From Department of Clinical Neuroscience
Karolinska Institutet, Stockholm, Sweden

A NEUROIMAGING PERSPECTIVE ON REGULATION OF EMOTION, REWARD, AND ATTENTION

Frida Bayard

Karolinska Institutet

Stockholm 2021

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2021

ISBN 978-91-8016-122-0

A neuroimaging perspective on regulation of emotion, reward, and attention

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Frida Bayard

The thesis will be defended in public at Karolinska Institutet, Stockholm, 21st of May 2021

Principal Supervisor:
Associate Professor, MD, Eva Henje
Karolinska Institutet,
Department of Clinical Neuroscience
Umeå University,
Child- and Adolescent Psychiatry,
Department of Clinical Science

Co-supervisors:
Associate Professor, MD, Predrag Petrovic
Karolinska Institutet,
Department of Clinical Neuroscience

PhD Christoph Abé
Karolinska Institutet,
Department of Clinical Neuroscience

Professor, MD, Martin Ingvar
Karolinska Institutet,
Department of Clinical Neuroscience

Opponent:
Associate Professor Anouk Scheres
Radboud University,
Behavioural Science Institute

Examination Board:
Associate Professor India Morrison
Linköping University,
Department of Biomedical and Clinical Sciences
Center for Social and Affective Neuroscience

Associate Professor Lisa Thorell
Karolinska Institutet,
Department of Clinical Neuroscience

Associate Professor Philippe Goldin
University of California Davis Healthcare System,
Betty Irene Moore School of Nursing

"The ultimate goal is to understand the human brain– that incredible three-pound package of tissue that can imagine the farthest reaches of the universe and the ultimate core of the atom but cannot fathom its own functioning. Each research project bites off a little piece of an immense puzzle"

Harold M. Schmeck, Jr., "Brain signals in test foretell action", The New York Times, Feb. 13, 1971. Copyright 1971 by the New York Times Company

POPULAR SCIENCE SUMMARY

We have all experienced emotional problems and difficulties in keeping our attention to boring tasks. However, the extent to which we experience these difficulties varies between individuals. The level of emotional and inattention problems are distributed across the population along a continuum; from low levels in healthy individuals to severe symptoms in psychiatric patients. High levels of emotional problems often coincide with high levels of inattention problems, and psychiatric diagnoses related to problems in those "symptom domains" often occur simultaneously in the same individual. Emotional symptoms characterized by rapidly shifting emotional states are present in psychiatric disorders such as conduct disorder in children and emotionally unstable personality disorder (also referred to as borderline personality disorder) in adults. Symptoms of inattention, and other "non-emotional" symptoms such as hyperactivity and impulsivity, are common in attention-deficit hyperactivity disorder (ADHD).

In this PhD project, we aimed to better understand how emotional problems–associated with rapidly shifting emotional states–and inattention problems relate to each other. In order to do so, we asked participants to fill out self-report questionnaires of their symptoms and behaviors related to problems in regulating emotions and attention. The participants also performed various behavioral tasks related to different aspects of emotional and attentional processing. Those tests were performed either on a computer, or while in a magnetic resonance imaging (MRI) scanner. Using a *functional* MRI technique allows visualizing activity in different parts of the brain while a person performs certain tasks. We also used *structural* MRI to measure volume of different parts of the brain that are thought to be specifically important in regulation of emotion and attention.

We investigated how emotional and inattention problems relate to each other in different study populations including both adolescents and adults, healthy participants and ADHD patients.

In the studies included in this PhD project we could show that smaller volume of specific "emotional" parts of the cortex of the brain related to higher levels of emotional problems in adolescents (**Study I**), but not in adults with and without ADHD (**Study II**). Similarly, we found that smaller "non-emotional" parts of the brain cortex were associated with higher levels of "non-emotional" problems in adolescents (**Study I**), but not in healthy adults or adults with ADHD (**Study II**). The fact that these associations could be observed in adolescents, but not in adults, could have a developmental explanation, since all the cortical regions investigated in this PhD project were "prefrontal" regions, which are among the last to mature. It is possible that when the brain development has "caught up", the relation between emotional and non-emotional problems and brain structure becomes more subtle, or even seizes to exist.

Deep inside the brain, a more primitive "reward region" called the ventral striatum, is located. Interestingly, we found that adults with a smaller ventral striatum reported higher levels of emotional problems (**Study II**). We also found that, in females, the higher levels of emotional problems that were reported by an individual, the less activation of the ventral striatum was seen while waiting for a reward (**Study III**). This kind of "hypoactivation" of the ventral

striatum is typical in ADHD patients, who often find waiting for a reward difficult. Our different findings relating the ventral striatum volume and function to *emotional* problems, rather than "non-emotional" problems, are interesting since this region of the brain has often been associated with ADHD, which traditionally has been considered primarily a "non-emotional" diagnosis–although "emotional" ADHD is becoming increasingly discussed.

In the final study of this PhD project, we could show that more activation in an "emotional" region of the brain during a task that depended on **both** emotional and non-emotional brain systems, was specifically related to higher levels of emotional problems of an individual, rather than non-emotional problems (**Study IV**). This study highlights the importance of investigating emotional and non-emotional symptoms and related processes in the brain *simultaneously*. Emotional and non-emotional processes in the brain never occur in isolation from each other. For example, driving a car requires many "non-emotional" skills such as proper attention and flexibly adapting the driving to changes in the environment. This might be easy when you are undisturbed and on your own, while it could be rather challenging if you are distracted by emotional input from a phone call or screaming children in the backseat. By using an experimental task targeting **both** emotional and non-emotional processes as in Study IV, we may, to some degree, separate processes that often occur at the same time in the brain, although the experimental setting will never mirror real world situations perfectly.

To conclude, it is difficult to separate emotional and non-emotional processes in the brain, but through the studies included in this PhD project, we have been able to start doing just that. If we increase our understanding of the underlying brain mechanisms that contribute to psychiatric symptoms in patients with conduct disorder, emotionally unstable (borderline) personality disorder and ADHD, we will hopefully help pave the way for the development of new, more individualized, treatments for the patients suffering from these disorders.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Vi har alla upplevt känslomässiga problem och svårigheter med att behålla uppmärksamheten på tråkiga uppgifter. Hur mycket och hur ofta vi upplever sådana svårigheter varierar dock mycket mellan individer. Graden av känslomässiga, eller *emotionella*, problem och uppmärksamhetsproblem är varierar över befolkningen, från låga nivåer hos friska individer, till svåra symptom hos psykiatriska patienter. Höga nivåer av emotionella problem förekommer ofta i kombination med en hög grad av uppmärksamhetsproblem och andra ”icke-emotionella” problem. Även psykiatriska diagnoser som inkluderar symptom i dessa symptomdomäner förekommer ofta tillsammans i en och samma individ. Emotionella symptom som karakteriseras av snabbt skiftande känslor förekommer i stor utsträckning hos barn med uppförandestörning och vuxna med emotionellt instabil personlighetsstörning, även kallad borderline personlighetsstörning. Uppmärksamhetsproblem och andra ”icke-emotionella” symptom, som till exempel hyperaktivitet och bristande impulskontroll, är vanligt förekommande i uppmärksamhetsstörning/hyperaktivitet (attention-deficit hyperactivity disorder; ADHD).

Genom detta doktorandprojekt ville vi öka förståelsen av hur emotionella problem, som till exempel snabbt skiftande känslor, och uppmärksamhetsproblem förhåller sig till varandra.

För att undersöka detta bad vi deltagare att fylla i självskattningsformulär avseende symptom och beteenden relaterade till reglering av känslor och uppmärksamhet. Deltagarna genomförde även beteendetester som speglade olika emotionella processer och uppmärksamhetsprocesser i hjärnan. Dessa tester gjordes antingen vid en dator eller i en magnetkamera (MR). Genom *funktionell* MR kan man få en bild av aktivitet i olika delar av hjärnan hos en person som gör olika uppgifter. Vi använde också *strukturell* MR för att mäta volymen av områden i hjärnan som anses särskilt viktiga för reglering av känslor och uppmärksamhet.

Vi undersökte hur emotionella problem och uppmärksamhetsproblem relaterar till varandra i olika populationer; ungdomar och vuxna, friska deltagare och ADHD-patienter.

Genom de olika studierna kunde vi visa att en mindre volym i vissa ”emotionella” delar av hjärnbarken relaterade till högre nivåer av emotionella problem hos ungdomar (**Studie I**), men inte hos vuxna med eller utan ADHD (**Studie II**). På ett liknande sätt kunde vi också visa att mindre volym i ”icke-emotionella” delar av hjärnbarken kunde kopplas till svårare ”icke-emotionella” problem hos ungdomar (**Studie I**), men inte hos vuxna med eller utan ADHD (**Studie II**). Anledningen till att dessa kopplingar kunde ses hos ungdomar, men inte hos vuxna, kan ha sin förklaring i hjärnans utveckling. De områden i hjärnan som nämnts ovan är alla belägna i pannloben, och är bland de områden i hjärnan som mognar allra sist. Det är möjligt att relationen mellan emotionella och icke-emotionella problem och strukturella förändringar i hjärnan minskar eller inte längre finns kvar när utvecklingen av hjärnan ”kommit ikapp”.

Vi undersökte också hur ett mer primitivt belöningscentrum beläget djupt inne i hjärnan, ventrala striatum, kunde relateras till emotionella och icke-emotionella problem. Vi kunde se

att vuxna med mindre volym i ventrala striatum också rapporterade högre nivåer av emotionella problem (**Studie II**). Vi kunde även se att kvinnliga deltagare med högre nivåer av emotionella problem också hade mindre aktivitet i ventrala striatum medan de väntade på att få en belöning (**Studie III**). Denna typ av ”hypoaktivering” i ventrala striatum är typiskt för patienter med ADHD som ofta har svårigheter med att vänta på en belöning. Våra resultat kopplar både volym och funktion i ventrala striatum till emotionella problem, snarare än till ”icke-emotionella” problem, och är intressanta i och med att detta område i hjärnan ofta förknippats med ADHD, som traditionellt har ansetts vara primärt en ”icke-emotionell” diagnos. Dock har även ”emotionell” ADHD alltmer uppmärksammats på senare tid.

I den sista studien ville vi undersöka om emotionella symptom specifikt kunde relateras till aktivering av ”emotionella” områden i hjärnbarken under ett test som engagerade **både** emotionella och icke-emotionella nätverk i hjärnan (**Studie IV**). Denna studie belyser vikten av att undersöka emotionella och icke-emotionella symptom och relaterade processer i hjärnan *samtidigt*. Emotionella och icke-emotionella processer i hjärnan sker aldrig helt separat från varandra. Ett exempel är bilkörning: att köra bil kräver många ”icke-emotionella” färdigheter, som till exempel uppmärksamhet och en förmåga att anpassa sig till en föränderlig omgivning. Detta kan vara relativt enkelt när det inte finns några störningsmoment och man är själv i bilen, men kan däremot vara betydligt svårare om man blir känslomässigt distraherad av till exempel telefonsamtal eller skrikande barn i baksätet. Genom den typ av experimentellt test som vi använde i Studie IV, vilket engagerar både emotionella och icke-emotionella processer, ökar förutsättningarna för att vi ska kunna separera processer som sker simultant i hjärnan, även om dessa test förstås aldrig helt kan avspegla de komplexa situationer vi möter i vardagen.

Sammanfattningsvis kan vi konstatera att det är svårt att separera emotionella från icke-emotionella processer i hjärnan, men genom studierna i detta doktorandprojekt har vi börjat göra det. Om vi kan öka förståelsen för de mekanismer i hjärnan som bidrar till psykiatriska symptom vid till exempel uppförandestörning, emotionellt instabil (borderline) personlighetsstörning och ADHD, kan vi förhoppningsvis bidra till utvecklingen av nya, mer effektiva och individuellt anpassade behandlingar för dessa patienter i framtiden.

ABSTRACT

Emotional symptoms and non-emotional symptoms such as inattention often co-occur. Each of these symptom domains covers symptoms that are distributed along a continuum across the population; from non-clinical levels to clinically significant psychiatric symptoms. In this PhD project, we have focused on emotional symptoms related to emotional *instability*, i.e. rapidly fluctuating emotional responses and behaviors. Emotional instability is common in psychiatric diagnoses such as conduct disorder (CD) in children and emotionally unstable personality disorder (EUPD) in adults. Similarly, non-emotional symptoms such as inattention, are common in attention-deficit hyperactivity disorder (ADHD). Since emotional instability symptoms and non-emotional symptoms often co-occur, so do many psychiatric diagnoses associated with them.

The overarching aim of this PhD project was to try to disentangle concurrent emotional and non-emotional neural processes, behaviors, and symptoms. We aimed to correlate emotional and non-emotional symptoms to neural and behavioral measurements, while adjusting for the other symptom domain, in order to tease out the *unique* contributions of each symptom domain and related neural correlates. The four studies included in the project address this overarching aim from slightly different angles, for example by including adolescents and adults, non-clinical and clinical populations, and structural and functional neuroimaging techniques. Our hypothesis was that emotional instability and non-emotional ADHD/inattention symptoms– and behavioral and neural correlates–could be disentangled to some degree.

Some neural regions were of particular importance to this PhD project. Lateral orbitofrontal cortex (lOFC), rostral anterior cingulate cortex (rACC), and ventral striatum (VS)/nucleus accumbens (NAcc) served as primarily "emotional" cortical and subcortical regions of interest (ROIs), and their structure and function were hypothesized to relate to emotional instability symptoms. Similarly, dorsolateral/dorsomedial prefrontal cortex (dl/dmPFC) and caudal anterior cingulate cortex (cACC) were chosen as primarily "non-emotional" ROIs, of which structure and function was hypothesized to be associated to non-emotional ADHD/inattention symptoms.

Study I investigated how structural brain measures in a large community sample of 14-year-olds correlated with emotional instability and non-emotional ADHD symptoms. We found that surface area (SA) of dl/dmPFC and cACC correlated negatively with non-emotional ADHD symptoms, when adjusting for emotional instability symptoms. Grey matter volume (GMV) of rACC correlated negatively with emotional instability symptoms, when adjusting for non-emotional ADHD symptoms.

Study II followed up on Study I by correlating structural cortical and subcortical brain measurements of adults with and without ADHD with emotional instability and non-emotional inattention symptoms. We observed a negative correlation between GMV of NAcc (and the caudate) and emotional instability symptoms, adjusting for non-emotional inattention symptoms. In contrast to Study I, we could not show any correlations between cortical brain

measurements and emotional instability or non-emotional inattention symptoms in this adult cohort.

Study III employed functional magnetic resonance imaging (fMRI) to investigate how neural activation (as estimated by the blood-oxygen-level-dependent (BOLD) response) during anticipation and outcome of reward related to emotional instability and non-emotional inattention symptoms in non-clinical adults. There were no correlations between VS activation during reward anticipation, or ACC and insula activation during reward outcome, and emotional instability or non-emotional inattention symptoms in the sample as a whole. However, in a subsample of females only, VS activation during reward anticipation correlated negatively with emotional instability symptoms, when adjusting for non-emotional inattention symptoms.

Finally, **Study IV** also used fMRI to investigate neural activation during emotional and non-emotional conflict processing, and how that activation related to emotional instability and non-emotional inattention symptoms, in a sample of non-clinical adults. Emotional instability symptoms correlated positively with rACC activation during emotional conflict adjustment (contrasted against non-emotional conflict adjustment), when correcting for non-emotional inattention symptoms. Activation in cACC/dmPFC during exposure to cognitive conflict, or dlPFC activation during non-emotional conflict adjustment, did not correlate with non-emotional inattention symptoms.

Taken together, we found partial support for our overarching hypothesis that emotional instability and non-emotional ADHD/inattention symptoms–and behavioral and neural correlates–may be disentangled to some degree. The findings from Study I through IV, in combination with new literature that has emerged since the start of this PhD project, led to a discussion on future possible separation of emotional and non-emotional symptoms and underlying neural mechanisms Understanding these mechanisms will hopefully help develop a deeper understanding of related psychiatric diagnoses, and help pave the way for new, more individualized, treatments.

LIST OF SCIENTIFIC PAPERS

I. **Frida Bayard***, Charlotte Nymberg Thunell*, Christoph Abé, Rita Almeida, Tobias Banaschewski, Gareth Barker, Arun L.W. Bokde, Uli Bromberg, Christian Büchel; Erin Burke Quinlan, Sylvane Desrivières, Herta Flor, Vincent Frouin, Hugh Garavan, Penny Gowland, Andreas Heinz, Bernd Ittermann, Jean-Luc Martinot, Marie-Laure Paillère Martinot, Frauke Nees, Dimitri Papadopoulos Orfanos, Tomáš Paus, Luise Poustka, Patricia Conrod, Argyris Stringaris, Maren Struve, Jani Penttilä, Viola Kappel, Yvonne Grimmer, Tahmine Fadai, Betteke van Noort, Michael N. Smolka, Nora C. Vetter, Henrik Walter, Robert Whelan, Gunter Schumann, Predrag Petrovic, the IMAGEN Consortium. Distinct brain structure and behavior related to ADHD and conduct disorder traits. *Molecular Psychiatry, 2020 Nov; 25(11):3020-3033 (e-pub Aug 2018).* *co-first authors

II. **Frida Bayard**, Christoph Abé, Eva Henje, Orestis Floros, Timea Sparding, Martin Ingvar, Mikael Landén*, Predrag Petrovic*. Smaller nucleus accumbens in ADHD patients and healthy individuals relates to emotional instability but not inattention. *Submitted.* *co-senior authors

III. **Frida Bayard**, Christoph Abé, Nathalie Wrobel, Martin Ingvar, Eva Henje, Predrag Petrovic. Emotional instability relates to ventral striatum activity during reward anticipation in females. *Frontiers of Behavioral Neuroscience, 2020, volume 14, article 76.*

IV. **Frida Bayard***, Orestis Floros*, Christoph Abé, Eva Henje, Martin Ingvar, Predrag Petrovic. Neural activation during emotional and non-emotional conflict processing and its relationship with symptoms of emotional instability and inattention. *Manuscript.* *co-first authors

CONTENTS

LIST OF ABBREVIATIONS

ADHD	attention-deficit hyperactivity disorder
APA	American Psychological Association
B-ADD	Brown Attention-Deficit Disorder scales
BDI	Beck Depression Inventory
BOLD	blood-oxygen-level-dependent
cACC	caudal anterior cingulate cortex
cC	congruent trial preceded by another congruent trial (Stroop task)
CD	conduct disorder
cI	incongruent trial preceded by a congruent trial (Stroop task)
dlPFC	dorsolateral prefrontal cortex
DSM-5	Diagnostic and Statistical Manual of mental disorders, 5th edition
EEG	electroencephalography
EUPD	emotionally unstable personality disorder (also referred to as borderline personality disorder)
fMRI	functional magnetic resonance imaging
GMV	grey matter volume
iC	congruent trial preceded by an incongruent trial (Stroop task)
ICD-10	International Classification of Diseases, 10th revision
IFC	inferior frontal cortex
IFG	inferior frontal gyrus
iI	incongruent trial preceded by another incongruent trial (Stroop task)
IPS	intraparietal sulcus
lOFC	lateral orbitofrontal cortex
mOFC	medial orbitofrontal cortex
mPFC	medial prefrontal cortex
MDD	major depressive disorder

MRI	magnetic resonance imaging
NAcc	nucleus accumbens
rACC	rostral anterior cingulate cortex
ROI	region of interest
PCC	posterior cingulate cortex
PET	positron emission tomography
PFC	prefrontal cortex
R-DoC	Research Domain Criteria
RT	response time
SA	surface area
SDQ	Strengths and Difficulties Questionnaire
SMA	supplementary motor area
TBV	total brain volume
vlPFC	ventrolateral prefrontal cortex
vmPFC	ventromedial prefrontal cortex
VS	ventral striatum

1 INTRODUCTION

The overall aim of this PhD project was to disentangle emotional instability symptoms and non-emotional attention-deficit hyperactivity disorder (ADHD)/inattention symptoms associated with top-down dysregulation, since these symptoms often co-occur. We aimed to investigate how the two different symptom domains related to behavioral measurements and underlying neural correlates, both structural and functional, with a focus on prefrontal cortical and subcortical brain regions, known to be involved in processing of emotion, reward, and attention.

When the symptoms mentioned above are severe, they may lead to clinical psychiatric morbidity, such as emotionally unstable personality disorder (EUPD), conduct disorder (CD), and ADHD. Since co-occurrence of emotional instability symptoms and non-emotional ADHD/inattention symptoms is common, so is comorbidity of psychiatric diagnoses associated with those symptoms. Psychiatric research is often performed in patient groups with categorical psychiatric diagnoses that paradoxically contain heterogeneous symptomatology due to the way the diagnostic classification systems are constructed. Therefore, the diagnostic entities do not necessarily relate to underlying neural alterations of transdiagnostic dimensional symptomatology. Using a dimensional approach to emotional instability and non-emotional symptom domains allows us to disentangle related processes more precisely, and to investigate associations between them, both on a behavioral and neural level and across both non-clinical and clinical populations.

Through four different studies, emotional and non-emotional processes have been investigated from different angles; including populations of adolescents and adults, non-clinical individuals and psychiatric patients; always with a dimensional approach to symptomatology and underlying neural processes. In **Study I**, structural brain measurements were correlated with emotional instability and non-emotional ADHD symptoms in a large community sample of 14-year olds across Europe. **Study II** followed up on this question by investigating how structure of cortical and subcortical brain regions related to emotional instability and non-emotional inattention symptoms in a sample spanning non-clinical adults to adult patients with ADHD. Further, **Study III** employed functional magnetic resonance imaging (fMRI) to investigate how reward processing in cortical and subcortical regions related to emotional instability symptoms in non-clinical adults. Finally, **Study IV** examined how neural processing of emotional and non-emotional cognitive conflicts, and associated behavioral measurements, related to emotional instability and non-emotional inattention symptoms.

I will start by presenting an overview of central concepts to this thesis, including regulation of emotion, reward, and attention, and the benefits of applying a dimensional approach in this context. Next, I describe psychiatric disorders in which altered emotional and non-emotional regulation capacities lead to clinically relevant problems. I further present a brief overview of the development of the human brain, especially in relation to the central concepts of this thesis.

This is followed by a section of methodological considerations relevant to the included studies, an overview of the main results, and a critical discussion of the studies included in this PhD project. Finally, I discuss implications for future research aiming to further disentangle emotional and non-emotional processing in the brain.

2 LITERATURE REVIEW

2.1 EMOTION REGULATION

2.1.1 What are emotions and why do we need them?

In general, emotions are thought of as responses within a human being to the surrounding environment, crucial for adapting to challenges and needs (3). Emotions are typically described as distinct from moods, which are more prolonged mental states (3). Some argue for the existence of discrete "core emotions" that are universally common (e.g. (4, 5)), while others suggest that each discrete emotion category is built up from many "basic psychological ingredients" that all relate to prior experience (e.g. (6)). Subsequently, there are different views of whether different basic emotions give rise to overlapping and/or partially distinct activation patterns in the brain (6, 7). The concept of *valuation* is central to emotion; given that the value of a particular stimulus is always determined relative to the outer and inner context of an individual (8).

2.1.2 What is emotion regulation?

One of the most widely used definitions of emotion regulation is "how individuals influence which emotions they have, when they have them, and how they experience and express them" (9, 10). Appraisal theory explains how a physiological response triggered by internal or external stimuli mediates an emotional response; a response that may be modulated by appraisal (9, 10). This approach suggests that emotions may be regulated at different levels, i.e. from the trigger that initiates an emotional response, through the physiological response, to the evaluation and interpretation of the response (3, 8, 10). Different conscious or unconscious emotion regulation strategies may target the different levels and related neurocircuitry. One could suppress behavior caused by emotions, or adapt attention to emotion or interpretation of emotion, which in turn adjusts emotional responding (3, 10, 11). Emotion regulation has been described within the reinforcement learning framework including perception of emotion, evaluation of emotion and finally action following emotion (8). The emotion undergoes a similar evaluation process once it has arisen, and thereby the emotion itself is regulated.

Box 1 Top-down control

Top-down control refers to the highest level of control by the cortex over physiological processes (1). Cortical regions involved in top-down control vary depending on the task at hand. Attentional top-down control and emotional top-down control involve partially shared, and partially distinct prefrontal cortical regions (2).

2.1.3 How is emotion regulated?

Gross and colleagues have proposed an overarching model for emotion regulation. It includes a cognitive "top-down" control system (See Box 1) regulating brain regions related to emotional reactivity and valuation (3, 8). Different types of cognitive control over emotional processes have been described. An overview of brain regions engaged in emotion processing is presented in Figure 1. Explicit emotion regulation, comprising insight and awareness (e.g. reappraisal) involves the frontoparietal executive network. This network includes the ventrolateral prefrontal cortex (vlPFC) that signals salience and thereby initiates appraisal, and the lateral orbitofrontal cortex (lOFC)–adjacent to and partially overlapping with vlPFC. The network also includes the dorsolateral prefrontal cortex (dlPFC) that is involved in diverse regulatory processes, parietal cortex, anterior insula, supplementary motor area (SMA) and pre-SMA (8, 12-14). Implicit emotion regulation that may occur without insight or awareness (e.g. emotional conflict processing) involves rostral anterior cingulate cortex (rACC) and the adjacent ventromedial prefrontal cortex (vmPFC). Both of these brain regions further modulate activation of regions related to emotional reactivity, valuation, and interoception such as amygdala, ventral striatum (VS), periaqueductal grey (PAG), anterior insula and caudal anterior cingulate cortex (cACC) (8, 12, 13, 15, 16). Many neurotransmitters are involved in emotion regulation, and serotonin has been especially highlighted in relation to OFC function (17).

