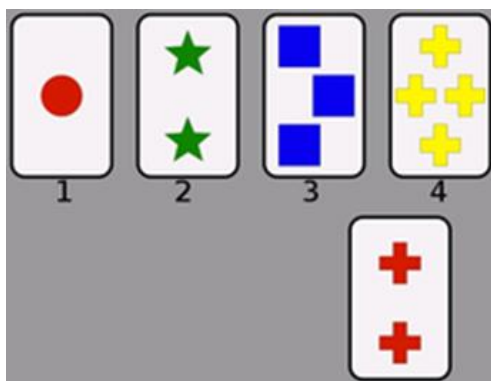


Figure 2.2 WCST task design

The “*Go no Go*” task (GnG) (Figure 2.3) is a measure of motor inhibition widely validated and extensively used in ADHD research (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; Rubia, Smith, & Taylor, 2007; Wahlstedt et al., 2009); its test-retest reliability is adequate, and it is used successfully to discriminate those with ADHD from typically developing controls (Wahlstedt et al., 2009). In this study the GnG task

is divided into two subtests of two minutes and 32 seconds each, each subtest measuring right and left-hand responses one at the time. Stimuli are presented in the middle of the screen for 300ms, with a 1.3 seconds blank screen in between. This task is administered in a block of 150 trials and the total duration was five minutes and four seconds. Participants are asked to either respond or inhibit a preponderant motor response according to the go or no-go stimuli showed on the computer screen. Specifically, participants need to press the appropriate arrow button (pointing left or right respective on the hand tested) as quickly as possible in the presence of a spaceship ("go" signal) and withhold their response in the presence of a green planet ("no go" signal). The spaceship is present in 73% of trials to induce a preponderant motor response, whereas the green planet is shown in only 27% of trials. Measures considered were Reaction Time to go signals and probability of inhibition, which is the percentage of responses to no-go signals (i.e. participant's response to the green planet) successfully inhibited. As complete data for both right and left hands was not available for all participants, only the dominant hand performance was considered.

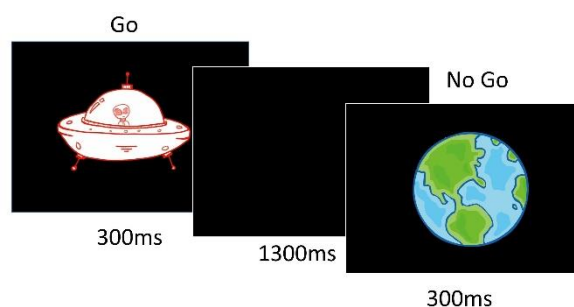


Figure 2.3 Go no Go task design

Hot EF tasks

The "*Card Playing Task*" (CPT) (Figure 2.4) is a measure of response perseveration when facing increasing loss, that indicates an individual's reward and punishment sensitivity (Newman, Patterson, & Kosson, 1987). To play, participants just need to click on the deck, and they are shown either a red (hearts or diamonds) or a black

(clubs or spades) card. If black, participants win £0.10 and they receive a feedback on the screen which says: "YOU WIN!"; if red, participants lose £0.10 and are shown a "YOU LOSE!" feedback on the screen. Participants start with no money and, on every trial, they are asked if they are willing to keep on playing the next card or to quit the game. The task involves a deck of 110 cards, divided in blocks of 10. The initial block has 100% probability of winning money but the probability of losing increases by 10% with each consecutive block, such that by the end of the task, punishment completely outweighs reward (Newman et al., 1987). More precisely, when the sum of £3.10 is reached, the deck of cards starts consistently to lose and ideally that is when participants should stop. The dependent variable was the total number of cards played before quitting as a measure of reward and punishment sensitivity.

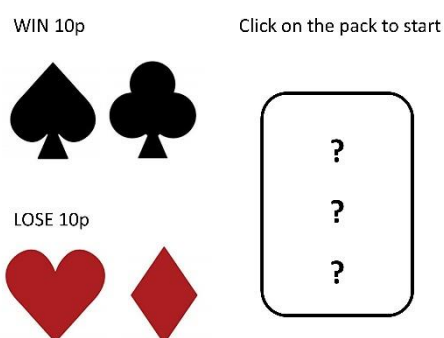


Figure 2.4 CPT Task Design

The “*Temporal Discounting Task*” (TDT) (Figure 2.5) measures the degree to which a reward is devalued in relation to its temporal delay, an index of impulsivity (Richards et al., 1999; Rubia, Halari, Christakou, & Taylor, 2009). In the TDT, participants choose, by pressing the relevant button, between a small and immediate monetary reward (ranging from £0 to £100) and a large reward (always £100) that is delayed by a week, a month, one year or two years. The TDT is composed of 20 trials for each type of delay and it lasts for 12 minutes; the rewards to choose from are randomly displayed for 4s on the right and left side of a computer screen, and each trial is

separated by an 8s blank screen. An algorithm is used to ensure equal number of immediate and delayed reward options are presented across the task, and it adjusts the immediate reward based on participant's previous choices to each of the four different delays. This adjustment determines the "indifference point", that is when the choice between the immediate and delayed reward is considered equivalent by the participant (Richards et al., 1999; Rubia et al., 2009). Typically reward discounting follows a hyperbolic function that depends on the amount, delay and k , a free impulsivity parameter calculated by fitting the hyperbolic function to the indifference point for each delay. Large values of k reflect a greater reward discounting (i.e., more impulsivity) (Richards et al., 1999). The dependent variables for this task were the difference in RT between delayed and immediate reward choice, and the Area Under the Curve (AUC) as a measure of impulsivity. The k parameter is normally the main impulsivity factor, however due to its hyperbolic function, it is associated with some measurement problems (e.g. very skewed distribution). The Area Under the Curve (AUC) is instead a good and a widely used alternative to measure temporal discounting (Myerson, Green, & Warusawitharana, 2006), whose values range from 0 to 1; larger AUC values represent less delay discounting (i.e. less impulsivity) (Myerson et al., 2006).

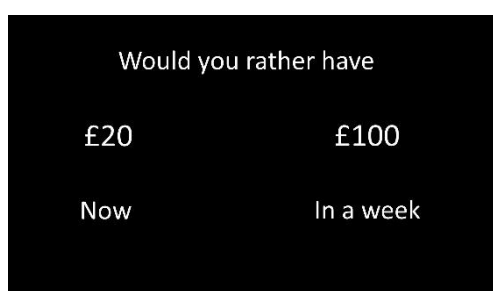


Figure 2.5 TDT task design

The "*Choice per Risk Task*" (CxR) is a measure of risk-taking behaviour and how it is affected by reward and punishment (Syngelaki, Moore, Savage, Fairchild, & van

Goozen, 2009). The aim of the CxR is to win as many points as possible by choosing between two wheels of fortune, an experimental wheel and a control wheel, displayed randomly on the right and left side of a computer screen. Each wheel has eight segments, each segment can make participants win or lose two different amounts of points (two or eight points for the experimental wheel and one point for the control wheel) at different probability (Figure 2.6). More precisely, the control wheel always has a 50% probability of winning or losing one point; thus, it has an equivalent number of segments (i.e., four segments) awarding or forfeiting one point (Figure 2.6). Contrarily, there are eight different types of experimental wheels that give a chance of winning or losing either two or eight points at a probability of 25% or 75%, depending on the wheel; some wheels are therefore riskier than others. Two additional positive and negative framing trial wheels are included to measure risk aversion and risk seeking, for a total of ten different types of experimental wheels. The negative framing trial (Figure 2.7) is characterised by a control wheel with a guaranteed possibility of gaining four points and an experimental wheel with 50% chance of winning either eight or zero points; whereas the positive framing trial has wheels with the same probability of losing the same amount of points on both the experimental and control wheels (Fairchild et al., 2009; Sully, Sonuga-Barke, Savage, & Fairchild, 2016; Syngelaki et al., 2009).

These wheels also differ on their relative Expected Value (ΔEV), that is the difference between the control and experimental wheel that the participant is presented with, providing information on how beneficial it is to choose the experimental wheel over the control one or vice versa. During each trial, participants with good decision-making skills and a reduced propensity to gamble are expected to choose the most favourable wheel based on the ΔEV , as that gives them the best chance of winning. For example, the control wheel has always an EV of 0, mathematically represented by the formula: $(0.5 \times 1) + (0.5 \times -1)$, where 0.5 is the probability of winning or losing, multiplied by the points the participant could gain or not. Whereas, an experimental wheel with 25%

chance of losing eight points and 75% probability of winning two points would have an EV of -0.5 ($(0.25 \times -8) + (0.75 \times 2)$). Therefore, in this example, it is safer to gamble on the control wheel than the experimental one, as their ΔEV is -0.5 relative to the experimental wheel.

The CxR task is composed of 4 blocks of 20 trials each (i.e. 80 trials in total); in each block the 10 different types of experimental wheels are presented twice, in a pseudo-randomised order. Participants choose a wheel by clicking with the mouse on the preferred wheel, which results in that wheel spinning and stopping on a particular segment awarding or forfeiting points. Each participant starts with 100 points at the beginning of each block and they are both given feedback on their choice and provided with the revised score for 2 seconds before the next trial. Several dependent measures were taken into account from this rich dataset. First, the overall propensity to gamble, measured as the percentage of times the experimental wheel was chosen as opposed to the control wheel. Second, participants' performance on six different types of experimental wheels, as a measure of risky decision-making. This measure is indexed by the number of times the experimental wheel was chosen for trial type *zero* and *three* which had value ± 8 and ∓ 2 with a probability of .25 or .75 of winning, respectively; for trial type *four* and *six* which had value $+8/+2$ and $-8/-2$ with a probability of .25 of winning, respectively; for trial *eight* which had values of 0 and -8 with a probability of .5 of winning and vice-versa (0; +8) for trial *nine* (positive and negative framing trials). Finally, participants' choice of the experimental over the control wheel after winning or losing small/big amounts (expressed as a percentage) was investigated, as an index of the impact of reward and punishment on risk-taking behaviour.

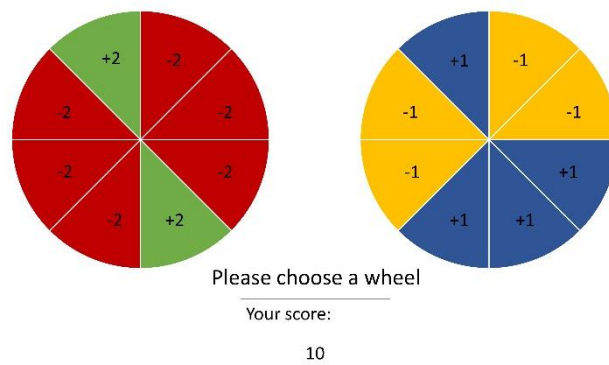


Figure 2.6 CxR task design, trial type six which had the experimental wheel with values of +2 and -2, with a probability of .25 of winning the + value.

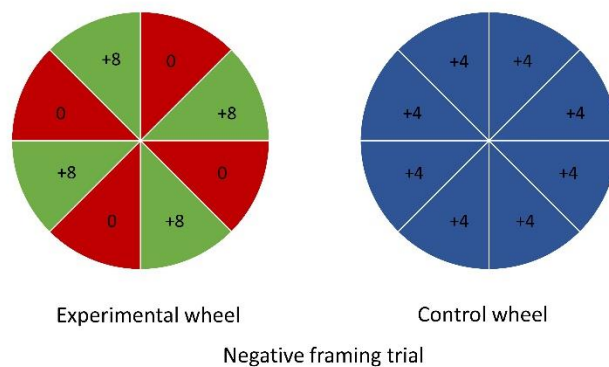


Figure 2.7 Negative framing trial design

The “*Ultimatum Game*” (UG) (Figure 2.8) is an economic decision-making computer game, often used as a measure of emotion regulation as it assesses decision-making performance in emotionally charged scenarios (Koenigs & Tranel, 2007; Northover, Thapar, Langley, & van Goozen, 2015a). The UG is composed of 22 trials; in each trial, participants are presented with a photograph of a fictional peer (the proposer), offering a way to split a sum of money. Participants (or responders) need to decide whether to accept or refuse the offer made by the proposer; across trials, this proposed split can either be more or less favourable to responders, ranging from being very fair (5/5 split) or moderately unfair (6/4, 7/3 split) to very unfair (8/2, 9/1 split). Participants are told that if they accept the proposer’s offer, both of them are

paid accordingly; if they refuse it, neither the responder nor the proposer gains money. To make it more believable, participants are told that these offers come from previous participants in the same study and at the end of the task, responders are asked to make their own offers to be stored in the database for future participants. The frequency of the offers is standardised by having two 5/5, two 6/4, six 7/3, six 8/2 and six 9/1 offers. Receipt of unfair offers is often associated with feelings of anger and other negative emotions which lead the responder to refuse them. This is considered an irrational emotionally driven decision (Koenigs & Tranel, 2007; Northover et al., 2015a), as the responder loses the possibility of making a utilitarian choice and gaining money, albeit less than the proposer. Optimal, emotion regulation strategies are therefore important to reduce the emotional arousal and make utilitarian decisions (Koenigs & Tranel, 2007; Northover et al., 2015a). The dependent variable considered was the percentage of moderately unfair (6/4; 7/3 split) offers accepted whose acceptance or refusal rate is more variable compared to those of truly fair (5/5 split) and very unfair (8/2; 9/3 split) offers, which almost all participants accept or reject, respectively.

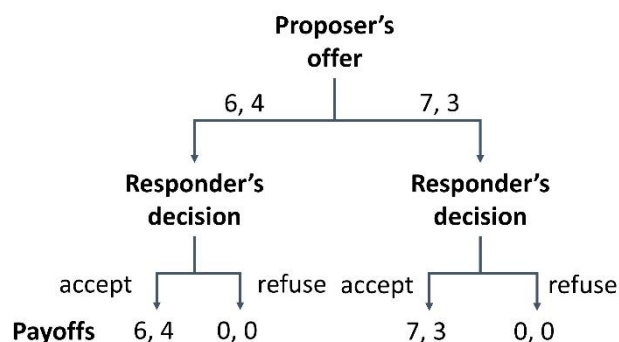


Figure 2.8 Graphic representation of the UG Moderately Unfair offers

Sociodemographic Measures

Participants age and IQ were re-assessed at follow-up. IQ was measured using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) and was based

only on vocabulary and matrix reasoning tests, measures of verbal comprehension and perceptual reasoning respectively. Previous studies also used the WASI to measure IQ (Northover, Thapar, Langley, Fairchild, & van Goozen, 2016; Northover et al., 2015a; Northover, Thapar, Langley, & van Goozen, 2015b; van Goozen et al., 2016).

2.3 Recruitment numbers

This section describes the number of participants recruited both at baseline and follow-up, providing the final sample sizes at these different time points. A flowchart of this recruitment procedure is shown in Figure 2.9.

2.3.1 Baseline

A final sample of 697 participants had data available for analysis; 17% were females ($n = 116$) and 83% were males ($n = 581$). Of these participants, only those with a DSM-IV ADHD diagnosis were selected ($n = 592$) and among these, 585 had irritable data available. To reduce the confounding effect of relatedness, 24 siblings were removed from this sample leading to a final sample size of 561 children with ADHD and irritability information. Notably, all participants met DSM-5 criteria for ADHD at baseline.

Additionally, information on maternal psychopathology was available for 467 mothers whose child took part in the baseline data collection.

2.3.2 Follow-up

Between 2013 and 2016, 483 families who participated to the SAGE study and agreed to be re-contacted for future research were considered eligible for this follow-up (i.e., had a male child aged 10-17 with an IQ within the normal range). 226 of these families

were traced and agreed to participate (47%), whereas 257 were either not found to be contacted or refused to take part in this follow-up (53%). An additional 46 participants, who expressed an interest in the SAGE study but were not seen at baseline, were recruited as they all had a clinical diagnosis of ADHD and had some overlapping information with the current baseline data, collected as part of previous research studies they participated in. The final sample size at follow-up changes across the individual studies included in this thesis and information about these changes is provided in the following chapters. Notably, all of the extra participants with a DSM-IV ADHD diagnosis also met the DSM-5 criteria at baseline.

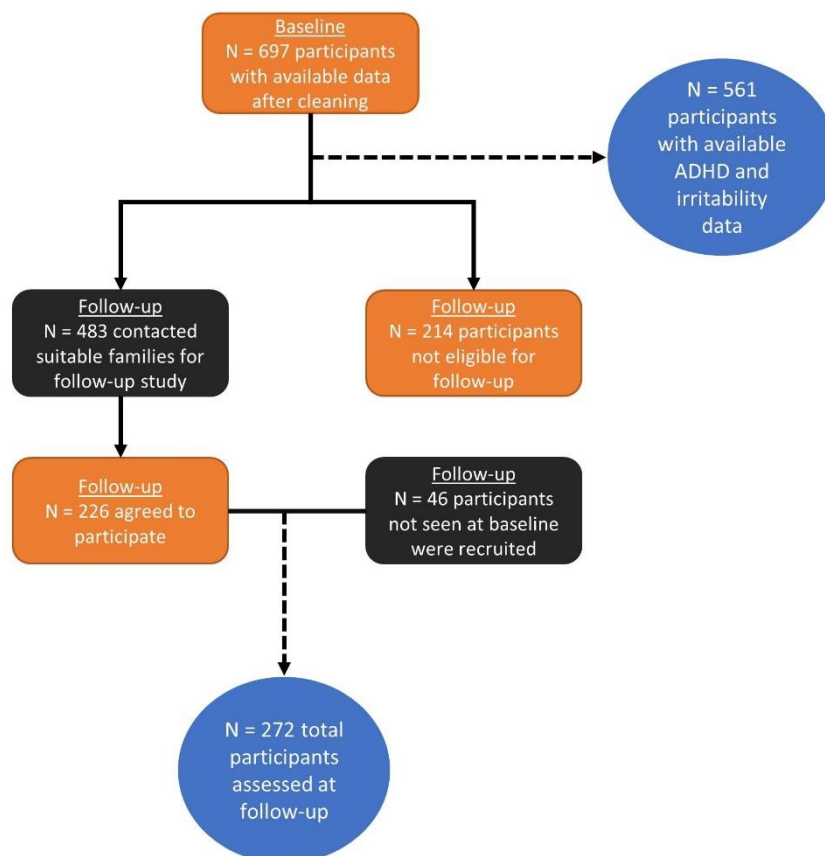


Figure 2.9 Flowchart of the recruitment procedure both at baseline and follow-up.

Further details regarding participant numbers, attrition and representativeness can be seen in Chapter 4, 5 and 6 alongside the relevant analyses.

Chapter 3

Investigating the Concept of Phasic and Tonic Irritability in Childhood ADHD

Chapter description

This chapter addresses the first aim of this thesis, which is to investigate the validity of a bi-dimensional construct of chronic and severe irritability in children with ADHD. This study is important as it also sets the way chronic and severe irritability is operationalised in the following studies of this thesis, either as a unitary construct or split into the two proposed components. Both the baseline and the follow-up data from this clinical ADHD sample is used in this chapter which focuses on clinical measures only. A brief overview of the samples and methods used is provided, with these elements described in more detail in Chapter 2.

3.1 Introduction

As discussed in Chapter 1, irritability has been defined as proneness to react with anger disproportionate to the situation and is subject to individual differences. This angry reaction can be displayed as temper tantrums and aggressive behaviours and/or as sullen, grumpy mood (Copeland et al., 2015; Leibenluft, 2017a; Vidal-Ribas et al., 2016). Irritability is also a cross-diagnostic symptom present in both internalizing and externalizing disorders (Stringaris, 2011); however, it has assumed unique diagnostic validity with the introduction of Disruptive Mood Dysregulation Disorder in the DSM-5 (American Psychiatric Association, 2013). Since the creation of the DMDD diagnostic label, chronic and severe irritability has acquired a greater importance. This interest is justified by the impairments across multiple areas of functioning associated with severe irritability both in childhood and in adulthood, even when adjusting for baseline psychopathology (Brotman, Kircanski, & Leibenluft, 2017; Vidal-Ribas et al., 2016) (see Chapter 1, section 1.1.4 for more details). Additionally, the clinical importance of irritability has been widely ascertained, as it is one of the most common reasons children are referred to mental health services, especially when conceptualised within aggressive and disruptive behaviours (Peterson, Zhang, Santa Lucia, King, & Lewis, 1996).

As suggested by the definition of irritability, this phenotype can include behavioural symptoms (i.e., temper tantrums) and/or persistent mood symptoms (e.g., grumpy mood). Both these behavioural and mood manifestations of irritability are core symptoms of DMDD, which is included in the Mood Disorder section of the DSM-5 (American Psychiatric Association, 2013). However, irritability, both as symptom and in the form of DMDD, is more commonly and highly associated with disruptive behaviours, especially ADHD and ODD (Brotman, Kircanski, & Leibenluft, 2017; Evans et al., 2017). It is therefore unclear whether chronic and severe irritability is

mainly a behavioural or a mood symptom and the homogeneity of this construct is questioned. In the 2014 NIMH workshop, which collected current knowledge on chronic and severe irritability, these mood and behavioural aspects were suggested to be different components of this phenotype (Leibenluft & Avenevoli, 2014). More precisely, group members defined two components of chronic and severe irritability: phasic and tonic irritability. The phasic dimension comprises episodic angry outbursts, which are intense and inconsistent with the developmental level; and the tonic dimension is conceived as chronic grumpy, grouchy, and angry mood that occur alone or in between temper outbursts (Brotman, Kircanski, & Leibenluft, 2017; Copeland et al., 2015; Leibenluft & Avenevoli, 2014; Vidal-Ribas et al., 2016). These distinct components of irritability are suggested to identify different subgroups of individuals, those who are euthymic and who display disruptive behaviours under minor provocation, and those with a constant negative mood (Blader et al., 2016). The distinction of phasic and tonic dimensions could also provide a possible explanation for the longitudinal associations of chronic and severe irritability with both internalising and externalising conditions (Eyre et al., 2019; Vidal-Ribas et al., 2016) (refer to Chapter 1, section 1.1.4 for more details). This is further suggested by a recent study that showed heterogeneity in developmental trajectories of severe irritability, with childhood onset and adolescent onset of irritability also linked to genetic liability for externalising (i.e., ADHD) and internalising (i.e., MDD) disorders, respectively (Riglin et al., 2019). This distinction suggests the existence of separate neurodevelopmental and mood types of severe irritability which fits well with the definition of phasic and tonic irritability. Whilst this theoretical definition has been proposed, whether phasic and tonic components are distinct in terms of defining characteristics and in their transition into externalising and internalising disorders over childhood has not been explored (Kessel et al., 2016; Leibenluft & Avenevoli, 2014; Vidal-Ribas et al., 2016).

As outlined in Chapter 1, ADHD is a common heterogeneous childhood condition leading to impairment in multiple settings (Cortese & Coghill, 2018; Thapar & Cooper, 2016). The core symptoms concern the dimensions of inattention and hyperactivity-impulsivity, however irritable symptoms are frequently observed in this population (Shaw et al., 2014) and prior to the DSM-III they were considered as diagnostic features of ADHD (Faraone et al., 2019). As shown in the general introduction, severe irritability is highly prevalent in youths with ADHD, that is also the most common condition associated with chronic and severe irritability in the form of SMD and DMDD (Faraone et al., 2019; Shaw et al., 2014); this is also confirmed at baseline in the same clinical ADHD sample used in this chapter (Eyre et al., 2017) (see Chapter 1, sections 1.1.4 and 1.2.3). The presence of severe irritability is also associated with poor functional outcomes in this clinical population. Preliminary evidence also suggests that irritability might be a source of clinical heterogeneity in ADHD, predisposing to both internalising and externalising conditions independently of comorbid conditions (see Chapter 1, section 1.2.3 for more details). Considering the clinical relevance and the high prevalence of severe irritability, children with ADHD seems to be an ideal sample to study chronic and severe irritability as currently conceptualised. This would also be beneficial to understand the heterogeneity of ADHD clinical correlates, which is problematic for several aspects of the research into this neurodevelopmental disorder (see Chapter 1, section 1.2 for details).

