The impact of affective functions on decision-making behaviour in adult ADHD

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Abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
ANOVA	Analysis of Variance
ANS	autonomic nervous system
APD	Antisocial Personality Disorder
aSCR	anticipatory skin conductance response
BART	Balloon Analogue Risk Task
BDI	Beck Depression Inventory
ben	expected benefit of specific situation outlined in the DOSPERT
BOLD	Blood-Oxygen-Level-Dependent
BPD	Borderline Personality Disorder
BSL	Borderline Symptom List
CAARS	Conners Adult ADHD Rating Scales
CD	Conduct Disorder
DAT 1	dopamine transporter 1
dlPFC	dorsolateral prefrontal cortex
DM	decision-making
DOSPERT	Domain-Specific Risk-Taking
DRD 4	DA receptor D4 gene
DZNE	German Centre for Neurodegenerative Diseases
EDA	elecetrodermal activity
EKF	Emotionale Kompetenz Fragebogen
FDR	false discovery rate
fMRI	functional magnetic resonance imaging
FWER	family-wise error rate
GLM	general linear model
HC	healthy control
HF	high frequency

HRV	heart rate variability
IGT	IOWA Gambling Task
LC	locus coeruleus
Mini-DIPS	Mini-Diagnostisches Interview bei psychiatrischen Störungen
MNI	Montreal Neurological Institute
mOFC	medial orbitofrontal cortex
MRI	magnetic resonance imaging
MWT-B	Mehrfachwahl-Wortschatz-Intelligenztest
ODD	Oppositional Defiant Disorder
PFC	prefrontal cortex
PNS	parasympathetic nervous system
prob	probability of engaging a risk behaviour (DOSPERT)
risk	perception of risk in the DOSPERT
rSCR	reactive skin conductance response
RT	reaction time
SCL	skin conductance level
SCR	skin conductance responses
SD	standard deviation
SNS	sympathetic nervous system
SP	sensitivity to punishment
SPSRQ	Sensitivity to Punishment and Sensitivity to Reward Questionnaire
SR	sensitivity to reward
STS	slice-to-slice
TD	total displacement
TE	echo time
TR	repetition time
vmPFC	ventromedial prefrontal cortex
WURS-k	Wender Utah Rating Scale

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental psychiatric disorder that often persists throughout a patient's life. ADHD is characterized by a particularly heterogeneous clinical profile, influenced not only by its progression over the years but also by differences between men and women. Deficits in affective functions, which are still rarely considered in adult patients, highlight these gender distinctions as symptoms attributed to emotional processes are more pronounced in female patients. Alongside cognitive functions, these emotional processes are critical in shaping behaviour, particularly in quick and intuitive decision-making and risk-engagement. Emotional arousal, which is coupled with changes in the autonomic nervous system, can modulate and guide unconscious decision-making behaviours. However, the extent to which impairments in decision-making behaviour in adult patients with ADHD depend on this interaction, and whether differences exist between male and female patients in terms of affective symptoms remains largely unexplored. Thus, this thesis aims to investigate the underlying mechanisms of affectively driven decision-making behaviour in adult patients with ADHD compared to healthy controls. Using measurements of physiological changes via skin conductance responses and neural changes via functional MRI, decision-making behaviour was examined in more detail across three consecutive studies. Behavioural data were collected through reaction times in a modified version of the Balloon Analogue Risk Task and self-assessment were gathered using self-report questionnaires that assessed emotional competence, risk attitude, and reward sensitivity. Analyses using a linear mixed-effects model demonstrated that increased risk-taking is not accompanied by an increase in physiological activity in adults with ADHD. Further analyses also revealed that this effect was primarily driven by female patients. Compared to self-reports from questionnaires, an impaired self-perception of one's own behaviour was also demonstrated. Neural correlates further substantiated the connection between physiological response and behaviour, indicating reduced neural activity in the region of the right precuneus and the right superior frontal gyrus in patients with

ADHD. Furthermore, hyperactive neural patterns were found in women compared to men within the patient group, emphasizing the critical role of the left insula in emotional processing across genders. Overall, this thesis underscores the significant role of affective processes during decision-making behaviour and highlights gender-specific differences in patients with ADHD. These differences can be attributed to an altered relationship between emotional processing of an event, physiological change and behaviour, primarily related to disturbed interoceptive perception and metacognitive functions. Based on this work, further studies are needed to explore the understanding and gender-specific effects of autonomic nervous system functions in adult ADHD. This could not only deepen our understanding of the behavioural difficulties in adult patients with ADHD but also provide an opportunity for individualized and transdiagnostic treatments.

Declaration

This is to certify that

(i) the thesis comprises only my original work towards the PhD, except where indicated;

(ii) due acknowledgement has been made in the text to all other material used;

(iii) the thesis is less than 100,000 words in length, exclusive of tables, figures, legends, bibliography, and appendices

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Eva Halbe 30/05/2024

Preface

This thesis is part of the pilot project of the Joint PhD program between the University of Bonn and the University of Melbourne, symbolizing the strength of international collaboration in advancing our understanding of decision-making in adults with ADHD. It represents research, supported by the Faculty of Medicine, the Institute of General Psychology I of the Rheinische Friedrich-Wilhelms-Universität Bonn, and the Clinic for Psychiatry and Psychotherapy at the University Hospital Bonn. The research was financially supported by the Clinic for Psychiatry and Psychotherapy at the University Hospital Bonn, the Institute of General Psychology I of the Rheinische Friedrich-Wilhelms-Universität Bonn, and the Bonn & Melbourne Academy for Excellence in Immunosciences (BM-AXIS).

This thesis is based on three studies (Chapter 3), which were conducted during my joint PhD candidateship, encompassing extensive research and analysis efforts, primarily self-conducted, including data collection, analysis, illustration creation, and writing of manuscripts and this thesis (> 90%). Co-authors and supervisors contributed with the help of providing technological support, feedback, and beneficial discussions. Chapter 3.1. contains the study design, statistical analyses, results and discussion from the original author-accepted manuscript published by “Altered interaction of physiological activity and behavior affects risky decision-making in ADHD” on the 20th of April 2023 (Halbe et al., 2023). Chapter 3.2. contains the design, statistical analyses results and discussion from the original manuscript submitted for publication to the Journal BMC Psychiatry on the 31st of July 2023 (in progress). Chapter 3.3. contains the design, statistical analyses results and discussion from the original manuscript submitted for publication to the Journal Brain and Behavior on the 4th of March 2024 (in progress).

In this thesis, the terms "gender" and "sex" are used interchangeably, reflecting a focus on biological differences between males and females.

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List of publications

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Chapter 1: Introduction

1.1 Attention-Deficit/Hyperactivity Disorder (ADHD)

Living with Attention-Deficit/Hyperactivity Disorder (ADHD) can feel like navigating life on an eight-lane highway, where the mind races at lightning speed, capturing every detail one moment at a time. ADHD enables individuals to absorb a variety of stimuli as quickly as a sponge, utilizing their boundless energy to embark on a series of impulsive and highly intuitive adventures. Individuals with ADHD find themselves in a world full of possibilities that they can create for themselves through their extensive creativity.

However, our society is also becoming increasingly fast-paced, requiring ever-greater levels of adaption, where the pressure to keep up with changing demands can be challenging. Furthermore, these increasing demands could lead to the described neurodiversity of individuals with ADHD becoming a source of suffering for them amidst our society. Particularly, young adults with ADHD frequently report feeling overwhelmed or a loss of body control in comparison to their peers. This comparison with peers can furthermore cause a damage of self-image due to their experienced challenges in life. The impact of negative emotions can not only affect the general well-being of patients but also influence their overall behaviour. As a neurodevelopmental condition, the characteristics of ADHD often accompanies the patients throughout their lives. In particular, the impact of affective functioning, which comprise not only the regulation of one's own emotions but also the emotional perception and assessment of the environment, takes on greater significance in ADHD in adulthood. However, as one of the most prevalent disorders, ADHD is a constant subject of current research and has garnered substantial attention from researchers, clinicians, and educators. The symptomology, diagnosis, neuropathology, treatment, and effects on those affected and their families are the subject of extensive research and discussion and will be reviewed in the following subchapters. Nevertheless, the diversity of the clinical profile also indicates that further research is needed to

gain a deeper understanding of the basis of the condition and to enable more differentiated diagnostics and more tailored treatment approaches.

1.1.1 Symptoms of ADHD and diagnostic criteria

ADHD is a neurodevelopmental disorder characterized by a pattern of primarily cognitive deficits and is often clarified by a triad of symptoms: hyperactivity, impulsivity, and inattention (APA - American Psychiatric Association, 2013). These core symptoms can be present in varying degrees of severity and are manifested by a deficit of perseverance in daily activities involving a high level of cognitive effort. The symptomology of ADHD is multifaceted and can manifest differently across individuals, affecting various aspects of their lives from childhood through adulthood (Biederman et al., 2012). ADHD is usually characterized by an early onset of symptoms that develop in the first five years of life. Individuals with ADHD often exhibit a pattern of frequently shifting between various activities, which can result in unfinished completion of tasks. In particular, activities that are perceived as less exciting can only be pursued by the patients with less attention and increased distractibility. Thus, patients with ADHD often report failings in their duties at school or workplace, driven by an increased tendency to make careless mistakes in various activities (Barkley, 1997; Willcutt, 2012). However, difficulties in maintaining attention do not uniformly affect all tasks; in terms of high interest, individuals with ADHD can experience hyperfocus and are deeply immersed in a subject matter. Furthermore, individuals with ADHD are often perceived as disorganized and exhibit scatterbrained behaviour leading to misplaced items or missed deadlines. This absent-mindedness can also be reflected in social contexts, so that individuals with ADHD are sometimes perceived as absent. Increased mind wandering can often be a result of the superimposition of increased stimulus perception (Lanier, Noyes, & Biederman, 2021). Further behavioural problems in social context can also be reflected by poorly regulated and/or exaggerated behaviour (Faraone et al., 2019). In children, these behaviours are also described as being hyperactive and impulsive

compared to their peers. This behaviour could manifest as inappropriate running or climbing, prematurely answering questions, interrupting conversations or activities, and struggling to wait patiently for one's turn. In adult patients, relaxation difficulties and inner restlessness occur more frequently (Banaschewski et al., 2017; Kooij et al., 2019). In addition, other common symptoms such as emotion regulation, emotional lability, and self-esteem problems develop (Christiansen et al., 2019). In social relationships, these behavioural difficulties can lead to distancing and lack of restraint, which can negatively affect interactions with parents and peers (Gardner & Gerdes, 2015). The behaviour caused by the symptoms can then be described as not corresponding to the age, intelligence and developmental level and as significantly deviating from peers. However, overall the clinical profile of ADHD is characterized by a heterogeneous pattern of symptoms that is not universal for patients, indicating that single deficits are often neither necessary nor sufficient to explain the clinical picture (Willcutt et al., 2005; Coghill et al., 2018).

The diagnosis is operationalized in clinical practice based on the evaluation of symptoms using the two major classification systems: The International Statistical Classification of Diseases and Related Health Problems (ICD-10; Dilling, 2015) and Diagnostic and Statistical Manual of Mental Disorders (DSM-5; Falkai et al., 2018). The guidelines of the two systems contain minor differences, so that the diagnostic process in the United States, which is classically based on the DSM criteria, can be distinguished from that in Europe, which is carried out using the ICD. Both, ICD-10 and DSM-5 requires at least 6 out of 9 symptoms of inattention, 3 out of 4 symptoms of hyperactivity, and 1 out of 4 symptoms of impulsivity, to receive a diagnosis of ADHD (F90.0). Furthermore, symptoms have to persist for at least 6 months with onset before 12 years of age (AWMF, 2017; Falkai et al., 2018). In contrast to the ICD-10, the DSM-5 furthermore distinguishes three different presentations of ADHD: mixed appearance (F90.2), predominantly impulsive appearance (F90.0), and predominantly hyperactive-impulsive appearance (F90.1). In addition, if the diagnostic criteria are not fully met, the DSM-5 allows a specification to be defined as partially remitted if distress is present. The specifics of the DSM-5 also

comprise ADHD in adulthood, by reducing the number of required symptoms after the age of 17. These modifications acknowledge that ADHD symptomatology can change throughout a patient's lifespan. Along with a highly individual clinical profile and often high intelligence level, which can lead to effective compensatory mechanisms, symptoms are also frequently overlooked in adulthood (Milioni et al., 2017). Therefore, in adulthood, it is important that a differentiated diagnosis takes place, which is not yet fully covered, especially by the ICD-10. However, since January 2022, the 11th version of the ICD has come into force but is not yet used in German hospitals for licensing reasons. The amendments intend to include an increasing number of diagnostic criteria as according to different presentations of ADHD (Gomez, Chen, & Houghton, 2023). Additionally, ADHD should then also be classified as a neurodevelopmental disorder and thus also take into account a certain persistence into adulthood.

Along with self-assessment in psychiatric and psychotherapeutic interviews, third-party assessments/observations by relatives or teachers are often consulted for diagnostic purposes (Heine & Exner, 2021). Furthermore, with regard to individual supplementation of the clinical profile, additional neuropsychological assessments such as the test battery for attention or attention stress tests can be carried out (Brickenkamp, 1994; Zimmermann & Fimm, 2009). During the diagnostic process, other psychiatric diseases that may cause the present symptoms must be considered (AWMF, 2017; Banaschewski et al., 2017). Particularly, ADHD is affected by difficulties of differential diagnoses due to a very high rate of comorbidities. Approximately 52% of diagnosed children exhibit at least one additional psychiatric disorder (Jensen & Steinhausen, 2015). Within affected children most common comorbid diagnoses are Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD). Further frequent disorders relate primarily to learning disabilities, such as dyslexia, written language disorder or mathematics disorder (Pham & Riviere, 2015). It is suspected that particularly disorders that occur in the range of developmental deficits share common neurobiological factors causing the high rate of comorbidities in ADHD. Thus as the development proceeds, the comorbidity pattern in ADHD changes over time. Longitudinal studies showed that although the probability of a comorbidity during

adulthood decreases, diagnoses are significantly more frequent in terms of mood disorders, substance abuse or personality disorder (Capusan et al., 2019; Meinzer et al., 2016; Miller et al., 2008; Sobanski, 2006; Yoshimasu et al., 2018). In this context, it is noteworthy that comorbid depression affects approximately 50% of all adults with ADHD and that this number is not just clearly higher than the prevalence in the general population, but is also 3 times higher compared to a comorbid depression with ADHD in childhood (Kessler et al., 2006; Fayyad et al., 2017; Mayer et al., 2021). This elevated risk for depressive symptoms suggests that the transition from childhood to adolescence is a particularly critical period for individuals with ADHD.

According to the heterogeneous symptom profile of patients with ADHD, treatment typically involves a multifaceted approach. Various treatment options have been established, which are used depending on the severity and clinical symptom profile as well as age and comorbidity (AWMF, 2017). A distinction is made between psychosocial, educational, psychotherapeutic, and pharmacological therapies. Stimulant medications, such as methylphenidate and amphetamines, are often effective in reducing symptoms by enhancing and balancing neurotransmitters in the brain (Cortese et al., 2018). However, it should be noted that some patients with ADHD do not respond to ADHD-specific medication or suffer from severe side effects of the medication (Nanda et al., 2023; Storebø et al., 2015). According to a meta-analysis in 2010 approximately 20% of patients with ADHD do not respond to stimulant medications, which are the most commonly prescribed treatment for ADHD (Faraone & Buitelaar, 2010). In addition, to pharmacological treatments, behavioural interventions, including cognitive-behavioural therapy play a crucial role in improving organizational skills, emotional impulsivity, time management, and social interaction (Young, Moghaddam, & Tickle, 2020). Moreover, alternative approaches like regular physical activity, neurofeedback, and usage of supplements and dietary strategies can further support individuals in managing ADHD symptoms effectively (Arns, Heinrich, & Strehl, 2014; Cooper et al., 2016; Nigg et al., 2012; Vysniauske et al., 2020). Given the heterogeneity of the clinical profile, it can therefore be crucial that treatment is carefully tailored to the individual needs of

each person and can consist of a multimodal approach across the overall treatment options.

1.1.2 Aetiology and neuropathology

In the course of research into the origin and development of ADHD, a variety of factors have been identified that may influence the development of the disorder. A considerable influence is exerted by the strong genetic component found (Franke et al., 2012). A number of monozygotic twin studies including both questionnaire measures of symptoms and symptom severity as well as genetic examination showing concordance rates between 0.6 and 0.9 (Biederman et al., 1990; Thapar et al., 1999). In a genome wide study, many genetic risk variants were identified, each contributing minimally to the overall risk of developing ADHD. This finding supports the theory that ADHD is predominantly polygenic, with multiple genetic variants—each with a slight effect—cumulatively elevating the risk for the disorder (Demontis et al., 2019). Further, the polygenic risk associated with ADHD correlates with broader psychopathology and is linked to various psychiatric conditions (Brikell et al., 2020). In families affected by ADHD, the presence of additional psychiatric symptoms is frequently observed, indicating a familial clustering of symptoms. Moreover, there is an elevated risk of encountering other psychiatric disorders within these families (Bradley & Golden, 2001). Thus, genetics play a significant role, particularly genes involved in the regulation of monoaminergic neurotransmission. The most replications in research on genetic aetiology of ADHD are made on variations in the DA receptor D4 gene (DRD4) and the gene encoding the dopamine transporter 1 (DAT1) (Swanson et al., 2000, 1998). In this context, the 7-repeat variant in exon 3 of the DRD 4 gene was shown to be associated with thinner right orbitofrontal, inferior prefrontal and posterior parietal cortex (Shaw et al., 2007; Swanson et al., 2000, 1998). Variation for the DAT1 gene is assumed to influence the regulation of density of transporters in the striatum and may thus affect the extracellular dopamine level (Schmidt et al., 2001; Bédard et al., 2010; Brown et al., 2010).

There are also findings on other potential genes associated with ADHD as the dopamine D5 receptor or SNAP-25, HTR1B genes (Faraone et al., 2001; Gizer, Ficks, & Waldman, 2009; Lowe et al., 2004). However, it is also evident that when considered individually, effects are weak and gene polymorphism is neither necessary nor sufficient to explain the development of ADHD. This indicates particularly that ADHD is of polygenic origin and can be classified as a genetically heterogeneous disorder. Furthermore, this approach can be closely linked to the high rate of comorbidities and reflect the phenotypic variability of ADHD presentations (Faraone & Biederman, 1999). Nevertheless, replicable results consistently demonstrate a strong correlation and evidence that, in particular, serotonergic genes are relevant for the development of ADHD (Bobb et al., 2006). According to the findings of altered dopamine and noradrenaline transport, ADHD is assumed to result from a dysregulation of the catecholaminergic neurotransmission system in the brain (Arnsten & Pliszk, 2011; Biederman & Spencer, 1999; Pliszka, McCracken, & Maas, 1996). In this context, lowered concentrations of noradrenaline and dopamine metabolites due to an increased re-uptake of dopamine in pre-synaptic neurons, resulting into a decreased extracellular level of dopamine, have been identified in individuals with ADHD (Gold et al., 2014; Volkow et al., 2001,2005). Both dopamine and noradrenaline are neurotransmitters crucial for maintaining mood and arousal. While low firing rate is associated with reduced arousal, phasic activation is mandatory when alertness is required (Foote, Aston-Jones & Bloom 1980; Finlay, Zigmond, & Abercrombie, 1995; Schultz, 1997; Aston-Jones, Rajkowski & Cohen, 2000). This relationship underscores the significance of neurotransmitter dynamics in maintaining cognitive and emotional balance. In the context of noradrenergic transmitter system’s pathology, it has been demonstrated that its functional connectivity is particularly important for the regulation information processing and attention (Aston-Jones, Rajkowski, & Cohen, 2000). This indicates that maintaining the proper functioning and balance of these neurotransmitter systems is essential for cognitive processes and the effective regulation of attention and arousal.

Neuroanatomically, imaging studies have identified structural and functional abnormalities in children, adolescents, and adults with ADHD. However, similarly to the heterogeneous symptom profile, there is also a high variability in the neuropathology among patients. Primarily, the prefrontal cortex (PFC) as a key region of the brain responsible for managing complex behaviours like planning, decision-making, and self-control, thus coordinating executive functions, has been found to play a central role in clinical picture of ADHD. These functions are regulated by certain neurotransmitters, mainly those belonging to the catecholamine group, such as dopamine and norepinephrine. Research has found that the PFC in individuals with ADHD is reduced in volume and functions, affecting its connections with other important brain areas like the caudate nuclei and the cerebellum, which also impact the control of attention and behaviour (Arnsten & Pliszk, 2011; Aston-Jones, Rajkowski & Cohen, 2000; Castellanos et al., 1994; Kesner & Churchwell, 2011; Filipek et al., 1997). The common issues of impulsivity and the difficulty in controlling reward-seeking behaviour are also related to the hypoactivity as well as the delayed maturation in the ageing process of the PFC (Brozoski et al., 1979; Shaw et al., 2011). A study on the norepinephrine transport availability in ADHD has furthermore indicated the crucial role of the locus coeruleus (LC), a brain area identified as the primary source of norepinephrine in the human brain. A reduced norepinephrine transporter availability, primary in fronto-parietal-thalamic-cerebellar regions has been shown to be associated with attentional deficits in patients with ADHD (Ulke et al., 2019). Additional findings also show reduced volume in the cerebellum in patients with ADHD. Studies have found reductions in lobules VII, IX, and X of the cerebellar vermis in individuals with ADHD. These reductions have been demonstrated to be negatively correlated with deficits in attention, suggesting a significant link between cerebellar anatomy and ADHD symptoms (Castellanos et al., 1996, 2002; Berquin et al., 1998; Hill et al., 2003; Mostofsky et al., 1998). Functional alterations in neural activity were also found in the dorsal anterior cingulate cortex which has been shown to play a crucial role in the cognition, motor control, and arousal state of individuals with ADHD (Bush, Luu, & Posner, 2000; Paus, 2001; Rubia et al., 1999). Overall, neuroanatomical findings in

children and adolescents primarily involve fronto-striatal and cerebral areas, regions rich in dopaminergic projections.

The extent to which environmental factors contribute to the development of ADHD remains unclear. Primarily, pre-, peri-, and postnatal influences are examined. Factors such as maternal stress, alcohol and nicotine consumption during pregnancy, premature births, and low birth weight are considered as potential risk factors (Banerjee, Middleton, & Faraone, 2007; AWMF, 2017; Banaschewski, 2017). Both emotional deprivation and general neglect may have an impact on the development of ADHD. However, it is not clear whether aversive parental behaviour is a reaction to the child's already exhibited behaviour or the actual effect on the development of an ADHD-specific abnormality (Biederman et al., 1996). Nevertheless, it can be argued that negative psychosocial conditions can be regarded as risk factors for the occurrence of ADHD and influence the course of the disorder. Conversely, an emotionally sensitive family environment with positive parenting behaviour can act as a protective factor in cases of increased genetic susceptibility (Schlack et al., 2007; AWMF, 2017). Furthermore, the exposure to environmental toxins have also found to be associated with ADHD. For instance, a recent meta-analysis found that elevated blood lead levels were associated with a four times higher probability of an ADHD diagnosis (Nilsen & Tulve, 2020). Another meta-analysis found artificial food dyes were associated with an increase in hyperactivity in children (Schab & Trinh, 2004).

Taken together, the aetiology and neuropathology of ADHD are a multifaceted and complex interplay of genetic and environmental factors. The complexity does not only predispose individuals to ADHD, but also suggests a shared vulnerability to a spectrum of psychiatric conditions within families affected by the disorder. Such understanding underscores the importance of considering both genetic predispositions and environmental exposures in the diagnosis, treatment, and management of ADHD, as well as in the broader context of mental health.

1.1.3 Prevalence and persistence of ADHD

Mental disorders play a crucial role in affecting a person's overall quality of life, often casting a long-lasting shadow over the individual's entire lifespan. This is particularly evident in neurodevelopmental disorders, where symptoms typically manifest during childhood and persist for life. Since the publication of the DSM-5 in 2013, ADHD is classified as a neurodevelopmental disorder (DSM-5; Falkai, 2018). With a prevalence of approximately 7%, ADHD is considered the most common neurodevelopmental disorder worldwide (APA - American Psychiatric Association, 2013). In 2014, the US Census Bureau announced that worldwide around 63 million youths between 5 and 19 years were affected by ADHD. Thus, at that time, ADHD affected approximately 26% of all children with a diagnosed mental illness (Polanczyk et al., 2015). However, resulting global prevalence according to different reviews on childhood, ADHD varies between 3.4 and 5.9 % (Catalá-López et al., 2012; Faraone et al., 2021; Fayyad et al., 2007; Francés et al., 2022; Wang et al., 2017). Variations in prevalence estimates are often attributed to methodological differences in diagnostics. It is important to consider, that there are diagnostic differences between the DSM, commonly used in North America, and the ICD-10 criteria, which is primarily utilized in Europe. However, study results also show no increase in the prevalence of ADHD in children and adolescents over the past three decades. Even though there is an increasing understanding of the disease, no increase in diagnoses has been registered (Faraone et al., 2021). Furthermore, the geographical region is also suggested to exhibit no significant effect on the prevalence. Thus, similar patterns in diagnosing ADHD were observed in North America and Europe, whereas a comparative evaluation with developing countries has proven to be difficult due to the limited availability of data (Biederman & Faraone, 2004; Polanczyk et al., 2014).

Due to the neurodevelopmental nature of ADHD, persistent symptoms and a continuing diagnosis into adulthood can be assumed. Previous studies, including prospective longitudinal follow-up research and comprehensive meta-analyses showed that a high proportion of individuals diagnosed with ADHD in

childhood continue to experience symptoms into their adulthood (Agnew-Blais et al., 2016; Caye et al., 2016; Moffitt et al., 2015). However, similar to estimates on ADHD in childhood, reported prevalence varies considerably. In 2020, a random-effects meta-analysis determined the pooled prevalence of ADHD to be 4.61%, encompassing a 2.58% prevalence of persistent diagnoses and a 6.8% prevalence of ADHD symptoms (regardless of whether they originated in childhood) (Song et al., 2021). These results are also in line with estimates from meta-analyses, reporting a pooled prevalence between 2.6% and 2.8% based on epidemiological data on adult patients with ADHD (Fayyad et al., 2017; Simon et al., 2009). Another epidemiologic study suggested that approximately 4% of adults from an US sample still meet full diagnostic criteria (Kessler et al., 2012). A longitudinal study reported that 21.9% of the children with ADHD still meet full criteria at age of 18 years (Agnew-Blais et al., 2016). However, probabilities of persistence can range up to 78% for meeting partial criteria of the diagnosis, which is furthermore dependent on the study design, the ratio of gender included, and the criteria used (full DSM-IV criteria, subsyndromal ADHD, impaired functioning, or remission with treatment) (Biederman et al., 2011). Significant predictors of persistence included exposure to maternal psychopathology and psychiatric comorbidities, particular oppositional defiant disorder, conduct disorder, bipolar disorder, and anxiety disorders (Biederman et al., 1996, 2011). Thus, as indicated, there is a decreasing prevalence of ADHD into adulthood, reflecting a remission of the disorder. This decrease may be attributed to a variety of factors, including neuronal maturation, the effectiveness of long-term treatment and management strategies, and the individual's adaptation and coping mechanisms. Furthermore, studies on ADHD in older adulthood showed that persistent symptoms may be associated with accelerated cognitive aging and an increased risk of dementia (Tzeng et al., 2019). In this context, individuals exhibiting both a high ADHD polygenic risk score and significant levels of Amyloid-ß deposition demonstrated notably lower cognitive performance compared to the impact of each factor on its own. Additionally, a high ADHD polygenic risk score was positively correlated with cerebrospinal fluid p-tau levels and fronto-parietal atrophy, as is typically observed in patients with

neurodegenerative disorders (Leffa et al., 2023). However, it is also evident that a significant number of patients retain or modify their symptomology. In this regard, it needs to be considered that the classification systems currently used, may not fully account for the altered manifestation of ADHD symptoms in adults. This underscores the importance of further research in adulthood to investigate the core components of ADHD, aiming to identify the specific elements responsible for the disorder's persistence into adulthood. Such investigations are also crucial for developing targeted interventions and refining diagnostic criteria, ultimately enhancing care and outcomes for adults with ADHD.

1.1.4 Gender differences

In the discourse on ADHD, the gender distribution among diagnosed individuals is highly relevant, particularly due to the significant imbalanced gender ratio reported. Numerous epidemiological studies represent that there are significantly more male patients than female patients. Thus, among childhood diagnoses there are reported gender ratios between boys and girls ranging from 2:1 to 4:1 (Catalá-López et al., 2012; Faraone et al., 2021; Sayal et al., 2018). The resulting apparent prevalence between boys and girls is often thought to derive from greater genetic vulnerability, endocrine factors or psychosocial contributors in boys (Hinshaw, 2018; Greven, Richards & Buitelaar, 2018). Furthermore, the "female protective effect" theory suggests that females need more genetic and environmental triggers for ADHD to manifest, leading to its lower prevalence in females and higher familial transmission when females are affected (Rhee & Waldman, 2004; Taylor et al., 2016). Females with ADHD are also often described by different behaviours, symptoms, and comorbidities compared to males. While boys tend to be particularly conspicuous due to externalizing behaviours, increasingly driven by impulsivity and hyperactivity, girls are significantly more often affected by internalizing impairments that manifest as inward-focused symptoms, such as inner restlessness and emotional instability. Thus, in girls there is a significantly weaker association with conduct disorder and

disruptive behaviour compared to boys (Biederman et al., 2004, 2005; Gaub & Carlson, 1997; Gershon, 2002). These gender-specific differences in the symptomology of ADHD might cause boys with behavioural difficulties to be more likely noticed. Since referrals, especially in childhood, are typically initiated by parents or teachers, boys tend to have higher clinical ascertainment rates than girls (Willcutt, 2012). In this context, study results indicated a tendency for greater compensatory behaviours and coping strategies in females, which might mask ADHD-related symptoms (Mowlem et al., 2019; Quinn & Madhoo, 2014). This is further supported by the higher rates of clinic referrals and a greater likelihood of boys with ADHD to receive stimulant treatment prescriptions. However, girls with ADHD are less frequently prescribed these treatments and typically begin medication intake at a later age than boys, despite no gender differences in medication effectiveness being reported so far (Dalsgaard et al., 2014; Hinshaw, 2007; Polanczyk et al., 2008; Sharp et al., 1999). Thus, the gender imbalance affects the understanding of the nature of ADHD and the factors that influence the diagnosis. Interestingly, this pronounced gender gap narrows when individuals with ADHD transition into adulthood, and the prevalence of males and females equalizes, whereby women are often described as the ‘silent minority’ (De Zwaan et al., 2012; Simon et al., 2009). Since in adulthood an assessment regarding an ADHD diagnosis is often intrinsically motivated and arises from one's own suffering in daily life, deficits related to internalizing functions such as inner restlessness, emotional instability, and affective impairments can be more accurately identified. Particularly, emotional lability and emotion dysregulation has been found be more severe in both girls and women compared to males (Quinn, 2011; Stepp et al., 2012). A recent study also showed that females are often referred for ADHD diagnoses due to emotional-related symptoms and are older at both their first clinic visit and at the time of diagnosis. Furthermore, it has been shown that females were more likely to receive non-ADHD related medication for emotional symptoms both before and after ADHD diagnosis (Klefsjö et al., 2021). It is also crucial to acknowledge that undiagnosed ADHD may heighten the risk of developing comorbid depressive disorders (Biederman et al., 2008; Biederman, Mick, & Faraone, 1998). This could explain why women

report significantly more difficulties in affective functions and are more likely to develop major depressive disorder, dysthymia or anxiety disorder (Biederman et al., 1994; Sobanski, 2006; Sprafkin, Weiss & Schneider, 2007; Wilens et al., 2009). Undiagnosed ADHD in females may also come along with more advanced compensatory mechanisms to manage their symptoms (Quinn & Madhoo, 2014). These learned mechanisms can also hinder later diagnosis and access to appropriate interventions and must be considered for treatment of ADHD in adulthood.

Research on maturation of the brain from childhood to young adulthood, reveals distinct growth trajectories for different brain lobes, with notable variations between boys and girls (Giedd et al., 1999; Thompson et al., 2005; Lenroot et al., 2007). Girls' brain regions often reach developmental peaks earlier and may exhibit more rapid maturation compared to boys. This divergence raises questions about the impact of gender on neurobiological and neuroanatomical changes, particularly in individuals with ADHD. While gender-specific investigations in ADHD are scarce, first findings suggest unique developmental patterns. Contrary to the delayed development observed in various brain areas among ADHD patients, the primary motor cortex appears to mature earlier, potentially linking to the pronounced hyperactivity symptoms in ADHD (Shaw et al., 2007). This early maturation and its relationship with symptom differences between genders imply that brain development in boys and girls with ADHD may follow distinct paths. Moreover, a gender-specific effect has been identified in the basal ganglia's volume as well as in subcortical and hippocampal volumes, showing structural neuronal reductions being more prominent in males with ADHD (Onnink et al., 2014; Qiu et al., 2009). Furthermore, hormonal influences, particularly those associated with the menstrual cycle, have also been found to impact ADHD-related symptoms, and further complicating our understanding of the disorder's clinical presentation across genders. A recent study posited that cyclical fluctuations in ovarian hormones, notably the sharp declines in oestrogen, might amplify ADHD symptoms by diminishing executive function and trait control during certain menstrual phases. The withdrawal of oestradiol, the predominant form of oestrogen, is thought to disrupt dopamine functioning in the

PFC. This disruption could lead to deficits in executive cognitive functions and the effective management of emotions and behaviours (Eng et al., 2024). Moreover, it is assumed that there might also be differences in the effectiveness of ADHD medications. Particularly, it has been observed that women exhibit increased sensitivity to stimulant medications during the follicular phase of their menstrual cycle, which is characterized by elevated oestrogen and reduced progesterone levels (Terner & de Wit, 2006).

These insights highlight the critical need to incorporate gender-specific considerations into ADHD research. Moreover, there is need for more tailored treatment approaches, particularly concerning the utility of stimulant medication with respect to medication dosage or type, according to developmental stages or hormonal cycle phases. This underscores the complex interaction between hormonal fluctuations and neurological processes in females. However, the majority of many previous and actual study results are also impacted by gender disparities. Thus, research on ADHD is still often relying on data predominantly from males and not reflecting a balanced gender ratio. This imbalance has led to gaps in the literature and a biased understanding of ADHD's clinical manifestations, as gender differences in behavioural problems are frequently overlooked. However, recent data showing a rise in prescription stimulant fills from 2016 to 2021, especially during the 2020–2021 period, indicate a shift. Notably, this increase is pronounced among adolescent and adult females, suggesting a growing awareness and recognition of ADHD in women (Danielson et al., 2023).

1.2 Autonomic nervous system

In the context of affective functions and arousal the autonomic nervous system (ANS) plays a crucial role in regulating states of wakefulness and alertness (Bellato et al., 2020). The ANS is part of the peripheral nervous system, which forms a communication network through its branches of nerves between the central nervous system and various body parts. Within that communication

network, the ANS is responsible for the regulation of involuntary physiological processes, such as blood pressure, heart rate, sweating, respiration, digestion, and pupil dilation. To do so, the ANS comprises the sympathetic, parasympathetic, and enteric nervous system (Karemaker, 2017; Sternini, 1997). Whereas the enteric nervous system is capable of acting independently and is responsible for regulating the gastrointestinal tract, the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) both contain afferent and efferent fibers that transmit information from and to the central nervous system. In their roles, the SNS and the PNS act as counterparts. When balanced, they maintain homeostasis within the body. When activated, the SNS triggers heightened alertness and activity, which includes increasing blood pressure, sweating, and initiation of glycogenolysis (Karemaker, 2017). It achieves this by releasing hormones like adrenaline and noradrenaline. Thus, sympathetic activity is often a response to stress in order to achieve a state of heightened alertness and physiological readiness, enabling the body to rapidly react to immediate threats or challenges. Conversely, the PNS conserves energy by reducing physiological responses in order to restore the body to calmness and maintains internal homeostasis by reversing the excitatory actions of the SNS (Kenney & Ganta, 2014). These autonomic psychophysiology processes have also been shown to be linked to distinct cognitive domains and interconnect information about internal states of bodily arousal with the central nervous system for feelings but also for behavioural actions (see Chapter 1.3.1. for further description). This interconnection is particularly mediated by the LC in the brainstem (Aston-Jones et al., 2000). In this context, several studies have demonstrated the significance of the interconnection between ANS, brainstem and cortical systems in regulation of behaviour and cognition (Gilzenrat et al., 2010; Murphy et al., 2014). Activations of these psychophysiological processes and thus assumptions about their effects on cognition can be objectified by recordings of heart rate, pupil dilation and electrodermal activity (Wass, de Barbaro, & Clackson, 2015). Particularly, the measurement of electrodermal activity, such as skin conductance responses, has been shown to be the most useful index of changes in sympathetic arousal that is tractable to emotional and cognitive states, as it is

the only autonomic psychophysiological variable that is not contaminated by parasympathetic activation (Boucsein, 2012).

1.2.1 Clinical implication of ANS functioning

Given the crucial role of the ANS in regulating almost every organ system of the human body, the clinical presentation of autonomic dysfunctions can be highly varied. The ANS plays a critical role in a wide range of physiological processes, ensuring the body's internal environment remains stable and responsive to changes. Moreover, the ANS is intricately connected with cognitive processes, influencing and being influenced by thought patterns, emotional responses, and behavioural decisions. Consequently, the involvement of the ANS can extend to a multitude of diseases, meaning that autonomic dysfunctions are often a component or a consequence in various pathological states. Clinical disorders of the ANS can be categorized as either focal or generalized, based on whether one or multiple autonomic segments are affected (Cardinali, 2018). Furthermore, in a clinical setting it is important to determine if the manifestations are predominantly due to sympathetic, parasympathetic, or mixed dysfunction. As previously described, neurotransmitters such as dopamine and noradrenaline (norepinephrine) modulate the functioning of the ANS. Dysfunctions in the reception or projection of these neurotransmitters are often associated with psychiatric diseases. Furthermore, studies have indicated that individuals with various psychiatric disorders face an approximately two to three times higher risk of developing cardiovascular diseases (Alvares et al., 2016; Garcia-Portilla et al., 2009; Saha, Chant, & McGrath, 2007). Reduced cardiac autonomic regulation is furthermore associated with severe consequences like reduction in heart rate variability (HRV) (Garcia-Portilla et al., 2009; Nicholson, Kuper, & Hemingway, 2006). In turn, there is also evidence that exposure to chronic stress can cause the development of psychiatric disorders, such as depression, anxiety, or substance abuse (Nemeroff & Vale, 2005; Santarelli et al., 2014). However, it is

not known whether the modification of these neurotransmitters is the cause or effect of mental illness.

A recent review demonstrated that altered autonomic function with a tendency of increased heart rate, reduced HRV and aberrant circadian changes are a common issue across psychiatric patients. The study highlights that physiological measures provide a valid transdiagnostic approach in representing dynamic biomarkers of stress system activity (Agorastos et al., 2023). Thus, stress-related disorders, such as post-traumatic stress disorder exhibit hypoactive functions in the PFC which causes an inhibition of the autonomic core centres like the hypothalamus and the brain stem (Falconer et al., 2008). Consequently, there is a reduction of high-order autonomic control associated with cognitive perception and emotional responses (Thayer & Lane, 2000). Accordingly, it has been shown that lower HRVs are associated with higher symptom severity of several psychiatric diseases (Agorastos et al., 2020). In patients with major depressive disorder, measures of HRV has been used as a biomarker for treatment stratification according to the varying effects of antidepressant treatment in different depression types (Kircanski, Williams, & Gotlib, 2019). Furthermore, there is evidence of specific psychiatric medications having a negative influence on, showing increased risk for cardiovascular diseases, which highlights the need for further considerations of physiological effects (Alvares et al., 2016). Variations in HRV have additionally been demonstrated as valid biomarkers in the prediction of cognitive impairments (Forte, Favieri, & Casagrande, 2019). Other physiological measurement techniques like pupillometry and electrodermal activity (EDA) have also proven to offer insights into cognitive processes and emotional states in psychiatric patients. For instance, individuals with depression exhibited sustained pupil dilation to negative stimuli indicating the prolonged processing of emotional information (Siegle et al., 2001). Furthermore, measures of EDA suggest shared pathology of autonomic dysfunctions in patients with anxiety and schizophrenia. In both groups, a greater frequency of spontaneous fluctuations in the EDA were found (Toone, Cooke, & Lader, 1981).

Studies on physiological measures, including HRV, pupil dilation, and EDA, alongside the biological principles of autonomic nervous processes, consistently indicate alterations in psychiatric diseases, revealing both disorder-specific changes and shared transdiagnostic patterns. These alterations highlight the intricate interplay between physiological responses and psychiatric conditions, suggesting that ANS dysregulation is a significant feature across various mental health disorders. Despite these insights, the clinical application of physiological measures in the diagnosis and management of psychiatric conditions remains underexplored. Although the significance of these measures could potentially enhance diagnostic processes and inform treatment strategies, an integration into routine clinical practice has not yet been realized.