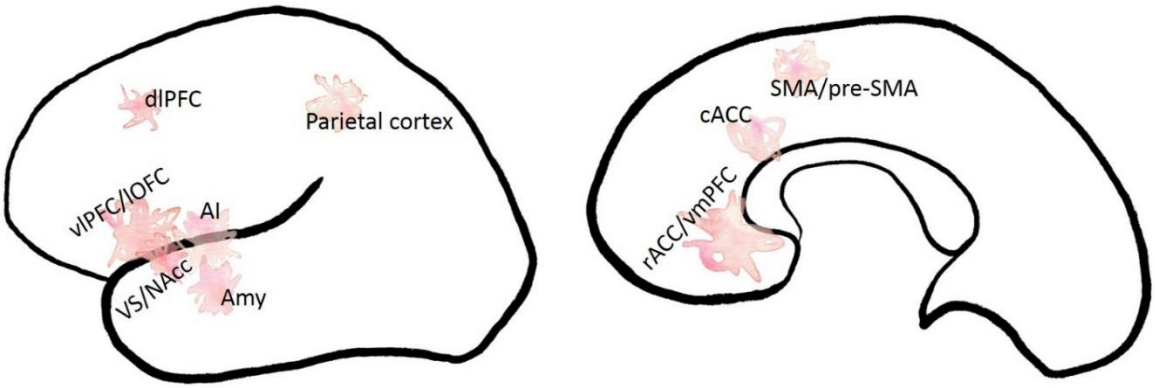


Figure 1 Regions involved in emotion processing. **Abbreviations**: AI = anterior insula, Amy = amygdala, cACC = caudal anterior cingulate cortex, dlPFC = dorsolateral prefrontal cortex, lOFC = lateral orbitofrontal cortex, NAcc = nucleus accumbens, rACC = rostral anterior cingulate cortex, SMA = supplementary motor area, vlPFC = ventrolateral prefrontal cortex, vmPFC = ventromedial prefrontal cortex, VS = ventral striatum

2.2 REWARD REGULATION

2.2.1 What is reward and why do we need it?

The ability to adequately process and evaluate reward is necessary to steer decisions in everyday life towards positively valenced stimuli and situations and avoid negatively valenced and potentially harmful stimuli and situations (18). Reward processing may involve anticipation of reward, the receipt of an expected/unexpected reward, and the subsequent valuation of the reward (19).

2.2.2 How is reward regulated?

Reward processing is associated with dopamine signaling. Dopaminergic pathways originate from brain stem/midbrain nuclei, project to basal ganglia structures, such as VS/nucleus accumbens (NAcc), and cortical networks, including OFC/vmPFC (19). However, many more regions–and neurotransmitter systems–are involved in processing of the different stages of reward, including anterior insula, rACC, dorsomedial prefrontal cortex (dmPFC)/SMA, and lateral frontoparietal areas (20, 21). Brain regions involved in reward processing are presented in Figure 2. Many of the regions are involved in several of the steps in reward processing, and despite mixed results, some distinctions have been suggested. Reward *anticipation* has been linked primarily to dopamine-dependent NAcc activation related to the concept of "wanting" (20-24). Dopamine-dependent VS/NAcc activation is essential in mediating the reward error signal that allows reward learning (25, 26). However, NAcc is also typically activated during reward *receipt*, and a subsection of the NAcc shell has been assigned as a "hedonic hotspot" linked to the concept of "liking" and related to the opioid neurotransmitter system (20-23, 27). Further, mOFC/vmPFC has been associated with the receipt of reward (21, 28-30), and together with ACC and anterior insula, more specifically with the subjective value and elicited feeling states related to the received reward (15, 16, 19, 21, 28, 29, 31, 32).

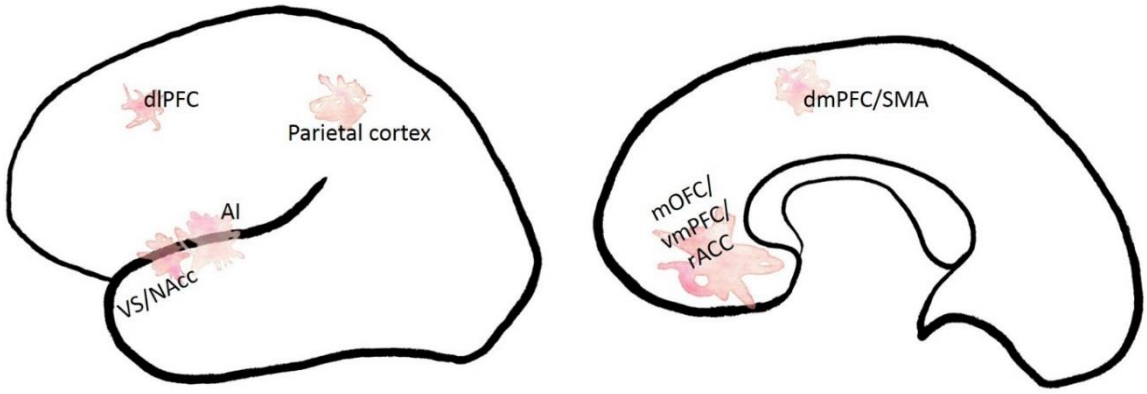


Figure 2 Regions involved in reward processing. **Abbreviations:** AI = anterior insula, dlPFC = dorsolateral prefrontal cortex, dmPFC = dorsomedial prefrontal cortex, mOFC = medial orbitofrontal cortex, NAcc = nucleus accumbens, rACC = rostral anterior cingulate cortex, SMA = supplementary motor area, vmPFC = ventromedial prefrontal cortex, VS = ventral striatum

2.3 ATTENTION REGULATION

2.3.1 What is attention and why do we need it?

"Attention is a multidimensional construct that refers to a state in which we have an optimal level of activation that allows selecting the information we want to prioritize in order to control the course of our actions" (36). Attention helps us focus on relevant input from the world around us, as well as inside of us, through appropriate selection of stimuli. Attention is also needed to identify situations in which control over automatic behaviors is required. Our attentive ability depends on our level of activation and motivation. Direction of attention may be automatic (stimulus-driven or bottom-up-mediated) or voluntary (goal-directed or top-down-mediated, see Box 1) and depends on the specific moment-to-moment circumstances. Attention may be driven by external stimulation or internal voluntary aims, and works in proximity with many executive functions (see Box 2).

Box 2 Executive function

Executive function is the ability to use top-down cognitive control mechanisms to make flexible choices and adapt our behavior in order to adjust to an ever-changing environment. Executive function depends on a distributed network, involving regions such as thalamus, basal ganglia and prefrontal regions. Examples of executive functions are attentional control, cognitive flexibility and working memory (33-35).

2.3.2 How is attention regulated?

Several neural systems are involved in regulation of the different aspects of attention (36-39). The underlying systems have been described using different nomenclature. Some refer to the alerting (arousal), orienting (sensory input selection) and executive attention (regulating processes to achieve the goal) networks (36-38), all of which interact (39). Attention regulation may also be described as an interplay between a salience network–related to arousal levels– and a central executive control network, which results in flexibly directing and maintaining attention to, and subsequently evaluating, relevant stimuli (40-42). Brain regions involved at different stages of attention processing are presented in Figure 3.

The **alerting network** is dependent primarily on locus coeruleus activation in the brain stem and the neurotransmitter norepinephrine, but also frontal cortex and parietal areas (36, 37, 39).

The orienting network modulates sensory processing, so that it is focused on attended stimuli rather than on distracting stimuli not associated with the task at hand. This network is highly dependent on the neurotransmitter acetylcholine (43). The orienting network consists of two

systems: the dorsal and ventral attention systems (44, 45). The dorsal attention system involves regions such as intraparietal sulcus (IPS), superior parietal cortex (SPC), and frontal eye fields (FEF) and has been associated with performance on top-down orienting tasks. The ventral attention system–proposed to be right-lateralized–involves temporoparietal junction (TPJ) and inferior frontal cortex (IFC)/vlPFC and medial frontal gyrus (mFG) and has been related to bottom-up activated attention; through external stimulation, such as an unusual stimulus or a warning signal. The dorsal and ventral attention systems interact to balance top-down and bottom-up influences. Regions comprised within the orienting network in turn modulate processing within sensory networks, so that attention is directed to appropriate stimuli and locations (36, 37).

The **executive control network**, or **executive attention network**, has been proposed to inlcude two independent neural networks. The first one is the cingulo-opercular network largely overlapping with the salience network, including cACC/medial superior frontal cortex and frontal operculum, extending into anterior insula. The second one is the frontoparietal network (similar to the "central executive network" (CEN)) including dlPFC, posterior parietal cortex (PPC), IPS, inferior parietal cortex (IPC), precuneus, and right midcingulate cortex (mCC) (36, 37, 39-42, 45, 46). The cingulo-opercular/salience network has been associated with general attention and maintaining required task information over longer periods of time, while the frontoparietal/CEN network has been related to cognitive control functions, such as trial-to-trial flexible response adjustment and decision making (47, 48).

Studies of conflict processing have led to another theory proposing one, rather than two, executive control networks (49, 50). This theory highlights the involvement of cACC in conflict "monitoring", while lateral prefrontal regions and rACC are involved in subsequent conflict resolution (49, 51-53). Others have described a single right-lateralized mid-cingulo/pre-SMA-insular-IFJ network as central for attentional control (54).

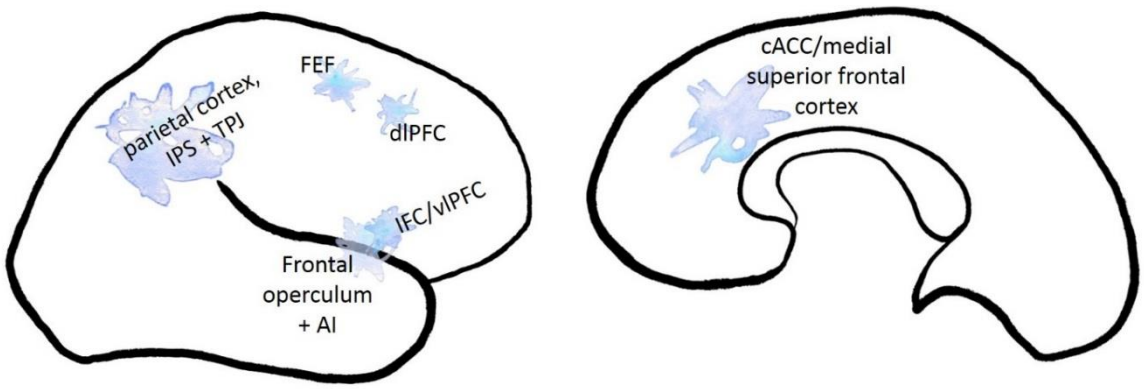


Figure 3 Regions involved in attention processing. The attention system has been proposed to be right lateralized, especially with regard to the IFC/vlPFC. **Abbreviations:** AI = anterior insula, cACC = caudal anterior cingulate cortex, dlPFC = dorsolateral prefrontal cortex, FEF = frontal eye fields, IFC = inferior frontal cortex, IPS = intraparietal sulcus, TPJ = temporoparietal junction, vlPFC = ventrolateral prefrontal cortex

Box 3 Dopamine and norepinephrine

Both emotional and non-emotional, such as attention, regulation systems are dependent on well-functioning dopamine signaling, which is important for assigning salience to different stimuli (23). The dopamine system works together with other neurotransmitter systems such as the norepinephrine system (55, 56). The dlPFC is one of the cortical regions highly dependent on catecholamine signaling in such a way that dopamine typically suppresses distracting signals ("noise"), while norepinephrine strengthens appropriate connections to achieve an optimal balance (56). The relation between catecholamine signaling and cognitive performance is suggested to follow an inverted U-shape function (56, 57), meaning that too little or too much catecholamines impairs performance. Dopamine availability increases in prefrontal regions until late adolescence/early adulthood, as top-down control capacity improves (34, 58-60).

2.4 BRAIN DEVELOPMENT

Study I of this thesis assesses brain morphology in relation to emotional instability and non-emotional ADHD symptoms in adolescents, while **Study II-IV** assess brain structure and function in adults. The following section gives a brief overview of the development of brain structure and function, with a focus on emotional and non-emotional processing.

2.4.1 Basics of neurodevelopment

During the first decades of life the brain undergoes significant neural reconstruction partly as an adaptive process to contextual influences. The total brain volume (TBV), including both grey and white matter, typically increases during childhood until adolescence, when pruning is causing a slight decrease of TBV. TBV then remains quite stable until the mid-thirties (61), after which the volume slowly declines as part of the natural aging process. Grey matter typically matures in a back-to-front direction, with lower-order somatosensory and visual cortices maturing first, followed by higher-order association and prefrontal cortices (62). The last cortical structure to fully develop is the orbitofrontal cortex (at around 25 years) (62), which is involved in emotion regulation and reward processing as described above.

Cortical thickness and surface area (SA) follow different developmental trajectories (63). On a global level, cortical grey matter volume (GMV) and cortical thickness typically decrease in a fairly linear fashion from childhood up till the mid-20's (63-65). SA has been shown to reach a peak at around 10 years of age after which it decreases, while other studies show a non-linear increase during adolescence (63, 65). Subcortical structure and function show more heterogeneous developmental tracts, and greater variability between individuals (63, 66).

2.4.2 Development of emotional and non-emotional processing

Despite complex neural developmental trajectories, in general, a rapid development of brain regions related to emotional processes, seems to be associated with the onset of puberty, interacting with the burst of neuro-endocrinological changes that occurs at that time (67). However, non-emotional cognitive skills that depend on prefrontal top-down control (See Box 1) co-vary with chronological age during development (68, 69). Altered connectivity between emotionally related subcortical regions and prefrontal cognitive control regions has also been reported (70). This mismatch in development results in a more affectively driven brain, without fully developed top-down cognitive control during adolescence (63, 71, 72).

The situation could be described as "starting the engines with an unskilled driver" (68), often resulting in increased sensation-seeking and engagement in risky behaviors (72-75). This type of behavior is associated with heightened dopaminergic reactivity (See Box 3), which also serves an adaptive function during adolescence, being a driving force of academic performance and prosocial behaviors (72, 76). With age, there is a shift towards more top-down regulated processing in the brain and emotion regulation capacity normally improves (69, 77).

2.5 WHAT HAPPENS WHEN REGULATION OF EMOTION, REWARD, AND ATTENTION FAILS?

Emotion dysregulation is a cardinal symptom in several psychiatric disorders. Emotional *instability* is one aspect of emotion dysregulation that refers to rapid changes of the emotional state, and impulsive emotional behavior (78). Symptoms of emotional instability are particularly common in patients with emotionally unstable personality disorder (EUPD), conduct disorder (CD), intermittent explosive disorder and antisocial personality disorder (79, 80).

Deficits in attention capacity and cognitive flexibility, hyperactivity and (non-emotional) impulsive behavior are also common across several psychiatric disorders, and the diagnosis most often associated with these problems is attention-deficit hyperactivity disorder (ADHD) (79).

Both emotional instability disorders (81-83) and ADHD (82-85) have also been related to altered processing of reward and reward related behavior.

Below, I summarize the main neural findings in patient groups typically associated with altered regulation of emotion, reward, and attention: EUPD (adults), CD (children), and ADHD.

2.5.1 Emotionally unstable personality disorder (EUPD)

EUPD (as described in International Classification of Diseases 10th Revision (ICD-10) (80)), is still referred to as borderline personality disorder by the Diagnostic and Statistical Manual of mental disorders 5th edition (DSM-5) (79). EUPD affects between 0.5 and 5.9% of the population (86, 87). It is a complex, heterogeneous disorder, often including psychiatric

comorbidity, in which emotional instability and difficulties in regulating emotions are central aspects (79, 80). Apart from having rapidly changing affective states, symptoms of anxiety and depression, EUPD patients often engage in self-harming and suicide related behaviors (79, 80, 87, 88).

It has been shown that patients with EUPD have smaller GMV in emotional cognitive control regions such as rACC (89, 90), and smaller GMV of lOFC has been reported in EUPD patients with a history of suicide attempts (90, 91). Additional structural deviances in EUPD patients include smaller GMV in hippocampi, amygdalae, right inferior frontal gyrus (IFG) pars opercularis, middle-superior temporal gyri, and bilateral insula (89-91).

fMRI studies including emotion processing tasks have reported varying results in EUPD patients. However, in general, EUPD patients show hyperreactivity to neutral and emotional stimuli in limbic regions such as amygdala, insula and ACC, and less prefrontal recruitment of for example OFC in reappraisal tasks as well as less recruitment of rACC in emotion conflict tasks and reward tasks (81, 92-101). In addition, hypofunction in cACC, rACC, dmPFC and dlPFC during interference processing in EUPD patients has been reported (102, 103), while others did not show any differences in activation in the same regions between EUPD patients and non-clinical controls (104).

2.5.2 Conduct disorder (CD)

CD occurs in 2-10% of children and adolescents under the age of 18, with higher prevalence in adolescents, and especially in boys (79). Problems related to CD include aggressive, antisocial, oppositional or defiant behaviors that violate rules and other people's rights. Many of these problems seem related to emotional dysregulation. There is a subgroup of CD, consisting of about 25% of the cases, presenting with callous-unemotional traits such as lack of empathy, guilt and emotion and low fear levels (105). This subgroup has been associated with a genetic vulnerability to antisocial behavior (106), distinct neural alterations (107), and has a more severe prognosis. Individuals in the CD subgroup with callous-unemotional traits do not show the typical emotional dysregulation problems that are within the scope of this PhD project.

Despite the heterogeneity of the CD patient group, the disorder has been associated with smaller GMV in amygdala, insula, medial superior frontal gyrus, ACC, and fusiform gyrus (108). Functional alterations during emotional and reward processing have been linked to CD in similar regions: lOFC, vmPFC, superior temporal lobes, amygdala, insula, hippocampus, ACC, and cerebellum (82, 83).

2.5.3 Attention-deficit hyperactivity disorder (ADHD)

The global prevalence of ADHD in children and adolescents is ca 5% (109). Around half of the affected individuals have symptoms that persist to adulthood (109). ADHD is commonly associated with executive dysfunction (See Box 2), inattention, impulsivity, and hyperactivity (79, 109-112). However, affective problems related to reward, motivation and emotion

regulation are being increasingly noted despite not being included in diagnostic criteria of ADHD (84, 113-119).

ADHD has been associated with a general delay in cortex maturation, especially in prefrontal cortex and ACC (120). Thinner cortex in medial prefrontal cortex (mPFC), dlPFC and cACC has been reported in adults with ADHD (121, 122). In addition, decreased functional activity in the frontoparietal network and the ventral attentional network has been observed in relation to ADHD during executive and attentional tasks (82, 111, 123, 124).

Furthermore, ADHD has been repeatedly related to altered reward processing (114-117). ADHD patients typically show less VS activation during reward anticipation compared to controls, while receipt of reward has been linked to a heightened activation in OFC in adult ADHD patients (84, 85).

2.6 DIMENSIONAL VERSUS CATEGORICAL DIAGNOSTICS

Just before the start of this PhD project, the Research Domain Criteria (RDoC) were proposed by the National Institute of Mental Health (NIMH) (125, 126). The approach highlights the drawbacks of classifying mental disorders by categorical symptom criteria, as done in the DSM (79) and ICD (80) systems. Although the DSM and ICD systems serve as important tools in clinical settings, they may hinder the elucidation of the underlying mechanisms related to psychiatric disorders, and subsequently, their treatment. The RDoC approach suggests that psychiatric disorders should be considered through a few distinct domains including several constructs, each of which should be well-validated through different "units of analysis": genes, molecules, cells, (neural) circuits, physiology, behavior, and self-report questionnaires. This framework encourages the investigation of the included domains across psychiatric diagnoses, and instead of using patient group status as independent variable, introducing a behavioral measure, or well-assessed non-clinical or clinical symptoms, related to a specific construct of a specific domain. At the start of the RDoC project, there were five suggested domains: negative valence domain, positive valence systems, cognitive systems, systems for social processes, and arousal/modulatory systems. However, the RDoC working group has, from the beginning, encouraged research to further develop the included domains and constructs–using a similar dimensional approach to specify new domains that could fit within the RDoC framework.

In line with the RDoC approach, the overarching hypothesis of this PhD project assumes that both emotional and non-emotional regulatory capacities are dimensionally distributed across the general population (127-129). At the end tail of the distribution of emotional instability and non-emotional symptoms, the likelihood of finding clinically diagnosed patients is higher. To learn about underlying neural mechanisms of emotional and non-emotional processing, patients with high levels of symptoms in the relevant domains may be studied. EUPD, CD and ADHD are all diagnoses in which altered neuroimaging findings related to emotional and non-emotional dysregulation have been reported. Across these diagnoses, comorbidity is common

and there is a large symptom overlap. In general, most neuroimaging studies performed in any one patient group have not investigated neural alterations in relation to dimensional symptom domains. Subsequently, previous studies in EUPD patients have not controlled for general attention capacity and ADHD traits, while studies including ADHD patients have seldom controlled for emotional regulation difficulties, making specific conclusions relating underlying neural correlates to either symptom domain difficult.

2.7 THE RELATION BETWEEN EMOTIONAL AND NON-EMOTIONAL REGULATION

Psychiatric disorders characterized by emotional instability, such as EUPD and CD, and ADHD–which is traditionally described as a non-emotional disorder–are often comorbid and show significant symptom overlap (130-132). Interestingly, emotion dysregulation has been noted in a subpopulation of ADHD patients (84, 119) and aberrant functioning in overlapping brain regions is reported in ADHD and EUPD (102).

2.7.1 The *cognitive core capacity theory*

The *cognitive core capacity theory* attempts to explain the high degree of comorbidity and symptom overlap between ADHD and disorders related to high levels of emotional instability (2). The theory suggests that individuals differ in various cognitive capacities, including top-down control dependent on prefrontal brain regions (See Box 1). Top-down control capacity is mirrored in behavior and various symptoms that are normally distributed across the population (127-129).

The *cognitive core capacity theory* suggests that although emotional and non-emotional top-down regulatory functions are closely interrelated, it is possible to separate the underlying processes to a certain degree (2). The model further suggests that problems of patients with EUPD/CD and ADHD, often found within the end tails of emotional instability and non-emotional symptom distributions, result from conceptually similar neural top-down dysregulation–with the difference being whether emotional or non-emotional (attentional/cognitive) regulatory processes are predominantly affected.

The *cognitive core capacity theory* further suggests that emotional and non-emotional neural networks are organized in a parallel fashion in an individual, both structurally and functionally. Consequently, if a person experiences problems related to dysfunction of one of these networks, a certain degree of problems in the parallel domain is likely to be experienced as well. For instance, some cases of ADHD may present with emotional dysregulation problems on subclinical levels–not accounted for by a comorbid diagnosis–and vice versa for patients with EUPD/CD (2, 113, 133).

The theory also suggests that there is an interplay between the emotional and non-emotional systems, allowing for a certain degree of compensation by the least affected system. For instance, it has been shown that patients with ADHD, characterized primarily by problems

related to the non-emotional domain, had increased lOFC volume (122), a region highly associated with emotional processing. A similar finding has been observed on a sub-clinical trait level (129).

2.7.2 Prefrontal brain regions of particular importance for the *cognitive core capacity theory*

Brain regions suggested to be central for emotional and non-emotional regulation by the *cognitive core capacity theory* are displayed in Figure 4 (2). The lOFC and the rACC are primarily related to emotion regulation processes associated with internal or interoceptive information–sometimes referred to as "hot" executive functions (2, 55, 82). The dlPFC and cACC are primarily involved in non-emotional regulation regarding external or exteroceptive information (53, 54)–sometimes referred to as "cool" executive functions (2, 55, 82). Both systems are highly dependent on dopamine and norepinephrine (55)(See Box 3).

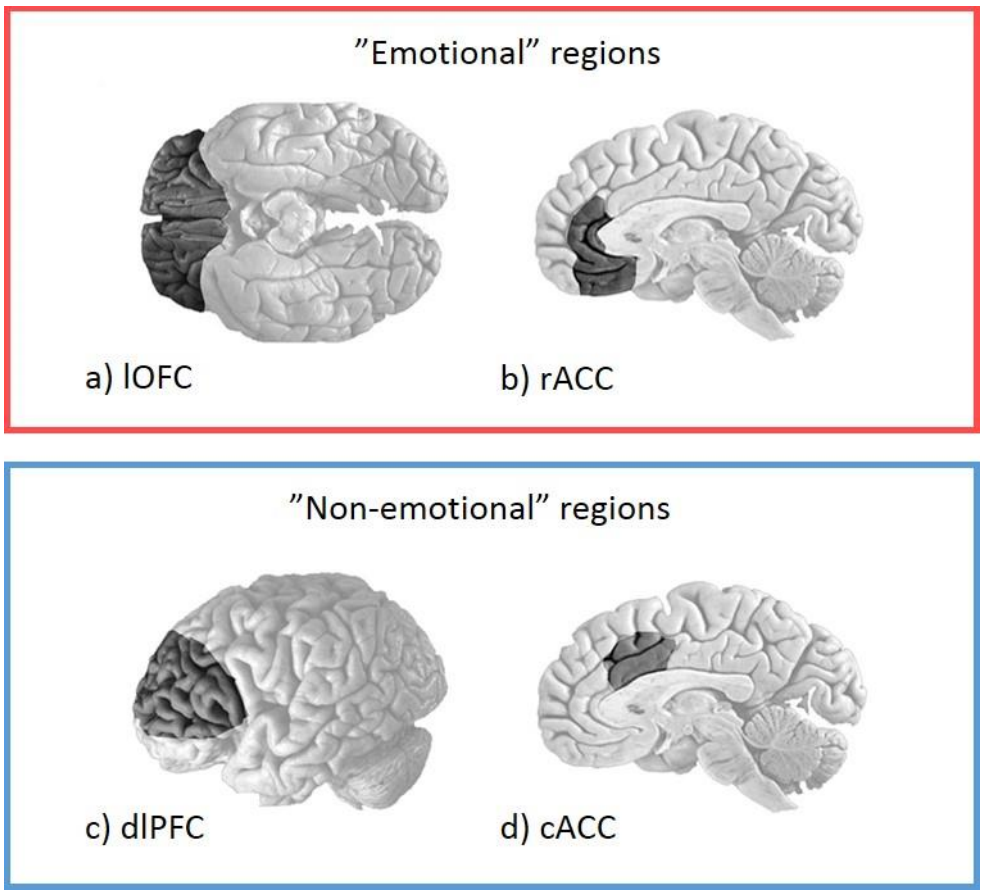


Figure 4 Prefrontal brain regions of interest in emotional (a, b) and non-emotional (c, d) regulation. Figure adapted from Petrovic and Castellanos 2016 (2). **Abbreviations:** cACC = caudal anterior cingulate cortex, dlPFC = dorsolateral prefrontal cortex, lOFC = lateral orbitofrontal cortex, rACC = rostral anterior cingulate cortex

2.8 IDENTIFIED KNOWLEDGE GAPS

The motivation for pursuing this PhD project was to improve the lives of patients with EUPD, CD, and ADHD, suffering from high levels of emotional and non-emotional dysregulation. This dysregulation often heavily impacts the lives of these patients, their families, and society at large. In order to intervene early and prevent future morbidity, it is crucial to better understand the underlying mechanisms. Increased understanding of the alterations of the neural mechanisms of–and relationship between–processing of emotion, reward, and attention in individuals with varying levels of emotional and non-emotional symptoms may contribute to better definitions of future patient phenotypes and improve treatment.