The phasic and tonic components of irritability have been previously explored together as symptoms included within the DMDD diagnosis, in both epidemiological and clinical samples (Axelson et al., 2012; Dougherty et al., 2014; Eyre et al., 2017; Mulraney et al., 2016). However, to the best of my knowledge, no study has specifically compared phasic and tonic irritability in a sample of children with ADHD. Copeland and colleagues (2015) were the first to directly compare these components but focused on an epidemiological sample. In an attempt to explore the validity of the

bi-dimensional structure of irritability, they assessed the prevalence, interplay, overlap and normative levels of phasic and tonic irritability in 1420 children derived from the Great Smoky Mountain Study (GSMS) and followed from 9 to 16 years of age. Across the eight waves of assessments, this study showed that both phasic and tonic irritability over childhood and adolescence were highly prevalent, in 51.4% and 28.3% respectively, with a high overlap between the two (22.8% of individuals endorsed both). Both phasic and tonic dimensions appeared to be equally accurate at identifying children with impaired functioning, or who were at risk for psychopathology (Copeland et al., 2015), perhaps indicating that the distinction between these dimensions was not clinically informative. The consistent overlap between phasic and tonic irritability has also been observed both in general psychiatric and epidemiological samples, in a study using dimensions of phasic and tonic irritability similarly operationalised as in Copeland's (2015) (Carlson et al., 2016; Copeland et al., 2015). Another recent study also explored tonic and phasic irritability, in a population twin study, showing that there are distinct genetic and unique environmental factors influencing tonic and phasic irritability (Moore et al., 2019). More specifically, tonic irritability seems to be influenced by genetic and unique environmental influences that are independent to risk factors associated with losing temper and temper tantrums, characteristics of phasic irritability (Moore et al., 2019). This suggests a difference between these two phenotypes at the aetiological level.

Whilst these findings are a first step in the study of phasic and tonic irritability, further investigation in clinical samples, including investigating the association with external validators, such as family history and developmental clinical outcomes (Copeland et al., 2015; Moore et al., 2019; Vidal-Ribas et al., 2016), are needed to ascertain the validity of their distinction.

In summary, little is known about the validity of phasic and tonic irritability in clinical samples such as in those with ADHD. This sample is ideal to research the taxonomy

of phasic and tonic irritability, especially in terms of different patterns of comorbidity and external validators of family history and long-term outcomes. This is due to the high prevalence of severe irritability, the functional and clinical outcomes associated with severe irritability in this clinical population and the need for information to help explaining the heterogeneity of ADHD. Thus, this is the first study investigating the cross-sectional prevalence of phasic and tonic irritability and exploring their associations with ADHD clinical correlates and maternal psychopathology. The longitudinal associations between phasic and tonic irritability with a range of clinical correlates were also explored. The aim was to ascertain the validity of the bi-dimensional structure of irritability in a sample of children with ADHD and additionally investigate whether one dimension was a stronger predictor of clinical correlates than the other. This then informed the conceptualisation of irritability for future subchapters.

3.2 Methods

3.2.1 Sample

In this study the baseline data from 561 children (details of the study are fully described in Chapter 2) was used. These children all had a diagnosis of ADHD, available irritability data and were aged 6-18 years (mean age 10.73, s.d. 2.98) at baseline. Data on current and childhood parental psychopathology was available for 467 mothers and for only 233 of fathers; thus, only maternal psychopathology was considered in this study. To investigate longitudinal elements of these research questions, follow-up data from a subset of 191 children aged 10-18 years (mean age 13.84, s.d. 1.83) was considered; these participants were previously assessed at baseline and had longitudinal clinical data available.

3.2.2 Irritability Measure

Phasic and tonic irritability presence was computed by extracting items from the ODD and Depression scales of the CAPA, consistent with the previous work of Copeland and colleagues (2015). Within the ODD section of the CAPA, the items related either to “Losing Temper” or “Temper Tantrums” were taken as symptoms of phasic irritability, whilst the tonic component was composed of symptoms of “Touchy or Easily Annoyed”, “Angry or Resentful”, and “Irritability”, taken from the CAPA Depression section.

The criteria utilised to assess the presence of these irritability dimensions were more stringent than those used by Copeland and colleagues (2015). Copeland and colleagues focused on a general population sample, allowing the use of broader criteria to assess the different dimensions of irritability. The present study however focused on a clinical population of children with ADHD therefore, in line with previous work (Eyre et al., 2017), more stringent criteria were necessary to avoid a too broad inclusion of cases and to identify more clinically relevant irritability. As described in Chapter 2, if either “Losing Temper” or “Temper Outburst” was present at the required frequency, for a period longer than 12 months and in more than one setting, phasic irritability was considered endorsed. Similarly, if “Touchy or Easily Annoyed”, “Angry or Resentful” or “Irritable Mood” was endorsed at the required frequency, duration and pervasiveness cut-offs, tonic irritability criteria were met (see Chapter 2, Table 2.1).

3.2.3 Psychopathology Measures

As previously described, child psychopathology was measured cross-sectionally using the CAPA, rated by parents (Angold & Costello, 2000). In particular, from the CAPA measures of ADHD, ODD, CD and Depressive symptom severity were generated by summing the relevant endorsed symptoms together. Notably, for this investigation, ODD and depression symptom scores excluded the irritability items to account for the overlap with the measure of chronic and severe irritability. Considering

that few individuals endorsed depressive symptoms, this measure was binary coded where 0 indicated the absence of symptoms and 1 indicating one or more symptom. The CAPA was also used to derive a research diagnosis of DSM-IV/5 ADHD and any anxiety disorder. It is important to consider that “any anxiety diagnosis” was a dichotomous variable, created combining the presence of Separation Anxiety Diagnosis, Generalised Anxiety Diagnosis or Social Anxiety Diagnosis to deal with the few cases per diagnostic category. A measure of ADHD impairment generated as described in Chapter 2 was also used. Parent-rated autistic symptoms and self-report psychopathic traits were collected from the ASQ (Berument et al., 1999) and the ICU (Andershed, Kerr, Stattin, & Levander, 2002) (see Chapter 2 for further details).

As detailed in Chapter 2, maternal psychopathology was assessed using self-report questionnaire and in particular, measures of current ADHD symptoms and childhood CD symptoms were considered. Additionally, maternal depression and anxiety symptoms were collected using the HADS (Zigmond & Snaith, 1983).

At follow-up, the parent version of the DAWBA structured interview (Goodman et al., 2000) was used to ascertain clinical symptoms of CD and ADHD. Symptom scores for CD and ADHD diagnoses were calculated according to the DSM-5 criteria (American Psychiatric Association, 2013). The parent-rated emotional, conduct, hyperactivity and impact subscales of the SDQ (Goodman, 1999) were also used.

3.2.4 Sociodemographic Measures

At baseline, demographic information related to child sex, age, full scale IQ and Social Economic Status were also collected and derived as detailed in Chapter 2.

3.3 Statistical Analyses

All analyses were conducted using SPSS version 23 (Corp, 2015) and STATA version 14 (StataCorp, 2015). First the prevalence of phasic and tonic irritability was assessed and their association with demographic factors such as sex, age, IQ and SES were considered.

Multiple linear and logistic regressions were performed to test whether the presence of either phasic and/or tonic irritability was associated with clinical correlates and maternal psychopathology at baseline and clinical outcomes at follow-up. Unadjusted analyses were followed by analyses including both types of irritability, demographic characteristics, ADHD symptom severity and baseline symptom measurement as covariates, where relevant.

A z-test was performed to determine whether phasic or tonic irritability was a stronger predictor of the clinical variables. To control for the effect of multiple testing when investigating the impact of both dimensions of irritability on clinical correlates, maternal psychopathology and clinical outcomes, Bonferroni correction was performed considering p-value thresholds of .006 (number of tests: 8); .01 (number of tests: 4) and .008 (number of tests: 6), respectively.

To assess how representative the follow-up characteristics of this clinical ADHD sample were of the baseline ones, Chi-square and t-test analyses were run across these two waves on the rates of phasic and tonic irritability, demographic characteristics and clinical variables assessed cross-sectionally.

Considering the size of these samples, the distribution of the variables of interest is not likely to be problematic as per the Central Limit Theorem (Field, 2013), however robust adjusted regressions were also used to check whether the results were different for those variables that violated the normality assumption (i.e., baseline children's CD symptoms, maternal CD symptoms in childhood, and SDQ hyperactivity).

3.4 Results

3.4.1 Prevalence of phasic and tonic irritability

At baseline, 83.1% of participants were males, with a mean IQ of 81.79 (s.d. 13.40). approximately half of the sample came from a family with low SES (54.6%). The mean symptom severity and disorder prevalence can be seen in Table 3.1.

The presence of any irritability symptoms was common in this clinical ADHD sample, 92.3% of parents endorsed at least one symptom of phasic irritability, while 81% reported at least one symptom of tonic irritability (Table 3.2). The application of frequency, duration and pervasiveness criteria qualified reduced this prevalence (Table 3.2). Using these criteria, severe and frequent phasic irritability was present in the 19.3% of children, whereas tonic irritability was present in 51.3%. There was much overlap between the two with 15.8% of the sample having both phasic and tonic irritability (Table 3.2).

	N (%)	MEAN (S.D.)
<i>BASELINE CHARACTERISTICS</i>		
CD DIAGNOSIS	119 (21.2%)	
ANY ANXIETY DIAGNOSIS	35 (6.4%)	
DEPRESSIVE SYMPTOMS	211 (38.3%)	
ADHD SYMPTOMS		15.36 (2.35)
ODD SYMPTOMS		2.29 (1.47)
CD SYMPTOMS		1.27 (1.65)
AUTISM SYMPTOMS		11.94 (6.62)
PSYCHOPATHY		35.04 (13.2)
<i>MATERNAL PSYCHOPATHOLOGY</i>		
CURRENT ADHD SYMPTOMS		5.48 (5.4)
CHILDHOOD CD SYMPTOMS		1.10 (1.75)
DEPRESSIVE SYMPTOMS		6.88 (4.24)
ANXIETY SYMPTOMS		9.84 (4.94)
<i>FOLLOW-UP CHARACTERISTICS</i>		
SDQ EMOTIONAL SCORE		5.34 (2.53)
SDQ CONDUCT		5.38 (2.42)
SDQ HYPERACTIVITY		9.05 (1.42)
SDQ IMPACT		5.45 (2.82)
ANY ADHD DIAGNOSIS	158 (83.2%)	
CD DIAGNOSIS	70 (36.8%)	

Table 3.1 Descriptive characteristics of the clinical ADHD sample at baseline, follow-up, and maternal psychopathology

SDQ = Strengths and Difficulties Questionnaire, S.D.= Standard Deviation.

	PHASIC N (%)	TONIC N (%)	DIMENSIONS N (%)
IRRITABILITY SYMPTOMS PRESENT	518 (92%)	451 (81%)	
FREQUENCY ≥ 3X/WEEK	315 (56%)	317 (57%)	
TIME LAPSE >12 MONTHS*	295 (53%)	286 (51%)	
SYMPTOMS PRESENT IN AT LEAST 2 SETTINGS*	111 (20%)	/	
FULL CRITERIA PREVALENCE	108 (19.3%)	286 (51.3%)	
ONLY ONE DIMENSION PRESENT	19 (3.4%)	198 (35.6%)	
NEITHER DIMENSION PRESENT			252 (45.2%)
BOTH DIMENSIONS PRESENT			88 (15.8%)
EITHER ONE DIMENSION PRESENT			217 (39%)

Table 3.2 Prevalence of phasic and tonic irritability and criteria

* at the required symptoms frequency.

3.4.2 Phasic and tonic irritability associations with clinical correlates at baseline

Cross-sectional analyses revealed that irritability and demographic factors did not seem to be inter-related, except for the association between phasic irritability and low SES (OR= 2.39, 95%CI= 1.3/4.3, $p=.003$). In this sample of children with ADHD, the presence of phasic irritability was associated with a three-fold increase in the likelihood of being diagnosed with CD (OR= 2.95, 95%CI= 1.6/5.4, $p<.001$), whilst those with tonic irritability had a greater than two-fold increase in the chance of displaying CD diagnosis (OR= 2.53, 95%CI= 1.4/4.5, $p=.002$). Tonic irritability was also associated with a three-fold increased risk of being diagnosed with anxiety disorders (OR= 3.3, 95%CI= 1.3/8.3, $p=.01$) (Table 3.3). Robust multiple regressions produced similar estimates for CD symptoms, which was independently predicted by both phasic and tonic irritability (unstandardized B= 1.06, $p=.001$; unstandardized B=

.54, $p = .002$, respectively). Z-tests revealed that there was no significant difference in the strength of association of phasic and tonic irritability for any of the clinical correlates considered (Table 3.3).

3.4.3 Phasic and tonic irritability associations with maternal psychopathology

Table 3.1 shows the means and standard deviations of the maternal psychopathology variables considered, whilst their association with phasic and tonic irritability are reported in Table 3.3. Phasic irritability seemed not to be significantly associated with any of the measures of maternal psychopathology. However, tonic irritability alone showed a significant association with maternal mood and anxiety symptoms. Bootstrapped estimates for maternal CD consistently show a non-significant association between phasic or tonic irritability with maternal CD symptoms (respectively: unstandardized $B = .14$, $p = .54$; unstandardized $B = .26$, $p = .14$). As shown by the z-tests, phasic irritability was not more strongly associated than tonic irritability with any of the maternal psychopathology variables considered (Table 3.3).

	MODEL	BETA/OR (95% CI)	ADJ- MODEL	BETA/OR (95% CI)	Z- TEST
BASELINE DATA					
ADHD SYMPTOMS	<i>Phasic</i>	B= 1.06 (.52, 1.61)***	<i>Phasic</i>	B= .59 (.02, 1.16)*	n.s.
	<i>Tonic</i>	B= 1.02 (.59, 1.44)***	<i>Tonic</i>	B= .78 (.34, 1.23)***	
ODD SYMPTOMS	<i>Phasic</i>	B= 1.20 (.87, 1.53)***	<i>Phasic</i>	B= .63 (.32, .95)***	n.s.
	<i>Tonic</i>	B= 1.18 (.93, 1.43)***	<i>Tonic</i>	B= .83 (.58, 1.08)***	
CD SYMPTOMS	<i>Phasic</i>	B= 1.31 (.94, 1.68)***	<i>Phasic</i>	B= .85 (.49, 1.21)***	n.s.
	<i>Tonic</i>	B= 1.05 (.75, 1.34)***	<i>Tonic</i>	B= .68 (.39, .96)***	
AUTISM SYMPTOMS	<i>Phasic</i>	B= 2.30 (.75, 3.85)**	<i>Phasic</i>	B= .87 (-.73, 2.47)	n.s.
	<i>Tonic</i>	B= 2.84 (1.64, 4.05)***	<i>Tonic</i>	B= 2.13 (.87, 3.39)***	
PSYCHOPATHY SYMPTOMS	<i>Phasic</i>	B= 8.23 (5.21, 11.3)***	<i>Phasic</i>	B= 4.37 (1.37, 7.37)**	n.s.
	<i>Tonic</i>	B= 8.91 (6.6, 11.2)***	<i>Tonic</i>	B= 6.68 (4.31, 9.05)***	
CD DIAGNOSIS	<i>Phasic</i>	OR= 4.23 (2.51, 7.2)***	<i>Phasic</i>	OR= 2.95 (1.63, 5.37)***	n.s.
	<i>Tonic</i>	OR= 3.73 (2.22, 6.26)***	<i>Tonic</i>	OR= 2.53 (1.41, 4.51)**	
ANY ANXIETY DIAGNOSIS	<i>Phasic</i>	OR= 1.14 (.45, 2.91)	<i>Phasic</i>	OR= .74 (.27, 1.98)	n.s.
	<i>Tonic</i>	OR= 3.4 (1.42, 8.14)**	<i>Tonic</i>	OR= 3.27 (1.29, 8.26)**	
DEPRESSIVE SYMPTOMS	<i>Phasic</i>	OR= 2.03 (1.25, 3.3)**	<i>Phasic</i>	OR= 1.51 (.89, 2.57)	n.s.
	<i>Tonic</i>	OR= 1.88 (1.27, 2.78)**	<i>Tonic</i>	OR= 1.44 (.94, 2.22)	

MATERNAL PSYCHOPATHOLOGY					
CURRENT ADHD SYMPTOMS	<i>Phasic</i>	B= .07 (-1.17, 1.30)	<i>Phasic</i>	B= -.08 (-1.38, 1.22)	n.s.
	<i>Tonic</i>	B= .36 (-.64, 1.35)	<i>Tonic</i>	B= .38 (-.67, 1.42)	
CHILDHOOD CD SYMPTOMS	<i>Phasic</i>	B= .25 (-.15, .65)	<i>Phasic</i>	B= .15 (-.28, .57)	n.s.
	<i>Tonic</i>	B= .30 (-.03, .62)	<i>Tonic</i>	B= .26 (-.08, .60)	
DEPRESSIVE SYMPTOMS	<i>Phasic</i>	B= 1.04 (.07, 2.01)*	<i>Phasic</i>	B= .55 (-.48, 1.55)	n.s.
	<i>Tonic</i>	B= 1.43 (.65, 2.20)***	<i>Tonic</i>	B= 1.29 (.48, 2.1)**	
ANXIETY SYMPTOMS	<i>Phasic</i>	B= 1.53 (.40, 2.66)**	<i>Phasic</i>	B= .75 (-.42, 1.92)	n.s.
	<i>Tonic</i>	B= 2.17 (1.28, 3.06)***	<i>Tonic</i>	B= 1.97 (1.04, 2.9)***	

Table 3.3 Univariate and multivariate logistic and linear regressions on clinical variables and maternal psychopathology.

The adjusted models (ADJ) were controlled for all the demographic factors, ADHD symptoms and the respective dimension of irritability, with the exception of ADHD symptoms controlled for IQ, SES, age and sex, only. Whereas maternal psychopathology adjusted models have been controlled only for the relevant type of irritability. $p < .05^*$; $p \leq .01^{**}$, $p \leq .001^{***}$

After Bonferroni: within-time phasic - ADHD symptoms and tonic - any anxiety diagnosis associations failed to reach significant threshold. No changes were observed for maternal psychopathology.

3.4.4 Phasic and tonic irritability associations with longitudinal clinical correlates

As a consequence of the initial inclusion criteria, demographic characteristics of this clinical ADHD sample significantly differed at baseline and follow-up (Table 3.4) (see Chapter 2 for more details on inclusion and exclusion criteria across the two waves). The clinical variables considered remained consistent across these two waves, although children with higher rates of tonic and phasic irritability were more likely to be included at follow-up (Table 3.4).

Overall, phasic and tonic irritability showed different patterns of association. Phasic irritability predicted ADHD diagnosis persistence, CD diagnosis in adolescence, whereas tonic irritability was a predictor of mood and anxiety symptoms, as rated by the emotional subscale of the SDQ, and a great impact at follow-up (Table 3.5). Tonic irritability was also the only significant predictor of SDQ hyperactivity symptom severity, which was also confirmed by the bootstrapped estimates of the robust multiple regression (unstandardized $B = .50$, $p = .031$). For all these clinical correlates, the z-tests revealed non-significant differences in the strength of association between phasic and tonic irritability across all variables (Table 3.5).

Following the application of the Bonferroni correction, many of the within-time associations between either phasic or tonic irritability with ADHD clinical correlates remained significant, the exceptions to this were associations between phasic irritability and ADHD symptoms and the associations between tonic irritability and any anxiety diagnosis (Table 3.3). Bonferroni correction did not impact on the pattern of associations observed for maternal psychopathology, where significant associations still reached the statistical threshold after correcting for multiple testing (Table 3.3). Counter to this, most longitudinal associations were no longer significant after applying the Bonferroni correction, apart for phasic irritability still predicting CD diagnosis (Table 3.5).

	BASELINE	FOLLOW-UP	T-TEST/X² P-VALUE
SEX (MALE)	289 (78.1%)	177 (92.7%)	p< .001
SES (LOW)	184 (58%)	81 (48.2%)	p< .05
IQ	80.15 (14.2)	85.04 (10.9)	p< .001
AGE	11.24 (3.15)	9.72 (2.31)	p< .001
ADHD SYMPTOMS	15.22 (2.44)	15.63 (2.15)	n.s.
ADHD IMPAIRMENT	6.75 (1.49)	6.93 (1.31)	n.s.
ODD SYMPTOMS	2.22 (1.43)	2.42 (1.54)	n.s.
CD SYMPTOMS	1.25 (1.63)	1.30 (1.68)	n.s.
ASQ SYMPTOMS	11.59 (6.32)	12.58 (7.11)	n.s.
TOTAL PSYCHOPATHY	35.03 (13.1)	35.06 (13.4)	n.s.
CD DIAGNOSIS	78 (21.1%)	41 (21.5%)	n.s.
ANY ANXIETY DIAGNOSIS	23 (6.4%)	12 (6.5%)	n.s.
DEPRESSIVE SYMPTOMS	137 (37.7%)	74 (39.4%)	n.s.
PHASIC IRRITABILITY	62 (16.8%)	46 (24.1%)	p< .05
TONIC IRRITABILITY	174 (47.4%)	112 (58.9%)	p< .05

Table 3.4 Prevalence rates, means and standard deviations of irritability dimensions, demographic and clinical variables considered at baseline. The results of the comparison of these estimates is also reported.

	MODEL	BETA/OR (95% CI)	ADJ- MODEL	BETA/OR (95% CI)	Z- TEST
SDQ: EMOTIONAL	<i>Phasic</i>	B= .59 (-.25, 1.43)	<i>Phasic</i>	B= .33 (-.53; 1.20)	n.s.
	<i>Tonic</i>	B= .90 (.17, 1.62)*	<i>Tonic</i>	B= .82 (.06; 1.57)*	
SDQ: CONDUCT	<i>Phasic</i>	B= 1.59 (.82, 2.37)***	<i>Phasic</i>	B= .65 (-.17, 1.47)	n.s.
	<i>Tonic</i>	B= 1.31 (.63, 1.99)***	<i>Tonic</i>	B= .63 (-.05, 1.32)	
SDQ: HYPERACTIVITY	<i>Phasic</i>	B= .20 (-.28, .67)	<i>Phasic</i>	B= -.12 (-.61, .37)	n.s.
	<i>Tonic</i>	B= .64 (.23, 1.04)**	<i>Tonic</i>	B= .51 (.08, .94)*	
SDQ: IMPACT	<i>Phasic</i>	B= .41 (-.54, 1.35)	<i>Phasic</i>	B= .11 (-.86, 1.08)	n.s.
	<i>Tonic</i>	B= .97 (.16, 1.78)*	<i>Tonic</i>	B= .95 (.10, 1.79)*	
ANY ADHD DIAGNOSIS	<i>Phasic</i>	OR= 5.66 (1.30, 24.7)*	<i>Phasic</i>	OR= 4.86 (1.09, 21.7)*	n.s.
	<i>Tonic</i>	OR= 2.08 (.96, 4.49)	<i>Tonic</i>	OR= 1.64 (.74, 3.61)	
CD DIAGNOSIS	<i>Phasic</i>	OR= 3.11 (1.56, 6.20)***	<i>Phasic</i>	OR= 2.75 (1.35, 5.61)**	n.s.
	<i>Tonic</i>	OR= 1.94 (1.04, 3.61)*	<i>Tonic</i>	OR= 1.55 (.81, 2.96)	

Table 3.5 Regressions and logistic regressions with clinical correlates at follow-up.

SDQ = Strengths and Difficulties Questionnaire. The adjusted models (ADJ) have been controlled for the relevant type of irritability. Additionally, SDQ Hyperactivity and SDQ Conduct have also been controlled for the relevant baseline symptoms. $p < .05^*$; $p \leq .01^{**}$, $p < .001^{***}$

After Bonferroni: only the longitudinal association between phasic irritability and CD diagnosis remained significant.

3.5 Discussion

The findings suggest that phasic and tonic irritability are highly prevalent in children with ADHD and are associated cross-sectionally with most of the clinical correlates tested, to an equal extent. Analyses of associations with external validators showed a different picture; phasic irritability was a consistent predictor of CD diagnosis in adolescents, whilst tonic was significantly associated with maternal internalising psychopathology. However, overall, phasic and tonic irritability did not significantly differ in the strength their associations and many of the longitudinal associations did not survive the Bonferroni correction.

In the present sample, the prevalence of tonic irritability was 51.3%, whilst phasic was 19.3%. 15.8% of children with ADHD showed both phasic and tonic symptoms. Tonic irritability was therefore the most frequent phenotype, whereas the phasic phenotype rarely appeared alone (in only 3.4% of cases). These prevalence rates differ from findings of Copeland and colleagues (2015), where phasic irritability alone was found to be more common than tonic: 51.4% and 28.3% respectively, with 22.8% reporting both. However, more stringent criteria than Copeland's (Copeland et al., 2015) were used in this clinical sample of youths with ADHD, and this was in line with previous work (Eyre et al., 2017). The application of less stringent criteria solely based on the presence or absence of irritability symptoms, as those used by Copeland and colleagues (2015), led to very similar results. Phasic irritability was more common than tonic irritability (92% and 81% respectively, see Table 3.2) but mostly these components greatly overlapped (78%, see Table 3.2). Thus, in addition to differences in the study population, the more stringent criteria used to assess phasic and tonic irritability in this study may account for these prevalence differences. This is further confirmed in a recent twin study showing higher rates of tonic irritability than phasic irritability when the frequency criteria was applied (Moore et al., 2019). Notably, tonic

and phasic irritability in Moore and colleagues' study (2019) were operationalised more similarly with this current study than Copeland's, as irritability cut offs based on frequency were applied (Copeland et al., 2015). As mentioned in the introduction of this chapter, the application of different cut-offs was considered important to operationalise phasic and tonic irritability in their chronic and severe facets, as well as to avoid over-diagnosing children with either dimension of irritability whose relevant symptoms were endorsed by the vast majority (see Table 3.2). Additionally, in the study of Mayes and colleagues (2015) tonic irritability was also found to be more common than phasic irritability in both children (17.3% vs. 13.4% on average) and adolescents (14.2% vs. 8.1% on average). However, it should be noted the aim of Mayes and colleagues' study (2015) was not to compare phasic and tonic irritability, which were also operationalised using different measures and items compared to both this current and Copeland's study (2015). Thus, taken together, the current findings find corroboration in several studies using both lenient and stringent cut-offs.