1.2.2 Autonomic nervous functioning in ADHD

A multitude of studies have shown ADHD to be a psychiatric condition linked to the altered functionality of the ANS. Summarized by a recent meta-analysis, it has been revealed that, using various measurement methods, patients with ADHD exhibit an overall hypoactivity of autonomic functions (Bellato et al., 2020). However, the literature in this regard in characterized by significant heterogeneity. Thus, dependent on the measurement method or condition (resting measurement or during task) used, hyperactivities have also been observed. This variability in ANS functionality could potentially be traced back to the heterogeneous clinical picture of ADHD. The extent to which hypoactive autonomic functions affect behaviour in patients with ADHD is not yet sufficiently explored. However, it is known that adequate emotional arousal, driven by sympathetic activity, is necessary to achieve a certain level of cognitive performance (Yerkes & Dodson, 1908). It is suspected that in patients with ADHD, a decreased arousal may be linked to higher-level cognitive deficits (Kuntsi & Klein, 2012; van der Meere, Börger, & Wiersema, 2010). Consequently, reduced arousal during monotonous or challenging cognitive tasks would explain poorer performance in ADHD. Furthermore, the diminished attentional resources

for relevant stimuli during a task could be related to a tonically hypo-aroused state. Conversely, the hyperactivity and impulsivity often observed in ADHD can be interpreted as potentially arising from autoregulatory processes aimed at enhancing arousal as a form of self-stimulation (Geissler et al., 2014). However, in order to accurately assess the relationship between cognitive performance which is also linked to the individual clinical profile of the patients, and the ANS functions, further research is needed, particularly regarding the causality between arousal and behaviour.

Furthermore, deficits in other autonomic functions are related to altered ANS regulation in patients with ADHD. For instance, a study on children with ADHD found a lower cortisol level in the patient group compared to controls. This down-regulation or delay in the daily cortisol cycle, crucial for the appropriate management of stress, represents an autonomic dysfunction in patients with ADHD, indicating an inappropriate regulation of the Hypothalamus-Pituitary-Adrenal axis. These low levels are presumed to be linked to a hypoaroused state, potentially underlying several core symptoms of ADHD. Additionally, the autonomously regulated circadian rhythm of sleep has been found to be altered in patients with ADHD (Isaksson et al., 2012). Patients describe their sleep as mainly superficial and disruptive. In this context, one study identified delayed melatonin secretion in patients with ADHD, which can lead to symptoms of restless sleep and frequent awakenings (Van Der Heijden et al., 2007). Consequently, an increased rate of daytime sleepiness has also been noted. It is important to consider that poor sleep routines and daytime fatigue can impair cognitive performance. A significant link between sleep behaviour and eating behaviour has also been established (Cortese et al., 2008). In this context, sleep deprivation has been shown to cause an increased level of ghrelin, a hormone that stimulates hunger and appetite (Carter et al., 2011). Coupled with reduced energy and symptoms of fatigue resulting from sleep difficulties, and a subsequent decrease in physical activity during the day, patients with ADHD face an elevated risk of excessive weight gain and obesity. This is further supported by a meta-analysis, which underscores the significant association between symptoms of ADHD and obesity (Cortese et al., 2016; Hanć & Cortese, 2018).

Taken together the relationship between ADHD and ANS functioning highlights a complex interplay of altered arousal affecting cognitive performance and behaviour. Furthermore, future research investigating autonomic functions and the diverse symptomology of ADHD could provide advanced understanding for treatment strategies in ADHD.

1.3 Decision-making (DM)

The process of decision-making (DM) has been a subject of profound interest for centuries. Rooted in the pioneering work of Daniel Bernoulli in 1738 (Bernoulli, 1954) and further developed through the economic theories of Von Neumann and Morgenstern, DM has traditionally been examined as a static process, primarily concerned with determining a single choice from a multitude of available courses of action (Edwards, 1961). DM in its rudimentary form can be quantified by assigning numerical values to potential outcomes and their associated probabilities. This quantification facilitates the computation of expected values, allowing a decision to be made in favour of the option whose sum has the greatest probability value product (Edwards, 1961). However, this weighing of values is primarily a matter of rational actions and causes DM to be based on expectations about the consequences. Despite static models describing how to decide, in psychology DM is regarded as a complex functioning of cognitive processes and is not always consistent with rational processes (Kahneman & Tversky, 1979; Wang & Ruhe, 2007). As the need for a decision arises due to internal or external demands of changes or the revisions of previous decisions, cognitive functions such as attention, comprehension, memorization, representation and problem-solving are required (Gigerenzer & Gaissmaier, 2011). In fact, DM is a highly complex interaction of various functions that is furthermore dependent on numerous environmental factors. Thus, not only the current circumstances, but also the current social and cultural influence can play a supporting role in decisions made and actions taken.

Human DM is deeply influenced by a range of psychological factors, including emotional biases, past experiences, and individual perceptions. These factors are often subconsciously processed and vary significantly between individuals, which makes it difficult to generalize findings or create predictive models (Tversky & Kahneman, 2013). The interindividual variability is also subject of our cognitive maturation across lifespan and can be modified by experiences we gain in everyday life. Therefore, actual DM is often overshadowed by "humanized" aspects that are difficult to define and objectify. Consequently, a gap emerges between the actual observable behaviour, known as descriptive DM, and the rational expected action, referred to as normative DM (Osborne & Rubinstein, 1994; Berger, 1980). This gap widens as subjective value becomes more involved during DM processes and represent a significant hurdle in convincing a decision maker to act and decide using normative techniques (Lipshitz, 1994). Therefore, strictly rational processes in DM apply only to an isolated form of decision types (e.g. strategic decisions by businesses, governments, and organizations). In practice, it is uncommon that DM relies only on these rational processes (Dillon, 1998). Instead, we make thousands of decisions every day that correspond to rather non-rational theories. These decisions can be unconscious and vary greatly from person to person. Understanding the basis of such DM behaviour requires a comprehensive understanding of neurobiological mechanisms and physiological interactions, which are not least an expression of our emotional processes. Such mechanisms can be repetitive, self-explaining and functioning within a single individual, but may manifest completely differently for another.

1.3.1 Somatic marker hypothesis

While the rational and logical aspects of DM have been extensively studied, there is another important function regarding the interplay between emotions, bodily sensations, and the choice we make. Thus, despite our deliberate cognitive ability to evaluate critically different options and retrieve previous situations, several

unconscious emotional processes are necessary and involved in the DM behaviour. Particularly quick and intuitive decisions require underlying processes that interact efficiently with emotional evaluation and physiological activity (Sonuga-Barke, 2002). This interaction was initially described by the somatic marker hypothesis (Damasio, 1996).

In the early 1990s, Antonio Damasio and his colleagues conducted extensive research on patients with brain lesions in the PFC. Indicated by the case of Phineas Gage, in particular, the relationship between dysfunctions of the ventromedial prefrontal cortex (vmPFC) and DM behaviour has been studied in more detail (Damasio et al., 1994). Due to an accident at work in 1848, Phineas Gage suffered a severe brain injury caused by an iron bar that pierced the left side of his skull. This caused an irreversible lesion in the area of vmPFC, which resulted in a significant change of his personality and behaviour. Gage became impulsive, irritable, and unreliable. His negatively accentuated affect also interfered with his DM behaviour and resulted in disadvantageous prospective decisions. These abnormalities could also be observed in other patients with lesions in the area of the vmPFC and demonstrated that the frontal lobes were linked to social conduct, judgment, DM, and personality (Bechara et al., 1994). Furthermore, it was known that the frontal lobes were linked to interoceptive and visceromotor functions (Terasawa, Fukushima, & Umeda, 2013). Thus, it could be assumed that behaviours such as DM are reliant on intact visceromotor functions as well as the interoceptive perception. Visceromotor functions refer to the regulation of bodily processes, such as heart rate, respiration, sweating, and other autonomic functions, which are intimately connected with our emotional states (Christopoulos, Uy, & Yap, 2019). This linkage is a key component of the mind-body connection and plays a significant role in how emotions are experienced and expressed. Based on these findings, Damasio and his team formulated the somatic marker hypothesis. They proposed that emotions and the physiological sensations associated with them, named “somatic markers” are responsible in guiding DM. Past experiences and related emotions as well as the accompanied bodily responses were integrated as a somatic marker. These markers reflect changes in our physiological and emotional states in response to

various life events (Damasio, 1996). They are a kind of implicit knowledge, elicited by the visceral response that reflect the anticipated value of the different choices. This provides a quick, intuitive, and subconscious guidance system that ensures making a more advantageous decision (Barrett et al., 2007; Brand et al., 2007; Damasio, 1996). When facing with a decision, the brain retrieves these encoded emotional and physiological markers associated with similar past situations. These markers then provide unconscious information about the potential consequences and risks of the decision and initiate a behavioural action. Thus, the relationship between visceromotor functions and emotions forms a feedback loop. Emotions can trigger changes in autonomic responses, and these bodily responses, in turn, can affect the intensity and duration of emotional experiences. Furthermore, the decision's outcome is experienced and associated with an emotional value, which in turn can become part of the feedback loop (Damasio, 1996).

In order to gain deeper insights in the role of the vmPFC and DM behaviour, Bechara, Damasio, and their colleagues designed a novel DM paradigm - the IOWA Gambling Task (IGT) (Bechara et al., 1994; Bechara et al., 1997; Bechara, Tranel, & Damasio, 2000; Maia & McClelland, 2004). The IGT is a card game designed to simulate real-life DM under uncertainty in order to control for the ability to predict future consequences of decisions (Bechara et al., 1994). Participants are presented with four decks of cards, each associated with different rewards and punishments. Two of the decks yield high immediate rewards but also carry high long-term losses, while the other two decks offer lower immediate rewards but lead to greater long-term gains. It is a test of an individuals' ability to learn from feedback and adjust their choices accordingly. It was demonstrated that patients with prefrontal lesions when compared to healthy controls were unable to prospect their own choice and seem to be guided by immediate prospect only (Bechara et al., 1994). According to the somatic marker hypothesis, it has been shown that patients cannot prevent a disadvantageous decision with the help of the intuition of their "gut feeling". This intuitive awareness of the outcomes of choices before they are consciously perceived can be measured by changes in the ANS that elicit a physiological activation. The

measurement of skin conductance responses (SCR), as an indicator of physiological activity, has become a viable method (see **Figure 1**) (Boucsein, 2012). Recordings of changes in the skin conductance during the performance of the IGT have demonstrated anticipatory changes in the physiology prior to DM as an indicator of the functioning of somatic markers. Thus, it has been shown that skin conductance increases before disadvantageous choices compared to advantageous choices, representing the bodily response that reflects emotional arousal. However, patients with bilateral damage to the vmPFC showed aberrant changes in their SCRs prior to a decision (Bechara et al., 1997). A meta-analysis from 2019, explored the relationship between anticipatory SCR (aSCR) and performance in the IGT by analysing data from various studies (Simonovic et al., 2019). The meta-analysis revealed a significant small-to-medium relationship between aSCR and IGT, supporting the notion that anticipatory physiological responses are associated with DM in the IGT. However, methodological inconsistencies, limited adherence to standardized protocols, and potential publication biases raised concerns about the reliability of these findings, highlighting the need for more rigorous approaches in future studies exploring the somatic marker hypothesis.

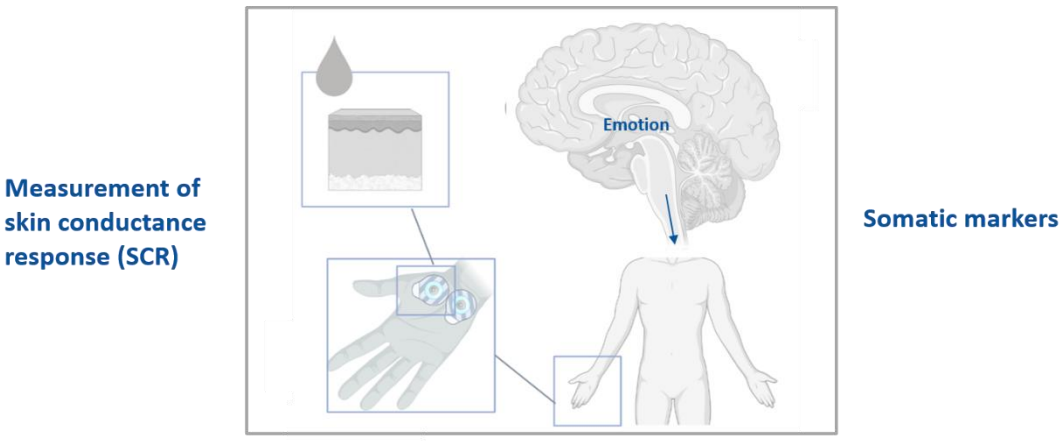

Figure 1: Measurement of skin conductance responses (SCR) as an indicator for somatic marker functioning.

At the neural level, Bechara, Damasio, and their colleagues describe the vmPFC, which encompasses the medial orbitofrontal cortex (mOFC), as the most crucial component of the network of neural systems responsible for DM behaviour and related affective processes. Nevertheless, DM relies on an interaction of large-scale systems that also include other cortical and subcortical components (see **Figure 2**) (Poppa & Bechara, 2018; Bechara, 2011). In this context, the vmPFC and mOFC can be described as an "integration system" that is responsible for successfully integrating information retrieved from other neural systems and initiating a visceral response to it. These extensive reciprocal connections enable the integration of internal emotional and cognitive information as well as external sensory information (Stuss & Knight, 2002). Past experiences including memories of past events or stimuli, as well as processes rehearsed by the working memory, are represented by the "memory system". It is thus assumed that functional connectivity exists between the dorsolateral prefrontal cortex (dlPFC) and the hippocampus from and to the integration system. Reciprocal projections with the “emotion system” are tasked with bringing the current affective state online. This system includes effector structures such as the hypothalamus and the autonomic brainstem nuclei to trigger changes in physiological activity. It also encompasses cortical structures such as the insular cortex, the posterior cingulate cortex and precuneus to receive afferent input about the visceral changes. Neurons, whose cell bodies are located in the brainstem, release neurotransmitters such as dopamine, serotonin, noradrenaline, and acetylcholine (Blessing & Gai, 1997). Modulated by the axon terminals of these neurons, cells throughout the cortex and striatum receive signals about neurotransmitter patterns, serving as a “motor/behavioural system” to initiate behavioural actions and cognition within the cortex (Li et al., 2010). These proposed neural mechanisms have been studied in several imaging studies using various DM paradigms. Although some limitations were demonstrated regarding the use of the original IGT, developed in context of the SMH, the vmPFC, the dlPFC, the mOFC, and the amygdala still emerged as key brain areas related to emotion and DM (Ernst et al., 2002; Fukui et al., 2005; Lawrence et al., 2009; Li et al., 2010; Northoff et al., 2006).

Overall, the somatic marker hypothesis posits that emotions play a crucial role in guiding our DM, especially in situations characterized by ambiguity and uncertainty. It suggests that the body's physiological responses to emotions provide us with valuable information, aiding in making more advantageous choices. This perspective has offered significant insights into the interplay between emotion and DM. However, the complex mechanisms underlying somatic marker functioning still require further empirical support. Additional research and the usage of advanced DM paradigms are necessary to expand our understanding of the neural systems involved.

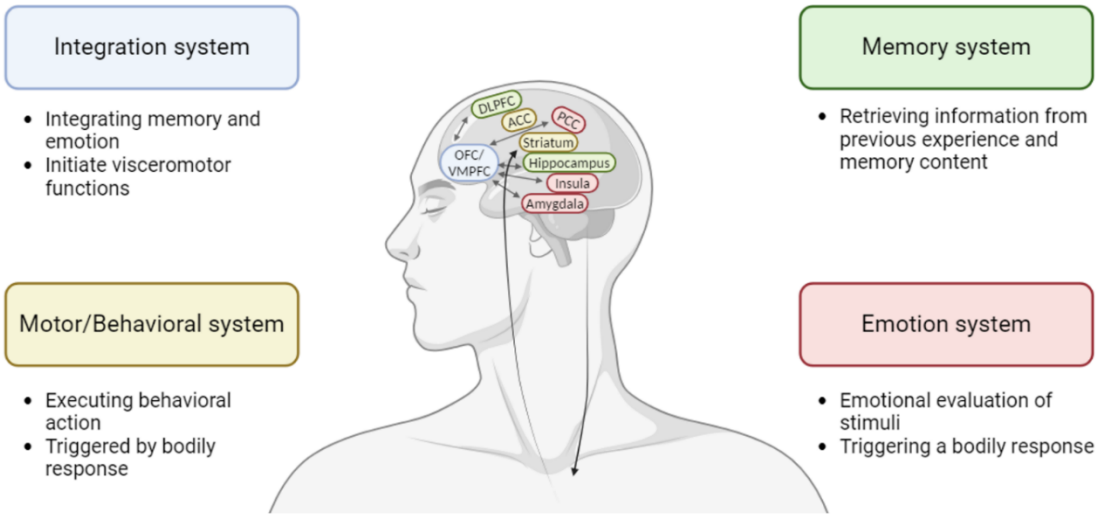

Figure 2: A schematic of the neural system and brain regions involved in decision-making according to the somatic marker hypothesis.

1.3.2 Decision-making in ADHD

Taken together, DM is a dynamic process that demands not only cognitive-analytical skills for the deliberate evaluation of different options, but also a synergetic interplay of emotion and physiology, especially in the context of quick, intuitive actions. Furthermore, DM is affected by complex interpersonal variability. Achieving advantageous decisions and taking appropriate actions requires a delicate balance – an ability to control inhibition, impulsivity, and attention,

coupled with the capacities for reflection, interoceptive awareness, and emotional competence. However, this intricate coordination between cognitive and affective processes raises a compelling question: What happens to DM behaviour when individuals experience impairments in these functions?

This question becomes particularly relevant when considering ADHD, a condition linked to various challenges in certain traits that may significantly affect DM abilities and behaviours. The complexity of DM behaviour, coupled with the heterogeneity in the clinical profiles of patients with ADHD, complicates the investigation of underlying mechanisms. Nevertheless, a substantial body of research has explored various facets of deficient DM behaviour in ADHD, contributing to an expanding understanding. Specifically, meta-analyses and reviews have revealed that deficits in executive functions and impulsivity control are associated with corresponding challenges in DM behaviour (Dekkers et al., 2021; Dekkers et al., 2016; Mäntylä et al., 2012; Mowinckel et al., 2015). Particularly, executive functions have been the focus of numerous studies on DM in ADHD. In individuals with ADHD, executive dysfunctions—such as deficits in working memory, cognitive flexibility, and planning/organization skills—impair the processing, adaptation, and forward-thinking essential for effective DM. This leads to difficulties in making both everyday choices and long-term decisions. Additionally, deficits in inhibition, another executive dysfunction closely associated with DM impairments in ADHD, entail a reduced ability to regulate responses and control impulsive behaviours. As a core symptom of ADHD, impulsivity in this context is tied to behavioural disinhibition, fostering an aversion to delay and resulting in rushed DM without adequate consideration of consequences. Since individuals with ADHD typically have difficulties controlling their immediate desires and reactions, short-term rewards are frequently prioritized over long-term goals. This conspicuousness is also often accompanied by impaired feedback processing. Thus, patients with ADHD commonly exhibit a reduced sensitivity towards negative decision outcomes and an enhanced focus on rewards which can appear often as reward seeking behaviour (Luman et al., 2008; Scheres et al., 2007). It is also assumed that impaired learning of valence and reward magnitude in ADHD diminishes the ability to prioritize decisions,

leading to choices driven by impulsivity or a lack of learned strategy (Ibanez et al., 2012). In terms of the intricate relationship between reward processing and impulsivity regarding DM behaviour, Berridge and colleagues introduced a compelling model referring to the differences between the “wanting” and “liking” of rewards. In this model, “wanting” refers to the motivation or desire for reward, while “liking” represents the hedonic pleasure derived from that reward. When applying this model to DM behaviour in ADHD, it may be assumed that patients' decisions are driven by an imbalance of "wanting" and "liking”. A combination of heightened “wanting” for immediate rewards and diminished “liking” for tasks that demand sustained attention can have a profound impact on DM behaviour in ADHD. They may exhibit a preference for activities that provide instant gratification or novel stimuli, even if their choices do not align with their long-term benefits (Berridge & Kringelbach, 2008). Another critical aspect of impulsive DM is the heightened tendency towards risky behaviour. It has been increasingly demonstrated that DM impairments in patients with ADHD are commonly associated with a propensity for risk-taking behaviours (Pollak et al., 2019). Consequently, individuals with ADHD often engage in activities that carry a significant risk of negative outcomes. Specifically, DM in risky situations requires an appropriate evaluation of the risks and the potential benefits/rewards associated with each option as well as the ability to retrieve information from past feedback to adjust future decisions. In this context, a recent meta-analysis explored the heightened propensity for risk engagement, particularly in relation to the increased "wanting" towards rewards, framing it as risk-seeking behaviour. This meta-analysis underscores the challenge in distinguishing whether DM deficits in ADHD stem from an intrinsic risk-seeking tendency or from difficulties in effectively evaluating the expected value of choices. The findings suggest that suboptimal DM in ADHD may not necessarily indicate risk-seeking behaviour but rather reflect executive functioning deficits, such as limitations in working memory and inhibitory control. These deficits complicate the ability to assess potential outcomes and resist impulsive choices (Dekkers et al., 2021). Furthermore, it has been observed that risk-taking is elevated in situations where the outcomes of decisions are uncertain. In this regard, affective functions are assumed to play

another crucial role, as they enable individuals to weigh emotional value of potential outcomes. This is particularly necessary to guide individuals' behaviour through complex choices fraught with ambiguity and uncertainty (Mäntylä et al., 2012; Shoham et al., 2016; Sonuga-Barke, 2002). Consequently, there is a strong indication that, alongside rational thinking, the assessment of risk is also based on internal sensations, often described as "gut feeling", and plays a significant role in our DM behaviour. Increased rates of risk-taking behaviour in patients with ADHD are frequently observed in areas such as risky driving, substance abuse, criminal activities, risky sexual behaviour and pathological gambling (Faregh & Derevensky, 2011; Flory et al., 2006; Lee et al., 2011; Pratt et al., 2002). The consequences of the disruptive DM behaviour extend far beyond the individual, impacting their social environment, financial stability, and causing challenges in educational and occupational settings. Moreover, these DM behaviours may lead to heightened burdens in terms of healthcare costs and public safety concerns (Hakkaart-van Roijen et al., 2007). The total socioeconomic cost of ADHD has been estimated to be billions of dollars, underscoring the need for increased public awareness and improved identification and treatment strategies to mitigate these costs (Sciberras et al., 2022). The patients themselves often experience significant distress due to their uncontrollable behaviours. This distress can manifest in various forms, including low self-esteem, anxiety, and depression. The feeling of not being in control can exacerbate feelings of frustration and inadequacy, leading to negative emotions that impact mental health and well-being. Moreover, the persistent struggle with self-regulation and impulsivity inherent in ADHD can lead to internal conflicts. The awareness of the mismatch between their intentions and actions often heightens their emotional distress, making it challenging to maintain a positive self-image (Cueli et al., 2020; Harpin et al., 2016).

At neural level, ADHD is associated with dysregulations in the dopamine system, which particularly affect the PFC and the striatum (see Chapter 1.1.2.). These areas have also been identified as crucial for cognitive control, motivation and reward processing in relation to DM behaviour (Berridge & Kringelbach, 2015). The PFC has been shown to be responsible for executive functions, such

as working memory, cognitive flexibility, planning, inhibition, and the regulation of attention and behaviour. The observed dopamine dysregulation in the PFC in individuals with ADHD can impair these executive functions, leading to difficulties in DM processes. Consequently, individuals with ADHD may struggle with tasks that require sustained attention, planning, and inhibition control, which are critical components of effective DM. In this context, particularly the dlPFC and its interaction with the dorsal striatum (particularly the caudate nucleus) were highlighted (Sonuga-Barke, 2005). Accordingly, dopamine as the key neuromodulator in the neural circuits of executive functions, is typically released mainly in the striatum and the PFC (Ziegler et al., 2016). However, study results identified a deficiency in dopamine signalling in individuals with ADHD which is further supported by the increasing effect of intrasynaptic dopamine by stimulants (Faraone, Biederman, & Mick, 2006; Volkow et al., 2001). Thus, hypoactivation in the PFC have been associated with difficulties in considering long-term consequences and inhibiting impulsive responses. Furthermore, reduced functional connection between brain areas such as PFC, anterior cingulate cortex, and the striatum were identified as cause of disturbances in the evaluation of choices and the regulation of behaviour (Bush et al., 1999; Cubillo et al., 2012; Dickstein et al., 2006; Tamm et al., 2004). However, neuroimaging studies examining neural activation to reward found hyperactivations in the region of the right anterior cingulate cortex in individuals with ADHD during the performance in the IGT (Ernst et al., 2003). It has also been shown that neural responsiveness regarding feedback processing and DM in ADHD is furthermore dependent on the feedback condition (Mesrobian et al., 2016). On delay discounting tasks it could be shown that rewards exhibited less neural activation in area of the mOFC (Wilbertz et al., 2012). Whereas neuroimaging during other rewarded tasks indicated decreased neural activity in the ventral and dorsal striatum (Furukawa et al., 2014; Pflichta & Scheres, 2014). Alternative perspectives on DM difficulties in individuals with ADHD highlight the issue of impaired signalling of delayed rewards, suggesting that the symptoms of ADHD are partly due to disturbances in motivational processes. Overall, these findings underscore the significant role of the fronto-ventral striatal reward circuits and the mesolimbic dopamine

pathways, which are crucial for reward processing, motivation, and the anticipation of future outcomes (Averbeck & O'Doherty, 2022; Cox & Witten, 2019). Thus, alterations in neural circuits, which are presumed to regulate attention and behaviour in response to rewards, may lead to diminished sensitivity to delayed rewards in individuals with ADHD (Sonuga-Barke, 2005).

However, although there is strong evidence of impaired DM behaviour in ADHD, supported by neural anomalies and observed daily behaviours, exploring the causes and underlying mechanisms presents significant challenges. While laboratory settings provide valuable insights into underlying mechanisms, the translation of findings to real-life scenarios is difficult (Groen et al., 2013). Most studies that have investigated DM in ADHD, particularly regarding risky behaviour, utilized the IGT (Bechara et al., 1994) (IGT). Several studies indicated impaired DM behaviour both in children and adults with ADHD, indicated by fewer advantageous choices in the IGT (Ernst et al., 2003; Garon, Moore, & Waschbusch, 2006; Toplak, Jain, & Tannock, 2005). However, compared to the Balloon Analogue Risk Task (BART), performance in the IGT revealed weaker effects of risk-taking behaviour (Mäntylä et al., 2012). This was further supported by other studies that found increased risky DM behaviour in patients with ADHD compared to healthy controls (Humphreys & Lee, 2011; Loya et al., 2019). Similar performance was also observed on the Game of Dice Task (Matthies, Philipsen, & Svaldi, 2012). However, when considering the existing literature, it is noteworthy that the findings reveal a lack of consistency across different tasks used. Existing tasks can be categorized, as either based on implicit or explicit behaviour, distinguishing between tasks requiring automatic, unconscious processes (implicit) and those that require conscious, deliberate processes (explicit). Frequently used tasks demanding explicit actions are, for example, the Cambridge Gamble Task (Robbins et al., 1998) and the Game of Dice Task (Brand et al., 2005), whereas the IGT and the BART represent typically implicit DM tasks. Interestingly, a meta-analysis on DM in ADHD revealed a significant effect of ADHD on impairments in the performance on implicit tasks, but not on explicit tasks (Dekkers et al., 2016). However, the fundamental cause or the interactions of functions that ultimately lead to a risk decision is still difficult to

detect in controlled experimental environments. This is further complicated by the heterogeneity in the clinical picture of ADHD. Not only does the individual spectrum of symptoms influence behaviour, but additional factors such as age, gender, and comorbidity also play a significant role. DM in individuals with ADHD can vary widely between children and adults, attributed to developmental changes, cognitive maturation, and the evolving demands of daily life. For instance, core symptoms of impulsivity and hyperactivity which can affect DM capabilities, generally diminish with age (Biederman & Faraone, 2000). In addition, it has been observed that common comorbidities in children with ADHD, such as Oppositional Defiant Disorder (ODD), Conduct Disorder (CD) or Antisocial Personality Disorder (APD) are associated with greater impairments in DM, particularly regarding risk engagement (Biederman et al., 2008; Groen et al., 2013; Humphreys & Lee, 2011; Ramos Olazagasti et al., 2013). Conversely, an increased probability of comorbid mood disorders in adult patients with ADHD indicate that in adulthood affective functions may have a more pronounced impact on impairments in DM.

Overall, impairments occurring in the DM of patients with ADHD refer to deficits in the underlying mechanisms of the dopaminergic mesocorticolimbic pathway which affects reward processing. Moreover, these impairments often lead to risk-taking behaviours, especially in situations characterized by a high degree of uncertainty in DM, which also highlights the crucial role of affective functions. However, study findings vary considerably due to the heterogeneity of symptoms and experimental conditions among individuals with ADHD.

1.4 Motivation, aims and hypotheses

ADHD is considered as the most common neurodevelopmental disorder worldwide (APA 2014). Patients with ADHD suffer from various cognitive and affective deficits that can have serious consequences, influencing social relationships as well as educational and occupational achievements. However, it must also be taken into account that the symptomology is subject to development,

which is primarily driven by the ongoing neural maturation into adulthood. Furthermore, gender-specific differences are also evident in the symptoms of ADHD, which are also reflected in behaviour and must be taken into account in diagnosis and treatment. For example, while men are more frequently affected by externalizing symptoms such as impulsivity and hyperactivity, which are associated with risk behaviour in many studies, women, on the other hand, suffer primarily from impaired internalizing functions. This constant change in the clinical profile, the developing or coexistence of comorbidities, as well as gender-specific variations still complicates the diagnostic process and causes a masking effect on the existing prevalence and gender ratio. Therefore, it is essential to obtain a deeper understanding of the nature of ADHD and the underlying causes of its diverse range of deficits. A frequently occurring characteristic of patients with ADHD in adulthood is impaired DM behaviour, which can often lead to risky behaviour. The resulting consequences of such increased risk-taking behaviour not only affect the patients themselves but can also have serious effects on their environment. In light of the basic principles, theories and mechanisms of DM behaviour and the emerging behaviours in ADHD during adulthood, it can be suggested that risk behaviour arises particularly when emotionally driven decisions are required. Underlying deficits in emotional competence as well as neural dysfunctions of the mesolimbic system may be responsible for these changes. Furthermore, results from self-reports reflect intact conscious, deliberate evaluation of risk whereas feedback and future outcomes cannot be correctly assessed. In addition, altered activities of the ANS can be observed, which, in accordance with the somatic marker hypothesis, is inevitably linked to the ability to make decisions.

Therefore, the following research questions can be formulated for the current thesis:

1. Are there differences in affectively driven DM behaviour between adults with ADHD and healthy controls and are these differences related to changes in physiological activity?

2. What impact does gender have on patients with ADHD in relation to affectively driven DM behaviour and the associated bodily function?
3. Are there differences in neural activation patterns in affectively driven DM behaviour between adults with ADHD and healthy controls as well as between males and females?

To address these questions, it is crucial to employ viable methods within the paradigm designed to explore affectively driven DM behaviour. While the IGT has been a widely employed tool to examine somatic marker functioning, there are still issues that call into question its effectiveness in investigating the somatic marker hypothesis. Thus, over the years of replicating studies, concerns arose primarily about the influence of conscious awareness on DM. Study results have indicated that participants are aware at an early stage about the outcome schedule. This potentially implicates that the IGT is relying more on explicit knowledge rather than non-conscious somatic markers (Bowman, Evans, & Turnbull, 2005; Maia & McClelland, 2004). Both psychophysiological and neuroimaging measurements have shown that the validation of somatic marker functioning remains elusive by usage of the IGT (Crone et al., 2004; Lin et al., 2008). Additionally, findings within specific clinical groups failed to be replicated, suggesting unreliability in using the IGT as a consistent measure of somatic marker functioning (Dunn, Dalgleish, & Lawrence, 2006). The variability in results across different studies and clinical conditions raises questions about the task's reliability in capturing the purported underlying mechanisms of DM. In turn the BART involves a dynamic and continuous risk manipulation which simulates a better real-life and real-time situation. Furthermore, this dynamic nature makes it particularly suitable for also capturing real-time physiological responses. Regarding the analysis, the BART is also suitable for a trial-by-trial analysis due to its short sequences in the process, allowing a more detailed examination of how DM evolves over the course of the task by respecting dynamic aspects like learning effects and habituation. In order to achieve a suitable version that can be performed during a functional magnetic resonance imaging (fMRI) measurement as well to decrease the cognitive effort but increase the intuitive affectively driven behaviour, we implemented a modified version of the BART in

all study designs within the current thesis. In this modified version, risk-taking is operationalized as the latency time to stop the inflation of an automatically growing balloon. Which means, that a decision must be made between continuing-to-inflate and actively stopping-further-inflation. Thus, longer latency times are associated with increased risky DM behaviour (see Chapter 2.3. for further description on the DM task) (Benjamin & Robbins, 2007; Henn et al., 2023; Hüpen et al., 2019; Hüpen et al., 2020; Lejuez et al., 2002). Overall, there is a limited number of studies exploring the affective dimensions of DM in ADHD. However, these studies have primarily focused only on the emotional processes associated with the evaluation and anticipation of feedback, whereas objective measurements of affective processes during DM are rarely considered (Bubier & Drabick, 2008; Dekkers et al., 2021, 2016; Ibanez et al., 2012; Mäntylä et al., 2012; Pollak et al., 2019). Some studies have underscored the crucial importance of autonomic functions in connection with cognitive performance (Geissler et al., 2014; Johnstone, Watt, & Clarke, 2010; Herpertz et al., 2001; Mayer, Wyckoff, & Strehl, 2016), however, only a few recent studies have examined the role of the ANS in patients with ADHD. Although meta-analyses have successfully demonstrated significant alterations in the activity using various measurements, the impact of these functions in connection with behavioural deficits in ADHD has not yet been thoroughly investigated. In this context, a hypo-activation was observed during the performance of cognitive tasks, but findings were highly heterogeneous, showing variability in study design, medication use, and samples (Bellato et al., 2020). Nevertheless, the specific relationship between emotion, bodily functions, and behaviour remains unexplored in the context of unconscious DM in adult patients with ADHD. Therefore, examining DM behaviour in patients with ADHD, accompanied by physiological measurements as indicators of ANS functioning using an innovative behavioural task can provide further understanding of the behavioural difficulties faced by adult patients with ADHD.

Furthermore, the usage of neuroimaging techniques provides a viable method to reveal insights into neural activation patterns in anticipation of DM. Thereby, the intricate involvement of various brain areas and functions, highlighting the interconnected network that underpins DM processes in the

context of ADHD can be visualized. Several psychiatric disorders have already been investigated in this way in DM behaviour. Interestingly, all disorders tested (substance abuse, pathological gambling, schizophrenia, obsessive-compulsive disorder, depression, ADHD) are suggested to share a common pathophysiology that involves the ventromedial region of the PFC (Bechara & Martin, 2004; Best, Williams, & Coccaro, 2002; Cavedini et al., 2002; Jollant et al., 2005; Malloy-Diniz et al., 2007; Sevy et al., 2007; Whitney et al., 2004). Furthermore, neuroimaging studies using the BART confirmed that mesolimbic as well as prefrontal regions are crucial for advantageous behaviour and indicated altered neural activation pattern in a psychiatric cohort. A study on patients with schizophrenia was the first to analyse the effects of risk evaluation and behaviour in BART under uncertainty (Purcell et al., 2023). However, so far, no study has examined neural processes of the anticipation of DM on basis of unconscious affective functions in adult ADHD. The utility of the BART investigating somatic marker functioning and affective processing in context of risky DM behaviour has been proven in some studies using healthy controls, indicating also the ability to predict real-world risk behaviour (Fukunaga, Brown, & Bogg, 2012; Kóbor et al., 2015; Li et al., 2020; Tannou et al., 2021; Wang et al., 2022). The role of the vmPFC and OFC as described key regions for integrating underlying emotional processes has also been demonstrated in neuroimaging studies using BART (Fukunaga et al., 2012; Rogalsky et al., 2012; Schonberg et al., 2012; Tannou et al., 2021).

Behavioural differences between males and females with ADHD have seldom been the subject of research. However, clinical reports and investigations into the symptomology across the patients during adulthood indicate that particular affective functions vary between genders. In this context, women predominantly suffer from dysregulation of their emotions or reduced affective processing, but the connection to ANS activity, representing arousal, remains underexplored. One study showed a decreased activation in skin conductance levels, that was more pronounced in women than in men (Hermens et al., 2004). Nonetheless, the impact of gender on the intricate interaction between interoceptive perception and DM is still unclear. In tasks assessing working memory and behavioural control, it has been demonstrated that females with

ADHD respond significantly slower and more variably with an increased tendency towards errors (Stibbe et al., 2020). Similar results were observed on delay discounting of real-time rewards in children with ADHD, where specifically girls exhibited atypical behaviour that could also be linked to poorer working memory and inhibitory control in this group (Patros et al., 2018). This finding is further supported by evidence of gender-specific anomalies in fronto-subcortical functional networks in girls with ADHD, showing atypical functional connectivity between the vmPFC and subcortical regions such as the striatum and amygdala, suggesting that girls exhibited heightened delay discounting (Rosch et al., 2018). At neuronal level, studies in children with ADHD suggest gender differences particularly in subcortical structures, indicating neurobiological mechanisms that predominantly cause impulsivity and hyperactivity in boys with ADHD (Wang et al., 2018). However a direct link to DM impairments has not yet been explored.

Given the aforementioned deficits in adult patients with ADHD regarding affective functioning, risky DM behaviour altered neural activation patterns, as well as the knowledge about gender differences and the intricate relationship between autonomic physiological response and emotional appraisal, the following hypotheses can be formulated:

a) Patients with ADHD exhibit more disadvantageous DM towards risky decisions, indicated by longer response rates, compared to healthy controls.
b) Disadvantageous DM behaviour is associated with altered physiological activity of the ANS.
c) Women with ADHD are more affected by deficits in affectively driven DM, which is associated with altered physiological activity of the ANS.
d) Altered affectively driven DM in adult patients with ADHD is associated with altered neural activity, particularly regarding the neural systems of the somatic marker functioning.
e) Gender differences in affectively driven DM behaviour are evident by altered neural activation patterns

Therefore, the aim of this thesis is to investigate DM behaviour in adults with ADHD, recognizing the often overlooked yet critical role of affective functions in patient behaviour. The conducted research studies specifically focus on the underlying mechanisms of arousal and affect and their influence on subsequent DM behaviour. Special attention is given to the significant role of the ANS in the dynamics of unconscious processes. Additionally, this thesis considers gender-specific differences in emotional processing among individuals with adult ADHD. It also represents the first study examining anticipatory processes in neural activity related to DM.

Chapter 2: Material and Methods

The following subchapters provide a comprehensive overview of the methods used in the three studies, encompassing the inclusion and exclusion criteria of subjects who participated in the studies, a description of the data collection and analyses, as well as a description of methods used for physiological and neural activation measurements. Data collection took place at the Department of Psychiatry and Psychotherapy of the University Hospital in Bonn and the German Centre for Neurodegenerative Diseases (DZNE) in Bonn. Data collection and analyses were carried out within three study phases corresponding to the three studies presented in Chapter 3. The specific methodologies employed for each study and applied analyses are reported in each corresponding method subchapter within Chapter 3: Results.