In 2014, when I started the PhD project, the *cognitive core capacity theory* (2) had already started to form, based on existing literature in the field and structural magnetic resonance imaging (MRI) findings made previously in the lab (129). However, there had not yet been any functional MRI studies designed to specifically disentangle the emotional from the non-emotional symptom domain, or correlating those symptoms with behavior and underlying brain activation. Subsequently, this became one of the main focuses of this PhD project, along with the aim to replicate the structural MRI findings (129) in larger samples, also including psychiatric patients.

3 RESEARCH AIMS

3.1 GENERAL AIM AND HYPOTHESES

The general aim of this PhD project was to disentangle emotional and non-emotional symptoms and investigate how these two symptom domains relate to underlying structural and functional brain correlates and associated behavioral measurements. Importantly, symptoms targeted in this project were primarily those of emotional *instability* (as opposed to other types of emotion dysregulation) and inattention (although non-emotional symptoms were more widely defined in **Study I** also to include other typical attention-deficit hyperactivity disorder (ADHD) symptoms).

The **first overarching hypothesis** was that emotional instability symptoms are associated with structural and functional alterations in brain regions engaged in emotional regulation, such as rostral anterior cingulate cortex (rACC) and lateral orbitofrontal cortex (lOFC), as well as subcortical regions connected to those, such as amygdala and ventral striatum (VS)/nucleus accumbens (NAcc), and associated behavioral measurements, also when controlling for the non-emotional symptom domain.

Similarly, the **second overarching hypothesis** was that non-emotional symptoms are associated to structural and functional alterations in brain regions involved in non-emotional attentional/cognitive control, such as caudal anterior cingulate cortex (cACC) and dorsolateral prefrontal cortex (dlPFC), and associated behavioral measurements, also when controlling for symptoms in the emotional instability domain.

We intended to test the hypotheses both in non-clinical and clinical populations using a dimensional approach to symptomatology in line with Research Domain Criteria (R-DoC), behavioral measurements and neural function related to the emotional instability and non-emotional domains.

3.2 SPECIFIC AIMS AND HYPOTHESES

The four studies included in this thesis investigate different aspects of the general hypotheses above. Specifically:

Study I aimed to investigate how emotional instability and non-emotional ADHD symptoms, including symptoms of inattention, related to underlying **structural** regional differences in the brain in a **community population** of **adolescents**. The hypotheses were that: 1) there are negative correlations between emotional instability symptoms and grey matter volume (GMV) of regions related to emotional regulation, such as rACC and lOFC, also when adjusting for non-emotional ADHD symptoms; 2) non-emotional ADHD symptoms correlate negatively with GMV of regions related to non-emotional attentional/cognitive control, such as cACC and

dorsolateral/dorsomedial prefrontal cortex (dl/dmPFC), also when adjusting for emotional instability symptoms; 3) behavioral performance associated to (non-emotional) motor impulse control and working memory capacity correlate with non-emotional ADHD symptoms while behavioral measurements related to processing of delayed rewards are mainly associated with emotional instability symptoms.

Study II aimed to disentangle **structural** neural correlates of emotional instability and non-emotional inattention symptoms in **adult patients with ADHD and in non-clinical adults.** The hypotheses were: 1) emotional instability symptoms correlate negatively with cortical and subcortical structure of rACC, lOFC, amygdala, and NAcc when adjusting for non-emotional inattention symptoms; 2) non-emotional inattention symptoms correlate negatively with cortical structure of cACC and dl/dmPFC when adjusting for emotional instability symptoms.

Study III aimed to study how emotional instability and non-emotional inattention symptoms related to different phases of **functional** neural processing of **reward**–both reward anticipation and reward outcome/receipt–in a **non-clinical adult** sample. The hypotheses were: 1) emotional instability symptoms are linked to a lower reward anticipation signal in VS/NAcc when adjusting for non-emotional inattention symptoms; 2) emotional instability symptoms, rather than non-emotional inattention symptoms, relate to activation of ACC and anterior insula during processing of reward outcome.

Study IV aimed to investigate how emotional instability and non-emotional inattention symptoms in **non-clinical adults** related to **functional** neural activation during different phases of **conflict processing** including both **emotional and non-emotional exposure to conflict and conflict adjustment**. The hypotheses were: 1) activation in cACC/dmPFC during exposure to emotional and non-emotional conflict correlate with non-emotional inattention symptoms, when adjusting for emotional instability symptoms; 2) rACC activation during emotional conflict adjustment correlate specifically with emotional instability symptoms, while dlPFC activation during non-emotional conflict adjustment correlate specifically with non-emotional inattention symptoms; 3) corresponding behavioral measurements of exposure to emotional and non-emotional conflict and conflict adjustment correlate similarly with symptoms of the respective domain.

4 METHODOLOGICAL CONSIDERATIONS

Below I describe and discuss the strengths and limitations of the methods of this PhD project, including the self-report questionnaires, behavioral tasks and neuroimaging techniques. Table 1 presents an overview of the methods applied and a specification of the hypotheses in relation to those methods. For further details of each assessment and technical specifications, see the included articles and manuscripts in the Appendix of this thesis.

Table 1 Overview of methods. For details, see articles/manuscripts in Appendix.

	Study I	**Study II**	**Study III***	**Study IV***
Assessment of emotional instability and non-emotional symptoms	**SDQ:** Emotional instability symptoms: *Conduct problems* subscale, referred to as *CD score* Non-emotional symptoms: *Hyperactivity/Inattention* subscale, referred to as *ADHD score*	**B-ADD:** Emotional instability symptoms: *Affect* subscale, referred to as *Emotion Instability* Non-emotional inattention symptoms: *Attention* subscale, referred to as *Inattention*		
Behavioral test/Cognitive assessment	Stop Signal test Spatial working memory task Delay discounting	-	MID task	Emotional and non-emotional Stroop task
Brain structures	**"emotional":** lOFC, rACC **"non-emotional":** dl/dmPFC, cACC	**"emotional":** lOFC, rACC, VS/NAcc, amygdala **"non-emotional":** dl/dmPFC, cACC	**"emotional":** VS/NAcc, ACC, anterior insula	**"emotional":** rACC **"non-emotional":** dlPFC, cACC
MRI technique	Structural	Structural	Functional: MID task	Functional: Emotional and non-emotional Stroop task

	Study I	Study II	Study III*	Study IV*
Main hypothesis	Structure of "emotional" brain regions correlates with *CD score*, while adjusting for *ADHD score*. Structure of "non-emotional" brain regions correlates with *ADHD score*, while adjusting for *CD score*.	Structure of "emotional" brain regions correlates with *Emotion Instability*, while adjusting for *Inattention*. Structure of "non-emotional" brain regions correlates with *Inattention*, while adjusting for *Emotion Instability*.	Activation within VS during reward anticipation correlates with *Emotion Instability*, when adjusting for *Inattention*. Activation within ACC and anterior insula during reward outcome correlates with *Emotion Instability*, when adjusting for *Inattention*.	Activation within "non-emotional" brain regions during exposure to both emotional and non-emotional conflict correlates with *Inattention*, while adjusting for *Emotion Instability*. Activation within rACC during emotional conflict adjustment correlates with *Emotion Instability*, while adjusting for *Inattention*. Activation within dlPFC during non-emotional conflict adjustment correlates with *Inattention*, while adjusting for *Emotion Instability*.
Other analyses	Correlating performance on behavioral tests with *CD* and *ADHD scores*. Do brain structure and test performance independently explain *CD* and *ADHD scores*?		Validation of our version of the MID task. Correlating behavioral measurements from the MID task with *Emotion Instability*, adjusting for *Inattention*.	Validation of our version of the Stroop task. Correlating behavioral measurements of the Stroop task with corresponding brain activation. Correlating behavioral measurements from the emotional and non-emotional Stroop task with *Emotion Instability* and *Inattention*, respectively.

* same participants included. **Abbreviations**: ADHD = attention-deficit hyperactivity disorder, cACC = caudal anterior cingulate cortex, CD = conduct disorder, dl/dmPFC = dorsolateral/dorsomedial prefrontal cortex, lOFC = lateral orbitofrontal cortex, MID = monetary incentive delay, MRI = magnetic resonance imaging, NAcc = nucleus accumbens, rACC = rostral anterior cingulate cortex, VS = ventral striatum

4.1 ASSESSING EMOTIONAL INSTABILITY AND NON-EMOTIONAL SYMPTOMS

In this PhD project, we were interested in relating brain structure and function to emotional *instability* and non-emotional symptoms. It should be noted that non-emotional symptoms were assessed slightly differently across the studies. In **Study I**, symptoms of inattention, hyperactivity, and impulsivity were included, whereas in **Study II-IV**, primarily symptoms of inattention were assessed. Below is a description and discussion of the different questionnaires used to assess these symptoms.

4.1.1 Strengths and Difficulties Questionnaire (SDQ)

Study I

Description: The SDQ consists of 25 questions divided into five subscales; *Emotional symptoms*, *Conduct problems*, *Hyperactivity/Inattention*, *Peer relationship problems*, and *Prosocial behavior* (134). For the purpose of this PhD project, the *Conduct problems* subscale and the *Hyperactivity/Inattention* subscale were of interest. The *Conduct problems* subscale assesses symptoms common in conduct disorder (CD), while the *Hyperactivity/Inattention* subscale assesses symptoms typically related to attention-deficit hyperactivity disorder (ADHD). The *Hyperactivity/Inattention* subscale may be further divided into *Hyperactivity/Impulsivity* (three questions) and *Inattention* (two questions). Both self- and parent-report scores were used in **Study I**.

Strengths: The questionnaire has been well validated to assess and capture specifically CD and ADHD symptoms in young populations (134). It is short and easy to administer and has been extensively used. Through inclusion of both emotional instability symptoms related to CD and non-emotional symptoms related to ADHD, the SDQ offers the opportunity to simultaneously assess these two symptom domains. Using both self-report and parent-report scores allows for a more nuanced and valid representation of symptomatology (135).

Limitations: The SDQ has not been designed to primarily assess dimensional traits, but has been shown to work well also for that purpose (136). The *Conduct problems scale* includes questions assessing callous traits, i.e., low levels of emotional reactivity rather than emotional *instability*, which could have influenced the results in **Study I**.

4.1.2 Brown Attention-Deficit Disorder scales (B-ADD)

Study II-IV

Description: The B-ADD self-report questionnaire consists of 40 items, divided into five subscales assessing different aspects of attention-deficit disorder (ADD) (not hyperactivity); *Activation* ("organizing, prioritizing, and activating to work"), *Attention* ("focusing, sustaining, and shifting attention to tasks"), *Effort* (regulating alertness, sustaining effort, and processing speed"), *Affect* ("managing frustration and modulating emotions"), and *Memory* ("utilizing working memory and accessing recall") (137). Higher subscale scores indicated more

difficulties in that particular domain. For the purpose of this PhD project, the *Affect* subscale (referred to as *Emotion Instability*) and the *Attention* subscale (referred to as *Inattention*) were used to assess the emotional instability symptom domain and non-emotional inattention symptom domain.

Strengths: The B-ADD questionnaire has been designed to assess different aspects of ADD, including inattention and emotional instability, and allows for a dimensional approach to these different aspects. It has previously been used to assess dimensional symptoms in a healthy population (129).

Limitations: The questionnaire has not been designed with the primary purpose of assessing the different symptom domains employing a dimensional perspective of symptoms within each domain. Within the *Emotion Instability* domain, there are two questions that rather relate to autistic features (item 30-31) and depression (item 29). We were interested in studying neural correlates of emotional *instability*, i.e. rapidly fluctuating emotions, and the inclusion of these additional questions might have affected our results. In previous publications, the results linking grey matter volume (GMV) of lateral orbitofrontal cortex (lOFC) to symptoms of emotional instability were more robust when those questions were removed (129).

4.1.3 Conclusions regarding symptom assessment

Using the SDQ and B-ADD scales to assess emotional instability and non-emotional symptoms was motivated, given the available questionnaires at the time of planning the studies included in this PhD project. However, there are many questionnaires available (some developed after the start of this PhD project) that assess different aspects of emotion regulation, including emotional reactivity and emotion regulation strategies, for example: Behavioral inhibition systems/Behavioral activation systems (BIS/BAS, including emotion reactivity (138)), Difficulties in Emotion Regulation Scale (DERS (139), M-DERS (140)), Emotion reactivity scale (ERS (141)), Perth Emotional reactivity scale (PERS, (142)), the Emotion Regulation Questionnaire (ERQ (143)), and Comprehensive Emotion Regulation Inventory (CERI (144)).

A similar issue arises regarding the non-emotional symptom domain. Through the questionnaires used in this PhD project, questions for the non-emotional symptom domain assessed both inattentive symptoms (B-ADD and SDQ), cognitive flexibility (B-ADD), and hyperactivity/impulsivity (SDQ). Those constructs could be investigated separately to further disentangle underlying neural correlates.

In summary, in order to better assess and target the exact constructs of interest, and relate to behavioral responses and underlying neural mechanisms, there is a need to develop new questionnaires, especially with regard to emotional instability, but also including a corresponding non-emotional domain. A questionnaire assessing emotional instability **and** non-emotional symptoms in a weighted and distinct way (allowing quantifying the level of orthogonality between these symptom domains) would have been ideal.

4.2 ASSESSING EMOTION REGULATION, REWARD PROCESSING, AND COGNITIVE CONTROL THROUGH COGNITIVE TESTING

The goal of this PhD project was to disentangle emotional instability and non-emotional symptoms in terms of behavioral responses and underlying neural processes of emotion regulation, reward processes, and non-emotional attention/cognitive control. In order to do so, we chose to use the tasks described below. The behavioral tasks included in **Study III** and **IV** were adapted specifically for these studies and therefore, our specific approach to these tasks is further discussed. The symptoms of interest are present to a high degree in patients with emotionally unstable personality disorder (EUPD), CD, and ADHD, and therefore, behavioral and neural findings in those patient groups are considered in relation to each task.

4.2.1 Stop Signal test

Study I

Description: The Stop Signal test (145, 146) has been widely used to assess primarily "non-emotional" motor impulse control, sometimes referred to as stopping impulsivity (147). Brain regions related to inhibition of motor responses are pre-supplementary motor area (SMA)/caudal anterior cingulate cortex (cACC), right ventrolateral prefrontal cortex (vlPFC)/inferior frontal cortex (IFC) extending into insula, and parietal regions (148-150).

Strengths: The Stop Signal test is a well validated and a simple task both to administer and perform. It is possible to use in different populations and in different settings. We were interested in investigating neural correlates of non-emotional problems often present in patients with ADHD. Patients with ADHD have been consistently reported to show a longer stop signal reaction time as compared to controls (151-153), while EUPD patients (154-156) and CD patients (151) typically do not, which suggests that the Stop Signal test may capture altered functioning specifically related to ADHD. Reduced activation in right inferior frontal gyrus (IFG), SMA and ACC has been observed in ADHD patients in relation to inhibitory processes during impulse control tasks (157). Taken together, the Stop Signal test properly assesses behavioral and neural correlates to non-emotional symptoms, which was one of the goals of this PhD project.

Limitations: Motor impulse control does not equate to all impulse control processes (147, 148), which should be considered when choosing the Stop Signal test for assessment. Several versions of the Stop Signal test are available, making comparison across studies difficult (158). The version used in **Study I** was adapted to a functional magnetic resonance imaging (fMRI) setting and to fit 14-year-olds (although we used only behavioral measurements in our analysis).

4.2.2 Delay discounting

Study I

Description: Delay discounting refers to the process in which a future reward is less valued the more distant in time it will be received (159). Delay discounting relates to choice impulsivity (147), which, apart from non-emotional impulsivity aspects, also involves more affectively charged processes (148). The tendency to discount a delayed reward is dependent on the balance between the subcortical reward system and prefrontal impulse control. Delay discounting processes depend on several brain regions–among them the ventral striatum (VS), lOFC, medial orbitofrontal cortex (mOFC), ACC, dorsolateral prefrontal cortex (dlPFC), vlPFC, and parietal cortices–and the connections between them (148, 160-164).

Strengths: The delay discounting assessment has been widely used in different formats (165). It is easy to administer (questionnaire format) and adapt reward levels and reward delay suitable to different populations. Patients with ADHD (166), EUPD (167, 168) and CD (169) tend to show high choice impulsivity, including steeper delay discounting, as compared to non-clinical controls. Taken together, this makes the delay discounting assessment a good choice for investigating behavioral responses related both to emotional instability and non-emotional symptoms.

Limitations: Real-world decisions might differ substantially from the responses regarding theoretical rewards in a questionnaire. The outcome of the delay discounting assessment depends both on emotional and non-emotional regulation capacity (148), which allows investigating both types of regulation simultaneously. Ideally, in order to study specific neural correlates of emotional processing capacity, a "pure" emotional processing task, or a task that includes separable emotional and a non-emotional parts that could be contrasted against each other, would have been preferred.

4.2.3 Monetary Incentive Delay (MID) task

Study III

Description: The MID task has been widely used to study reward anticipation and reward receipt, often in an fMRI setting (170, 171). Details of the version of the MID task used in **Study III** of this PhD project are presented in Figure 5.

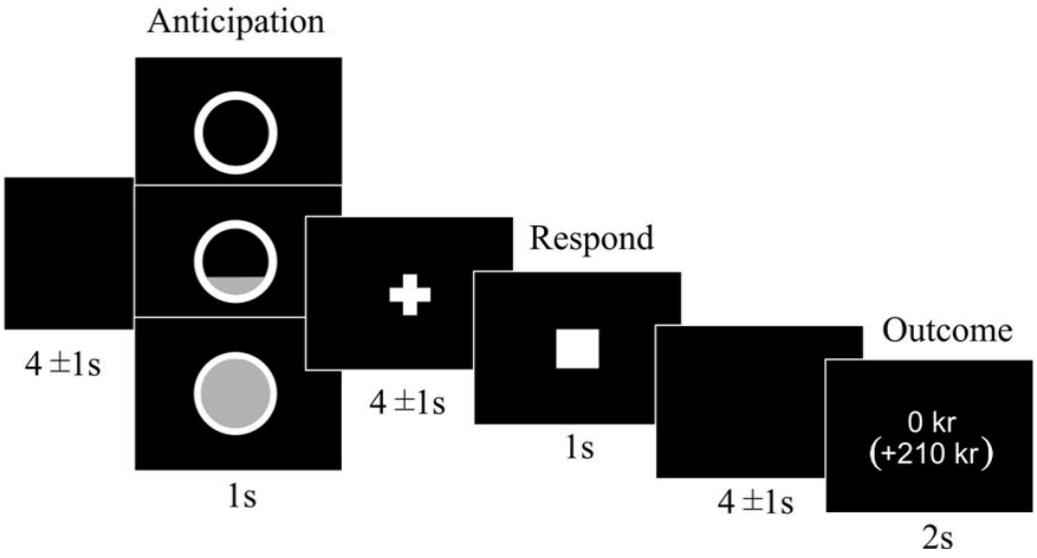


Figure 5 The Monetary Incentive Delay (MID) task used in this PhD project, adapted from Knutson et al. (170, 171). In each trial, the participant may win 0, 10 or 50 Swedish crowns (SEK). 10 SEK is equivalent to approximately 1 Euro. Figure adapted from Bayard et al. 2020 (172). For further details regarding our version of the MID task, see article related to **Study III** in Appendix.

Strengths: The MID task has been widely used and is an established fMRI task with consistently reported activations in VS during reward anticipation (21). The MID task also allows investigating changes in neural activation in response to increasing reward levels (170). Furthermore, the task has been used frequently to test ADHD patients, showing hypoactivation in VS during reward anticipation, but varying activation during reward outcome as compared to non-clinical controls (85, 173-179). EUPD has not been extensively studied by using the MID task, but blunted reward anticipation activation in VS has been reported (81, 180, 181).

Limitations: Many different versions of the MID task exist. Some separate the anticipation phase from the outcome phase through proper jittering (e.g. (182)), while many do not (see details of studies included in meta-analysis by Oldham et al. (21)), making differentiation between neural activation during the different phases of reward processing difficult. Furthermore, baseline trials are defined differently, which makes interpretation and comparison of results difficult.

Our specific approach: We used the original version of the MID task (170, 171) and adapted jittering to properly separate the anticipation from the outcome phase, since we were interested in studying both phases. We further used neutral trials only (without possibility to win) as baseline trials, against which we compared activation during reward processing. We did not include all no-win outcome trials in our analyses, which has sometimes been done previously, since we assumed that those trials would also represent disappointment, when failing to receive an anticipated reward. The reasons for including two different reward levels in our task, while collapsing them in the analyses were: 1) to keep the task more interesting for the participants; 2) allowing to confirm that the activation in VS during reward anticipation was actually related to the reward level, thereby increasing the likelihood that we were studying what we aimed to

study; 3) the possibility to use the same task in larger samples in the future, and then separate the two reward levels in the analysis. We first confirmed that the main activations of the task were in line with previous studies, and subsequently ran analyses testing our specific hypotheses.

In order to get enough power for the analysis, the task had to be rather long in an fMRI setting. We divided it into two sessions, hoping that it would decrease boredom. Most participants reported being highly motivated throughout the task due to the relatively high levels of (real) reward.

4.2.4 Emotional and non-emotional Stroop task

Study IV

Description: The Stroop task may be used to study conflict processing, which is dependent on higher cognitive control functions, including regulation of attention. The task allows investigation of processes both related to exposure to conflicting stimuli, such as conflict monitoring, conflict generation or immediate conflict regulation, from here on referred to simply as *exposure to cognitive conflict*, and *adjustment* of conflict processing following previous conflicting stimuli. Different versions of the classic color-word Stroop task (183) have been used to study *exposure to cognitive conflict* and *conflict adjustment* in humans. The classic version of the task presents the subject with incongruent (conflicting) stimuli (for example the word "green" printed with yellow ink) or congruent (non-conflicting) stimuli (for example the word "blue" printed with blue ink). The task is to report the color of the ink and ignore the meaning of the word. Incongruent trials typically result in longer response times (RT) and more errors. Incongruent trials preceded by another incongruent trial (iI) typically result in comparably shorter RTs and less errors than incongruent trials preceded by a congruent trial (cI). This results from cognitive control processes being recruited during the previous incongruent trial and has been interpreted as an adjustment effect (49, 50, 53).

Efforts have also been made to study *exposure to* emotional *cognitive conflict* and *conflict adjustment* using a face + word Stroop task (51, 52), see Figure 6. Activation during *exposure to* both emotional and non-emotional *cognitive conflict* (51, 52) and more general interference related activation (49, 50, 52, 53, 184-190) have been reported within cACC and adjacent dmPFC; both part of the non-emotional control systems (2). Amygdala activation has been reported uniquely in relation to *exposure to* emotional *cognitive conflict* (51, 52). DlPFC activation has been mainly associated with non-emotional *conflict adjustment* (52, 53, 185), while rACC activation has been proposed to relate to emotional *conflict adjustment* rather than non-emotional *conflict adjustment*, and exert top-down control over the amygdala, reducing amygdala activation in response to conflict (52).

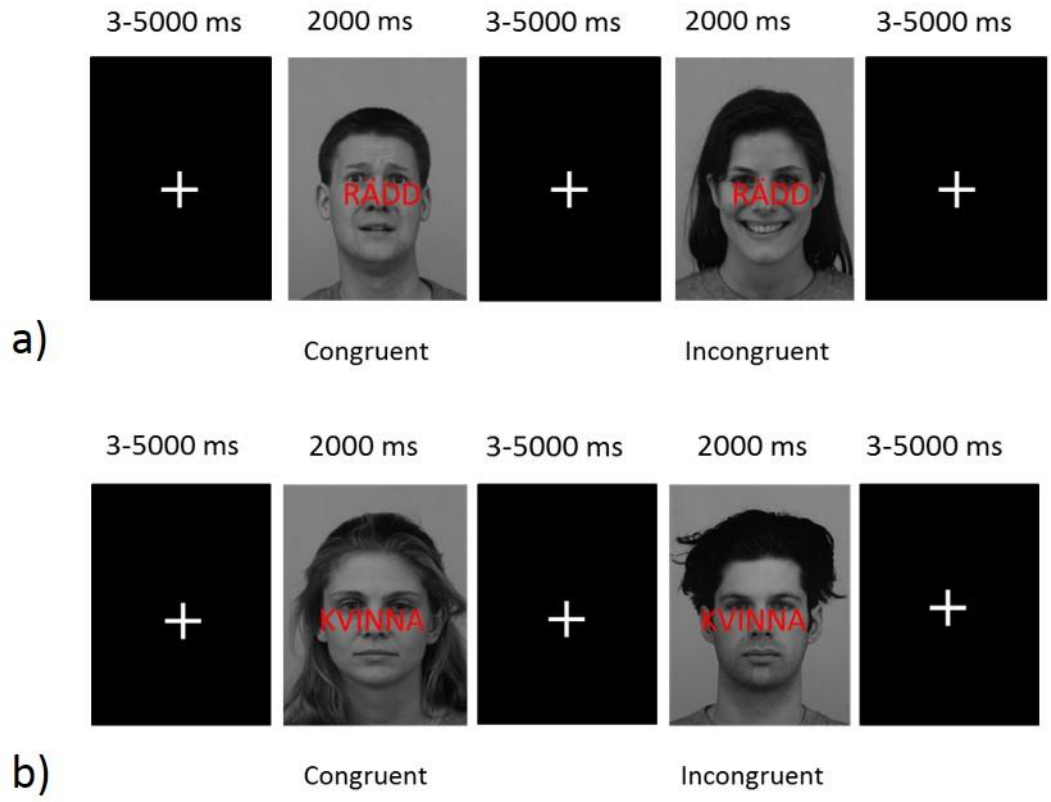


Figure 6 Example of the **a)** emotional and **b)** non-emotional Stroop task, adapted from a previous version of the task (51, 52), used in this PhD project. The emotional trials consisted of pictures of male and female faces with a happy or fearful expression, overlaid by the word RÄDD (fearful) or GLAD (happy). The non-emotional trials consisted of pictures of male and female faces with neutral expressions, overlaid by the word MAN (Swedish word for man) or KVINNA (Swedish word for woman). Participants were instructed to press different buttons for happy and fearful faces (a), and male and female faces (b), while ignoring the word superimposed on the picture. For further details regarding our version of the Stroop task, see Floros et al. (192) and manuscript related to **Study IV** in Appendix.