Cross-sectionally, the multivariate regression analyses show a similar pattern of associations for both phasic and tonic irritability to the clinical correlates considered, questioning the usefulness of their distinction. The absence of significant cross-sectional associations between either of irritability dimensions and depressive symptom presence and anxiety diagnosis is somewhat surprising. The comorbidity between ADHD and symptoms of depression and anxiety is consistent within the scientific literature (Schatz & Rostain, 2006; Spencer, Biederman, & Wilens, 1999), as well as the comorbidity between irritability and depression and anxiety symptoms and disorders (Brotman, Kircanski, & Leibenluft, 2017). Previous findings have also shown that DMDD, as a proxy for severe irritability, is significantly associated with anxiety symptoms and diagnosis (Eyre et al., 2017, 2019; Mulraney et al., 2016) and with depressive symptoms in children with ADHD (Eyre et al., 2017, 2019). Similar patterns of association were also observed in this sample of pre-pubertal children with

ADHD (Eyre et al., 2017, 2019). However, this is the first study to investigate associations with phasic and tonic components of irritability separately. Furthermore, depression is relatively uncommon in childhood and the risk of which increases over adolescence, with a greater prevalence found especially after puberty (Thapar, Collishaw, Pine, & Thapar, 2012). With a mean age of 10.73 (s.d. 2.98), the majority of the current sample had not yet reached the typical age of onset for depression (Eyre et al., 2017). This is also supported by the very few depressive symptoms endorsed by individuals in this sample. Similarly, any anxiety diagnosis was only present in the 6.4% of the current sample which also showed a greater male preponderance. Overall, sex differences are not shown in pre-pubertal children with anxiety disorder, except for separation anxiety that does appear to be more common in female than males in childhood (Hayward & Sanborn, 2002; Pine & Fox, 2015). Separation anxiety was amongst the disorders added into the “any anxiety disorder variable” used in this study that might have contributed to reduce the power to find a significant association.

Additionally, findings associated with external validators (i.e. maternal psychopathology and longitudinal associations), used to further and more robustly explore the distinction between dimensions of irritability over and above cross-sectional associations, do not seem to consistently support the distinction between tonic and phasic irritability. Considering only those associations that survive Bonferroni correction, maternal psychopathology analyses revealed that mothers with symptoms of depression and anxiety are more likely to have children with tonic irritability, consistent with the theoretical conceptualisation of tonic irritability as a persistent negative mood symptom. However, tonic irritability does not seem to be associated with emotional symptoms longitudinally. Phasic irritability seems to be linked to disruptive behaviours predicting CD diagnosis at follow-up, but it does not seem to be associated with disruptive symptoms when considering maternal

psychopathology or at follow-up. Thus, the independent contribution of phasic and tonic irritability seems very limited considering these external validators, whilst furthermore the longitudinal associations between phasic and tonic irritability and clinical correlates do not seem to be independent of the effect of comorbid symptoms at baseline as evidenced in Table 3.5. Floor effects might have driven some of these non-significant findings; for instance, only few mothers endorsed CD symptoms in childhood which is not surprising considering that disruptive behaviours are more commonly observed in males and that CD symptoms were investigated retrospectively (Carlson, Tamm, & Gaub, 1997; Newman et al., 1996; Nock, Kazdin, Hiripi, & Kessler, 2006). Additionally, this clinical sample was smaller at follow-up than it was at baseline which might account for the non-survival of the longitudinal associations. These inconsistencies in terms of pattern of associations of phasic and tonic irritability both within and across time thus limit the possibility to draw stronger conclusions; more studies are needed to validate the bi-dimensional nature of chronic and severe irritability, especially those looking at longitudinal associations and using larger samples.

There are several strengths to this study. In particular, the analyses run on irritability and outcome variables were independent of the influence of ADHD symptom severity. The same consideration applies to the measure of ODD and depressive symptoms, which were disentangled from irritability items. Another strength of this study is the validity of criteria used to assess the presence of phasic and tonic irritability. They partially replicate those used in the study by Copeland and colleagues (2015) and are also adapted to a sample of children with ADHD in line with previous studies (Eyre et al., 2017). This study also benefited from a large sample size and careful characterisation of clinical constructs using well validated assessment measures. Finally, external validators (i.e. maternal psychopathology and longitudinal data) have been used alongside the cross-sectional data to increase the consistency of the

present findings. There are also a number of limitations that should be considered. Phasic and tonic irritability were measured indirectly by using the CAPA interview. Although the criteria used are aligned to those in the original conceptualisation of tonic and phasic irritability (Leibenluft & Avenevoli, 2014) and previous studies (Copeland et al., 2015; Eyre et al., 2017), researchers have stressed the need of having measures specifically designed to capture each dimension (Leibenluft & Avenevoli, 2014; Vidal-Ribas et al., 2016). ODD symptoms at follow-up were also excluded from the analysis due to different scoring systems, and baseline ODD CAPA diagnosis was also not looked at, as it was not feasible to disentangle the non-irritable symptoms due to high overlap with the current measure of irritability. The use of different assessment measures across time points may also have limited the robustness of these results. In the light of these limitations, further research is therefore necessary to corroborate these findings.

This is the first study to compare phasic and tonic irritability in a clinical sample and specifically, in childhood ADHD. Cross-sectional analyses seem to suggest that at the clinical level, separating tonic and phasic irritability may not be useful due to their similar predictive power in term of strength and associations with clinical correlates. Similarly, analyses using external validators in the form of maternal psychopathology and longitudinal outcomes failed to provide strong conclusion about the theoretical distinction between these components of irritability. Taken together these results suggest that irritability might just be a marker of severity in ADHD. Therefore, within clinical practice, separating tonic and phasic irritability may not be useful in identifying children at future risk for internalising or externalising disorders. Although considering the pioneering nature of this study, more research is needed to validate these findings. Considering the purpose of this thesis, separating phasic and tonic irritability does not seem to be justified, thus chronic and severe irritability in the following chapters would be considered as a unitary construct.

Chapter 4

Investigating the cognitive markers of childhood chronic and severe irritability in a sample of adolescents with ADHD

Chapter description

This chapter addresses the second aim of this thesis which is to investigate the impact of childhood chronic and severe irritability on Hot, as opposed to Cool, Executive Functions in a sample of adolescents with ADHD. In this chapter only participants with available follow-up data are considered, which focuses on cognitive measures. A brief description of the clinical and demographic variables, and cognitive tasks is provided although these are described more comprehensively in Chapter 2.

4.1 Introduction

The previous chapter looked at the proposed phasic and tonic dimensions of chronic and severe irritability and their associations with clinical correlates of ADHD, in childhood. Following these analyses, it does not seem to be justified to conceptualise irritability bi-dimensionally and so a single construct will be utilised. Nonetheless, the associations between chronic and severe irritability with a range of clinical correlates were observed, supporting the relevance of this construct in youths with ADHD. However, little is known about how irritability mediates risk for future psychiatric conditions and about its pathophysiology (Avenevoli, Blader, & Leibenluft, 2015). Research on pathophysiological mechanisms of irritability is a new frontier and great importance is given to the concept of “frustration” to which irritability is closely intertwined (Brotman, Kircanski, & Leibenluft, 2017; Leibenluft, 2017b). In fact as explained in the general introduction (Chapter 1, section 1.1.1), irritability can be conceptualised as a lower tolerance to react with anger often precipitated by frustrating circumstances; such as situations where a desired and expected reward is withheld (Brotman, Kircanski, & Leibenluft, 2017; Leibenluft, 2017b). Deficits in reward processing may in turn increase the exposure to frustration for youth with severe irritability as such impairments would hinder the attainment of the desired reward. This paradigm seems to be supported by previous findings that youth with severe irritability show impairments in reward learning, reward prediction error, expected value representation and aberrant sensitivity to rewards (Brotman, Kircanski, & Leibenluft, 2017; Leibenluft, 2017b; Vidal-Ribas et al., 2016). However, research in this area is far from clear and findings are mixed; impairments are often found at neurophysiological level but overall they are not supported by behavioural results (Adleman et al., 2011; Dickstein et al., 2007; Perlman et al., 2015; Rau et al., 2008) and it is noted that some cognitive tasks used do not actually tap reward-related processes (Dickstein et al., 2007). More specifically, significant behavioural findings

are found for a-specific measures of cognitive performance, such as overall task accuracy, rather than for measures that are more strictly linked to reward processing impairments (e.g., change in reward contingencies) (Adleman et al., 2011; Dickstein et al., 2007). Furthermore, previous work comparing children with SMD, BD and typically controls found that cognitive performance of severely irritable youths seems to differ either from controls or from other clinical groups, without showing a unique characterisation associated with chronic and severe irritability (Dickstein et al., 2007). Additionally, some of the evidence claimed to support deficits in reward learning in this population were obtained using Cool EF tasks, thus cognitive processes that occur in unemotional contexts, such as the ID/ED task tapping cognitive flexibility (Brotman, Kircanski, & Leibenluft, 2017; Dickstein et al., 2007). Some previous research also focuses on emotional (i.e. anger) (Gagne & Goldsmith, 2011) and behavioural (i.e. disruptive/antisocial behaviours) correlates of irritability, rather than on irritability as currently conceptualised (Finger et al., 2011; White et al., 2014, 2013). Some studies also suggest that reward-related impairments in youth with severe irritability may also be mediated by deficits in cognitive control processes such as behavioural inhibition (Brotman, Kircanski, & Leibenluft, 2017; Brotman, Kircanski, Stringaris, et al., 2017; Leibenluft, 2017b). However, previous findings comparing severely irritable children, those with BD and healthy controls did not find any compelling differences in the behavioural performance of the different groups on a motor inhibition task, as well as when comparing children with high and low trait anger (Deveney et al., 2012; Liu et al., 2015). This ultimately suggests that it may be reward processing impairments that are more relevant for youths with severe irritability.

An additional limitation of these previous findings is that overall their construct of irritability has often been based on Severe Mood Dysregulation, a proxy for chronic and severe irritability with a hyperarousal component that greatly overlaps with ADHD symptoms (Adleman et al., 2011; Deveney et al., 2012; Dickstein et al., 2007; Rich et al., 2007). Because of the convergence between ADHD and SMD, it is difficult to

partial out the contribution of ADHD to these results, something also indicated by the high prevalence of ADHD diagnosis in different samples of children with SMD studied, ranging between 77% to 85% (Adleman et al., 2011; Deveney et al., 2012; Dickstein et al., 2007; Rich et al., 2007). Further research is therefore needed to test the hypothesis that there is an association between decision-making and reward-related processes with severe irritability, and this may be especially relevant in those with ADHD.

Neuropsychological impairments found in previous studies for those with irritability are also common in children with ADHD. As mentioned in Chapter 1, ADHD is a heterogeneous neurodevelopmental disorder that shows variability in core symptom presentation, co-occurring conditions and neuropsychological deficits (Thapar & Cooper, 2016; Wahlstedt et al., 2009). At the cognitive level, children with ADHD do not show a specific neuropsychological profile, rather they display a variety of impairments in Executive Functions (Castellanos et al., 2006; Thapar & Cooper, 2016). As mentioned in the general introduction (Chapter 1, section 1.3.1), EFs are conceptualised as a top-down cognitive abilities that regulate goal directed activities and can be split into “Cool” and “Hot” components. Whilst Cool EFs are used when facing abstract and decontextualized problems, Hot EFs refer to emotionally engaging cognitive processes (Castellanos et al., 2006). To date, the literature on children with ADHD has mainly focused on the Cool EFs, whereas recent evidence also points to the important role played by motivational and reward-related processes (Hot EFs) (Dekkers et al., 2016; Mowinckel et al., 2015; Sjöwall & Thorell, 2018; Willcutt et al., 2005). Children with ADHD, compared to typically developing controls, show the most robust deficits in Cool EF processes of inhibitory control, attention, working memory and vigilance, and Hot EF processes of decision-making and reward processing (Baroni & Castellanos, 2015; Thapar & Cooper, 2016). Notably, previous work found Hot EF deficits also in youths with disruptive behaviours (i.e., ODD/CD) (Alegria,

Radua, & Rubia, 2016; Fairchild et al., 2009; Sully et al., 2016), some of these studies used an identical task to the one considered in this current study, such as the Choice per Risk Task (Fairchild et al., 2009; Sully et al., 2016). The presence of disruptive behaviours seems associated with impaired Hot EFs also in those with ADHD (Northover et al., 2015a). More precisely, the presence of disruptive behaviours (i.e., ODD/CD) seems to worsen Hot cognitive functioning in those with ADHD compared to children with ADHD alone (Dekkers et al., 2016; Groen, Gaastra, Lewis-Evans, & Tucha, 2013). The study of neuropsychological impairments in ADHD is particularly important in order to try to understand possible sources of the heterogeneity of this condition and in turn identify underlying risk pathways.

As noted previously, irritable symptoms are frequently observed in children with ADHD (Krieger, Leibenluft, Stringaris, & Polanczyk, 2013) with a prevalence ranging between 57% and 92% (Eyre et al., 2017). Irritability in those with childhood ADHD is also associated with greater impairment, poorer outcome and higher rates of comorbid conditions (Biederman, Spencer, et al., 2012; Eyre et al., 2017; Faraone et al., 2019; Shaw et al., 2014). Studies aiming to understand the sources of comorbidity between irritability and ADHD which focus on neuropsychological mechanisms are however scarce and far from conclusive.

A study by Sjöwall and colleagues (2013) looked at the overlap between Emotional Dysregulation and neuropsychological deficits showing that 44% of children with ADHD have both emotion regulation impairments and neuropsychological deficits. Emotion Dysregulation and impairments in emotion recognition significantly contribute to discriminate children with ADHD from controls. This contribution seems to be independent of neuropsychological deficits and the effect is consistent even when controlling for behavioural and emotional problems (Sjöwall et al., 2013). Banaschewski and colleagues (2012) showed that ADHD and Emotional Lability are associated with the same neuropsychological indicators, however the relationship

between neuropsychological functions and Emotional Lability was completely mediated by ADHD symptom severity. Both bottom-up emotional reactivity and top-down regulatory mechanisms are also suggested as possible reasons for the overlap between ADHD and Emotional Dysregulation (Shaw et al., 2014). In terms of bottom-up processes, individuals with ADHD show difficulties in both orienting attention to emotionally relevant stimuli and in the evaluation of rewards, as demonstrated by the aberrant neurophysiological activity and poor performance in delay aversion tasks (Shaw et al., 2014). This suggests an enhanced emotionality that could give rise to Emotional Dysregulation in ADHD (Shaw et al., 2014). Top-down mechanisms are also impaired in individuals with ADHD as supported by studies that showed their difficulties in engaging cognitive control strategies to downregulate emotional reactivity (Shaw et al., 2014). In fact, children with ADHD show both a poor parasympathetic response to emotional stimuli, as indexed by physiological indicator of emotion regulation, and impairments in allocating their attention to or away from emotional stimuli, which is important to regulate emotional arousal (Shaw et al., 2014). However, these bottom-up and top-down impairments provide only indirect evidence for the co-occurrence of Emotion Dysregulation in ADHD. Furthermore, all these studies have conceptualised irritability within broader phenotypes such as Emotional Lability and Emotional Dysregulation, where symptoms, such as hot temper, tearfulness and mood swings are included in addition to irritability symptoms (Banaschewski et al., 2012; Shaw et al., 2014; Sjöwall et al., 2013). Finally, tasks included in these previous studies were mainly within the Cool EF domain and for Hot EFs only delay aversion has been considered (Banaschewski et al., 2012; Sjöwall et al., 2013). As suggested by the previous paradigm of irritability, Hot EFs could be a more promising line of research to understand pathophysiological mechanisms of severe irritability. Further research is therefore needed to understand the source of co-occurrence between ADHD and severe irritability with a more circumscribed

operationalisation of this phenotypes and tasks that comprise a broader variety of Hot EF tasks.

Based on these knowledge gaps, it appears important to disentangle neuropsychological markers specific to ADHD, those specific to severe irritability and to understand shared mechanisms explaining their co-occurrence. This was the broad aim of this study. To the best of my knowledge, this is the first study investigating neuropsychological markers of severe irritability in a sample of youths with ADHD. The aim was to see whether chronic and severe childhood irritability had a specific pattern of association with adolescents' Cool and Hot EFs. Based on the paradigm of severe irritability (Brotman, Kircanski, Stringaris, et al., 2017; Leibenluft, 2017b), it was hypothesised that childhood severe irritable symptoms would be specifically associated with Hot EFs but not with Cool EFs in adolescence. I also wanted to examine if the significant associations between childhood chronic and severe irritability and adolescence Hot EF measures were present over and above childhood ADHD symptom severity. The importance of this study lies on the possibility to understand sources of heterogeneity within ADHD and neurocognitive markers specific to irritability, ultimately being able to investigate the impact that this phenotype has on ADHD at a cognitive level.

4.2 Methods

4.2.1 Sample

The sample utilised in this chapter comprised of 219 adolescents with a clinical diagnosis of ADHD and with childhood irritability and cognitive data available. Participants were aged 10-18 years (mean age 14.04, s.d. 1.90), the majority of whom were taking medication for ADHD (78.8%), although they were asked to suspend it 24h prior to testing. 205 of these participants were youths included in the SAGE study

who were followed up between two to five years later (mean 2.59; s.d. .91) (see Chapter 2 for further details), whereas the remaining 14 were extra participants included as having the same clinical and irritability baseline information, as CAPA was used as part of their original assessment. At follow-up, 14 SAGE participants with a baseline DSM-III-R ADHD diagnosis were also included; broadening the criteria of inclusion for this clinical ADHD sample was decided as using more stringent criteria (i.e., only baseline participants with a DSM-IV/5 diagnosis) led to an important drop in sample size, due to little availability of cognitive data. Finally, it is important to notice that 18.3% of this sample no longer met ADHD diagnostic criteria at follow-up, as opposed to 75.8% with persistent ADHD and 5.9% who did not have follow-up information available on ADHD diagnostic status.

4.2.2 Clinical Measures

As reported in Chapter 2, information on ADHD research diagnosis and symptoms was collected at baseline using the parent version of the CAPA (Angold & Costello, 2000) and at follow-up using the parent version of the DAWBA (Goodman et al., 2000). Similarly, parent rated CD symptoms were collected at follow-up using the DAWBA (Goodman et al., 2000).

A composite score of chronic and severe irritability was extracted at baseline using five items from the ODD and the Depression section of the CAPA. These items were “Losing temper” and “Temper Tantrums” from the ODD section and “Touchy or Easily Annoyed”, “Angry or Resentful”, and “Irritability” from the Depression session. Cut-offs based on frequency, pervasiveness and onset were applied to identify a more severe phenotype of irritability, consistent with previous work (Eyre et al., 2017) (refer to Chapter 2 for further details). The continuous score ranged from 0-4, as no participants endorsed the “Irritability” item.

4.2.3 Cognitive tasks

The cognitive tasks used in this study and described below are illustrated in further details in Chapter 2.

Cool EF tasks

The “*Wisconsin Card Sorting Test*” is a measure of set-shifting where participant’s need to adapt their response to feedbacks on how to sort correctly a deck of cards (Greve, 2001). The outcome measures were total number of errors and number of perseverative errors.

The “*Go no Go*” task measures behavioural inhibition and asks participants to either respond or withheld their preponderant motor response depending on the stimuli showed on the computer screen (Rubia et al., 2007). The outcome measures were RT to go signals and probability of inhibition in relation to performance using participants’ dominant hand.

Hot EF tasks

The “*Card Playing Task*” targets reward and punishment sensitivity (Newman et al., 1987). Participants are asked to play with a deck of cards with a progressively decreasing probability of winning and decide when to stop. The outcome measure was the total number of cards played before quitting.

The “*Temporal Discounting Task*” measures impulsivity expressed as reward devaluation as a function of its temporal delay (Richards et al., 1999; Rubia et al., 2009). Participants are asked to choose between an immediate reward and a reward delayed over a week, a month, a year, or two years. The outcome measures were the RT difference in choosing between a delayed and an immediate reward and the Area Under the Curve as an index of impulsivity. AUC values range from 0 to 1; the larger

AUC values, the lesser the delay discounting (i.e. less impulsivity) (Myerson et al., 2006).

The “*Choice per Risk Task*” measures how reward and punishment impact on risk-taking behaviours (Syngelaki et al., 2009). Participants need to win as many points as possibly by gambling on either one of two wheels of fortune that differ in their probability of winning and losing. The outcome measures were 1) the overall propensity to gamble; 2) participants’ risky decision-making on six different trials; 3) participants’ gambling behaviour after winning or losing small/big amounts.

The “*Ultimatum Game*” is a measure of emotion regulation (Koenigs & Tranel, 2007; Northover et al., 2015a) where participants are playing against a fictional opponent who suggest a way to split a sum of money that participants can either accept or refuse. The outcome measure was the percentage of moderately unfair (6/4; 7/3) offers accepted.

4.2.4 Sociodemographic Measures

Demographic information related to age and IQ (at follow-up), sex and SES were considered and collected as described in Chapter 2.

4.3 Quality Control of Cognitive Data

Before inclusion, data was analysed for Quality Control (QC) that consisted in identifying outliers, looking at testing notes for each participant and checking participant’s raw data where needed. Notably, testing notes were comments and observation made by the researchers during the child assessment about children level of engagement and behaviour during tasks. The initial sample composed of 220 participants with complete cognitive and childhood irritability data and z-scores were

computed to identify outliers, defined as scores over ± 3 standard deviations from the mean. All outlying participants showed poor commitment to the relevant tasks, as indicated either by performance consistently lacking variability and/or by comments in testing notes (e.g., participant was not focused, chatting throughout the task; half way through participant closed his eyes and was just pressing randomly), with the exception of two participants whose outlying scores seemed to have no recorded explanation. The scores of these two individuals were then replaced with the most extreme score within two standard deviations from the mean, whereas the task scores of the remaining outlying participants were removed from the database. Better and poorer than average performers also had their testing notes and cognitive performance checked on relevant tasks; if a response pattern indicative of poor engagement was identified, subjects' task scores were removed, whereas if the pattern of response varied and suggested a certain logic being followed, the participant scores were left in. Additionally, where z-scores were within the normal range, but testing notes described participants' poor performance (e.g. "responding with eyes closed"), the relevant task scores were removed. Conversely, for vague testing notes (e.g. "subject doesn't seem to be paying attention") and z-scores within the normal range, scores were included in the analyses unchanged. For cases with z-scores within the normal range, but no performance variability (suggesting no commitment to the task), relevant scores were removed. Finally, data for one subject was completely removed as the testing note suggested a generalised struggle across all cognitive tasks, which was consistent with generalised outlying scores. The final sample was composed of 219 adolescents with complete irritability data. Cognitive data available varied from a minimum of 116 participants to a maximum of 208 participants, this is due to participants' lack of compliance, technical problems that failed to record scores, removal of poor quality of data, as well as testing protocol changes. In particular, protocol changes affected the data collection for the UG task and the CxR task, the first one was discontinued. This was done to reduce the testing

time, whilst introducing new measures to enhance data collection of other relevant information.

4.4 Data Analysis

Analyses were conducted using SPSS version 23 (Corp, 2015). Initially, multiple and logistic regressions were performed to explore the association between the measure of chronic and severe irritability in childhood and demographic characteristics, whilst controlling for the effect of the relevant demographic factors and ADHD symptoms at follow-up. Additionally, multiple linear regressions were undertaken in a two-stage model to test the hypothesis that childhood chronic and severe irritability predicts CPT, TDT and UG (Hot EF tasks) but not WCST nor GnG (Cool EF tasks) performance in adolescents. In the first stage, Cool and Hot EFs were individually regressed onto childhood chronic and severe irritability; whereas in the second stage adjusted models were run controlling for demographic factors, and ADHD and CD symptom severity at follow-up. Notably, all variables were normally distributed. Consistent with previous literature (e.g., Dennis et al., 2009; Fry, Langley, & Shelton, 2020; Sjöwall & Thorell, 2018), the effect of the IQ was not partialled out due to the variance overlap with EF measures. The Bonferroni correction was performed to account for multiple testing, setting the p-value threshold to .006 (number of tests: 8).