2.1 Participants

Participants in the current study were recruited over two years from the outpatient clinic for adult patients with ADHD at the Department of Psychiatry and Psychotherapy, University Hospital in Bonn, and through the study applicant pool (pool of registration forms from people who had expressed their interest in participating in a future study) there. Additional recruitment methods included public advertisements on the internet and via flyers. Detailed information on the number of subjects recruited and included in the three studies, as well as reasons for the exclusion of individual subjects from further participation, is listed in **Table 1**. All participants met the inclusion criteria of being between 18 and 60 years of age and were fluent in German language. Furthermore, participants were excluded if they had a diagnosis of neurological disease, depressive disorder, borderline personality disorder, or other psychiatric disease with psychosis. Participants assigned to the patient group met the full DSM-V criteria for ADHD diagnosis (F90) (APA - American Psychiatric Association, 2013). Participants assigned to the healthy control (HC) group did not meet diagnostic criteria for

psychiatric diseases. In addition to the clinically assigned diagnosis, psychiatric symptoms, and comorbidities of all subjects were assessed using the brief diagnostic interview (Margraf & Schneider, 2009). Furthermore, the Beck Depression Inventory-II (Beck, Steer, & Brown, 1996) and the Borderline Symptom List-95 (Bohus et al., 2001) were used to specifically control for symptoms of major depressive disorder and borderline personality disorder. To gain deeper insight into the clinical profile of the patients, ADHD-specific symptoms were also evaluated using the Wender Utah Rating Scale (Retz-Junginger et al., 2002) for childhood ADHD, and the Conners Adult Rating Scale (Conners et al., 1999) for adult ADHD (see Chapter 2.2. for further descriptions). Participants with deviations from the normal range values (± 1 SD) in the questionnaires or with incomplete data were excluded from further analyses. Demographic information regarding age, gender, educational level, and medication intake was documented using a self-designed demographic questionnaire. Verbal intelligence was assessed using the “Rasch-Skalierung des Mehrfachwahl-Wortschatztests (Metzler & Schmidt, 1992) to determine the intelligence quotient. Participants in the patient group with regular ADHD-specific medication intake were asked to discontinue use for 24 hours prior to their participation in the study, which was additionally verified by oral questioning on the study day. Participants recruited for study 3 additionally underwent a medical pre-examination concerning their physical and mental suitability for MRI measurement, carried out by medical study doctors at the German Centre for Neurodegenerative Diseases (DZNE) in Bonn. The study was approved by the Ethics Committee of the Medical Faculty of the University of Bonn (122/21) and all participants gave their oral and written informed consent for participation. Participants were compensated for their time and involvement in the study, receiving an expense allowance of 10 euros per hour. The study was conducted by myself and two student assistants, ensuring that all patient data were treated with strict confidentiality and processed in a pseudonymised manner to protect participants' privacy and adhere to ethical standards. This approach involved assigning a unique identifier to each participant's data, allowing for the analysis

without revealing personal information, thereby maintaining the integrity of the data while safeguarding participant anonymity.

Table 1: Overview of the inclusion and exclusion of participants in all three studies.

Study	Recruited	Included	Excluded	Reasons of exclusion
1	n = 30 HC n = 29 ADHD	n = 28 HC n = 28 ADHD	n = 2 HC n = 1 ADHD	Missing data, acute suicidality, extreme outlier values
2	Participants of study 1 + n = 5 HC n = 1 ADHD	n = 33 HC n = 29 ADHD	-	-
3	n = 21 HC n = 21 ADHD	n = 20 HC n = 18 ADHD	n = 1 HC n = 3 ADHD	Missing data, movement distortions during MRI measurement

2.2 Questionnaires

As previously described, various questionnaires were used to inquire about clinical symptoms in more detail, primarily to examine the inclusion and exclusion criteria of the participants (see **Table 2**). Assessments about ADHD related symptoms in adulthood were conducted using the long version of **the Conners Adult ADHD Rating Scales (CAARS)** in German language, which is a comprehensive self-report questionnaire to assess ADHD related symptoms in adults aged 18 years and older (Conners et al., 1999) The CAARS consists of 66 items covering scales of inattention/memory problems, hyperactivity/motor restlessness, impulsivity/emotional instability, and self-concept problems. Responses were given by estimates about frequency of the behaviours and feelings described by the items using ratings from 0 to 3 (1 = not at all; 1 = a little/sometimes; 2 = strong/frequent; 3 = very strong/very frequent). Three additional scales assess symptoms related to ADHD in adults, based on the DSM-IV criteria established by the American Psychiatric Association (1991). These include scales for inattention symptoms, hyperactivity/impulsivity symptoms, and total ADHD symptomatology. Additionally, an ADHD index is available, which evaluates items that most effectively distinguish between adults

with ADHD and those without the condition. An inconsistency index is also included to identify arbitrary or careless responses. Normalized values, which indicate clinical abnormalities, are determined based on gender and age. The questionnaire demonstrates acceptable to very good internal consistency ranging from Cronbach's α > .70 and Cronbach's α > .85. The retest reliability was significant and very high (r = .74 to .93), indicating a high stability of the scales.

To assess retrospective childhood ADHD-related symptoms, the short version of **the Wender Utah Rating Scale (WURS-k)** was used. This questionnaire is a self-report tool on the presence and severity of ADHD symptoms that individuals may have experienced during their childhood, specifically between the ages of 8 and 10 years (Retz-Junginger et al., 2002). The questionnaire comprises 25 items that are to be rated on a scale from 0 to 4 (0 = does not apply; 1 = less pronounced; 2 = moderately pronounced; 3 = clearly pronounced; 4 = strongly pronounced). The scores of the individual items are summed up, with a score of 30 and above from the total of 21 items being considered indicative of ADHD. The remaining four items are combined to form a deceit score, indicating potential dishonesty in the responses from a score of eight and above. The retest reliability was estimated at r = .85, and Cronbach's α, as a measure of internal consistency, was found to be α = 0.91.

Comorbid depressive symptoms were assessed by the second version of **the Beck Depression Inventory (BDI-II)** in German language, which is a widely used self-report to assess the presence and severity of depressive symptoms in adolescents and adults (Beck et al., 1996). The BDI consists of 21 items each addressing a specific symptom or attitude related to depression such as sadness, pessimism, sense of failure, dissatisfaction, guilt, expectations of punishment, self-dislike, self-accusations, suicidal ideas, crying, irritability, social withdrawal, indecisiveness, body image change, work inhibition, sleep disturbance, fatigue, appetite loss, weight loss, somatic preoccupation, and loss of libido. Respondents are asked to evaluate how they have been feeling over the past two weeks, rating each item on a scale from 0 to 3, with higher scores indicating more severe depressive symptoms. The total score is obtained by summing the

scores of all items, providing an overall measure of depression severity. The BDI's scoring system categorizes depression into different levels: 0–9 indicates minimal depression; 10–18 indicates mild depression; 19–29 indicates moderate depression; 30–63 indicates severe depression. The retest reliability of the BDI was estimated at $r \geq .75$ and Cronbach's α was found to be $\alpha \geq .84$.

In order to assess symptoms regarding the Borderline Personality Disorder (BPD), **the Borderline Symptom List 95 (BSL-95)** was used, which is a self-report to assess the severity and spectrum of symptoms associated with BPD (Bohus et al., 2001). The BSL-95 consists of 95 items that cover a wide range of BPD-related symptoms, including affective instability, identity disturbance, negative relationships, self-harm, suicidal behaviour, impulsivity, chronic feelings of emptiness, and efforts to avoid abandonment. Respondents are asked to rate the frequency and intensity of these symptoms over the past week on a scale from 0 to 4 (0 = not at all; 1 = a little; 2 = quite a bit; 3 = strong; 4 = very strong). The total score is calculated by summing the ratings across all items, with higher scores indicating a more severe expression of BPD symptoms. The retest reliability of the BDI was estimated at $r = .84$ and Cronbach's α was found to be $\alpha = .97$.

In order to obtain a comprehensive overview of other psychiatric diseases, the "**Mini-Diagnostisches Interview bei psychiatrischen Störungen" (Mini-DIPS)** was used, which is a diagnostic tool to assess a wide range of psychiatric symptoms (Margraf & Schneider, 2009). Designed for use in both clinical and research settings, the Mini-DIPS facilitates a structured interview process that guides the interviewer through a series of questions tailored to diagnose major psychological disorders according to the criteria outlined in DSM. The interview covers a broad spectrum of psychiatric conditions, including anxiety disorders, mood disorders, obsessive-compulsive disorder, traumatic stress disorder, eating disorders, sleeping disorders, substance use disorders, and psychotic disorders. In each category, the guided questions about individual symptoms can be used to evaluate whether there is a conspicuousness with regard to a diagnosis.

Personal details were collected with the help of a **self-designed demographic questionnaire**. This included the following information: date of birth; age; gender; handedness; family status; school education; current occupational activity; medication intake; history of mental illness. Furthermore, verbal intelligence is assessed using version B of the **"Mehrfachwahl-Wortschatz-Intelligenztest" (MWT-B)**, which is a psychometric tool to assess vocabulary knowledge (Metzler & Schmidt, 1992). This assessment tool comprises of a series of multiple choice questions including a list of five words. Among these, only one is a real word, while the others are plausible but fictitious. Participants are asked to identify the real word in each list, with the total number of correct identifications serving as a measure of their verbal intelligence and language proficiency.

In addition to the clinical and demographic questionnaires, further self-reports were used to provide deeper insights into behavioural self-assessment (see **Table 2**). First, the **"Emotionale Kompetenz Fragebogen" (EKF)** was employed to investigate individuals' management of their own emotions and their interactions with the emotions of others (Rindermann, 2009). This questionnaire provides insights in the recognition and understanding of personal emotions as a basis for enhancing learning experiences, modifying DM behaviour, and potentially identifying perceptual distortions in various situations. The EKF questionnaire is utilized for capturing emotions across a broad spectrum and detailing them into various facets. It comprises four subscales assessing (a) recognition of one's own emotions (15 items), (b) recognition of emotions in others (17 items), (c) regulation and control of one's own feelings (13 items), and (d) emotional expressiveness (17 items). Thus, in total the questionnaire consists of 62 items, with responses measured on a five-point Likert scale ranging from "strongly disagree" (1) to "strongly agree" (5). In addition, an overall value can be calculated by standardizing and averaging the four subscales. This overall value can be described as general emotional competence. The assumed factor structure has been confirmed by Rindermann (2009), showing high reliability across the scales (average Cronbach's $\alpha = .91$) and moderate stability over a year (average $r = .69$).

Second, the German version of **the Domain-Specific Risk-Taking (DOSPERT)** questionnaire is utilized to subjectively assess and operationalize risk behaviour (Weber, Blais, & Betz, 2002). In order to capture risk behaviour in various facets and to consider factors that may have an impact on the behaviour, the DOSPERT includes 40 items across six dimensions: recreation, health, social, ethics, investment, and gambling. The dimensions are assessed using eight items each, except for the financial dimensions (gambling and investment), which use four items each. Responses are quantified using a Likert scale ranging from 1 ("no benefit at all"/"very unlikely"/"very low risk") to 5 ("very high benefit"/"very likely"/"very high risk"). Thus, in total the questionnaire consists of 40 items, in which each item asks about the likelihood of engaging in a certain risk behaviour (prob), the perception of risk (risk), and the expected utility of a specific situation (ben). The DOSPERT calculates scores for the subscales, resulting in total scores for probability, benefit, and risk perception for each participant, with a maximum possible score of 200 (40 items x 5). The German version of the DOSPERT was validated in a study with 532 participants, showing moderate reliability overall. The highest reliability was observed in the gambling dimension (Cronbach's α = .82 for prob, Cronbach's α = .85 for risk, Cronbach's α = .83 for ben), while the lowest reliability was in the social dimension (Cronbach's α = .51 for prob, Cronbach's α = .63 for risk, Cronbach's α = .56 for ben).

Thirdly, in order to assess individual differences in behavioural inhibition and activation systems describing personality dimensions related to the sensitivity to punishment and sensitivity to reward, a German version of **the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ)** was utilized (German version: Hewig, Hagemann, & Riemann, n.d.; publicly available in: Hahn, 2007). This questionnaire was developed as a tool to measure the distinct motivational systems based on Gray's biopsychological theory of personality (Gray, 1982). Therefore, the SPSRQ consists of two main scales each consisting of 24 items: Sensitivity to Punishment (SP) and Sensitivity to Reward (SR). The SP subscale measures an individual's tendency to respond to signals of punishment, non-reward, or novel stimuli that might lead to negative

outcomes, reflecting the behavioural inhibition system which regulates aversive motives. The SR subscale assesses an individual's propensity to respond to signals of reward or positive reinforcement, reflecting the behavioural activation system which regulates approach behaviours towards potentially rewarding stimuli. Thus, in total the questionnaire consists of 48 items that are assigned to either sensitivity towards punishment or sensitivity towards reward. The questions are dichotomous, with each "yes" being scored with one point and each "no" with zero points. The ratio of the total sums indicates which category is predominant. A higher ratio towards SP items indicates a higher sensitivity to cues of punishment, making an individual more likely to avoid potential threats or negative outcomes, whereas higher ratio towards SR items suggests a strong motivation to seek out rewards, leading to more approach-oriented behaviours. The questionnaire demonstrates acceptable to good internal consistency being Cronbach's $\alpha = .83$ for SP and Cronbach's $\alpha = .77$ for SR (Torrubia et al., 2001).

Table 2: Questionnaires used to collect clinical symptoms, demographic information, and self-assessment.

Clinical Questionnaires	Assessed function	Reference
Conners Adult Rating Scale (CAARS)	ADHD symptoms in adulthood	*Conners et al., 1999*
Wender Utah Rating Scale - Kurzversion version (WURS-k)	ADHD symptoms in childhood	*Retz-Junginger et al., 2002*
Beck Depression Inventory-II (BDI-II)	Depressive symptoms	*Beck, Steer, & Brown, 1996*
Borderline Symptom List-95 (BDL-95)	Symptoms of Borderline Personality Disorder	*Bohus et al., 2001*
Diagnostisches Kurzinterview bei psychischen Störungen (Mini-DIPS)*[1]	Brief interview for psychiatric symptoms	*Margraf, 1994*
Demographic questionnaires		
Self-designed demographic questionnaire	Assessment of age, gender, handedness, family status, school education, current occupational activity, medication intake, history of mental illness	
Rasch-Skalierung des Mehrfach-Wortschatz-Intelligenztest (MWT-B)*[2]	Assessment of the verbal intelligence	*Metzler, P., & Schmidt, K.-H. (1992)*
Additional questionnaires		
Emotionale Kompetenz Fragebogen (EKF)	Self-assessment of emotion recognition and regulation	*Rindermann, 2009*
Domain-specific Risk-taking Scale (DOSPERT-G – German version)	Assessment of risk estimation and related benefits	*Weber, Blais, & Betz, 2002*
The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ – unpublished German version)	Assessment of feedback sensitivity	*German version: Hewig, Hagemann, & Riemann, n.d.; publicly available in: Hahn, 2007*

All questionnaires (except *[1] and *[2]) were collected in the form of a self-assessment as a selfreport.

*[1] represents an interview conducted by the investigator.

*[2] represents a neuropsychological, objective test procedure

2.3 Decision-making task: Balloon Analogue Risk Task (BART)

The DM task employed in all three studies was a modified version of the well-established Balloon Analogue Risk Task (BART) was employed. The modified version is a computerized experimental task designed with the software Presentation (www.neurobs.com) to specifically investigate risky DM under uncertainty. Originally conceptualized by Lejuez et al., (2002), the BART has been instrumental in probing the nuances of risky DM behaviours within a controlled laboratory setting. The task is recognized for its robust validity in assessing risk propensity (Groen et al., 2013; Li et al., 2020) and its demonstrated correlation with real-world risk-taking (Humphreys & Lee, 2011; Lejuez et al., 2002). The task involves a two-choice mechanism, where participants decide between increasing a sum of money or cashing out the amount already accrued. The potential for monetary increase is contingent upon further inflation of a balloon, which also elevates the risk of its explosion, resulting in the loss of collected earnings within that trial. Unlike the original paradigm's binary choice, this modified version employs a single-action response. The balloon inflates automatically and dynamically throughout the decision phase, with the escalating risk of explosion correlated to its increasing size. Participants are thus encouraged to intuitively press a response button in order to achieve a saving/cashout of the already collected money. Notably, the inflation duration remains constant at 5000 ms across all trials. The occurrence of a balloon explosion or the immediate effect of a button press remains undisclosed to the participant in real-time. A feedback screen displayed for 2500 ms subsequently reveals the monetary outcome (gain or loss). Each trial begins with a brief display (500 ms) indicating the trial's maximum potential earnings, with color coding (grey for low and yellow for high rewards) signalling the magnitude of the reward within the current trial. Following the decision phase a fixation cross appears (250 ms), followed by the feedback display. Should the button press precede the balloon explosion, the participant is provided with positive feedback regarding the collected money. Conversely, if the button is pressed after the balloon has exploded, a graphic depicting a burst balloon is shown, alongside a notification

that no money was earned in that trial. Each participant completed a total of 60 trials of the modified version of the BART, evenly divided into 30 trials each for low and high reward conditions (see **Figure 3**). Each trial lasts 8.5 seconds, resulting in a total duration of 8.5 minutes to complete the paradigm.

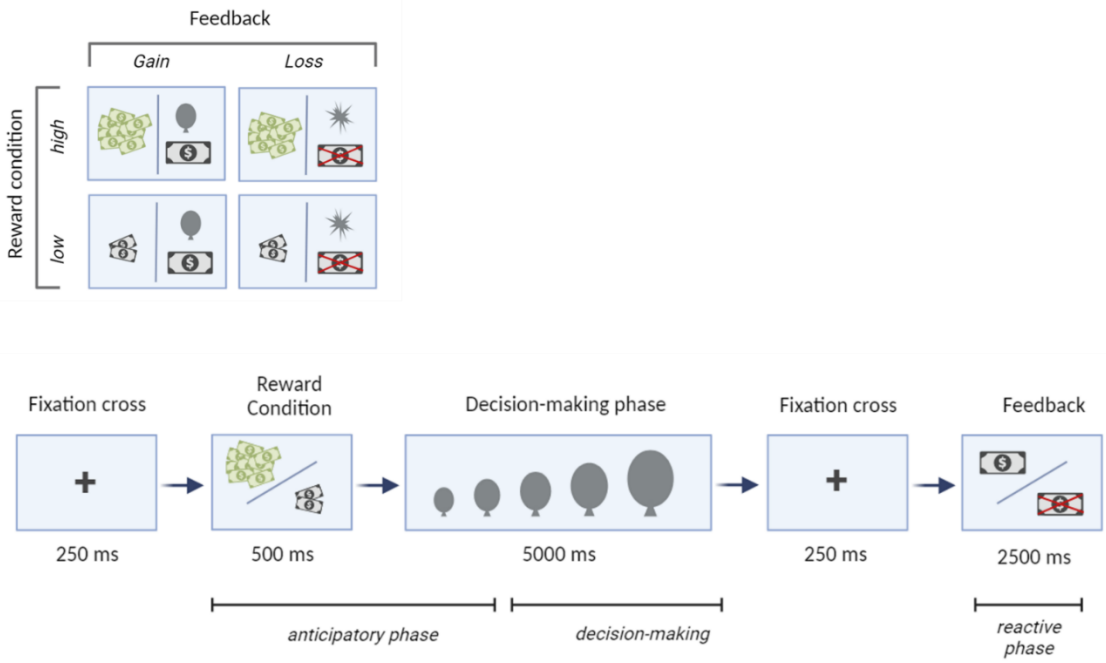

Figure 3: Overview of one trial of the modified version of the Balloon Analogue Risk Task (BART; bottom) and trial variations by reward condition and outcome (top).

2.4 Skin conductance

Skin conductance measurement is a valuable physiological technique widely utilized in the fields of psychology, neuroscience and medicine (Boucsein, 2012). It provides recordings of electrodermal activities that represent electrical processes on the skin. The skin conductance response (SCR) describes how well skin conducts electricity when a small external direct current of constant voltage is applied. Thus, skin conductance can be qualified by applying an electrical potential between two points on the skin and measuring the resulting current flow between them. A change in the electrical conductivity of the skin results from the sweat secretion from the finest eccrine sweat glands in the skin that depict a

dynamic response of the ANS and is particularly sensitive to affective and emotional processes (Andreassi, 2006; Bradley & Lang, 2007; Boucsein, 2012). Emotional arousal induces ANS activity that stimulates physiological responses such as sweating. The extent of sweat secretion by the glands thus also determines the extent of SC change. Since sweat is an electrolyte solution from a chemical point of view, an increased secretion also leads to an increase in the conductivity of the skin (Boucsein, 2012). Thus, changes of the skin conductance can be used as a reliable biomarker of physiological arousal, which is controlled by the ANS and associated with the generation and processing of emotions. Following the principle of physiological measurements, continuous recordings during the performance of the modified BART were used as an indicator of an automatic somatic response due to an emotional arousal in Studies 1 and 2 of this thesis.

2.4.1 Acquisition

For the measurements, two disposable snap (Ag-AgCl) electrodes (11 mm diameter) were attached to the palm (thenar and hypothenar) of the participant's non-dominant hand. The palmar location for skin conductance measurements has proven to be particularly effective, as it has the highest density of sweat glands in the skin next to the soles of the feet (Frewin & Downey, 1976; Saga, 2002). Before attaching the electrodes, a pea-sized amount of 0.5% saline paste in a neutral base (0.05 molar NaCl) was applied to both electrodes to increase the conductivity and thus the measurement capability. The electrodes were additionally attached to the hand using adhesive strips to prevent them from dislocating or loosening during the measurement. The resulting recordings can be analysed in terms of tonic activity, which describes the skin conductance level (SCL) over a specific time interval, or phasic activity, which describes the skin conductance responses (SCRs) to rapid, event-related changes (Dawson, Schell, & Filion, 2007; Nagai et al., 2004). Furthermore, SCRs can be categorized into specific changes, such as those related to events or stimuli, and non-specific

SCRs. These event-related physiological responses are utilized to gain deeper insights into the affective state and its interaction with autonomic processes at specific time points during the DM task. However, it must be considered that SCRs reflect only a change in intensity related to emotional arousal; they do not allow for the evaluation of whether these stimuli are positive or negative (Critchley, 2002; Boucsein, 2012) .The recordings are continuously taken during the performance of the modified BART, at a sampling rate of 5,000 Hz and with a direct current excitation of 0.5 V, using a Biopac MP150 system (Biopac Systems Inc., Goleta, CA, United States).

2.4.2 Preprocessing

With the help of the software AcqKnowledge, which serves as acquisition and analysis program of the Biopac system, measurements are captured and can be further processed in subsequent steps. The signals of the skin conductance activity are transmitted via the wireless PPG/EDA BioNomadix Transmitter to this software. Furthermore, the recordings are synchronized with the BART sequence via digital input ports sent by the Presentation® software of neurobehavioural systems. Thus, event triggers for the reward condition (high/low), feedback display (gain/loss), button press (indicating reaction time), as well as the start and endpoint of each trial, are transmitted to the recording tracks in AcqKnowledge to determine SCRs. A transition latency is set at 2 ms to separate quickly successive triggers from one another, and additional low pass filtering of 1 Hz is applied for noise reduction. Non-relevant triggers are extracted from the tracks, thus further analyses are performed on the recording tracks with the following event triggers: reward condition (high/low) as anticipatory SCR (aSCR); feedback display (gain/loss) as reactive SCR (rSCR). All tracks are descriptively examined for artefacts (e.g. due to movement or sources of interference). Tracks not responding or those with less than a third of the relevant events assigned to an SCR are excluded from further analyses. Further preprocessing is performed with the Ledalab toolbox (V.3.4.8) of Matlab, including smoothing (Gaussian method)

and a downsampling to 20 Hz. Using a continuous decomposition analysis (CDA), relevant phasic SCRs are extracted from the signal tracks (Benedek & Kaernbach, 2010). The CDA also determines the integral under the curve of each SCR (ISCR), which represents the cumulative phasic activity within the aSCRs and rSCRs and is used as a physiological value in further analyses. For peak detection a minimum amplitude criterion of 0.05 µS is used. Each SCR amplitude within a time window of 1-6 s after the appearance of the condition, as well as 1-3 s after the display of feedback, is used for further analyses.

2.5 Functional magnetic resonance imaging (fMRI)

Functional magnetic resonance imaging (fMRI) is a neuroimaging procedure based on the mechanism of magnetic resonance imaging (MRI). The basic principle of MRI concerns the magnetic property of hydrogen molecules in an organism (Plewes & Kucharczyk, 2012). Due to the natural nuclear spin of these protons a magnetization is generated. By usage of an external magnetic field and high-frequency pulses (HF-impulses) in the radio frequency range, the magnetization of protons can be modified. These changes of the magnetization can be recorded and are used to generate structural imaging of tissues. Therefore, particularly the relaxation back to the initial state after deflection of the magnetization is utilized (Van Geuns et al., 1999). The different tissue types vary in their relaxation time and thus enable a structural differentiation which become visible on the images in different shades of grey. The relaxation time is described by the duration until the longitudinal magnetization has built up after excitation by the HF pulse (T1) and by the duration of reduction of the transverse magnetization (T2). To highlight a specific tissue type, the HF-pulse sequence and usage of gradient coils is chosen to amplify the signal recording. Thus, important characteristics of MRI sequences are the duration between HF-pulse and measurement of signal (echo time = TE) and the duration between the successive HF-pulses (repetition time = TR) (Schenck, 1996). In order to map functional changes due to neural activity, the blood flow and oxygen saturation becomes a major factor during the recording and represent the Blood-Oxygen-

Level-Dependent (BOLD) – contrast (Ogawa et al., 1990). The BOLD-contrast is thus based on metabolic processes that are initiated by increased brain activity and the resulting change in blood flow. During the generation of a neuronal action potential, increased levels of energy and oxygen are required for cellular processing. In addition, due to glycolysis, the recycling of the released neurotransmitter produces by-products that cause a dilation of the surrounding capillary vessels and induce an increase in cerebral blood flow. However, the decisive measure of this contrast is mainly based on the ratio of “new” oxygenated blood and “old” deoxygenated blood that have different magnetic properties. In blood, oxygen is bound to the iron complex of haemoglobin and exhibits a diamagnetic state, whereas haemoglobin is paramagnetic in its deoxygenated state. Diamagnetic and paramagnetic states do have different impacts on inhomogeneities of the magnetic field resulting in different signal intensities (Pauling & Coryell, 1936). This distinct resolution based on the magnetic property of the blood is described as T2*-weighted imaging that indirectly reflects neuronal activity (Kim & Bandettini, 2006).

2.5.1 Acquisition

Based on the principles of fMRI, the measurements of neural activity during the performance on the modified BART represent changes in the blood flow due to an increase of metabolic processing. Emerging changes can then be evaluated more precisely on a statistical level related to the performance and at group level. The measurements for study 3 of the current thesis are conducted using a Siemens 3T scanner (Magnetom Skyra, Siemens, Erlangen, Germany) equipped with a 32-channel head array for whole-brain high-resolution signal reception. All MRI measurements are performed at the Institute for German Centre for Neurodegenerative Diseases (DZNE) in Bonn. Functional images, which captured the BOLD signal, are acquired using a rapid 3-dimensional echo planar imaging sequence that combined CAIPIRINHA acceleration and water-selective fat suppression (Stirnberg et al., 2017) with the following parameters: repetition

time 1500 ms, echo time 30 ms, flip angle 16°, matrix size 120 x 120 x 78, voxel size 1.8 x 1.8 x 1.8 mm3, oblique-axial slice orientation approximately along the anterior-posterior commissure, anterior-posterior phase encoding direction, slice parallel imaging acceleration factor 6, CAIPI shift 2. Each participant completes 60 trials of the modified BART, resulting in a total duration of 12 minutes. After the functional scans, individual high-resolution T1-weighted anatomical images are obtained using a magnetization-prepared rapid gradient echo (ME-MP-RAGE) sequence that combined CAIPIRINHA acceleration and elliptical sampling (Brenner et al., 2014) with the following parameters: repetition time 2560 ms, inversion time 1100 ms, flip angle 7°, matrix size 320 x 320 x 224, voxel size 0.8 x 0.8 x 0.8 mm3, sagittal slice orientation, slice parallel imaging acceleration factor 2, CAIPI shift 1, Turbofactor 180, acquisition time 6 min 52 s. Using the software Presentation, the paradigm is projected onto a display screen at the back of the scanner and participants view the task through a mirror that was fixated on top of the coil. Responses within the task are made by pressing a button on a joy-stick using the thumb of the right hand.

2.5.2 Preprocessing

In order to reduce spatial and temporal artefacts that may occur during the measurement with MRI, the image data are preprocessed by a series of transformation steps that consider the possible effects of variability (see **Figure 4**). The software Statistical Parametric Mapping software v7219 (SPM12, Functional Imaging Laboratory, London, UK) was used for preprocessing and the subsequent analyses of the data. Initially, the data is assessed regarding motion artefacts. Therefore, motion artefacts are corrected by realignment of the SPM preprocessing. To do so, all functional scans are aligned to a reference scan to ensure consistent brain positioning across the entire series. This process involves estimating and correcting for small movements and rotations of the head that occur during the scanning session, improving the accuracy of subsequent analyses. Strong motion artefacts are also identified by the toolbox “Motion

Fingerprint", which detects motion variability by values of total displacement (TD) and mean slice-to-slice parameter (STS) of each participant (Wilke, 2012). Subjects with displacement parameters greater than 3 mm are excluded from further analyses. Following, differences in the acquisition time between slices are corrected by slice-time correction that creates a continuous signal of the volumes via phase-shifting of the signal waves. This correction accounts for the fact that different slices of the brain are acquired at slightly different times within each scanning sequence. The motion-corrected images are then co-registered to merge the functional images with the structural images for each participant, thus aligning orientation and space of the data. To enable comparability between subjects, the co-registered images are normalized to the standard brain template, the Montreal Neurological Institute (MNI)-152 template (Maintz & Viergever, 1998). Moreover, this step enables comparability with other research results, as it allows comparison of analysis results with the MNI coordinates of other studies. To do so, the structural images are first segmented, which classifies single voxels to one of six specific tissue types; grey matter, white matter, cerebrospinal fluid (CSF), soft tissue and skull (Ashburner & Friston, 1999). This tissue classification thus assists in Normalization to enable an improved alignment of individual images to a standardized template. Finally, the images are smoothed with a Gaussian kernel (5-mm full width at half-maximum) and filtered with a high-pass filter with the cut-off set at 128s to remove low-frequency fluctuations.

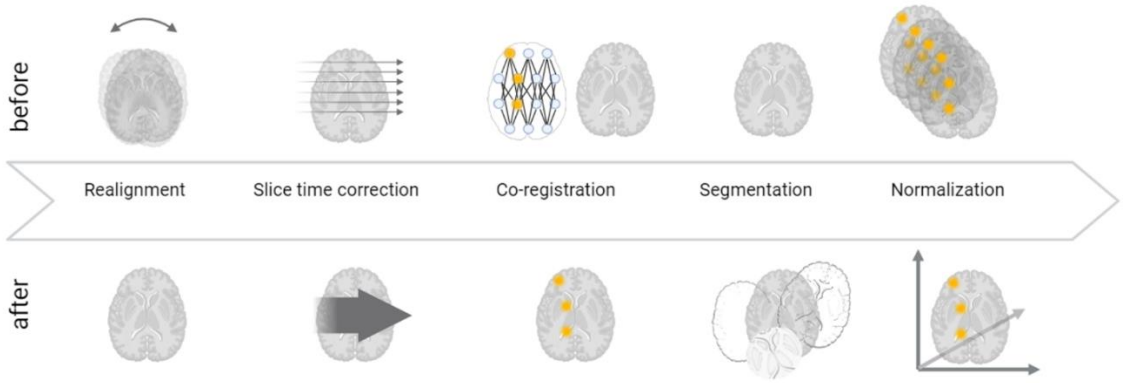

Figure 4: Flowchart showing the preprocessing pipeline by illustrating the input (top) and output (bottom) of each preprocessing step.

2.6 Statistical analyses

The successful execution of a research study depends not only on the careful design of experiments and data collection, but also on the sophisticated application of robust statistical analysis. In this section, the methodological foundations that are presented enable the transformation of raw data into meaningful insights. The statistical analyses used in the studies serve as the central component and provide a rigorous framework for examining, interpreting and deriving conclusive results. The following chapters provide insights into the basis of the different approaches used for analysing the collected data. Therefore, three types of statistical methods (Analysis of Variance; general linear model; linear mixed-effects model) were assigned to the basis of linear regression modelling. The methods presented refer to the various approaches to data to be analysed, which can be traced back to the commonality of linear models. The methods differ in terms of which assumptions are met and which variables must be taken into account for analysis. The analysis of variance is primarily used to analyse group differences in behavioural or self-report values. General linear models, on the other hand, are used to identify differences in neural activation pattern using a mass univariate approach. Finally, linear mixed-effects models

can be used to account for possible random effects that may arise from repeated measurements.

2.6.1 Linear regression models

Linear models are a statistical method used to explore the relationship between a target variable and observed influencing variables. The target variable (Y) is also known as the dependent variable or response value. The influencing variables, which are known to affect *Y*, are denoted as $x_1,...,x_n$ or independent variables. In the data collected from a conducted study, *Y* is measured or observed n- times, corresponding to the sample size. In linear models, these target variables ($y_1,...,y_n$) must be collected independently of each other, with each observation unit Y_i being assigned values $x_{i1},...,x_{ik}$. This relationship between the dependent variable Y_i and the independent variable(s) $x_{i1},...,x_{ik}$ is modelled as a linear equation, and the statistical goal is to find the best-fitting line (regression line) that describes the data with least variance to the measured data. Mathematically, the linear model following the linear regression can be modelled as follows:

$$Y_i = \beta_0 + \beta_1 x_i + \varepsilon_i$$

As described, Y_i represents the dependent variable and x_i the independent variable (predictor value). Additionally, β_0 is the y-intercept, which is the value of Y when x = 0. Next β_1 describes the slope that represents the change in Y for a one-unit change in X. Together, β_0 and β_1 are the regression coefficients that are objective to estimate in a manner that minimize the sum of squared differences between the observed and predicted Y values. Lastly, ε is the error term accounting for unobserved factors, affecting Y that influence the dependent variable but are not explicitly included in the model. This value, also known as the residual, takes into account the error in the estimation and describes the distance between the predicted value (in accordance with the regression line) and the true measured value. In a well-fitted linear regression model, the error

term should ideally exhibit certain properties, such as having a mean of zero and being homoscedastic (constant variance). Analysing the residuals (the differences between observed and predicted values) can provide insights into the appropriateness of the model and whether the assumptions underlying linear regression are met (Su, Yan, & Tsai, 2012).

2.6.1.1 Analysis of Variance

A specialized method of the linear regression model to analyse group mean differences between a dependent variable (Y) and one or more independent variables (x) is the Analysis of Variance (ANOVA). Therefore, the ANOVA focuses on identifying differences between the respective means of the independent variables by comparing means across different groups or categories of a categorical independent variable. Therefore, it is a multivariate analytical method that tests whether the means of multiple independent groups differ significantly. The principle of this procedure is based on the t-test, which, however, examines only two means in direct comparison. In contrast, ANOVA involves multiple variables and considers the issue of type-I errors while multiple testing. Variance analyses are frequently used in market research or in medical and psychological research. Based on this, it can be assessed, for example, whether an existing diagnosis has an impact on a specific measurement parameter. ANOVA is employed when data has been collected on a categorical independent variable and a quantitative dependent variable. Mathematically, ANOVA follows the principle of linear regression:

$$Y_{ij} = \mu + \alpha_i + \varepsilon_{ij}$$

Y_{ij} represents the individual score of a person (j) in group (i). The one-way ANOVA model is driven by three factors. First, μ describes the effect of constant factors (graphical intercept) - these influences are the same for every individual and can also be expressed as the population mean; an effect that everyone shares. Second, α_i is the effect of the independent variable, which can also be described as the group factor or treatment, with 'i' indicating the specific

treatment. Third, ε_{ij} is the effect of remaining or residual factors, which can also be described as individual differences or often seen as error. This effect accounts for a certain variance within one group that is dependent on an additional unspecified individual factor. Overall, the question sought to be answered by the ANOVA is where a certain variation in Y_{ij} comes from. The resulting null hypothesis can be modulated as follows:

$$H_0: \mu_1 = \mu_2 = \ldots = \mu_{i.}$$

It describes in case the null hypothesis (H_0) of ANOVA is true, there is no difference between group means (each μ representing one group), indicating that the treatment (α) does not influence Y_{ij}. On the other hand, the alternative hypothesis (H_a) states that there is a significant difference between the independent variables (H_a: not all μ_i are equal). The alternative hypothesis is accepted as soon as only two of the tested groups differ and thus the null hypothesis can be rejected. To ensure the validity of statistical results, certain assumptions must be met. For this purpose, the dependent variable (Y) must first be defined as a continuous (interval or ratio) level of measurement and the independent variables as categorical (nominal or ordinal) variables. The relationship between the dependent variable and the independent variables should be linear and can be tested through graphical representation using a scatterplot (Eid, Gollwitzert, & Schmitt, 2013). Additionally, the observations within each group and between groups should be independent of each other. Furthermore, the ANOVA assumes that the populations from which the samples are drawn follow a normal distribution. Normality can be statistically tested by the Shapiro-Wilk Test, Anderson-Darling Test or Kolmogorov-Smirnov Test. The null hypothesis of these tests is that the data follows a normal distribution. If the p-value is greater than the chosen significance level (e.g., 0.05), rejecting the null hypothesis failed, suggesting normality. However, the ANOVA is robust against violation of the assumption of normality. With a sufficiently large sample size (usually considered to be 30 or more), the Central Limit Theorem suggests that the sampling distribution of the sample mean will be approximately normal, even if the underlying population distribution is not (Cuesta & Muñiz, 1999). If normal

distribution is violated and the sample size is not large enough, a non-parametric test (e.g. Mann-Whitney-U-Test) can also be used when testing two independent samples with at least ordinal scaled characteristics. Finally, it must be assumed that all samples have been drawn from populations with the same dispersion. This assumption, also known as homoscedasticity, posits that the variances of the populations being compared are approximately equal. Violations of homogeneity of variance can affect the accuracy of ANOVA results. The Levene's test is commonly employed to assess homogeneity of variance. It tests the null hypothesis that variances of the population are equal, meaning that if the test is significant, the null hypothesis must be rejected and the variances are demonstrated as unequal (Eid, Gollwitzert, & Schmitt, 2013). The statistical model of ANOVA classically refers to one independent variable that is tested (one-way ANOVA). However, this model can also be extended and allows two (two-way ANOVA) or more (N-way ANOVA) independent variables to be tested. It furthermore allows to explore the interaction between the two independent variables. Interactions suggest that distinctions are not consistent across all categories of the independent variables. Furthermore, multivariate ANOVA (MANOVA) can also be used to include multivariate dependent variables in the analysis. A multivariate normal distribution can also be assumed for a given univariate normal distribution (Finch, 2005; Razali & Wah, 2011). It also assumes the independence of the observations found within each group and that the variances of the dependent variables must be equal. Data collected in the form of questionnaires or behavioural parameters from Studies 1-3 are processed this way using SPSS Statistics 22 (IBM, Armonk, NY, USA). Further description of the exact use of the statistical model can be found in the subchapter “Methods” of each study (see Chapter 3).

2.6.1.2 General linear model

An alternative statistical method grounded in linear regression to analyse group mean differences is the general linear model (GLM), presenting an expanded

representation of the depicted relationships. In principle, the assumptions outlined in Chapter 2.6.1.1 still apply when conducting a GLM, but it offers enhanced robustness, particularly in the face of deviations from normality, linearity, and homoscedasticity.

GLM is a common approach when analysing fMRI datasets and formulates the time series as a linear combination of various signal components. In this context, it is examined whether brain activity in each voxel shown by the hemodynamic responses is (linearly) related to the different experimental conditions of the paradigm used. Thus, the data are treated by a model function with a known shape but unknown amplitude. The GLM allows to use one or more independent variables (in the context of fMRI analyses they are also described as regressors), to fit an expected model to the measured variable/dependent variable. Mathematically, the GLM applied for data of neural activation also follows the linear regression model, taking into account possible multiple regressors:

$$Y = \beta_0 + \beta_1 X_{i1} + \beta_2 X_{i2} + \ldots + \beta_n X_{in} + \varepsilon_i$$

As shown in Chapter 2.6.1.1., β_0 is the constant variable or intercept capturing the mean level of fMRI signal across time. Following, $\beta_{1...n}$ representing the beta weights that represent the estimated amplitude of the neural response associated with a specific condition. Positive beta weights indicate an increase in neural activity associated with the experimental condition, while negative beta weights suggest a decrease in neural activity. Thus, the magnitude of a beta weight reflects the strength of the relationship and is multiplied by the predictor variable (X), which is the design matrix including the task regressors that represent the various conditions of interest in the paradigm used. Errors occurring by signal noises are respected by the error term ε. Alternatively, β_1, ..., βn represent the beta weights assigned to the predictor variables (X) in the regression equation which can be summarized in a matrix. This results in a concise form similar to linear regression, where *n* is the number of data points acquired for each time interval *i*.

$$Y_i = \beta X_i + \varepsilon_i = \begin{pmatrix} Y1 \\ Y2 \\ \vdots \\ Yn \end{pmatrix} = \begin{pmatrix} \beta 1 \\ \beta 2 \\ \vdots \\ \beta n \end{pmatrix} * \begin{pmatrix} X11 & \cdots & X1p \\ X21 & \cdots & X2p \\ \vdots & \ldots & \vdots \\ Xnp & \ldots & Xnp \end{pmatrix} + \begin{pmatrix} \varepsilon 1 \\ \varepsilon 2 \\ \vdots \\ \varepsilon n \end{pmatrix}$$

Consequently, the equation represents Y as the acquired hemodynamic response signal from a single voxel as a function of time and can be expressed by the design matrix (the sum of one or more experimental variables x) multiplied by a weighting factor β, while accounting for signal noise through a random error term ε. As each vector within the design matrix X represents one regressor that is thought to have an impact on the neural activation corresponds, the number of regressors included depends on the number of conditions of interest provided by the task. In order to examine the neural activation pattern in the whole brain the GLM is implemented for each voxel of the fMRI dataset and summarized in a statistical map that encompasses all voxels and their corresponding test statistics (see **Figure 5**).