Strengths: The Stroop effect is well-established, both behaviorally (183) and in fMRI studies (54). An emotional Stroop task very similar to our version has already been used in fMRI settings (51, 52). This specific version of the task allows studying emotional and non-emotional interference processing in parallel. Both emotional and non-emotional conflict processing and other types of interference processing have repeatedly been related to activation in cACC and adjacent regions (49-53, 184-187). Interference processing has been associated with hypoactivation of cACC/dorsomedial prefrontal cortex (dmPFC) in patients with ADHD (102, 191), and with hypofunction in cACC, rACC, dmPFC and dlPFC in patients with EUPD (102, 103).

Limitations: While performing the current version of the Stroop task, many complex processes such as face processing, responding, and keeping several rules "online" in working memory occur simultaneously. Some separation could be achieved by precise contrast specification, such as contrasting emotional faces with neutral faces; thereby removing all activity related to

general facial processing. However, disentangling attentional regulation from other executive functions is not possible by using this version of the Stroop task.

Our specific approach: The Stroop version employed in this PhD project has been slightly modified compared to previous versions (See Figure 6, and Floros et al. (192) for details of our version of the task and (51) and (52) for previous versions). We believe the changes made have improved the task in the following ways: 1) Neutral faces were employed in the non-emotional blocks of the task (rather than emotional faces as previously done (51, 52)) in order to better distinguish between emotional and non-emotional processing; 2) We used a slightly different approach to defining *exposure to cognitive conflict* than previously. We contrasted trials with the highest amount of conflict (cI) against trails with the lowest amount of conflict (cC), compared to others who have used iI (adjusted conflict processing) instead of cC as reference. We believe our approach better represents the construct we intended to study; 3) We did not model errors in the fMRI model, since we believed it could potentially remove some of the variance related to conflict processing, i.e. the construct of interest (expecting more errors when conflict level is particularly high); 4) Our version of the task included a different set of facial expression pictures, as well as words in Swedish, which potentially could have affected the responses.

Finally, in order to collect enough data to achieve power for meaningful analyses, the duration of the task was relatively long, and some participants expressed declining motivation towards the end.

4.2.5 Conclusions regarding assessment of emotion regulation, reward processing, and cognitive control

Different tasks aim to induce different emotional or non-emotional processing or states. However, non-emotional processing may be accompanied by some degree of emotional frustration and processing, while emotional processing typically involves aspects of non-emotional regulation, such as shifting attention to relevant stimuli. When several neural processing systems are involved, or the functioning of one neural system is related to a vast repertoire of processes, disentangling processes uniquely related to emotional instability and non-emotional symptoms requires careful consideration. By adapting precise aspects of the chosen tasks in certain directions, i.e., adding "more emotional" or "more non-emotional" cognitive load, allows disentangling underlying neural processes at least to some extent. This was accomplished by using the emotional and non-emotional versions of the Stroop task in **Study IV**. However, we could not produce a similar separation of the domains within the delay discounting assessment in **Study II** or the MID task in **Study III**.

The cognitive tests included in this PhD project could all be used in future studies, although some modifications might be desirable. The Stop Signal test in **Study I** was adapted to an fMRI setting, and not a "standard" behavioral version as provided by Verbruggen et al. (146). However, both these versions have been tested in large samples and could be used in their current form. The delay discounting assessment (**Study I**) focuses on varying the (hypothetical)

duration of a delayed reward and results in an "indifference point" for each participant, mirroring the time point when a delayed larger reward is judged "equivalent" to a specific smaller immediate reward. This measurement could be complemented with an assessment of delay gratification, which rather assesses how long an individual can wait for a larger reward, such as in the classic Marshmallow test (193). Delay gratification tasks typically result in number of points corresponding to the tendency to choose smaller immediate or larger delayed rewards (e.g., (194)), or number of choices made favoring the immediate to delayed reward option (e.g., (116)). Both delay discounting and delay gratification relate to choice impulsivity (166), but may add complementing views of related processes. The modified version of the MID task that we employed in **Study III** evoked robust main activation in expected regions and could therefore be used in its current format in future studies. Regarding the emotional and non-emotional Stroop task employed in **Study IV**, recent studies have pointed to additional potential brain regions of importance in conflict processing, such as IFG and anterior insula (184-187). Those regions, as well as the networks they form part of, should be considered in future studies on interference processing. Recently, it has been shown that behavioral *variability* measurements extracted from the Stroop task may be more related to emotional instability and non-emotional inattention symptoms (192), as compared to response times (RT) investigated in **Study IV**. Variability in neural activation during the Stroop task as measured by fMRI, corresponding to the behavioral variability measurements, could be further investigated in future studies including this task.

A general problem that arises with regard to any research study involving behavioral assessment is the validity of the results in relation to the "real world". In order to study any neural process there is a need to precisely specify and isolate the process as much as possible from other related processes. However, in the real world, no neural processes occur in isolation, and it is therefore difficult to generalize experimental research findings to real world situations.

4.3 IMAGING METHODS TO STUDY NEURAL STRUCTURE AND FUNCTION

There are several imaging methods available to study the brain. I will briefly explain why I believe that structural and functional MRI are the best choices for the current PhD project, despite their limitations, as compared to other imaging modalities.

4.3.1 Structural MRI

Strengths: MRI offers the best structural resolution available without exposing participants to high levels of ionizing radiation. Resolution has improved much over the past few years, and the standard magnetic field strength today is 3 Tesla (T), even though 7 T is becoming increasingly used in research. MRI is a non-invasive technique and more powerful analysis tools are appearing rapidly. Large pooled datasets are emerging, allowing for mega-analyses including several thousands of participants (e.g. the IMAGEN (195) and ENIGMA consortia (196)).

Limitations: There are several technical limitations and typical problems related to MRI, such as signal-to-noise ratio, and (in)homogeneity of the magnetic field applied (197). Structural MRI studies are still sometimes limited by small sample sizes that, in combination with flexible processing of raw data results in overestimated effect sizes and low reproducibility (198-200).

4.3.2 Functional MRI

Strengths: fMRI makes it possible to indirectly visualize and investigate brain activation, with higher spatial resolution than electroencephalography (EEG) and positron emission tomography (PET), and with no exposure to ionizing radiation, no invasive procedures and short preparation to collect data. Standardized pipelines for processing of data have emerged and are constantly developing, aiming at creating more comparable results and encourage replication (e.g. fMRIPrep pipeline (201)). Large consortia are emerging that aim to pool large fMRI datasets (e.g. the IMAGEN (195) and the ABCD study (202))

Limitations: If structural MRI data may be analyzed in many different ways, functional MRI offers an even greater analysis flexibility, which has recently been shown to give rise to highly divergent results (198). Factors highlighted as of certain importance to the varying results within fMRI studies are smoothing techniques, the software used, methods applied to correct for multiple comparisons, typically low statistical power, excessive exploratory analyses, which are not subsequently presented as such, but rather as based on pre-defined hypotheses, software errors, insufficient study reporting and lack of independent replications (198-200). Nevertheless, larger sample sizes are becoming more common in the field (199) and Botvinick-Nezer and colleagues suggested that pooling unthresholded statistical maps from fMRI studies could be one way to improve reliability (198). Still, it is difficult, and costly, to pool large datasets, since fMRI tasks seldom employ the exact same version of the intended task and behavioral measurements.

Moreover, the blood-oxygen-level-dependent (BOLD) signal assessed by fMRI, modelled by the hemodynamic response function (HRF) (or other), and further represented in the form of statistical maps, is only an indirect measure of brain activation, possible through the magnetic properties of oxygenated versus deoxygenated blood. The BOLD signal is a relatively slow response with a duration of 20-30 seconds and cannot match the actual neural transmission rate or the temporal resolution of EEG and magnetoencephalography (MEG). In addition, even if assuming that the BOLD signal from a region correctly represents neural activation, it is still not possible to say whether the underlying activation is of excitatory nature, or rather the opposite. Furthermore, despite being a non-invasive procedure, fMRI scanning involves a relatively long period of lying still in a confined space surrounded by loud noise. Even small head movements interact with signal acquisition and further, it is difficult to mimic a real world setting under these circumstances.

4.3.3 What could be improved?

Choosing a functional imaging method today often involves a certain trade-off between ideal spatial and temporal resolution. To address this problem, it has become more common to

combine imaging methods, for example EEG and fMRI (185, 203). Combining structural and functional MRI may also be valuable, since structural alterations do not necessarily invoke functional alterations, or vice versa, even though there is some level of correlation between structural and functional connectivity (204). Another approach could be to use PET or MR spectroscopy in addition to fMRI in order to elucidate what neurotransmitters (excitatory or inhibitory) are involved in the processes captured by fMRI. Applying each of these combinations could potentially compensate for the limitations related primarily to the fMRI technique.

In addition, since investigating brain regions in isolation might obstruct the interpretation of results, I believe it would be of value to follow-up on our studies with structural and functional network analyses for validation, given that we chose a limited number of pre-defined ROIs to represent parts of the relevant networks in each study.

4.4 ETHICAL CONSIDERATIONS

The studies included in this PhD project all involved human participants, which required several ethical considerations. Participation in all studies within the project was voluntary and participants could choose to withdraw their participation at any time. All participants included in **Study I-IV** gave written informed consent to participate in the respective study.

In **Study I**, we had access to a large European multi-center dataset through the IMAGEN consortium and the data had been collected elsewhere, according to European ethical regulations (195). We applied to the IMAGEN consortium to be granted access to the anonymized data for our specific research questions, according to their standard procedures. Even though the participants had all given consent to be part of the IMAGEN dataset, as well as future studies including that dataset, they still had not given informed consent to participation in our specific study. The IMAGEN dataset has not been made publicly available, due to concerns that the data could possibly be used to investigate un-ethical questions.

In **Study III**, we studied reward processing, and wanted to create a "real" sense of reward in the participants by offering them an amount of money. However, there was still an upper limit of maximum reimbursement and the choice to participate should not solely depend on the monetary re-imbursement, in agreement with ethical guidelines.

Until now, no known risks of MRI have been reported. However, the time spent in the scanner was quite long for **Study III** and **IV**, possibly causing discomfort. We divided the scanning into two sessions, and it was also possible to add extra breaks. Another ethical aspect of MR-scanning is the possible incidental pathological neural findings. We followed standard protocol at the MR Center at Karolinska Hospital in Solna, where all T2 scans of our participants were examined by a neuroradiology specialist. In case of any incidental findings, the participant was contacted and invited to clinical assessment.

There are several ethical considerations that are common to various scientific fields of research. The problems mentioned above, in relation to fMRI research, are relevant also within other areas: analysis flexibility, limited sample size, excessive exploratory analyses and insufficient study reporting (198, 199, 205). Lack of independent replication, including high rates of false findings, is not limited to the field of neuroscience, but has received much attention lately within diverse research fields (198-200, 205-208), as has publication bias (209, 210). One of several steps towards increasing reproducibility and reliability in fMRI research is to pre-register studies and hypotheses (198, 199). We pre-registered the overarching hypotheses for **Study III** and **IV** at Clinicaltrials.gov. The registered version concerned extended research including psychiatric patients with EUPD and ADHD. Another measure contributing to decreasing the effects of analysis flexibility and to increasing reproducibility within the fMRI field, is through open access of data and analysis scripts (198, 199). As for the studies in which we were responsible for data collection (**Study III** and **IV**), data and analyses scripts were available upon request. In the future, it would be of interest to share data and analyses more actively and openly.

5 MAIN RESULTS

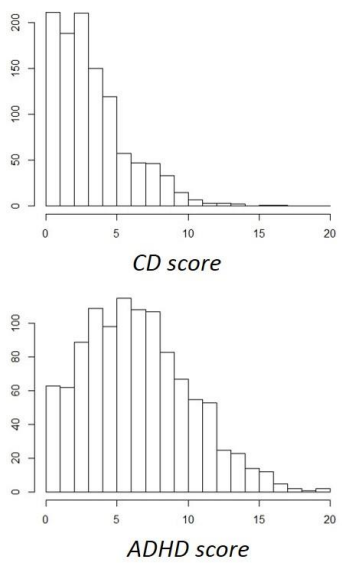
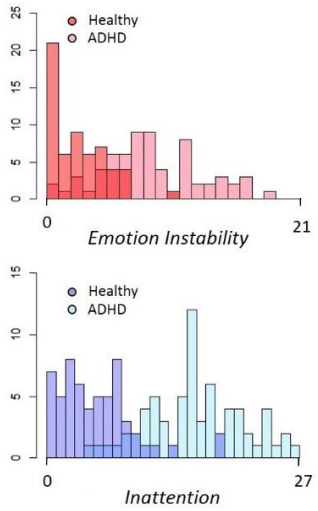
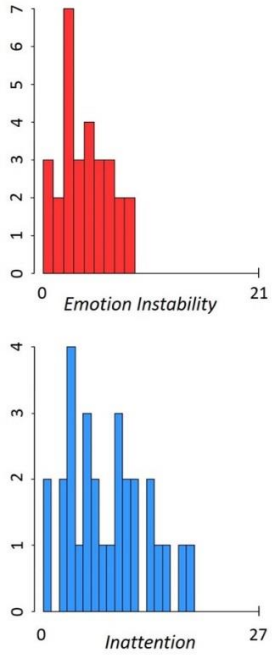
Below I present participant demographics (Table 2) and main results (Table 3) of the studies included in this PhD project. I then briefly discuss the results in the light of their general validity. Functional and structural magnetic resonance imaging (MRI) results also require some general comments in this section, while further discussion of results in relation to the hypotheses follow in the Discussion section. For details, see the respective articles and manuscripts in Appendix.

Table 2 Summary demographics

	Study I	**Study II**	**Study III and IV***
Number of participants	1093	130	29
Age (years)	Mean 14.47 (SD = 0.39)	**Non-clinical:** mean 43.5 (SD = 12.7) **ADHD patients:** mean 34.1 (SD = 10.0)	Mean 28.94 (SD = 6.47)
Sex	n = 616 females n = 477 males	**Non-clinical:** n = 29 females, n = 30 males **ADHD patients:** n = 34 females, n = 37 males	n = 15 females n = 14 males
Emotional instability and non-emotional symptoms	*CD score*: mean 3.70 (SD = 2.60) *ADHD score*: mean 6.90 (SD = 3.75)	**Non-clinical:** *Emotion Instability*: mean 2.98 (SD = 2.42) *Inattention*: mean 5.69 (SD = 4.13) **ADHD patients:** *Emotion Instability*: mean 9.16 (SD = 4.18) *Inattention*: mean 16.41 (SD = 5.08)	*Emotion Instability*: mean 4.59 (SD = 2.37) *Inattention*: mean 8.59 (SD = 5.03)
Type of study population	Adolescent community sample	Non-clinical adults (n = 59) and adults with ADHD (n = 71)	Non-clinical adults

* same participants included. **Abbreviations:** ADHD = attention-deficit hyperactivity disorder, CD = conduct disorder, SD = standard deviation

Table 3 Summary of main results

	Study I	Study II	Study III*	Study IV*
Emotional instability and non-emotional symptom distributions				
Correlation between symptom domains	There was a significant correlation between *CD score* and *ADHD score*: r = 0.549, p < 0.001	There was a significant correlation between *Emotion Instability* and *Inattention*: r = 0.73, p < 0.001	There was not a significant correlation between *Emotion Instability* and *Inattention*: r = 0.27, p = 0.16	

	Study I	Study II	Study III*	Study IV*
Behavioral results	**Stop Signal test:** *ADHD score* (driven primarily by inattention symptoms) explained a unique part of the variance of SSRT, while *CD score* did not. **Delay discounting:** each of *ADHD score* and *CD score* explained a unique part of the variance of the k-coefficient ("indifference" time point). **Spatial working memory task:** Each of *ADHD score* and *CD score* symptoms explained a unique part of the variance of number of errors.	-	There was a suggested correlation between response time speeding (baseline RT – mean Win RT) and *Emotion Instability*, when controlling for *Inattention* ($p = 0.08$)	There were no correlations between behavioral measurements and *Emotion Instability* or *Inattention*.
Main imaging result, testing main hypotheses	**Structural MRI:** GMV of rACC correlated negatively with *CD score*, when controlling for *ADHD score*. SA of dl/dmPFC and cACC correlated negatively with *ADHD score*, when controlling for *CD score*.	**Structural MRI:** There was a negative correlation between NAcc volume and *Emotion Instability*, when controlling for *Inattention*.	**Functional MRI:** There were no correlations between activation in VS during reward anticipation, or ACC or insula activation during reward outcome, and *Emotion Instability* or *Inattention* in the whole sample.	**Functional MRI:** *Emotion Instability* correlated positively with activation within rACC for the contrast (Emotional > Neutral conflict adjustment), when controlling for *Inattention*.

	Study I	Study II	Study III*	Study IV*
Other results	SSRT from the Stop Signal test and "non-emotional" brain structures (dl/dmPFC and cACC) each uniquely explained a part of the variance of *ADHD score*. "Emotional" brain structures (rACC) and k-coefficient from delay discounting questionnaire each explained a unique part of the variance in *CD score*. A localized GMV cluster within the left lOFC correlated negatively with *ADHD score*, also when adjusting for *CD score* (corrected for multiple comparisons on whole brain level).	There was a negative correlation between caudate volume and *Emotion Instability*, when controlling for *Inattention*. There was a suggested positive correlation between lOFC thickness and *Inattention*, when controlling for *Emotion Instability*.	Behavioral measurements and main fMRI activations were in line with previous literature. Insula was activated during reward outcome, but also during outcomes representing disappointment. **Exploratory:** In females, there was a negative correlation between activation in VS during reward anticipation and *Emotion Instability*, controlling for *Inattention*.	**Validation of task - behavior:** There was a significant difference in RT between high conflict level trials and low conflict level trials. There was a significant RT difference between high conflict adjustment trials and low conflict adjustment trials. **Validation of task - fMRI:** We could not re-produce robust main fMRI activations for the contrasts of interest. However, the RT difference between neutral high conflict trials and neutral low conflict trials correlated with mean neutral conflict monitoring activation in cACC, strengthening the notion that our version of the task was valid.

* same participants included. Figures adapted from the respective articles/manuscripts, found in Appendix. **Abbreviations**: ADHD = attention-deficit hyperactivity disorder, cACC = caudal anterior cingulate cortex, CD = conduct disorder, dl/dmPFC = dorsolateral/dorsomedial prefrontal cortex, GMV = grey matter volume, lOFC = lateral orbitofrontal cortex, MRI = magnetic resonance imaging, NAcc = nucleus accumbens, rACC = rostral anterior cingulate cortex, RT = response time, SA = surface area, SSRT = stop signal reaction time

Functional and structural magnetic resonance imaging (MRI) results require some general comments. When considering the included studies together, there was one specifically interesting finding: ventral striatum (VS)/nucleus accumbens (NAcc) structure (**Study II**) and function (**Study III**) related to emotional instability symptoms, when adjusting for non-emotional inattention symptoms, even in the cohort including attention-deficit hyperactivity disorder (ADHD) patients (**Study II**). However, the correlation between functional activation and emotional instability symptoms in **Study III** could only be observed in an exploratory analysis in females (n = 15), and not in the sample as a whole, which makes further interpretation tentative until the results are replicated in larger samples.

In **Study I**, grey matter volume (GMV) of rACC correlated negatively with emotional instability symptoms, when controlling for non-emotional ADHD symptoms, while surface area (SA) of dorsolateral/dorsomedial prefrontal cortex (dl/dmPFC) and caudal anterior cingulate cortex (cACC) correlated negatively with non-emotional ADHD symptoms, when controlling for emotional instability symptoms in 14-year-olds. We did not find a correlation between GMV, SA, or cortical thickness of lateral orbitofrontal cortex (lOFC) and emotional instability symptoms (**Study I** and **II**). However, in exploratory vertex-wise analyses within the pre-defined lOFC region of interest (ROI), there were localized GMV clusters bilaterally, extending into vlPFC, that correlated negatively with emotional instability symptoms, also when controlling for non-emotional ADHD symptoms, in adolescents (**Study I**). However, these local clusters did not survive correction for multiple comparisons on whole brain level. In addition, in the exploratory vertex-wise analysis within the bilateral lOFC ROI, there was a negative correlation between GMV clusters in both left and right lOFC (located anteriorly to the clusters that correlated with emotional instability symptoms) and non-emotional ADHD symptoms, when adjusting for emotional instability symptoms, in adolescents (**Study I**). The correlation in the left lOFC survived correction for multiple comparisons on whole brain level. Similar correlations between emotional instability and non-emotional inattention symptoms and SA and cortical thickness of the same prefrontal ROIs were **not** found in adults with and without ADHD (**Study II**). However, in **Study II**, no vertex-wise analysis was performed, which might have obscured more localized correlations within the pre-defined ROIs.

In **Study IV**, we could not re-produce previously reported robust main activations in expected locations for the contrasts of interest (51, 52), although behavioral outcomes from the task reflected the desired Stroop effect. There may be several reasons for this. First, the main activations observed in our version of the Stroop task were located in expected regions, albeit weak, suggesting that it may simply be a matter of small sample size in combination with small effect size. Second, we used a slightly different analytic approach in defining the functional MRI (fMRI) model (including neutral–rather than emotional–faces in the non-emotional blocks, and another trial type as baseline when defining the contrast representing exposure to cognitive conflict. For further details see Methodological considerations). In addition, the studies on which we based our version of the Stroop task had not included many participants (51, 52), and recently, a study employing this same version of the Stroop task presented a lack of reliable fMRI results despite presence of reliable behavioral results (211), suggesting main

fMRI activations might in fact not be as robust as previously inferred. Recently, behavioral studies have shown that there is a large response variability within each condition, and that studying such variability may be more sensitive than using a simple contrast approach (192, 212). Further replication of the main activations related to the current version of the Stroop task are necessary in order to draw more specific conclusions.

Behavioral results were mixed with regard to our pre-defined hypotheses. **Study I** could demonstrate a correlation between non-emotional ADHD symptoms, and not emotional instability symptoms, and performance on a motor impulse control task (Stop Signal test), while both emotional instability and non-emotional ADHD symptoms correlated with performance in the delayed discounting assessment as well as in a working memory task. **Study III** revealed a non-significant ($p = 0.08$) correlation between response time speeding in a reward anticipation task (monetary incentive delay (MID) task) and emotional instability symptoms, but not non-emotional inattention symptoms. No correlations between behavioral measurements of conflict processing and emotional instability or non-emotional inattention symptoms were noted in **Study IV**.

Finally, before proceeding to the Discussion section, I would like to repeat that when interpreting the results, the limitations of the different studies as described in Methodological considerations should be acknowledged. Some of the results are based on exploratory analyses, and not pre-defined hypotheses. However, *in order to be able to discuss the results further, I will assume that the results could be replicated in larger samples, even though this is not yet certain.*

6 DISCUSSION

6.1 MAJOR FINDINGS IN RELATION TO HYPOTHESES

The general aim of this PhD project was to disentangle symptoms of emotional instability and non-emotional symptoms associated with attention-deficit hyperactivity disorder (ADHD)–such as inattention–and investigate how the different symptom domains related to behavioral measurements and underlying neural correlates–both structural and functional. We focused on the processing and regulation of emotion, reward, and attention in prefrontal cortical regions. However, we also wanted to study subcortical alterations tied to the emotional instability and non-emotional ADHD/inattention symptom domains.

6.1.1 Results related to the first overarching hypothesis

We found partial support for the first overarching hypothesis that postulated that emotional instability symptoms are associated with structural and functional alterations in brain regions engaged in emotional regulation, as well as subcortical regions connected to those, also when adjusting for the non-emotional symptom domain.

6.1.1.1 Rostral anterior cingulate cortex (rACC) and emotional instability symptoms

rACC grey matter volume (GMV) correlated negatively with emotional instability symptoms, also when adjusting for non-emotional ADHD symptoms in adolescents (**Study I**), while we did not see this correlation in adults with and without an ADHD diagnosis (**Study II**). We also found a correlation between rACC activation during emotional conflict adjustment (relative to non-emotional conflict adjustment) and emotional instability symptoms, adjusting for non-emotional inattention symptoms (**Study IV**), although this result should be treated with caution given the small sample size.

6.1.1.2 Lateral orbitofrontal cortex (lOFC) and emotional instability symptoms

We did not observe any correlations between GMV, surface area (SA) or cortical thickness of the lOFC region of interest (ROI) and emotional instability symptoms (**Study I** and **II**). However, there was one localized cluster in each lOFC, extending into ventrolateral prefrontal cortex (vlPFC) that correlated negatively with emotional instability symptoms, also when adjusting for non-emotional ADHD symptoms (**Study I**). However, these two clusters did not survive whole brain correction for multiple comparisons.