4.4.1 Analysis on Choice per Risk task

Notably, the CxR task measured in adolescence was analysed comparing two groups: adolescents with ADHD and adolescents with ADHD and one or more symptoms of childhood severe irritability (ADHD vs. ADHD + I), consistently with previous studies (Fairchild et al., 2009; Sully et al., 2016; Syngelaki et al., 2009). These irritable and non-irritable groups were compared using a t-test on their propensity to gamble on the experimental wheels across trials (including the framing wheels). A mixed ANOVA

was used to analyse participants' risky decision-making in a 6 (trial type) \times 2 (group: ADHD + I vs. ADHD) design. These six trials selected were those where the optimal choice was less obvious: trial *zero* ($\Delta EV = 0.5$), trial *three* ($\Delta EV = -0.5$), trial *four* ($\Delta EV = -4$), trial *six* ($\Delta EV = -1$), trial *eight* ($\Delta EV = 0$; - frame) and trial *nine* ($\Delta EV = 0$; + frame), as undertaken previously (Sully et al., 2016). The four trials excluded all showed a lack of variability due to ceiling and flooring effects. 2 (Outcome: loss vs. win) \times 2 (Magnitude: large vs. small) \times 3 (Group: ADHD vs. ADHD+I) mixed-design ANOVA was also conducted to investigate participants' choice of risky wheel after losing a big or a small amount, or winning big or small, respectively. Significant group effects in mixed-design ANOVAs were followed-up using Bonferroni pairwise comparisons. Additional mixed-design analyses of covariance for both trial type and behavioural outcome were conducted to control for the effect of demographic, and ADHD and CD symptoms in adolescents. Notably, sex was not controlled for as all participants who were tested on CxR were males.

4.4.2 Bayesian Analyses

Bayesian analyses were conducted using JASP (version 0.9.2) (Jasp Team, 2018) to further validate the main findings obtained using a frequentist approach. The Bayesian approach complements the classic statistics by assessing the plausibility of either the null hypothesis (H_0) or the alternative hypothesis (H_1); whereas the classic p-value has a much less direct evidence in support of the alternative hypothesis (Marsman & Wagenmakers, 2017; Quintana & Williams, 2018). For the current Bayesian analysis, since this is the first study looking at cognitive markers of irritability, previous knowledge was unavailable to set up prior features in JASP, therefore the software's default options were used to conduct these analyses. Additionally, the Bayes Factor (BF_{10}) is used, that is the ratio of the experimental hypothesis to the null hypothesis (Marsman & Wagenmakers, 2017; Quintana & Williams, 2018). The values of the BF_{10} range from 0 to ∞ and they are interpreted following the

conventional guidelines (Quintana & Williams, 2018; van Doorn et al., 2019), for which a BF_{10} between 1 and 3 indicates equal support for both the rival hypotheses, BF_{10} values ranging from 3 to 10 suggest moderate evidence for H_1 , and finally BF_{10} greater than 10 and 30 points toward strong and very strong evidence for H_1 , respectively. Any BF_{10} value above 100 is considered to be extremely in favour of H_1 (Quintana & Williams, 2018; van Doorn et al., 2019). Conversely, the reciprocal scores provide evidence in favour of H_0 , similarly ranging from anecdotal to extreme support (Quintana & Williams, 2018; van Doorn et al., 2019).

As some adolescents ($n = 18$; 8.2%) did not stop their ADHD medication 24h prior testing, sensitivity analyses were performed to see if there was a change in the results by excluding these participants.

4.5 Results

At follow-up, this clinical ADHD sample was composed of 94% males and 46% of participants had a low SES. Associations between demographic characteristics and childhood chronic and severe irritability revealed that this phenotype was significantly associated with lower IQ (unstandardized $B = -1.96$, $p = .025$), whereas there was only a trend with low SES (OR= 1.36, 95% CI= 1.00, 1.84, $p = .049$) and there was no significant association with age (unstandardized $B = .082$, $p = .542$) or sex (OR= .871, 95% CI= .467/1.624, $p = .664$). Nonetheless, SES, age and sex were still used as covariates. Demographic characteristics by ADHD irritable and non-irritable groups are reported in Table 4.1.

	ADHD (N= 83)	ADHD+I (N= 136)	p-value
IQ	89.64 (13.75)	86.13 (11.7)	n.s
AGE	14.25 (1.82)	13.90 (1.92)	n.s
SES (LOW)	30 (37%)	61 (51%)	< .05
SEX (MALE)	79 (93%)	130 (95%)	n.s
ADHD SYMPTOMS AT FOLLOW-UP	10.9 (4.54)	13.49 (4.20)	< .001
CD SYMPTOMS AT FOLLOW-UP	1.91 (2.33)	3.05 (2.73)	< .05

Table 4.1 Clinical and demographic characteristics of the ADHD alone and ADHD & irritability groups.

Means or number are reported with standard deviations or percentage within brackets.

4.5.1 Multiple regression results

As shown in Table 4.2, overall childhood irritability did not predict Hot (CPT, TDT and UG) or Cool (WCST and GnG) EFs in adolescents with ADHD. This was consistent when controlling for demographic factors, and CD and ADHD symptom severity at follow-up. A significant association between severe irritability in childhood and WCST perseverative error (Cool EF measure) in adolescence did not withstand Bonferroni correction ($p = .006$).

	N	MODEL	UNSTANDARDIZED BETA (95% CI)
COOL EFs			
WCST TOTAL ERRORS	N= 173	Unadjusted Model	B= 1.24 (.21, 2.27)*
		Adjusted Model	B= 1.02 (-.04, 2.09)
WCST PERSEVERATIVE ERRORS	N= 173	Unadjusted Model	B= .73 (.17, 1.29)*
		Adjusted Model	B= .69 (.11, 1.28)*
GNG RT TO GO SIGNALS	N= 185	Unadjusted Model	B= 1.71 (-4.76, 8.17)
		Adjusted Model	B= 1.04 (-5.60, 7.67)
GNG PROBABILITY OF INHIBITION	N= 185	Unadjusted Model	B= 1.05 (-1.81, 3.91)
		Adjusted Model	B= 1.51 (-1.18, 4.20)
HOT EFs			
CPT TOTAL NUMBER OF CARDS	N= 208	Unadjusted Model	B= 1.31 (-3.05, 5.67)
		Adjusted Model	B= 1.49 (-3.17, 6.14)
TDT RT DIFFERENCE DELAYED - IMMEDIATE CHOICE	N= 176	Unadjusted Model	B= -.91 (-22.8, 21.0)
		Adjusted Model	B= -4.94 (-28.5, 18.6)
TDT AUC	N= 176	Unadjusted Model	B= -.02 (-.05, .01)
		Adjusted Model	B= -.02 (-.06, .01)
UG MODERATELY UNFAIR OFFERS ACCEPTED	N= 116	Unadjusted Model	B= -.07 (-.13, -.01)*
		Adjusted Model	B= -.05 (-.11, .02)

Table 4.2 Pattern of associations between severe irritability and Cool and Hot EF measures.

WCST = Wisconsin Card Sorting Test task, GnG = Go no Go task, CPT = Continuous Performance Task, TDT = Temporal Discounting Task, UG = Ultimatum Game. RT = Reaction Time, AUC = Area Under the Curve. Adjusted models were corrected for age, sex, SES, and ADHD and CD symptom severity in adolescence.

* Significant at < .05

4.5.2 Choice per Risk results

The t-test revealed no difference in the propensity to gamble between the non-irritable ADHD and irritable ADHD groups ($t(1, 149) = -1.243, p = .216$). Results of the mixed ANOVAs and mixed analyses of covariance are reported in Table 4.3. For both trial type and outcome after large/small loss/win, overall there was no main effect of group (i.e., no difference between ADHD+I and ADHD groups), and no significant interaction. There was a significant main effect of outcome and trial type. Pairwise comparisons on outcome suggested that participants who lost a large amount of money gambled more in subsequent trials than those who won a large amount ($p = .004$), although the main effect of outcome was no longer significant after adding covariates. The pattern of main effect of trial type is reported in Figure 4.1; overall adolescents chose the risky wheel significantly less on trial 1 than both trial 2 and 5 and significantly more than trial 3 and 4. Participants' decision-making was overall significantly riskier on trial 2 than any other trial, except trial 5. Trial 3 and trial 4 do not differ to one another, but participants gambled less on these wheels than they did on the rest of trials. Finally, adolescents chose the risky wheel more often on trial 5 than trial 6. Notably, this pattern was overall consistent in unadjusted and adjusted models.

Sensitivity analyses excluding adolescents who had not withdrawn their medication did not alter the findings, especially once applied the Bonferroni correction (see Appendix 4.1, Appendix 4.2, Appendix 4.3).

	MODEL (N= 151)			ADJUSTED MODEL (N= 121)		
	F	p	EF size	F	p	EF size
TRIAL TYPE	F (5, 149) = 281.41	p < .001	$\eta_p^2 = .654$	F (5, 119) = 10.46	p < .001	$\eta_p^2 = .083$
IRRITABILITY GROUPS	F (1, 149) = 1.281	p = .260	$\eta_p^2 = .009$	F (1, 119) = 1.583	p = .211	$\eta_p^2 = .014$
TRIAL TYPE * IRRITABILITY GROUPS	F (5, 149) = 1.129	p = .343	$\eta_p^2 = .008$	F (5, 119) = 2.085	p = .066	$\eta_p^2 = .018$
	F	p	EF size	F	p	EF size
OUTCOME	F (3, 149) = 3.711	p = .012	$\eta_p^2 = .024$	F (3, 119) = 1.469	p = .223	$\eta_p^2 = .013$
IRRITABILITY GROUPS	F (1, 149) = 2.984	p = .086	$\eta_p^2 = .020$	F (1, 119) = 2.814	p = .096	$\eta_p^2 = .024$
OUTCOME * IRRITABILITY GROUPS	F (3, 149) = .969	p = .407	$\eta_p^2 = .006$	F (3, 119) = 1.699	p = .167	$\eta_p^2 = .015$

Table 4.3 CxR mixed ANOVAs and mixed analysis of covariance results for trial type and outcome.

Adjusted models were corrected for age, SES, and ADHD and CD symptom severity in adolescence

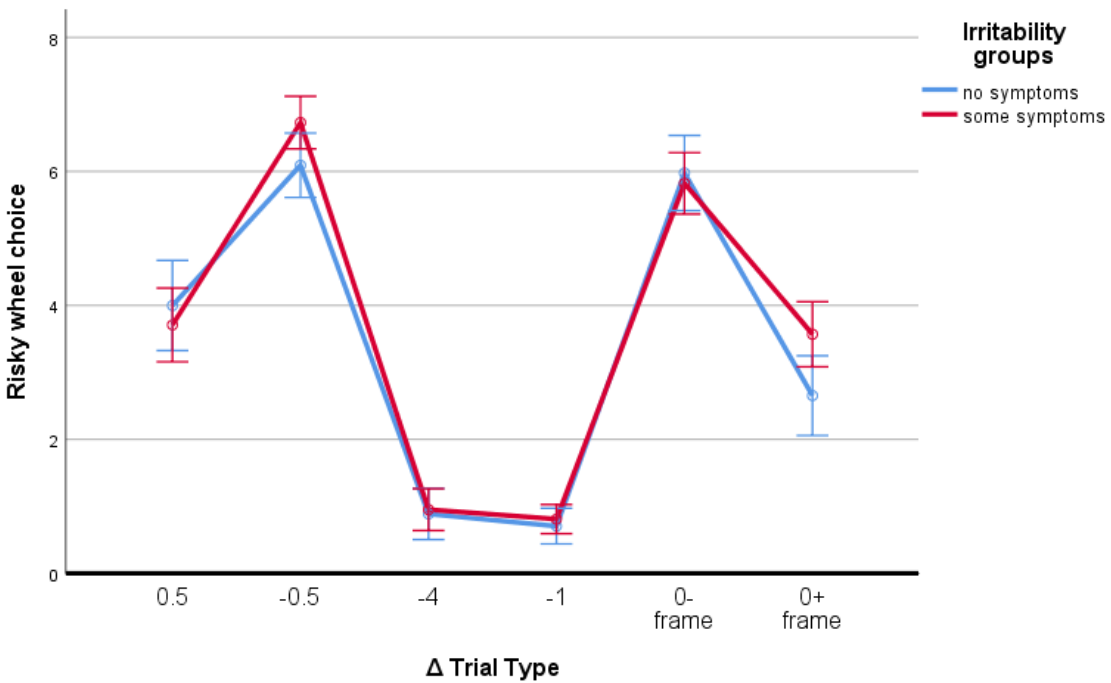


Figure 4.1 Risky decision-making mean values across 6 different trial types, split into groups.

Different trial type Δ Expected Values are reported on the x axis, whereas the y axis shows mean values of the number of times participants have chosen the experimental wheel per each trial type. -frame and + frame represent the positive and negative frame trials, respectively.

4.6 Bayesian Results

4.6.1 Multiple regression Results

For the Bayesian multiple regressions, the unadjusted models with irritability as sole predictor were compared against the null model (Table 4.4). Additionally, adjusted models including predictor and covariates (i.e., irritability, age, sex, SES, ADHD and CD symptom severity) were compared against the model including covariates only (i.e., age, sex, SES, ADHD and CD symptom severity) to see if irritability was a predictor of cognitive performance over and above the effect of covariates. This could be obtained using Bayes factor transitive property and thus dividing the model including predictor and covariates (i.e., irritability, and clinical and demographic factors) by the model with covariates only (i.e., age, sex, SES, ADHD and CD symptoms) (Quintana & Williams, 2018). Considering the unadjusted models, the BF_{10} for the WCST (Cool task) ranged from 3.1 to 4.9, suggesting these results being 3 to 5 times more likely under H_1 than H_0 . The absolute value of the BF_{10} for the rest of the tasks considered was small, providing either anecdotal evidence for both H_0 and H_1 or, more commonly, moderate support for H_0 over H_1 . Adjusted models seemed overall to be preferable to the unadjusted models due to improvements in BF_{10} , although for the majority of tasks they provided anecdotal evidence for both rival hypotheses. An exception is represented by WCST total errors whose BF_{10} worsened from moderate support for H_1 to anecdotal evidence. Notably, BF_{10} for TDT AUC (Hot EF) and WCST Perseverative errors (Cool EF) adjusted models was moderately in favour of H_1 .

COOL AND HOT EFs**MODEL'S BF_{10} (BF CLASSIFICATION RANGE)**

	N	Null	Childhood Irritability	Childhood irritability & covariates
WCST TOTAL ERRORS	N= 147	1.000	3.13 (3-10)	1.58 (1-3)
WCST PERSEVERATIVE ERRORS	N= 147	1.000	4.85 (3-10)	3.51 (3-10)
GNG RT TO GO SIGNALS	N= 157	1.000	0.27 (0.1-0.33)	0.46 (0.33-1)
GNG PROBABILITY OF INHIBITION	N= 157	1.000	0.21 (0.1-0.33)	0.33 (0.33-1)
CPT TOTAL NUMBER OF CARDS	N= 175	1.000	0.18 (0.1-0.33)	0.50 (0.33-1)
TDT RT DIFFERENCE DELAYED – IMMEDIATE CHOICE	N= 150	1.000	0.16 (0.1-0.33)	0.46 (0.33-1)
TDT AUC	N= 150	1.000	0.56 (0.33-1)	3.25 (3-10)
UG MODERATELY UNFAIR OFFERS ACCEPTED	N= 92	1.000	2.21 (1-3)	0.56 (0.33-1)

Table 4.4 Bayesian results for multiple regressions.

WCST = Wisconsin Card Sorting Test task, GnG = Go no Go task, CPT = Continuous Performance Task, TDT = Temporal Discounting Task, UG = Ultimatum Game; RT = Reaction Time, AUC = Area Under the Curve; BF = Bayes Factor.

Covariates are age, sex, SES, and ADHD and CD symptom severity at follow-up.

4.6.2 Choice per Risk results

Bayesian mixed ANOVA and mixed analysis of covariance results for the CxR task are reported in Table 4.5. For unadjusted models, both the main effects alone and the full model with main effects and interaction term were compared to the null model. For full models, main effects were included alongside the interaction term, as evidence from a previous study indicated that models with interactions without main effects are implausible (Rouder, Engelhardt, McCabe, & Morey, 2016). Adjusted models were however compared against the model including covariates only, to partial out their effect, similar to the previous Bayesian multiple regression analysis (see section 4.6.1). For risky decision-making across different trials, there was strong support for the main effect of trial type only, provided by the extreme BF_{10} , which remained consistent after controlling for covariates. The BF_{10} for adjusted and unadjusted models including both main effects and interaction term was extremely in favour of the H_1 over the H_0 , although this seemed to be driven by trial type. In fact, the BF_{10} of the full mixed ANOVA model, once accounted for the variance explained by trial type, was .004 (BF_{10} of the full model = $7.827e+176$ divided by BF_{10} of the model with main effect of trial type only = $1.792e+179$). Similarly, the BF_{10} of the full mixed ANCOVA model, once accounted for the variance explained by trial type, was .061 ($8.2e+146 / 1.346e+148$). These results suggest extreme and strong support for H_0 , respectively. In terms of gambling after the outcome of the risky choice, the main effects of outcome and ADHD irritable and non-irritable groups were anecdotal, after controlling for covariates, whereas the BF_{10} for the full mixed ANOVA and ANCOVA models supported H_0 strongly and moderately, respectively.

MODELS (N= 121)	BF ₁₀ (BF CLASSIFICATION RANGE)		
	Null Model	BF ₁₀ Unadjusted Model	BF ₁₀ Adjusted Model
TRIAL TYPE	1.000	1.792e+179 (BF ₁₀ > 100)	1.346e+148 (BF ₁₀ > 100)
CHILDHOOD IRRITABILITY	1.000	0.117 (0.1-0.33)	.109 (0.1-0.33)
TRIAL TYPE + CHILDHOOD IRRITABILITY + TRIAL TYPE * CHILDHOOD IRRITABILITY	1.000	7.827e+176 (BF ₁₀ > 100)	8.2e+146 (BF ₁₀ > 100)
	Null Model	BF ₁₀ Unadjusted Model	BF ₁₀ Adjusted Model
OUTCOME	1.000	3.181 (3-10)	2.75 (1-3)
CHILDHOOD IRRITABILITY	1.000	0.358 (0.33-1)	0.5 (0.33-1)
OUTCOME + CHILDHOOD IRRITABILITY + OUTCOME * CHILDHOOD IRRITABILITY	1.000	0.075 (0.03-0.1)	0.126 (0.1-0.33)

Table 4.5 Bayesian results for CxR task on trial type and outcome.

Adjusted models were controlled for age, SES, and ADHD and CD symptom severity at follow-up.

BF = Bayes Factor.

4.7 Discussion

This is the first longitudinal study testing the hypothesis of an association between childhood chronic and severe irritability and adolescents' Hot executive functioning. Overall results obtained using a frequentist approach show that baseline childhood chronic and severe irritability does not predict Hot EFs as opposed to Cool EFs in adolescence. In fact, all the analyses undertaken led to non-significant results following Bonferroni correction. This was independent of the role played by ADHD symptom severity or demographic factors, suggesting that childhood severe irritability *per se* does not seem to have any effect on Hot or Cool EF performance in a sample of adolescents with ADHD. Bayesian analysis however suggests that these findings need further validation as many results provided anecdotal evidence and thus were insensitive to detect an effect (Quintana & Williams, 2018; van Doorn et al., 2019). An exception is represented by WCST Perseverative errors and TDT AUC which provides support for H_1 . This seems inconsistent with the results obtained using the frequentist approach, however it should be noted that Bayesian analyses conducted with JASP, yielded slightly different results as this software handles missing using a listwise deletion, thus it further reduced the availability of cognitive data. Caution is therefore needed when interpreting these favourable results for H_1 .

Considering the uniqueness of this study, it adds to previous research in the field of ADHD and neurocognitive markers of irritability. The results obtained support those studies that failed to find significant behavioural differences comparing children with severe irritability and controls on cognitive performance (Adleman et al., 2011; Dickstein et al., 2007; Perlman et al., 2015; Rau et al., 2008), ultimately rejecting the hypothesis that irritability is associated with Hot EFs. They are also consistent with previous research in ADHD populations where irritability failed to show an association with cognitive markers, over and above ADHD symptom severity (Banaschewski et

al., 2012). These results are however in contrast with previous evidence in favour of this theory linking irritability and Hot cognitive functions (Brotman, Kircanski, & Leibenluft, 2017; Leibenluft, 2017b; Vidal-Ribas et al., 2016). It should be noted that this previous research focused on a narrow range of Hot cognitive tasks or used tasks that did not actually tap Hot cognitive processing (Adleman et al., 2011; Dickstein et al., 2007). Conversely this current study used a broad range of well validated measures to assess Cool and Hot EFs. It is therefore possible that the different results obtained reflect a more comprehensive assessment that enables a greater insight on the impact of severe irritability on cognitive performance. Previous significant results were in children with SMD (Adleman et al., 2011; Deveney et al., 2012; Dickstein et al., 2007; Rich et al., 2007). Considering the strong overlap of this phenotype with ADHD, it is possible that significant associations between SMD and Hot executive functioning might have actually been driven by ADHD symptom severity. This is further confirmed by previous findings showing ADHD and Emotional Lability being associated with the same cognitive parameters (Banaschewski et al., 2012). The discussion of these previous findings is also strongly limited by the different operationalisations of irritability, referred to as Emotional Lability/Dysregulation, within SMD or defined by its emotional and behavioural correlates. These inconsistencies prevent me from systematically comparing findings between previous studies, as well as between this current study and others as, for reasons detailed in Chapter 2 a stringent definition of irritability was used in this thesis.

These non-significant findings also inform the debate on irritability (Evans et al., 2017) by highlighting that, in a sample of adolescents with ADHD, irritability may not be clinically relevant from a cognitive perspective over and above ADHD diagnosis and symptom severity. However, there could be other pathophysiological mechanisms associated with irritability that should be investigated in an attempt to assess the clinical relevance of this phenotype at the cognitive level in those with ADHD.

As suggested by previous reviews (Brotman, Kircanski, & Leibenluft, 2017; Brotman, Kircanski, Stringaris, et al., 2017; Leibenluft, 2017b), severe irritability is intertwined with the Frustrative Non-Reward that considers those showing severe irritability as having a lower tolerance and an aberrant response to frustration. Thus, it is possible that cognitive markers of severe irritability may be strictly connected to this concept of FNR, as opposed to broader deficits in reward processing. Previous studies investigating responses to blocked reward attainment, with tasks specifically designed to induce frustration, showed consistent findings; compared to controls, children with severe irritability display a greater emotional response to frustration with a negative impact on cognitive performance, supported both at neurophysiological and behavioural level (Rich et al., 2011, 2007). These neurophysiological results are also supported in a sample of kindergarten aged children with externalising problems (Gatzke-Kopp et al., 2015). Additionally, as mentioned in the general introduction, the EF model is only one of the disrupted neuropsychological pathways possibly leading to ADHD. The default-mode network hypothesis has acquired a greater importance in ADHD literature (Liddle et al., 2011; Sonuga-Barke & Castellanos, 2007); failure to regulate the default-mode network seems to be characteristics of those with ADHD, possibly explaining lapses of attention, performance variability or impulsive behaviour interfering with goal-directed activities (Liddle et al., 2011; Sonuga-Barke & Castellanos, 2007). Similarly, those with ADHD show consistent problems in the state-regulation activity, displayed as poor effort regulation, vigilant attention, arousal and activation that may disrupt cognitive processes (Sergeant, 2000, 2005; Wahlstedt et al., 2009). Thus, future research on the overlap between ADHD and irritability could investigate other pathophysiological mechanisms to the EF model to test the impact of severe irritability in youths with ADHD. Finally, the negative impact of irritability in ADHD could act through a social rather than cognitive pathway. Studies on Emotion Dysregulation showed a consistent link with social problems in children with ADHD. Cross-sectionally peer problems, functional impairment and comorbid conditions in

those with ADHD are partially mediated by Emotion Dysregulation (Anastopoulos et al., 2011; Sjöwall & Thorell, 2014); whereas longitudinally irritability in adolescents is predictive of poor educational attainment and lower Social Economic Status at 20 years follow-up (Stringaris et al., 2009).