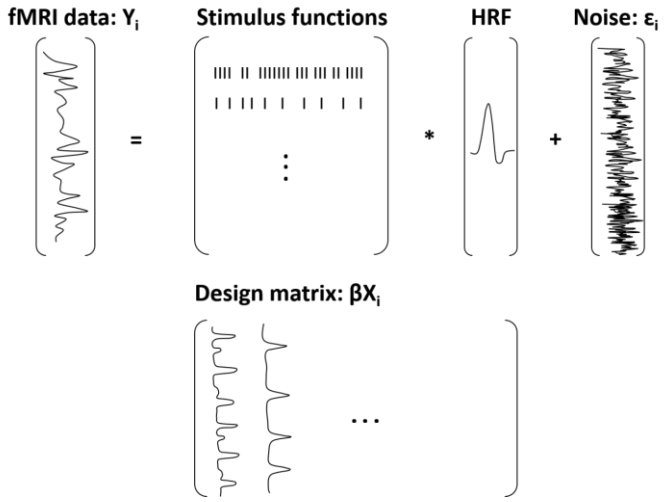

Figure 5: Simplified representation of the composition of the GLM with fMRI data.

However, this procedure results in an immense number of multiple comparisons with an increased probability for a type-1 error (false positives-(Genovese, Lazar, & Nichols, 2002). There are different approaches controlling this false positive rate depending on whether it controls family-wise error rate (FWER) or false discovery rate (FDR) (Lindquist & Mejia, 2015). The FWER correction is commonly based on the approach of the random field theory (Worsley et al., 2004), which controls the probability of making one or more false discoveries in a set of tests or comparisons, resulting in a more conservative approach (Hayasaka & Nichols, 2004). In turn, the FDR, as the more liberal approach is the expected value ratio of errors we have made, thus controlling the number of false positive voxels among the subset of voxels labelled as significant (Genovese et al., 2002). The FDR approach that is most commonly used in fMRI analysis is the Benjamini-Hochburg procedure (Benjamini et al., 2001). Both approaches assumes that all tests (for each voxel) are independent. However, in fMRI data a certain voxel is mostly similar to its neighbour voxel, resulting in similar response patterns of neighbouring voxels. This characteristic can also be extended to the factor of time series of each voxel. Another, approach that particularly considers the dependency of neighbouring voxels in the dataset is the cluster correction procedure (Woo, Krishnan, & Wager, 2014). Thereby, adjacent activated voxels are grouped into clusters and correction is performed for the number of resulting clusters that are tested.

For whole data analysis, the GLM is conducted as two-level hierarchical analysis, providing estimations individually (within-subject) in the 1st level analysis, and estimation across subjects (between-group) in the 2nd level analysis. Further description of the exact use of the statistical model can be found in the subchapter “Methods” of each study (see Chapter 3).

2.6.1.3 Linear mixed effects model

Another powerful tool in statistical analysis is the linear mixed-effects model. This statistical analysis is also based on the linear regression model and exemplified

by ANOVA (see Chapter 2.6.1.1.), can be extended through the application of linear mixed-effects models (Harrington & Reubold, 2018). This approach is particularly valuable for datasets that contain observations with a degree of dependency, where the observed correlation may arise from a clustering within the observations. This is often the case when data include repeated measurements for the units of observations, or when units of observation are otherwise grouped together. In contrast to linear models, which model Y as a function of the independent variable α and are suitable for data from a single homogeneous group without underlying structure, observations often belong to smaller subgroups nested within a larger population. Consequently, the assumption of independence is violated, and moreover some of the variation might be explained by the subgroup to which an observation belongs. This kind of data structure, including subgroups, introduces the idea of fixed versus random effects. Fixed effects (or general effects) usually apply to all observations in the dataset and represent the effects of primary interest. Random effects (or specific effects) apply to a particular group, creating subgroups in the dataset. These effects can be challenging to define and determine and might change in accordance with the research question. However, they provide a way to control the non-independence that arises from a nested data structure and to account for possible differences between the groups of the factor. Thus, an analysis using a mixed model may not meet the assumption of independence, as the random effects may be able to explain a certain dispersion and variance within the dataset. Both random intercepts and random slopes are components that account for such individual variation. A random intercept captures variability in the baseline of the dependent variable across different subjects or groups, while a random slope accounts for variability in the relationship between the independent variable(s) and the dependent variable. Mathematically, linear mixed-effects models can be expressed as follows:

$$Y_{ij} = \mu + \alpha_i + cz + \varepsilon_{ij}$$

This function also describes the constant variable as the intercept (μ), the independent variable (α), and the error (ε). It now also includes the random effect

(cz), which takes into account possible clusters within the distribution. The assumption of a continuous dependent variable and one or more categorical independent variables, as well as normality and linearity, still applies to linear mixed-effects models (Baayen, Davidson, & Bates, 2008). To achieve a reliable and adequate convergence of the model, a minimum number of 60 observations is expected. However, this minimum number also depends on the number of factors used and increases with their number (Harrington & Reubold, 2018). Nevertheless, it can be taken into account that the usage of mixed models is shown to increase the power in comparison to e.g. a repeated measures ANOVA (Aarts et al., 2015). This can be achieved by collecting multiple measures of the same individual. Therefore, the analysis with linear mixed-effects model is conducted as trial-by-trial. In contrast to a standardized analysis method for calculating group differences in performance of various repeated trials, such as an ANOVA with repeated measures, the mixed model includes all individual values in the calculation (instead of averaging over the repeated measures). At the same time, it takes into account the repeated measures and the strong variability of the dependent variables and effects over time (Harrington & Reubold, 2018). A recommended approach for implementing linear mixed models on a trial-by-trial basis, incorporating random intercepts and random slopes, involves utilizing the RStudio software (https://www.rstudio.com/) along with the lme4 package (Bates et al., 2015). In this framework, the trial number can be incorporated as a repeated measurement, treated as a random factor. Further description of the exact use of the statistical model can be found in the subchapter “Methods” of each study (see Chapter 3).

2.6.2 Power analysis

In the conceptualization of a scientific study, conducting a power analysis to determine the required sample size is an essential step. Based on the research design and the chosen statistical method, it is possible to determine how many subjects need to be included in order to achieve robust results. For the

determination of the minimum sample size required for the studies, we utilized G*Power (version 3.1.9.5; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany; http://www.gpower.hhu.de/), a tool enabling the use of statistical power analyses according to different research designs. Therefore, the choice of effect sizes, reflecting the magnitude of an empirical effect, was based on a comprehensive review of previous literature in the relevant research field, ensuring that the sample size calculation is based on empirical evidence.

The comprehensive literature review considering studies using the BART as DM paradigm, revealed small-to-medium effect sizes with Cohen's d reaching up to 0.46 (Dekkers et al., 2016). The variation in effect sizes underscores the complexity of measuring risky DM and the influence of study design on observed effects. The modified version of the BART used in the studies of the current thesis represent a more tailored approach, incorporating two within-subject factors and employs a repeated measures design, where each participant engages in 60 trials. This design is comparable to the methodological framework of Bornovalova et al. (2009) reporting a moderate effect of Cohen's f = .19. Thus, a priori power analysis for repeated measures ANOVA with two groups and two within-subjects factor, with an alpha of $\alpha = 0.05$, indicate that a total of 58 participants would suffice for a robust examination of our hypotheses.

2.7 Study design

In order to address the research questions presented in Chapter 1.4., the PhD project was structured into three distinct phases, each phase was dedicated examining a specific research question. The study design provided a multilayered approach of a comprehensive understanding of the impact of affective functions on DM in adult ADHD. The study design thus aimed to measure both the objective and visible aspects of DM behaviour (displayed behaviour and self-reports), as well as the underlying processes involved in the body (physiological activity) and the brain (neuronal activity) (see **Figure 6**).

The primary goal of the first study phase was to explore DM behaviours in patients with ADHD compared to HC, as outlined in the first research question. This objective was aligned with the first research question. Participants' performance on the modified BART was assessed to investigate DM behaviour. In addition to performance-based assessments, participants' subjective evaluations of their behaviours were collected using questionnaires. These assessments provided insights into behavioural awareness and facilitated comparisons with underlying functions and mechanisms. The evaluation was further extended by monitoring physiological processes; SCR were continuously recorded during BART performance. These recordings highlighted changes indicative of internal bodily reactions necessary for initiating behaviours. Moreover, variations in skin conductance were observed, reflecting sympathetic nervous system responses, denoting emotional states. Analysing the interplay between objective and subjective aspects of DM behaviour and physiological processes intended to reveal the impact of affective functions and undeliberate DM behaviours.

The second study phase focused on the second research question. Building upon the measurements from the first phase, a specialized focus on gender was introduced. This approach aimed to gain a deeper understanding of the variability in results, which could potentially explain certain observed effects.

The third study phase addressed the third research question by utilizing fMRI to investigate the neural mechanisms and circuits underlying the observed behaviours. This phase built upon the insights gained from the previous phases, exploring differences in neural responses during DM anticipation. Differences in neural activation patterns between patients with ADHD and HC, including gender-specific variations, were examined. By analysing these patterns with respect to the somatic marker hypothesis, a deeper understanding of the interplay between various neural systems involved in making advantageous decisions was gained.

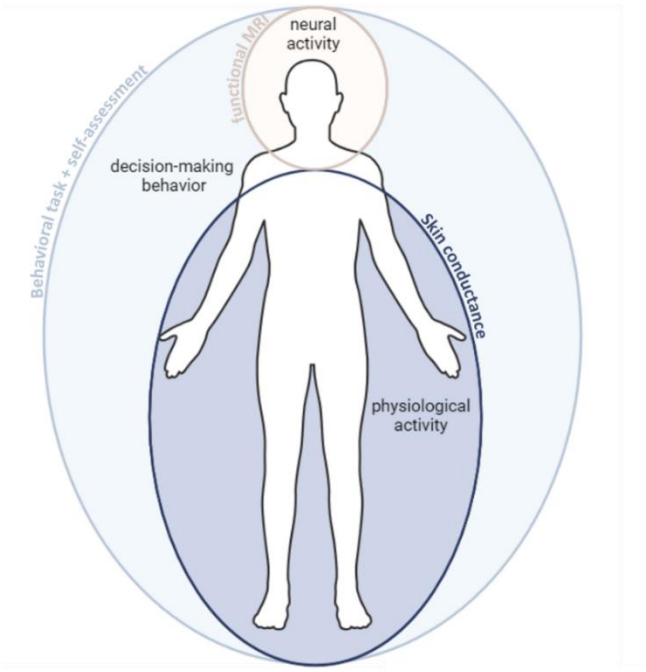

Figure 6: Illustration of measurements drawn following the research design.

Chapter 3: Results

This chapter is structured based on the three studies, which correspond to the three research questions presented in Chapter 1.4. (see **Table 3**). Each subchapter provides a summarized version of its respective manuscript, which has been either submitted or published in a scientific journal. At the beginning, all paragraphs derived directly from the author-accepted version of the original manuscript are listed, along with all co-authors involved and their contributions to the study.

Table 3: Overview of the three studies.

Study	Author	Key points
Altered interaction of physiological activity and behaviour affects risky decision-making in ADHD.	Eva Halbe[1] Fabian Kolf[1] Alina Sophie Heger[1] Philippa Hüpen[2,3] Moritz Bergmann[1] Behrem Aslan[1] Ben J. Harrison[4] Christopher G. Davey[4] Alexandra Philipsen[1] Silke Lux[1]	• Altered changes in physiological activity during a risky decision-making task • Indication of an aberrant relationship between bodily response and risky behaviour in adults with ADHD • Higher emotional arousal in ADHD participants before decision-making and after feedback display • Risky behaviour was greater in HC than in individuals with ADHD • Positive correlation between anticipatory skin conductance responses and reaction time in HC, whereas this correlation was negative in ADHD
Gender differences in physiological correlates of affectively driven decision-making behaviour in adult ADHD	Eva Halbe[1] Alina Sophie Heger[1] Fabian Kolf[1] Philippa Hüpen[2,3] Moritz Bergmann[1] Ben J. Harrison[4] Christopher G. Davey[4] Silke Lux[1] Alexandra Philipsen[1]	• Altered interaction between physiological activity and risky behaviour in women with ADHD • Female patients with ADHD showed a significantly greater risk engagement in the BART compared to male patients • No gender differences in skin conductance responses in the group of ADHD, whereas male HCs exhibit significantly greater physiological responses compared to female HCs • Reduced sensitivity towards their own bodily responses in women with ADHD
Neural correlates and gender-specific effects of affectively driven processes underlying	Eva Halbe[1] Alec Jamieson[4] Moritz Bergmann[1]	• Altered neural activity in adult patients with ADHD with gender-specific differences during the anticipation of a risky decision

decision-making in adult ADHD	Aylin Mehren[1,5] Ben J. Harrison[4] Christopher G. Davey[4] Tony Stöcker[6] Alexandra Philipsen[1] Silke Lux[1]	• Patients with ADHD exhibited reduced activation in the right precuneus and the right superior frontal gyrus compared to healthy controls • Gender-specific effects were exclusively observed within the ADHD group • Increased neural activity in females compared to males in areas including the dorsolateral prefrontal cortex, left insula, right caudate, right cuneus, and precuneus

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[2] Department of Psychiatry, Psychotherapy and Psychosomatics, Faculty of Medicine, RWTH Aachen University, Aachen, Germany
[3] JARA - Translational Brain Medicine, Aachen, Germany
[4] Department of Psychiatry, University of Melbourne, Melbourne, VIC, Australia
[5] Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behavior, Radbound University Nijmegen Medical Centre, Nijmegen, The Netherlands
6 **German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany**

3.1 Study 1: Altered interaction of physiological activity and behaviour affects risky decision-making in ADHD

This chapter encompasses a condensed introduction, the main motivation, and methodological approaches. The paragraphs describing the study design, analyses, results, and discussions are derived directly from the author-accepted version of the original manuscript, which has been published in Frontiers in Human Neuroscience (see **Appendix A**).

Halbe E, Kolf F, Heger AS, Hüpen P, Bergmann M, Aslan B, Harrison BJ, Davey CG, Philipsen A and Lux S (2023) Altered interaction of physiological activity and behavior affects risky decision-making in ADHD. Front. Hum. Neurosci. 17:1147329. doi: 10.3389/fnhum.2023.1147329.

The first study addresses the research question: "Are there differences in affectively driven DM behaviour between adults with ADHD and healthy controls and are these differences related to changes in physiological activity?" In the context of the rarely considered affective processes in relation to deficits in risk-taking behaviour, the modified version of the BART was intended to assess behaviour based precisely on such functions. By continuously recording of skin conductance, we gained insight into the underlying affective processes, as changes in physiology are seen as indicators of changes in arousal. Overall, the

following study showed that adult patients with ADHD exhibit altered changes in their physiological activity during a risky DM task. Additionally, it can be assumed that alterations in behaviour are driven by an aberrant relationship between bodily response and subsequent behaviour. The study was carried out in collaboration with the following co-authors: Eva Halbe, Fabian Kolf, Alina Sophie Heger, Philippa Hüpen, Moritz Bergmann, Behrem Aslan, Ben J. Harrison, Christopher G. Davey, Alexandra Philipsen, Silke Lux.

Eva Halbe was responsible for the majority of the work in this study and conceive the study and its design with the support of Silke Lux and Philippa Hüpen. Data acquisition and analysis were performed by Eva Halbe with help of Fabian Kolf and Alina Sophie Heger. Moritz Bergmann, Ben Harrison, Christopher Davey, Silke Lux and Alexandra Philipsen then supported Eva Halbe in interpreting the results. Behrem Aslan was responsible for the recruitment and initial screening of patients for this study. Finally, Eva Halbe wrote the first draft of the manuscript.

3.1.1 Introduction

ADHD, recognized as one of the most common psychiatric disorders, primarily affects cognitive functions related to attention, impulsivity, and a tendency towards hyperactive behaviour (Polanczyk et al., 2007, 2014; Must et al., 2013). Consequently, individuals with ADHD experience impairments in self-regulatory processes, impacting their ability to plan work and complete daily activities, as well as in psychosocial interactions. In adults with ADHD, these impairments often extend to DM behaviour, frequently resulting in risky behaviours (Flory et al., 2006; Thompson et al., 2007; Gibbins et al., 2010; Francx et al., 2015; Faregh & Derevensky, 2011).

However, investigating risky DM behaviour in adult patients with ADHD in experimental settings presents numerous challenges, including inconsistent results and the difficulty of capturing everyday behavioural deficits (Mowinckel et al., 2015; Dekkers et al., 2016). These challenges are further compounded by the

unclear role of neuropsychological functions in risk-taking and the varied methodologies employed across studies. Additionally, most DM paradigms predominantly require high cognitive-analytical functions. However, affective dysfunctions, which are prevalent in adults with ADHD, receive less attention, highlighting the need for further research into the impact of affective functions on DM (Brand et al., 2007; Figner et al., 2009; Mäntylä et al., 2012; Crowley et al., 2010). Research indicates that while cognitive deficits in patients may decrease into adulthood, particularly with development, impairments in emotional competence increase, exacerbating socio-emotional challenges and leading to a higher predisposition towards affective comorbidities (Halperin & Schulz, 2006; Bresner et al., 2009; Shushakova, Ohrmann, & Pedersen, 2018; Materna et al., 2019; Beheshti, Chavanon, & Christiansen, 2020).

The Dual Pathway Model, as described by Sonuga-Barke in 2002, identifies two distinct signalling pathways involved in DM: the cognitive-analytic functions, also referred to as 'cold functions,' and the intuitive-affective functions, known as 'hot functions'. In this regard, particularly quick and intuitive decisions often rely on “hot functions”, necessitate a high level of affective input, and may result in disadvantageous decisions or a heightened propensity for risk-taking (Sonuga-Barke, 2002; Mäntylä et al., 2012; Shoham et al., 2016). Such behaviours are coupled to functions of the ANS, causing changes in the physiological activity in order to modulate the behaviour (Damasio, 1996; Figner & Murphy, 2011; Christopoulos, Uy, & Yap, 2019; Bellato et al., 2020). By usage of measurements such as SCR, emotional arousal related to DM behaviour can be captured. Therefore, the current study aims to detect reactive changes in the SCR (rSCR) and anticipatory changes in the SCR (aSCR) to explore the effects of affective functions the risky DM behaviour.

Previous studies have identified inconsistent ANS patterns in individuals with ADHD (Bellato et al., 2020). However, no study so far has investigated the linkage between physiological response and risky DM in adults with ADHD. Given the presumption of dysfunctional affective processes in ADHD, it can be assumed that either (1) alterations in anticipatory (aSCR) and reactive (rSCR) skin

conductance responses do not manifest during risky DM, or (2) increases in aSCRs are not associated with advantageous behavioural outcomes. The current study aimed to explore these interconnections by continuously recording SCRs during the performance in a modified version of the BART, which is designed to provoke emotional arousal and intuitive behaviour (Hüpen et al., 2019, 2020; Henn et al., 2023). Furthermore, self-assessment was utilized to explore awareness of one's own risky DM behaviour and emotional competence.

3.1.2 Materials and methods

In the present study, we employed a modified version of BART as the DM behaviour paradigm. A more detailed description of the paradigm's structure and procedure is provided in Chapter 2.3. Furthermore, we conducted a continuous measurement of skin conductance, which is elaborated in Chapter 2.4. The inclusion and exclusion criteria for participants are listed in Chapter 2.1. In total data from 56 subjects (28 patients with ADHD and 28 HCs) were included in the data analysis. The following tools were utilized in this study:

- Modified version of the BART (see Chapter 2.3.)
- Measurement of SCR (see Chapter 2.4.)
- Questionnaires (see Chapter 2.2.)
    - CAARS
    - WURS-k
    - BDI-II
    - BSL-95
    - Mini-DIPS
    - Self-designed demographic questionnaire
    - MWT-B
    - EKF
    - DOSPERT

In order to investigate the research questions on the basis of the materials used, different consecutive analyses are used (see **Figure 7**). Unconscious (blue

pathway) and conscious (red pathway) processes from stimulus onset to decision making were examined. As the appearance of the balloon (stimulus) provokes a change in the aSCR that modifies the representing behavior via RT, it should be investigated whether differences occur in the physiological activity (model 1), the behavior (model 2) or whether the behavior is also influenced by the aSCR (model 3). Since feedback also has an impact on hot function guided DM, we also investigated whether differences in rSCR are present (model 4). Two additional analyses should provide information on whether the participants' own behavior is perceived (additional analysis 1) and how their own affective functions are assessed (additional analysis 2).

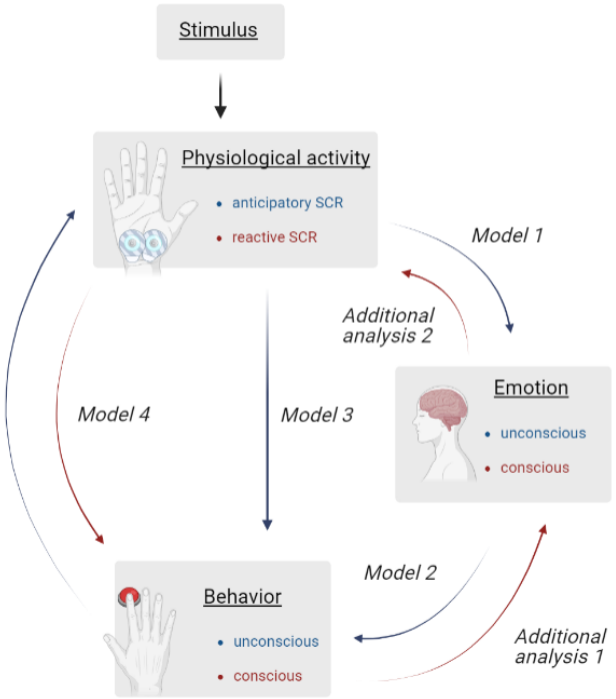

Figure 7: Illustration of the sequential analyses investigating unconscious (blue) and conscious (red) processes during risky decision making. To visualize the process to be investigated, six analyses are shown and assigned via arrow description (Model 1-4; Additional Analyses 1 & 2). The measurement variables belonging to the analysis are highlighted in the boxes "Physiological Activity", "Emotion" and "Behavior".

In order to investigate behavioral and psychophysiological differences between ADHD and HC, we used linear mixed effects model containing interaction terms of the fixed effects and random intercepts for participants and trials. Group (ADHD; HC) and reward condition (high; low) were included as fixed effects in the models. A “Non-responder” was not excluded from analyses as the lack of SCR might represent an actual psychophysiological activity. All models were fitted using the R (R Core Team, 2015) package lme4 (Bates et al., 2015). For post hoc comparisons, we used the emmeans package (Lenth, 2016) to account for means and corrected p values. Additional analyses were performed for the evaluation of the two questionnaires (DOSPERT; EKF). Therefore, we used univariate Analysis of Variance (ANOVA) with total scores of each questionnaire being the dependent variable and group (ADHD; HC) representing the independent variable.

3.1.3 Results

3.1.3.1 Demographics

There were no significant differences between HC and ADHD in age, gender distribution, verbal intelligence (as assessed by the WST; Metzler & Schmidt, 1992) and years of education (see **Table 4**). In terms of the clinical screening and the psychiatric symptoms, ADHD had greater levels of self-reported ADHD-related symptoms (Mann-Whitney-U = 769.5, n1 = n2 = 28, $p < 0.001$ two-tailed), depression (Mann-Whitney-U = 535, n1 = n2 = 28, $p = 0.018$ two-tailed) and BPD-related symptoms (Mann-Whitney-U = 584.5, n1 = n2 = 28, $p = 0.002$ two-tailed).

Table 4: Demographic and clinical characteristics of patients with ADHD and healthy controls (HCs).

		Median		*Mann-Whitney-U-Test*	
Parameter		HC (n=28)	ADHD (n=28)	*U*	*p*
Age (years)		27.00	30.50	431.5	0.516
Verbal IQ (WST)		33.00	32.00	376.5	0.798
Education (years)		18.00	16.00	287	0.178
CAARS	Hyperactivity	8.50	24.50	734.5	<0.001 ***
	Inattention	8.00	25.00	720.5	<0.001 ***
	Impulsivity	6.00	19.50	754.5	<0.001 ***
	Self-conception	4.50	11.50	633.5	<0.001 ***
WURS-k		12.00	40.00	748	<0.001 ***
BDI		2.00	4.50	535	0.018 *
BSL		2.00	12.00	584.5	0.002 **
		Frequency		**Chi-squared-Test**	
Gender (m/f)		9/19	16/12		p = 0.053

Abbreviations: ADHD = Attention-deficit-/hyperactivity disorder; HC = healthy controls; WST = Wortschatztest; CAARS = Conners Adult Rating Scale; WURS-k = Wender Utah Rating Scale; BDI = Beck depression inventory; BSL = borderline symptom list; m = male; f = female; *p < .05, **p < 0.01, ***p < 0.001.

3.1.3.2 Unconscious pathway (blue)

Model 1 investigating differences in the aSCRs, revealed a significant main effect of group (ß=-0.12, SE=0.05, t=-2.63, p<0.001). Post hoc analysis showed higher aSCR in ADHD compared to HC ($M_{Difference,ADHD-HC}$= 0.09, SE=0.03, t=2.79, p=0.005), indicating higher emotional arousal preceding a decision (see **Figure 8**). Model 2 accounting for the behavioral differences on basis of the RT, revealed a significant main effect of group (ß=219.51, SE=39.88, t=5.5, p<0.001) and reward condition (ß=215.36, SE=38.36, t=5.61, p<0.001). Post hoc analyses showed higher RTs in HC ($M_{Difference,ADHD-HC}$= -222, SE=29.3, t=-7.59, p<0.001) and under high reward condition ($M_{Difference,low-high}$= -218, SE=27.2, t=-8.02,

p<0.001), indicating greater risky DM but also a dependence of behavior on the level of reward in both groups (see **Figure 9**).

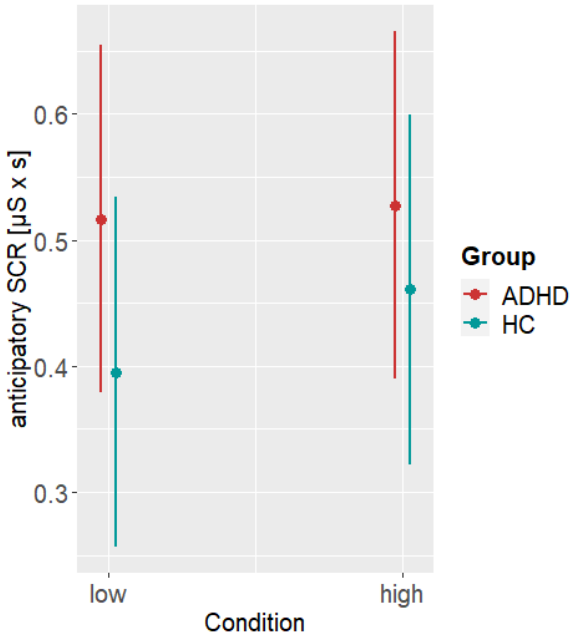

Figure 8: Post hoc results of model 1. Representing the anticipatory skin conductance responses (aSCRs) per group (ADHD, HC) and reward condition (low, high).

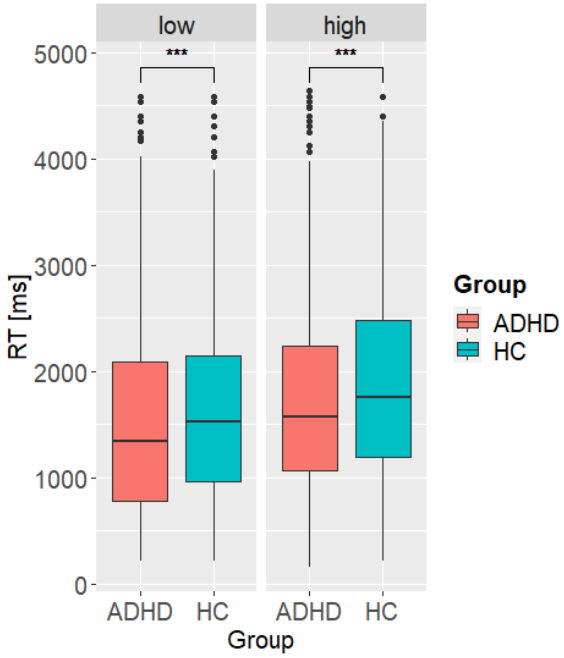

Figure 9: Post hoc results of model 2. Representing the reaction time (RT) per group (ADHD, HC) and reward condition (low vs high). ***p < 0.001.

An additional model was used to investigate whether RT is influenced by changes in aSCR. Here, model 3 revealed a significant main effect of aSCR (ß=-55.37, SE=28.03, t=-1.98, p=0.048), reward condition (ß=208.91, SE=43.65, t=4.79, p<0.001) and group (ß=162, SE=44.38, t=3.66, p<0.001). Furthermore, a significant interaction effect of group and aSCR was found (ß=107.17, SE=41.91, t=2.56, p=0.011). Post hoc analyses showed that RT of HC and ADHD seem to diverge from each other as the aSCR increases, with relationship of aSCR and RT tend to be positive in HC and being negative in ADHD ($M_{Difference,ADHD-HC}$= -222, SE=29.4, t=-7.57, p<0.001). Results indicate risky DM is associated with emotional arousal in HC but not in ADHD (see **Figure 10**). Please see **Table 5** for all other parameter estimates.

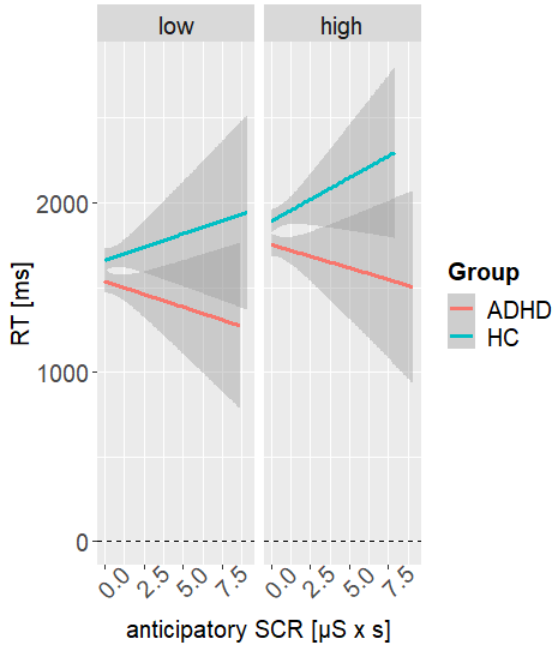

Figure 10: Interaction effect of model 3. Representing the simple slopes for the interaction of anticipatory skin conductance responses (aSCRs) at the factor variables reward condition (high, low) and group (ADHD, HC).

3.1.3.3 Conscious pathway (red)

Model 4 investigating differences in the rSCRs, revealed significant main effects of group (ß=-0.14, SE=0.05, t=-2.66, p=0.008) and feedback (ß=-0.11, SE=0.05, t=-2.32, p=0.02). Post hoc analyses showed higher rSCRs in ADHD ($M_{Difference,ADHD-HC}$=0.098, SE=0.04, t=2.7, p=0.007) and after loss display ($M_{Difference,loss-gain}$= 0.07, SE=0.03, t=2.03, p=0.042), indicating higher emotional arousal in loss trials with this being more pronounced in ADHD (see **Figure 11**). Please see Table 2 for all other parameter estimates.

The univariate ANOVA for the total score of propensity of risk engagement (additional analysis 1) did not reveal a significant difference of group ($F_{(1,54)}$=0.285, p=0.6, η2=0.005). Results indicate the same propensity of risk engagement in ADHD and HC. The ANOVA for the self-assessment of emotional competence (additional analysis 2) revealed a significant difference between ADHD and HC ($F_{(1,54)}$=23.1, p < 0.001, partial η2= 0.3), indicating a higher emotional competence in HC (see **Figure 12**).

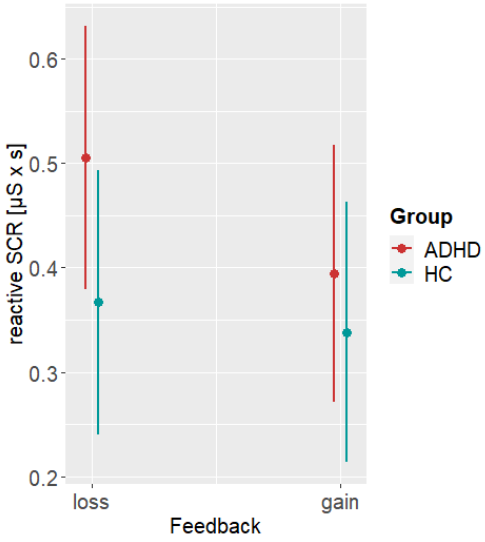

Figure 11: Post hoc results of model 4. Representing the reactive skin conductance responses (rSCRs) per group (ADHD, HC) and reward condition (low, high).

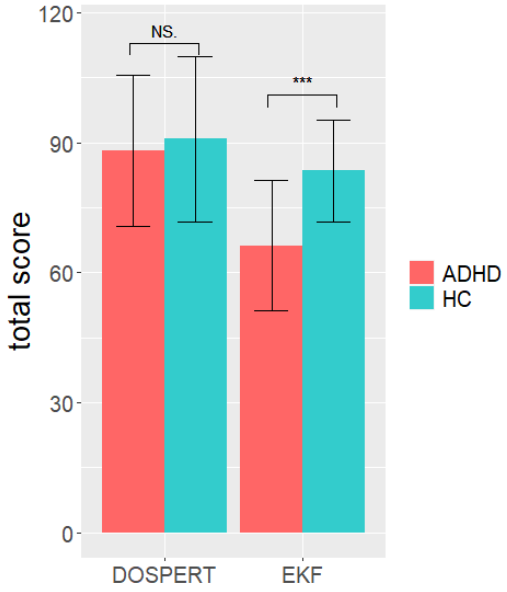

Figure 12: Univariate ANOVA results. Representing the total scores in the questionnaires Domain Specific Risk Taking (DOSPERT) and „Emotionale Kompetenz Fragebogen“(EKF) per group (ADHD, HC). Error bars represent standard errors of the means. NS $p > 0.05$, *** $p < 0.001$.

Table 5: Parameter estimates from the linear mixed effects model analyses.

	Model	b	SE	t	CI 95%	p
Model 1	(Intercept)	0.52	0.07	7.34	[0.38, 0.65]	< 0.001 ***
	Group	-0.12	0.05	-2.63	[-0.21, -0.03]	<0.001 ***
	Condition	0.01	0.04	0.25	[-0.08, 0.1]	0.8
	Group x Condition	0.05	0.06	0.86	[-0.07, 0.18]	0.39
Model 2	(Intercept)	1327.45	81.08	16.37	[1168.5, 1486.4]	< 0.001 ***
	Group	219.51	39.88	5.5	[141.32, 297.71]	< 0.001 ***
	Condition	215.36	38.36	5.61	[140.15, 111.31]	< 0.001***
	Group x Condition	4.85	54.3	0.09	[-101.61, 111.31]	0.929
Model 3	(Intercept)	1438.17	79.33	18.13	[1282.63, 1593.72]	< 0.001 ***
	aSCR	-55.37	28.03	-1.98	[-110.32, -0.41]	0.048 *
	Condition	208.91	43.65	4.79	[123.33, 294.5]	< 0.001 ***
	Group	162.63	44.38	3.66	[75.62, 249.65]	< 0.001 ***
	aSCR x Condition	13.55	39.38	0.34	[-63.66, 90.77]	0.73
	aSCR x Group	107.17	41.91	2.56	[24.99, 189.34]	0.011 *
	Condition x Group	18.5	61.27	0.3	[-101.63, 138.63]	0.76
	aSCR x Condition x Group	0.52	58.14	0.009	[-113.48, 114.51]	0.99
Model 4	(Intercept)	0.51	0.06	7.86	[0.38, 0.63]	< 0.001 ***
	Group	-0.14	0.05	-2.66	[-0.24, -0.04]	0.008 **
	Feedback	-0.11	0.05	0.05	[-0.21, -0.02]	0.02 *
	Group x Feedback	0.08	0.07	0.07	[-0.05, 0.22]	0.23

Note: Linear mixed-effects model with group (ADHD, HC) as fixed factor in every model. Reward condition (high, low) was additionally included as fixed factor in model 1-3. Feedback (gain, loss) was additionally included as fixed factor in model 4. Anticipatory skin conductance response (aSCR) was additionally included as fixed factor in model 3. Dependent variables were aSCR in model 1, mean reaction time (RT) in model 2,3 and reactive skin conductance response (rSCR) in model 4.

Abbreviations: CI = confidence interval; SE = standard error; *p < .05, **p < 0.01, ***p < 0.001.

3.1.4 Discussion

The present study investigated whether there is a potential causal relationship of affective pathways and abnormal risky DM behavior in adult ADHD. Therefore, different phases of hot function-guided DM were analyzed and compared between adult ADHD and HC on the basis of behavior, physiological activity, and self-assessment.

Results showed higher emotional arousal in ADHD indicated by elevated SCRs preceding a DM. These findings are consistent with the observation of hyperactivity of the autonomic nervous system being increasingly associated with motoric hyperactivity and impulsive behavior in ADHD. These results were suggested to reflect an over-activation of autonomic functions (Wilbertz et al.

2013). It is discussed whether hyperactivity of somatic functions in ADHD serves to induce a stimulating environment in order to promote a certain stability of vigilance (Geissler et al., 2014). In addition, these hyperarousal activities can also be related to a reduced ability of downregulating excessive arousal. However, other findings showed that during the performance of monotonous tasks, quick exhaustion may occur, which is then characterized by hypoactivity of bodily responses (Geissler et al., 2014; Kuntsi & Klein, 2012). It can therefore be assumed that, depending on the demands and excitement of the task; emotional arousal can be either hyper-/ or hypo-threshold.

Regarding the available effect of somatic markers at this point, high aSCRs would be expected to be associated with high risk behaviors, as the somatic response will increase with increased risk engagement in order to avoid disadvantageous behavior (Dawson et al., 2011; Garon et al., 2006; Starcke et al., 2009; Wright & Rakow, 2017). However, in the present study risky behavior could not be detected in ADHD. Instead, HCs with overall higher RTs, showed significantly greater risky DM than ADHD. At this point, it can be questioned whether the modified BART accurately reflects daily risky DM and whether it is a valid measurement under laboratory conditions. Moreover, the BART primarily examines risk engagement in the context of financial behaviors and therefore cannot represent all domains of potential daily risk taking behaviors. In addition, recent meta-analyses also highlight the fact that behavioral results of many studies represent rather a suboptimal DM behavior than a risk-seeking DM behavior in ADHD (Dekkers et al. 2021, Roberts et al. 2021). In this context, the underlying mechanism regarding the disentanglement of disadvantageous decisions and risk-seeking decisions reflect an additional important aspect in the field of DM and need to be considered in further studies (Dekkers et al. 2021). On the other hand, the behavior shown could also reflect an action that demonstrates shorter RT according to the Intolerance of Uncertainty that was found to be a transdiagnostic construct in psychiatric disorder (Gramszlo et al. 2018). Subsequently, not the risky DM behavior itself is an interesting outcome, but rather the relationship and interconnection of bodily response and DM.

Thus, in order to investigate how the somatic response influences behavior we analyzed the relation of aSCRs and RT. Results showed that risk engagement in HC coincides with increased aSCR, representing the correlation of disadvantageous behavior and higher SCRs (Dawson et al., 2011; Garon et al., 2006; Starcke et al., 2009; Wright & Rakow, 2017). In turn, increased risk engagement in ADHD was associated with lower aSCR. This negative correlation of RT and aSCR in ADHD confirms the hypothesis about an altered relation between affective state and behavior. However, the strongest affective responses were observed at low RTs. Thus, it is shown that as risk-engagement increases, affectivity decreases, however quick responses tend to elicit the greatest arousal. This suggests that the physical response shown may be related to additional factors than risk. Therefore, it can be assumed that in adult ADHD, there is a missing interconnection between bodily response and behavior regarding risky DM. Nevertheless, further emotionally arousing functions involved in this BART need to be examined.

To understand further aspects of hot function-guided DM, SCRs in response to feedback were also investigated. In this context, the somatic response reflects the evaluation and emotional arousal towards feedback. Results of the rSCRs indicate that feedback is evaluated more emotionally arousing for ADHD than to HC. We could also identify that the feedback of loss is more arousing than gain across both groups. The high rSCRs are also consistent with findings of previous studies on reward sensitivity in ADHD. It was shown that hyperarousal during feedback is associated with weaker inhibitory abilities (Iaboni et al., 1997; Masunami et al., 2009). Furthermore, also in HC it could already be shown that gains produce higher physiological activity (Lole et al., 2012). The impact of feedback, whether it appears as a gain or a loss, can moreover encourage behavioral adaptation. In their prospect theory, Kahneman and Tversky (1979) describe higher emotional arousal and motivation towards loss outcomes. This motivation is accompanied by a decreased propensity to risky DM and is particularly evident in mixed gain/loss prospects. However, it could also be shown that norepinephrine plays a significant role in risk appraisal and propensity (Trepel, Fox, & Poldrack, 2005). Accordingly, it was found that a central

norepinephrine blockade decreases the sensitivity to risk-taking significantly (Rogers et al., 2004). Relating this to the underactivity of norepinephrine in ADHD, it seems plausible that reduced risk-taking is caused by the norepinephrine deficiency. Reflecting the elevated rSCRs and the reduced risky DM behavior it can be assumed that the autonomic signal might not get properly transferred to the central nervous system (Critchley & Garfinkel, 2018).