6.1.1.3 Subcortical structures and emotional instability symptoms

As for subcortical regions, ventral striatum (VS)/nucleus accumbens (NAcc) was smaller in relation to emotional instability symptoms in adults with and without ADHD after adjusting for non-emotional inattention symptoms (**Study II**). VS/NAcc was also less activated during reward anticipation (**Study III**) in relation to subclinical symptoms of emotional instability after adjusting for non-emotional inattention symptoms, but only in an exploratory analysis of

female subjects (**Study III**). In addition, an exploratory analysis revealed a negative correlation between adjacent caudate volume and emotional instability symptoms, when adjusting for non-emotional inattention symptoms, in adults with and without ADHD (**Study II**).

6.1.1.4 Cognitive tests and emotional instability symptoms

Emotional instability symptoms explained a unique part of the variance of delay discounting and working memory performance (**Study I**). However, emotional instability symptoms were only related to behavioral measurements of reward processing on a trend significant level ($p = 0.08$, **Study III**), and not significantly related to behavioral measurements corresponding to emotional conflict processing (**Study IV**).

6.1.2 Results related to the second overarching hypothesis

We found partial support for the second overarching hypothesis which stated that non-emotional symptoms are associated to structural and functional alterations in brain regions involved in non-emotional attentional/cognitive control, also when adjusting for symptoms in the emotional instability domain.

6.1.2.1 Caudal anterior cingulate cortex (cACC), dorsolateral/dorsomedial prefrontal cortex (dl/dmPFC) and non-emotional ADHD/inattention symptoms

Non-emotional ADHD symptoms related to smaller SA of cACC and dl/dmPFC in adolescents, after adjusting for emotional instability symptoms (**Study I**), but non-emotional inattention symptoms did not correlate with cACC or dl/dmPFC structure in adults with and without an ADHD diagnosis (**Study II**). We did not observe any correlations between functional activation in cACC during exposure to cognitive conflict and non-emotional inattention symptoms, nor any correlation between dlPFC activation during non-emotional conflict adjustment and non-emotional inattention symptoms in non-clinical adults (**Study IV**).

6.1.2.2 Cognitive tests and non-emotional ADHD/inattention symptoms

We found a correlation between behavioral performance on a motor impulse control task, a delay discounting assessment, and a working memory task and non-emotional ADHD symptoms, when adjusting for emotional instability symptoms (**Study I**). We did not observe significant correlations between behavioral measurements related to conflict processing and non-emotional inattention symptoms (**Study IV**).

6.2 OUR FINDINGS IN A WIDER PERSPECTIVE

Below I discuss our findings in relation to processing and regulation of emotion, reward, and attention (and related executive functions such as cognitive flexibility and inhibition). Since many brain regions are involved in diverse processes and included within several regulatory networks, I have chosen to use each region as a starting point for the discussion. A short

summary of discussion points, also in relation to methodological considerations, for each study included in this PhD project is presented in Table 4.

Table 4 Summary discussion

	Study I	**Study II**	**Study III***	**Study IV***
Strengths	Large community sample	ADHD patients included	Updated version of the MID task	Updated version of the Stroop task
Limitations	Emotional instability symptoms as assessed by the *Conduct problems* subscale of the SDQ also include callous-unemotional symptoms.	Medication and comorbidity in patients.	Small sample of non-clinical participants, limiting the range of symptom distribution within each domain.	Small sample of non-clinical participants, limiting the range of symptom distribution within each domain.
Suggested follow-up through future studies	Longitudinal approach to follow developmental changes. Further investigate how pubertal status influences the results. Biological versus chronological age. Sex differences.	Include patients characterized primarily by high levels of emotional instability, with or without comorbid ADHD. Include behavioral test correlates.	Larger sample, include patients with high levels of emotional instability, and non-emotional ADHD/inattention symptoms.	Further develop the Stroop task to evoke robust main fMRI activations. Larger sample, include patients with high levels of emotional instability, and non-emotional ADHD/inattention symptoms.

* same participants included. **Abbreviations:** ADHD = attention-deficit hyperactivity disorder, CD = conduct disorder, MID = monetary incentive delay, SDQ = Strengths and Difficulties Questionnaire

6.2.1 Reward processing

6.2.1.1 VS/NAcc: related to emotional instability

We observed correlations between both VS structure (**Study II**) and function (**Study III**) and symptoms of emotional instability in adults, when adjusting for inattention, including participants both with and without an ADHD diagnosis. ADHD diagnosis has been related to altered structure (213) and function in VS (85, 173, 174, 177, 178, 214, 215). Symptoms of hyperactivity and impulsivity have been shown to correlate both negatively with VS activation during reward anticipation within mixed samples of non-clinical and ADHD individuals (173, 214, 216), ADHD patients only (174, 215), non-clinical females (177) and positively with VS activation within the healthy population (85). Also inattentive symptoms (177), and an inattentive subgroup of ADHD patients (176), have been related to hyporesponsiveness during reward anticipation in VS. Further, others have reported no differences in VS responsiveness during reward anticipation between ADHD patients and non-clinical controls (217, 218). In adults with ADHD, in contrast to children with ADHD, no structural differences have been reported in VS as compared to controls (213). However, hypoactivation in VS during reward anticipation has been related to a transdiagnostic emotional trait in the form of Beck Depression Inventory (BDI) score across different psychiatric patient groups (217, 219). Our results in **Study II** and **III** further support the notion that alterations of VS structure and activation during reward anticipation could be associated with an emotionally related trait (despite differently defined in this PhD project as compared to the study by Hägele et al. (217)), even in ADHD patients. Together with mixed results with regard to VS responsiveness during reward anticipation in patients with ADHD, and in relation to symptoms of hyperactivity/impulsivity and inattention, these findings further highlight the need to acknowledge emotionally related problems also within ADHD patients.

6.2.1.2 Reward processing: beyond NAcc

In **Study III**, we employed the extensively used monetary incentive delay (MID) task (170, 171). For the reward anticipation phase, we observed similar main activations in VS as previously reported (21). For the outcome phase, however, we observed activation in bilateral insula and rACC, but not in VS, OFC/ventromedial prefrontal cortex (vmPFC), posterior cingulate cortex (PCC), right amygdala and medial prefrontal cortex (mPFC) as reported previously (21). One reason for these discrepant findings could be the use of different type of trials as baseline. We contrasted successful reward outcome against neutral outcome (no outcome was expected), similarly to a previous study reporting results in line with ours (182). When comparing the "failed" reward outcome trials (also contrasted against neutral baseline), we observed activation within bilateral insula and rACC, which overlapped with activation during successful reward outcome trials. This finding supports the notion that bilateral insula and rACC have a more general role across several reward processes, such as reward evaluation and associated feeling states (15, 16, 19, 29).

Historically, the NAcc has been the "classic" subcortical reward processing region, but with advanced knowledge of the topological organization of cortical input to basal ganglia, adjacent regions such as rostral and medial caudate and rostral putamen are being increasingly acknowledged in reward and emotion processing (220, 221). It has been suggested that the caudate might be related to anticipation of loss (21, 222). Moreover, within the original Knutson studies employing the MID task the caudate was activated during the reward anticipation phase, while the adjacent NAcc was associated with the level of reward (170, 171), and VS peak activation related to reward anticipation has been located both within the NAcc and the caudate (85). In **Study II**, we reported a negative correlation of caudate GMV, in addition to NAcc GMV, and emotional instability symptoms in non-clinical participants and patients with ADHD. The caudate has been suggested to be smaller in children and adolescents with ADHD as compared to controls (213, 223), and in children with heightened genetic risk for ADHD (224), while caudate volume in adult patients with ADHD has been reported to not differ from that of controls (213), or even be larger (223). These discrepant findings may, in part, be due to the correlation to emotional instability symptoms, which have not been assessed in the above mentioned studies. The caudate has been highlighted in emotionally related disruptive behavior disorders (225), further strengthening the idea of the caudate being related to emotional processing, at least in adults. However, connectivity between subdivisions along the striatum connect to different prefrontal regions (the NAcc shell connects primarily to vmPFC, slightly more dorsal sections of the NAcc connect to lOFC, while further dorsal VS sections connect to cACC, and the caudate connects to dlPFC (19)), suggesting a somewhat emotional–non-emotional organization, similarly to the organization of ACC where emotional processes are primarily related to rACC, while non-emotional processing are primarily related to cACC (226). It remains to be elucidated how the understanding of this topological organization may be merged with the above mentioned findings in clinical populations and associated symptoms, and in relation to different aspects of reward processing.

6.2.2 Cortical regions related to emotional instability and non-emotional ADHD/inattention symptoms

In line with our overarching hypotheses, we found negative correlations between cortical structure and emotional instability and non-emotional ADHD/inattention symptoms in adolescents (**Study I**), but could not observe similar correlations in adults with and without ADHD (**Study II**). This is in line with previous findings in children/adolescents versus adults with ADHD (227). We further found support for our hypothesis that emotional instability symptoms correlated negatively with rACC activation during emotional conflict adjustment (**Study IV**), but we did not find a strong link between emotional instability and activation in rACC/vmPFC or insula during reward outcome (**Study III**), or between non-emotional symptoms of inattention and activation in dlPFC or cACC during conflict processing (**Study IV**). These mixed findings, with regard to our pre-defined hypotheses, may be due to the dependence of prefrontal top-down control on dispersed regions connecting functionally to many subcortical regions, rather than to specific subcortical regions related to exclusive

symptom domains. For that reason, below I will discuss our findings in relation to literature in the field, focusing on one prefrontal brain region at a time.

6.2.2.1 Emotional–and non-emotional–processing within lOFC

We found negative correlations between GMV of clusters within both left and right lOFC ROIs and emotional instability symptoms in adolescents (but not significant across the whole lOFC ROI, and the clusters did not survive correction for multiple comparisons on whole brain level) (**Study I**). We found no correlation between lOFC morphology and emotional instability in adults with and without ADHD (**Study II**). Previous studies have shown that emotionally unstable personality disorder (EUPD) patients, known to present with high levels of emotional instability (among other heterogeneous symptoms), have smaller lOFC (89), especially pronounced in relation to suicidality (90, 91), thinner lOFC (extending into medial orbitofrontal cortex (mOFC)) (228), blunted lOFC activation in relation to suicidality (229) and aggressive behavior (230), as compared to controls. The discrepant findings could be due to that structural alterations in lOFC may only be detected in individuals with especially high levels of emotional instability symptoms, such as in EUPD. It is also possible that the lOFC alterations seen in symptomatically heterogeneous EUPD patients are not related to emotional instability, specifically.

We also observed a negative correlation between GMV in bilateral clusters within the lOFC ROI (located anteriorly to the clusters that correlated with emotional instability symptoms) and non-emotional ADHD symptoms, when adjusting for emotional instability symptoms, in adolescents (**Study I**). The cluster in the left lOFC survived correction for multiple comparisons on whole brain level. These exploratory results could indicate that regulatory processes within lOFC also relate to non-emotional ADHD symptoms, despite the lOFC primary role in emotional regulation. A large study from the ENIGMA consortium showed smaller lOFC SA in children (< 14 years old) with ADHD as compared to controls, but no differences in lOFC structure between adolescents and adults with ADHD and controls (227). However, level of emotional instability symptoms was not reported in this study and could have impacted the results. Whether the localization of non-emotional regulatory processes within the lOFC overlap with processes related more specifically with emotional regulation or not, remain to be further investigated.

In contrast, there was a suggested correlation in the opposite direction between lOFC thickness and inattention symptoms in adults with and without ADHD (**Study II**), which could indicate a compensatory mechanism as reported previously (65, 103). lOFC has been related to top-down emotional regulation (17, 21, 115), but two meta-analyses did not report the involvement of lOFC across several types of emotional reappraisal tasks, but instead the adjacent (sometimes described as overlapping) more lateral vlPFC (22, 147). lOFC has been related to flexible reinforcement learning and reward processing (28), evaluation of context-appropriate emotional value of stimuli (also more medial parts of OFC) and the selection of a subsequent goal-orienting response (17, 21). Further, the representation of value of rewards has been associated to medial regions of OFC, while lOFC has been related to representation of value of

punishments, which may be employed in further flexible reinforcement learning (28). Since lOFC engages in a vast repertoire of processes, it is potentially difficult to correlate its function and structure with one specific symptom domain, and this may be one reason why we did not find strong correlations between lOFC structure and a simple measure of emotional instability symptoms.

It is worth noting that the discrepancy in findings might also, partially, be due to differing nomenclature and definitions of lOFC versus ventrolateral prefrontal cortex (vlPFC) in the previous literature (17, 21, 22, 147, 148). The activations during reappraisal in two meta-analyses were located outside of the lOFC as we defined it (22, 147).

6.2.2.2 Non-emotional–and emotional–processing within dl/dmPFC

In line with the second overarching hypothesis, SA of dl/dmPFC correlated negatively with non-emotional ADHD symptoms in adolescents (**Study I**). In contrast, we did not find a similar correlation between non-emotional inattention symptoms and either thickness or SA of the same dl/dmPFC ROI in adults with and without ADHD (**Study II**). This is in line with recent literature that reported structural differences within these regions in children with ADHD, but not in adults with ADHD, as compared to controls (227). Dl/dmPFC has been related both to attentional regulation and other instances of executive function, such as cognitive flexibility, inhibition and working memory (35, 37, 231), but also to emotional regulation (8, 12-14, 232, 233). Overlapping areas within dl/dmPFC seem to engage in several executive function domains, but there is some specificity within this large region (231). While the lateral dlPFC has been associated with keeping rules of a task "online" in working memory, response selection, inhibition, flexibility in shifting focus (231) and adapting responses (49, 50), the medial dmPFC has been implicated in quite different processes, including complex social cognitive tasks, theory of mind, empathy and moral reasoning, as well as being a key node in the default-mode network (DMN) (234). Negative correlations between GMV and non-emotional ADHD symptoms were observed in exploratory analyses across both lateral and medial sections of the large dl/dmPFC ROI in **Study I** and could suggest that subtle alterations of the PFC, rather than specific localized differences, might influence an overarching attentional/cognitive regulatory capacity. This general deficit could, in turn, also influence emotional processes that depend on attentional control.

Since the dl/dmPFC ROI definition employed in **Study I** and **II** entails a very large brain area that is involved in a vast number of diverse processes, it is not possible to draw any conclusions regarding what symptoms or behavior more local alterations in structure and function may relate to. However, in **Study IV**, the dlPFC ROI was limited to match activation related to the Stroop task, but still we could not observe either an expected main activation in response to neutral conflict adjustment (See Methodological considerations and Results sections), or a correlation between the activation and non-emotional inattention symptoms.

6.2.2.3 Emotional, non-emotional, and reward processing within rACC and cACC

In line with the first overarching hypothesis, our results suggest that smaller rACC (**Study I**) and more activation during emotional conflict adjustment (**Study IV**) might relate to higher levels of emotional instability symptoms. In line with the second overarching hypothesis, smaller cACC SA related to higher levels of non-emotional ADHD symptoms in adolescents (**Study I**). These results support the division of the ACC into a rostral emotional part and a caudal cognitive part (226).

Contrary to the first overarching hypothesis, we did not find any correlation between rACC activation during reward outcome and emotional instability symptoms (**Study III**). Apart from limitations discussed in Methodological considerations, another reason that we did not find support for our hypothesis could be that activation of rACC, and adjacent vmPFC/mOFC, is related to reward value processing (19, 29) and activation therein might not be dimensionally related to emotional *instability* per se. Instead, activation during reward outcome in rACC, might be related to the participant's general evaluation of reward, which might be better assessed by, for instance, a dimensional measurement of depressive or anhedonic tendencies, known to be related to aberrant valence processing of rewards (235)(See section 6.3.2 Major depressive disorder–an example of a primarily internalizing disorder).

In contrast to our second overarching hypothesis, cACC activation during emotional and non-emotional conflict processing did not relate to non-emotional inattention symptoms (**Study IV**). There are several possible reasons for this. First, the Stroop task employed in **Study IV** elicited relatively weak main activations in response to conflict, which makes interpretation of further correlations between activation and symptoms difficult. Second, it might be that a dimensional measure of inattention (including measures of cognitive flexibility in Brown Attention-Deficit Disorder scales (B-ADD)) does not properly represent the function of cACC, at least not during a Stroop task. Further, despite being able to show a negative correlation between SA of cACC and non-emotional ADHD symptoms in adolescents (**Study I**), a similar correlation was not present in adults with and without ADHD (**Study II**), in line with a previous meta-analysis (227). It has been reported that in early childhood, the size of right ACC is the best predictor of conflict solving ability, but with age behavioral measurements of conflict solving are most related to white matter connections (236). Furthermore, the exact role of cACC has been debated since it is, often together with adjacent mPFC and anterior insula, involved in such diverse processes as perception of physical and social pain, reward processing, conflict processing, error detection, and theory of mind (37).

6.2.3 Discussion of cortical regions not included in the main hypotheses

Through the course of this PhD project, a few brain regions that were not the primary focus of the overarching hypothesis have stood out. Below, I discuss the anterior insula and vlPFC in relation to findings in our studies and existing literature.

6.2.3.1 Anterior insula

The insula is one of the brain regions that differs the most between humans and other primates (237). It is located at an ideal spot to integrate information from diverse other neural regions and its main functions are related to interoceptive processes and hedonic value thereof, mapping body states that are relevant to maintain homeostasis (15, 16, 238). The anterior insula, and adjacent vlPFC, has been shown to be involved across several types of emotion regulation strategies (233). This anterior section of the insula is specifically involved in integrating interoceptive signals with emotional, cognitive and reward-related signals from regions such as the amygdala, ACC, dlPFC and VS, resulting in a subjective "feeling state" (15, 16, 238). The anterior insula is involved in flexibly attributing salience to stimuli important to the individual under varying circumstances.

The anterior insula has further been related to reward value, both in relation to external and internal types of reward (8). The region is involved in coding positive and negative reward (20) and in anticipation and receipt of reward (20, 21). Our findings in **Study III** are in line with this notion in that the anterior insula was activated both during receipt of rewards, but also in response to failure to receive an expected reward, which could be interpreted as disappointment. Both situations involve a representation of the "feeling state", despite different valence.

Contrary to our hypothesis, we did not find a correlation between anterior insula activation during reward outcome and symptoms of emotional instability (**Study III**). High levels of emotional instability symptoms have been related to smaller bilateral anterior insula in non-clinical participants (129). Moreover, two of the most robust findings in patients with EUPD, characterized by high levels of emotional instability symptoms, are smaller volume (90) and increased reactivity (92, 239, 240) in anterior insula, even though others have not reported hyperreactivity in anterior insula in EUPD (95, 96, 241). However, EUPD involves complex heterogeneous symptoms and larger neural alterations in anterior insula within the EUPD patient group have been related to level of suicidality (90, 91), and traits of impulsivity and aggression have been suggested to relate to anterior insula alterations in EUPD patients with varying levels of suicidality (91). Furthermore, smaller bilateral insular cortex has been related to a vast array of psychiatric disorders (242). In addition, higher levels of depressive symptoms–including trait anhedonia–have been related to *reduced* reactivity and connectivity of anterior insula (243, 244). Taken together, this suggests that anterior insula structure and function could be investigated in relation to *both* emotional instability and depressive symptoms in future studies in order to elucidate its role in relation to different types of emotional symptoms.

6.2.3.2 vlPFC

The vlPFC has been implicated to serve a role in inhibitory control across cognitive and emotional tasks (245). The region has both afferent and efferent connections to amygdala and sensory cortices, as well as afferent connections from anterior insula (232).

It might be useful to consider the vlPFC, in addition to the adjacent (sometimes described as overlapping) lOFC, in relation to emotional instability and non-emotional ADHD/inattention symptoms. The main reasons that the lOFC was one of the four pre-defined cortical ROIs in this PhD project, were that the lOFC has been related to complex emotion regulation, rather than non-emotional processing (2). Further, smaller lOFC has been observed in patients with EUPD–a patient group characterized by emotional instability (among other heterogeneous symptoms) (89, 90), and also in relation to emotional instability symptoms in a non-clinical sample (129). Recently, also blunted lOFC activation related to level of suicidality (229) and aggressive behavior (91, 230) has been reported in patients with EUPD, supporting the appropriateness of our choice of lOFC as an "emotional ROI". Function of the vlPFC, on the other hand, has been consistently reported in relation **both** to emotional reappraisal tasks (8, 12, 14, 233), as well as in non-emotional motor impulse control (148, 245) and in relation to ADHD (54, 246), without controlling for non-emotional ADHD/inattention and emotional instability aspects, respectively. The localized bilateral clusters within the lOFC ROI that correlated negatively with emotional instability symptoms, adjusting for non-emotional ADHD symptoms, in exploratory analyses in **Study I** (but did not survive whole brain correction for multiple comparisons), extended into the vlPFC region. However, GMV, SA and cortical thickness of a bilateral vlPFC ROI in adolescents did not correlate either with emotional instability or non-emotional ADHD symptoms in an exploratory analysis (**Study I**). It would be of interest to further specify how different emotional and non-emotional processes, and related symptoms, interact with each other within the vlPFC.

6.2.4 Age effects and development

We found support for correlations between dlPFC/dmPFC, cACC, rACC as well as within more localized clusters of lOFC and the hypothesized symptom domains in adolescents (**Study I**), but not in adults (**Study II**). This is in line with previous studies suggesting smaller structures cortically in children with ADHD as compared to controls, but not in adults (213, 227). Despite different questionnaires being used to assess emotional instability and non-emotional symptoms in **Study I** and **II** (See Methodological considerations), there are other possible reasons for these discrepant findings. Prefrontal cortical regions are among the last to mature, suggesting that alterations present during early stages of brain development might be attenuated at later stages. In addition, delayed cortical maturation has been reported in ADHD (120) and subsequently, cortical alterations are more pronounced as compared to normally developing non-clinical individuals during adolescence. In adults, cortical development may have reached full maturation also in individuals with ADHD, and differences may not be as pronounced, at least not structurally. Further, adolescents in general display heightened levels of impulsivity compared to adults–a trait that serves an important function in exploration of the world during this time of life (76). Baseline levels of impulsivity across a non-clinical population of adolescents versus one of adults might differ, and complicate comparisons between these populations.

6.3 A TRANSDIAGNOSTIC APPROACH TO ALTERED EMOTION REGULATION AND REWARD PROCESSING

Research of recent years has further highlighted the heterogeneity of both EUPD and ADHD patient groups, as well as high genetic correlations between several psychiatric disorders (247, 248). Dimensional approaches have become more common in trying to increase the understanding of underlying neural regulation mechanisms in many psychiatric disorders. Below I describe neural similarities across psychiatric disorders, and the increasing consensus of applying a transdiagnostic approach within psychiatric research. I further summarize some of the most robust findings in relation to major depressive disorder (MDD), included here as an example of a primarily internalizing emotional disorder. Internalizing symptoms are also of importance in EUPD and ADHD, in addition to the externalizing/impulsive traits that are commonly described.

6.3.1 Similarities across psychiatric disorders

All the brain regions highlighted in this PhD project are also implicated in other psychiatric disorders, and not only associated to EUPD/CD and ADHD. Several psychiatric disorders have been related to functional alterations in emotional processing, such as hyperactivation in amygdala extending into hippocampus, and hypoactivation in prefrontal regions such as dmPFC/vmPFC/ACC, and right vlPFC/OFC (249). Reduced GMV has also been reported across several psychiatric disorders in cACC and bilateral anterior insula (242). Sprooten et al. could show that no brain region was functionally uniquely related to any one psychiatric diagnosis in tasks covering all of the five Research Domain Criteria (RDoC) domains, respectively, though the partially overlapping neural profiles of different psychiatric disorders differed (250). The same study could not relate any specific neural activation pattern to separate RDoC constructs in a whole-brain analysis (250).

A transdiagnostic approach with regard to emotional processing across several psychiatric disorders has been proposed (249, 250). Moreover, it has even been suggested to include emotion regulation as a sixth RDoC domain (251), which might help in further elucidating more specific underlying neural networks related to emotion regulation.

6.3.2 Major depressive disorder–an example of a primarily internalizing disorder

Depressive symptoms are common and sometimes persistent across many psychiatric diagnoses, including EUPD (88) and ADHD (252). Unlike EUPD and ADHD, which are related to persistent traits of impulsivity/instability of attention and emotions, often expressed as externalizing symptoms, typical MDD rather relates to a generally lowered mood and anhedonia in adults that is often–but not always–of periodic character. Importantly, irritability is also included in the diagnostic criteria of MDD in the Diagnostic and Statistical Manual of mental disorders, 5th edition (DSM-5) (79), and is even a core symptom of adolescent, but not adult, depression (79). MDD has been associated with structural and functional alterations in diverse brain regions, of which many are related to emotion regulation and reward processing.

A recent meta-analysis reported thinner cortices in adults with MDD as compared to controls across diverse brain regions such as bilateral mOFC, fusiform gyrus, insula, rACC, PCC, left middle temporal gyrus, right inferior temporal gyrus, and right cACC (253). Functional magnetic resonance imaging (fMRI) studies have reported mixed prefrontal activations in response to reward in MDD patients as compared to controls (within OFC, dlPFC, vmPFC, ACC, middle frontal gyrus, inferior frontal gyrus (IFG), rACC, and dmPFC) (254-257). Subcortical alterations have also been observed in relation to MDD, such as smaller hippocampi, and a trend towards smaller amygdalae in patients with early onset MDD (258). fMRI studies in MDD have consequently reported hyporesponsiveness to reward in VS (254) and the caudate (256, 257). Amygdala hyperreactivity to punishments (254) and increased amygdala and ACC activation in response to negative emotional cues (255) are also robust findings in MDD. A negative correlation between depressive symptoms (as measured by BDI (219)) and VS activation during reward anticipation across several psychiatric disorders (217) has been reported, and level of depressive symptoms, including anhedonia, has been suggested to correlate negatively with VS (259), anterior insula and lOFC activation (243), as well as connectivity between ACC and striatal regions and right anterior insula (244). In contrast, others have not found correlations between cortical (253) or subcortical (258) alterations and overall depressive symptom severity. However, MDD is a heterogeneous disorder and self-report questionnaires span diverse symptoms, from increased irritability to lowered mood, which are likely to relate to different underlying neural mechanisms, possibly explaining the mixed neuroimaging findings in relation to depressive traits.