This study has several strengths. It is innovative as it is the first study looking at neurocognitive markers of chronic and severe irritability in ADHD, exploring potential pathological mechanisms leading to impairment in this population. It benefits from a clear and circumscribed operationalisation of chronic and severe irritability, as opposed to looking at facets of this construct (e.g., trait anger, emotional lability, or dysregulation). A wide range of well validated cognitive tasks was also used, thus Cool and Hot cognitive functioning were accurately tapped, ultimately enhancing the possibility to directly compare these two cognitive aspects. Nonetheless, the results of this study should be considered in light of several limitations. Firstly, chronic and severe irritability is measured through a parent-rated questionnaire, whereas EFs are measured in the laboratory. These different measurement systems could possibly explain non-significant results due to the lack of consistency between parent-rated and lab-assessed measures (Sjöwall & Thorell, 2018). A multi-method approach might therefore provide more accurate evidence of the impact of chronic and severe irritability on neuropsychological functions in ADHD. Secondly, this is a post hoc study and the measures available were originally chosen to address a different aim. Thus, a comprehensive scale specifically designed to tap chronic and severe irritability could not be used; this measure was derived from available clinical interview subscales. Additionally, the EF tasks were initially selected as well validated in ADHD population and not as direct measures of cognitive markers of irritability. Thirdly, this study lacks both a comparison and a control group which would complement the study of the cognitive markers of irritability by looking at the impact of chronic and severe irritability on Hot cognitive functioning both in the general population and in other clinical

samples. The lack of typically developing controls also limits the possibility to compare EF performances, ultimately being unable to refine these analyses to those actually showing EF impairments. Fourthly, despite this study was accessible to a large number of families with ADHD at baseline, participant drop-out, protocol changes and QC checks negatively impacted the availability of cognitive data at follow-up, that was further reduced for the Bayesian analysis. Thus, investigating the same research questions in a larger sample might enable more definitive conclusion. Finally, it is possible that the wide age range of this current sample can have biased these results at least in respect to certain tasks. Although chronic and severe irritability was not associated with age, age was correlated with cognitive performance on GnG and WCST.

In conclusion this is the first study to longitudinally investigate an association between reward-related impairments and chronic and severe irritability, as suggested by the neuroscientific conceptualisation of this phenotype. Despite the broad range of well validated Cool and Hot EF measures used, these results failed to support the initial hypothesis; childhood chronic and severe irritability does not seem to be associated with later impairments in Hot cognitive processing, in youths with ADHD. This conclusion is supported by both the classic frequentist approach and the Bayesian approach. This hypothesis was however explored using a variable-centred approach, as group performance on individual tasks was considered. The associations between chronic and severe irritability and Hot cognitive functioning can also be explored using a person-centred approach, thus taking into account the cognitive performance at the individual level. This might be beneficial to produce more robust results as it is explained more in details in the next subchapter, where the association between chronic and severe irritability and Hot EFs using a person-centred approach is investigated.

4.8 A person-centred approach to the study of Hot cognitive functioning and chronic and severe irritability

4.8.1 Introduction

Counter to my hypotheses, results of the previous study failed to show an association between childhood chronic and severe irritability and Hot cognitive markers in adolescents with ADHD; these non-significant results however would benefit of further investigation to enable a better insight on their interpretation. It could in fact be that these non-significant findings are the results of methodological caveats relating to the way in which Hot EFs were characterized; applying a different study design to the same research question could inform of the robustness of these findings. This is also consistent with the concept of “triangulation of evidence”, a highly encouraged practice of using a multitude of different approaches to corroborate results, to increase the replicability of science, and to avoid artefacts (Munafo & Smith, 2018).

One methodological caveat possibly affecting the results of the previous study could be that the decision to look at Hot EF tasks individually might have masked the effect of an association between adolescents' Hot cognitive functioning and childhood chronic and severe irritability in this ADHD sample. This stems from previous evidence showing small effect sizes associated with the investigation of individual cognitive tasks (DeVito et al., 2008; Sjöwall & Thorell, 2018; Willcutt et al., 2005), suggesting that looking at participants' performance across multiple tasks combined might increase the power to detect significant effects. As the previous analyses in this chapter were the first to compare those with ADHD and chronic and severe irritability and those with ADHD alone, inferences about this caveat come from case-control studies on cognitive impairments that only show small to medium Cohen's *d* effect

sizes when comparing ADHD to typically developing controls on individual cognitive tasks (DeVito et al., 2008; Sjöwall & Thorell, 2018; Willcutt et al., 2005). More specifically, a meta-analysis comparing children with ADHD to controls on Cool EFs (behavioural inhibition, sustained attention, set-shifting, planning and working memory) single task performance revealed only medium average effect sizes, observed especially for motor inhibition, sustained attention, spatial working memory and planning (Willcutt et al., 2005). Most importantly, case-control differences on set-shifting skills showed a small effect size (Willcutt et al., 2005); it should be noted that it is the only measure of Cool EFs overlapping with the previous study, as in both cases set-shifting abilities were measured using the Wisconsin Card Sorting Test, whereas the remaining variables considered by this meta-analysis differ from the ones used in this thesis. These case-control differences of small to medium effect sizes are also not accounted for by intelligence, population source, ADHD comorbid symptoms or academic functioning (Willcutt et al., 2005). Additionally, as suggested by twin and family studies, ADHD symptoms and scores on individual Cool EF tasks show a small proportion of common genetic influences, possibly explaining their small to medium correlation; there is a consistent proportion of variance explained by unique genetic and environmental influences for each phenotype (Doyle et al., 2005; Willcutt et al., 2005). Hot executive functioning has been less systematically investigated, although case-control studies suggest those with ADHD performing worse on delay aversion, decision-making and risk adjustment than controls with medium and large effect sizes (DeVito et al., 2008; Sjöwall & Thorell, 2018). It should however be noted that these effect sizes were obtained using different Hot EF tasks, and to a certain extent measures (e.g., risk adjustment), to the ones used in this thesis. Importantly, youths with ADHD show impairments in emotional functioning, a concept related to irritability, compared to controls with just a small effect size (Sjöwall & Thorell, 2018). Despite the fact that this evidence comes from a different study design (i.e., case-control comparisons) compared to the analyses in this thesis, these findings can still illustrate

the effect size caveat when looking at individual cognitive tasks that could even be exacerbated when looking within a sample of youths with ADHD. It is therefore possible that a specific focus on single Cool and Hot EF tasks within ADHD might have exposed this methodological caveat to a greater extent, ultimately leading to non-significant findings related to the cognitive markers of chronic and severe irritability in this population. Thus, work is needed that focuses on cognitive performance across multiple tasks combined to enhance the detection of larger effect sizes and this is what the current study aimed to do.

Another methodological caveat is that the previous study of this chapter used a variable-centred approach whose intrinsic methodological limitations could have led to non-significant results. The same research question about the Hot cognitive markers of childhood chronic and severe irritability within adolescence ADHD could therefore benefit from a person-centred approach instead. A variable-centred approach focuses on individual variables and relationships between them, in the attempt of predicting outcomes (Muthén & Muthén, 2000). Thus, this describes the approach used previously in this chapter when comparing youths with childhood chronic and severe irritability and ADHD to those with ADHD alone, as consistent impairments across individuals were looked at the individual cognitive task level. Conversely, a person-centred approach is data-driven with a greater focus on relationships between individuals, as it aims at grouping individuals into homogeneous categories based on their different and similar pattern of responses across multiple variables of interest (Muthén & Muthén, 2000). Using a person-centred approach as opposed to a variable-centred one is not intrinsically better but rather, these approaches can be complementary and used to address the same research question from a different perspective (Howard & Hoffman, 2018). However, as they are reliant on different methods, using a person-centred approach as opposed to a variable-centred one could have methodological advantages. There

are four main benefits associated with this approach that are relevant in this chapter:

1) A person-centred approach is more specific than a variable-centred one due to their different assumption of homogeneity (Howard & Hoffman, 2018). This means that whilst a variable-centred approach assumes that the sample of interest is homogeneous; a person-centred approach assumes that a sample could be characterized by different subpopulations of homogeneous individuals. Using a person-centred approach could therefore identify sample characteristics with a greater level of specificity. Considering the previous study of this chapter, using a person-centred approach would enable a deeper insight on the characteristics of the current ADHD sample that could consist of subgroup of individuals with different Hot cognitive profiles, differently associated with childhood chronic and severe irritability. Counter to this, considering the current ADHD sample as unitary by using a variable-centred approach could have reduced the ability of identifying Hot cognitive markers of this chronic and severe phenotype of irritability by reducing the overall variability of this sample. 2) A person-centred approach is data-driven, thus with the advantage of not being reliant on arbitrary thresholds and biased theoretical constructs, compared to a variable-centred one (Lambek et al., 2018; Sjöwall & Thorell, 2018). The ADHD sample used in the previous analyses of this chapter was reasonably, but still arbitrarily, split into irritable and non-irritable groups of adolescents with ADHD, forcing the cognitive variability within these pre-determined groups. Using a person-centred approach would entail a flexible and assumption-free reorganisation of this sample into different categories based on their differences and similarities at the cognitive level, possibly providing a greater insight on Hot cognitive markers of childhood chronic and severe irritability in adolescents with ADHD. Cut-offs and constructs could in fact be clinically useful but quite reductionist and potentially unable to identify the underpinnings of complex multifaceted psychiatric conditions such as ADHD (Lambek et al., 2018; Marquand, Wolfers, Mennes, Buitelaar, & Beckmann, 2016). 3) A person-centred approach often follows a data reduction principle as it

investigates variance captured by latent variables (Oberski, 2016). This suggests that using a person-centred approach would not require the Bonferroni adjustment for multiple comparisons which is a conservative measure (Simes, 1986) that could have further reduced the power to detect an effect, especially combined with previous disadvantages associated with a variable-centred approach. 4) A person-centred approach considers a higher proportion of variance compared to a variable-centred one, as it encapsulates common variance shared by indicators of the homogeneous categories identified (Geiser, 2013). This overall variance is not simply the sum of each individual indicator variance, as suggested by the fact that the accuracy of the model to identify homogeneous categories of individuals, is not equal to the combined accuracy of individual indicators (Asparouhov & Muthén, 2018). Considering Hot cognitive tasks individually (i.e., variable-centred approach) could have reduced the amount of variance potentially explained by childhood chronic and severe irritability, whereas a greater variability could increase both the power of this predictor to detect an effect and effect sizes. This is further confirmed by previous works including youths with ADHD that report greater effect sizes using a person-centred approach on Cool and Hot EFs than when neuropsychological measures are compared either in DSM-defined or case-control groups (Gomez, Gomez, Winther, & Vance, 2014; Lambek et al., 2018; Rommelse, van der Meer, Hartman, & Buitelaar, 2016). Considering these methodological caveats related to a variable-centred approach, it appears clear that the complementary person-centred one could be beneficial to further investigate the relationship between chronic and severe irritability and Hot cognitive functioning.

Previous studies have used a person-centred approach to identify cognitively homogeneous subgroups of youths with ADHD (Fair, Bathula, Nikolas, & Nigg, 2012; Gomez et al., 2014; Rajendran, O'Neill, Marks, & Halperin, 2015; Rommelse et al., 2016; Van Hulst, De Zeeuw, & Durston, 2015), although no one to date has considered irritability as a class predictor nor considered a wide range of Hot EF tasks,

only. These studies in fact focused on both Cool and Hot EFs, and additionally, the Hot tasks considered only tapped reward sensitivity and delay aversion (Lambek et al., 2018; Van Hulst et al., 2015), rather than a broad range of Hot EFs as those used in the current thesis. Findings from these previous studies are also mixed in terms of the usefulness of stratifying childhood ADHD based on different cognitive profiles (Lambek et al., 2018; Van Hulst et al., 2015). One study identified three classes with different profiles of cognitive control and timing in a sample of youths with ADHD, but these classes showed very similar profiles on reward sensitivity (Van Hulst et al., 2015). Conversely, another study was able to distinguish four different cognitive profiles ranging from high to very poor performance across all Cool and Hot indicators (working memory, set-shifting and delay aversion) (Lambek et al., 2018). Cool EFs have been more consistently studied than Hot EFs, and different profiles were found for working memory impairments (High, Moderate and Average) (Fair et al., 2012; Gomez et al., 2014), Reaction Time variability, output speed, temporal information processing and arousal (Fair et al., 2012) within childhood ADHD. Finally, different profiles were also reported with qualitatively different impairments on attention, neuropsychological functions and level of motor activity in pre-schoolers with ADHD (Rajendran et al., 2015). None of these studies using a person-centred approach has considered possible predictors of these different cognitive profiles. Only associations with clinical and functional outcomes were investigated with mixed findings on the prognostic and clinical relevance of the cognitive profiles identified (Fair et al., 2012; Gomez et al., 2014; Lambek et al., 2018; Rajendran et al., 2015; Rommelse et al., 2016; Van Hulst et al., 2015). It is important to note that the majority of evidence coming from these previous studies has been obtained applying a Latent Profile Analysis (LPA), a widely used technique in a person-centred approach. LPA identifies latent classes composed of individuals with similar profiles across a range of continuous class indicators (e.g. neuropsychological measures). This technique provides information about the most likely class membership for each individual

(Nylund & Muthén, 2007), a parameter used to group those with similar profiles together based on their observed pattern of responses, ultimately being able to minimize differences within each class and maximize differences across classes (Nylund & Muthén, 2007). LPA also assumes conditional independence whereby within a latent class, all the class indicators are considered to be independent to one another and any observed correlation between these indicators are considered to be entirely due to the latent class (Nylund & Muthén, 2007).

To summarise, looking at individual cognitive tasks in youths with ADHD is associated with small to medium effect sizes and a person-centred approach might be beneficial to address the same research questions compared to a variable-centred one, but this approach is under-researched in ADHD, especially in the domain of Hot EFs. As previous non-significant findings might have been limited by a series of methodological caveats, mostly obtained using a variable-centred approach, a further investigation using the complementary person-centred approach might be particularly beneficial for an accurate interpretation. Therefore, the aim of this current analysis was to use Latent Profile Analysis to identify homogeneous Hot cognitive profiles in this current sample of adolescents with ADHD and to see if they were predicted by childhood chronic and severe irritability. This analysis focused on Hot EFs only, as the theoretical rationale links impairments in motivational and reward processing (Hot EFs) to chronic and severe irritability specifically. Therefore, distinct profiles in Cool EFs are not of interest and were previously used just as control measures (refer to section 4.1 for further details). As this is the first study to include a broad range of Hot EF tasks, no hypothesis was made in terms of LPA number of profiles; whereas, childhood chronic and severe irritability was expected to predict at least one of the poor Hot cognitive profiles possibly identified.

4.8.2 Methods

Sample

The original sample was composed of 219 adolescents with ADHD, aged 10-18 years (mean age 14.04, s.d. 1.90) whose details are provided in the previous analyses (see Chapter 4, section 4.2.1). One subject was found to have missing data on all Hot cognitive variables taken into account and it was therefore excluded, leaving a total sample size of 218 participants for this exploratory LPA analysis.

Measures

Childhood chronic and severe irritability measure was derived by extracting relevant items from the Oppositional Defiant Disorder and Depression sections of the CAPA as previously described (see Chapter 4, section 4.2.2).

The Hot cognitive tasks and variables used are: total card played from the CPT; RT differences between delayed and immediate reward choice and the AUC from the TDT; behavioural outcome after large/small loss/win from the CxR; and percentage of moderately unfair offers accepted from the UG (see Chapter 2 for a full description of these tasks). These measures were consistent with the ones considered in the previous study of this chapter, with the exception of the CxR task whereby overall propensity to gamble and risky decision-making across six different trials were excluded. The outcome after a large/small loss/win was in fact the main variable of interest; looking at single trials individually in an LPA is also not as informative as looking at the overall trend in a mixed ANOVA as done previously. These are the reasons that led to the exclusion of CxR overall propensity to gamble and risky decision-making across trial types.

4.8.3 Statistical Analysis

All statistical analyses on Hot EF tasks (CPT, TDT, CxR, UG) were performed using Mplus software, version 8.21 (Muthén & Muthén, 2018). It should be considered that the LPA does not provide an accurate index of absolute fit of the model, although it provides indexes of relative fit comparing models with different classes to one another that guide the decision on the best class model (Nylund & Muthén, 2007). These relative fit indexes can be grouped into both Information Criteria (IC) and likelihood-based indexes and among these, the most reliable ones are the Bayesian Information Criterion (BIC) and Akaike's Information Criterion (AIC), for the IC, and the Lo-Mendell-Rubin (LMR) and the Bootstrapped Likelihood Ratio Test (BLRT), for the likelihood-based criteria (Nylund & Muthén, 2007). Lower values of both BIC and AIC indicate a better fit when comparing competing models; whereas LMR and BLRT provide a p-value that indicates if the fit of the model with the higher number of classes is significantly better than the neighbouring model (Nylund & Muthén, 2007). Model parameters were obtained using the Maximum Likelihood (ML) estimator and high starting values were chosen to ensure the validity of each latent profile solution (Geiser, 2013). Model entropy was also estimated as a measure of classification accuracy; entropy values range between 0 and 1, with values closer to 1 indicating a neater class distinction (Asparouhov & Muthén, 2018). LPA model estimations are less prone to bias with large values of entropy, suggesting that the classes identified are adequately different to one another with negligible or no classification error (Asparouhov & Muthén, 2018). An entropy value of at least .60 is shown to identify sufficiently separate profiles (Asparouhov & Muthén, 2014). Univariate entropy was also estimated as a measure of the contribution of single indicators in discriminating the classes; the greater the univariate entropy (ranging from 0 to 1), the more informative an individual indicator in identifying different profiles (Asparouhov & Muthén, 2018). Although not relevant to the decision regarding the best LPA model, the proportion of individuals per class and classification accuracy, which is the

average latent class probabilities for most likely latent class membership, were reported as they provide a useful descriptive summary of the model profiles. Once the best LPA model was chosen, childhood chronic and severe irritability was added as profile predictor using the R3STEP procedure, which is an automatic approach to estimate the predictive power of this phenotype without changing the latent profile formation (Asparouhov & Muthén, 2018; Vermunt, 2010).

4.8.4 Results

As shown in Table 4.6, both LMR and BLRT suggested that the fit of the 2-class model was significantly better than considering the cognitive performance of this current sample as cognitively homogeneous. This model was also preferable than a 3-class model as indicated by all relative fit indexes considered, with the exception of AIC, which is known to be less accurate than both BIC and BLRT (Nylund & Muthén, 2007) (Table 4.6). Furthermore, both the overall entropy and the accuracy of participants' classification into different profiles were worse for the 3-class model than for the competing 2-class model. The 2-class model was therefore the best solution to fit this data, suggesting that adolescents with ADHD showed two distinct Hot cognitive profiles.

RELATIVE MODEL FIT INDEXES	2-CLASS MODEL	3-CLASS MODEL
AIC	4010.775	4008.606
BIC	4095.387	4123.678
LMR P-VALUE	.000	.714
BLRT P-VALUE	.000	.707
ENTROPY	.78	.74
% OF PARTICIPANT PER CLASS	.50/.50	.43/.42/.15
CLASS ACCURACY	.94/.92	.92/.91/.68

Table 4.6 Two and three-class model fit statistics for LPA on Hot executive functioning

AIC = Akaike's Information Criterion, BIC = Bayesian Information Criterion, LMR = Lo-Mendell-Rubin, BLRT = Bootstrapped Likelihood Ratio Test.

Considering the univariate entropy, there was only one measure that had a moderate univariate entropy which was CPT total number of cards played (.768); whereas this parameter was negligible for all of the remaining individual Hot indicators, ranging from less than .001 to .053. This suggests that only CPT had a consistent contribution in defining the 2-class model, whereas the remaining indicators did not have any influence in differentiating the two Hot cognitive profiles. This was further confirmed by looking at the class characteristics reported in Table 4.7, where mean values were very similar across the majority of Hot tasks with the exception of CPT. Participants in class 1 were in fact characterised by a smaller number of cards played (i.e., better performance) on CPT than those in class 2, suggesting that the Hot cognitive profile of those in class 1 was characterised by a greater sensitivity to reward and punishment than those in class 2.

INDICATOR MEANS (S.D.)		
	Profile 1	Profile 2
CPT CARDS	31.1 (14.73)	88.14 (16.43)
TDT LN	-.53 (153.71)	20.57 (148.90)
TDT AUC	.62 (.21)	.62 (.20)
CXR LL	.55 (.22)	.58 (.21)
CXR SL	.54 (.25)	.56 (.25)
CXR LW	.49 (.16)	.49 (.14).
CXR SW	.52 (.18)	.53 (.16)
UG MU	.39 (.34)	.64 (.28)

Table 4.7 Descriptive statistics for the two profiles identified by the LPA.

CPT = Card Playing Task; TDT = Temporal Discounting Task; CxR = Choice per Risk task; UG = Ultimatum Game; Cards = total number of cards played; LN = RT differences between late and

immediate reward choice; AUC = Area Under the Curve; LL = large loss; SL = small loss; LW = large win; SW = small win; MU = Moderately Unfair offers accepted.

Finally, childhood chronic and severe irritability was a significant predictor of neither of the two cognitive profiles identified, as revealed by the R3STEP approach ($p = .334$). This suggests that chronic and severe irritability in childhood did not predict adolescents' likelihood of displaying greater or lower sensitivity to reward and punishment, as represented by the two cognitive profiles emerged.

4.8.5 Discussion

Overall results of the Latent Profile Analysis suggest that the cognitive performance on Hot executive tasks of adolescents with ADHD can be split into two distinct cognitive profiles. However, this distinction seems to be driven only by differences in reward and punishment sensitivity as measured by the CPT. Class 1 shows in fact a better performance on this task only, compared to class 2; the negligible contributions of all other indicators suggests a lack of cross-task variability that ultimately question the usefulness of these two profiles. Finally, contrary to the initial hypothesis, childhood chronic and severe irritability does not seem to be a predictor of the poorer Hot cognitive profile (class 2) and it significantly predicts neither of these Hot cognitive profiles.

Comparing these findings to the previous literature, they are in contrast with those obtained by Van Hulst and colleagues (2015), who failed to identify ADHD subgroups with different reward and punishment sensitivity profiles. However, it should be considered that this current study differs from Van Hulst's (2015) in terms of tasks used, number of classes identified, and LPA information considered. Reward and punishment sensitivity was measured in their previous research using a modified version of the Monetary Incentive Delay (Van Hulst et al., 2015), originally designed

as a measure of reward anticipation rather than sensitivity (Knutson, Adams, Fong, & Hommer, 2001). During this task, participants just need to guess where a sum of money would be by choosing between two stimuli, followed by a rigged outcome unrelated to their responses, and the variable of interest was the RT differences in rewarded and non-rewarded condition (Van Hulst et al., 2015). The CPT task used in this current study engages participants more actively by asking them to decide when to stop which reflect a great interest in the behavioural expression of reward and punishment sensitivity (i.e., total number of cards played) rather than in a more non-specific measure; RT is in fact a low-order cognitive process, underlying multiple cognitive activities. It should also be noted that in Van Hulst and colleagues' study (2015), two profiles out of the 5-class best fit model identified were excluded due to their small sample size, and this arbitrary model reduction could have reduced their possibility of identifying different profiles based on reward and punishment sensitivity. Finally, in this current analysis, univariate entropy was also considered as an objective measure to look at the indicator's contribution to the profile identification, whereas van Hulst and colleagues (2015) did not use similar objective parameters to support the negligible role of reward and punishment sensitivity.

The current findings are also in contrast with a previous study by Lambek and colleagues (2018) who found significant profile differences for delay aversion. However, it should be considered that delay aversion was a factor score obtained combining multiple tasks, whereas in this current study just one individual task tapping temporal discounting (i.e. TDT) was used. Furthermore, albeit similar, the concepts of delay aversion and temporal discounting are different. Delay aversion refers to the motivational effort to avoid delay (Lambek et al., 2018); whereas temporal discounting is the devaluation of a reward as a function of delay (Myerson et al., 2006). It should however be noted that this is the first study to use LPA on a broad range of Hot EF tasks, thus the conceptual and methodological differences when comparing results of

this study to previous literature limit the possibility of discussing these findings thoroughly.

Additionally, considering that the Hot cognitive profiles identified were based only on participants' score on CPT, it is not surprising that childhood chronic and severe irritability was not a significant predictor in this LPA analysis. Findings from the previous analysis in section 4.5.1 looking at individual tasks, already showed childhood chronic and severe irritability failing to predict adolescents' performance on CPT.