Risk engagement was also investigated by self-assessment using the domain of probability of risk engagement of the DOSPERT questionnaire. Results showed no differences in the self-awareness of risky DM behavior. Contrary to the postulated daily behavior in ADHD, self-assessment does not seem to be perceived as an altered behavior. However, it should be noted that in the current study only the subdomain “probability of risk engagement” was used for a group comparison. Thus, a general evaluation of risky DM based on the DOSPERT results is limited. As questionnaires mostly comprise a subjective and consciously driven self-assessment, it can be assumed that on a conscious level, there are smaller differences in the risk-engagement between HC and ADHD. Consequently, it can be assumed that more unconscious, emotional-motivational driven processes, thus control the increased risky DM behavior in ADHD that is postulated in daily life. This is further supported by the self-assessment of emotional competence using the EKF questionnaire. Results indicated an impaired ability of emotional regulation, perception, understanding, and expression in ADHD that are important requirements for a proper hot function-guided decision (Sonuga-Barke, 2002). Moreover, risky DM is not only guided by previous experience of loss and gain, but also by the potential reward amount. Different studies have shown that with increasing magnitude of reward the risk avoidance also increases (Christopoulos et al., 2019; Hüpen et al., 2019; Kahneman, 2003; Van Leijenhorst et al., 2010). However, the present study indicates greater risk-engagement under high reward conditions, demonstrated by longer RTs, but not by changes in skin conductance. There was, however, no group difference and both ADHD and HC showed greater risky behavior under high reward conditions. Similar results were also shown in studies on ADHD and on Borderline Personality Disorder, arguing that the range between reward

conditions was too narrow (Hüpen et al., 2020; Luman, Oosterlaan, & Sergeant, 2008).

Overall, the measurement of SCRs has been shown to be a robust method to easily detect subconscious emotional arousal in anticipation and evaluation of DM. It yields a continuous measure that is related to activity in the sympathetic branch of the autonomic nervous system (Figner & Murphy, 2011). However, similar to many other indirect measurement methods, there are also some limitations. Subsequently, it must be taken into account that some participants can be “non-responders” (Figner & Murphy, 2011). In this study, we decided to include all measurements in the analyses as our statistical model corrected for individual differences in SCRs (Hüpen et al., 2019). Furthermore, there are contradictory recommendations on the pretreatment of the skin, whether the skin should be treated with water, oil or nothing at all before attaching the electrodes (Boucsein, 2012). We decided to follow the BIOPAC guidelines and used the saline paste supplied. Medication intake was also proven to affect activity of the autonomic nervous system (Bellato et al., 2020). Therefore, medication effect on behavioral results should be considered in future studies. Additionally, despite the potential individual lack of activity, there might also be environmental disturbances on the electrodermal recording that affect the signal. For instance, it was shown that electromagnetic noises such as overhead lights can disturb the signal and cause unrelated changes in the SCRs. We tried to avoid these artefacts by using low-pass filters and conducting the study in interference-free rooms, but a potential effect cannot be ruled out when considering the results. Furthermore, since the present study focuses on risky behavior in adults with ADHD it is important to consider that there may be limited comparability with child studies. Behavioral deficits in children may be deferred due to the delayed cortical maturation but may not persist in adulthood (Dekkers et al., 2016; Koscielniak, Rydzewska, & Sedek, 2016; Whelan & Mchugh, 2009). In addition, a possible effect of comorbidities on the results must also be taken into account. For instance, patients with Antisocial Personality Disorder are also affected by deficits in affective functions (Glenn, Johnson & Raine, 2013). Since the Mini-DIPS does not assess personality disorders, additional questionnaires should be included in

future studies. Moreover, it should be taken into account that the present study investigated the specific functionality of emotional competence, but ADHD is particularly characterized by a heterogeneity of dysfunctions. However, the effectiveness of hot functions is still underrepresented in behavioral studies on ADHD. To gradually shed more light on this topic, future studies should specifically examine demographic effects such as age, gender, and education in relation to the ability of affective functioning in adult ADHD.

In conclusion, the present study is the first to investigate hot functions as underlying mechanisms for risky DM in adult ADHD. Results show significantly higher arousal before a DM and after feedback display in ADHD. However, ADHD participants were unable to use this physiological information to modify behavior. This finding is also confirmed by self-reports that showed a weaker ability in the perception of arousal and emotion in ADHD, whereas self-reported risk behavior was not altered compared to HC. Further research is needed to investigate how emotional processing can be influenced or improved in ADHD. However, our research underlines the importance of considering emotional therapeutic technics in the work with patients with ADHD.

3.2 Study 2: Gender differences in physiological correlates of affectively driven decision-making behaviour in adult ADHD

This chapter encompasses a condensed introduction, main motivation, and methodological approaches. The paragraphs describing the study design, analyses, results, and discussions are derived directly from the author-accepted version of the original manuscript, which has been submitted to BMC Psychiatry.

The second study addresses the research question: "What impact does gender have on patients with ADHD in relation to affectively driven DM behaviour and the associated bodily function?" This study aims to build on the findings from Study 1 by examining the behavioural differences and associated changes in physiological response between men and women separately. Additionally, the cohort from Study 1 was expanded by 6 subjects (1 patient with ADHD and 5

HCs). Overall, this study indicates gender-specific differences in risky DM behaviour, physiological activity, and the relationship between bodily response and subsequent behaviour. The study was carried out in collaboration with the following co-authors: Eva Halbe, Alina Sophie Heger, Fabian Kolf, Philippa Hüpen, Moritz Bergmann, Ben J. Harrison, Christopher G. Davey, Silke Lux, and Alexandra Philipsen.

Eva Halbe was responsible for the majority of the work in this study and conceive the study and its design with the support of Silke Lux and Philippa Hüpen. Subject recruitment, data acquisition and analyses were performed by Eva Halbe with help of Alina Sophie Heger and Fabian Kolf. Moritz Bergmann, Ben Harrison, Christopher Davey, Silke Lux and Alexandra Philipsen then supported Eva Halbe in interpreting the results. Finally, Eva Halbe wrote the first draft of the manuscript.

3.2.1 Introduction

ADHD is a neurodevelopmental disorder with males being significantly more likely to be diagnosed compared to females. In longitudinal studies on childhood ADHD, the imbalanced gender ratio can reach up to 9:1 (boys:girls) (Gaub & Carlson, 1997; Gershon, 2002). The symptoms of ADHD are diverse and can persist into adulthood in up to 57% of cases, with the clinical manifestation changing significantly over time; while hyperactivity and impulsivity may decrease, internalizing difficulties like emotional dysregulation tend to increase, particularly in female patients who also report greater deficits in emotional competencies compared to their male counterparts (Must et al., 2013; Kessler et al., 2006; Francx et al., 2015; Fayyad et al., 2017).

Research on gender differences in ADHD symptomology is limited, but findings suggest that adult women with ADHD exhibit less hyperactivity, impulsivity, and other externalizing difficulties, and more deficits in affective competences (Gaub & Carlson, 1997; Gershon, 2002, Yoshimasu et al., 2018).

This gender disparity in diagnosis and treatment, influenced by internalizing symptoms more common in girls, complicates ADHD diagnosis, suggesting potential underdiagnosis in females and highlighting the need for more research on clinical indicators specific to female patients with ADHD (Ginsberg et al., 2014; Mao & Findling, 2014). These observed deficits in affective functioning in women with ADHD also suggest gender-specific impairments in daily life, particularly in situations requiring a high level of affective functioning. For instance, as shown in our previous study, risky DM in closely tied to motivational-emotional processing (Halbe et al., 2023). Studies investigating risky DM behaviour in HC have shown an increased risk behaviour in male subjects, whereas studies including patients with ADHD have identified more frequent risk behaviour in women with ADHD (Byrnes et al., 1999; Bolla et al., 2004). Furthermore, there are indications that deficits in affect, related to a psychiatric disorder may predict pathological gambling in females but not in males (Dannon et al., 2006). However, to date, no study has investigated the relationship between gender-specific impairments in affective functions and risky DM behaviour in adults with ADHD.

Using the valuable method of recording SCR, this study aimed to explore changes in emotional arousal processed unconsciously before making a decision, to uncover the underlying mechanisms of risky DM behaviour in ADHD (Starcke et al., 2009; Wright & Rakow, 2017; Christopoulos, Uy, & Yap, 2019). We focued on gender-specific effects to deepen our understanding of how affective functions impact behavioural deficits and to address the lack of attention to gender disparities in ADHD. Therefore, we analysed both between-group effects (ADHD vs HC) and within-group effects (male vs female) in 1) self-assessment on risky behaviour, emotional competence, and feedback sensitivity, 2) affective driven behavioural performance on a modified version of the BART, 3) physiological processes prior to DM and during feedback measured by SCR and 4) interconnection of body response and behaviour.

3.2.2 Methods

In the second study, the sample from Study 1 was extended by 5 HCs and 1 patient with ADHD to achieve a balanced gender distribution in both groups. The methods for assessing performance in the modified BART and the parallel measurement of skin conductance remained consistent with Study 1. The study design of the BART (see Chapter 2.3.) includes two different reward magnitude conditions (high and low) to account for potential effects on risk behaviour. However, no effect of reward condition on behaviour as well as on SCRs was found in Study 1. Consequently, the effect of reward condition was not considered in this study. In contrast, the focus of this study was primarily on analysing gender differences. Additionally, two further questionnaires were incorporated to evaluate the objectively measured self-assessment. Consequently, the following tools were utilized in this study:

- Modified version of the BART (see Chapter 2.3.)
- Measurement of SCR (see Chapter 2.4.)
- Questionnaires (see Chapter 2.2.)
    - CAARS
    - WURS-k
    - BDI-II
    - BSL-95
    - Mini-DIPS
    - Self-designed demographic questionnaire
    - MWT-B
    - EKF
    - DOSPERT
    - SPSRQ

Group comparisons regarding results in self-assessment of emotional competence were performed using a multifactorial univariate Analysis of Variance (ANOVA) with group (ADHD; HC) and gender (male; female) as independent variables. Analyses of self-assessment in the three subdomains of

the DOSPERT (prob; risk; ben) and the two subdomains of the SPSRQ (SP; SR) were performed using multifactorial multivariate Analyses of Variance (MANOVA) with group (ADHD; HC) and gender (male; female) as independent variables. Assumptions of homogeneity of variances were tested using Levene Test. Post hoc group comparisons were calculated using Tukey HSD test. Analyses of the behavioral data and physiological measures were performed using linear effects model that contain interaction terms of the fixed effects and random intercepts for participants and trials. In order to analyze group differences related on gender, both variables were included as fixed factor in every model. Reaction time (RT), anticipatory SCRs and reactive SCRs were each included as dependent variables in three separate models. As additional fixed effect, feedback (gain; loss) was included in the model investigating reactive changes in SCRs, whereas reward condition (high; low) was included in models investigating behavior, anticipatory SCRs and their relation. All analyses were performed using R (R Core Team, 2015). As the reward condition did not reveal sufficient effects in the models, it was excluded from the models for further interpretation of results. Model effect sizes were calculated. Therefore, the total explanatory power is described by the conditional R^2, whereas the part related power to fixed effect is described by the marginal R^2.

3.2.3 Results

3.2.3.1 Demographics

The group of patients with ADHD were comparable to the group of HC on gender ratio ($\chi^2(1) = 1.004$, $p = 0.316$, $\phi = 0.127$). There were no significant group differences with regard to age and years of education (see **Table 6**). Screening of depressive and borderline symptoms by clinical questionnaires did not reveal any abnormalities in either group. Thus, no subject was excluded for further data analyses.

Table 6: Demographic characteristics and clinical ADHD symptoms.

Parameter	**Median**				**Mann-Whitney-U-Test**	
	ADHD		HC			
	males[1] (n = 16)	females[2] (n = 13)	males[3] (n = 14)	females[4] (n = 19)	within-group comparison	Between-group comparison
Age (years)	31.50	27.00	30.00	26.00	$^{1=2}$ U = 87.5, p = .48 $^{2=3}$ U = 88.5, p = .11	$^{1=3}$ U = 110, p = .95 $^{2=4}$ U = 115.5, p = .76
Education (years)	16.50	16.25	18.00	16.50	$^{1=2}$ U = 95.5, p = .98 $^{2=3}$ U =76.5, p = .11	$^{1=3}$ U = 74, p = 0.2 $^{2=4}$ U = 108, p = 1
CAARS[a)] (**Hyperactivity**)	23.50	24.00	11.00	9.00	$^{1=2}$ U = 93.5, p = .65 $^{2=3}$ U = 95, p = .17	$^{1>3}$ U = 195, p < .001 $^{2>4}$ U = 220, p < .001
CAARS (**Inattention**)	25.50	22.00	12.50	8.00	$^{1=2}$ U = 88.5, p = .5 $^{2=3}$ U = 100.5, p = .24	$^{1>3}$ U = 194.5, p < .001 $^{2>4}$ U = 230, p < .001
CAARS (**Impulsivity**)	19.00	20.00	6.00	6.00	$^{1=2}$ U = 98, p = .81 $^{2=3}$ U = 108, p = .38	$^{1>3}$ U = 200, p < .001 $^{2>4}$ U = 233, p < .001
CAARS (**Self-conception**)	13.00	11.00	5.50	4.00	$^{1=2}$ U = 98.5, p = .81 $^{2=3}$ U = 118.5, p = .6	$^{1>3}$ U = 172, p < .001 $^{2>4}$ U = 210.5, p = .012
WURS-k[b)]	15.50	40.00	15.50	11.00	$^{1=2}$ U = 96.5, p = .75 $^{2=3}$ U = 93, p = 0.15	$^{1>3}$ U = 204, p < .001 $^{2>4}$ U = 240, p < .001

[a)] Conners Adult Rating Scale
[b)] Wender Utah Rating Scale
[*1] = ADHD males; [2] = ADHD females; [3] = HC males, [4] = HC females

3.2.3.2 Self-assessment

The ANOVA for the total score of emotional competence (EKF) revealed no significant effect of gender ($F_{(1,58)} = 1.67$, $p = 0.202$), while there was a significant effect of group ($F_{(1,58)} = 18.33$, $p < 0.001$). Results indicated higher emotional competence in HC ($M = 82.29 \pm 12.17$) compared to ADHD ($M = 66.81 \pm 14.97$). The MANOVA for total scores of the DOSPERT revealed no significant effect of group in all three subdomains (prob: $F_{(1,58)} = 1.74$, $p = 0.19$; risk: $F_{(1,58)} = 0.02$, $p = 0.88$; ben: $F_{(1,58)} = 0.29$, $p = 0.59$). However, there was a significant effect of gender in the subdomain probability of risk engagement (prob: $F_{(1,58)} = 6.28$, $p = 0.015$), whereas risk estimation (risk: ($F_{(1,58)} = 1.19$, $p = 0.28$) and evaluation of benefit (ben: $F_{(1,58)} = 0.041$, $p = 0.841$) did not significantly differ between males and females (see **Table 7**). Results showed significant higher probability of risk engagement (prob) in males ($M = 97.4 \pm 20.34$) compared to females ($M = 85.72 \pm 18.02$). The MANOVA for total scores for sensitivity to reward (SR) and sensitivity to punishment (SP) revealed no significant effect of gender (SR: $F_{(1,58)} = 1.97$, $p = 0.17$; SP: $F_{(1,58)} = 0.06$, $p = 0.81$) and no significant effect of group (SR: $F_{(1,58)} = 0.01$, $p = 0.92$; SP: $F_{(1,58)} = 3.05$, $p = 0.09$).

Table 7: Group comparison of total scores of self-reported questionnaires.

Parameter	Mean (SD)				Analysis of Variance		
	ADHD		HC		Group comparison		*Post-hoc*
	males[1] (n = 16)	females[2] (n = 16)	males[3] (n = 14)	females[4] (n = 19)	F	p	
EKF [a)]	64.3 (16.9)	69.9 (12.2)	80.4 (12.7)	83.7 (11.9)	$F_{(3,58)} = 7.26$	< .001	1,2 < 3,4
DOSPERT[b)] **(prob)**	93 (16.12)	83.6 (18.1)	102.4 (23.9)	87.2 (18.3)	$F_{(3,58)} = 2.61$	.06	NS
DOSPERT (risk)	132.6 (25.9)	135.3 (25.2)	127.8 (15.4)	138.2 (24.3)	$F_{(3,58)} = 0.57$	.64	NS
DOSPERT (ben)	99.9 (18.1)	99.9 (24.2)	98.1 (17)	95.9 (22.8)	$F_{(3,58)} = 0.14$	.94	NS
SP [c)]	10.6 (5.9)	11.8 (7)	8.9 (4.9)	8.4 (4.9)	$F_{(3,58)} = 1.12$	.35	NS
SR [d)]	10 (3.25)	9.54 (4.7)	10.86 (4.24)	8.47 (83.71)	$F_{(3,58)} = 1.04$	.38	NS

[a)] Emotionale-Kompetenz-Fragebogen
[b)] Domain Specific Risk Taking
[c)] Sensitivity to punishment
[b)] Sensitivity to reward
[*1] = ADHD males; [2] = ADHD females; [3] = HC males, [4] = HC females

3.2.3.3 Decision-making behavior

The first linear effects model investigated group differences in risky DM on basis of the RT in the BART according to gender (see **Figure 13, Table 8**). The model revealed a significant main effect of group (ß = -116.64, SE = 54.59, t = -2.14, p = 0.033) and gender (ß = -498.39, SE = 60.37, t = -8.26, p < 0.001) with a conditional effect size of $R^2 = 0.54$ and a marginal effect size of $R^2 = 0.03$. Furthermore, there was a significant interaction effect of group and gender (ß = 610.44, SE = 98.83, t = 6.18, p < 0.001). Post hoc analyses indicated significant higher RT in females compared to males in the group of ADHD ($M_{ADHD,female-male}$= 498, SE = 60.4, p < 0.001), whereas RT was not significantly different between gender in the group of HC ($M_{HC,female-male}$= -112, SE = 62.6, p = 0.073).

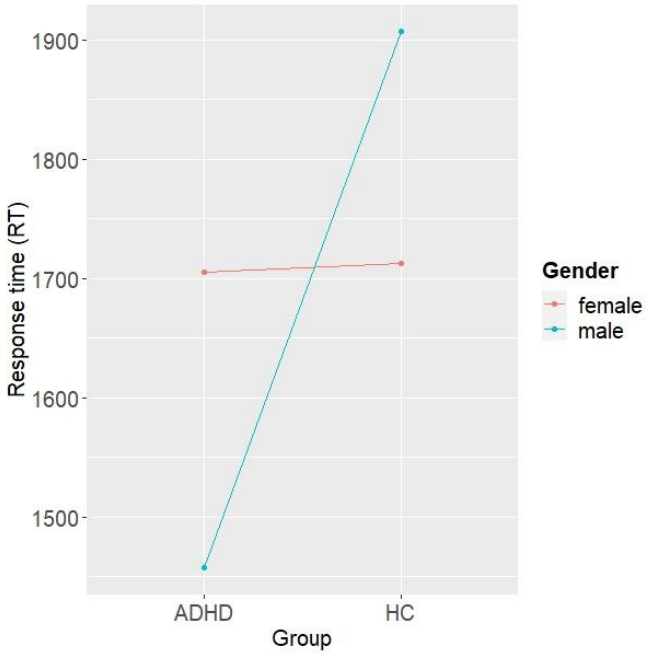

Figure 13: Interaction effect of reaction time (RT). Representing group differences (ADHD, HC) for mean RT in females (red) and males (blue).

3.2.3.4 Physiological activity

The second linear effects model investigated group and gender differences in arousal during feedback display on basis of the reactive SCRs and according to the feedback (see **Table 8**). The model revealed a significant main effect of gender (ß = 0.44, SE = 0.1, t = 4.58, p < 0.001) with a conditional effect size of R^2 = 0.6 and a marginal effect size of R2 = 0.01. Furthermore, there was a significant interaction effect of group, gender, and feedback (ß = 0.34, SE = 0.14, t = 2.48, p = 0.013). Post hoc analyses indicated significant higher reactive SCRs during loss feedback in males ($M_{male,loss\text{-}gain}$= 0.12, SE = 0.05, p = 0.019) and with a more prominent effect in ADHD compared to HC ($M_{ADHD,loss\text{-}gain}$= 0.15, SE = 0.05, p = 0.019).

The third linear effects model investigated group and gender differences in arousal prior to DM on basis of the anticipatory SCRs (see **Table 8**). The model revealed a significant main effect of group (ß = -0.16, SE = 0.07, t = -2.34, p = 0.02) with a conditional effect size of R^2 = 0.45 and a marginal effect size of R^2 =

0.01. Furthermore, there was a significant interaction effect of group and gender (ß = 0.32, SE = 0.12, t = 2.63, p = 0.009). Post hoc analyses indicated significant higher anticipatory SCRs in males in the group of HC ($M_{HC,female-male}$= -0.4, SE= 0.08, p < 0.001) and no gender differences in the group of ADHD.

3.2.3.5 Behaviour and physiology

The fourth linear effects model investigated the impact of anticipatory SCRs on the RTs and the differences in groups and gender (see **Figure 14, Table 8**). The model revealed again a main effect of group and gender, but also for anticipatory SCR (ß = -129.16, SE = 31.27, t = -4.13, p < 0.001), with a conditional effect size of R^2 = 0.42 and a marginal effect size of R^2 = 0.04. Furthermore, the model revealed a significant interaction of anticipatory SCR and group (ß = 195.41, SE = 43.38, t = 4.51, p < 0.001) and anticipatory SCR and gender (ß = 144.06, SE = 41.53, t = 3.47, p < 0.001). There was also a significant three-way interaction effect of anticipatory SCR, gender and group (ß = -202.08, SE = 54.77, t = -3.69, p < 0.001). Post hoc analyses indicated decreasing RT in HC when anticipatory SCR is high in males, whereas there is no SCR related change in RT in females ($M_{HC,female-male}$= -156, SE = 64.9, p = 0.016). An opposite effect is indicated in the group of ADHD, with increasing RT when anticipatory SCR is high in males and decreasing RT when anticipatory SCR is high in females ($M_{ADHD,female-male}$= 464, SE = 61.4, p < 0.001).

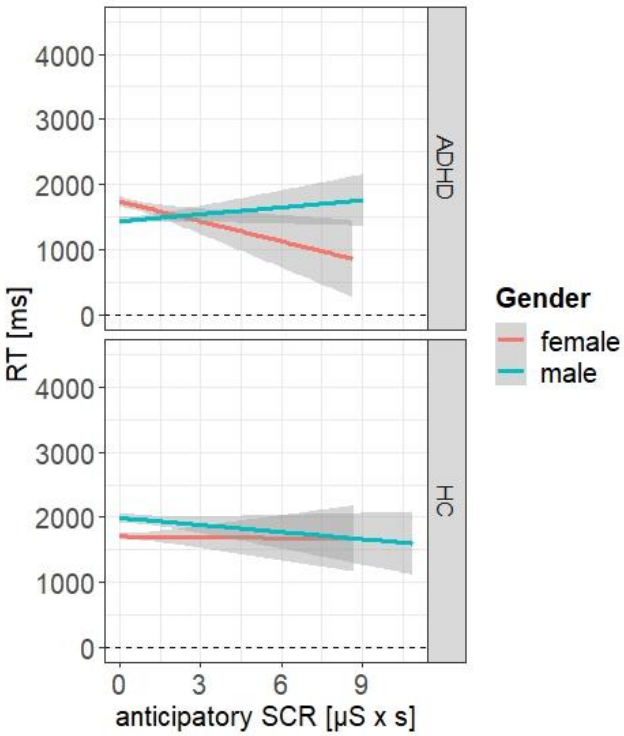

Figure 14: Interaction effect of anticipatory SCR and reaction time (RT). Representing the simple slopes for the interaction at the factor variables group (ADHD, HC) dependent on gender (male, female).

Table 8: Parameter estimates from the linear mixed effects model analyses.

Model		b	SE	t	CI 95%	p
RT [a]	Group	-116.64	54.59	-2.14	[-223.67, -9.62]	0.033
	Gender	-498.39	60.37	-8.26	[-616.75, -380.03]	< 0.001
	Group x Gender	610.44	98.83	6.18	[416.68, 804.21]	< 0.001
rSCR [b]	Group	0.01	0.09	0.13	[-0.16, 0.18]	0.897
	Feedback	0.03	0.07	0.42	[-0.11, 0.17]	0.678
	Gender	0.44	0.1	4.58	[0.25, 0.62]	< 0.001
	Group x Feedback	-0.05	0.09	-0.55	[-0.24, 0.13]	0.582
	Group x Gender	-0.11	0.15	-0.76	[-0.4, 0.18]	0.446
	Gender x Feedback	-0.29	0.1	-2.97	[-0.48, -0.1]	0.003
	Group x Feedback x Gender	0.34	0.14	2.48	[0.07, 0.61]	0.013
aSCR [c]	Group	-0.16	0.07	-2.34	[-0.3, -0.03]	0.02
	Gender	0.08	0.08	1.05	[-0.07, 0.23]	0.293
	Group x Gender	0.32	0.12	2.63	[0.08, 0.57]	0.009
aSCR x RT	aSCR	-129.16	31.27	-4.13	[-190.46, -67.86]	< 0.001
	Group	-184.21	58.12	-3.17	[298.17, -70.25]	0.002
	Gender	-538.23	64.98	-8.28	[-665.63, -410.83]	< 0.001
	aSCR x Group	195.41	43.38	4.5	[110.36, 280.47]	<0.001
	aSCR x Gender	144.06	41.53	3.47	[62.64, 225.48]	<0.001
	Group x Gender	724.48	103.07	7.03	[522.39, 926.57]	< 0.001
	aSCR x Group x Gender	-202.08	54.77	-3.69	[-309.46, -94.69]	<0.001

[a] response time
[b] reactive skin conductance response
[c] anticipatory skin conductance response
Note: Linear mixed-effects model with group (ADHD, HC) as fixed factor in every model. Gender (female, male) was additionally included as fixed factor in every model. Investigating risky behavior based on the RT, a model was fitted with RT as dependent variable. Investigating physiological response for feedback, a model was fitted including feedback as additional fixed effect and reactive SCR as dependent variable. Investigating physiological response anticipating DM, a model was fitted with anticipatory SCR as dependent variable. Investigating the interaction of physiology and behavior, a model was fitted including anticipatory SCR as additional fixed effect and RT as dependent variable.

3.2.4 Discussion

The present study investigated gender differences in affective-motivational driven behaviour related to physiological processes in adult patients with ADHD compared to HC. Results were furthermore examined with respect to the self-assessment in emotional competence, risk perception and feedback sensitivity. The current study reflects an increased impairment in affective functions in women with ADHD, regarding the physiological activity but also the related behaviour guided by the bodily response.

Using questionnaires, we revealed insight into self-awareness of risky DM behaviour in ADHD. Regarding self-assessment of emotional competence, the results showed significant group differences indicating a reduced ability for recognizing and treating own/other feelings in patients with ADHD. These results confirm the frequently observed and reported deficits in affective functions (Beheshti, Chavanon, & Christiansen, 2020; Shushakova, Ohrmann, & Pedersen, 2018). However, the imbalanced gender ratio in affective symptoms as well as the often shown altered sensitivity to feedback in ADHD were not confirmed by the results. On the other hand, significantly higher scores on self-assessed probability of risk engagement (prob) were found in males, whereas this gender effect did not differ between both groups. As a previous study has indicated, gender-specific symptoms may appear differently on subjective and objective measures (Slobodin & Davidovitch, 2019). In this context, reports from teachers showed greater psychiatric internalizing deficits in boys, whereas most clinical measures identified more severe affective impairment in females (Biederman et al., 2008). Another study also confirms these inhomogeneities and emphasizes the need for complementary objective measures in screening of ADHD symptoms (Emser et al., 2018). Consequently, the results of the current study do not indicate strong evidence for gender differences in the self-assessment. Nevertheless, as ratings in questionnaires represent a subjective and consciously made evaluation, the results reveal an interesting insight in the self-awareness of feelings and behaviour in adult ADHD. Thus, deficits regarding affective functions seem to be perceived, whereas risky behaviour does not appear to be deliberately engaged. Accordingly, it is emphasized that underlying unconsciously affective processes may cause a deficient effect of internal interconnections and result in an aberrant DM behaviour.

Investigating to what extent risky DM is objectively reflected, the performance in the modified BART was analysed with respect to gender. The results indicate that behaviour considerably depends on gender. Thus, male HCs and female patients with ADHD showed significantly greater risky DM behaviour, indicated by the RT than male patients with ADHD and female HCs. These gender-dependent behavioural effects are known in HC, whereas the present

study is the first to demonstrate that gender differences in affective driven risky DM behaviour exist in adult ADHD. Since the modified version of the BART used in the current study is intended to require unconscious, intuitive DM behaviour with help of undeliberate affective functions, the hypothesis can be confirmed that in particular women with ADHD are affected by deficits in emotional-driven DM. Nevertheless, it seems contradictory that the least risky DM behaviour was found in the group of male patients with ADHD. A possible interpretation that is often used to explain the reduced applicability of daily life behaviours to laboratory settings, is that patients have learned behavioural strategies to cope with their instincts (Mowinckel et al., 2015). Taken together, however, it appears that exhibited behaviour alone is not sufficient to explain gender differences in ADHD.

The further exploration of the underlying affective processes measured by the skin conductance in response to feedback stimuli in the task and the undeliberate anticipation of DM, indicated overall higher responsiveness of the ANS in males than in females in both ADHD and HC. These gender-related differences were also reported in previous studies that for instance indicate attenuated sympatho-adrenal activation in women (Hinojosa-Laborde et al., 1999). The current study showed that elicited effects in the reactive SCRs were more prominent during negative feedback compared to positive feedback with a greater effect in the ADHD group. Such a blunted relation of positive emotional experience and sympathetic response was also reviewed by a recent meta-analysis (Behnke et al., 2022). Furthermore, greater physiological responses to losses than to gains have also successfully shown in studies on DM behaviour (Hochman & Yechiam, 2011; Kreibig, 2010). Although the self-assessment results in the current study did not indicate increased sensitivity to punishment, there is some evidence in the literature that patients with ADHD perceive emotional stimuli as more arousing than HC and are particularly distracted by stimuli with negative valence (Köchel et al., 2015; López-Martín et al., 2013; Mauri et al., 2020; McQuade & Breaux, 2017). Regarding physiological activity during anticipating DM, men showed higher amplitudes than females in both groups. Consequently, the current results support the hypothesis that

increasingly women with ADHD have deficits in the autonomic response towards external stimuli that might cause affective dysfunctions.

To further explore the extent to which altered gender-specific physiological activity modifies behaviour, anticipatory SCRs were also analysed in relation to subsequent behaviour. Results indicated a negative association of anticipatory SCR and RT in male HC and female ADHD, whereas the correlation was shown to be positive in male ADHD and was not present in female HC. The relationship between DM and anticipatory changes in the physiological activity has been proven in previous studies in context of conditioned learning of reward and punishment contingencies but also in laboratory settings where no learning was required (Bechara et al., 1997; Crone et al., 2004; Guillaume et al., 2009). However, this interconnection between the preceding physiological response and the behaviour is difficult to generalize for both types of DM (affective-driven and cognitive-driven). While deliberate risk-taking (choosing inflation versus cashout) in the original BART is associated with a positive correlation of risky behaviour and anticipatory SCR, results in the modified version of BART indicate a negative correlation of disadvantageous behaviour and physiological activity. Here, less risky performance, as seen in male ADHD and female HC, could be traced back to an intrinsic warning signal of the ANS. Whereas in the original BART the behaviour shown is usually correlated with the general individual bodily function, in the current study anticipatory activity was associated with the subsequent behaviour in each trial (Henn et al., 2023; Hüpen et al., 2019, 2020). Thus, the results reflect more the temporal sequence of physiology and behaviour. Therefore, this relationship suggests a certain sensitivity to bodily response, implying that individuals with a positive correlation of anticipatory SCR and RT are more sensitive to their bodily functions and thus less risky. The present results indicate a reduced sensitivity towards their own bodily responses in women with ADHD, which could consequently cause increased risky DM behaviour.

However, some limitations must be taken into account considering results of physiological parameters. In this context, individual but also environmental influences on the measurements can occur. Therefore, we tried to keep the

measurement conditions as stable as possible using an interference-free examination room. By evaluating integral changes in SCR, individual variation should be reduced in the current study, but it must still be considered that potential non-responders could distort between group effects (Figner & Murphy, 2011). A recent review on physiological abnormalities in patients with ADHD, medications were identified to have effects on autonomic functions. Stimulants were shown to cause an upregulation of the ANS that counteract the hypoaroused state. This excitatory effect of ADHD-specific medications has also been demonstrated after discontinuation of the medications (Idrees et al., 2023). In addition, the clinical profile of ADHD is characterized by a heterogeneity of symptoms, which means that deficits in the functioning of affective processes do not necessarily apply to all ADHD patients. Moreover, regarding the subdivision of gender, the small sample size must also be taken into account as a limitation as it can intricate a generalization of the results.

In summary, the present study was the first to demonstrate gender-dependent effects of affective functioning on undeliberate DM behaviour in adult patients with ADHD. The results showed that particularly women with ADHD tend to engage in risky DM behaviour in the paradigm used and that this behaviour can be traced back to alterations in the relation between activity of the ANS and intuitive behaviour. However, with future research it should be further investigated if this effect is related to a triggered increase in sensitivity to their own bodily functions. Additionally, the stimulant effect of ADHD-specific medication on autonomic functions should be further explored in the context of DM behaviours. Overall, this study indicates that a greater focus addressing gender-specific deficits is needed in diagnosis and treatment of adults with ADHD.

3.3 Study 3: Neural correlates and gender-specific effects of affectively driven processes underlying decision-making in adult ADHD

This chapter encompasses a condensed introduction, main motivation, and methodological approaches. The paragraphs describing the study design,

analyses, results, and discussions are derived directly from the author-accepted version of the original manuscript, which has been submitted to Brain and Behavior (see **Appendix B** for submitted supplementary material).

The third study addresses the research question: "Are there differences in neural activation patterns in affectively driven DM behaviour between adults with ADHD and healthy controls as well as between males and females?" This study aims to extend the previous findings from Studies 1 and 2 by investigating neural correlates during the anticipation of DM, with an additional focus on gender-specific effects. Therefore, behavioural and neuroimaging data from 38 participants were included in this study (see Chapter 2.1.). Overall, this study identified altered neural activity in adult patients with ADHD, noting gender-specific differences during the anticipation of a risky decision. The study underscores the importance of the right precuneus and right superior frontal gyrus in relation to metacognitive functioning and interoceptive awareness. Furthermore, increased neural activity was found in females with ADHD compared to males with ADHD in the area including the dlPFC, left insula, right caudate, right cuneus, and precuneus. This study was carried out in collaboration with the following co-authors: Eva Halbe, Alec Jamieson, Moritz Bergmann, Aylin Mehren, Ben J. Harrison, Christopher G. Davey, Tony Stöcker,Alexandra Philipsen, and Silke Lux.

Eva Halbe was responsible for the majority of the work in this study and conceive the study and its design with the support of Silke Lux and Alec Jamieson. Subject recruitment and data acquisition were performed by Eva Halbe with help of Moritz Bergmann. Tony Stöcker provided the MRI scanner, developed the sequence script, and offered support for technical inquiries. Data analyses wereperformed by Eva Halbe supported by Alec Jamieson, Ben Harrison, and Aylin Mehren. Moritz Bergmann, Ben Harrison, Christopher Davey, Silke Lux and Alexandra Philipsen then supported Eva Halbe in interpreting the results. Finally, Eva Halbe wrote the first draft of the manuscript.

3.3.1 Introduction

ADHD is associated with persistent cognitive impairments and an increased tendency towards risky DM behaviour, influenced by the core symptoms of the patients (Polanczyk et al., 2014, Dekkers et al., 2016, Pollak et al., 2019). Alongside impairments such as feedback perception, impulsivity and disinhibition, this heightened vulnerability to increased risk-taking is also driven by deficits in affective processes (Sonuga-Barke, 2002; Winstanley, Eagle, & Robbins, 2006; Scheres et al., 2007; Ströhle et al., 2008; Mäntylä et al., 2012). The somatic marker hypothesis posits an interconnection between affective processes, physiological activity, and behaviour, suggesting that DM is intrinsically guided by unconscious processes (Damasio, 1996; Figner & Murphy, 2011). In previous studies, we found altered interactions between bodily responses and risky DM behaviour in adults with ADHD, which has also been shown to be highly dependent on gender (Halbe et al., 2023). Additionally, despite evidence suggesting gender differences in affective dysfunctions among ADHD patients, research often generalizes findings across genders, leaving the impact of gender on affectively driven DM behaviour in ADHD underexplored.

Neuroimaging studies exploring somatic marker functioning have highlighted the role of the vmPFC in DM, where damage leads to deficits in choosing advantageous outcomes. Other key areas such as the dlPFC, amygdala, insula, posterior cingulate cortex, and OFC have been found to be associated with anticipatory processes of DM (Rao et al., 2008; Li et al., 2010; Li et al., 2020; Tannou et al., 2021; Wang et al., 2022). These findings underscore the importance of the interconnection between emotion and memory as well as integrative processes in generating advantageous DM behaviour. However, research on DM in ADHD has predominantly focused on neural mechanisms of feedback processing, neglecting the role of unconscious processes preceding DM. Nevertheless, there are indications that reduced neural activity in the area of the vmPFC and dlPFC is associated with risky DM in individuals with ADHD (Nejati et al., 2020). Building on our previous findings and the knowledge of aberrant ANS functions in adult patients with ADHD, this study aims to further

explore the neural processes preceding DM by usage of fMRI during performance on the modified BART. Analyses of this study aim for a more extensive exploration of underlying processes of affective functions as well as gender-specific effects related to risky DM behaviour in adult ADHD.

3.3.2 Methods

In the third study, performance on the modified version of the BART was examined during a functional MRI measurement. Data from 38 participants (18 patients with ADHD and 20 HCs) were analysed to assess neural activation patterns during the anticipation phase of the DM paradigm. Additionally, the effect of gender on neural activation patterns and questionnaires on self-assessment were exploratively investigated through further analyses. The following tools were used in this study:

- Modified version of the BART (see Chapter 2.3.)
- Measurement of functional MRI (see Chapter 2.4.)
- Questionnaires (see Chapter 2.2.)
    - CAARS
    - WURS-k
    - BDI-II
    - Mini-DIPS
    - Self-designed demographic questionnaire

For the fMRI data analysis, an event-related design was utilized. Therefore, all event triggers of the BART were included as regressors in first-level analyses capturing the timing of the appearance of the balloon and the display of the feedback in relation to the reward condition (high; low) and the outcome (pos; neg) in the previous trial: high_pos_start; low_pos_start; high_neg_start; low_neg_start; pos_feedback; neg_feedback. All further steps in the analysis were performed with respect to the anticipatory phase of DM. Regarding the research question of the current study, all anticipatory regressors were considered as one in order to determine the contrast image "Start". Additionally,

motion parameters from the preprocessing were incorporated as multiple regressors of no interest in the analyses. All contrast images were used to perform a two-sample t-test (ADHD vs HC) for group-level analyses. An initial whole brain voxel threshold of 0.001 uncorrected with no restriction to cluster size was applied. Significances in neural activity changes were considered for multiple testing on cluster level (corrected pFWE < 0.05).

An additional 2x2 full-factorial analysis was performed, including group (ADHD; HC) and gender (female; male) as factors to explore gender dependent effects during the anticipation of DM. Brain regions were labelled using the toolbox Automated Anatomical Labelling 3 (AAL3; Rolls et al., 2020) in Matlab R2022a (The MathWorks, Inc.). Behavioral data regarding the performance in the BART were analyzed using SPSS Statistics 22 (IBM, Armonk, NY, USA). A two-way Analysis of Variance (ANOVA) was conducted to examine the effects of gender and group on the mean of RT. Gender (male; female) and group (ADHD; HC) were considered as independent variables, while RT served as the dependent variable. Assumptions of normal distribution and homogeneity of variances were assessed prior to conducting the ANOVA. RT of both reward conditions (low; high) were considered together so that the behavioral data were considered independent of reward level.