MDD is presented herein as an example of internalizing disorders. Comorbidity with other internalizing disorders, especially generalized or social anxiety disorders (79), is common. Since MDD and anxiety disorders also share underlying neurobiological alterations (242, 249) and treatment options are overlapping, a dimensional approach seems favorable also regarding associated internalizing traits.

6.4 WHAT IS EMOTIONAL INSTABILITY–REALLY?

It is clear from the literature that the definition of emotional instability varies extensively. We employed the definition by American Psychological Association (APA) describing emotional instability as "a tendency to exhibit unpredictable and rapid changes in emotions" (78), but other constructs are overlapping. Some examples are: 1) *labile affect* that is described as "highly variable, suddenly shifting emotional expression"(78); 2) *emotional reactivity* that includes concepts of activation, intensity and duration and that may result in frequent changes in emotions and moods if excessive (e.g., (141, 142, 260)); 3) *emotional lability*/*affect lability* that are similar to APA's definition of emotional instability, but also includes exaggerated behavior in response to emotions (e.g. (261, 262)). In addition, the concept of *affect tolerance* is referring to the ability to experience highly charged emotions and still react in a calm and constructive manner in a given situation (263, 264). Finally, *dissociative states* (a defense mechanism in which […] ideas and feelings are separated from the rest of the psyche (78))

often occurring as a result of developmental trauma, are relevant when discussing what emotional instability really is. Below I describe some of the issues related to defining emotional instability that I have come across during this PhD project.

6.4.1 Emotional reactivity versus emotion regulation

Emotional instability may be defined as rapid changes in emotional state, and related impulsive emotional behavior. Our approach to assessing emotional instability using the Strengths and Difficulties Questionnaire (SDQ) and B-ADD scales focused mostly (but not exclusively) on externalizing impulsive emotional symptoms and behaviors. The first overarching hypothesis of this PhD project stated that emotional instability symptoms are a result of failure of prefrontal top-down control mechanisms to exert proper control over emotional responses further downstream in the neural networks. This approach infers that when robust top-down control mechanisms are available, intense emotional reactivity may still be present, albeit flexibly adjusted by prefrontal brain regions resulting in low levels of emotional symptoms (265), relating to the concept of *affect tolerance* (263, 264). The approach further implies that low levels of emotional reactivity would not result in emotional impulsivity, even when prefrontal control mechanisms are not robust.

6.4.2 Emotional instability and reactivity in EUPD patients

In this PhD project, findings from research involving EUPD patients, including limbic hyperreactivity and less recruitment of prefrontal regions during emotion regulation (81, 92-101), have been interpreted as representing correlates of high levels of emotion instability symptoms. However, EUPD is a highly heterogeneous disorder, and recent studies of relatively large samples have reported inconsistent measurements of emotional reactivity (physiological responses, behavior, and self-report measurements) in various experimental settings in patients with EUPD (266), and no robust differences in "affective neural signatures" (regarding emotional reactivity) between patients with EUPD, patients with complex post-traumatic stress disorder), and controls (267). (Note, however, that the studies by Bortolla et al. (266) and Sicorello et al. (267) did not investigate emotion *regulation*, but rather emotional *reactivity*, and (267) is a pre-print at this stage) Considering the mixed neural findings in patients with EUPD, it is of importance to define, assess, and investigate specifically the emotional *instability* trait, while controlling for other possibly confounding factors, commonly present in psychiatric populations, including EUPD.

6.4.3 Internalizing aspect of emotional instability

It should be noted that internalizing symptoms related to emotional instability may be underrated, since these symptoms do not affect people in the surroundings to the same extent as externalizing symptoms do. Typical internalizing symptoms of emotional instability in patients with EUPD (not assessed in the studies included in this thesis) are rapidly shifting internal emotional states, unstable self-image, and unstable interior representations of relationships (79, 80). In order to clarify how emotional instability is represented on a neural level, the internalizing aspects should be quantified more thoroughly in addition to

externalizing traits. It is of interest to better understand how internalizing and externalizing emotional instability symptoms relate to each other on a neural level.

6.5 LINKING EMOTION REGULATION, REWARD PROCESSING, AND ATTENTION

The original overarching hypothesis was built on the assumed existence of two parallel neural systems–one primarily emotional, one primarily non-emotional–interacting with each other, but at the same time working independently. One system included top-down emotional control through lOFC and rACC of "downstream"/subcortical regions such as insula/amygdala. The other system included top-down regulation through dlPFC/cACC of secondary regions further "downstream" in the attentional networks (2, 55, 82).

It has been argued that affective and cognitive executive neural networks cannot be disentangled, since these domains share underlying neurobiology to such a large extent (268). However, several models have recently been suggested that further link emotion regulation to reward processing (269), reinforcement learning (8), and implicit versus explicit processing (270). Below I describe one of those models proposed by Beauchaine and Zisner (269, 271) that focuses on the separation between internalizing and externalizing symptom domains, and then relate this model to the *cognitive core capacity theory*, which was central to this PhD project (2).

6.5.1 Internalizing and externalizing symptom domains in psychiatry

According to the model proposed by Beauchaine and Zisner, psychiatric symptoms and behaviors may be divided into transdiagnostic internalizing and externalizing domains (269, 271). The internalizing domain covers constructs such as anxiety, depression and withdrawal, while the externalizing domain includes impulsivity, aggression, delinquency, substance dependencies, and approach-related behaviors. The model does not address non-emotional attentional regulation specifically, but focuses on the subdivision of emotionally related processing. The model suggests that approach-related emotions and behavior depend on NAcc and are regulated by diverse prefrontal regions such as dlPFC, OFC and ACC, while avoidance-related emotions and behaviors depend on amygdala and are regulated by somewhat overlapping regions such as vlPFC, vmPFC/mOFC and ACC. The approach-related system is associated with the dopamine dependent "wanting" concept (22, 24) and externalizing symptoms, while the avoidance-related system including the amygdala, relates to internalizing symptoms. However, the two systems are also closely interconnected and altered connectivity between OFC and amygdala has been linked to emotional lability.

In line with our overarching hypothesis based on the *cognitive core capacity theory* (2), the model presented by Beauchaine and Zisner (269) suggests that psychiatric disorders are often linked to a general transdiagnostic deficient prefrontal regulation capacity through altered connectivity to subcortical regions. Beauchaine and Zisner further propose that both internalizing and externalizing regulation are dependent on largely overlapping, prefrontal regions such as dlPFC, OFC and ACC (269), and that the dopamine system is at the core of

commonly comorbid symptoms such as impulsivity, anhedonia, and irritability (271). Recent studies also highlight the overlap between regions associated with cognitive control and emotional processing across several psychiatric disorders, for example the anterior insula and vlPFC (249).

6.5.2 Clinical diagnoses within an internalizing/externalizing framework

The psychiatric disorders of the ICD and DSM systems used as examples within the *cognitive core capacity theory* (2), may also be helpful in describing how an introduction of an internalizing/externalizing domain could alter the framework (Table 5). The main addition to the previous framework is the internalizing emotional quadrant referring to symptoms such as anhedonia, anxiety, and rapidly shifting internal emotional states.

Table 5 Examples of psychiatric diagnoses and typical symptoms within an updated framework including an internalizing/externalizing domain

	Emotional	**Non-emotional**
Internalizing	*Diagnosis:* **MDD, EUPD** *Typical symptom:* **Anhedonia, anxiety, rapidly shifting internal emotional state**	*Diagnosis:* **ADHD – inattentive type** *Typical symptom:* **Inattention**
Externalizing	*Diagnosis:* **EUPD, CD** *Typical symptom:* **Aggressive behavior**	*Diagnosis:* **ADHD – combined type** *Typical symptom:* **Hyperactivity, impulsivity**

Diagnoses are examples related to especially high levels of the domain typical symptom, but not necessarily with symptoms exclusive to that domain. Grey color indicates domains covered by the overarching hypotheses and assessments of this PhD project, based on the *cognitive core capacity theory* (2). **Abbreviations**: ADHD = attention-deficit hyperactivity disorder, CD = conduct disorder, EUPD = emotionally unstable personality disorder, MDD = major depressive disorder

6.5.3 Considering ”stability” of symptoms

Another domain that could be considered is “stability” of symptoms, i.e. whether a symptom is primarily characterized by its variability/instability or rather marked by a stable shift from normal levels. An “unstable” symptom, whether internalizing or externalizing, could indicate fluctuating prefrontal top-down control, and might be context-dependent. In contrast, a “stable” symptom may arise from generally blunted (anhedonia), or generally increased (anxiety), subcortical emotional reactivity. Especially the internalizing emotional domain could potentially benefit from this further specification, since both unstable (e.g. rapidly shifting emotional state) and stable symptoms (e.g. increased anxiety levels as seen in generalized anxiety disorder (GAD)) are common. Further, from a developmental perspective, adolescent

major depressive disorder (MDD) might be more “unstable” and characterized by mood swings or irritability to a larger extent than “stable” anhedonic adult MDD (79).

Finally, “stability” of symptoms can also be discussed in relation to persistence of symptoms over time. Many symptoms in EUPD and ADHD, whether internalizing or externalizing, are typically persistent for long periods of time, and often even of trait-like character. In contrast, symptoms during an isolated depressive episode or a panic attack, are rather of transient nature. This difference in persistence of symptoms might be mirrored in underlying neural mechanisms too.

7 CONCLUSIONS

I believe the major strength of this PhD project is the consistent dimensional approach to the symptom domains, behavioral performance and underlying neural structure and function. This is in line with the Research Domain Criteria (RDoC) (125, 126), aligned with the tendency of moving away from categorical diagnoses within psychiatric research (79, 80). It has been suggested recently to include *emotion regulation* as an additional construct within the RDoC framework (251), which I believe could make it even more relevant.

Another strength of this PhD project is that we were able to study the same overarching hypotheses, from different angles, employing both structural and functional magnetic resonance imaging (fMRI), in different samples, including adolescents and adults, patients and non-clinical individuals.

We found partial support for the first overarching hypothesis relating structure and function of lateral orbitofrontal cortex (lOFC), rostral anterior cingulate cortex (rACC) and ventral striatum (VS)/nucleus accumbens (NAcc) to symptoms of emotional instability, adjusting for non-emotional attention-deficit hyperactivity disorder (ADHD)/inattention symptoms. Further, we found partial support also for the second overarching hypothesis linking structure, but not function, of dorsolateral prefrontal cortex (dlPFC) and caudal anterior cingulate cortex (cACC) to non-emotional symptoms, adjusting for symptoms of emotional instability. The suggested relationship between VS structure (both NAcc and caudate) and activation during reward anticipation and symptoms of emotional instability, could potentially be a first step towards shifting the view of reward processing across psychiatric disorders, including ADHD.

7.1 FUTURE PERSPECTIVES

Following from the conclusions and the discussion in the previous section, it would be interesting to study how internalizing/externalizing symptoms, as well as symptom "stability" relate to emotional and non-emotional regulatory systems in the brain. In order to do so, there is a need to develop a self-report questionnaire that mirrors those constructs properly on a symptom level before it is meaningful to relate symptomatology to performance on behavioral tests and underlying neural correlates.

Another point that requires some discussion is that throughout the analyses in this PhD project, a region of interest (ROI) approach was first employed followed by whole brain exploratory analyses. This choice was based on the rationale that the isolated regions were selected as representatives of larger networks. In order to further elucidate which cortical regions exert (deficient) control of subcortical regions, a functional and structural network approach could be employed in future studies. Both prefrontal and subcortical regions are connected to a large

number of other brain regions and studying each of them in isolation limits the possibility to interpret the results.

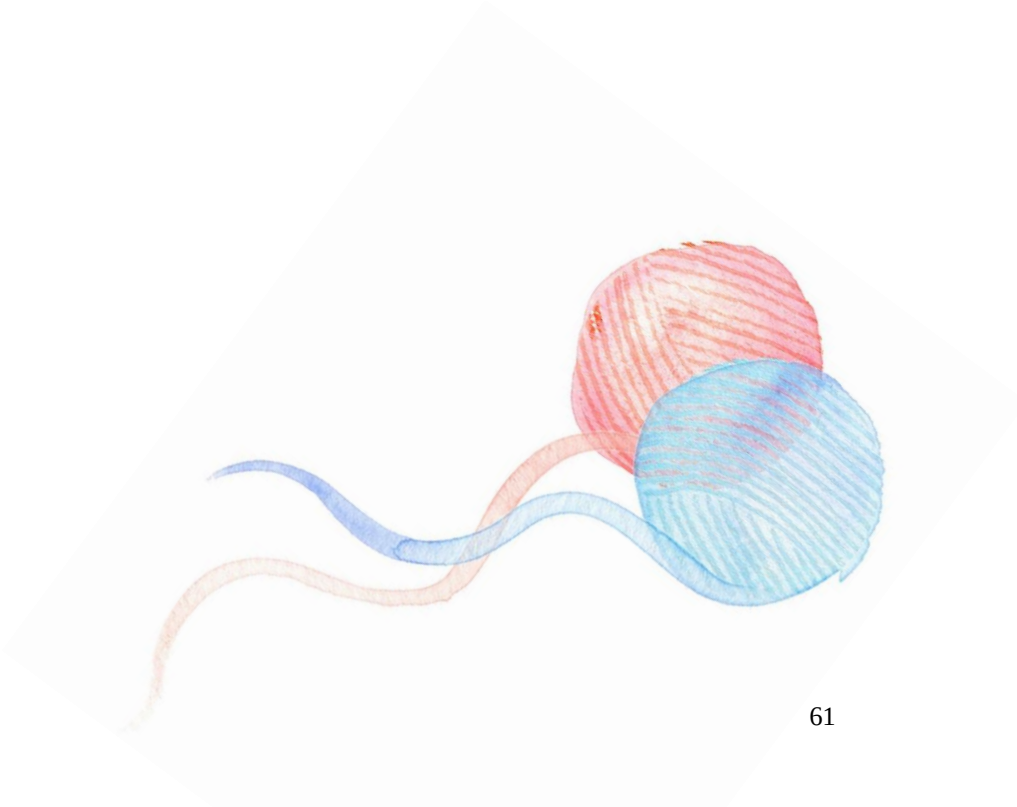
Another important direction is to investigating potential sex differences in regulation of emotion, reward, and attention. Several of the psychiatric disorders discussed in this thesis show a higher prevalence in males (ADHD (272, 273) and conduct disorder (CD) (274)) or in females (emotionally unstable personality disorder (EUPD (275, 276), major depressive disorder (MDD) (277, 278), and anxiety disorders (279-281)). We observed a correlation between emotional instability symptoms and reward anticipation activation in VS in females only (n = 15) in an exploratory analysis (**Study III**). Despite the unreliability of those results due to limited sample size, together with previously reported sex differences in relation to reward (282) and emotion processing (283, 284), and the influence of hormonal fluctuations during the menstrual cycle on these processes (285), this suggests that a sex difference approach towards regulation of emotion, reward, and attention should be further explored.

A developmental aspect was incorporated in this thesis through **Study I**, which investigated a community sample of 14-year-olds. Since **Study I** was cross-sectional, there were limitations to what developmental effects we could investigate, but the study gave rise to many questions regarding the effect of development in relation to our overarching hypothesis. One important aspect in studying adolescents is considering chronological age versus biological age. Different neural networks and associated capacities follow developmental trajectories related to chronological age, such as cognitive functions, while other neural networks follow a developmental trajectory related to biological age and puberty, such as reward systems (67, 68). I believe it is specifically important to study adolescents in relation to regulation of emotion, reward, and attention in order to capture this dynamic development. In addition, a developmental approach could potentially help elucidate why emotional instability symptoms arise in the first place. It has been suggested that early traumatic experiences could pave the way for susceptibility to emotional instability and impulsive behavior later in life (286, 287). Understanding the development of emotional instability and related morbidity could hopefully result in earlier intervention in relation to several disorders often arising during childhood (ADHD and CD) or adolescence (EUPD, MDD, anxiety).

In addition, no matter how thoroughly we assess symptoms, behaviors, and even genetics, in relation to psychiatric disorders, there are always confounding factors that cannot be measured or adjusted for. It is difficult to control for contextual factors such as life stress, and other related/modulating genetic, epigenetic and environmental factors (288-290). As an example, it has been shown that attention systems are modulated by environmental factors (36), and a supportive environment may serve a protective function and contribute to resilience towards development of several psychiatric disorders (291, 292).

Finally, how do all the experimental findings discussed in this thesis relate to the real world? There will always be a discrepancy between the precise behavioral and neural mechanisms that we (believe we) investigate experimentally–often through indirect measurements–and the complex situations encountered in the real world. Science brings tiny pieces of the puzzle at a

time, and as long as we do not over interpret their meaning, or draw conclusions from the pieces in isolation, I believe we will be able to eventually understand the brain better, at least a little bit.



8 ACKNOWLEDGEMENTS

First of all, my warmest thank you to **Eva Henje**, for being my main supervisor and unofficial mentor, following along on this rather long ride. Thank you for all scientific discussions, guidance, and new perspectives, but also everything else including Muir Woods and talks about life in general. I look forward to what is coming next–for both of us!

Thank you **Predrag Petrovic**, for being both my main supervisor and co-supervisor. I have really enjoyed discussing science with you! I also had the great opportunity to participate in several exciting scientific conferences (and associated Gruyère fondue!) thanks to you. I will forever be impressed by your never-ending optimism and passion for science.

Christoph Abé, thank you for being the best co-supervisor one could possibly wish for. You taught me so much: statistics, programming, writing, handling academia… You always took the time to help me out with very different types of matters. And thanks to you following your dreams, making music and art, I have at least one cool friend ;) You really inspire me!

Martin Ingvar, thank you for helping keep this project on track and sharing your knowledge of scientific procedures and quality in your role as co-supervisor.

Charlotte Nymberg Thunell, and **Eva Serlachius**, thank you for acting as co-supervisors for a part of this PhD project. Charlotte, you introduced me to (very) large datasets and taught me a fair deal about statistics. Eva, thank you for showing that it is possible to create a nurturing, welcoming, and pretty (!) research environment.

Thank you **Nathalie Wrobel** for being my unofficial co-supervisor and teaching me a lot about fMRI and programming. I am so very lucky to have shared an office with you–someone else who knows the importance of a decent snack! Also, after several "let me Google that for you", I finally learnt how to do just that myself ;)

Thank you **Camilla Hallek** and **David Mataix-Cols** for being my external mentors throughout this project. I appreciate very much that you were willing to spend time listening to my concerns and offer advice on how to navigate in academia, on clinical work, and on life in general.

Mimmi Wernman–the queen of f*cking everything ☺ Thank you for all the help over the years and knowing the importance of gardening, but above all, thank you for being you and sticking to it.

Thank you **Rita Almeida**, **Jonatan Berrebi**, **Rouslan Sitnikov**, and other staff at MRC, for helping out with statistics and MRI related issues.

I would also like to thank everyone who has been around in the Osher corridors during my PhD years. A special thanks to **Jens**, always up for coffee, politics, literature, garden shows, (listening to) planting ideas, and lately even textiles, and **Isabel**: thank you for always taking

time for tea/coffee and listening to my complaints regarding many different things, including R. Thank you to all of you who have been around for work-related matters, but also friendly chats: **Orestis**, **Alexander**, **Kasim**, **Torbjörn**, **Angelica**, **Silvia**, **Jeanette**, **Aisha**, **Moa**, **Maria**, **William**, **Pär**, **Alva**, **Eleni**, **Arjan**, **Lau**, **Mikkel**, **Fanny**, **Cassia**, **Gustav**, and also **Eva**, **Peter**, **Karin**, **Mats,** and **Daniel**. I would also like to take the opportunity to apologize to all of you that I have shared an office with over the years, and disturbed by endless talking: **Sofia**, **Annelie**, **Philip** (but you are quite talkative yourselves), **Björn**, and **Anaïs**.

Thank you also to all of you over at the Psychology department: **Moa**, **Irem**, **Giorgia**, **Arnaud**, **Martin**, **Neda**, **Behzad**, **Robin**, **Lisa**, **Elin**, **Artin**. Thank you for keeping my mood up by inspirational conversations, and cake, of course. An especially warm thank you to **Danja**, for sharing this journey with me in so many ways.

And: **Sandra**! Thank you for being my programming duck, and friend, through it all ☺

None of the studies included in this PhD project would have been possible without the engagement of participants. I am very grateful that you all chose to participate.

Finally, I would like to thank my friends and family for tolerating both my complaints and praise for science, and especially **Martin**, **Arvid,** and **Edvin**, for reminding me of what is *really* important.

9 REFERENCES

1. Roepstorff A, Frith C. What's at the top in the top-down control of action? Script-sharing and 'top-top' control of action in cognitive experiments. Psychol Res. 2004;68(2-3):189-98.
2. Petrovic P, Castellanos FX. Top-Down Dysregulation-From ADHD to Emotional Instability. Front Behav Neurosci. 2016;10:70.
3. Ochsner KN, Gross JJ. The cognitive control of emotion. Trends Cogn Sci. 9. England 2005. p. 242-9.
4. Ekman P. An argument for basic emotions. Cognition and Emotion. 1992;6(3-4):169-200.
5. Ekman P, Cordaro D. What is Meant by Calling Emotions Basic. Emotion Review. 2011;3(4):364-70.
6. Lindquist KA, Wager TD, Kober H, Bliss-Moreau E, Barrett LF. The brain basis of emotion: a meta-analytic review. Behav Brain Sci. 2012;35(3):121-43.
7. Kirby LAJ, Robinson JL. Affective mapping: An activation likelihood estimation (ALE) meta-analysis. Brain and cognition. 2017;118:137-48.
8. Etkin A, Buchel C, Gross JJ. The neural bases of emotion regulation. Nat Rev Neurosci. 2015;16(11):693-700.
9. Gross JJ. The Emerging Field of Emotion Regulation: An Integrative Review. Review of General Psychology. 1998;2(3):271-99.
10. Gross JJ. The Extended Process Model of Emotion Regulation: Elaborations, Applications, and Future Directions. Psychological Inquiry. 2015;26(1):130-7.
11. McRae K, Gross JJ. Emotion regulation. Emotion. 2020;20(1):1-9.
12. Kohn N, Eickhoff SB, Scheller M, Laird AR, Fox PT, Habel U. Neural network of cognitive emotion regulation--an ALE meta-analysis and MACM analysis. NeuroImage. 2014;87:345-55.
13. Ochsner KN, Silvers JA, Buhle JT. Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. Ann N Y Acad Sci. 2012;1251:E1-24.
14. Buhle JT, Silvers JA, Wager TD, Lopez R, Onyemekwu C, Kober H, et al. Cognitive reappraisal of emotion: a meta-analysis of human neuroimaging studies. Cerebral cortex (New York, NY : 1991). 2014;24(11):2981-90.
15. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci. 2002;3(8):655-66.
16. Craig AD. Interoception: the sense of the physiological condition of the body. Current opinion in neurobiology. 2003;13(4):500-5.
17. Roberts AC. The importance of serotonin for orbitofrontal function. Biol Psychiatry. 2011;69(12):1185-91.
18. Lutz K, Widmer M. What can the monetary incentive delay task tell us about the neural processing of reward and punishment? Neuroscience and Neuroeconomics. 2014:33.
19. Haber SN, Knutson B. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology. 2010;35(1):4-26.
20. Liu X, Hairston J, Schrier M, Fan J. Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional neuroimaging studies. Neurosci Biobehav Rev. 2011;35(5):1219-36.
21. Oldham S, Murawski C, Fornito A, Youssef G, Yucel M, Lorenzetti V. The anticipation and outcome phases of reward and loss processing: A neuroimaging meta-analysis of the monetary incentive delay task. Hum Brain Mapp. 2018;39(8):3398-418.

22. Berridge KC, Robinson TE. Parsing reward. Trends in neurosciences. 2003;26(9):507-13.
23. Berridge KC. The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology. 2007;191(3):391-431.
24. Berridge KC. Evolving Concepts of Emotion and Motivation. Front Psychol. 2018;9:1647.
25. Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature. 2006;442(7106):1042-5.
26. Schultz W. Dopamine reward prediction error coding. Dialogues in clinical neuroscience. 2016;18(1):23-32.
27. Berridge KC, Kringelbach ML. Pleasure systems in the brain. Neuron. 2015;86(3):646-64.
28. Kringelbach ML, Rolls ET. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Progress in neurobiology. 2004;72(5):341-72.
29. Kable JW, Glimcher PW. The neural correlates of subjective value during intertemporal choice. Nat Neurosci. 2007;10(12):1625-33.
30. Peters J, Buchel C. Neural representations of subjective reward value. Behav Brain Res. 2010;213(2):135-41.
31. O'Doherty J, Kringelbach ML, Rolls ET, Hornak J, Andrews C. Abstract reward and punishment representations in the human orbitofrontal cortex. Nat Neurosci. 2001;4(1):95-102.
32. Peters J, Buchel C. Episodic future thinking reduces reward delay discounting through an enhancement of prefrontal-mediotemporal interactions. Neuron. 2010;66(1):138-48.
33. Barkley RA. Executive Functions: What They Are, How They Work, and Why They Evolved. New York, NY: Guilford Press; 2012.
34. Diamond A. Executive functions. Annu Rev Psychol. 2013;64:135-68.
35. Stuss DT. Functions of the frontal lobes: relation to executive functions. J Int Neuropsychol Soc. 2011;17(5):759-65.
36. Rosario Rueda M, P. Pozuelos J, M. Cómbita L. Cognitive Neuroscience of Attention. From brain mechanisms to individual differences in efficiency. AIMS Neuroscience. 2015;2(4):183-202.
37. Petersen SE, Posner MI. The attention system of the human brain: 20 years after. Annu Rev Neurosci. 2012;35:73-89.
38. Posner MI, Rothbart MK. Research on attention networks as a model for the integration of psychological science. Annu Rev Psychol. 2007;58:1-23.
39. Xuan B, Mackie MA, Spagna A, Wu T, Tian Y, Hof PR, et al. The activation of interactive attentional networks. NeuroImage. 2016;129:308-19.
40. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci. 2007;27(9):2349-56.
41. Young CB, Raz G, Everaerd D, Beckmann CF, Tendolkar I, Hendler T, et al. Dynamic Shifts in Large-Scale Brain Network Balance As a Function of Arousal. J Neurosci. 2017;37(2):281-90.
42. Uddin LQ, Supekar KS, Ryali S, Menon V. Dynamic reconfiguration of structural and functional connectivity across core neurocognitive brain networks with development. J Neurosci. 2011;31(50):18578-89.
43. Sarter M, Hasselmo ME, Bruno JP, Givens B. Unraveling the attentional functions of cortical cholinergic inputs: interactions between signal-driven and cognitive modulation of signal detection. Brain Res Brain Res Rev. 2005;48(1):98-111.