The lack of common variability in terms of Hot cognitive functioning is more surprising than this non-significant association, especially considering the great heterogeneity that characterises ADHD at a cognitive level (Nigg et al., 2005). However, as mentioned in the general introduction, it should be noted that only a small subset of youths with ADHD seem to be cognitively impaired showing a worse performance on cognitive tasks compared to controls (Nigg et al., 2005; Sjöwall et al., 2013; Sjöwall & Thorell, 2018). Additionally, among those who do show neuropsychological deficits; children with ADHD more commonly display impairment in Cool EFs (working memory, behavioural inhibition, set-shifting, RT variability) than they do on Hot EFs (delay aversion, emotional functioning) (Sjöwall et al., 2013; Sjöwall & Thorell, 2018); although it should be considered that Hot EFs are understudied compared to Cool EFs. It is therefore possible that this current sample was under-characterised in terms of Hot cognitively impaired youths with ADHD, without being able to fully understand its extent, as the Hot EF measures used mostly lack standardised norms and a control group was not available to define the criteria of impairment. Thus, the possibility of investigating the impact of childhood chronic and severe irritability on Hot cognitive functioning in this sample of adolescents with ADHD might have been greatly reduced. Another possible explanation for the under identification of common variance across Hot tasks, relates to Reaction Time variability characteristic of

cognitive performance of youths with ADHD (Castellanos et al., 2005). RT variability is considered as a moment-to-moment fluctuations in cognitive performance, measured within a time frame of multiples of seconds, that are shown to be larger and more frequent in individuals with ADHD, leading to greatly variable performance and randomness of behaviour (Castellanos et al., 2005). Therefore, it could be that the difficulty in extracting shared variance across tasks encountered in this current study could be due to the cognitive performance inconsistency at task level, which reflects great intra-individual RT variability of those with ADHD. This is also suggested by the large and overlapping standard deviations (e.g. TDT RT) observed in this ADHD sample as an indication of the overall variability at single time points.

These findings need to be considered in light of several strengths and limitations. The great value of this study is that it is the first attempt to conduct an LPA on a broad range of Hot cognitive functions, and the first to investigate childhood chronic and severe irritability as a possible predictor of these profiles, in a large sample of adolescents with ADHD. Even though some of the methodological caveats discussed in relation to the analyses in section 4.7 were addressed by using a person-centred approach, some of the previous limitations still stand. These mainly refer to the post hoc nature of this data; lack of comparison and control groups; the measurement of chronic and severe irritability; the choice of EF tasks and measures, well-validated in ADHD but possibly inadequate to tap chronic and severe irritability; and finally the wide age range that even in this study might have reduced the possibility to detect common variance across Hot EF tasks and to investigate the predictive power of irritability defined as chronic and severe (refer to the 4.7 section of Chapter 4 for further explanation).

In conclusion this is the first study conducting an exploratory LPA on a broad range of Hot EF tasks and looking at childhood chronic and severe irritability as a profile

predictor, in a clinical sample of adolescents with ADHD. The use of a person-centred approach to investigate the same research questions has led to similar conclusions; overall these results failed to show great cognitive variability and childhood chronic and severe irritability did not predict either of the profiles identified. Investigating different EFs, and social and neuropsychological processes might be more relevant leading to more promising results. However, considering the pioneering nature of these studies, findings are far from conclusive. Similarly, irritability is a cross-diagnostic symptom, investigating its cognitive markers in both externalising and internalising conditions could give better insight about pathophysiological mechanisms of this phenotype across different samples. Addressing these aspects in future research could improve the theoretical models of ADHD and provide a better understanding of the clinical relevance of irritability across conditions, being ultimately useful in clinical practice. A person-centred approach could still be particularly beneficial in this field, ultimately leading to a better understanding of the architecture of complex neurodevelopmental disorders, to identify different aetiological pathways and treatment response which the limitations associated to variable-oriented methods might constitute a barrier to.

Despite these non-significant results, chronic and severe irritability appears to be highly relevant for individuals with ADHD as supported by previous research (see Chapter 1, section 1.2.3) and backed up by Chapter 3 results, showing this phenotype to be associated with poor clinical outcomes, in this population. This supported the investigation of cognitive markers, and whilst at the cognitive-behavioural level results have been inconclusive, additional work assuming a different perspective, such as looking at biological underpinnings, might yield different results. This is addressed in the following chapter of this thesis that aimed to explore shared genetic risk between chronic and severe irritability and Hot cognitive functioning, possibly enhancing the

understanding of Hot EFs as pathophysiological markers of this clinically relevant phenotype.

Chapter 5

Irritability common genetic contributions to Hot cognitive functioning in a sample of adolescents with ADHD

Chapter description

This chapter addresses the third and final aim of this thesis which is to investigate the impact of common genetic risk associated with irritability on Hot, as opposed to Cool, cognitive functioning, in a sample of adolescents with ADHD. In this chapter, participants from the clinical ADHD sample, whose data was available at follow-up, and the United Kingdom (UK) Biobank sample were considered. Details about The UK Biobank sample are provided below.

5.1 Introduction

As previously discussed, chronic and severe irritability is defined as an intense and disproportionate anger reaction, compared to peers, when facing negative stimuli (Brotman, Kircanski, & Leibenluft, 2017; Brotman, Kircanski, Stringaris, et al., 2017). This phenotype is particularly relevant in Attention Deficit Hyperactivity Disorder being very prevalent (up to 92% of those with ADHD report irritable symptoms) (Eyre et al., 2017) and being associated with worse clinical and functional outcomes than those with ADHD alone (Biederman, Petty, et al., 2012; Biederman, Spencer, et al., 2012; Shaw et al., 2014). The importance of severe irritability in ADHD is also supported from a genetic perspective, as demonstrated by Polygenic Risk Score (PRS) analysis/studies. PRS is a composite score of individual common genetic risk for a specific phenotype of interest, obtained by summing an individual's set of risk alleles across the genome, weighted by their effect size (Wray et al., 2014). These risk alleles are detected by GWAS in the so called "discovery sample"; this is a sample used to identify risk alleles associated with the phenotype under investigation, at different PRS p-value thresholds (Wray et al., 2014). The presence of these risk alleles is then investigated in an independent (i.e., target) sample and they are combined to identify each individual's genetic risk for that specific phenotype (Wray et al., 2014). PRS is then used to investigate the relationship between multiple PRSs for different phenotypes, or to determine individuals' susceptibility to a trait or disease as a difference in PRS between cases and controls for a given phenotype, or as a proportion of variance explained for a continuous trait. Evidence shows an association between ADHD PRS and severe irritability, both in general population samples and in the clinical sample of individuals with ADHD used in this thesis and assessed at baseline (Riglin et al., 2017). Notably in this previous work, severe irritability was operationalised in a very similar way to that in this thesis. This reported association withstands ADHD and Conduct Disorder symptom correction, suggesting that the

effect of ADHD PRS on severe irritability is independent of core and comorbid symptoms and that similar biological underpinnings might link these two clinical phenotypes (Riglin et al., 2017).

Greater attention has recently been given to cognitive impairments as potential pathophysiological mechanisms of severe irritability, in particular Hot executive functioning (e.g., reward processing, decision-making) as opposed to Cool executive functioning (e.g., set-shifting and behavioural inhibition) (Brotman, Kircanski, & Leibenluft, 2017; Brotman, Kircanski, Stringaris, et al., 2017; Leibenluft, 2017b) (this is described in details in Chapter 1, section 1.3.3 and Chapter 4 introduction). Both Cool and Hot Executive Functions appear to be consistently heritable as demonstrated by twin studies. In particular, genetic influences are observed for Cool EFs, namely working memory, cognitive flexibility, inhibition, and selective and sustained attention both cross sectionally (Ando, Ono, & Wright, 2001; Anokhin, Heath, & Myers, 2004; Anokhin, Heath, & Ralano, 2003; Friedman et al., 2008; Kuntsi et al., 2006; Lee et al., 2012; Singer, MacGregor, Cherkas, & Spector, 2006) and longitudinally (Anokhin, Golosheykin, Grant, & Heath, 2010; Polderman et al., 2007). The cognitive performance on these different set of Cool EF tasks seems also to be determined by a shared pool of genetic influences that is more heritable than individual genetic contributions to single tasks (Ando et al., 2001; Engelhardt, Briley, Mann, Harden, & Tucker-Drob, 2015; Friedman et al., 2008; Hagenaars et al., 2016; Lee et al., 2012). Candidate genes, mostly dopaminergic and serotonergic genes, have also been studied in association with Cool EFs, although overall there has been a failure to replicate significant results (Greene, Braet, Johnson, & Bellgrove, 2008). Conversely, genetic and environmental influences on Hot EFs have been less extensively studied, although a previous twin study found consistent genetic contributions to risky decision-making both within and across time (Tuvblad et al., 2013). Similarly to Cool EFs, specific genetic candidates linked to the dopaminergic

system have been found to be associated with Hot cognitive processing (Frank, Moustafa, Haughey, Curran, & Hutchison, 2007; Yacubian & Büchel, 2009). In particular, the catechol-O-methyltransferase (COMT) enzyme, involved in synaptic dopamine degradation, seems to play a key role in reward processing and reward learning both at the behavioural and neural level in the general population (Boettiger et al., 2007; Foti & Hajcak, 2012; Frank et al., 2007; Yacubian & Büchel, 2009). Similarly, the genotype of the serotonin transporter gene was found to affect the behavioural and neural sensitivity to decision-making bias (Roiser et al., 2009). However, candidate genes are not ideal to study genetic contributions especially for complex phenotypes, as they are often chosen *a priori*, explain overall a very small proportion of genetic variance and findings are difficult to replicate (Duncan & Keller, 2011; Franke, Neale, & Faraone, 2009; Kendler, 2013). Conversely, GWAS and PRS studies can provide more robust evidence on genetic influences for a specific phenotype without aprioristic assumptions, allowing researchers to look across a large number of genes (GWAS) and combining the small risk effects carried by individual genes (PRS). These improvements brought by GWAS and PRS methods are supported by previous work looking at common genetic risk of cognitive functioning using both a GWAS and PRS approaches. GWASs on Cool cognitive functioning were able to identify genes enriched in the brain and involved in mechanisms such as neuronal development, synaptic function and immune system, and neurological conditions, such as Alzheimer's disease (Davies et al., 2016; Debette et al., 2015). Notably none of the genetic candidates previously associated with Cool EFs (i.e., memory performance) met the statistical significant threshold in GWAS analysis (Debette et al., 2015). Additionally, the heritability of the significant Single Nucleotide Polymorphisms identified in the GWAS explained up to 31% of genetic variance (Davies et al., 2016). Thus, the combined effect of common genes, informed by GWAS results and indexed by PRS, can be a more promising approach in investigating genetic influences on cognitive functioning.

Like cognitive functioning, preliminary evidence from twin studies suggests that severe irritability is also influenced in a consistent proportion (up to 89%, see Chapter 1, section 1.1.5) by genetic risk factors (Coccaro et al., 1997; Roberson-Nay et al., 2015; Stringaris, Zavos, et al., 2012). No study to date has however considered severe irritability PRS influences on EFs. Previous work has in fact looked at other PRSs to investigate cognitive functioning variability in the general population. These PRSs were linked to several clinical conditions, such as neuropsychiatric disorders (e.g., autism, depression, schizophrenia) and physical health disorders (e.g., Body Mass Index, coronary artery disease), finding overall a small proportion of cognitive variance explained by these common genetic risks (Bearden & Glahn, 2017; Hagenaars et al., 2016). Additionally, no study to date has looked at the contributions of severe irritability PRS to cognitive variation in a sample of individuals with ADHD; this is particularly relevant considering the overlap of Hot cognitive impairments across these two phenotypes, and their co-occurrence (see Chapter 4 for more details). The common genetic risk most frequently investigated as a potential source of variation in cognitive functioning in those with ADHD is ADHD PRS. For instance, a previous study by Martin, Hamshere and colleagues (2015) found that PRS for ADHD in a general population sample was significantly associated with performance on working memory but not inhibitory control or emotion recognition tasks. A more recent community sample study by Nigg and colleagues (2018) confirmed that PRS for ADHD does not seem to be linked to behavioural inhibition, although it is consistently associated with working memory and vigilance that partially mediate the association between genetic liability for ADHD and ADHD diagnosis. However, ADHD PRS in relation to cognitive variability was found to explain less than 1% of cognitive variation (Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2015). Taken together, these findings show that the PRSs considered so far are able to explain only a small proportion of cognitive variability, suggesting that there might be other PRS,

such as genetic liability for chronic and severe irritability, that could account for a larger proportion of cognitive variation, especially in those with ADHD.

To conclude, chronic and severe irritability is common in ADHD and impairing, possibly due to its negative impact on cognitive functioning. Both Hot and Cool cognitive functions show genetic influences and irritability PRS could explain part of cognitive performance differences between individuals. No study to date has however looked at PRS associated with irritability, especially in relation to Hot cognitive functioning, in ADHD and this is particularly relevant, considering the frequent co-occurrence of irritability and the Hot cognitive deficits shared by these two phenotypes. This study therefore is the first one aiming to see in a sample of adolescents with ADHD 1) if irritability PRS was linked to baseline chronic and severe irritability measured in childhood; 2) if irritability PRS affected adolescents' cognitive performance on a wide range of Cool and Hot EF tasks. The hypothesis was that irritability PRS would be associated with childhood chronic and severe irritability and with a poorer cognitive performance on Hot EF tasks only. PRS was computed in this current sample of adolescents with ADHD (target sample) using unpublished, but publicly available, irritability GWAS data from the UK Biobank sample (discovery sample) which has not previously been explored. No published GWAS data could be used to compute PRS as no one has specifically tapped severe irritability; previous studies looked at phenotypes that are only marginally related to irritability (e.g., Emotional Lability/Dysregulation) (Greenwood et al., 2012, 2013; Powers et al., 2016; Tielbeek et al., 2017; Ward et al., 2019) (see Chapter 1, section 1.1.1 for more information). Despite the lack of cognitive differences found at the behavioural level in the previous study of this thesis (see Chapter 4), the current research question is nonetheless important. Whilst in the previous study, the focus was on phenotypic associations between chronic and severe irritability and cognitive functioning, this study aimed to understand the underlying genetic liability of this phenotype. More

precisely, the aim was to link irritability common genetic risk to irritable symptom severity and to Hot cognitive functioning in ADHD, informing of underlying biological processes that can be used to develop clinical interventions. Because of this focus switch from behaviour to genetics, this study might still yield significant results, despite the non-significant behavioural findings of the previous chapter.

5.2 Methods

5.2.1 Samples

Discovery sample – UK Biobank sample

The discovery sample for this analysis was the UK Biobank, an independent longitudinal sample and the largest one available for irritability. It is composed of over 500,000 individuals from the general population, recruited between 2006 and 2010 all across Great Britain and who are still being followed up (Sudlow et al., 2015). Those who took part in the study had to sign an informed consent and ethical approval for this large longitudinal study was obtained by the National Health Service (NHS) National Research Ethics service (Ref 16/NW/0274). This population-based cohort was composed of participants aged 40 to 69 who underwent a comprehensive and multimodal (questionnaires, physical and functional measurement) clinical, cognitive, sociodemographic and genetic assessment to understand physical and psychiatric health-related outcomes (Sudlow et al., 2015). Notably, the UK Biobank grants open access to health data collected. For the present study, 345,231 individuals of both sexes were considered in the discovery sample (46.3% were males and 53.7% were females) as they all had genome-wide genotyped irritability data available. Notably, no additional exclusion criteria were applied.

Target sample – ADHD sample

The target sample was the clinical ADHD sample at follow-up, previously used in this thesis, composed of 204 adolescents with an ADHD clinical diagnosis and with complete and available data on chronic and severe irritability, cognitive measures, and genetic information (see Chapter 4 for further details). Participants had a mean age of 14.02 (s.d. 1.87) and 94.1% of them were males.

5.2.2 Measures

Discovery sample – UK Biobank sample

Clinical measure. In the UK Biobank sample, the measure of irritability was composed of a single self-reported item “are you an irritable person?”, to which 28.1% of participants answered “yes” and 71.9% “no”.

Target sample – ADHD sample

Clinical measures. ADHD research diagnosis was made at baseline and at follow-up using the parent-rated version of the CAPA (Angold & Costello, 2000) and the DAWBA (Goodman et al., 2000) respectively (see Chapter 2, section 2.2 for more details). At baseline, 93.6% of participants met a DSM-IV/5 ADHD research diagnosis (American Psychiatric Association, 2013). At follow-up, 81.8% continued to meet a DMS-IV/5 ADHD diagnosis, whereas 18.2% no longer met diagnostic criteria.

A composite score of childhood chronic and severe irritability was computed summing responses across 5 items (“Losing Temper”, “Temper Tantrums”, “Touchy or Easily Annoyed”, “Angry or Resentful” and “Irritability”) taken from the Depression and the Oppositional Defiant Disorder sections of the parent rated CAPA (Angold & Costello, 2000). The total score ranged from 0 to 4 as no one endorsed irritable mood. Cut-offs based on frequency, pervasiveness and duration are applied to definite irritability in its severity and chronicity, as done previously (Eyre et al., 2017) (more details are provided in Chapter 2, section 2.2.1).

Cognitive measures. Cool and Hot EF measures and variables are described in detail in Chapter 2. Briefly, two tasks were used to tap Cool EFs: the Wisconsin Card Sorting Test and the Go no Go as measures of set-shifting and behavioural inhibition, respectively. The variables considered were WCST total errors, WCST perseverative errors, GnG RT to go signals and GnG probability of inhibition. In terms of Hot EFs, Card Playing Task and Choice per Risk tasks were used to measure sensitivity to and risk-taking following different degrees of reward and punishment. Temporal Discounting Task and the Ultimatum Game were also used to tap reward devaluation and emotion regulation. The Hot EF variables considered were: CPT total card played, CxR behavioural outcomes after winning or losing big or small amounts of money, TDT RT difference between delayed and immediate reward, TDT AUC, and UG percentage of moderately unfair offers accepted.

Sociodemographic measures. Demographic information related to age and IQ at follow-up, sex, and Social Economic Status were also collected (see Chapter 2 for further details).

5.3 Genotyping and Quality Control of Genetic Data

2.3.3 Discovery sample – UK Biobank sample

Participants at the UK Biobank were asked to provide a blood sample to be genotyped. Genotyping was carried out by Affymetrix Research Services Laboratory (High Wycombe, UK) and two extremely similar arrays (the Affymetrix UK BiLEAVE Axiom array and Affymetrix UK Biobank Axiom® array) were both used to genotype participants (Bycroft et al., 2018). Quality Control for this discovery sample was conducted by Affymetrix and the Wellcome Trust Centre for Human Genetics. QC

entails the exclusion of participants based on different parameters such as missingness, relatedness, sex mismatch, non-British ancestry, population structure and many others (Bycroft et al., 2018; The UK Biobank, 2015). A GWAS looking at the association between common genetic variants and irritability in the UK Biobank was conducted by the Neale Lab research group, who produced the related GWAS summary statistics (e.g., genetic variants, p-value and effect size of their association with irritability) and made it publicly available on their website (Neale lab, 2018). I downloaded this summary statistics data that resulted in 13,791,467 SNP variants retained as being associated with irritability and I then performed additional QC checks on it. In particular, I applied the following SNP exclusion parameters: SNPs with a Minor Allele Frequency (MAF) under 5%; SNPs with imputation quality probability (INFO) less than 80%; multi-allelic, duplicate or ambiguous (where it is not clear what base is associated with the minor or major allele) SNPs, sex chromosome variants, and those with a low confidence interval. This extra and rigorous quality check ensured the retainment of good quality genetic data that resulted in 5,933,889 SNP variants retained. These SNPs were used to compute PRS in the target sample.

2.3.4 Target sample – ADHD sample

As noted in Chapter 2, either a peripheral blood or saliva sample was collected from all SAGE study participants and their parents at baseline for the purpose of genetic analysis. This clinical ADHD sample was then genotyped in batches using two different arrays (Illumina Human660W-Quad BeadChip and a customised version of the PsychChip), and rigorous imputation and QC procedures were performed within each batch by Dr Leon Hubbard and Dr Joanna Martin. This was done prior to this analysis and as part of a separate ongoing project combining different clinical samples of individuals with ADHD and their families ($n = 1,988$; 919 children with ADHD, 671 mothers, and 398 fathers), including the clinical ADHD sample used in this thesis, with both baseline and follow-up data, ($n = 204$). Briefly, SNPs were aligned to the

Haplotype Reference Consortium data using GenomeHarmoniser, SNPs were removed if they had MAF under 1%, genotyping rate less than 95%, or Hardy-Weinberg Equilibrium (HWE) $p < 1 \times 10^{-6}$, and individuals were removed if they had missingness greater than 5%, sex discrepancy, or were duplicate samples. Then the samples were imputed using the Michigan Imputation Server (using Eagle v2.4 for phasing, Minimac4 for imputation, and the HRC V1.1 imputation reference panel). After imputation, dosage data were converted to best guess genotype data using Plink2. Additionally, post-imputation data and individual QC filters were applied as follows. SNPs with a MAF less than 1%, INFO less than 80%, ambiguous (Cytosine-Thymine/Adenine-Guanine) variants, SNPs with inconsistent alleles (i.e., duplicate position or multiallelic SNPs) and deviating from HWE at $p < 1 \times 10^{-5}$ were removed. In terms of individual QC, individuals with a genotype probability less than 90% and disproportionate level of missingness (i.e., greater than 3%) were also removed. Additionally, family relationships were confirmed using the Identity By Descent (IBD) index and Mendel analyses in PLINK. SNPs over five Mendel errors (suggesting close genetic relatedness) and samples that did not index the expected family structure were excluded. The PCAiR method was employed to perform Principal Component (PC) Analysis, whilst accounting for the kinship information in the sample (Conomos, Miller, & Thornton, 2015); based on this analysis, those with a non-European ancestry were excluded. PCAiR was also run on the final set of markers to derive PCs to use as covariates. A GWAS of batch was run on unrelated samples. SNPs associated with batch ($p < .01$) were excluded from all batches. A total of 3,335,041 SNPs in this comprehensive sample of individuals with ADHD, analysed prior to this current study, passed the QC and filter procedures. I supported the production of this data by double checking the demographic information on participants' ethnic background to retain only those with a British ancestry to avoid artefacts.

5.4 Polygenic Risk Score Calculation

PRS was also calculated in the comprehensive target sample of individuals with ADHD ($n=1,988$) which includes the clinical sample used in this thesis and recruited at follow-up. This was undertaken by Dr Joanna Martin using the UK Biobank GWAS summary statistics as the discovery sample using PLINK software (Purcell et al., 2007). The discovery sample (described in section 5.2.1) provided SNPs whose risk alleles were significantly associated with irritability and only SNPs in common between discovery and target samples were retained. Relatively common (i.e., MAF greater than 5%) SNPs were clumped considering alleles that were in relative linkage equilibrium, thus with an R^2 threshold of .2, within a distance threshold of 500 kilobases. These thresholds ensured the identification of relatively independent set of SNPs, while retaining the most significant SNP in each LD (Linkage Disequilibrium) block and led to a total of 14,259 SNPs retained (at a PRS threshold of $p < .05$). Additionally, PRS was computed using several p-value thresholds ($p < .00001$, $p < .001$, $p < .01$, $p < .05$, $p < .1$, $p < .5$, $p < 1$) used to select the most associated SNPs (Martin, Hamshere, et al., 2015; Riglin et al., 2019; Wray et al., 2014). Finally, PRS was calculated for each individual in the target sample, summing their risk alleles for each SNPs weighted by the SNP effect size (i.e., log of the odds ratios) in the GWAS discovery sample. I then took the PRSs generated previously in this broad target sample and extracted the information that was relevant for my smaller sample of 204 adolescents with ADHD. In particular, I matched each participant's ID with the respective genetic, cognitive, demographic and clinical data and excluded related individuals (i.e., siblings) to ensure the production of robust results. I further used the information produced by the PRS calculation in this broad ADHD target sample to inform my methodological choices (e.g., the PRS main threshold) and I then conducted all the data analysis process and result interpretation as follows.

5.5 Data analysis

As this is the first study on common genetic risk of irritability, previous empirical evidence informing on the PRS p-value threshold to best capture phenotypic variance was not available. A PRS threshold of $p < .05$ was chosen to define risk alleles for primary analyses as opposed to other p-values ($p < .00001$, $p < .001$, $p < .01$, $p < .1$, $p < .5$, $p < 1$). This threshold is in line with previous work using PRS linked to different phenotypes (e.g., Riglin et al., 2019). It is also a PRS threshold that is not too conservative nor too lenient in terms of number of risk alleles included, as observed in PRS data extracted from the broader sample of individuals with ADHD ($n = 1,988$) (see Appendix 5.1 for the number of SNPs at each PRS p-value threshold). Notably, PRS were standardized using Z-score transformation, by subtracting the sample mean from each score and then dividing by the standard deviation. Multiple linear regressions were then performed to test the association between irritability PRS with chronic and severe irritability as operationalised in the target sample, and irritability PRS with Hot and Cool EF measures. These multiple regressions were undertaken whilst controlling for the effect of covariates, in particular batch effects and the first five PCs. Correlations were conducted looking at associations between irritability PRS and clinical symptoms (e.g., ADHD and CD symptoms at follow-up) to see whether these phenotypes also needed to be controlled for (see Chapter 2 for information on how ADHD and CD scores were obtained). Demographic factors were not considered as covariates to avoid overcorrecting, thus reducing the power to detect an effect, based on the lack of associations between severe irritability and demographic characteristics observed in the previous chapter (see Chapter 4, section 4.5). IQ was also excluded for the same reasons explained in Chapter 4 (see section 4.4). All the variables were normally distributed. Notably, the first five PCs were used as covariates as these captured the majority of ancestry-related variance (see Appendix 5.2), although sensitivity analyses were performed controlling for all ten PCs.