3.3.3 Results

3.3.3.1 Risky decision-making behavior

In total, thirty-eight participants (n = 20 HC, n = 18 ADHD) were included in the following analyses of behavioral and fMRI data. One HC and two patients with ADHD were excluded due to excessive movement parameters. Another patient with ADHD was excluded due to severe comorbid affective symptoms. There were no significant differences between the groups in age, gender and educational level. Patients with ADHD scored significantly higher on the clinical questionnaires in terms of ADHD symptomatology and depression (see **Table 9**). Sixteen patients with ADHD took stimulant medications (Elvanse, Medikinet,

Methylphenidate, and Ritalin) regularly for a period of at least two weeks. These medications were discontinued 24 hours before participation in the study. All participants completed 60 trials of the modified version of the BART. In order to investigate risky DM behavior, RT during the DM phase of the paradigm was compared between groups and gender. On average, females in the HC group showed a RT of 1610.74 ms (SD = 497.64 ms), whereas males in the HC group showed a RT of 1970.19 ms (SD = 447.61 ms). In the group of patients with ADHD, mean RT was 1538.09 ms (SD = 441.45 ms) for females and 2148.07 ms (SD = 748.55) for males. Using a two-way ANOVA, no significant effect of group was identified ($F_{(1,34)}$ = 0.091, p = 0.76, η2 = 0.003), whereas a significant effect of gender was found ($F_{(1,34)}$ = 7.74, p = 0.009, η2 = 0.186). With no significant effect of the interaction of group and gender ($F_{(1,34)}$ = 0.52, p = 0.477, η2 = 0.015), gender differences in RT did not appear to differ between groups.

Table 9: Demographic, clinical and behavioural variables.

Parameter		**Median**		***Mann-Whitney-U-Test***	
		HC (n=20)	ADHD (n=18)	*U*	*p*
Age (years)		19.25	19.78	185	.897
Education (years)		18.15	15.78	116.5	.488
CAARS[a)]	Hyperactivity	10.55	27.92	331.5	< .001
	Inattention/memory	10.61	27.86	330.5	< .001
	Impulsivity	11.61	26.81	311.5	< .001
	Self-conception	13.87	24.42	268.5	.002
WURS-k[b)]		11.32	26.53	298	< .001
BDI[c)]		14.95	23.28	248	.019
		Frequency		**Chi-squared-Test**	
Gender (m/f)		10/10	8/10		χ 2 = 0.117

[a)] Conners Adult ADHD Rating Scale
[b)] Wender Utah Rating Scale
[c)] Beck Depression Inventory
Note: The median was used as measure of central tendency due to the non-normally distributed nature of the variables.

3.3.3.2 Functional MRI data

The main focus of the analyses was to examine brain activation patterns during the anticipation phase of DM using the contrast “Start”. For the HC group the whole brain analysis revealed significant activation in the frontal lobe, including right inferior and bilateral middle frontal gyri as well as bilateral middle parts of the temporal lobe. Further significant activation patterns were found in bilateral postcentral, precentral, and left paracentral gyri. Subcortical activation patterns were observed in the left putamen and right caudate (see **Table 10**). Moreover, the cluster with peak activation in the left precentral gyrus was found to extend into the region of the left insula (see supplementary material for further details). For the ADHD group the whole brain analysis revealed activation in the right middle part of the cingulate, left middle frontal gyrus, and right middle temporal gyrus (see **Table 10**). Activation in the cingulate also extended into the right insula (see supplementary material for further details).

To identify alterations in the functional activity pattern in the patient group compared to HC, the between-group contrasts (HC > ADHD; ADHD > HC) for the anticipation phase were analyzed. The whole brain analysis revealed significantly higher activation in HC compared to ADHD, whereas no increased activation patterns were found in ADHD compared to HC. Increased activation in HC compared to ADHD was found in two clusters with peak activation in the right precuneus and the right superior frontal gyrus (see **Figure 15, Table 10**). Moreover, the cluster with peak activation in the right precuneus extended into the region of the right paracentral lobule (see supplementary material for further details). In order to evaluate whether these group differences were driven by a hyperactivation in the HC group or hypoactivation in the ADHD group, peak beta values for both groups were extracted and compared for illustrative purposes (see **Figure 16**). The results indicate increased activation in the HC group, whereas activation appears to decrease during DM anticipation in the ADHD group.

An additional exploratory analysis was performed in order to identify effects of gender during the anticipation of DM. Therefore, a whole brain full

factorial analysis was performed with group and gender as between-subject factors. The analysis revealed no significant interaction effect between group and gender, indicating that the differences in neuronal activity between groups were not significantly affected by gender. However, according to our previous study results, it was of particular interest to investigate gender differences within the ADHD group, as we hypothesized that gender might play a role in the neural activity of patients with ADHD. For this purpose, we further examined gender differences within the groups (see **Table 11**). In females compared to males with ADHD, we observed increased neural activity during anticipation of DM in various clusters located in the frontal lobe including bilateral dorsolateral and bilateral middle frontal parts (see **Figure 17**). Further significant activation patterns were found in the left insula, right cuneus and precuneus, as well as the left precentral and lingual gyrus. Subcortical activation patterns were found in the region of the right caudate (see supplementary material for further details). No significant group differences were found when comparing ADHD and HC within females and males separately.

Table 10: Brain activations associated with the anticipation of decision-making within groups (HC; ADHD) and compared between groups (HC>ADHD; ADHD>HC).

	Peak MNI coordinates			$p_{FWE\text{-}corr}$ (cluster level)	Z_E (peak-level)	Cluster size
	x	y	z			
HC						
R. Inferior frontal gyrus, opercular part	60	12	16	< .001	5.75	335
L. Middle frontal gyrus	4	10	50	< .001	5.73	8343
L. Precentral gyrus	-36	14	8	< .001	5.3	1039
L. Putamen	-24	6	-6	< .001	5.05	496
R. Middle temporal gyrus	46	-60	6	< .001	5.05	290
R. Postcentral gyrus	56	-12	24	< .001	4.97	250
L. Middle temporal gyrus	-50	-60	10	< .001	4.87	250
R. Caudate	15	8	-2	< .001	4.72	563
R. Middle frontal gyrus	36	38	30	< .001	4.64	757
L. Paracentral lobule	-6	-30	60	< .001	4.62	544
R. Crus II of cerebellar hemisphere	44	-78	-36	< .001	4.54	754
L. Postcentral gyrus	-66	-14	10	.002	4.52	209
L. Crus I of cerebellar hemisphere	-52	-64	-34	< .001	4.49	319
L. Lobule VIII of cerebellar hemisphere	-24	-64	-54	< .001	4.14	275
R. Postcentral gyrus	30	-42	52	.031	4.07	123
R. Precentral gyrus	38	-14	60	.026	4.06	128
ADHD						
R. Middle Cingulate & paracingulate gyri	22	6	20	.001	5.3	241
L. Middle frontal gyrus	-34	40	18	.001	4.7	231
R. Middle temporal gyrus	46	-66	2	.021	4.63	133
HC>ADHD						
R. Precuneus	16	-40	56	.01	4.36	154
R. Superior frontal gyrus, dorsolateral	20	60	6	.041	4.23	115
ADHD>HC						
not significant						

* L. = left hemisphere; R. = right hemisphere

Note: Initial voxel threshold was set as uncorrected ($p < 0.001$) for within-group and between-group comparisons. Reported activation patterns are FWE-corrected ($p < 0.05$) on cluster level. See supplementary material for further details of significant clusters.

Table 11: Gender-related brain activation patterns associated with the anticipation of decision-making. Displayed are the main effect of gender and within-group gender comparisons, as revealed by the full factorial analysis with gender and group as between-subject factors.

	Peak MNI coordinates			$p_{FWE\text{-}corr}$ (cluster level)	Z_E (peak-level)	Cluster size
	x	y	z			
ADHD female>male						
R. Lobule VI of cerebellar hemisphere	8	-78	-18	< .001	5.14	335
R. Crus I of cerebellar hemisphere	42	-42	-34	< .001	4.87	459
R. Caudate	22	-18	22	< .001	4.86	637
R. Superior frontal gyrus, dorsolateral	10	30	28	< .001	4.81	1512
L. Insula	-48	2	-4	.002	4.67	216
R. Cuneus	10	-74	36	< .001	4.44	296
L. Superior frontal gyrus, dorsolateral	-16	30	22	.011	4.41	157
R. Middle frontal gyrus	30	36	28	< .001	4.41	484
L. Lobule VIII of cerebellar hemisphere	-36	-44	-46	.002	4.34	211
Lobule VI of Vermis	8	-66	-36	.001	4.27	226
L. Precentral gyrus	-36	0	62	< .001	4.26	455
R. Precuneus	-6	-68	58	< .001	4.25	943
L. Lingual gyrus	-18	-64	-14	.008	4.15	169
L. Middle frontal gyrus	-34	54	-14	< .001	4.14	266
L. SupraMarginal gyrus	-54	-14	28	.023	3.97	135
L. Crus I of cerebellar hemisphere	-30	-66	-24	.002	3.86	212
ADHD male>female	not significant					
HC female>male	not significant					
HC male>female	not significant					

* L. = left hemisphere; R. = right hemisphere

Note: Initial voxel threshold was set as uncorrected ($p < 0.001$) for the full factorial analysis. Reported activation patterns are FWE-corrected ($p < 0.05$) on cluster level. See supplementary material for further details of significant clusters.

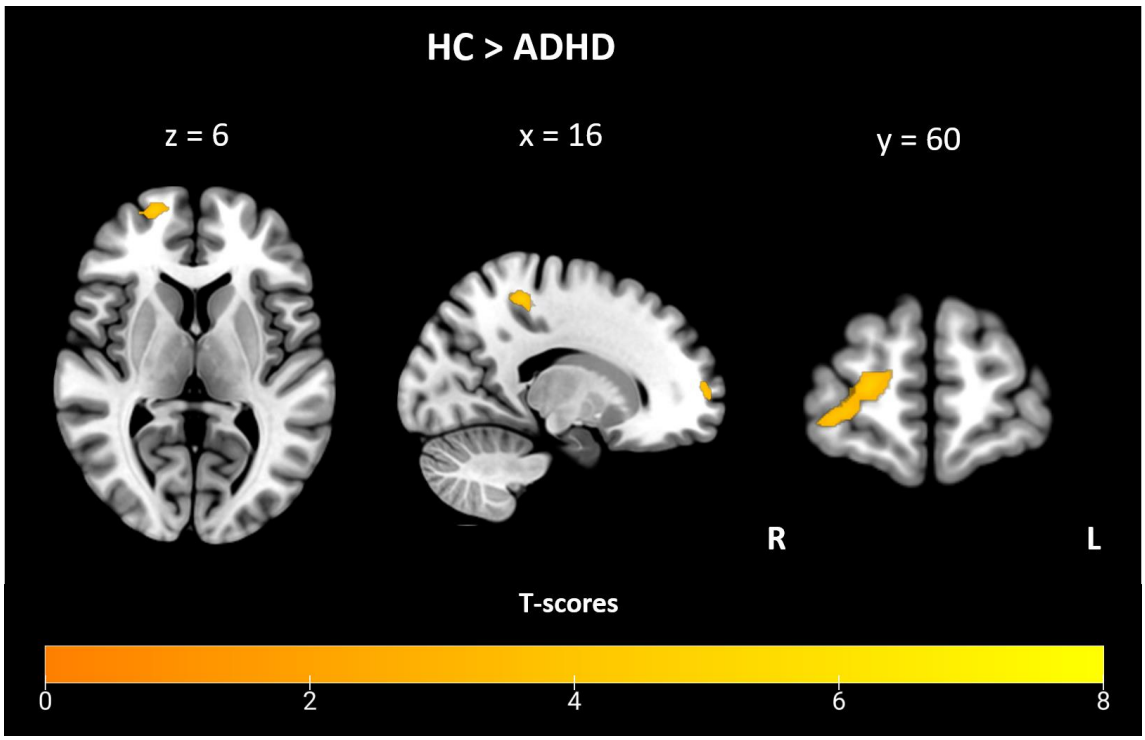

Figure 15: Brain activation associated with anticipation of decision-making for the contrast HC > ADHD ($p < 0.05$, FWE-corrected on cluster level, initial voxel threshold 0.001 uncorrected).

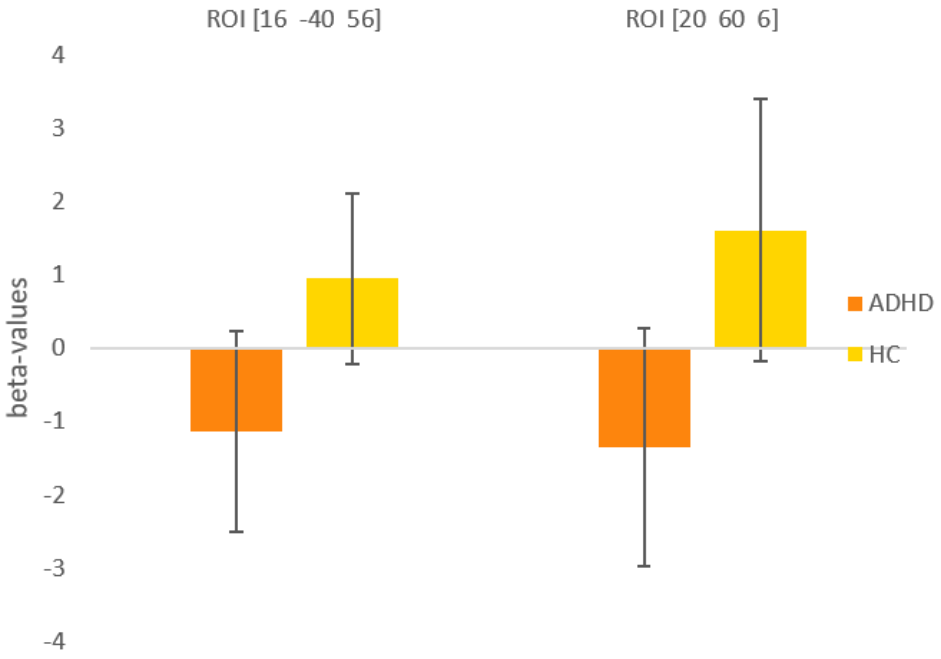

Figure 16: Mean beta values (± standard deviation = error bars) of peak coordinates in the two significant clusters comparing neural activation between ADHD (orange) and HC (yellow). ROI [16 -40 56] reflects the region of the right precuneus. ROI [20 60 6] reflects the region of the right superior frontal gyrus.

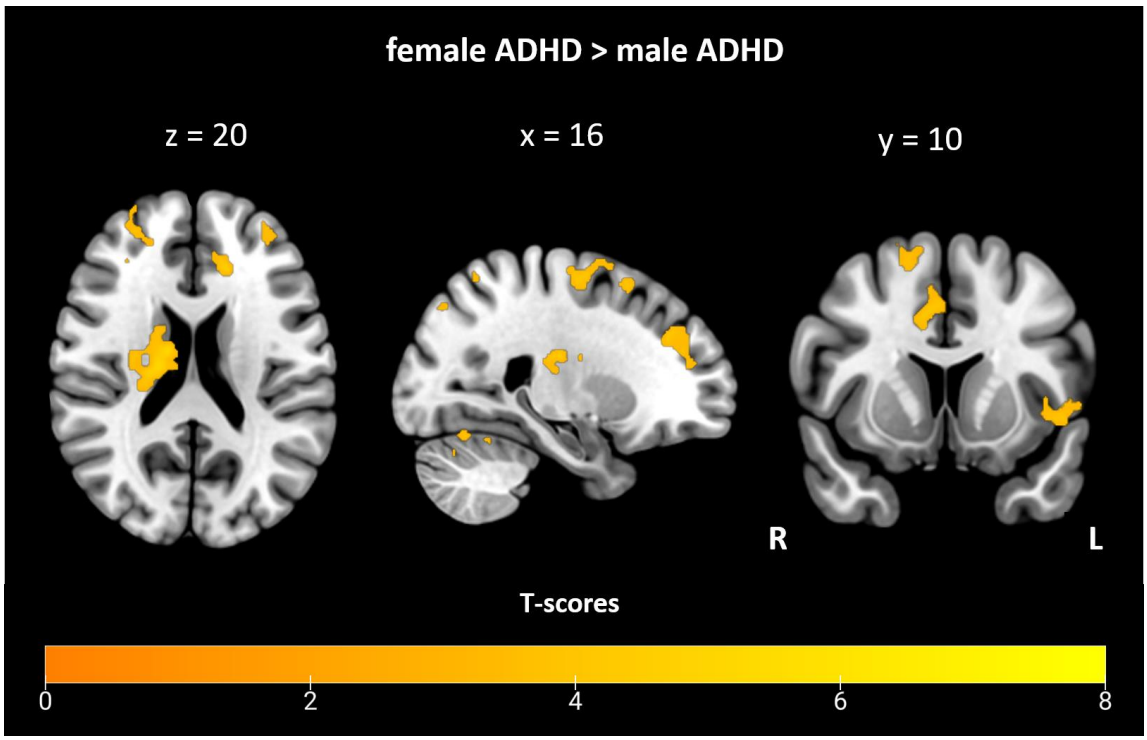

Figure 17: Brain activation associated with anticipation of decision-making in the contrast female > male of the within group comparison of the full factorial analysis in ADHD ($p < 0.05$, FWE-corrected on cluster level, initial voxel threshold 0.001 uncorrected).

3.3.4 Discussion

The current study is the first to examine whether adult patients with ADHD demonstrate altered neural activity prior to making a risky decision. Using fMRI during the performance of a modified version of the BART, we found significantly lower activation in the right precuneus and right superior frontal gyrus in adult patients with ADHD compared to HC. Moreover, we explored whether there were gender-dependent differences during the anticipation phase of DM. Results indicated no gender effect in the HC group, whereas in females compared to males with ADHD neural activity was increased within the dorsolateral prefrontal cortex (dlPFC), left insula, right caudate, right cuneus and precuneus. These results provide evidence that individuals with ADHD exhibit altered neural activity

immediately before making a decision, which may suggest impaired unconscious affectively driven DM behavior.

In the context of the somatic marker hypothesis, specific neural correlates have been reported, with particular emphasis on the vmPFC and OFC, as key regions critical for the integration processes underlying somatic marker functioning (Bechara et al., 2005; Verdejo-García & Bechara, 2009). However, in the current study we did not observe significant activation differences in these regions between individuals with ADHD and HC. Instead, we identified differences in activation patterns of the right precuneus and the right superior frontal gyrus during the anticipation of DM. A possible explanation for this discrepancy could be that the majority of studies addressing the somatic marker hypothesis have been based on the IOWA Gambling Task. The paradigm used in the current study was a modified version of the BART, which has not yet been utilized in any neuroimaging studies. In contrast to the original BART, the modified version was designed to favor more intuitive DM behaviour (Henn et al., 2023). Since it does not require a choice between two possible options, it likely involves lower cognitive-analytical functioning. On the other hand, in patients with ADHD we found decreased activation in the right superior frontal gyrus, a region known to be involved in various cognitive functions, including reward anticipation, response inhibition, and cognitive control (Friedman & Robbins, 2022; Geier et al., 2010; Ridderinkhof et al., 2004). Furthermore, the superior frontal gyrus has also been identified as a crucial component in the integration of cognitive and affective information (Eshel et al., 2007; Gray, Braver, & Raichle, 2002; Ridderinkhof et al., 2004; Van Leijenhorst et al., 2010). However, neural correlates in the preceding processes of DM are largely unexplored in ADHD. Notably, previous research has identified reduced volume and impaired connectivity of the superior frontal gyrus in ADHD (Vilgis et al., 2016; Zhao et al., 2020). Consequently, the results of the current study suggest that impairments in affectively driven DM in ADHD may be more likely associated with hypoactivity in the superior frontal gyrus.

Additionally, we observed hypoactivity in the right precuneus in patients with ADHD. The right precuneus has been shown to be involved in functions such as self-reflection and awareness in previous studies (Farrow et al., 2001; Johnson et al., 2002; Matthys et al., 2012). It has also been implicated in accessing interoceptive states and the experience of emotions (Terasawa, Fukushima, & Umeda, 2013). Importantly, the right precuneus is part of the neural network responsible for metacognitive abilities. Specifically, its functional connectivity with the medial anterior prefrontal cortex has been shown to be related with metacognitive assessment of memory (Baird et al., 2013; McCurdy et al., 2013). This suggests that the right precuneus plays a crucial role in our awareness of internal sensations, emotional experiences, and metacognitive reflection. In the context of the somatic marker hypothesis, the right precuneus appears to be relevant due to its involvement in the integration of emotion, somatic perception, and memory – all of which are critical components of affectively driven DM. A dysfunctional interaction in these processes can explain disadvantageous DM behaviour (Damasio, 1996). Furthermore, our findings of decreased activity in the right precuneus align with previous research indicating reduced gray matter volume in this region among individuals with ADHD. This reduced neural activity may contribute to deficient neurocognitive abilities, potentially leading to behavioral impairments in ADHD (Noordermeer et al., 2017; Noordermeer, Luman, & Oosterlaan, 2016).

In summary, both the right precuneus and the right superior frontal gyrus have been shown to be involved in important functions in the context of somatic marker processing. Our findings of decreased neural activity in these regions in individuals with ADHD suggest potential mechanisms underlying impaired affectively driven DM. Moreover, our study highlights the relevance of these regions even before conscious DM, shedding light on subconscious processes that may contribute to DM impairments in ADHD. However, both regions are part of broader networks of brain regions involved in higher-order cognitive functions, and further research on functional connectivity is needed to reveal further insights into subconscious processes in ADHD.

In our exploratory analysis, we also found that neural activity during the anticipatory phase of DM depends on gender in patients with ADHD. Activation in females was increased compared to males, with the most pronounced differences noted in regions implicated in the neurobiology of ADHD. Specifically, the dlPFC and the insula are frequently considered as neural bases for impairments in executive function as well as emotional regulation (Arnsten & Rubia, 2012; Lemiere et al., 2012; Norman et al., 2016; Seidman et al., 2005). Furthermore, gender differences in activation patterns were also observed in the right precuneus, suggesting that the hypoactivity found in the group comparison was primarily driven by males with ADHD. This aligns with existing literature indicating increased tendency for risk-taking in males compared to females (Barasinska, Badunenko & Schäfer, 2011; Byrnes, Miller, & Schafer, 1999; Eckel & Grossman, 2008). However, these gender differences were evident only in the ADHD group and were not identified in the HC group. Consequently, it could be assumed that males with ADHD experience more pronounced neural dysfunction and related ADHD symptoms. This observation contrasts with our initial hypothesis that women, due to increased impairment of affective functions, would exhibit stronger neural dysfunctions during the anticipation phase. However, a study examining the neural relationship between the somatic marker hypothesis and various emotional intelligence parameters showed a negative correlation in this context. Individuals with better abilities in emotional competence exhibited reduced functional activation during performance and less reactivity in response to emotional stimuli, indicating a greater neural efficiency (Killgore & Yurgelun-Todd, 2007). Taken together, the current results suggest gender-specific differences in neural activity preceding DM, which were only observed in individuals with ADHD. Nevertheless, comparing these findings with existing literature remains challenging as most studies on ADHD still have an unbalanced gender ratio and are predominantly based on male participant data.

For the behavioral parameters of the task, measured by reaction time to DM, we found no significant group differences between HC and ADHD. This indicates that there are no behavioral abnormalities related to risky DM in ADHD. Previous studies have also shown that it is difficult to identify difficulties in real-

life DM in adult patients with ADHD (Dekkers et al., 2016b; Mowinckel et al., 2015). In this context, it should be noted that in a meta-analysis, the effect size for differences between HC and ADHD in gambling tasks was found to be small-to-medium (Dekkers et al., 2020). Although the BART is restricted to examining primarily financial domains of DM behavior, a recent review has shown that the BART is the most sensitive task for detecting risk-taking behaviour in psychiatric disorders (Harmon, Haas, & Peterkin, 2021). Furthermore, study results were found to vary between subjective claims and objective measurements (Emser et al., 2018). However, taken together, these inhomogeneities highlight the need for further research in the field of impairments in DM behaviors in ADHD. Thus, the current findings indicate that, unconscious underlying processes and the integration of physiology and emotion may be an essential component.

Considering the current findings, there are some limitations that need to be taken into account. The exploratory full factorial analysis examining the effects of gender on neural activity was based on only a small sample size in the four subgroups due to the two factors included. This limited sample size could also have contributed to the lack of a significant effect found in the interaction of gender and group. Consequently, the results should be interpreted cautiously and can only serve as preliminary indicators of a potential effect. Furthermore, it must be considered that ADHD is a heterogenous disorder with individual variations in symptoms and their impacts, so that the current sample may not fully represent the entire population of individuals with ADHD and further studies with larger sample sizes are needed.

Overall, the present study represents the first investigation into neural correlates in patients with ADHD in anticipation of DM, aiming to provide deeper insights into risky behavior. The current findings suggest that more attention should be given to the right precuneus and superior frontal gyrus concerning metacognitive functioning and interoceptive awareness. Furthermore, the results underscore the complexity of ADHD and the importance of considering gender-specific neurobiological factors in research and clinical practice. However, further research is needed to explore additional neural processes involved in the

interplay between emotion, physiology, and DM, as well as to gain further insights into gender-dependent differences. In this context, future studies should emphasize the examination of integrative processes during the anticipation of behavioral actions. Combining physiological and neuroimaging measures can offer a more comprehensive view of the temporal interaction in these processes.

Chapter 4: General discussion

The aim of the present thesis was to investigate the DM behaviour of adult patients with ADHD. The focus was primarily on quick and intuitive decisions and the associated potential engagement of risky behaviour when making decisions. An important indicator for such decisions is unconscious affective processes that take effect shortly before a decision is made. To objectify and examine affective functionality and the associated emotional arousal, skin conductance and neural activity were measured. These measurements aimed not only to reveal insight into differences between patients with ADHD and HC but also into gender differences. This approach was intended to provide further understanding of the impact of affective processes and uncover possible variability within males and females suffering from ADHD.

Study 1 pioneered the exploration of 'hot functions' (emotional processes) in adult ADHD, particularly in the context of risky DM. A key finding was that individuals with ADHD showed significantly higher arousal both before DM and after receiving feedback. However, this heightened arousal did not translate into altered behaviour, indicating a difficulty in utilizing physiological cues for behavioural modification in the patient group. Additionally, self-reports revealed a diminished ability in ADHD individuals to perceive arousal and emotions, despite no significant difference in self-reported risk behaviour compared to HC. This underscores the potential benefit of incorporating emotional therapeutic techniques in ADHD treatment and highlights the need for further research into improving emotional processing in ADHD.

Study 2 extended the previous findings by demonstrating gender-dependent effects on affective functioning and intuitive DM in adult ADHD patients. Notably, it was found that women with ADHD were more inclined towards risky DM behaviours, linked to alterations in the ANS's activity and intuitive behaviour. This study calls for further investigation into the potential impact of heightened bodily function sensitivity and the influence of ADHD-specific medications on autonomic functions in DM behaviours. The findings

advocate for a gender-specific approach in the diagnosis and treatment of ADHD in adults, emphasizing the necessity of addressing these unique deficits.

Study 3 marks the first investigation into the neural correlates of DM anticipation in ADHD, providing valuable insights into risky behaviour. Significant attention was drawn to the role of the right precuneus and superior frontal gyrus in metacognitive functioning and interoceptive awareness. The study highlighted the complexity of ADHD and the critical need to consider gender-specific neurobiological factors in both research and clinical practice. Future research is encouraged to achieve a deeper understanding of the neural processes encompassing emotion, physiology, and DM, particularly focusing on gender-dependent differences. The integration of physiological and neuroimaging measures in future studies is suggested to offer a more comprehensive understanding of the temporal interactions in these processes.

In the following subchapters, the results of the three studies will be examined and discussed in their entirety. In particular, the aspects of emotion and DM, other potential impact factors on cognitive functions, the understanding of consciousness and unconsciousness, and the role of the ANS regarding clinical implication will be discussed in more detail.

4.1 Emotion and decision-making

For a long time, scientists paid little attention to the impact of emotions on DM. Nowadays, numerous theories assert that emotions, alongside cognition, play a decisive role in controlling and regulating behaviour. However, the principles and significance of human relationships, feelings, and intuition, compared to the reliability and our understanding of the laws of nature, are far less predictable and quantifiable. Unlike static mechanisms or physical circumstances, emotions are dynamic and fluctuating, varying not only among individuals but also within the same person across different contexts (Toda, 1980). As a result, disciplines ranging from philosophy to neuroscience are increasingly attempting to understand the impact of emotions on judgment and DM, although much remains

to be understood. By the 1990s, it became apparent that various DM processes, especially those involving significant risk and uncertainty, are influenced by underlying biases and emotions that operate on a subconscious level. The importance of emotional processes has been further emphasized with the foundation of the somatic marker hypothesis (Damasio, 1996; see Chapter 1.3.1.).

Given that adult patients with ADHD are associated with heightened risk-taking behaviour, impaired DM abilities in daily life, and the often exhibit dysfunctions in their emotional competence, we aimed to explore this interconnection of emotional arousal and risky DM behaviour. To do so, Study 1 of this thesis was designed to measure emotional arousal as a manifestation of ANS functioning using SCRs. It also aimed to analyse changes induced by emotional arousal in these responses in relation to subsequent DM behaviour. The results of this study were the first to shed light on this crucial interconnection in DM behaviour among adult patients with ADHD. We identified a heightened arousal state preceding and following a DM event (indicated by the somatic responses of aSCRs and rSCRs) in the group of patients with ADHD. As highlighted in Chapter 3.1.4., integrating these findings into the existing body of literature is somewhat constrained, due to the complex nature of this field. On one hand, previous studies have identified hyperactivity in autonomic somatic functions in patients with ADHD, suggesting a deficient downregulation of these functions. On the other hand, there is a contrasting body of evidence pointing to hypoactivity, attributed to insufficient external stimulation (Geissler et al., 2014). These conflicting findings present a challenge in aligning our results with the broader literature, as it encompasses both ends of the activity spectrum: from hypoactivity due to inadequate stimulation to hyperactivity resulting from an inability to adequately downregulate somatic functions. A recent meta-analysis also reflects this inconsistency, reviewing a number of studies investigating various types of physiological measurements as indicators of emotional arousal for comparison (Bellato et al., 2020). Although the majority of these studies indicate a hypoactive ANS in patients with ADHD, they often rely on baseline measurements or responses to individual stimuli. Thus, Study 1 of the current

thesis is the first to investigate the connection between bodily function and DM behaviour in ADHD. Our results suggest that quick and affectively driven DM behaviour under potential risk-taking leads to hyperactivation of autonomic somatic functions in adults with ADHD. However, in order to use the enhanced arousal to avoid further risk engagement, Study 1 demonstrated an aberrant relationship between physiological changes and DM behaviour in the patient group compared to the HCs. The observed negative correlation (see Chapter 3.1.3.2.) suggests that the perception of changes in physiology is either not coupled with, or is only weakly associated with, behavioural control. This implies that no internal warning signal (such as an increase in physiological response) is recognized as the risk increases. According to the somatic marker hypothesis, these study results suggest a deficient integration of emotion, physiology and behaviour in patients with ADHD. A diminished capacity for emotional control in individuals with ADHD aligns with results from a previous study showing reduced ability on tasks requiring cognitive appraisal and expressive suppression (Liu et al., 2022). The study indicated that individuals with ADHD have an increased tendency to struggle with managing their emotions, especially in situations that demand cognitive reappraisal (changing one’s emotional responses by reinterpreting the meaning of a situation) and expressive suppression (inhibiting the outward signs of one’s internal emotions). Additionally, a recent systematic review highlighted that emotion dysregulation in ADHD is caused by an inadequate top-down regulation of emotional reactivity by higher cortical regions (Soler-Gutérrez, Pérez-Gonález, & Mayas, 2023). Both studies suggest that adults with ADHD might use maladaptive emotion regulation strategies compared to HC. Thus, it could be inferred that the potential reliance on alternative mechanisms to process emotional arousal leads to an aberrant correlation between bodily response and behaviour. Taken together, Study 1 demonstrates that access to the representation of one's own emotional state and the perception of physiological changes can be assumed to be impaired in adults with ADHD.

However, the results of Study 2 (see Chapter 3.2.3.) further clarify this interconnection. The findings indicate that the overall overactivation of autonomic functions in patients with ADHD might be due to gender-dependent differences

in the ANS functions. Although no significant gender differences in physiological changes prior to DM (aSCRS) were observed in the patient group (see Chapter 3.2.3.4.), a significant negative correlation between physiological responses and subsequent behaviour (as observed in Study 1) was found only in women with ADHD. This implies that women with ADHD primarily contribute to the negative correlation between risky DM behaviour and physiological emotional arousal observed in Study 1. It suggests that women with ADHD may face greater deficits in emotional competence and struggle more to use affective information adequately. This aligns with research suggesting that adult females with ADHD are more prone to affective disorders and emotional dysfunctions (Biederman et al., 2004, 2005, 2008; Biederman, Mick, & Faraone, 1998; Gaub & Carlson, 1997; Gershon, 2002; Quinn, 2011; Stepp et al., 2012). A possible cause for a disturbed interaction in the use of bodily signals and behaviour could be the increased fluctuation rate of oestrogen in women (caused by the menstrual cycle). Previous studies have already shown that there is a dynamic interplay between ADHD-specific symptoms – particularly those affecting executive function – and the menstrual cycle, revealing significant fluctuations that align with hormonal changes (Eng et al., 2024). This variability in executive functioning, closely tied to hormonal cycles, suggests a broader impact on the integration of bodily reactions in DM. In this context, research by Amandusson and Blomqvist (2013) has underscored a compelling link between oestrogen levels and perception. This connection not only highlights the role of oestrogen in modulating sensory and pain responses, it also suggests a potential underlying factor for diminished bodily sensitivity observed in females. However, given the limited research on gender differences in ADHD, it remains challenging to fully understand the significance of the observed altered relation of emotional arousal and DM behaviour. Thus, the contrasting activity patterns in the use of autonomic somatic signals between genders found in Study 2, not only add a layer of complexity to our understanding of ADHD, but also raise fundamental questions about the underlying mechanisms that drive these differences.

Study 3 aimed to thoroughly investigate this issue by examining patterns of neural activity. Initially, significant group differences in neural activity were

observed, demonstrating that hypoactivity in the right precuneus and right superior frontal gyrus during the anticipation of DM could lead to potential impairments in DM behaviour in ADHD. However, as also observed in Studies 1 and 2, these impairments in DM behaviour were not reflected in the behavioural data. This discrepancy raises questions about whether laboratory conditions, as often discussed in other studies, limit the investigation of behavioural difficulties in patients with ADHD (further discussed in Chapter 4.2.). It should, nevertheless, be considered, that differences in neural processes when affective-driven behaviour is required suggest strong indications of deficits in processing of interoceptive perception and metacognitive functioning (see Chapter 3.3.4.). Furthermore, the full factorial analysis highlighted significant gender differences in neural activity preceding DM, exclusively found in the group of patients with ADHD. In this context, increased neural activity in the area of the left insula, right cuneus and precuneus, left precentral and lingual gyrus, as well as the right caudate was associated with the anticipation of DM only in women with ADHD. These findings from Study 3 provide further insights into the complex interplay between neural activity and DM processes in women with ADHD. In line with several previous studies, the left insula can be highlighted as a crucial component in affect processing and has also been linked to affective dysfunctions in patients with ADHD (Cortese et al. 2021). Furthermore, a recent meta-analysis emphasizes the dorsal mid-insula as a transdiagnostic, domain-general difference in interoceptive processing and viscerosensory functions, suggesting that disrupted mid-insular activation may represent a neural marker of psychopathology across various psychiatric disorders (Nord, Lawson, & Dalgleish, 2021). Research also points to unusual connectivity between the dorsal mid-insula and prefrontal areas, such as the superior frontal gyrus, impacting affective processing in psychiatric conditions (Sliz & Hayley, 2012; Avery et al., 214; Yin et al., 2018). However, studies on insula activity in ADHD show mixed results, with some indicating increased response to negative stimuli, while others report reduced left insula activity alongside increased right insula activity (Vetter et al., 2018; Yu et al., 2023). Our findings from Study 3 provide further insights into the complex interplay between neural activity and DM

processes in women with ADHD and highlighting the crucial role of the left insula. However, these results contradict the broader literature and our initial assumptions. Based on the previously obtained results from Study 2, it was assumed that the altered relationship between emotion and behaviour in the female patient group might also be associated with reduced neural activity in core areas relevant for affective functions or integration (according to the somatic marker hypothesis). However, the observed increase in neural activity during the anticipation of DM contradicts the expected reduction, for instance, in the left insula, a crucial region for emotional processes (Craig, 2011). In this regard, it should also be considered, that the results of the physiological activity (from Study 2) indicated rather increased and unimpaired emotional processing, matching this enhanced neural activation pattern. Given this discrepancy, it could be assumed that, in women with ADHD, emotional processing may not be conventionally impaired, but could instead be characterized by atypical neural engagement patterns during decision-related anticipation. The involvement of the left insula suggests a potentially heightened emotional responsiveness in these patients. This could imply that emotional processing in women with ADHD involves an overactivation of neural circuits associated with emotional and somatic feedback, which might influence DM processes differently from those in neurotypical populations or even in men with ADHD. A possible explanation could be an impaired projection and perception of physiological processes and body awareness. In this context, increased insula activation, as seen in Study 3, has been associated with higher level of alexithymia in a group of healthy participants (Wiebking & Northoff, 2015). Here, the intriguing finding discussed suggests that hyperactivation in the insula due to enhanced processing of emotional information, may not necessarily lead to increased effectiveness. Thus, the heightened activity in response to interoceptive signals might represent a compensatory mechanism within the salience network, aiming to adjust for potential deficits in processing these internal cues. In a study of patients with generalised anxiety disorder, increased insula activity has been linked to psychopathological hypersensitivity, where heightened sensitivity to somatic states results in diminished affect in context of an anxiety disorder (Cui et al.,

2020). Furthermore, the activation of the right cuneus and precuneus, along with the left precentral and lingual gyrus, indicates a more complex neural network at play, encompassing areas related to visual processing, attention, and motor planning. Overall, the findings suggest that the anticipatory phase of DM in women with ADHD may involve a broader array of cognitive and emotional integrations, possibly reflecting a compensatory mechanism or a distinct cognitive style, with potentially different consequences between genders within the patient group.

Another important concept concerning emotion and DM that needs to be considered is the dual pathway model (Sonuga-Barke, 2002). As outlined in Chapter 3.1.1., this model proposes two distinct systems of thinking. System 1 operates automatically, quickly, and often unconsciously, facilitating intuitive and emotional responses. This system efficiently supports quick judgments and spontaneous actions. Conversely, System 2 is characterized by slower, more deliberate, and conscious processing, involving analytical and logical reasoning. It comes into play during complex problem-solving and situations requiring careful contemplation. The interaction between both systems influences our DM process, suggesting that DM results from the complementary functions of both systems and requires a dynamic interplay between emotional and cognitive mechanisms. An overreliance on the emotional system can lead to impulsive decisions without adequate consideration of consequences, whereas overdependence on the cognitive system can result in analysis paralysis or deficits in empathy and social interaction. This also means when the cognitive system is overwhelmed by multiple factors, impairing attentional resources, DM can become impaired (De Neys, Schaeken, & d'Ydewalle, 2005; De Neys & Pennycook, 2019). In light of the results from Studies 1 and 2, which revealed increased SCR, it could be inferred that heightened emotionality influences the DM behaviour of patients with ADHD compared to the HCs. According to the dual pathway model, this increased emotionality indicates an imbalanced relationship between the two systems, potentially leading to unfavourable DM behaviour. The observation that the shown RTs, i.e. the risk behaviour, were even significantly lower in patients with ADHD compared to HC, implies that the imbalance between the two systems

favours emotionally impulsive functions. The enhanced emotionality, as evidenced by increased levels of physiological activity, particularly in tasks offering rewards, aligns with findings from other studies on ADHD. Specifically, research in feedback processing has indicated that the intensified emotional arousal of immediate rewards can be attributed to a type of reward seeking behaviour in ADHD (Shoham et al., 2016). This effect of increased reactive emotional arousal during the feedback display was also evident in the results of the present studies. However, while previous studies have demonstrated the influence of both systems, disentangling deficits of both systems in context of DM behaviour in individuals with ADHD remains a complex challenge (Schulze et al., 2021).

Despite this common theory, it should also be noted that new principles such as the Triple Pathway Theory view DM behaviour not solely based on the interplay between emotion and cognition. The Triple Path Model, introduced by Gary Klein emphasizes three distinct pathways to gain insights: contradictions (noticing inconsistencies with current beliefs), connections (forming new insights through coincidences), and creative desperation (challenging assumptions under pressure). This model expands our understanding of how insights that influence DM can be derived from diverse sources and situations (Klein, 2013). On this basis, the altered physiological response, as well as the altered relationship between physiological change and DM behaviour might suggest a different processing route in the Triple Path Model. In this context, patients with ADHD might process contradiction differently, potentially impacting how they recognize and resolve inconsistencies in their DM environment. Consequently, the perception of possible trigger points that correspond to one of the three pathways may not be uniformly recognized or weighted. For example, a contradiction that arises during the processing of a task may not be perceived at all or may be perceived differently by patients with ADHD, and thus also be accompanied by a deviating physiological response. According to this theory, a crucial aspect in this context is the need to modify the perception of specific triggers. However, the increased responsiveness indicated by significantly higher skin conductance, contrasts with the impaired perception of certain triggers.