44. Vossel S, Geng JJ, Fink GR. Dorsal and ventral attention systems: distinct neural circuits but collaborative roles. Neuroscientist. 2014;20(2):150-9.
45. Power JD, Cohen AL, Nelson SM, Wig GS, Barnes KA, Church JA, et al. Functional network organization of the human brain. Neuron. 2011;72(4):665-78.
46. Posner MI, Rothbart MK, Voelker P. Developing brain networks of attention. Curr Opin Pediatr. 2016;28(6):720-4.
47. Dosenbach NU, Fair DA, Miezin FM, Cohen AL, Wenger KK, Dosenbach RA, et al. Distinct brain networks for adaptive and stable task control in humans. Proc Natl Acad Sci U S A. 2007;104(26):11073-8.
48. Dosenbach NU, Fair DA, Cohen AL, Schlaggar BL, Petersen SE. A dual-networks architecture of top-down control. Trends Cogn Sci. 2008;12(3):99-105.
49. Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD. Conflict monitoring and cognitive control. Psychol Rev. 2001;108(3):624-52.
50. Mansouri FA, Tanaka K, Buckley MJ. Conflict-induced behavioural adjustment: a clue to the executive functions of the prefrontal cortex. Nat Rev Neurosci. 2009;10(2):141-52.
51. Etkin A, Egner T, Peraza DM, Kandel ER, Hirsch J. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron. 2006;51(6):871-82.
52. Egner T, Etkin A, Gale S, Hirsch J. Dissociable neural systems resolve conflict from emotional versus nonemotional distracters. Cerebral cortex (New York, NY : 1991). 2008;18(6):1475-84.
53. Kerns JG, Cohen JD, MacDonald AW, 3rd, Cho RY, Stenger VA, Carter CS. Anterior cingulate conflict monitoring and adjustments in control. Science (New York, NY). 2004;303(5660):1023-6.
54. Cieslik EC, Mueller VI, Eickhoff CR, Langner R, Eickhoff SB. Three key regions for supervisory attentional control: evidence from neuroimaging meta-analyses. Neurosci Biobehav Rev. 2015;48:22-34.
55. Arnsten AF, Rubia K. Neurobiological circuits regulating attention, cognitive control, motivation, and emotion: disruptions in neurodevelopmental psychiatric disorders. J Am Acad Child Adolesc Psychiatry. 2012;51(4):356-67.
56. Arnsten AF. Catecholamine influences on dorsolateral prefrontal cortical networks. Biol Psychiatry. 2011;69(12):e89-99.
57. Cools R, D'Esposito M. Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biol Psychiatry. 2011;69(12):e113-25.
58. van den Bos W, Cohen MX, Kahnt T, Crone EA. Striatum-medial prefrontal cortex connectivity predicts developmental changes in reinforcement learning. Cerebral cortex (New York, NY : 1991). 2012;22(6):1247-55.
59. Li SC. Neuromodulation of behavioral and cognitive development across the life span. Dev Psychol. 2012;48(3):810-4.
60. Padmanabhan A, Luna B. Developmental imaging genetics: linking dopamine function to adolescent behavior. Brain and cognition. 2014;89:27-38.
61. Hedman AM, van Haren NE, Schnack HG, Kahn RS, Hulshoff Pol HE. Human brain changes across the life span: a review of 56 longitudinal magnetic resonance imaging studies. Hum Brain Mapp. 2012;33(8):1987-2002.
62. Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, et al. Dynamic mapping of human cortical development during childhood through early adulthood. Proc Natl Acad Sci U S A. 2004;101(21):8174-9.
63. Mills KL, Tamnes CK. Methods and considerations for longitudinal structural brain imaging analysis across development. Dev Cogn Neurosci. 2014;9:172-90.

64. Ducharme S, Albaugh MD, Nguyen TV, Hudziak JJ, Mateos-Perez JM, Labbe A, et al. Trajectories of cortical thickness maturation in normal brain development--The importance of quality control procedures. NeuroImage. 2016;125:267-79.
65. Vijayakumar N, Allen NB, Youssef G, Dennison M, Yucel M, Simmons JG, et al. Brain development during adolescence: A mixed-longitudinal investigation of cortical thickness, surface area, and volume. Hum Brain Mapp. 2016;37(6):2027-38.
66. Crone EA, Elzinga BM. Changing brains: how longitudinal functional magnetic resonance imaging studies can inform us about cognitive and social-affective growth trajectories. Wiley Interdiscip Rev Cogn Sci. 2015;6(1):53-63.
67. Guyer AE, Silk JS, Nelson EE. The neurobiology of the emotional adolescent: From the inside out. Neurosci Biobehav Rev. 2016;70:74-85.
68. Dahl RE. Adolescent brain development: a period of vulnerabilities and opportunities. Keynote address. Ann N Y Acad Sci. 2004;1021:1-22.
69. Rubia K. Functional brain imaging across development. Eur Child Adolesc Psychiatry. 2013;22(12):719-31.
70. Aldao A, Gee DG, De Los Reyes A, Seager I. Emotion regulation as a transdiagnostic factor in the development of internalizing and externalizing psychopathology: Current and future directions. Development and psychopathology. 2016;28(4pt1):927-46.
71. Somerville LH, Casey BJ. Developmental neurobiology of cognitive control and motivational systems. Current opinion in neurobiology. 2010;20(2):236-41.
72. Blakemore SJ. Inventing ourselves. The secret life of the teenage brain. Great Britain: Penguin Random House, Transworld Pulblishers, Doubleday; 2018.
73. Bjork JM, Pardini DA. Who are those "risk-taking adolescents"? Individual differences in developmental neuroimaging research. Dev Cogn Neurosci. 2015;11:56-64.
74. Schneider S, Peters J, Bromberg U, Brassen S, Miedl SF, Banaschewski T, et al. Risk taking and the adolescent reward system: a potential common link to substance abuse. Am J Psychiatry. 2012;169(1):39-46.
75. van Duijvenvoorde AC, Op de Macks ZA, Overgaauw S, Gunther Moor B, Dahl RE, Crone EA. A cross-sectional and longitudinal analysis of reward-related brain activation: effects of age, pubertal stage, and reward sensitivity. Brain and cognition. 2014;89:3-14.
76. Telzer EH. Dopaminergic reward sensitivity can promote adolescent health: A new perspective on the mechanism of ventral striatum activation. Dev Cogn Neurosci. 2016;17:57-67.
77. Silvers JA, McRae K, Gabrieli JD, Gross JJ, Remy KA, Ochsner KN. Age-related differences in emotional reactivity, regulation, and rejection sensitivity in adolescence. Emotion. 2012;12(6):1235-47.
78. VandenBos GR, & American Psychological Association. APA dictionary of psychology. Washington, DC: American Psychological Association; 2007.
79. DSM-5. Diagnostic and statistical manual of mental disorders : DSM-5. Arlington, Va.: American Psychiatric Association; 2013.
80. WHO. International Classification of Diseases, 10th Revision (ICD-10). Geneva: World Health Organization; 2016.
81. Enzi B, Doering S, Faber C, Hinrichs J, Bahmer J, Northoff G. Reduced deactivation in reward circuitry and midline structures during emotion processing in borderline personality disorder. The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry. 2013;14(1):45-56.
82. Rubia K. "Cool" inferior frontostriatal dysfunction in attention-deficit/hyperactivity disorder versus "hot" ventromedial orbitofrontal-limbic dysfunction in conduct disorder: a review. Biol Psychiatry. 2011;69(12):e69-87.
83. Rubia K, Smith AB, Halari R, Matsukura F, Mohammad M, Taylor E, et al. Disorder-specific dissociation of orbitofrontal dysfunction in boys with pure conduct

disorder during reward and ventrolateral prefrontal dysfunction in boys with pure ADHD during sustained attention. Am J Psychiatry. 2009;166(1):83-94.
84. Shaw P, Stringaris A, Nigg J, Leibenluft E. Emotion dysregulation in attention deficit hyperactivity disorder. Am J Psychiatry. 2014;171(3):276-93.
85. Plichta MM, Scheres A. Ventral-striatal responsiveness during reward anticipation in ADHD and its relation to trait impulsivity in the healthy population: a meta-analytic review of the fMRI literature. Neurosci Biobehav Rev. 2014;38:125-34.
86. SBU. Dialektisk beteendeterapi (DBT) vid borderline personlighetsstörning. Stockholm: Statens beredning för medicinsk utvärdering (SBU) 2005; SBU Alert-rapport nr 2005-07.
87. Leichsenring F, Leibing E, Kruse J, New AS, Leweke F. Borderline personality disorder. Lancet. 2011;377(9759):74-84.
88. Kohling J, Ehrenthal JC, Levy KN, Schauenburg H, Dinger U. Quality and severity of depression in borderline personality disorder: A systematic review and meta-analysis. Clin Psychol Rev. 2015;37:13-25.
89. Soloff P, Nutche J, Goradia D, Diwadkar V. Structural brain abnormalities in borderline personality disorder: a voxel-based morphometry study. Psychiatry Res. 2008;164(3):223-36.
90. Soloff PH, Pruitt P, Sharma M, Radwan J, White R, Diwadkar VA. Structural brain abnormalities and suicidal behavior in borderline personality disorder. Journal of psychiatric research. 2012;46(4):516-25.
91. Soloff P, White R, Diwadkar VA. Impulsivity, aggression and brain structure in high and low lethality suicide attempters with borderline personality disorder. Psychiatry Res. 2014;222(3):131-9.
92. Krause-Utz A, Winter D, Niedtfeld I, Schmahl C. The Latest Neuroimaging Findings in Borderline Personality Disorder. Current psychiatry reports. 2014;16(3).
93. Koenigsberg HW, Fan J, Ochsner KN, Liu X, Guise KG, Pizzarello S, et al. Neural correlates of the use of psychological distancing to regulate responses to negative social cues: a study of patients with borderline personality disorder. Biol Psychiatry. 2009;66(9):854-63.
94. Mauchnik J, Schmahl C. The latest neuroimaging findings in borderline personality disorder. Current psychiatry reports. 2010;12(1):46-55.
95. Schulze L, Schmahl C, Niedtfeld I. Neural Correlates of Disturbed Emotion Processing in Borderline Personality Disorder: A Multimodal Meta-Analysis. Biol Psychiatry. 2016;79(2):97-106.
96. Mitchell AE, Dickens GL, Picchioni MM. Facial emotion processing in borderline personality disorder: a systematic review and meta-analysis. Neuropsychol Rev. 2014;24(2):166-84.
97. Schulze L, Domes G, Kruger A, Berger C, Fleischer M, Prehn K, et al. Neuronal correlates of cognitive reappraisal in borderline patients with affective instability. Biol Psychiatry. 2011;69(6):564-73.
98. Silbersweig D, Clarkin JF, Goldstein M, Kernberg OF, Tuescher O, Levy KN, et al. Failure of frontolimbic inhibitory function in the context of negative emotion in borderline personality disorder. Am J Psychiatry. 2007;164(12):1832-41.
99. Holtmann J, Herbort MC, Wustenberg T, Soch J, Richter S, Walter H, et al. Trait anxiety modulates fronto-limbic processing of emotional interference in borderline personality disorder. Front Hum Neurosci. 2013;7:54.
100. Jacob GA, Zvonik K, Kamphausen S, Sebastian A, Maier S, Philipsen A, et al. Emotional modulation of motor response inhibition in women with borderline personality disorder: an fMRI study. Journal of psychiatry & neuroscience : JPN. 2013;38(3):164-72.
101. Wingenfeld K, Rullkoetter N, Mensebach C, Beblo T, Mertens M, Kreisel S, et al. Neural correlates of the individual emotional Stroop in borderline personality disorder. Psychoneuroendocrinology. 2009;34(4):571-86.

102. Sebastian A, Jung P, Krause-Utz A, Lieb K, Schmahl C, Tuscher O. Frontal dysfunctions of impulse control - a systematic review in borderline personality disorder and attention-deficit/hyperactivity disorder. Front Hum Neurosci. 2014;8:698.
103. Winter D, Krause-Utz A, Lis S, Chiu CD, Lanius RA, Schriner F, et al. Dissociation in borderline personality disorder: Disturbed cognitive and emotional inhibition and its neural correlates. Psychiatry Res. 2015;233(3):339-51.
104. van Eijk J, Sebastian A, Krause-Utz A, Cackowski S, Demirakca T, Biedermann SV, et al. Women with borderline personality disorder do not show altered BOLD responses during response inhibition. Psychiatry Res. 2015;234(3):378-89.
105. Frick PJ, Stickle TR, Dandreaux DM, Farrell JM, Kimonis ER. Callous-unemotional traits in predicting the severity and stability of conduct problems and delinquency. Journal of abnormal child psychology. 2005;33(4):471-87.
106. Viding E, Fontaine NM, McCrory EJ. Antisocial behaviour in children with and without callous-unemotional traits. J R Soc Med. 2012;105(5):195-200.
107. Carlisi CO, Moffitt TE, Knodt AR, Harrington H, Ireland D, Melzer TR, et al. Associations between life-course-persistent antisocial behaviour and brain structure in a population-representative longitudinal birth cohort. The Lancet Psychiatry. 2020;7(3):245-53.
108. Rogers JC, De Brito SA. Cortical and Subcortical Gray Matter Volume in Youths With Conduct Problems: A Meta-analysis. JAMA psychiatry. 2016;73(1):64-72.
109. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. Lancet. 2005;366(9481):237-48.
110. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull. 1997;121(1):65-94.
111. Bush G. Attention-deficit/hyperactivity disorder and attention networks. Neuropsychopharmacology. 2010;35(1):278-300.
112. Sonuga-Barke EJ. The dual pathway model of AD/HD: an elaboration of neuro-developmental characteristics. Neurosci Biobehav Rev. 2003;27(7):593-604.
113. Castellanos FX, Sonuga-Barke EJ, Milham MP, Tannock R. Characterizing cognition in ADHD: beyond executive dysfunction. Trends Cogn Sci. 2006;10(3):117-23.
114. Luman M, Tripp G, Scheres A. Identifying the neurobiology of altered reinforcement sensitivity in ADHD: a review and research agenda. Neurosci Biobehav Rev. 2010;34(5):744-54.
115. Solanto MV, Abikoff H, Sonuga-Barke E, Schachar R, Logan GD, Wigal T, et al. The ecological validity of delay aversion and response inhibition as measures of impulsivity in AD/HD: a supplement to the NIMH multimodal treatment study of AD/HD. Journal of abnormal child psychology. 2001;29(3):215-28.
116. Thorell LB. Do delay aversion and executive function deficits make distinct contributions to the functional impact of ADHD symptoms? A study of early academic skill deficits. J Child Psychol Psychiatry. 2007;48(11):1061-70.
117. Yu X, Sonuga-Barke E, Liu X. Preference for Smaller Sooner Over Larger Later Rewards in ADHD: Contribution of Delay Duration and Paradigm Type. J Atten Disord. 2015.
118. Nigg JT, Casey BJ. An integrative theory of attention-deficit/ hyperactivity disorder based on the cognitive and affective neurosciences. Development and psychopathology. 2005;17(3):785-806.
119. Skirrow C, Asherson P. Emotional lability, comorbidity and impairment in adults with attention-deficit hyperactivity disorder. J Affect Disord. 2013;147(1-3):80-6.
120. Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci U S A. 2007;104(49):19649-54.

121. Shaw P, Malek M, Watson B, Greenstein D, de Rossi P, Sharp W. Trajectories of cerebral cortical development in childhood and adolescence and adult attention-deficit/hyperactivity disorder. Biol Psychiatry. 2013;74(8):599-606.
122. Seidman LJ, Biederman J, Liang L, Valera EM, Monuteaux MC, Brown A, et al. Gray matter alterations in adults with attention-deficit/hyperactivity disorder identified by voxel based morphometry. Biol Psychiatry. 2011;69(9):857-66.
123. Cortese S, Kelly C, Chabernaud C, Proal E, Di Martino A, Milham MP, et al. Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. Am J Psychiatry. 2012;169(10):1038-55.
124. Makris N, Biederman J, Monuteaux MC, Seidman LJ. Towards conceptualizing a neural systems-based anatomy of attention-deficit/hyperactivity disorder. Developmental neuroscience. 2009;31(1-2):36-49.
125. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC medicine. 2013;11:126.
126. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010;167(7):748-51.
127. Crosbie J, Arnold P, Paterson A, Swanson J, Dupuis A, Li X, et al. Response inhibition and ADHD traits: correlates and heritability in a community sample. Journal of abnormal child psychology. 2013;41(3):497-507.
128. Das D, Cherbuin N, Butterworth P, Anstey KJ, Easteal S. A population-based study of attention deficit/hyperactivity disorder symptoms and associated impairment in middle-aged adults. PloS one. 2012;7(2):e31500.
129. Petrovic P, Ekman CJ, Klahr J, Tigerstrom L, Ryden G, Johansson AG, et al. Significant grey matter changes in a region of the orbitofrontal cortex in healthy participants predicts emotional dysregulation. Soc Cogn Affect Neurosci. 2016;11(7):1041-9.
130. Anckarsäter H, Stahlberg O, Larson T, Hakansson C, Jutblad SB, Niklasson L, et al. The impact of ADHD and autism spectrum disorders on temperament, character, and personality development. Am J Psychiatry. 2006;163(7):1239-44.
131. Philipsen A, Limberger MF, Lieb K, Feige B, Kleindienst N, Ebner-Priemer U, et al. Attention-deficit hyperactivity disorder as a potentially aggravating factor in borderline personality disorder. Br J Psychiatry. 2008;192(2):118-23.
132. Distel MA, Carlier A, Middeldorp CM, Derom CA, Lubke GH, Boomsma DI. Borderline personality traits and adult attention-deficit hyperactivity disorder symptoms: a genetic analysis of comorbidity. Am J Med Genet B Neuropsychiatr Genet. 2011;156B(7):817-25.
133. Castellanos FX, Tannock R. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat Rev Neurosci. 2002;3(8):617-28.
134. Goodman R. Psychometric properties of the strengths and difficulties questionnaire. J Am Acad Child Adolesc Psychiatry. 2001;40(11):1337-45.
135. Goodman R, Ford T, Simmons H, Gatward R, Meltzer H. Using the Strengths and Difficulties Questionnaire (SDQ) to screen for child psychiatric disorders in a community sample. Br J Psychiatry. 2000;177:534-9.
136. Goodman A, Goodman R. Strengths and difficulties questionnaire as a dimensional measure of child mental health. J Am Acad Child Adolesc Psychiatry. 2009;48(4):400-3.
137. Brown TE. Brown Attention-Deficit Disorder Scales (Manual). San Antonio, TX: The Psychological Corporation; 1996.
138. Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS Scales. Journal of personality and social psychology. 1994;67(2):319-33.

139. Gratz KL, Roemer L. Multidimensional assessment of emotion regulation and dysregulation: Development, factor structure, and initial validation of the difficulties in emotion regulation scale. J Psychopathol Behav Assess. 2004;26(1):41-54.
140. Benfer N, Bardeen JR, Fergus TA, Rogers TA. Factor Structure and Incremental Validity of the Original and Modified Versions of the Difficulties in Emotion Regulation Scale. J Pers Assess. 2019;101(6):598-608.
141. Nock MK, Wedig MM, Holmberg EB, Hooley JM. The emotion reactivity scale: development, evaluation, and relation to self-injurious thoughts and behaviors. Behav Ther. 2008;39(2):107-16.
142. Preece D, Becerra R, Campitelli G. Assessing Emotional Reactivity: Psychometric Properties of the Perth Emotional Reactivity Scale and the Development of a Short Form. J Pers Assess. 2019;101(6):589-97.
143. Gross JJ, John OP. Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. Journal of personality and social psychology. 2003;85(2):348-62.
144. Thorell LB, Tilling H, Sjowall D. Emotion dysregulation in adult ADHD: Introducing the Comprehensive Emotion Regulation Inventory (CERI). J Clin Exp Neuropsychol. 2020;42(7):747-58.
145. Logan GD, Cowan WB, Davis KA. On the ability to inhibit simple and choice reaction time responses: a model and a method. Journal of experimental psychology Human perception and performance. 1984;10(2):276-91.
146. Verbruggen F, Logan GD, Stevens MA. STOP-IT: Windows executable software for the stop-signal paradigm. Behav Res Methods. 2008;40(2):479-83.
147. Winstanley CA, Eagle DM, Robbins TW. Behavioral models of impulsivity in relation to ADHD: translation between clinical and preclinical studies. Clin Psychol Rev. 2006;26(4):379-95.
148. Bari A, Robbins TW. Inhibition and impulsivity: behavioral and neural basis of response control. Progress in neurobiology. 2013;108:44-79.
149. Rae CL, Hughes LE, Weaver C, Anderson MC, Rowe JB. Selection and stopping in voluntary action: a meta-analysis and combined fMRI study. NeuroImage. 2014;86:381-91.
150. Cai W, Ryali S, Chen T, Li CS, Menon V. Dissociable roles of right inferior frontal cortex and anterior insula in inhibitory control: evidence from intrinsic and task-related functional parcellation, connectivity, and response profile analyses across multiple datasets. J Neurosci. 2014;34(44):14652-67.
151. Lipszyc J, Schachar R. Inhibitory control and psychopathology: a meta-analysis of studies using the stop signal task. J Int Neuropsychol Soc. 2010;16(6):1064-76.
152. Alderson RM, Rapport MD, Kofler MJ. Attention-deficit/hyperactivity disorder and behavioral inhibition: a meta-analytic review of the stop-signal paradigm. Journal of abnormal child psychology. 2007;35(5):745-58.
153. Lijffijt M, Kenemans JL, Verbaten MN, van Engeland H. A meta-analytic review of stopping performance in attention-deficit/hyperactivity disorder: deficient inhibitory motor control? Journal of abnormal psychology. 2005;114(2):216-22.
154. Linhartova P, Latalova A, Bartecek R, Sirucek J, Theiner P, Ejova A, et al. Impulsivity in patients with borderline personality disorder: a comprehensive profile compared with healthy people and patients with ADHD. Psychological medicine. 2020;50(11):1829-38.
155. Linhartova P, Sirucek J, Ejova A, Bartecek R, Theiner P, Kasparek T. Dimensions of Impulsivity in Healthy People, Patients with Borderline Personality Disorder, and Patients with Attention-Deficit/Hyperactivity Disorder. J Atten Disord. 2021;25(4):584-95.
156. Barker V, Romaniuk L, Cardinal RN, Pope M, Nicol K, Hall J. Impulsivity in borderline personality disorder. Psychological medicine. 2015;45(9):1955-64.

157. Hart H, Radua J, Nakao T, Mataix-Cols D, Rubia K. Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. JAMA psychiatry. 2013;70(2):185-98.
158. Huizenga HM, van Bers BM, Plat J, van den Wildenberg WP, van der Molen MW. Task complexity enhances response inhibition deficits in childhood and adolescent attention-deficit/hyperactivity disorder: a meta-regression analysis. Biol Psychiatry. 2009;65(1):39-45.
159. Ainslie G. Specious reward: a behavioral theory of impulsiveness and impulse control. Psychol Bull. 1975;82(4):463-96.
160. Peters J, Buchel C. The neural mechanisms of inter-temporal decision-making: understanding variability. Trends Cogn Sci. 2011;15(5):227-39.
161. van den Bos W, Rodriguez CA, Schweitzer JB, McClure SM. Connectivity strength of dissociable striatal tracts predict individual differences in temporal discounting. J Neurosci. 2014;34(31):10298-310.
162. van den Bos W, McClure SM. Towards a general model of temporal discounting. Journal of the experimental analysis of behavior. 2013;99(1):58-73.
163. Figner B, Knoch D, Johnson EJ, Krosch AR, Lisanby SH, Fehr E, et al. Lateral prefrontal cortex and self-control in intertemporal choice. Nat Neurosci. 2010;13(5):538-9.
164. McClure SM, Laibson DI, Loewenstein G, Cohen JD. Separate neural systems value immediate and delayed monetary rewards. Science (New York, NY). 2004;306(5695):503-7.
165. Kirby KN, Petry NM, Bickel WK. Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. Journal of experimental psychology General. 1999;128(1):78-87.
166. Patros CH, Alderson RM, Kasper LJ, Tarle SJ, Lea SE, Hudec KL. Choice-impulsivity in children and adolescents with attention-deficit/hyperactivity disorder (ADHD): A meta-analytic review. Clin Psychol Rev. 2016;43:162-74.
167. Amlung M, Marsden E, Holshausen K, Morris V, Patel H, Vedelago L, et al. Delay Discounting as a Transdiagnostic Process in Psychiatric Disorders: A Meta-analysis. JAMA psychiatry. 2019;76(11):1176-86.
168. Paret C, Jennen-Steinmetz C, Schmahl C. Disadvantageous decision-making in borderline personality disorder: Partial support from a meta-analytic review. Neurosci Biobehav Rev. 2017;72:301-9.
169. White SF, Clanton R, Brislin SJ, Meffert H, Hwang S, Sinclair S, et al. Reward: empirical contribution. Temporal discounting and conduct disorder in adolescents. Journal of personality disorders. 2014;28(1):5-18.
170. Knutson B, Adams CM, Fong GW, Hommer D. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J Neurosci. 2001;21(16):RC159.
171. Knutson B, Fong GW, Adams CM, Varner JL, Hommer D. Dissociation of reward anticipation and outcome with event-related fMRI. Neuroreport. 2001;12(17):3683-7.
172. Bayard F, Abe C, Wrobel N, Ingvar M, Henje E, Petrovic P. Emotional Instability Relates to Ventral Striatum Activity During Reward Anticipation in Females. Front Behav Neurosci. 2020;14:76.
173. Scheres A, Milham MP, Knutson B, Castellanos FX. Ventral striatal hyporesponsiveness during reward anticipation in attention-deficit/hyperactivity disorder. Biol Psychiatry. 2007;61(5):720-4.
174. Strohle A, Stoy M, Wrase J, Schwarzer S, Schlagenhauf F, Huss M, et al. Reward anticipation and outcomes in adult males with attention-deficit/hyperactivity disorder. NeuroImage. 2008;39(3):966-72.
175. Stoy M, Schlagenhauf F, Schlochtermeier L, Wrase J, Knutson B, Lehmkuhl U, et al. Reward processing in male adults with childhood ADHD--a comparison between drug-naïve and methylphenidate-treated subjects. Psychopharmacology. 2011;215(3):467-81.