Sensitivity analyses were also conducted considering the remaining PRS p-value thresholds (i.e., $p < .00001$, $p < .001$, $p < .01$, $p < .1$, $p < .5$, $p < 1$) to ensure robustness of results. Consistent with the sensitivity results obtained in the previous chapter (see Chapter 4), analyses were not re-run excluding those who did not suspend their medication 24h prior cognitive assessment. Bonferroni correction was applied to correct for multiple testing in relation to cognitive functioning ($p < .004$, number of tests: 12).

5.6 Results

Demographic characteristics of this sample are reported in Table 5.1. Of note, based on the correlation results, ADHD and CD symptoms at follow-up were not included as covariates in multiple regressions due to the lack of association with irritability PRS ($r = .5$, $p = .49$; $r = .01$, $p = .93$, respectively).

	MEAN (S.D.)	N (%)
AGE	14.02 (1.87)	
IQ	87.70 (12.6)	
SES (LOW)		83 (46.4%)
SEX (MALES)		192 (94.1%)
CHRONIC AND SEVERE IRRITABILITY SYMPTOMS AT BASELINE	1.14 (1.09)	
ADHD SYMPTOMS AT FOLLOW-UP	12.69 (4.46)	
CD SYMPTOMS AT FOLLOW-UP	2.61 (2.66)	

Table 5.1 Descriptive statistics of the target sample

5.6.1 PRS association with chronic and severe irritability symptoms

Multiple regression results showed that irritability PRS was significantly associated with a greater chronic and severe irritability symptom severity ($B = .164$, $95\%CI = .013/.315$, $p = .033$). This common genetic risk explained 2.3% of phenotypic variance.

5.6.2 PRS association with cognitive functioning

As shown in Table 5.2, irritability PRS did not seem to be associated with any of the cognitive measures considered, except for CxR gambling after small loss. In particular, irritability PRS was related to an increased risk-taking after losing a small amount of money and was able to explain 3.5% of CxR gamble after small loss variance ($R^2 = .035$). However, this association failed to reach statistical significance once corrected for multiple comparisons (Bonferroni p -value $< .004$).

	N	UNSTANDARDIZED BETA (95% CI)
COOL EFs		
WCST TOTAL ERRORS	N= 162	B= .73 (-.43, 1.89)
WCST PERSEVERATIVE ERRORS	N= 162	B= .13 (-.51, .76)
GNG RT TO GO SIGNALS	N= 173	B= .51 (-6.54, 7.56)
GNG PROBABILITY OF INHIBITION	N= 173	B= -.78 (-3.85, 2.28)
HOT EFs		
CPT TOTAL NUMBER OF CARDS	N= 194	B= -1.09 (-5.84, 3.66)
TDT RT DIFFERENCE DELAYED - IMMEDIATE CHOICE	N= 165	B= -1.53 (-25.07, 22.00)
TDT AUC	N= 165	B= -.004 (-.04, .03)

UG MODERATELY UNFAIR OFFERS ACCEPTED	N= 108	B= -.02 (-.08, .05)
CXR GAMBLING AFTER LARGE LOSS	N= 143	B= .02 (-.02, .05)
CXR GAMBLING AFTER SMALL LOSS	N= 143	B= .05 (.01, .09)*
CXR GAMBLING AFTER LARGE WIN	N= 143	B= -.001 (-.03, .02)
CXR GAMBLING AFTER SMALL WIN	N= 143	B= -.003 (-.03, .03)

Table 5.2 Associations between irritability PRS and Hot and Cool cognitive functioning.

Adjusted models were corrected for the first five PC and batch effects.

* Significant at $< .05$

5.6.3 Sensitivity analysis results

Sensitivity analysis controlling for all ten PCs demonstrated that the results obtained were robust (see Appendix 5.3). Similarly, sensitivity analysis using different PRS p-value thresholds yielded the same results when looking at cognitive functioning (see Appendix 5.4), whereas inconsistent findings were obtained for chronic and severe irritability symptom severity (Figure 5.1). As shown in Figure 5.1, a significant association between irritability PRS and the phenotype of irritability was found using a PRS threshold less than .1 ($p = .021$), whereas there was a trend towards significance for $p < .00001$, $p < .5$, and $p < 1$ PRS thresholds ($p = .058$, $p = .054$ and $p = .072$, respectively). Finally using the remaining PRS p-value thresholds did not yield significant results.

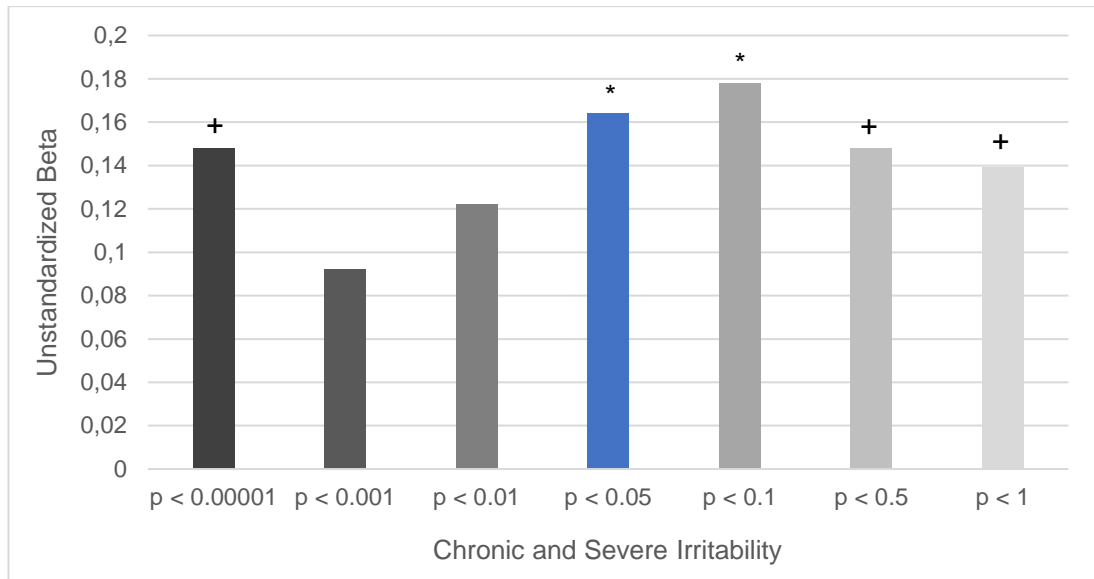


Figure 5.1 Sensitivity analysis of the association between irritability PRS and chronic and severe irritability using different PRS p-value thresholds.

Beta reported refers to Adjusted model, thus including the first five PC and batch effects as covariates.

Blue bar = main threshold chosen

* = p significant at $< .05$; + = trend towards significance

5.7 Discussion

This is the first study exploring the link between PRS for irritability, the construct of chronic and severe irritability, and cognitive functioning in a sample of adolescents with ADHD. Taken together these findings provide partial support for the initial hypotheses. More specifically, the first hypothesis seems to be supported as irritability PRS is shown to be associated with greater chronic and severe irritability symptom severity, independent of the effect of covariates. However, irritability PRS does not seem to be associated either with Cool or Hot EFs considered, failing to support the second hypothesis of this study.

Previous twin studies have shown that the heritability of severe irritability is between 31% to 89%, depending on age and sex (Coccaro et al., 1997; Roberson-Nay et al., 2015; Stringaris, Zavos, et al., 2012) (see Chapter 1, section 1.1.5). This current study provides for the first-time insight on the genetic architecture of irritability, showing that

common genetic variants account for 2.3% of the variability of this phenotype. However, this result needs to be considered with caution, considering that sensitivity analysis using different PRS p-value thresholds only show partial support. The role of common genetic variants for the phenotype of chronic and severe irritability also suggests the importance of additive effects, considered by the PRS analysis, although as expected, they fail to account for the entirety of the earlier heritability estimate found by twin studies. The problem of this missing heritability is not new in genetic studies and there might be different explanations for it (Manolio et al., 2009). Firstly, it is possible that additional variants related to the irritability risk still need to be discovered. More precisely, there might be rare genetic variants (present in less than 5% of the population) with bigger effect sizes, or more common genetic variants with very small effects sizes that GWAS does not have enough power to detect and link to the phenotype under consideration (Maher, 2008; Manolio et al., 2009; Plomin, 2013; Zuk, Hechter, Sunyaev, & Lander, 2012). Secondly, Copy Number Variants, rare mutations in the DNA structure, such as duplication or deletion of DNA strands, might also help explaining the missing heritability (Maher, 2008; Manolio et al., 2009). Thirdly, GWAS does not consider gene-gene interactions (i.e., epistasis) according to which the effects of combined genes is able to account for a bigger proportion of genetic variance than each gene alone (Maher, 2008; Manolio et al., 2009). Finally, the accuracy of current heritability estimates should also be considered. Previous work has found that the current heritability estimates might be overinflated mostly due to the assumption that genetic variants have an additional effect, disregarding interaction effects (Zuk et al., 2012). If the heritability is smaller, this means that the proportion of genetic variance explained by common genetic risk could be larger than the one currently detected by genetic studies (Zuk et al., 2012). Thus, despite the small proportion of variance explained, these pioneering findings might be beneficial to the missing heritability issue, being a starting point for the investigation of additional

common and rare variants, interactions effects, and underlying biological mechanisms of this clinically relevant phenotype.

Additionally, common genetic variants associated with irritability do not account for the cognitive performance variability in those with ADHD, failing to add up to the heritability explained by other phenotypes' PRS found in previous studies (Ando et al., 2001; Anokhin et al., 2004, 2003; Friedman et al., 2008; Kuntsi et al., 2006; Lee et al., 2012; Singer et al., 2006; Tuvblad et al., 2013). Although non-significant associations were expected for Cool EFs, the lack of significant findings for Hot EFs was surprising. This might suggest that irritability common genetic risk does not have a pleiotropic effect broadly involving cognitive functioning, but rather it might impact more specifically a different neurocognitive mechanism underpinning chronic and severe irritability. As mentioned in the general introduction (see Chapter 1, section 1.3.3), frustration and the related Frustrative Non-Reward paradigm are key components of chronic and severe irritability (Brotman, Kircanski, & Leibenluft, 2017; Brotman, Kircanski, Stringaris, et al., 2017; Leibenluft, 2017b). Thus, the genetic underpinning of chronic and severe irritability might specifically affect frustration, as opposed to Hot executive functioning more generally. Additionally, irritability PRS might be linked to cognitive functioning via gene-environment interactions, that are not accounted for by PRS and GWASs (Maher, 2008; Plomin, 2013). The importance of the environment in the aetiology of severe irritability has been ascertained by previous twin studies (Coccaro et al., 1997; Roberson-Nay et al., 2015; Stringaris, Zavos, et al., 2012). Amongst the environmental factors, negative parenting, characterised by hostility and conflict, might be particularly relevant for irritability; preliminary evidence has shown its impact on children's irritability symptoms (Oliver, 2015; Waxmonsky et al., 2016). Parenting seems to be a crucial environmental factor also in those with ADHD. The NICE guidelines recommend parent training for those with ADHD and comorbid disruptive behaviours (ODD, CD) as it has shown to be

effective in reducing such symptoms (National Institute for Health and Care Excellence, 2018); as mentioned in the general introduction, irritability can also be considered amongst disruptive behaviours. Parenting is also important for children's emotional development and acquisition of self-regulation skills (Kiff, Lengua, & Zalewski, 2011; Waxmonsky et al., 2016). These skills are tested during Hot cognitive performance since Hot EF tasks take place in emotionally charged scenarios (Zelazo & Carlson, 2012; Zelazo & Muller, 2002). Thus, parenting is a factor worth investigating in future studies, especially studying its potential interaction with genetic liability (such as that captured by PRS) for irritability leading to poor Hot executive functioning.

These findings need to be considered in the light of a number of strengths and limitations. Firstly, the UK biobank identified irritability with a single item asking people whether they considered themselves to be irritable or not. The measure of irritability considered in this sample of adolescents with ADHD is more complex, tapping multiple items and considering especially the chronic and severe facets of this phenotype, disregarded by the UK Biobank. The different operationalisation of irritability might have led to biased PRS as the GWAS was conducted on a less variable measure of irritability, that was neither chronic nor severe. Secondly, the age of the UK biobank sample is much older than the age of this current sample (age range: 40-69 vs. 10-18) and from the literature, it appears clear that severe irritability is subject to developmental changes over time (Riglin et al., 2019) and tends to decrease with age (Copeland et al., 2015; Mayes et al., 2015). Thus, it is not surprising that only 28.1% of adults in the UK Biobank endorsed irritable symptoms, even without applying severity cut offs, such as pervasiveness, duration, and frequency. This suggests that those endorsing a clinically relevant type of irritability amongst the UK Biobank sample might be even fewer. The healthy volunteer selection bias for the UK biobank sample has been reported by previous work,

pointing out that this sample is comprised of individuals with better sociodemographic and health-related characteristics than the UK general population (Fry et al., 2017). This potentially small proportion of participants in the “case” group might have reduced the possibility to detect more clinically relevant SNPs as being associated with chronic and severe irritability. Finally, this study might be underpowered overall, and this is due to the size of the target sample that it is not as big as it is recommended (i.e., around 2,000 individuals) to find a significant effect (Wray et al., 2014). However, several previous studies had a potentially underpowered target sample, as they used a sample size of less than 2,000 individuals, including those looking at cognitive functioning (Gisbert et al., 2019; Hamshere, Langley, et al., 2013; Martin, O’Donovan, et al., 2015; Nigg et al., 2018; Riglin et al., 2017; Stergiakouli et al., 2015). This suggests that the sample size used in this thesis is in line with previous work. Despite the different operationalisation of irritability and sample characteristics, a significant association between irritability PRS and chronic and severe irritability was still found. This suggests that the UK biobank discovery sample was powerful enough to enable the detection of significant findings and that their less variable measure of irritability is akin to the chronic and severe irritability operationalised in this thesis, ultimately validating the measure used which is a remarkable finding. Previous work has reported the necessity of having a big discovery sample to increase the accuracy of PRS calculation, and this methodological indication is well represented by the big size of UK biobank (Wray et al., 2014). Finally, the sensitivity analysis yielded fairly consistent results in linking irritability PRS to chronic and severe irritability phenotype, although replicating this study is highly important.

In conclusion this is the first study, conducted on a sample of adolescents with ADHD, showing that chronic and severe irritability has an underpinning common genetic risk, although the pathway linking genetic liability to chronic and severe symptom severity does not seem to involve neither Hot nor Cool cognitive functioning. However, it is too

early to discount the contribution of irritability PRS to cognitive functioning in those with ADHD as future more powerful studies might find different results. Similarly, considering the role of parenting in gene-environment interactions as well as different neurocognitive markers such as frustration might yield important findings that can be translated into clinical interventions. Additionally, considering the pioneering nature of this study, the inconsistency of sensitivity analysis results and the highly different characteristics of the discovery and the target sample used, replicating this study is also deemed necessary. In particular, future studies should focus on a discovery sample of adolescents, with a similar operationalisation of irritability to the one used in this study, such as The Avon Longitudinal Study of Parents and Children (ALSPAC), a prospective birth cohort study.

Chapter 6

General Discussion

6.1 Result summary

The overall aim of this PhD was to explore the nature, pathophysiological mechanisms, and aetiology of chronic and severe irritability in a sample of youths with ADHD, in the attempt to further understand heterogeneity within this population. This overarching aim was broken down into smaller ones. In particular, the first study reported in Chapter 3 explored the proposed bi-dimensional conceptualisation of chronic and severe irritability, consisting of phasic and tonic dimensions. This was achieved by looking at different patterns of associations with co-occurring clinical symptoms, cross-sectionally, longitudinally and taking into account maternal psychopathology. Overall, this study showed that phasic and tonic irritability were both present in the current sample of children with ADHD (19.3% and 51.3%, respectively), although phasic irritability was rarely endorsed alone (in 3.4% only). Additionally, cross-sectional associations revealed that these two dimensions of chronic and severe irritability were associated with most of the clinical correlates considered, to an equal extent. When looking at longitudinal associations and maternal psychopathology, despite initial evidence pointing towards phasic irritability predicting externalizing symptoms and tonic predicting internalizing symptoms, these results were deemed not to be strong enough to support a distinction between these two dimensions. Based on these results, chronic and severe irritability was considered as a unidimensional construct in the following studies of this thesis.

Chapter 4 addressed the underpinnings of chronic and severe irritability at the cognitive level over time. In line with previous work, it was hypothesized that this

phenotype measured in childhood was associated with Hot as opposed to Cool EFs in adolescents with ADHD. However, the results obtained suggested that the pathophysiological mechanisms of chronic and severe irritability do not involve either Cool or Hot cognitive functioning. Similar conclusions were drawn when using a person-centred approach.

The third and final aim covered in Chapter 5 explored the genetic architecture of chronic and severe irritability and its association with irritable symptom severity and cognitive functioning in youths with ADHD. Common genetic risk in the form of irritability PRS was found to be associated with baseline chronic and severe irritability symptom severity, explaining up to 2.3% of phenotypic variance. However, irritability PRS did not impact on cognitive functioning in adolescents with ADHD (Hot or Cool EFs), suggesting that impairing biological mechanisms of chronic and severe irritability in this population do not act through this cognitive pathway.

6.2 Interpretation of results

6.2.1 Importance of Chronic and Severe Irritability in ADHD

Overall, the results obtained did not support the clinical usefulness of splitting chronic and severe irritability into phasic and tonic dimensions in those with ADHD. This is mainly suggested by the a-specific associations of both these dimensions with most of the clinical symptoms considered (Chapter 3 results), although future studies possibly utilising longitudinal designs and with bigger samples are necessary for further validation. Nonetheless, chronic and severe irritability in Chapter 3 appeared to identify children with greater psychiatric symptom severity overall. At the phenotypic level, these findings also seem in line with previous literature conducted on ADHD that showed severe irritability being associated with both internalising and

externalising conditions (e.g., Anastopoulos et al., 2011; Rosen et al., 2015) (for more details see Chapter 1, section 1.2.3). This supported the importance of exploring pathophysiological markers associated with this phenotype in the attempt to possibly identify pathways leading to impairment. This was achieved in Chapter 4, which found that, counter to the initial hypothesis, Hot cognitive functioning is not a pathophysiological marker of chronic and severe irritability. Similar to these findings, at the cognitive level, there are other studies that failed to show Hot EFs as pathophysiological markers of severe irritability (Adleman et al., 2011; Dickstein et al., 2007; Perlman et al., 2015; Rau et al., 2008) (for more details see Chapter 4 introduction). Additionally the studies within this thesis failed to identify biological underpinnings specifically linked to chronic and severe irritability at the cognitive level, despite genetic factors seemed to be associated with behavioural manifestations of this phenotype (Chapter 5). This inconsistency between the relevance of chronic and severe irritability at the behavioural level and the failure to identify its pathophysiological underpinnings might suggest that this phenotype is simply a marker of severity in those with ADHD, as opposed to a relevant pathophysiological marker leading to impairment. Thus, one might conclude that considering this phenotype within more complex constructs, especially ODD, might be more clinically relevant for those with ADHD. This approach is consistent with previous work that has been critical of the DMDD diagnosis (Evans et al., 2017) and with the ICD-11 that considers irritability as a specifier of ODD diagnosis (World Health Organization, 2018).

It should be considered, however, that severe irritability in the literature has been assessed with different measures and cut-off criteria (e.g., Axelson et al., 2012; Dougherty et al., 2014; Mayes et al., 2016), it is often conceptualised within broader phenotypes (e.g., ODD, Emotional Dysregulation / Lability) (Evans et al., 2017; Liu et al., 2019; Shaw et al., 2014; Sobanski et al., 2010), and this is actually the first study

investigating the nature, pathophysiological mechanisms and biological underpinnings of chronic and severe irritability in those with ADHD, whilst operationalised consistently with previous work (e.g., Copeland et al., 2015; Eyre et al., 2017). Thus, considering the pioneering nature of this PhD work, whether chronic and severe irritability is only a marker of severity and might be better conceptualised within more complex phenotypes in those with ADHD is far from being fully understood. Longitudinal studies with large sample sizes and with measures designed specifically to tap chronic and severe irritability and its features (i.e., phasic and tonic dimensions and pathophysiological markers) are needed and might yield different results. This thesis relied on pre-existing data and the measurement of chronic and severe irritability and its dimensions was derived post hoc, although this method and the operationalisation of chronic and severe irritability was consistent with previous work (Copeland et al., 2015; Eyre et al., 2017, 2019). More comprehensive measures of chronic and severe irritability are now available and were specifically developed to tap this phenotype, such as the Affective Reactivity Index (Stringaris, Goodman, et al., 2012). Therefore, future studies should preferably utilise these specific measures, as opposed to retrospective ones, or should compare them to ensure they are tapping the same constructs.

The use of existing data, rather than that explicitly designed to assess chronic and severe irritability, also applies to the cognitive tasks utilised in this PhD project. The follow-up data was collected as part of a project with different initial aims than to explore chronic and severe irritability; thus, the EF tasks available are validated in ADHD but might not have been ideal to specifically tap pathophysiological markers of irritability at the cognitive level. Despite the current non-significant findings, the final study of this thesis shows that there is a common genetic risk linked to irritability, associated with chronic and severe irritability symptom severity in youths with ADHD. This suggests that there might be pathophysiological markers still to be discovered

that might lead to impairment in those with ADHD, ultimately supporting the relevance of chronic and severe irritability in the pathophysiology of this neurodevelopmental disorder, as opposed of being just a marker of severity. For instance, as discussed previously in Chapter 1 section 1.3.3, response to frustration (i.e., FNR) might be a more promising neurocognitive marker of chronic and severe irritability in those with ADHD, as it is a paradigm that well represents this phenotype at the neurocognitive level and it is supported by preliminary evidence (Deveney et al., 2013; Leibenluft, Blair, et al., 2003; Perlman et al., 2015; Rich et al., 2011, 2007). However, pathophysiological markers other than Hot cognitive functions could not be explored due to the post hoc nature of the available data; focusing on tasks that elicit frustration is therefore needed for future studies. Similarly, environmental factors (e.g., parenting) linked to chronic and severe irritability as a pathological pathway leading to impairment in those with ADHD should also be considered (see Chapter 4 and Chapter 5 discussions, and Chapter 1 section 1.3.3). Overall, more research on the pathological mechanisms and risk factors associated with this phenotype, consistently conceptualised, is therefore necessary to further understand the role of chronic and severe irritability in youths with ADHD.

6.2.2 Understanding ADHD heterogeneity

The a-specific associations of tonic and phasic irritability with a variety of clinical correlates and the failure to identify cognitive markers of chronic and severe irritability also seem to suggest that this phenotype might not be a relevant source of heterogeneity in those with ADHD, both at the clinical and the cognitive level.

A possible explanation involves the heterogeneity of ADHD in terms of core symptoms presentation. Previous research has suggested that, compared to the combined and inattentive subtypes, the hyperactive-impulsive subtype might be more linked to Hot cognitive impairments (Castellanos et al., 2006) as well as Emotional Lability (Skirrow

& Asherson, 2013; Sobanski et al., 2010). At follow-up the prevalence of individuals with hyperactive-impulsive ADHD subtype was only around 9%, which has prevented the conduction of further analysis on this clinical group only. It could be that looking at clinical correlates and neurocognitive markers of chronic and severe irritability in this specific ADHD subtype might lead to different results. Alternatively, a dimensional measure of hyperactive-impulsive symptoms could have been utilised in this thesis to explore the link between the hyperactive-impulsive subtype and chronic and severe irritability. However, the sample used in this PhD project is composed of youths with a clinical ADHD diagnosis, therefore they all show high ADHD symptoms, including hyperactivity-impulsivity. Thus, the little variability of symptoms in the hyperactive-impulsive domain might make it harder to detect differences. Additionally, individuals with ADHD within clinical practice have a complex clinical and functional profile, focusing on one subset of symptoms would not reflect the complexity of this neurodevelopmental disorder, ultimately being less useful for clinicians and those with the condition. This is also supported by the proportion of youths with ADHD without chronic and severe irritability that was around a third of the clinical sample considered throughout the chapters of this thesis. This suggests that this phenotype is common in this clinical sample, encompassing all the different ADHD subtypes. Thus, chronic and severe irritability is not likely to be relevant only for those with the hyperactive-impulsive subtype. Looking at just the hyperactive-impulsive subtype would therefore consist in splitting up ADHD further, instead of accounting for the heterogeneity of this condition as a whole. It is also important to note that the DSM-5 does not support the ADHD distinction into subtypes due to their heterotypic continuity over time (American Psychiatric Association, 2000, 2013; Cortese & Coghill, 2018; Willcutt et al., 2012). Finding ways to reduce this heterogeneity, such as identifying sources of variability, instead of looking at different facets of ADHD either with a categorical or dimensional perspective, seems to be more clinically relevant and reflective of the heterogeneous nature of this neurodevelopmental disorder.