Taken together, the findings highlight an altered relationship between emotion and DM behaviour in ADHD, predominantly driven by women. This alteration challenges conventional models and emphasizes the need for further research to dissect the intricate interplay between emotions and behavioural decisions in ADHD, particularly in female patients. In this context, future research should also consider hormonal influences to fully understand their implications for ADHD symptomatology and the integration of bodily states in cognitive processes. Our results on neural data have highlighted the crucial role of the left insula in the context of emotional responses and DM. However, the unexpected patterns of neural activity necessitate further investigations to understand the complex dynamics between emotions and DM behaviours, as well as the gender-related differences in affective functions.

4.2 The complexity of decision-making

The complexity of researching DM behaviour extends beyond the difficulties in measuring individual emotional processes that might impact decisions. For years, scientists have explored the neurobiological foundations and effects of DM behaviour, consistently contributing new theories and insights into the underlying mechanisms and signalling pathways. The complexity of this field increases when examining daily life impairments under laboratory conditions and when investigating intuitive and unconsciously driven behaviour, which may also be influenced by various situational environmental conditions. In this context, the behavioural results of Studies 1, 2, and 3, included in this thesis do not fully capture the commonly observed impaired DM behaviour in individuals with ADHD. Previous studies have emphasized the need for new empirical paradigms to bridge the gap between economic and naturalistic risk-taking, highlighting the importance of tasks that can enable the investigation of behavioural and neural factors predicting naturalistic risk-taking behaviours (Schonberg, Fox, & Poldrack, 2010). Additionally, the literature provide evidence that tasks with realistic rewards are more sensitive in reflecting ADHD-related deficits (Scheres,

Lee, & Sumiya, 2008). Thus, the non-significant group differences observed in Studies 1-3 might be due to unsuitable laboratory conditions. This underscores the importance to develop new methodologies that more accurately reflect real-world conditions and behaviours, particularly those influenced by intuitive and unconscious processes.

Interestingly, a significant difference in the RT was observed in Study 1, even indicating higher risk-taking in the HC group. In other words, significantly less risky DM behaviour was observed in the group of patients with ADHD. The aforementioned complexity of interpersonal and external factors that could affect DM behaviour (see Chapter 1.3.) may provide a possible explanation, as these factors can be considerably more complex in psychiatric cohorts. This variability can complicate the identification of consistent patterns or effects on DM processes. Many psychiatric disorders, including ADHD, are associated with cognitive distortions and altered perceptions, which may vary with the disorder's severity, the individuality of symptoms, and the presence of drug and psychotherapeutic treatments or comorbidities (Millan et al., 2012). These factors can not only distort objective measurements, such as the potential long-term effect of stimulants on the ANS, but can also impair self-perception and thus affect self-reports (Christiansen et al., 2019). Particularly, in patients with ADHD, the heterogeneity in clinical profile can play a major role in studies on DM behaviour. For instance, the typically occurring symptom of impulsivity must be taken into account when investigating DM behaviours. It needs to be considered that impulsivity plays a critical role especially in performance requiring quick actions and intuition that demands underlying unconscious functions. Impulsivity is characterized by actions that are poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation and often result in undesirable outcomes. Impulsive behaviour has also been linked to delayed maturation of the PFC and impaired reward processing, referring to dysfunctions in the dopamine system (Shaw et al., 2011). Furthermore, as describes in Chapter 1.3.2. impulsivity could result from heightened "wanting" or motivation of immediate reward, coupled with diminished "liking" or pleasure from those rewards, especially in tasks requiring sustained attention (Berridge & Kringelbach, 2008).

This could have led to quicker DM, as demonstrated by the behavioural data in Studies 1-3, where individuals with ADHD prioritize immediate reward or novel stimuli, potentially disregarding long-term consequences. Investigations of impulsive DM behaviour in ADHD have often utilized delay discounting tasks, which have revealed emerging behavioural alterations towards impulsive choices (Knutson et al., 2001). Referring to the dual pathway model, impulsivity is conceptualized as stemming from deficits in both cognitive control and emotional regulation. Cognitive deficits may lead to challenges in inhibiting impulsive actions and in making thoughtful decisions. Concurrently, difficulties in emotional regulation can intensify impulsivity, as it might reduce the ability to effectively manage and respond to emotional states (Sonuga-Barke, 2003). This dual deficit could have come into play and needs to be considered in relation to the behavioural data presented.

Another important aspect affecting the complexity of investigations on DM in ADHD is the heterogeneity in symptom profiles between men and women. In this context, previous research has already emphasized that there are potential types of decisions that are beneficial for women compared to men and vice versa (Bechara et al., 2005). For instance, studies have shown that risky DM behaviour, such as gambling, differs between boys and girls (Hooper et al., 2004; Overman, 2004). Accordingly, a meta-analysis on HC showed increased risk-taking in males compared to females (Byrnes, 1999). Notably, although Study 2 observed increased risk-taking behaviour among men in the HC group, women in the patient group exhibited a significantly greater tendency towards risky behaviour. Compared to the assumption that deficits in affective regulation and perception may result in altered behavioural patterns in women, it is also plausible that a higher prevalence of impulsive symptoms in men with ADHD contributes to their lower RTs. Furthermore, gender differences in ADHD symptoms can also be observed in other cognitive functions. Studies suggest that women with ADHD often experience more symptoms of inattention compared to men with ADHD (Robison et al., 2008). Inattention can be characterized as a lack of focus, awareness, or responsiveness to environmental stimuli, often due to factors such as distractibility. Patients with ADHD frequently struggle to maintain attention on

tasks or may easily be distracted by extraneous stimuli (Schoechlin & Engel, 2005). Therefore, it must be considered that overall performance on DM tasks is affected by a shift in attention and an impaired perception and subsequent processing of relevant information. Since the paradigm used is designed to be simple and monotonous to ensure good comparability and efficient investigation of behavioural, physiological, and neural changes, low stimulation during the performance could have led to unfocused action. However, the relationship between cognitive performance and arousal is not limited to patients with impaired attention, but can also be observed in HC subjects (Yerkes & Dodson, 1908). At the neural level, the pathology of inattention may arise from aberrant activation within the PFC or the anterior cingulate cortex, contributing to difficulties in adapting to changes in task demands (Friedman & Robbins, 2021). A lack of arousal and the resulting lack of focus is also a consequence of dysfunctions in the noradrenaline neurotransmitter system. Particularly noradrenergic pathways from the locus coeruleus to the cortex are critical in regulating attention and response inhibition (Bari et al., 2020). Furthermore, individuals with ADHD often exhibit differences in how they process sensory information, which can manifest as either hypersensitivity or hyposensitivity to sensory stimuli. These sensory processing issues can contribute to the symptoms of inattention seen in ADHD. Accordingly, overstimulation due to hypersensitivity might lead to distraction and difficulties in concentration and attention (Fassbender et al., 2009). In addition, the precuneus was found to play a role in integrating sensory information with thoughts, memories, and experiences (Cavanna & Trimble, 2006). Therefore, in line with the current finding of hypoactivity in the right precuneus in patients with ADHD, it could be assumed that during the performance, these patients were less able to integrate sensory input with personal awareness. Further consideration was given to the fact that this neural activation pattern in the precuneus was also evident in the gender difference within the patient group, with male patients with ADHD exhibiting reduced neural activity. However, it should be noted that according to results from the CAARS questionnaire, there were no significant differences in terms of impulsivity or inattention between men and women with ADHD.

Taken together, it remains challenging to determine whether altered affectively driven DM behaviour relies on the inability to perceive and be aware of interoceptive information, the lack of focus due to inattention, or the inability to inhibit responses due to the symptom of impulsivity.

4.3 Unconscious and conscious processing

In the field of decision neuroscience, research into unconscious processes demands a comprehensive understanding of the intricate principles of consciousness and unconsciousness. Although the somatic marker hypothesis highlights the importance of unconsciously linking emotions, previous experiences, and physical reactions in DM, it is still crucial to consider the role of rational deliberation and awareness. Even when affective functions operate effectively at an unconscious level, there should be an awareness of one's actions and their consequences (Damasio, 1996). In some situations, the human body reacts with an innate response pattern, commonly known as the fight-or-flight response, where hyperarousing stimuli (e.g., encountering a snake) trigger a conditioned reaction (Cannon, 1914). Related to the somatic marker hypothesis, such stimuli can also provoke a full response solely by a cognitive representation (without actually facing this stimulus), a phenomenon termed the "as-if body loop". This process allows us to anticipate an expected bodily response without the actual physiological involvement (Dunn, Dalgleish, & Lawrence, 2006). This mechanism enables quick and unconscious DM, bypassing the slower, more conscious processes typically associated with the traditional "body loop," where emotions are experienced through physiological changes in the body. In the context of the as-if-body loop, the brain, particularly regions like the amygdala and the PFC, plays a crucial role in processing emotional content and generating what might be considered a 'virtual' body response. Consequently, traditional physiological measures, such as skin conductance, might not capture processes based on the as-if body loop.

The insights from distinguishing between the body loop and the as-if-body loop are crucial, particularly when considering the findings from Studies 1 and 2. Alterations in DM processes might occur independently of observable changes in skin conductance, suggesting that quick RTs, especially in trials involving a certain reward condition, could indicate an innate response mechanism akin to the as-if-body loop. In individuals with ADHD, who are often characterized by impulsivity and a propensity for quick DM, there is frequently a lack of reflection in thought processes (Butzbach et al., 2021). The cognitive processing according to the “shortcut” provided by the as-if body loop, facilitated by the amygdala aligns with these characteristics, suggesting that individuals with ADHD might rely more heavily on this fast-acting, unconscious DM system. Furthermore, differences in the neural activation pattern observed in Study 3 could also be referred to this understanding. The precuneus, known for its involvement in self-consciousness, aspects of memory retrieval, and the visualization of experiences, plays a key role in integrating information from various sources to construct cohesive self-awareness (Schmitz et al., 2006; Baird et al., 2013; McCurdy et al., 2013). Its reduced activation in the group of patients with ADHD might suggest decreased engagement in self-referential processing or the visualization of potential outcomes, which could indicate a less introspective or reflective DM strategy, potentially associated with the as-if-body loop pathway. Additionally, the region of the superior frontal gyrus, which is associated with higher cognitive functions, was also found to be hypoactivated in the group of patients with ADHD. This could lead to decreased reliance on executive control and might reflect a preference for more impulsive and immediate response. Overall, these findings suggest a more complex interplay between conscious and unconscious processing in DM, possibly indicating adaptive or compensatory mechanisms in individuals with ADHD that obscure some of the hypothesized results.

In order to examine the complexities of consciousness and unconsciousness, questionnaires were included to measure subjective self-reports about personal behaviour. As outlined in the methodology of Study 1 (see Chapter 3.1.2.), these questionnaires were utilized to bridge the gap between unconscious processes and conscious self-reflection of their own behaviours. A

previous study highlighted a discrepancy between conscious awareness of one's behaviour and actual performance, finding significant differences in error processing, particularly in the awareness of errors among individuals with ADHD compared to matched HCs. This study underscored that relying solely on self-reports might not fully capture the extent of behavioural difficulties in ADHD, emphasizing the need to incorporate objective measures for comprehensive understanding (O'Connell et al., 2009). To assess possible discrepancies regarding the risky behaviour, the DOSPERT questionnaire was included in Studies 1 and 2. Previous studies have validated the DOSPERT, demonstrating its sensitivity to realistic behavioural parameters (Shou & Olney, 2023; Brailovskaia et al., 2018). In this context, DOSPERT scores have been associated with increased impulsivity and sensation seeking. However, the current findings from Studies 1 and 2 did not show significant differences in DOSPERT scores between ADHD and HC, which contradicts existing literature that suggests an increased engagement in risky behaviours among adults with ADHD (Faregh & Derevensky, 2011; Flory et al., 2006; Lee et al., 2011; Pratt et al., 2002; Pollak et al., 2019). This further emphasizes the assumption of reduced self-reflection in one's own behaviour in adults with ADHD. Regarding self-assessment in ratings of one's own benefits (ben) in the DOSPERT, a previous study identified higher perceived benefits in patients with ADHD (Shoham et al., 2016). It was discussed that DM processes might be influenced more by the appealing aspects of risky behaviours rather than a diminished perception of risk (Pollak et al., 2019). Results from Study 2 also demonstrated that individuals with ADHD rate the benefits of scenarios higher, though these differences were not statistically significant. Nonetheless, because the perceived risk in these situations remained consistent across surveys, this indicates a shift in focus toward potential benefits among the ADHD group, which may obscure their recognition of associated risks. Overall, this indicates that risky behaviour might occur more due to a shift in focus rather than an inadequate perception of the situation.

Another questionnaire utilized to explore self-assessment of their own behaviour, specifically concerning awareness of feedback sensitivity, was the

SPSRQ (Sensitivity to Punishment and Sensitivity to Reward Questionnaire). This questionnaire was developed to operationalize the major motivational systems underlying behaviour and personality by regulating aversive and appetitive motives (Torrubia et al., 2001). There is evidence that feedback sensitivity in patients with ADHD is often skewed, with a preference for immediate rewards and a diminished response to punishment (Luman et al., 2008; Scheres et al., 2007). Contrary to expectations based on findings from previous studies, the results of the SPSRQ in Study 2 reveal neither gender nor group differences, which may also indicate a diminished self-awareness of feedback sensitivity among participants with ADHD. Moreover, no gender differences were identified, which further suggests that particularly women with ADHD may be impaired in their self-perception. Since increased risk-taking behaviour was observed in women with ADHD compared to men with ADHD in the behavioural data, these findings further demonstrate a discrepancy between subjective and objective measures of feedback sensitivity. This suggests that women with ADHD, in particular, may be impaired in their self-perception. Considering the gender differences in externalizing and internalizing behavioural characteristics, as well as variations in neural functions related to reward processing, it can be assumed that more intricate underlying mechanisms may exist. Exploring and understanding feedback sensitivity in patients with ADHD is crucial, particularly for optimizing treatment strategies. The discrepancies between subjective experiences of feedback sensitivity and objective responses may complicate self-regulation and adaptive behaviour adjustments in response to feedback, highlighting the complexity of ADHD and the challenges in understanding and treating it (Sonuga-Barke, 2005; Owens et al., 2007). For instance, psychotherapeutic interventions can be tailored to enhance the recognition and management of external stimuli more effectively and considering different strategies for males and females. Accordingly, a previous study has shown that children with low levels of impulsive negative behaviour respond best to behavioural interventions that use reward contingencies, suggesting the significance of examining individual neuropsychological profiles when treating ADHD (Van Langen et al., 2020). However, further research is needed to

understand gender differences in feedback sensitivity and the importance of tailored ADHD treatment. With regard to feedback processing and the sensitivity attributed to an outcome, prior expectations play a crucial role. It is known that positive feedback triggers dopamine release. However, if a positive outcome is anticipated, the increase in dopamine levels occurs at the time of expectation rather than at the time of receiving the reward itself (Faller, 2010). Based on the increased perceived benefit (ben)-scores in the DOSPERT for patients with ADHD observed in Study 2, it could be inferred that these patients tend to have more positive expectations, even under risky conditions. This increased expected utility of their own actions thus differs from that of the general population who, according to prospect theory, tend to behave in a risk-averse manner when outcomes are uncertain (Kahneman & Tversky, 1984). Consequently, this implies that dopamine release is diminished when an actual reward is presented. Moreover, a recent study using a mouse model demonstrated that when large reward expectations are not met, unexpected reward omission leads to a decrease in dopamine concentration, particularly in the ventral striatum region (Shikano et al., 2023). A lack of dopamine can be associated not only with reduced cognitive performance but also with metacognitive capacity, which is strongly linked to dopaminergic regulation (Joensson et al., 2015). Altogether, this might have caused a perpetual cycle where patients with ADHD engage in increased risk behaviour to compensate for their own dopamine deficiency, have particularly high expectations of potential rewards, and experience further decline in dopamine concentration when these expectations are unmet.

Overall, while primarily focused on the unconscious processes of DM in ADHD, the data presented in Studies 1-3 also shed light on the critical aspect of conscious self-awareness of one’s own behaviour. Self-report data indicate diminished self-perception in patients with ADHD, particularly among female patients concerning their attitudes towards risk and feedback sensitivity. Further research is needed to gain a deeper understanding of the relation between metacognition, expectations, and feedback processing. However, the current results suggest that addressing individual profiles of self-reflection abilities can lead to targeted interventions potentially improving DM strategies.

4.4 The impact of physiological responses – clinical implication

The significance of the ANS in the relationship between arousal and cognition was comprehensively discussed in Chapter 4.1. Studies 1 and 2 demonstrated not only a relationship between ANS function (an indicator of arousal) and behaviour, but also an alteration in patients with ADHD. This alteration is particularly evident in the deficient relationship observed in women with ADHD.

At neural level, ANS functions are linked to the interplay between arousal and cognition, especially involving activation patterns in the LC. This small nucleus, located in the brainstem, is the main source of noradrenaline and thereby a crucial mediator interconnecting the bodily state (homeostasis between PNS and SNS) and the central nervous system (Bast, Poustka, & Freitag, 2018). Thus, arousal is regulated by noradrenergic projections from the LC, which are also directly related to cognitive processes. (Zhang et al., 2013; Murphy et al., 2014). According to the Yerkes-Dodson-Law, a phasic release of noradrenaline causes an increase in arousal which in turn is related to task-focused attention. In contrast, low-rewarding stimuli are associated with tonic release resulting in disengagement from the current task. Consequently, surrounding stimuli are unconsciously sought out to provide the necessary stimulation for concentrated performance and sustained attention (Yerkes & Dodson, 1908). However, in patients with ADHD, external stimulation is often inadequately absorbed, which may also affect hyperactive autonomic function, resulting in overstimulation and feelings of being overwhelmed. On the other hand, indications of hypoactive functions of the ANS can promote self-stimulation, such as through impulsive, risky behaviour (Bellato et al., 2020). In this context, it can be assumed that inhibited rise of emotionality, as indicated by the negative correlation of physiological activity and subsequent behaviour in the results of Studies 1 and 2, causes a diminished ability to sustain attention on relevant cues of risk factors and thus resulting in intrinsic impairment to recognise potential risk. However, the extent to which altered activity in the ANS in patients with ADHD is also associated with a reduction in cognitive performance is not yet fully understood, and further research is needed.

Changes in autonomic functions have also been demonstrated in other psychiatric disorders. For instance, patients with major depressive disorder exhibited reduced physiological activity indicating a dysregulation of the balance between sympathetic and parasympathetic nervous system activity (Wang et al., 2013). The relationship that a decrease in affective functions is associated with reduced ANS functioning, as observed in women with ADHD in Study 2, might be an interesting approach to use ANS functions as transdiagnostic clinical markers. Thus, measurements of autonomic functions could potentially be used in clinical diagnostics to differentiate between different symptomatic profiles of affected patients. Physiological measurements could thus continue to be used as an objective tool in the assessment of comorbid conditions. However, the findings of Study 2 also indicate that different ANS profiles may also exist between ADHD males and ADHD females, which may also be a helpful indicator in the diagnosis of ADHD. Thus, based on the results presented in the current thesis, important distinctions can be made not only between patients with ADHD and HCs but also between the genders within the patient group. Furthermore, the hypofunction of the ANS is also shown by an increased susceptibility for patients with ADHD to suffer from sleep disorder, allergies, asthma, difficulties in regulating appetite, and hypertension, all which is controlled by autonomic functions (Faraone et al., 2021). Consequently, physiological measurements can also be a useful preventive tool in monitoring other clinically relevant abnormalities.

The significance of autonomic functions for behavioural action and for a performance that requires sustained attention also becomes relevant when considering the effects of ADHD-specific medication on physiological responses. A recent meta-analysis indicated that ADHD-specific pharmacological treatments (e.g. methylphenidate) enhance an upregulation ANS, thus increasing arousal in patients which may result in improvements in cognitive performance (Idrees et al., 2023). By inhibiting the reuptake of neurotransmitters norepinephrine and dopamine in presynaptic neurons, it increases their concentration in the synaptic cleft (Hannestadt et al., 2010). This action leads to heightened arousal and stimulation of the ANS, manifesting in increased heart rate, skin conductance, and blood pressure. A similar effect has also been found for antidepressants, and

the usage of ANS measurements has been shown to be an efficient biomarker for treatment stratification (see Chapter 1.2.1; Kircanski, Williams, & Gotlib, 2019). Additional interventions, such as vagus nerve stimulation or trigeminal nerve stimulation were also found to have an upregulating effect on the ANS. Both techniques reveal an increase in the LC activity and consequently enhance transmitter release to induce arousal (Zaehle & Krauel, 2021; De Cicco et al., 2018; Farrand et al., 2023). The reduction in neural activity in prefrontal regions, such as the superior frontal gyrus shown by Study 3, may also be driven by the widespread projections of the LC. The bi-directional connection of LC and PFC reflects that the prefrontal regions are under significant control of noradrenergic projections from the LC, highlighting that optimal levels of noradrenaline are necessary for working memory functions and the regulation of autonomic functions (Sara, 2009). Thus, enhancing LC activity via vagus or trigeminal nerve stimulation could lead to improved behaviour and autonomic regulation in patients with ADHD. This underscores the therapeutic potential of modulating noradrenergic pathways for conditions such as ADHD, which are associated with dysregulated autonomic and cognitive processes.

Taken together, physiological measurements could supplement clinical diagnostics to make predictions about unconscious emotional processes and potential behavioural effects, as well as effects in the context of comorbid disorders. Beyond the use of stimulants, vagus nerve or trigeminal nerve stimulation could be a promising approach to enhance autonomic functions. Further examination in neural activity and SCR could also explore the role of the LC in cognitive and emotional processes, particularly in regards to metacognition and interoception. Insights into LC projections could reveal how alterations in this neural pathway contribute to psychiatric and neurological conditions, potentially guiding more targeted therapeutic interventions. Understanding these mechanisms may enhance our comprehension of the complex interplay between brain, physiology, and cognitive-emotional experiences in various disorders.

4.5 Limitations

In transitioning to the critical evaluation of the presented research, it is necessary to consider its limitations. The limitations of the three studies have been briefly outlined in the respective chapters of the discussion (see Chapters 3.1.4, 3.2.4, and 3.3.4). These limitations will be summarized in the following section. Additionally, cross-study limitations and considerations related to study design, methodology, and analysis will be discussed.

One of the major considerations that needs to be taken into account is the number of subjects who participated in the presented studies. The sample size plays a crucial role in discussions of validity, reliability, and generalizability of research findings. One of the most significant consequences of small sample sizes is the reduction in statistical power, which is the probability of correctly rejecting a false null hypothesis. This implies that relatively small sample sizes can increase the risk of a Type II error (false negative). Additionally, there is the increasing challenge of ensuring that the study cohort is representative of the general population. In research on ADHD, this difficulty in generalisation can be further complicated by the heterogeneity of the clinical picture. Consequently, “small sample size bias” needs to be considered when evaluating effect sizes to avoid overestimation and inflated expectations. However, adopting advanced statistical methods that are more robust to the effects of small sample sizes, such as considering repeated measures and potential cluster formation using mixed models, or the applying FWE-correction at cluster level when considering multiple comparisons in neuroimaging analyses, can mitigate these issues.

Moreover, the three studies presented could also be affected by additional interfering factors. These may initially occur as within-group variability in the patient group, whereby influencing factors such as comorbidity, medication intake or symptom severity can impact the data collected. In this context, the long-time effects of ADHD-related medication use on ANS function are not yet clear. As described in Chapter 4.4., regular medication use can have upregulating effects on autonomic somatic functions (Bellato et al., 2020; Idrees et al., 2023).

However, even though all patients were asked to cease medication intake 24 hours prior their participation in the study, potential long-time effects might still influence their behaviour. Another potential interfering factor could be the age of participants. Although age was normally distributed in all three studies and did not differ between groups, previous research indicates an impact of age on behaviour as well as on physiological measures. Regarding the measurements of skin conductance, a diminished amount of sweating per gland with increased age has been shown to relate to a decrease in the number of active eccrine sweat glands (Fenske & Lober, 1986; Balin & Pratt, 1989). Furthermore, this reduction in sweating per gland in relation to age is more pronounced in males than in females (Morimoto, 1978). In terms of disadvantageous DM behaviour in the BART, a previous study found a linear decline in performance, trending towards riskier behaviour among individuals aged 13 to 17 years (Collado et al., 2014). However, compared to older adults risky DM behaviour on the BART has been found to decrease (Koscielniak, Rydzewska, & Sedek, 2016). Another previous study also indicates that gender affects skin conductance measures, particularly in interaction which changing environmental conditions, such as time of day or season of the year (Venables & Mitchell, 1996). From a methodological point of view, there may also be other individual effect in the response rate of physiological and neuronal measurements. Further external factors such as the principle investigator, experimental management or experimental environment may have had a possible influence on the collected data (Boucsein, 2012).

In addition, the study design used must also be considered as a possible limitation across all studies. This includes the frequently mentioned usability of the paradigm employed. It is important to note that the modified paradigm used, unlike the original version, distinguished between trials with different reward conditions. However, no effects of the rewards conditions were found regarding group differences in behaviour and SCR. Therefore, the factor of reward condition was excluded in Study 2. Contrary to expectations that behaviour and biophysiological data depend on reward magnitude, it can be suggested that the modified paradigm might not sensitively capture the nuances of how rewards influence DM in ADHD. This could be due to various factors such as the task's

design, the specific measures of risk engagement used, or the homogeneity of the sample in terms of their sensitivity to reward. Furthermore, the aspect of feedback processing was only infrequently considered in this thesis. Various studies have already demonstrated that feedback processing is a crucial factor during DM behaviour in patients with ADHD and might influence the findings of this study (Dekkers et al., 2021; Groen et al., 2013). However, the primary objective of this research was to examine anticipatory processes and their influence on DM behaviour in individuals with ADHD. This focus was intended to address a gap in the literature regarding how affective anticipatory mechanisms contribute to the propensity for risky decisions in ADHD. Given the finite resources and constraints inherent in any research project, such as time and funding, it was necessary to prioritize certain aspects over others. However, since the collected data contains information on feedback processing, it should be further analysed in the future to provide deeper insights into interesting and important issues within this context.

In summary, it is essential to interpret the results within the context of the aforementioned limitations. Additionally, this thesis represents only a condensed part of the collected data, which was utilized to examine the specific hypotheses. This indicates that further analyses of the available data are necessary, as well as follow-up studies with larger samples that can extend the findings presented. Nevertheless, the three studies have made a significant contribution to research in the field of decision neuroscience in ADHD and have provided first insights into a previously unexplored topic.

4.6 Conclusion

In conclusion, this thesis firstly explores the impact of affective functions during anticipatory processes of DM behaviour in adult patients with ADHD. By implementing three subsequent study phases (Studies 1-3), this thesis explores the complex interplay of emotional arousal, biophysiological processes, and DM behaviour. Comparisons of SCRs, neural activity patterns, RTs, and self-reports

between a group of adult patients with ADHD and a matched group of HC, as well as between genders were performed. We identified an altered processing of arousal and bodily signals when anticipating DM. Findings from Study 1 demonstrated that increased risk-taking is not accompanied by an increase in physiological activity in adults with ADHD. This can be interpreted as deficient internal warning signals and a diminished capacity for emotion regulation in patients. These maladaptive strategies suggest an underlying dysfunction in how individuals with ADHD process and respond to emotion-evoking events, potentially exacerbating DM difficulties. Building on these findings, Study 2 extended our understanding of gender-specific dynamics regarding this interplay of emotion and physiological processes. Results confirmed that the negative correlations observed in the patient group were predominantly driven by women. This aligns with literature that notes inhibited emotional processing and affective dysfunctions, particularly in females with ADHD. Study 3 further expanded the exploration to the neural correlates, finding reduced activity in the region of the right precuneus and superior frontal gyrus, areas that are critical for metacognitive functions and interoceptive awareness. Interestingly, while hypoactivity was expected to be more pronounced in females, it was the male participants who exhibited these patterns, suggesting that gender may influence the neural pathways involved in ADHD differently. Increased activity in the left insula among females can be discussed as deriving from stronger feelings of negative affect, highlighting the crucial role of the left insula in female patients and an area of interest for further investigations in this field.

This thesis emphasizes the relevance of gender-specific differences among patients with ADHD, which are evident not only in bodily processes but also impact DM behaviour. In this context, the present results emphasize the importance of considering symptoms that are of an emotional nature. This thesis highlights the importance of individualized treatment and acknowledges affective dysfunctions as a crucial characteristic in the symptomology of ADHD in adulthood. Furthermore, the findings on ANS measurements indicate that physiological measures might be a viable additional tool in diagnostic, particularly in terms of assessing efficiency of ADHD-specific medications. For instance,

measurements of physiological activities could be used to understand and identify individual behavioural patterns that are processed unconsciously and therefore cannot be verbalized.

However, it remains challenging to disentangle whether altered affectively driven DM behaviour relies on the inability to awareness and perception of interoceptive information, the lack of focus due to inattention or the inability to inhibit due impulsivity. In future studies, it would be particularly interesting to investigate the relationship between oestrogen fluctuations during the menstrual cycle in women with ADHD and the related interplay of emotion, physiology, and behaviour. Additionally, further studies are needed to investigate the possible long-term effects of ADHD-specific medication on ANS functions and which alternative therapy methods could influence this interaction. Furthermore, measures of SCR can provide a useful approach to explore transdiagnostic mechanisms to broaden our understanding of overlapping clinical practices with different psychiatric conditions.

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Appendix A: Published version Study 1

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Altered interaction of physiological activity and behavior affects risky decision-making in ADHD

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Background: Adult attention-deficit/hyperactivity disorder (ADHD) is often associated with risky decision-making behavior. However, current research studies are often limited by the ability to adequately reflect daily behavior in a laboratory setting. Over the lifespan impairments in cognitive functions appear to improve, whereas affective functions become more severe. We assume that risk behavior in ADHD arises predominantly from deficits in affective processes. This study will therefore aim to investigate whether a dysfunction in affective pathways causes an abnormal risky decision-making (DM) behavior in adult ADHD.

Methods: Twenty-eight participants with ADHD and twenty-eight healthy controls completed a battery of questionnaires regarding clinical symptoms, self-assessment of behavior and emotional competence. Furthermore, skin conductance responses were measured during the performance in a modified version of the Balloon Analogue Risk Task. A linear mixed-effects model analysis was used to analyze emotional arousal prior to a decision and after feedback display.

Results: Results showed higher emotional arousal in ADHD participants before decision-making ($\beta = -0.12$, SE = 0.05, $t = -2.63$, $p < 0.001$) and after feedback display ($\beta = -0.14$, SE = 0.05, $t = -2.66$, $p = 0.008$). Although risky behavior was greater in HC than in ADHD, we found a significant interaction effect of group and anticipatory skin conductance responses regarding the response behavior ($\beta = 107.17$, SE = 41.91, $t = 2.56$, $p = 0.011$). *Post hoc* analyses revealed a positive correlation between anticipatory skin conductance responses and reaction time in HC, whereas this correlation was negative in ADHD. Self-assessment results were in line with the objective measurements.

Conclusion: We found altered changes in physiological activity during a risky decision-making task. The results confirm the assumption of an aberrant relationship between bodily response and risky behavior in adult ADHD. However, further research is needed with respect to age and gender when considering physiological activities.

KEYWORDS

attention deficit and hyperactivity disorder, risky decision-making behavior, skin conductance response (SCR), autonomic nervous system, physiological activity, affective functions, emotional arousal, balloon analogue risk task (BART)

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder with a prevalence of 5% worldwide (Polanczyk et al., 2007). ADHD presents with heterogeneous symptomatology characterized by inattention, impulsivity, and hyperactivity. Patients are also significantly affected in several aspects of daily life including work performance, planning, decision-making (DM), and psychosocial interactions (Must et al., 2013; Polanczyk et al., 2014). A meta-analysis on longitudinal studies has shown that up to 50% of diagnosed children still meet partial ADHD-related symptoms by the age of 25 (Faraone et al., 2006). However, across the lifespan the main symptom of hypermotoric behavior shifts to an inner restlessness, inattention, and emotional dysregulation (Gibbins et al., 2010; Francx et al., 2015). Furthermore, it is noteworthy that adult ADHD has an increasing tendency to engage in risky behavior that derives from inadequate DM. Those heightened risk taking behaviors are seen particularly in situations of risky driving, risky sexual behavior and pathological gambling (Flory et al., 2006; Thompson et al., 2007; Faregh and Derevensky, 2011).

Investigating risky behavior in the context of disadvantageous decisions is challenging in an experimental setting and study results are often inconsistent and do not reflect the daily behavioral deficits of ADHD (Mowinckel et al., 2015; Dekkers et al., 2016). It is often not clear which neuropsychological functions are responsible during the performance of risk-taking paradigms. Furthermore, the wide variety of methodologies makes it difficult to compare different studies with each other. However, according to the Dual Pathway Model (DPM) it is known that two different signaling pathways are involved in the development of behavioral actions: including cognitive-analytic functions (*cold functions*) and the intuitive-affective functions (*hot functions*) (Sonuga-Barke, 2002). The most common decision-making paradigms; IOWA Gambling Task (IGT), Columbia Card Task (CCT-cold), and Game of Dice Task (GDT) involve cognitive-analytic functions, whereas the Balloon Analogue Risk Task (BART) and Colorado Balloon Game (CBG) can be associated with more affective-emotional driven behavior (Lejuez et al., 2002; Brand et al., 2007; Figner et al., 2009; Crowley et al., 2010; Mäntylä et al., 2012).

Due to the heterogeneity in study results regarding risky DM in ADHD, as well as the lack of focus on *hot function* driven behavioral impairments, further research on affective functioning is needed. Additionally, based on the prefrontal recovery hypothesis (Halperin and Schulz, 2006), it has been shown that developmental improvements in cognitive control functions may favor a reduction in behavioral disturbances in adult ADHD (Groen et al., 2013; Mowinckel et al., 2015). Conversely, significant increases in impaired emotional competence can be observed and are known to negatively affect the patients' socio-emotional life (Shushakova et al., 2018; Materna et al., 2019; Beheshti et al., 2020). Moreover, these emotional difficulties are also a risk factor for the development of affective comorbidities, such as major depressive disorder (Bresner et al., 2009). It can thus be assumed that impairments of *cold functions* in adulthood diminish, whereas dysfunctions in emotional control and regulation become more prevalent (Shushakova et al., 2018; Materna et al., 2019; Beheshti et al., 2020; Mayer et al., 2021). This leads to the assumption that heightened risk-taking in adult ADHD that arises from deficits in DM ability may result from an impairment in *hot functions*.

Referring to the DPM, hot functions describe particular behavior that arise quickly and intuitively (Sonuga-Barke, 2002; Mäntylä et al., 2012; Shoham et al., 2016), in which perceived stimuli are transmitted directly from the sensory system to the amygdala (Damasio et al., 2000). Due to this activation of the limbic system, the autonomic nervous system is stimulated and induces physiological responses such as modulations in heart rate, sweating, breathing and eye blinking (Figner and Murphy, 2011; Bellato et al., 2020). These physiological changes, in turn, are perceived by the body in the form of a feedback loop which can then elicit a behavioral action (Christopoulos et al., 2019). Thus, the signaling pathway of hot functions is composed of an interconnection of perception of the stimulus, activation of the autonomic nervous system and physiological changes. Although these processes are not consciously experienced, this interconnection to a certain stimulus can be *learned* and stored as somatic markers in the brain, according to prominent theories (Damasio, 1996). Thus, the somatic response can also act as an early-warning-system that guides subconscious decisions from the learned connection of the stimulus and body reaction.

A promising measurement technique to detect somatic marker functioning and anticipatory physiologically changes, is the recording of skin conductance responses (SCR) (Starcke et al., 2009; Wright and Rakow, 2017; Christopoulos et al., 2019). When emotional arousal occurs the electrical property of the skin changes due to the increased sweat secretion. This can be detected by applying an external direct current with constant voltage to the skin (Boucsein, 2012; Uddin et al., 2017). It is important to determine at

which timepoint during a DM process a change in skin conductance occurs. In the present study changes that follow a decision are described as *reactive* SCR (rSCR) whereas changes that precede a decision are described as *anticipatory* SCR (aSCR). Although SCRs represent emotional arousal, it cannot be clearly assessed whether an rSCR follows a positive or negative feedback (Figner and Murphy, 2011). It has only be shown that highly evaluated feedback (either being high rewards or high punishments) were associated with increased SCR amplitudes (Wilkes et al., 2010; Lole et al., 2012). In addition, risky behavior was found to decrease when rSCR was already elevated in the previous trial (Masunami et al., 2009; Wright and Rakow, 2017). Regarding aSCRs, it is well documented that disadvantageous DM behavior is associated with higher amplitudes (Garon et al., 2006; Starcke et al., 2009; Dawson et al., 2011; Wright and Rakow, 2017). Thus, it can be shown that when a high risk condition is present, an increased amplitude in aSCR represents an implicit perception of risk (Guillaume et al., 2009; Rogalsky et al., 2012; Wright and Rakow, 2017; Agren et al., 2019).

There are only a few studies which have investigated the relationship between electrodermal activity and risky DM behavior in adult ADHD. However, results indicated an altered psychophysiological activity in the context of behavioral impairment in adult ADHD (Lazzaro et al., 1999; Lackschewitz et al., 2008; Matthies et al., 2012; Ziegler et al., 2016). Furthermore, a recent systematic review investigating autonomic nervous system function in ADHD identified altered activity patterns at rest but also during task performance. Results were not consistent and showed both hypoactive and hyperactive patterns in ADHD compared to healthy controls (HC) (Bellato et al., 2020). To date, however, much of the research in this area has mainly focused on abnormalities in rSCR regarding feedback sensitivity. In these studies, results indicated greater risky DM in conditions of punishment (DeVito et al., 2008; Masunami et al., 2009), whereas rSCRs have been shown to decrease in response to an error feedback or the omission of rewards (Iaboni et al., 1997; O'Connell et al., 2004). In contrast, hyperactivity of the rSCR is partially observed after rewarding feedback (Masunami et al., 2009; Bellato et al., 2020). However, to the best of our knowledge, no study so far has investigated somatic responses as an anticipatory correlate that guides a quick and intuitive behavior in adult ADHD. Assuming dysfunctional affective processes in ADHD, it can therefore be suggested that (1) alterations of aSCR and rSCR do not occur during risky DM; or (2) increases in aSCRs are not linked to advantageous behavioral actions.

The aim of the present study was to investigate whether a dysfunction in affective pathways is associated with an altered risky DM behavior in adult ADHD. To address this, we analyzed SCRs as well as the relationship between aSCRs and task-behavior. Therefore, we used a modified version of the Balloon Analogue Risk Task (BART) to demand hot function-guided risky decision behavior (Hüpen et al., 2019). The BART has been demonstrated to induce naturalistic risky DM (Lejuez et al., 2002). Moreover, the modified version was designed to trigger emotional arousal and intuitive guided behavior, and to investigate DM depending on the reward magnitude (Hüpen et al., 2019, 2020). Additionally, questionnaires were used to investigate self-assessment of risky behavior and emotional competence.

2. Materials and methods

2.1. Participants

Fifty-nine participants [n = 30 HC and n = 29 patients with ADHD] were recruited for the current study and met the following inclusion criteria: aged between 18 and 60 years, fluent German language skills, no neurological diseases, no depressive disorder, no borderline personality disorder, or other psychiatric disorder with psychosis. The patient group was recruited from the outpatient clinic of the Department of Psychiatry and Psychotherapy of the University Hospital Bonn and met the full DSM-V criteria (APA, 2013). Participants ceased taking ADHD-specific medications 24 h prior to the start of the experiment which was additionally objectified by oral questioning on the study day. HCs were recruited via public advertisement on the Internet and flyers. Psychiatric symptoms and comorbidities were assessed by a brief diagnostic interview (Mini-DIPS; Margraf and Schneider, 1994), the Beck Depression Inventory-II (BDI-II; Beck et al., 1996) and the Borderline Symptom List-95 (BSL-95; Bohus et al., 2001). ADHD-related psychopathology was quantified by the Conners Adult Rating Scale (CAARS; Conners et al., 1999) and the validated short version of the Wender Utah Rating Scale (WURS-k; Retz-Junginger et al., 2002). Following data collection, three participants (n = 2 HC, n = 1 ADHD) were excluded from the subsequent analyses due to missing measurement data, acute suicidality, or extreme outlier values. The study was approved by the Ethics Committee of the Medical Faculty of the University of Bonn (122/21) and all participants gave oral and written informed consent.