176. Edel MA, Enzi B, Witthaus H, Tegenthoff M, Peters S, Juckel G, et al. Differential reward processing in subtypes of adult attention deficit hyperactivity disorder. Journal of psychiatric research. 2013;47(3):350-6.
177. Stark R, Bauer E, Merz CJ, Zimmermann M, Reuter M, Plichta MM, et al. ADHD related behaviors are associated with brain activation in the reward system. Neuropsychologia. 2011;49(3):426-34.
178. Kappel V, Lorenz RC, Streifling M, Renneberg B, Lehmkuhl U, Strohle A, et al. Effect of brain structure and function on reward anticipation in children and adults with attention deficit hyperactivity disorder combined subtype. Soc Cogn Affect Neurosci. 2015;10(7):945-51.
179. van Hulst BM, de Zeeuw P, Bos DJ, Rijks Y, Neggers SF, Durston S. Children with ADHD symptoms show decreased activity in ventral striatum during the anticipation of reward, irrespective of ADHD diagnosis. J Child Psychol Psychiatry. 2017;58(2):206-14.
180. Herbort MC, Soch J, Wustenberg T, Krauel K, Pujara M, Koenigs M, et al. A negative relationship between ventral striatal loss anticipation response and impulsivity in borderline personality disorder. NeuroImage Clinical. 2016;12:724-36.
181. Vollm B, Richardson P, McKie S, Elliott R, Dolan M, Deakin B. Neuronal correlates of reward and loss in Cluster B personality disorders: a functional magnetic resonance imaging study. Psychiatry Res. 2007;156(2):151-67.
182. Dillon DG, Bogdan R, Fagerness J, Holmes AJ, Perlis RH, Pizzagalli DA. Variation in TREK1 gene linked to depression-resistant phenotype is associated with potentiated neural responses to rewards in humans. Hum Brain Mapp. 2010;31(2):210-21.
183. Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935; 18:643-62.
184. Song S, Zilverstand A, Song H, d'Oleire Uquillas F, Wang Y, Xie C, et al. The influence of emotional interference on cognitive control: A meta-analysis of neuroimaging studies using the emotional Stroop task. Sci Rep. 2017;7(1):2088.
185. Hinault T, Larcher K, Zazubovits N, Gotman J, Dagher A. Spatio-temporal patterns of cognitive control revealed with simultaneous electroencephalography and functional magnetic resonance imaging. Hum Brain Mapp. 2019;40(1):80-97.
186. Chen T, Becker B, Camilleri J, Wang L, Yu S, Eickhoff SB, et al. A domain-general brain network underlying emotional and cognitive interference processing: evidence from coordinate-based and functional connectivity meta-analyses. Brain Struct Funct. 2018;223(8):3813-40.
187. Xu M, Xu G, Yang Y. Neural Systems Underlying Emotional and Non-emotional Interference Processing: An ALE Meta-Analysis of Functional Neuroimaging Studies. Front Behav Neurosci. 2016;10:220.
188. Bush G, Frazier JA, Rauch SL, Seidman LJ, Whalen PJ, Jenike MA, et al. Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the Counting Stroop. Biol Psychiatry. 1999;45(12):1542-52.
189. Bush G, Whalen PJ, Rosen BR, Jenike MA, McInerney SC, Rauch SL. The counting Stroop: an interference task specialized for functional neuroimaging--validation study with functional MRI. Hum Brain Mapp. 1998;6(4):270-82.
190. Haas BW, Omura K, Constable RT, Canli T. Interference produced by emotional conflict associated with anterior cingulate activation. Cognitive, affective & behavioral neuroscience. 2006;6(2):152-6.
191. Hwang S, White SF, Nolan ZT, Craig Williams W, Sinclair S, Blair RJ. Executive attention control and emotional responding in attention-deficit/hyperactivity disorder--A functional MRI study. NeuroImage Clinical. 2015;9:545-54.
192. Floros O, Axelsson J, Almeida R, Tigerstrom L, Lekander M, Sundelin T, et al. Vulnerability in Executive Functions to Sleep Deprivation Is Predicted by Subclinical

Attention-Deficit/Hyperactivity Disorder Symptoms. Biol Psychiatry Cogn Neurosci Neuroimaging. 2020.
193. Mischel W, Shoda Y, Rodriguez MI. Delay of gratification in children. Science (New York, NY). 1989;244(4907):933-8.
194. Patros CH, Alderson RM, Lea SE, Tarle SJ, Kasper LJ, Hudec KL. Visuospatial working memory underlies choice-impulsivity in boys with attention-deficit/hyperactivity disorder. Res Dev Disabil. 2015;38:134-44.
195. Schumann G, Loth E, Banaschewski T, Barbot A, Barker G, Buchel C, et al. The IMAGEN study: reinforcement-related behaviour in normal brain function and psychopathology. Molecular psychiatry. 2010;15(12):1128-39.
196. Ching CRK, Hibar DP, Gurholt TP, Nunes A, Thomopoulos SI, Abe C, et al. What we learn about bipolar disorder from large-scale neuroimaging: Findings and future directions from the ENIGMA Bipolar Disorder Working Group. Hum Brain Mapp. 2020.
197. Seixas D, Lima D. Accuracy, reliability, validity and limitations of functional and structural magnetic resonance imaging data. Cortex. 2011;47(10):1266-9.
198. Botvinik-Nezer R, Holzmeister F, Camerer CF, Dreber A, Huber J, Johannesson M, et al. Variability in the analysis of a single neuroimaging dataset by many teams. Nature. 2020;582(7810):84-8.
199. Poldrack RA, Baker CI, Durnez J, Gorgolewski KJ, Matthews PM, Munafò MR, et al. Scanning the horizon: towards transparent and reproducible neuroimaging research. Nature Reviews Neuroscience. 2017;18(2):115-26.
200. Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, et al. Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci. 2013;14(5):365-76.
201. Esteban O, Markiewicz CJ, Blair RW, Moodie CA, Isik AI, Erramuzpe A, et al. fMRIPrep: a robust preprocessing pipeline for functional MRI. Nat Methods. 2019;16(1):111-6.
202. Casey BJ, Cannonier T, Conley MI, Cohen AO, Barch DM, Heitzeg MM, et al. The Adolescent Brain Cognitive Development (ABCD) study: Imaging acquisition across 21 sites. Dev Cogn Neurosci. 2018;32:43-54.
203. Rosenkranz K, Lemieux L. Present and future of simultaneous EEG-fMRI. MAGMA. 2010;23(5-6):309-16.
204. Straathof M, Sinke MR, Dijkhuizen RM, Otte WM. A systematic review on the quantitative relationship between structural and functional network connectivity strength in mammalian brains. J Cereb Blood Flow Metab. 2019;39(2):189-209.
205. Silberzahn R, Uhlmann EL, Martin DP, Anselmi P, Aust F, Awtrey E, et al. Many Analysts, One Data Set: Making Transparent How Variations in Analytic Choices Affect Results. Advances in Methods and Practices in Psychological Science. 2018;1(3):337-56.
206. Ioannidis JP. Why most published research findings are false. PLoS medicine. 2005;2(8):e124.
207. Simmons JP, Nelson LD, Simonsohn U. False-positive psychology: undisclosed flexibility in data collection and analysis allows presenting anything as significant. Psychol Sci. 2011;22(11):1359-66.
208. Collaboration OS. PSYCHOLOGY. Estimating the reproducibility of psychological science. Science (New York, NY). 2015;349(6251):aac4716.
209. Jones CW, Handler L, Crowell KE, Keil LG, Weaver MA, Platts-Mills TF. Non-publication of large randomized clinical trials: cross sectional analysis. BMJ. 2013;347:f6104.
210. Fanelli D. Negative results are disappearing from most disciplines and countries. Scientometrics. 2011;90(3):891-904.

211. Hassel S, Sharma GB, Alders GL, Davis AD, Arnott SR, Frey BN, et al. Reliability of a functional magnetic resonance imaging task of emotional conflict in healthy participants. Hum Brain Mapp. 2020;41(6):1400-15.
212. Borella E, de Ribaupierre A, Cornoldi C, Chicherio C. Beyond interference control impairment in ADHD: evidence from increased intraindividual variability in the color-stroop test. Child Neuropsychol. 2013;19(5):495-515.
213. Hoogman M, Bralten J, Hibar DP, Mennes M, Zwiers MP, Schweren LSJ, et al. Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis. The Lancet Psychiatry. 2017;4(4):310-9.
214. Carmona S, Hoekzema E, Ramos-Quiroga JA, Richarte V, Canals C, Bosch R, et al. Response inhibition and reward anticipation in medication-naive adults with attention-deficit/hyperactivity disorder: a within-subject case-control neuroimaging study. Hum Brain Mapp. 2012;33(10):2350-61.
215. Furukawa E, Bado P, Tripp G, Mattos P, Wickens JR, Bramati IE, et al. Abnormal striatal BOLD responses to reward anticipation and reward delivery in ADHD. PloS one. 2014;9(2):e89129.
216. Nymberg C, Jia T, Lubbe S, Ruggeri B, Desrivieres S, Barker G, et al. Neural mechanisms of attention-deficit/hyperactivity disorder symptoms are stratified by MAOA genotype. Biol Psychiatry. 2013;74(8):607-14.
217. Hägele C, Schlagenhauf F, Rapp M, Sterzer P, Beck A, Bermpohl F, et al. Dimensional psychiatry: reward dysfunction and depressive mood across psychiatric disorders. Psychopharmacology. 2015;232(2):331-41.
218. von Rhein D, Cools R, Zwiers MP, van der Schaaf M, Franke B, Luman M, et al. Increased neural responses to reward in adolescents and young adults with attention-deficit/hyperactivity disorder and their unaffected siblings. J Am Acad Child Adolesc Psychiatry. 2015;54(5):394-402.
219. Steer RA, Clark DA, Beck AT, Ranieri WF. Common and specific dimensions of self-reported anxiety and depression: the BDI-II versus the BDI-IA. Behaviour research and therapy. 1999;37(2):183-90.
220. Haber SN, Behrens TE. The neural network underlying incentive-based learning: implications for interpreting circuit disruptions in psychiatric disorders. Neuron. 2014;83(5):1019-39.
221. Arsalidou M, Duerden EG, Taylor MJ. The centre of the brain: Topographical model of motor, cognitive, affective, and somatosensory functions of the basal ganglia. Human Brain Mapping. 2013;34(11):3031-54.
222. Mattfeld AT, Gluck MA, Stark CE. Functional specialization within the striatum along both the dorsal/ventral and anterior/posterior axes during associative learning via reward and punishment. Learning & memory (Cold Spring Harbor, NY). 2011;18(11):703-11.
223. Greven CU, Bralten J, Mennes M, O'Dwyer L, van Hulzen KJ, Rommelse N, et al. Developmentally stable whole-brain volume reductions and developmentally sensitive caudate and putamen volume alterations in those with attention-deficit/hyperactivity disorder and their unaffected siblings. JAMA psychiatry. 2015;72(5):490-9.
224. Alemany S, Jansen PR, Muetzel RL, Marques N, El Marroun H, Jaddoe VWV, et al. Common Polygenic Variations for Psychiatric Disorders and Cognition in Relation to Brain Morphology in the General Pediatric Population. J Am Acad Child Adolesc Psychiatry. 2019;58(6):600-7.
225. Alegria AA, Radua J, Rubia K. Meta-Analysis of fMRI Studies of Disruptive Behavior Disorders. Am J Psychiatry. 2016;173(11):1119-30.
226. Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci. 2000;4(6):215-22.

227. Hoogman M, Muetzel R, Guimaraes JP, Shumskaya E, Mennes M, Zwiers MP, et al. Brain Imaging of the Cortex in ADHD: A Coordinated Analysis of Large-Scale Clinical and Population-Based Samples. Am J Psychiatry. 2019;176(7):531-42.
228. Sampedro F, Farres CCI, Soler J, Elices M, Schmidt C, Corripio I, et al. Structural brain abnormalities in borderline personality disorder correlate with clinical severity and predict psychotherapy response. Brain imaging and behavior. 2021.
229. Soloff PH, Chowdury A, Diwadkar VA. Affective interference in borderline personality disorder: The lethality of suicidal behavior predicts functional brain profiles. J Affect Disord. 2019;252:253-62.
230. Soloff PH, Abraham K, Burgess A, Ramaseshan K, Chowdury A, Diwadkar VA. Impulsivity and aggression mediate regional brain responses in Borderline Personality Disorder: An fMRI study. Psychiatry Res Neuroimaging. 2017;260:76-85.
231. Niendam TA, Laird AR, Ray KL, Dean YM, Glahn DC, Carter CS. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. Cognitive, affective & behavioral neuroscience. 2012;12(2):241-68.
232. Ray RD, Zald DH. Anatomical insights into the interaction of emotion and cognition in the prefrontal cortex. Neurosci Biobehav Rev. 2012;36(1):479-501.
233. Morawetz C, Bode S, Derntl B, Heekeren HR. The effect of strategies, goals and stimulus material on the neural mechanisms of emotion regulation: A meta-analysis of fMRI studies. Neurosci Biobehav Rev. 2017;72:111-28.
234. Eickhoff SB, Laird AR, Fox PT, Bzdok D, Hensel L. Functional Segregation of the Human Dorsomedial Prefrontal Cortex. Cerebral cortex (New York, NY : 1991). 2016;26(1):304-21.
235. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci Biobehav Rev. 2011;35(3):537-55.
236. Fjell AM, Walhovd KB, Brown TT, Kuperman JM, Chung Y, Hagler DJ, Jr., et al. Multimodal imaging of the self-regulating developing brain. Proc Natl Acad Sci U S A. 2012;109(48):19620-5.
237. Bauernfeind AL, de Sousa AA, Avasthi T, Dobson SD, Raghanti MA, Lewandowski AH, et al. A volumetric comparison of the insular cortex and its subregions in primates. J Hum Evol. 2013;64(4):263-79.
238. Namkung H, Kim SH, Sawa A. The Insula: An Underestimated Brain Area in Clinical Neuroscience, Psychiatry, and Neurology. Trends in neurosciences. 2017;40(4):200-7.
239. Ruocco AC, Amirthavasagam S, Choi-Kain LW, McMain SF. Neural correlates of negative emotionality in borderline personality disorder: an activation-likelihood-estimation meta-analysis. Biol Psychiatry. 2013;73(2):153-60.
240. Ruocco AC, Carcone D. A Neurobiological Model of Borderline Personality Disorder: Systematic and Integrative Review. Harv Rev Psychiatry. 2016;24(5):311-29.
241. Schulze L, Schulze A, Renneberg B, Schmahl C, Niedtfeld I. Neural Correlates of Affective Disturbances: A Comparative Meta-analysis of Negative Affect Processing in Borderline Personality Disorder, Major Depressive Disorder, and Posttraumatic Stress Disorder. Biol Psychiatry Cogn Neurosci Neuroimaging. 2019;4(3):220-32.
242. Goodkind M, Eickhoff SB, Oathes DJ, Jiang Y, Chang A, Jones-Hagata LB, et al. Identification of a common neurobiological substrate for mental illness. JAMA psychiatry. 2015;72(4):305-15.
243. Keller J, Young CB, Kelley E, Prater K, Levitin DJ, Menon V. Trait anhedonia is associated with reduced reactivity and connectivity of mesolimbic and paralimbic reward pathways. Journal of psychiatric research. 2013;47(10):1319-28.
244. Philippi CL, Motzkin JC, Pujara MS, Koenigs M. Subclinical depression severity is associated with distinct patterns of functional connectivity for subregions of anterior cingulate cortex. Journal of psychiatric research. 2015;71:103-11.

245. Tabibnia G, Monterosso JR, Baicy K, Aron AR, Poldrack RA, Chakrapani S, et al. Different forms of self-control share a neurocognitive substrate. J Neurosci. 2011;31(13):4805-10.
246. Norman LJ, Carlisi C, Lukito S, Hart H, Mataix-Cols D, Radua J, et al. Structural and Functional Brain Abnormalities in Attention-Deficit/Hyperactivity Disorder and Obsessive-Compulsive Disorder: A Comparative Meta-analysis. JAMA psychiatry. 2016;73(8):815-25.
247. O'Donovan MC, Owen MJ. The implications of the shared genetics of psychiatric disorders. Nat Med. 2016;22(11):1214-9.
248. Brainstorm C, Anttila V, Bulik-Sullivan B, Finucane HK, Walters RK, Bras J, et al. Analysis of shared heritability in common disorders of the brain. Science (New York, NY). 2018;360(6395).
249. McTeague LM, Rosenberg BM, Lopez JW, Carreon DM, Huemer J, Jiang Y, et al. Identification of Common Neural Circuit Disruptions in Emotional Processing Across Psychiatric Disorders. Am J Psychiatry. 2020;177(5):411-21.
250. Sprooten E, Rasgon A, Goodman M, Carlin A, Leibu E, Lee WH, et al. Addressing reverse inference in psychiatric neuroimaging: Meta-analyses of task-related brain activation in common mental disorders. Hum Brain Mapp. 2017;38(4):1846-64.
251. Fernandez KC, Jazaieri H, Gross JJ. Emotion Regulation: A Transdiagnostic Perspective on a New RDoC Domain. Cognit Ther Res. 2016;40(3):426-40.
252. Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry. 2006;163(4):716-23.
253. Schmaal L, Hibar DP, Samann PG, Hall GB, Baune BT, Jahanshad N, et al. Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA Major Depressive Disorder Working Group. Molecular psychiatry. 2017;22(6):900-9.
254. Ng TH, Alloy LB, Smith DV. Meta-analysis of reward processing in major depressive disorder reveals distinct abnormalities within the reward circuit. Translational psychiatry. 2019;9(1):293.
255. Groenewold NA, Opmeer EM, de Jonge P, Aleman A, Costafreda SG. Emotional valence modulates brain functional abnormalities in depression: evidence from a meta-analysis of fMRI studies. Neurosci Biobehav Rev. 2013;37(2):152-63.
256. Zhang WN, Chang SH, Guo LY, Zhang KL, Wang J. The neural correlates of reward-related processing in major depressive disorder: a meta-analysis of functional magnetic resonance imaging studies. J Affect Disord. 2013;151(2):531-9.
257. Keren H, O'Callaghan G, Vidal-Ribas P, Buzzell GA, Brotman MA, Leibenluft E, et al. Reward Processing in Depression: A Conceptual and Meta-Analytic Review Across fMRI and EEG Studies. Am J Psychiatry. 2018;175(11):1111-20.
258. Schmaal L, Veltman DJ, van Erp TG, Samann PG, Frodl T, Jahanshad N, et al. Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. Molecular psychiatry. 2016;21(6):806-12.
259. Gorwood P. Neurobiological mechanisms of anhedonia. Dialogues in clinical neuroscience. 2008;10(3):291-9.
260. Becerra R, Campitelli G. Emotional Reactivity: Critical Analysis and Proposal of a New Scale. International Journal of Applied Psychology, . 2013;3(6):161-8.
261. Posner J, Kass E, Hulvershorn L. Using stimulants to treat ADHD-related emotional lability. Current psychiatry reports. 2014;16(10):478.
262. Moore SR, Gresham LS, Bromberg MB, Kasarkis EJ, Smith RA. A self report measure of affective lability. Journal of neurology, neurosurgery, and psychiatry. 1997;63(1):89-93.

263. Bernstein A, Zvolensky MJ, Vujanovic AA, Moos R. Integrating anxiety sensitivity, distress tolerance, and discomfort intolerance: a hierarchical model of affect sensitivity and tolerance. Behav Ther. 2009;40(3):291-301.
264. Sashin JI. Affect tolerance: A model of affect-response using catastrophe theory. Journal of Social and Biological Structures. 1985;8(2):175-202.
265. Shapero BG, Abramson LY, Alloy LB. Emotional Reactivity and Internalizing Symptoms: Moderating Role of Emotion Regulation. Cognit Ther Res. 2016;40(30):328-40.
266. Bortolla R, Cavicchioli M, Fossati A, Maffei C. Emotional Reactivity in Borderline Personality Disorder: Theoretical Considerations Based on a Meta-Analytic Review of Laboratory Studies. Journal of personality disorders. 2020;34(1):64-87.
267. Sicorello M, Herzog J, Wager TD, Ende G, Müller-Engelmann M, Herpertz SC, et al. Affective neural signatures do not distinguish women with emotion dysregulation from healthy controls: A mega-analysis across three task-based fMRI studies. 2021.
268. Rohr CS, Dreyer FR, Aderka IM, Margulies DS, Frisch S, Villringer A, et al. Individual differences in common factors of emotional traits and executive functions predict functional connectivity of the amygdala. NeuroImage. 2015;120:154-63.
269. Beauchaine TP, Zisner A. Motivation, emotion regulation, and the latent structure of psychopathology: An integrative and convergent historical perspective. International journal of psychophysiology : official journal of the International Organization of Psychophysiology. 2017;119:108-18.
270. Braunstein LM, Gross JJ, Ochsner KN. Explicit and implicit emotion regulation: a multi-level framework. Soc Cogn Affect Neurosci. 2017;12(10):1545-57.
271. Zisner A, Beauchaine TP. Neural substrates of trait impulsivity, anhedonia, and irritability: Mechanisms of heterotypic comorbidity between externalizing disorders and unipolar depression. Development and psychopathology. 2016;28(4pt1):1177-208.
272. Davies W. Sex differences in attention Deficit Hyperactivity Disorder: candidate genetic and endocrine mechanisms. Front Neuroendocrinol. 2014;35(3):331-46.
273. Mowlem FD, Rosenqvist MA, Martin J, Lichtenstein P, Asherson P, Larsson H. Sex differences in predicting ADHD clinical diagnosis and pharmacological treatment. Eur Child Adolesc Psychiatry. 2018.
274. Maughan B, Rowe R, Messer J, Goodman R, Meltzer H. Conduct disorder and oppositional defiant disorder in a national sample: developmental epidemiology. J Child Psychol Psychiatry. 2004;45(3):609-21.
275. Sansone RA, Sansone LA. Gender patterns in borderline personality disorder. Innovations in clinical neuroscience. 2011;8(5):16-20.
276. Sher L, Rutter SB, New AS, Siever LJ, Hazlett EA. Gender differences and similarities in aggression, suicidal behaviour, and psychiatric comorbidity in borderline personality disorder. Acta Psychiatr Scand. 2019;139(2):145-53.
277. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA : the journal of the American Medical Association. 2003;289(23):3095-105.
278. Lim GY, Tam WW, Lu Y, Ho CS, Zhang MW, Ho RC. Prevalence of Depression in the Community from 30 Countries between 1994 and 2014. Sci Rep. 2018;8(1):2861.
279. Christiansen D, editor Examining Sex and Gender Differences in Anxiety Disorders2015.
280. Maeng LY, Milad MR. Sex differences in anxiety disorders: Interactions between fear, stress, and gonadal hormones. Horm Behav. 2015;76:106-17.
281. McLean CP, Asnaani A, Litz BT, Hofmann SG. Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. Journal of psychiatric research. 2011;45(8):1027-35.

282. Becker JB, Chartoff E. Sex differences in neural mechanisms mediating reward and addiction. Neuropsychopharmacology. 2019;44(1):166-83.
283. Stevens JS, Hamann S. Sex differences in brain activation to emotional stimuli: a meta-analysis of neuroimaging studies. Neuropsychologia. 2012;50(7):1578-93.
284. Sacher J, Neumann J, Okon-Singer H, Gotowiec S, Villringer A. Sexual dimorphism in the human brain: evidence from neuroimaging. Magn Reson Imaging. 2013;31(3):366-75.
285. Sacher J, Okon-Singer H, Villringer A. Evidence from neuroimaging for the role of the menstrual cycle in the interplay of emotion and cognition. Front Hum Neurosci. 2013;7:374.
286. Corrigan FM, Fisher JJ, Nutt DJ. Autonomic dysregulation and the Window of Tolerance model of the effects of complex emotional trauma. Journal of psychopharmacology (Oxford, England). 2011;25(1):17-25.
287. Krause-Utz A, Erol E, Brousianou AV, Cackowski S, Paret C, Ende G, et al. Self-reported impulsivity in women with borderline personality disorder: the role of childhood maltreatment severity and emotion regulation difficulties. Borderline personality disorder and emotion dysregulation. 2019;6:6.
288. Casey BJ, Jones RM, Levita L, Libby V, Pattwell SS, Ruberry EJ, et al. The storm and stress of adolescence: insights from human imaging and mouse genetics. Developmental psychobiology. 2010;52(3):225-35.
289. Beauchaine TP, Hinshaw SP. RDoC and Psychopathology among Youth: Misplaced Assumptions and an Agenda for Future Research. J Clin Child Adolesc Psychol. 2020;49(3):322-40.
290. Beauchaine TP, Constantino JN. Redefining the endophenotype concept to accommodate transdiagnostic vulnerabilities and etiological complexity. Biomarkers in medicine. 2017;11(9):769-80.
291. Yule K, Houston J, Grych J. Resilience in Children Exposed to Violence: A Meta-analysis of Protective Factors Across Ecological Contexts. Clin Child Fam Psychol Rev. 2019;22(3):406-31.
292. Darling Rasmussen P, Storebo OJ, Lokkeholt T, Voss LG, Shmueli-Goetz Y, Bojesen AB, et al. Attachment as a Core Feature of Resilience: A Systematic Review and Meta-Analysis. Psychol Rep. 2019;122(4):1259-96.