Despite the current non-significant findings, there is preliminary evidence about the importance of chronic and severe irritability as a source of clinical heterogeneity, especially internalising symptoms, in those with ADHD (Eyre et al., 2017, 2019). This stems from previous work with a very similar operationalisation of this phenotype as the one used in this thesis, and conducted in the same clinical ADHD sample considered at baseline and follow-up and used across these current experimental chapters (Eyre et al., 2017, 2019). This research found that chronic and severe irritability in youths with ADHD is cross-sectionally linked to anxiety and depression symptom severity; chronic and severe irritability risk for developing depression symptoms was also confirmed longitudinally (Eyre et al., 2017, 2019). Thus, another reason for the results of this thesis to not identify irritability related heterogeneity in those with ADHD at the cognitive level might lie with the pathophysiological marker considered. Empirical evidence shows that threat processing impairments, such as orientation bias to threatening stimuli and tendency to interpret ambiguous stimuli as threatening, are very common in individuals with severe anxiety (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & Van Ijzendoorn, 2007; Miers, Blöte, Bögels, & Westenberg, 2008; Sonuga-Barke, Cortese, Fairchild, & Stringaris, 2016). Similar impairments in threat processing are also observed in those with severe irritability and are thus suggested as possible pathophysiological markers of this clinical phenotype; the rationale being that imminent threat often elicits sullen aggressive responses that are often a behavioural display of severe irritability (Brotman, Kircanski, & Leibenluft, 2017; Leibenluft, 2017b). Thus, it might be worth looking at threat processing as a possible source of cognitive heterogeneity linking ADHD, chronic and severe irritability and risk for internalizing disorders, especially considering that anxiety and depression frequently co-occur and that anxiety tends to precede later depression (Thapar et al., 2012).

Finally, considering chronic and severe irritability as a marker of severity means that those with ADHD and comorbidity irritability are also likely to have a number of other co-occurring conditions or behaviours. In individuals with this complex and severe clinical profile, chronic and severe irritability might not be as relevant in explaining ADHD heterogeneity. For instance, as mentioned in Chapter 4 introduction, disruptive behaviours (namely, ODD/CD) in individuals with ADHD seem to be associated with greater impairments in Hot EFs compared to those with ADHD alone (Dekkers et al., 2016; Groen et al., 2013). Thus, a distinction into an ADHD alone and ADHD with comorbid disruptive behaviours might account for the heterogeneity at the cognitive level more than chronic and severe irritability. However, considering the novelty of this thesis more research is needed before discarding chronic and severe irritability as a source of clinical and cognitive heterogeneity in those with ADHD. Future studies should definitely consider using cognitive tasks specifically designed to tap chronic and severe irritability, as well as different pathophysiological pathways (e.g., Hot cognitive functioning, threat processing and FNR) that can lead to poor cognitive and clinical outcomes in youths with ADHD.

6.3 Implications

As illustrated in the general introduction, ADHD heterogeneity is problematic, especially for the development of tailored interventions (see Chapter 1, section 1.2). The role of emotional impairments in this population has long been recognised (e.g., Faraone et al., 2019; Shaw et al., 2014) and recently there is an increased interest in investigating chronic and severe irritability, a common condition in those with ADHD (e.g., American Psychiatric Association, 2013; Brotman, Kircanski, & Leibenluft, 2017; Leibenluft, 2011). Among others, the nature, pathophysiological markers and risk factors were considered as research priorities for the study of chronic and severe irritability (Leibenluft & Avenevoli, 2014). All these aspects were addressed altogether

in this thesis for the first time. In addition to having implications in the research field by filling in these knowledge gaps and providing initial empirical evidence related to the field of ADHD and chronic and severe irritability, this thesis also aimed to investigate topics that had a translational element. Thus, this work aimed to further inform clinical practice and the development of future interventions. Based on the findings obtained across the three individual studies included, there is insufficient evidence for clinicians to consider chronic and severe irritability as bi-dimensional construct in those with ADHD. Similarly, future interventions are not advised to include cognitive training tapping Hot EFs as these results suggest that these are not relevant to the pathological pathway associated with chronic and severe irritability in those with ADHD. Nonetheless, clinicians should be aware of the high prevalence of chronic and severe irritability in those with ADHD and that common genetic risk influences chronic and severe irritability symptom severity in this population. Such information might be used to improve communication about the nature of ADHD to those with the condition, their family members, and relevant professionals (e.g., teachers) in the attempt to increase awareness and reduce stigma.

6.4 Strengths and limitations

The strengths and limitations of this PhD thesis are mostly detailed in each individual experimental chapter discussions (see Chapter 3, Chapter 4 and Chapter 5). In addition to large sample size, well validated and comprehensive measures, this study has further methodological strengths. Firstly, this thesis benefits of innovative methods in the field of developmental psychology such as the use of Bayesian analysis that were able to compare the results obtained against the experimental hypothesis and not only the null hypothesis (Chapter 4). Secondly, the use of both a variable-centred and data-driven approach to validate the findings obtained showed that results are robust and not method specific (Chapter 4). This methodological

choice of replicating the findings observed also fits well in a time where science is facing a replication crisis and replication is considered essential to this field (Munafo & Smith, 2018). Finally, as mentioned above, the novelty of this thesis is also a strength as it aims to fill the knowledge gaps related to the problem of heterogeneity in psychiatric research and chronic and severe irritability that is clinically relevant as well as understudied.

Limitations should also be considered for the interpretation of these findings. Previous research showed that irritability symptoms tend to decrease with age (see Chapter 1, section 1.1.3), thus it could be that looking at longitudinal associations to identify pathophysiological mechanisms of chronic and severe irritability could have reduced the power to detect an effect, due to fewer adolescents with ADHD endorsing this phenotype. Additionally, Hot and Cool EF tasks correlate at phenotypical level and partially overlap at the neuroanatomical level (see Chapter 1, section 1.3.1). This suggests that it might be difficult to pull out Hot compared to Cool cognitive processing, although this thesis used well-validated tasks employed in previous research on ADHD and shown to be effective in measuring the cognitive aspects considered in this thesis. On a similar note, whether or not the cognitive measures used in this thesis share genetic risk with chronic and severe irritability is not currently known. Focusing on tasks specifically linked to this phenotype at the genetic and/or phenotypic level might have enhance the possibility to identify neurobiological and cognitive underpinnings of chronic and severe irritability in those with ADHD. Additionally, the sample size in this thesis is large at baseline (N = 561) but it is more than halved at follow-up (N from 191 to 219, depending on the chapter). Follow-up data was nonetheless collected on a sample size that is comparable if not greater than samples included in previous longitudinal studies (e.g., Agha, Zammit, Thapar, & Langley, 2017a; Deveney et al., 2015; Eyre et al., 2019). However, considering the number of multiple comparisons, the longitudinal design, and approaches used, the

sample size at follow-up might have not been sufficient to detect an effect about the bi-dimensional nature of chronic and severe irritability and its cognitive markers. More precisely, in Chapter 3 there was preliminary evidence pointing towards a distinction between tonic and phasic irritability that was however negatively impacted by correcting for multiple testing (i.e., the Bonferroni correction) which led to insufficient evidence. Similarly, in Chapter 4, Bayesian analysis only suggested anecdotal evidence for both rival hypothesis without being able to dismiss H_0 . It is also possible that the wide heterogeneity of ADHD at the cognitive level might require larger sample size to pull out different cognitive profiles in LPA analysis, although once again the sample size of this thesis is in line with previous studies (e.g., Lambek et al., 2018; Rajendran et al., 2015; Van Hulst et al., 2015). Further limitations, already outlined in Chapter 3, Chapter 4 and Chapter 5 discussions, include the wide age range of this clinical ADHD sample both at baseline and follow-up, chronic and severe irritability was measured post-hoc, the heterogeneity of cognitive impairments was not fully taken into account lacking a control group, and cognitive measures were selected based on validated ADHD cognitive impairments as opposed to chronic and severe irritability.

6.5 Future directions

Considering the findings obtained by the studies included in this thesis, it can either be that 1) chronic and severe irritability is bi-dimensional and a relevant source of heterogeneity in this clinical ADHD sample, but the power to detect an effect is low. For instance, preliminary evidence in Chapter 3, suggested a different longitudinal pattern for phasic and tonic irritability, however these dimensions did not appear to differ after correcting for multiple testing. In addition to the Bonferroni correction, the power was reduced due to the sample size reduction at follow-up that was further reduced with the Bayesian analysis. 2) chronic and severe irritability is unidimensional

and simply a marker of severity, instead of a relevant source of heterogeneity and pathophysiological marker, in those with ADHD. Considering the novelty, and the strengths and limitations of this PhD project, any interpretation in either direction should be cautious; more evidence is thus needed to draw stronger conclusions. Future studies should attempt to replicate these findings using a larger prospective sample, a more comprehensive measure of severe irritability and its proposed constructs, and cognitive tasks specifically designed to tap this phenotype at the cognitive level, whilst still looking at external validators (e.g., longitudinal associations and maternal psychopathology). This might increase the power to detect a significant effect. Similarly, future work should also focus on different neurocognitive markers (e.g., FNR and threat processing) and environmental factors (e.g., parenting and peer problems) related to chronic and severe irritability that appear to be particularly relevant in those with ADHD as well. Using different clinical samples might also be useful to explore the different characteristics of chronic and severe irritability encompassing different diagnosis, in line with the RDoC approach. Future research might benefit from using a multi-method approach consistently with what was done in this thesis that employs both a person-centre and a variable-centred approach, as well as a frequentist and Bayes approach for data analysis. Additionally, looking at multiple level of analysis consistently with this thesis that combines both behavioural, cognitive and genetic perspectives should be retained in future work as this would offer a comprehensive perspective on the topics covered in this thesis. These recommendations would ultimately advance the understanding of ADHD heterogeneity and chronic and severe irritability, both very relevant aspects in psychiatric research.

6.6 Conclusion

Overall, the conclusion drawn from the results of this thesis is that chronic and severe irritability seems to have a unidimensional nature, it is influenced by common genetic risk, and Hot cognitive functioning might not be a pathophysiological marker of this phenotype leading to impairment in youths with ADHD. These results have implications both in the research and clinical field; they help fill knowledge gaps in the field of ADHD and chronic and severe irritability and inform clinical practice and future interventions.

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Appendices

Chapter 4

The following tables show the results of the same set of analyses (using a frequentist approach) included in Chapter 4, conducted on the clinical sample of adolescents with ADHD at follow-up, excluding 18 participants who did not suspend their medication 24h prior testing (n= 201).

Appendix 4.1

Pattern of associations between severe irritability and Hot and Cool EFs

	N	MODEL	UNSTANDARDIZED BETA (95% CI)
COOL EFs			
WCST TOTAL ERRORS	N= 162	Unadjusted Model	B= 1.30 (.28, 2.32)*
		Adjusted model	B= 1.03 (-.04, 2.10)
WCST PERSEVERATIVE ERRORS	N= 162	Unadjusted Model	B= .81 (.27, 1.35)**
		Adjusted model	B= .75 (.17, 1.33)*
GNG RT TO GO SIGNALS	N= 174	Unadjusted Model	B= 2.40 (-.016, 8.81)
		Adjusted model	B= 2.27 (-4.32, 8.85)
GNG PROBABILITY OF INHIBITION	N= 174	Unadjusted Model	B= 1.20 (-1.67, 4.07)

		Adjusted model	B= 1.68 (-1.04, 4.39)
<i>HOT EFs</i>			
CPT TOTAL NUMBER OF CARDS	N= 191	Unadjusted Model	B= 1.89 (-2.45, 6.24)
		Adjusted model	B= 2.05 (-2.60, 6.69)
TDT RT DIFFERENCE DELAYED - IMMEDIATE CHOICE	N= 164	Unadjusted Model	B= -.70 (-22.7, 21.3)
		Adjusted model	B= -5.58 (-29.3, 18.2)
TDT AUC	N= 164	Unadjusted Model	B= -.02 (-.05, .01)
		Adjusted model	B= -.023 (-.05, .01)
UG MODERATELY UNFAIR OFFERS ACCEPTED	N= 107	Unadjusted Model	B= -.07 (-.13, -.01)*
		Adjusted model	B= -.05 (-.12, .01)

Adjusted models were corrected for age, sex, SES, and ADHD and CD symptom severity in adolescence.

* Significant at < .05

** Significant at < .01

Appendix 4.2

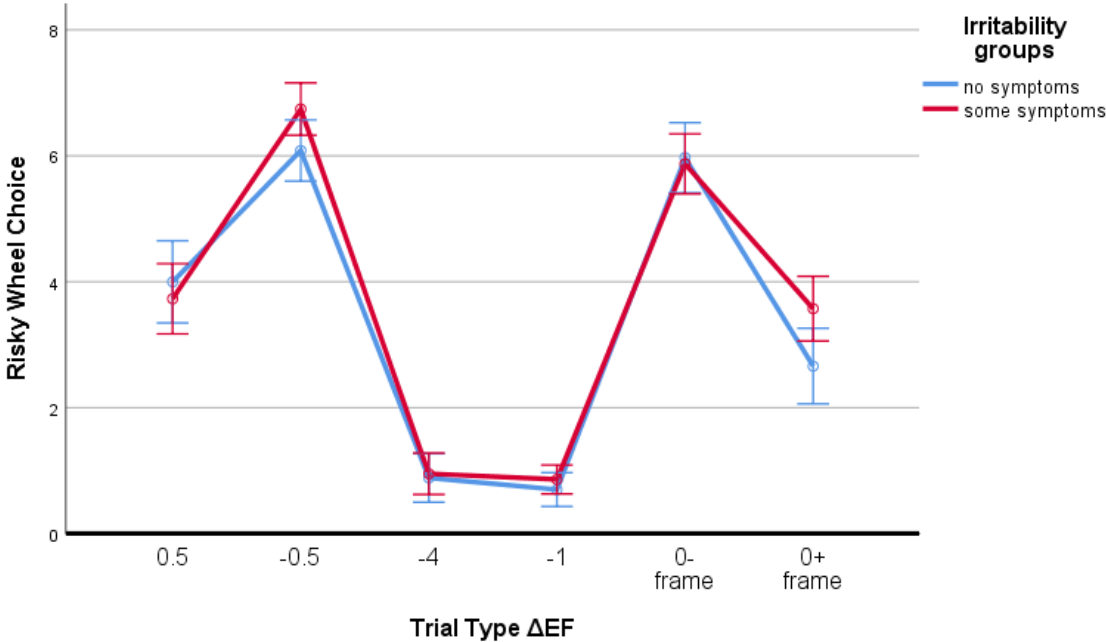
Mixed ANOVAs and mixed ANCOVA results for trial type and outcome

	MODEL (N= 142)			ADJUSTED MODEL		
	F	p	EF size	F	p	EF size
TRIAL TYPE	F (5, 140) = 272.96	p < .001	$\eta_p^2 = .661$	F (5, 116) = 11.27	p < .001	$\eta_p^2 = .094$
IRRITABILITY GROUPS	F (1, 140) = .870	p = .353	$\eta_p^2 = .006$	F (1, 116) = 1.948	p = .166	$\eta_p^2 = .018$
TRIAL TYPE * IRRITABILITY GROUPS	F (5, 140) = 1.010	p = .410	$\eta_p^2 = .007$	F (5, 116) = 1.916	p = .090	$\eta_p^2 = .017$
	F	p	EF size	F	p	EF size
OUTCOME	F (3, 140) = 3.082	p = .027	$\eta_p^2 = .022$	F (3, 113) = 1.395	p = .244	$\eta_p^2 = .013$
IRRITABILITY GROUPS	F (1, 140) = 1.610	p = .207	$\eta_p^2 = .011$	F (1, 113) = 2.173	p = .143	$\eta_p^2 = .020$
OUTCOME * IRRITABILITY GROUPS	F (3, 140) = .464	p = .708	$\eta_p^2 = .003$	F (3, 113) = 1.328	p = .265	$\eta_p^2 = .012$

Adjusted models were corrected for age, SES, and ADHD and CD symptom severity in adolescence

Appendix 4.3

Risky decision-making mean values across six different trial types by group



Δ Expected Values are reported on the x axis, whereas the y axis shows mean values of the number of times participants have chosen the experimental when per each trial type. -frame and + frame represent the positive and negative frame trials, respectively.

Chapter 5

The following tables and figures integrate the methods and illustrate sensitivity analysis results related to Chapter 5.

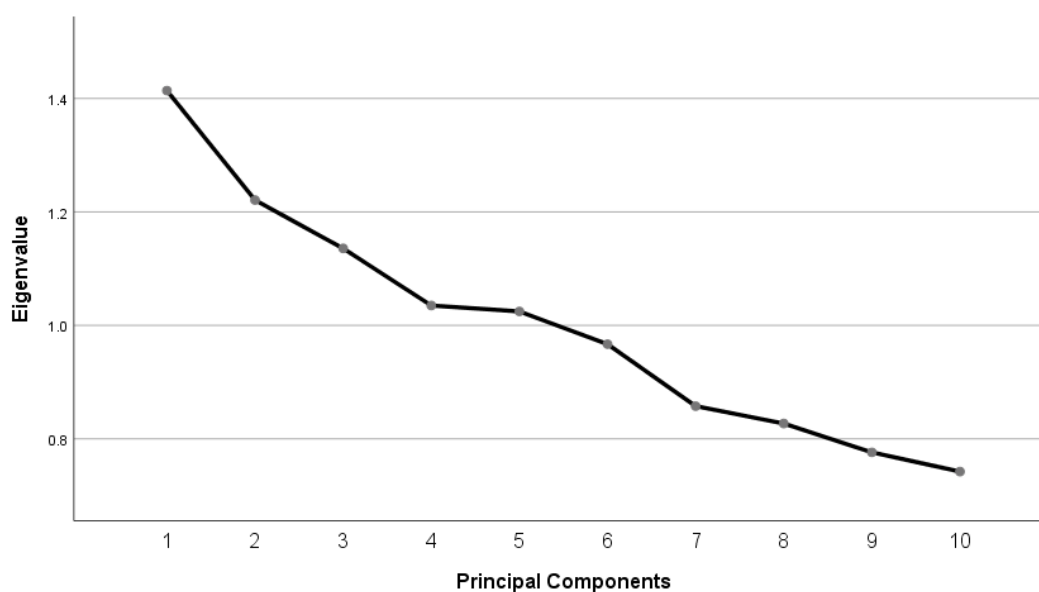
Appendix 5.1

Number of SNPs by PRS p-value thresholds

PRS P-VALUE THRESHOLDS	NUMBER OF SNPS
1.0	81154
0.5	60845
0.1	22337
0.05	14259
0.01	5192
0.001	1333
0.00001	174

Appendix 5.2

Scree Plot of Eigenvalues associated with the ten PCs



When combined, the first five PCs explained up to 58.3% of the ancestry-related variance, whereas the remaining five did not appear to have a substantial contribution all having an eigenvalue less than 1.

Appendix 5.3

Sensitivity analysis results correcting for all ten PCs.

UNSTANDARDIZED BETA (95% CI)

<i>CLINICAL MEASURE</i>	
CHRONIC AND SEVERE IRRITABILITY	B= .16 (.01, .32)*
<i>COGNITIVE MEASURES</i>	
WCST TOTAL ERRORS	B= .69 (-.49, 1.86)
WCST PERSEVERATIVE ERRORS	B= .08 (-.56, .72)
GNG RT TO GO SIGNALS	B= .82 (-6.31, 7.95)
GNG PROBABILITY OF INHIBITION	B= -.72 (-3.80, 2.36)
CPT TOTAL NUMBER OF CARDS	B= -1.76 (-6.52, 3.00)
TDT RT DIFFERENCE DELAYED - IMMEDIATE CHOICE	B= -2.92 (-26.8, 20.9)
TDT AREA UNDER THE CURVE	B= -.001 (-.03, .03)
UG MODERATELY UNFAIR OFFERS ACCEPTED	B= -.02 (-.09, .05)
CXR GAMBLING AFTER LARGE LOSS	B= .02 (-.02, .05)
CXR GAMBLING AFTER SMALL LOSS	B= .04 (.002, .09)*
CXR GAMBLING AFTER LARGE WIN	B= -.001 (-.03, .02)
CXR GAMBLING AFTER SMALL WIN	B= -.006 (-.04, .02)

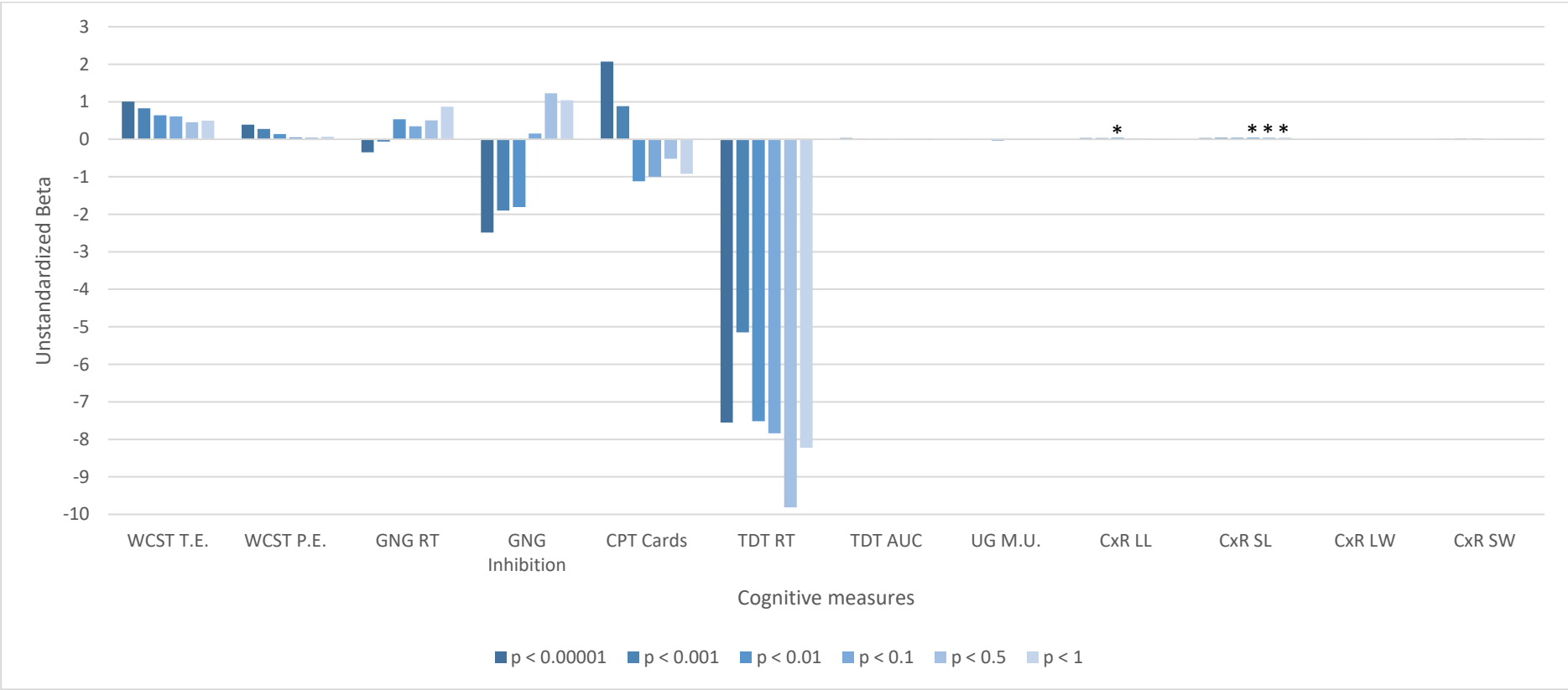
Beta values are reported for Adjusted model that, other than the ten PCs, also includes batch effects.

* significant at $p < .05$.

Overall irritability PRS was significantly associated with chronic and severe irritability symptoms but neither with Cool nor Hot EF measures, except for CxR gambling after small loss. This association failed to reach statistical significance after the Bonferroni correction, ultimately confirming results obtained when correcting only for the first five PCs.

Appendix 5.4

Sensitivity analysis on the association between irritability PRS with Cool and Hot EFs at different PRS p-value thresholds



the Beta value reported refers to the Adjusted model corrected for the first five PCs and batch effects.

* = significant at $p < .05$.

This graph shows that irritability PRS did not seem to be associated with neither Cool nor Hot EFs consistently across all the different PRS p-value thresholds. Exceptions are represented by the associations between irritability PRS with CxR gambling after large loss at $p < .01$ PRS threshold and irritability PRS with CxR gambling after small loss at $p < .1$ $p < .5$ and $p < 1$ PRS thresholds. However, all of these associations are no longer significant after Bonferroni correction, consistently with the initial results.