2.2. Materials

2.2.1. Risky decision-making paradigm: Balloon Analogue Risk Task

In the present study a modified version was used which is intended to measure hot function-guided risky DM behavior (Hüpen et al., 2019). Participants are presented with a dynamically growing balloon on a screen for a duration of 5,000 ms. The increasing size of the balloon coincides with an increasing amount of money and a greater risk of the balloon exploding. Participants are asked to press a response button at a self-determined timepoint in order to gain as much money as possible. As the inflation duration is the same on every trial the balloon explosion is not visually presented to the participants. Following this time interval, a fixation cross (250 ms) is shown followed by the feedback display for 2,500 ms. In case of positive feedback, the amount of the collected money is presented. For negative feedback, the participant will be presented with a burst balloon and "0.00 Euros were won" if the determined timepoint was after the explosion point of the balloon. The total amount (sum of trials so far) appears additionally with every feedback. Each trial is also assigned with a certain gain condition (high or low reward). For this, it is shown by color whether the maximum potential trial gain is a high or low condition. The participant is instructed about the linear relationship of the money increase and explosion probability as well as the reward conditions. In total, every participant perform 60

trials (30 trials per each reward condition). For further information, see Henn et al. (2023).

2.2.2. Self-assessment of risk behavior and emotional competence

To investigate self-assessment of risk perception and behavior (Domain Specific Risk Taking; DOSPERT), as well as emotional competence ("Emotionale Kompetenz Fragebogen"; EKF) two self-report questionnaires were used. A subsequent comparison and analysis with the actual behavior in the DM task provides a further insight into the awareness of the participants' own behavior. The German validated version of the DOSPERT includes 40 items, representing daily situations that are assigned to one of the following subdomains: Investment, Gambling, Health, Recreational, Ethical and Social (Weber et al., 2002). Using a Likert-Scale (1–5), participants should specify the probability of engagement, the estimated risk and the personal benefit of every item. The EKF includes 62 items on self-assessment of emotional-competence-demanding events divided into four categories: Recognizing own feelings, recognizing emotions of others, regulation and control of own feelings and emotional expressivity (Rindermann, 2009). Ratings were scored using a Likert-Scale (1–5). For the analyses, we used the total score of the emotional competence and the total score of the propensity of risk engagement.

2.2.3. SCR data acquisition and preprocessing

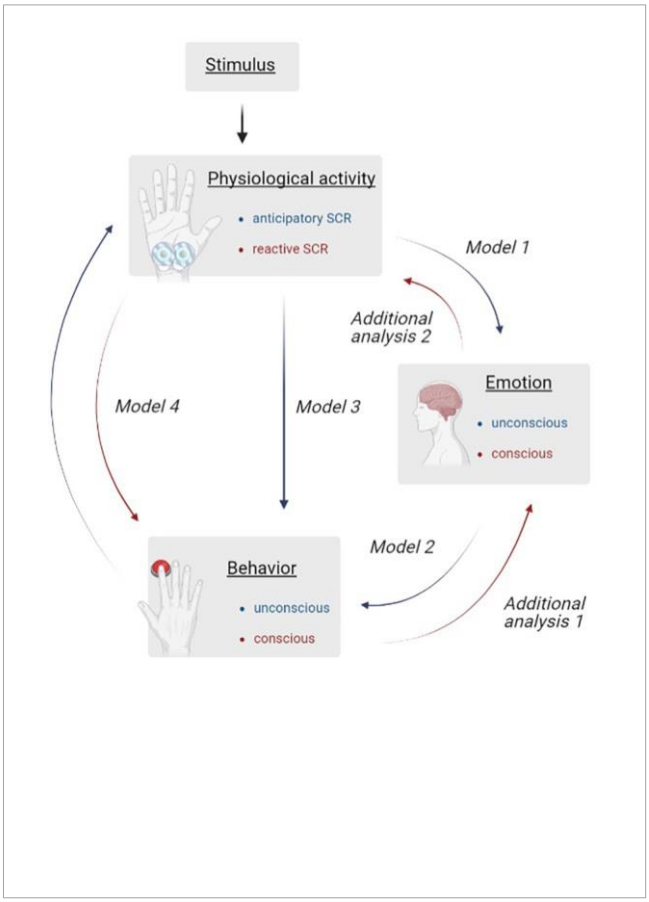
Skin conductance was recorded using a Biopac MP150 system (Biopac Systems Inc., Goleta, CA, United States). Recordings were taken at 5,000 Hz and a direct current excitation of 0.5 V. Two disposable snap (Ag-AgCl) electrodes (11 mm diameter), prepared with a 0.5% saline paste in a neutral base (0.05 molar NaCl) were attached to the thenar and hypothenar eminence of the non-dominant hand. Signals of the skin conductance activity were transmitted via the wireless PPG/EDA BioNomadix Transmitter to the software AcqKnowledge (acquisition and analysis program). The recordings were synchronized with the BART sequence via digital input ports sent by the Presentation® software of neurobehavioral systems. Trigger for the reward condition (high/low), feedback display (gain/loss), response timepoint as well as start-/endpoint of the trial were transformed. To do so, a transition latency was set for 2 ms, and an additional low pass filtering of 1 Hz was applied. Further preprocessing was performed with Ledalab toolbox (V.3.4.8) of Matlab, including smoothing (Gaussian method) and a downsampling to 20 Hz. Using a continuous decomposition analysis (CDA) relevant phasic skin conductance responses (SCR) were extracted from the signal tracks (Benedek and Kaernbach, 2010). The integral of the skin conductance responses (ISCR) was used as a measure for the analyses. As the short peaks in activity represents the phasic driver, one response window was defined 1–6 s with condition display (at the beginning of each trial) and one 1–3 s with feedback display (at the end of each trial). For peak detection, a minimum amplitude criterion of 0.05 μS was used.

2.3. Research design

In order to investigate the research questions on the basis of the materials used, different consecutive analyses are used (see **Figure 1**). Unconscious (green pathway) and conscious (red pathway) processes from stimulus onset to decision making were examined. As the appearance of the balloon (stimulus) provokes a change in the aSCR that modifies the representing behavior via RT, it should be investigated whether differences occur in the physiological activity (model 1), the behavior (model 2) or whether the behavior is also influenced by the aSCR (model 3). Since feedback also has an impact on hot function guided DM, we also investigated whether differences in rSCR are present (model 4). Two additional analyses should provide information on whether the participants' own behavior is perceived (additional analysis 1) and how their own affective functions are assessed (additional analysis 2).

2.4. Statistical analysis

In order to investigate behavioral and psychophysiological differences between ADHD and HC, we used linear mixed effects model containing interaction terms of the fixed effects and random intercepts for participants and trials. Group (ADHD; HC) and reward condition (high; low) were included as fixed effects in the models. A "Non-responder" was not excluded from analyses as the lack of SCR might represent an actual psychophysiological activity. All models were fitted using the R (R Core Team, 2014) package lme4 (Bates et al., 2015). For *post hoc* comparisons, we used the emmeans package (Lenth, 2016) to account for means and corrected *p*-values. Additional analyses were performed for the evaluation of the two questionnaires (DOSPERT; EKF). Therefore,



we used univariate Analysis of Variance (ANOVA) with total scores of each questionnaire being the dependent variable and group (ADHD; HC) representing the independent variable.

3. Results

3.1. Demographics

There were no significant differences between HC and ADHD in age, gender distribution, verbal intelligence (as assessed by the WST; Metzler and Schmidt, 1992) and years of education (see **Table 1**). In terms of the clinical screening and the psychiatric symptoms, ADHD had greater levels of self-reported ADHD-related symptoms (Mann–Whitney-$U = 769.5$, $n1 = n2 = 28$, $p < 0.001$ two-tailed), depression (Mann–Whitney-$U = 535$, $n1 = n2 = 28$, $p = 0.018$ two-tailed) and BPD-related symptoms (Mann–Whitney-$U = 584.5$, $n1 = n2 = 28$, $p = 0.002$ two-tailed).

3.2. Unconscious pathway (blue)

Model 1 investigating differences in the aSCRs, revealed a significant main effect of group ($\beta = -0.12$, SE = 0.05, $t = -2.63$, $p < 0.001$). *Post hoc* analysis showed higher aSCR in ADHD compared to HC ($M_{Difference,ADHD-HC} = 0.09$, SE = 0.03, $t = 2.79$, $p = 0.005$), indicating higher emotional arousal preceding a decision (see **Figure 2**). Model 2 accounting for the behavioral differences on basis of the RT, revealed a significant main effect of group ($\beta = 219.51$, SE = 39.88, $t = 5.5$, $p < 0.001$) and reward condition ($\beta = 215.36$, SE = 38.36, $t = 5.61$, $p < 0.001$). *Post hoc* analyses showed higher RTs in HC ($M_{Difference,ADHD-HC} = -222$, SE = 29.3, $t = -7.59$, $p < 0.001$) and under high reward condition ($M_{Difference,low-high} = -218$, SE = 27.2, $t = -8.02$, $p < 0.001$), indicating greater risky DM but also a dependence of behavior on the level of reward in both groups (see **Figure 3**).

An additional model was used to investigate whether RT is influenced by changes in aSCR. Here, model 3 revealed a significant main effect of aSCR ($\beta = -55.37$, SE = 28.03, $t = -1.98$, $p = 0.048$), reward condition ($\beta = 208.91$, SE = 43.65, $t = 4.79$, $p < 0.001$) and group ($\beta = 162$, SE = 44.38, $t = 3.66$, $p < 0.001$). Furthermore, a significant interaction effect of group and aSCR was found ($\beta = 107.17$, SE = 41.91, $t = 2.56$, $p = 0.011$). *Post hoc* analyses showed that RT of HC and ADHD seem to diverge from each other as the aSCR increases, with relationship of aSCR and RT tend to be positive in HC and being negative in ADHD ($M_{Difference,ADHD-HC} = -222$, SE = 29.4, $t = -7.57$, $p < 0.001$). Results indicate risky DM is associated with emotional arousal in HC but not in ADHD (see **Figure 4**). Please see **Table 2** for all other parameter estimates.

3.3. Conscious pathway (red)

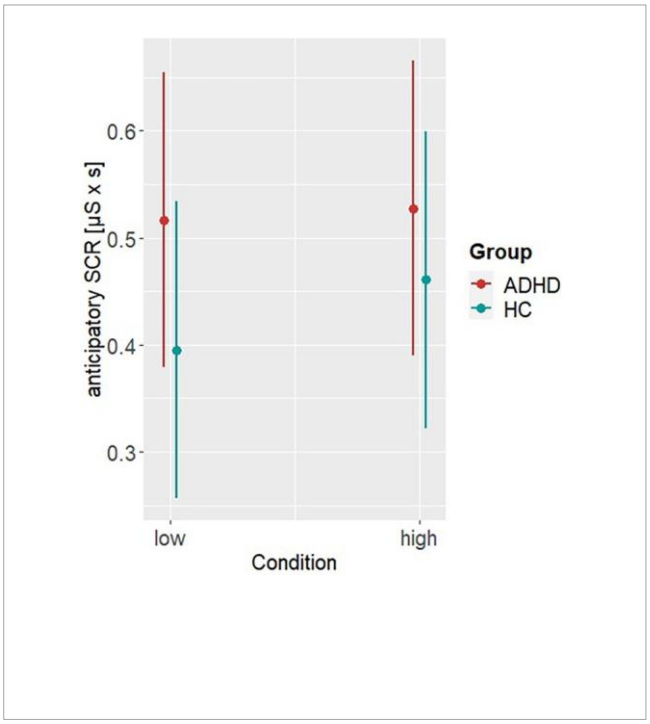
Model 4 investigating differences in the rSCRs, revealed significant main effects of group ($\beta = -0.14$, SE = 0.05, $t = -2.66$, $p = 0.008$) and feedback ($\beta = -0.11$, SE = 0.05, $t = -2.32$, $p = 0.02$). *Post hoc* analyses showed higher rSCRs in ADHD ($M_{Difference,ADHD-HC} = 0.098$, SE = 0.04, $t = 27$, $p = 0.007$) and after loss display ($M_{Difference,loss-gain} = 0.07$, SE = 0.03, $t = 2.03$, $p = 0.042$), indicating higher emotional arousal in loss trials with this being more pronounced in ADHD (see **Figure 5**). Please see **Table 2** for all other parameter estimates.

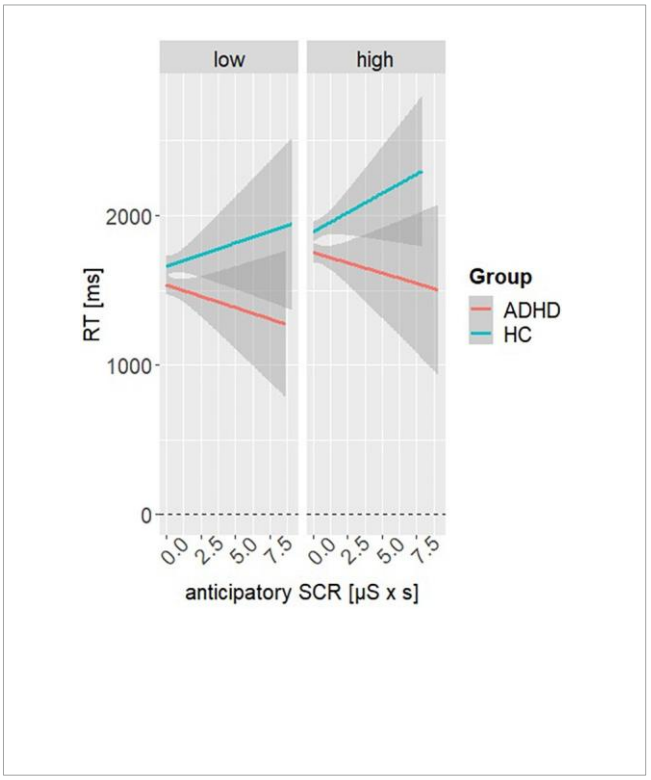
The univariate ANOVA for the total score of propensity of risk engagement (additional analysis 1) did not reveal a significant difference of group [$F_{(1,54)} = 0.285$, $p = 0.6$, $\eta 2 = 0.005$]. Results indicate the same propensity of risk engagement in ADHD and HC. The ANOVA for the self-assessment of emotional competence (additional analysis 2) revealed a significant difference between ADHD and HC [$F_{(1,54)} = 23.1$, $p < 0.001$, partial $\eta 2 = 0.3$], indicating a higher emotional competence in HC (see **Figure 6**).

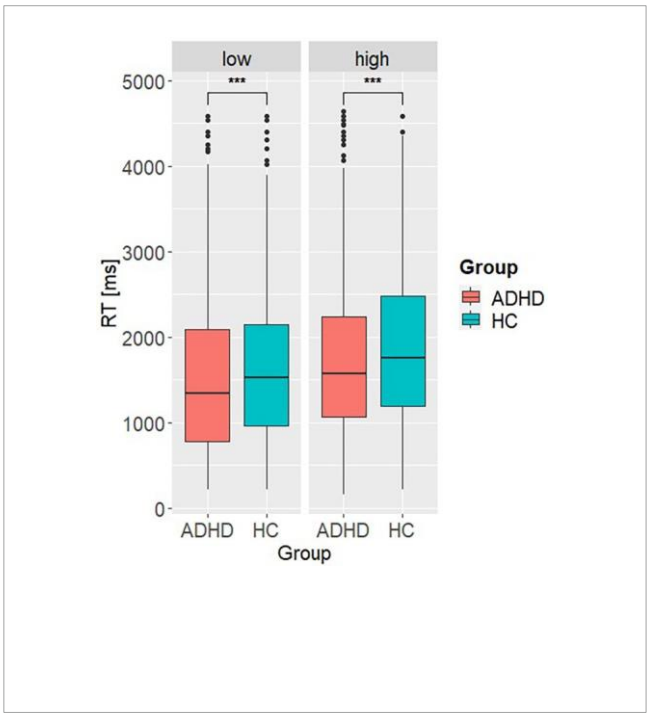
TABLE 1 Demographic and clinical characteristics of patients with ADHD and healthy controls (HCs).

		Median		Mann–Whitney-U-test	
Parameter		HC ($n = 28$)	ADHD ($n = 28$)	*U*	*p*
Age (years)		27.0	30.5	431.5	0.516
Verbal IQ (WST)		33.0	32.0	376.5	0.798
Education (years)		18.0	16.0	287	0.178
CAARS	Hyperactivity	8.5	24.5	734.5	<0.001
	Inattention	8.0	25.0	720.5	<0.001
	Impulsivity	6.0	19.5	754.5	<0.001
	Self-conception	4.5	11.5	633.5	<0.001
WURS-k		12.0	40.0	748	<0.001
BDI		2.0	4.5	535	0.018
BSL		2.0	12.0	584.5	0.002
		Frequency		Chi-squared-test	
Gender (m/f)		9/19	16/12		$\chi^2 = 3.54$

ADHD, attention-deficit-/hyperactivity disorder; HC, healthy controls; WST, Wortschatztest; CAARS, Conners Adult Rating Scale; WURS-k, Wender Utah Rating Scale; BDI, beck depression inventory; BSL, borderline symptom list; *m* = male; *f* = female.







4. Discussion

The present study investigated whether there is a potential causal relationship of affective pathways and abnormal risky DM behavior in adult ADHD. Therefore, different phases of hot function-guided DM were analyzed and compared between adult ADHD and HC on the basis of behavior, physiological activity, and self-assessment.

Results showed higher emotional arousal in ADHD indicated by elevated SCRs preceding a DM. These findings are consistent with the observation of hyperactivity of the autonomic nervous system being increasingly associated with motoric hyperactivity and impulsive behavior in ADHD. These results were suggested to reflect an over-activation of autonomic functions (Wilbertz et al., 2012). It is discussed whether hyperactivity of somatic functions in ADHD serves to induce a stimulating environment in order to promote a certain stability of vigilance (Geissler et al., 2014). In addition, these hyperarousal activities can also be related to a reduced ability of downregulating excessive arousal. However, other findings showed that during the performance of monotonous tasks, quick exhaustion may occur, which is then characterized by hypoactivity of bodily responses (Kuntsi and Klein, 2012; Geissler et al., 2014). It can therefore be assumed that, depending on the demands and excitement of the task; emotional arousal can be either hyper-/or hypo-threshold.

Regarding the available effect of somatic markers at this point, high aSCRs would be expected to be associated with high risk behaviors, as the somatic response will increase with increased risk engagement in order to avoid disadvantageous behavior (Garon et al., 2006; Starcke et al., 2009; Dawson et al., 2011; Wright and Rakow, 2017). However, in the present study risky behavior could not be detected in ADHD. Instead, HCs with overall higher RTs, showed significantly greater risky DM than ADHD. At this point, it can be questioned whether the modified BART accurately reflects daily risky DM and whether it is a valid measurement under laboratory conditions. Moreover, the BART primarily examines risk engagement in the context of financial behaviors and therefore cannot represent all domains of potential daily risk taking behaviors. In addition, recent meta-analyses also highlight the fact that behavioral results of many studies represent rather a suboptimal DM behavior than a risk-seeking DM behavior in ADHD (Dekkers et al., 2021; Roberts et al., 2021). In this context, the underlying mechanism regarding the disentanglement of disadvantageous decisions and risk-seeking decisions reflect

TABLE 2 Parameter estimates of the linear mixed effects model analyses.

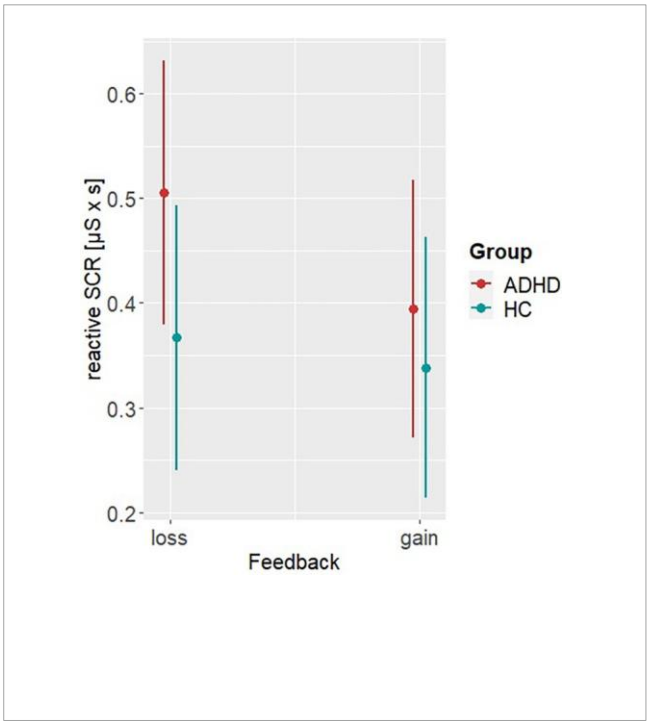
Model		*b*	SE	*t*	CI 95%	*p*
Model 1	Intercept	0.52	0.07	7.34	[0.38, 0.65]	<0.001
	Group	−0.12	0.05	−2.63	[−0.21, −0.03]	<0.001
	Condition	0.01	0.04	0.25	[−0.08, 0.1]	0.8
	Group × condition	0.05	0.06	0.86	[−0.07, 0.18]	0.39
Model 2	Intercept	1327.45	81.08	16.37	[1168.5, 1486.4]	<0.001
	Group	219.51	39.88	5.5	[141.32, 297.71]	<0.001
	Condition	215.36	38.36	5.61	[140.15, 111.31]	<0.001
	Group × condition	4.85	54.3	0.09	[−101.61, 111.31]	0.929
Model 3	Intercept	1438.17	79.33	18.13	[1282.63, 1593.72]	<0.001
	aSCR	−55.37	28.03	−1.98	[−110.32, −0.41]	0.048
	Condition	208.91	43.65	4.79	[123.33, 294.5]	<0.001
	Group	162.63	44.38	3.66	[75.62, 249.65]	<0.001
	aSCR × condition	13.55	39.38	0.34	[−63.66, 90.77]	0.73
	aSCR × group	107.17	41.91	2.56	[24.99, 189.34]	0.011
	Condition × group	18.5	61.27	0.3	[−101.63, 138.63]	0.76
	aSCR × condition × group	0.52	58.14	0.009	[−113.48, 114.51]	0.99
Model 4	Intercept	0.51	0.06	7.86	[0.38, 0.63]	<0.001
	Group	−0.14	0.05	−2.66	[−0.24, −0.04]	0.008
	Feedback	−0.11	0.05	0.05	[−0.21, −0.02]	0.02
	Group × feedback	0.08	0.07	0.07	[−0.05, 0.22]	0.23

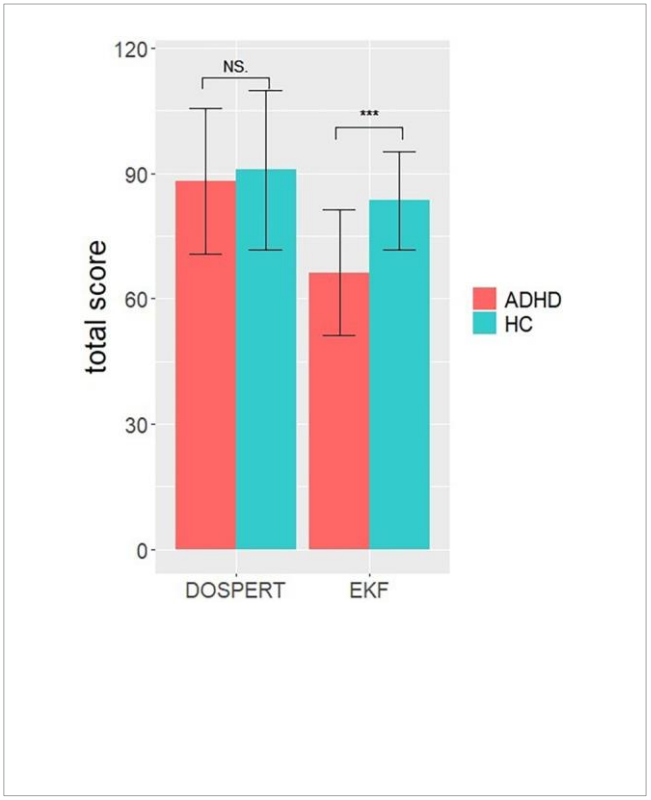
Linear mixed-effects model with group (ADHD, HC) as fixed factor in every model. Reward condition (high, low) was additionally included as fixed factor in model 1–3. Feedback (gain, loss) was additionally included as fixed factor in model 4. Anticipatory skin conductance response (aSCR) was additionally included as fixed factor in model 3. Dependent variables were aSCR in model 1, mean reaction time (RT) in model 2 and 3 and reactive skin conductance response (rSCR) in model 4. CI, confidence interval; SE, standard error.

an additional important aspect in the field of DM and need to be considered in further studies (Dekkers et al., 2021). On the other hand, the behavior shown could also reflect an action that demonstrates shorter RT according to the Intolerance of Uncertainty that was found to be a transdiagnostic construct in psychiatric disorder (Gramszlo et al., 2018). Subsequently, not the risky DM behavior itself is an interesting outcome, but rather the relationship and interconnection of bodily response and DM.

Thus, in order to investigate how the somatic response influences behavior we analyzed the relation of aSCRs and RT. Results showed that risk engagement in HC coincides with increased aSCR, representing the correlation of disadvantageous behavior and higher SCRs (Garon et al., 2006; Starcke et al., 2009; Dawson et al., 2011; Wright and Rakow, 2017). In turn, increased risk engagement in ADHD was associated with lower aSCR. This negative correlation of RT and aSCR in ADHD confirms the hypothesis about an altered relation between affective state and behavior. However, the strongest affective responses were observed at low RTs. Thus, it is shown that as risk-engagement increases, affectivity decreases, however quick responses tend to elicit the greatest arousal. This suggests that the physical response shown may be related to additional factors than risk. Therefore, it can be assumed that in adult ADHD, there is a missing interconnection between bodily response and behavior regarding risky DM. Nevertheless, further emotionally arousing functions involved in this BART need to be examined.

To understand further aspects of hot function-guided DM, SCRs in response to feedback were also investigated. In this context, the somatic response reflects the evaluation and emotional arousal toward feedback. Results of the rSCRs indicate that feedback is evaluated more emotionally arousing for ADHD than to HC. We could also identify that the feedback of loss is more arousing than gain across both groups. The high rSCRs are also consistent with findings of previous studies on reward sensitivity in ADHD. It was shown that hyperarousal during feedback is associated with weaker inhibitory abilities (Iaboni et al., 1997; Masunami et al., 2009). Furthermore, also in HC it could already be shown that gains produce higher physiological activity (Lole et al., 2012). The impact of feedback, whether it appears as a gain or a loss, can moreover encourage behavioral adaptation. In their prospect theory, Kahneman and Tversky (1979) describe higher emotional arousal and motivation toward loss outcomes. This motivation is accompanied by a decreased propensity to risky DM and is particularly evident in mixed gain/loss prospects. However, it could also be shown that norepinephrine plays a significant role in risk appraisal and propensity (Trepel et al., 2005). Accordingly, it was found that a central norepinephrine blockade decreases the sensitivity to risk-taking significantly (Rogers et al., 2004). Relating this to the underactivity of norepinephrine in ADHD, it seems plausible that reduced risk-taking is caused by the norepinephrine deficiency. Reflecting the elevated rSCRs and the reduced risky DM behavior it can be assumed that the autonomic signal might not get





properly transferred to the central nervous system (Critchley and Garfinkel, 2018).

Risk engagement was also investigated by self-assessment using the domain of probability of risk engagement of the DOSPERT questionnaire. Results showed no differences in the self-awareness of risky DM behavior. Contrary to the postulated daily behavior in ADHD, self-assessment does not seem to be perceived as an altered behavior. However, it should be noted that in the current study only the subdomain "probability of risk engagement" was used for a group comparison. Thus, a general evaluation of risky DM based on the DOSPERT results is limited. As questionnaires mostly comprise a subjective and consciously driven self-assessment, it can be assumed that on a conscious level, there are smaller differences in the risk-engagement between HC and ADHD. Consequently, it can be assumed that more unconscious, emotional-motivational driven processes, thus control the increased risky DM behavior in ADHD that is postulated in daily life. This is further supported by the self-assessment of emotional competence using the EKF questionnaire. Results indicated an impaired ability of emotional regulation, perception, understanding, and expression in ADHD that are important requirements for a proper hot function-guided decision (Sonuga-Barke, 2002). Moreover, risky DM is not only guided by previous experience of loss and gain, but also by the potential reward amount. Different studies have shown that with increasing magnitude of reward the risk avoidance also increases (Kahneman, 2003; Van Leijenhorst et al., 2010; Christopoulos et al., 2019; Hüpen et al., 2019). However, the present study indicates greater risk-engagement under high reward conditions, demonstrated by longer RTs, but not by changes in skin conductance. There was, however, no group difference and both ADHD and HC showed greater risky behavior under high reward conditions. Similar results were also shown in studies on ADHD and on Borderline Personality Disorder, arguing that the range between reward conditions was too narrow (Luman et al., 2008; Hüpen et al., 2020).

Overall, the measurement of SCRs has been shown to be a robust method to easily detect subconscious emotional arousal in anticipation and evaluation of DM. It yields a continuous measure that is related to activity in the sympathetic branch of the autonomic nervous system (Figner and Murphy, 2011). However, similar to many other indirect measurement methods, there are also some limitations. Subsequently, it must be taken into account that some participants can be "non-responders" (Figner and Murphy, 2011). In this study, we decided to include all measurements in the analyses as our statistical model corrected for individual differences in SCRs (Hüpen et al., 2019). Furthermore, there are contradictory recommendations on the pretreatment of the skin, whether the skin should be treated with water, oil or nothing at all before attaching the electrodes (Boucsein, 2012). We decided to follow the BIOPAC guidelines and used the saline paste supplied. Medication intake was also proven to affect activity of the autonomic nervous system (Bellato et al., 2020). Therefore, medication effect on behavioral results should be considered in future studies. Additionally, despite the potential individual lack of activity, there might also be environmental disturbances on the electrodermal recording that affect the signal. For instance, it was shown that electromagnetic noises such as overhead lights can disturb the signal and cause unrelated changes in the SCRs. We tried to avoid these artifacts by using low-pass filters and conducting the study in interference-free rooms, but a potential effect cannot be ruled out when considering the results. Furthermore, since the present study focuses on risky behavior in adults with ADHD it is important to consider that there may be limited comparability with child studies. Behavioral deficits in children may be deferred due to the delayed cortical maturation but may not persist in adulthood (Whelan and Mchugh, 2009; Dekkers et al., 2016; Koscielniak et al., 2016). In addition, a possible effect of comorbidities on the results must also be taken into account.

For instance, patients with Antisocial Personality Disorder are also affected by deficits in affective functions (Glenn et al., 2013). Since the Mini-DIPS does not assess personality disorders, additional questionnaires should be included in future studies. Moreover, it should be taken into account that the present study investigated the specific functionality of emotional competence, but ADHD is particularly characterized by a heterogeneity of dysfunctions. However, the effectiveness of hot functions is still underrepresented in behavioral studies on ADHD. To gradually shed more light on this topic, future studies should specifically examine demographic effects such as age, gender, and education in relation to the ability of affective functioning in adult ADHD.

In conclusion, the present study is the first to investigate hot functions as underlying mechanisms for risky DM in adult ADHD. Results show significantly higher arousal before a DM and after feedback display in ADHD. However, ADHD participants were unable to use this physiological information to modify behavior. This finding is also confirmed by self-reports that showed a weaker ability in the perception of arousal and emotion in ADHD, whereas self-reported risk behavior was not altered compared to HC. Further research is needed to investigate how emotional processing can be influenced or improved in ADHD. However, our research underlines the importance of considering emotional therapeutic technics in the work with patients with ADHD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Medical Faculty of the University of Bonn. The patients/participants provided their written informed consent to participate in this study.

Author contributions

EH, SL, and PH contributed to the conception and design of the study. EH, FK, and AH acquired the data and performed data analyses. PH designed the paradigm and performed data analyses. EH, MB, BH, CD, SL, and AP contributed to data interpretation and discussion of results. BA recruited patients with ADHD for study participation. EH wrote the first draft of the manuscript. All authors read and approved the submitted version.

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Conflict of interest

AP declares that she served on advisory boards, gave lectures, performed phase-3 studies, and received travel grants within the last five years from MEDICE Arzneimittel, Pütter GmbH and Co., KG, Takeda, Boehringer, Janssen-Cilag, and has authored books and articles on ADHD published by Elsevier, Hogrefe, Schattauer, Kohlhammer, Karger, Oxford Press, Thieme, Springer, and Schattauer.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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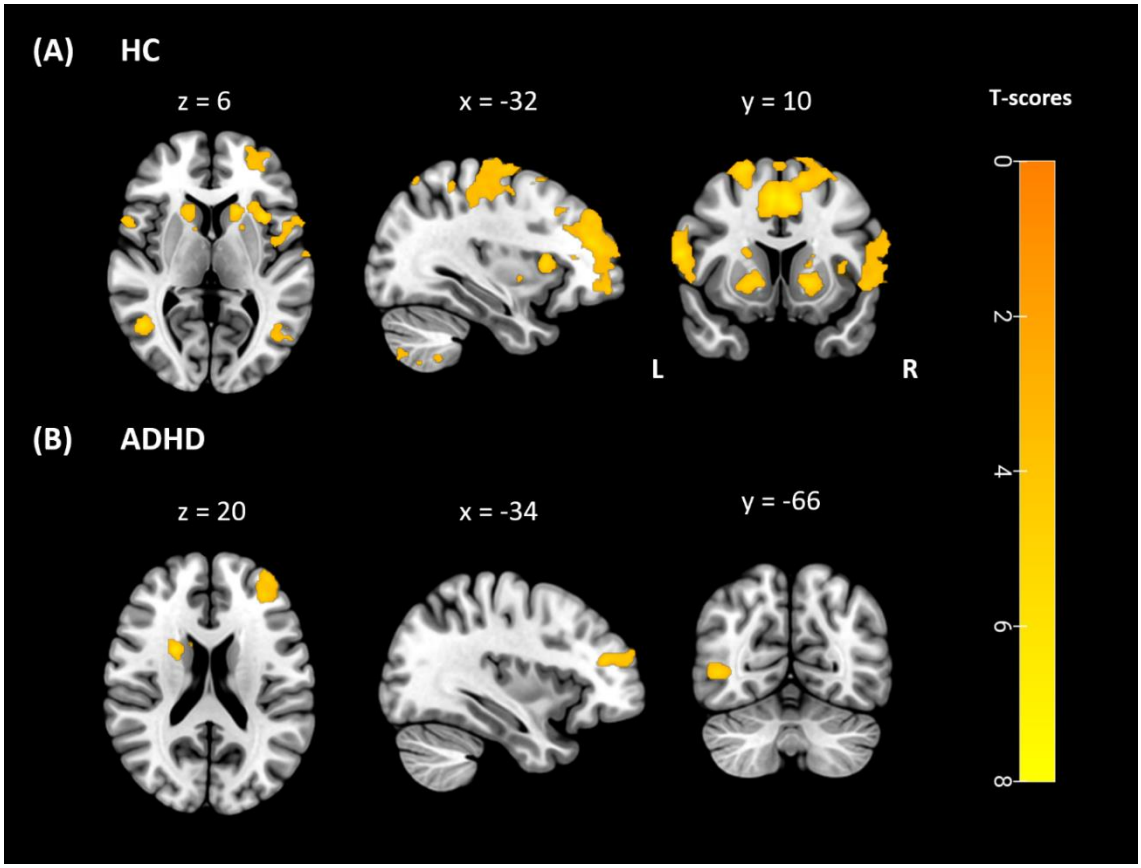
Appendix B: Supplementary material Study 3

Neural correlates and gender-specific effects of affectively driven processes underlying decision-making in adult ADHD.

Halbe, E., Jamieson, A., Bergmann, M., Mehren, A., Harrison, B.J., Davey, C. G., Stöcker, T., Philipsen, A., Lux, S,



Supplementary Figure 18: Brain activation associated with anticipation of a decision-making. Within-group activation patterns for (A) healthy controls (HC) and (B) patients with ADHD ($p < 0.05$, FWE-corrected on cluster level, initial voxel threshold 0.001 uncorrected).

Supplementary Table 2

Gender comparison of brain activation during the anticipation of decision-making within the patient group

Contrast	Region of peak activation	Regions comprised in the cluster	MNI coordinates (x, y, z)	Cluster size	t-statistic	z-statistic	p*
ADHD female > ADHD male	R. Lobule VI of cerebellar hemisphere	Lobule VI of vermis Lobule VII of vermis R. Crus I of cerebellar hemisphere R. lingual gyrus R. Lobule IV, V of cerebellar hemisphere L. Crus I of cerebellar hemisphere R. fusiform gyrus L. Crus II of cerebellar hemisphere	8,-78,-18	335	6.38	5.14	<.001
	R. Crus I of cerebellar hemisphere	R. Lobule VI of cerebellar hemisphere R. inferior temporal gyrus R. Fusiform R. Crus II of cerebellar hemisphere	42, -42, -34	459	5.91	4.87	<.001
	R. caudate nucleus	R. Thalamus, ventral lateral R. Thalamus, pulvinar medial R. Thalamus, mediodorsal medial magnocellular L. Thalamus, pulvinar medial R. Thalamus, ventral posterolateral	22, -18, 22	637	5.9	4.86	<.001

Contrast	Region of peak activation	Regions comprised in the cluster	MNI coordinates (x, y, z)	Cluster size	t-statistic	z-statistic	p*
		R. Thalamus, lateral posterior L. Thalamus, mediodorsal medial magnocellular R. Thalamus, pulvinar anterior L. Thalamus, pulvinar anterior R. Thalamus, anteroventral nucleus R. Thalamus, pulvinar lateral R. Thalamus, mediodorsal lateral parvocellular L. Thalamus, mediodorsal lateral parvocellular L. Thalamus, ventralposterolateral L. Thalamus, lateral posterior L. Hippocampus					
	R. Frontal Sup 2	R. supplementary motor area R. middle cingulate & paracingulate gyri L. supplementary motor area L. middle cingulate & paracingulate gyri R. Anterior cingulate cortex, supracallosal R. middle frontal gyrus 2 R. precentral gyrus L. superior frontal gyrus, medial L. anterior cingulate cortex, supracallosal	10, 30, 28	1512	5.81	4.81	<.001

Contrast	Region of peak activation	Regions comprised in the cluster	MNI coordinates (x, y, z)	Cluster size	t-statistic	z-statistic	p*
	L. Insula	L. temporal pole: superior temporal gyrus L. superior temporal gyrus L. rolandic operculum L. inferior frontal gyrus, opercular part L. inferior frontal gyrus, triangular part L. IFG pars orbitalis	-48, 2, -4	216	5.58	4.67	.002
	R. Cuneus	R. Precuneus R. superior occipital gyrus R. superior parietal gyrus	10, -74, 36	296	5.22	4.44	<.001
	L. superior frontal gyrus 2	L. superior frontal gyrus, medial R. inferior frontal gyrus, opercular part	-16, 30, 22	157	5.17	4.41	.011
	R. middle frontal gyrus 2	R. superior frontal gyrus 2 R. inferior frontal gyrus, opercular part	30, 36, 28	484	5.17	4.41	<.001
	L. Lobule VIII of cerebellar hemisphere	L. Lobule VIIB of cerebellar hemisphere L. Lobule VI of cerebellar hemisphere L. Crus I of cerebellar hemisphere L. Crus II of cerebellar	-36, -44, -46	211	5.06	4.34	.002

Contrast	Region of peak activation	Regions comprised in the cluster	MNI coordinates (x, y, z)	Cluster size	t-statistic	z-statistic	p*
		hemisphere					
	Lobule VI of vermis	R. Lobule VIII of cerebellar hemisphere Lobule VIII of vermis Lobule IX of vermis R. Lobule IX of cerebellar hemisphere Lobule IV, V of vermis R. Lobule VI of cerebellar hemisphere L. Lobule IV, V of cerebellar hemisphere R. Crus I of cerebellar hemisphere Lobule X of vermis	8, -66, -36	226	4.96	4.27	.001
	L. precentral gyrus	L. postcental gyrus L. superior frontal gyrus 2 L. superior frontal gyrus L. middle frontal gyrus 2 L. Paracentral Lobule	-36, 0, 62	455	4.95	4.26	<.001
	R. Precuneus	L. Precuneus L. middle cingulate & paracingulate gyri R. superior parietal gyrus R. middle cingulate & paracingulate gyri	-6, -68, 58	943	4.93	4.25	.002

Contrast	Region of peak activation	Regions comprised in the cluster	MNI coordinates (x, y, z)	Cluster size	t-statistic	z-statistic	p*
		L. Paracentral Lobule R. Paracentral Lobule R. posterior cingulate gyrus					
	L. Lingual	L. Lobule VI of cerebellar hemisphere	-18, -64, -14	169	4.78	4.15	.008
	L. middle frontal gyrus 2	L. inferior frontal gyrus, triangular part L. superior frontal gyrus 2	-34, 54, 14	266	4.77	4.14	<.001
	L. supramarginal gyrus	L. postcental gyrus L. superior temporal gyrus L. inferior parietal gyrus, excluding supramarginal and angular gyri L. rolandic operculum	-54, -14, 28	135	4.52	3.97	.023
	L. Crus I of cerebellar hemisphere	L. Lobule VI of cerebellar hemisphere L. interior temporal gyrus L. Fusiform	-30, -66, -24	212	4.36	3.86	.002

*FWE-corrected on cluster level (initial voxel threshold .001 uncorrected)