Biological Substrates of Waiting Impulsivity in Children and Adolescents with and without ADHD

Biologische Substrate der Warte-Impulsivität bei Kindern und Jugendlichen mit und ohne ADHS

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Abbreviations

ACC	Anterior Cingulate Cortex
Acc	Accuracy
ADHD	Attention-Deficit/Hyperactivity Disorder
AMY	Amygdala
ANOVA	Analysis of Variance
CBCL	Child Behavior Checklist
dlPFC	Dorsolateral Prefrontal Cortex
DSM-V	5th Diagnostic and Statistical Manual of Mental Disorders
FDR	False Discovery Rate
fMRI	Functional Magnetic Resonance Imaging
H/I	Hyperactivity/Impulsivity
HC	Hippocampus
IA	Inattention
IFG	Inferior Frontal Gyrus
MANCOVA	Multiple Analysis of Covariance
MFG	Middle Frontal Gyrus
Mot_Ind	Motivation Index
NAcc	Nucleus Accumbens
PCR	Polymerase Chain Reaction
PFC	Prefrontal Cortex
PR	Premature Responses
RDoC	Research Domain Criteria
RT	Reaction Time
RT_rew	Reaction Time during Rewarded Trials
RTV	Reaction Time Variability
sMRI	Structural Magnetic Resonance Imaging
SNP	Single Nucleotide Polymorphism
TDC	Typically Developing Control Subjects
TPH2	Tryptophan Hydroxylase 2
vlPFC	Ventrolateral Prefrontal Cortex
vmPFC	Ventromedial Prefrontal Cortex

SUMMARY

Focus of the present work were the questions whether and how the concept of waiting impulsivity (WI), defined as the ability to regulate a response in anticipation of reward and measured by the 4-choice serial reaction time task (4-CSRTT), may contribute to our understanding of Attention-Deficit/Hyperactivity Disorder (ADHD) and its neurobiological underpinnings.

To address this topic, two studies were conducted: in a first study, the relationship between 4-CSRTT behavioral measures, neural correlates and ADHD symptom domains, i.e. *inattention* (IA) and *hyperactivity/impulsivity* (H/I) was explored in a pooled sample of 90 children and adolescents with (*n*=44) and without (*n*=46) ADHD diagnosis. As expected, IA was associated with dorsolateral prefrontal brain regions linked with executive functions and attentional control, which was evident on the structural and the functional level. Higher levels of both IA and H/I covaried with decreased activity in the right ventrolateral prefrontal cortex (PFC), a central structure for response inhibition. Moderation analyses revealed that H/I-related decreased activation in this region did not map linearly on difficulties on the behavioral level: brain activation was a significant predictor of task accuracy only, when H/I symptoms were low/absent but not for clinically relevant ADHD symptoms. Further, H/I was implicated in dysfunctional top-down control of reward evaluation. Both symptom domains correlated positively with hippocampus (HC) activity in anticipation of reward. In addition, for high H/I symptoms, greater activation in the HC was found to correlate with higher motivation on the behavioral level, indicating that reinforcement-learning and/or contingency awareness may contribute to altered reward processing in ADHD patients.

In a second study, the possible serotonergic modulation of WI and the ADHD-WI relationship was addressed in a sub-sample comprising 86 children and adolescents of study I. The effects of a functional variant in the gene coding for the rate-limiting enzyme in the

synthesis of brain serotonin on behavior and structure or function of the WI-network was investigated. Moderation analyses revealed that on the behavioral level, a negative correlation between accuracy and IA was found only in GG-homozygotes, whereas no significant relationship emerged for carriers of the T-allele. This is in line with previous reports of differential effects of serotonergic modulation on attentional performance depending on the presence of ADHD symptoms. A trend-wise interaction effect of genotype and IA for regional volume of the right middle frontal gyrus was interpreted as a hint towards an involvement of the PFC in this relationship, although a more complex mechanism including developmental effects can be assumed. In addition, interaction effects of genotype and IA were found for brain activation in the amygdala (AMY) und HC during performance of the 4-CSRTT, while another interaction was found for H/I symptoms and genotype for right AMY volume. These findings indicate a serotonergic modulation of coding of the emotional value of reward during performance of the 4-CSRTT that varies depending on the extent of psychopathology-associated traits.

Taken together, it was shown that the 4-CSRTT taps distinct domains of impulsivity with relevance to ADHD symptomatology: (proactive) response inhibition difficulties in relation with anticipation of reward. Furthermore, the two symptom domains, IA and H/I, contribute differently to WI, which emphasizes the need to distinguish both in the research of ADHD. The results of study II emphasized the relevance of serotonergic transmission especially for attentional control and emotional processing. Although the present findings need replication and further refinement in more homogenous age groups, the use of the 4-CSRTT with a dimensional approach is a very promising strategy, which will hopefully extend our understanding of impulsivity-related mental disorders in the future.

ZUSAMMENFASSUNG

Im Mittelpunkt der vorliegenden Arbeit steht das Konzept der Warte-Impulsivität (WI), definiert als die Fähigkeit der Antwort-Inhibition, während eine Belohnung erwartet wird, welche mittels des 4-choice serial reaction time task (4-CSRTT) erfasst werden kann. Es sollte untersucht werden ob und auf welche Weise WI und der 4-CSRTT genutzt werden können, um die neurobiologischen Grundlagen der Aufmerksamkeits-Defizit/Hyperaktivitäts-Störung (ADHS) besser zu verstehen.

Es wurden zwei Studien durchgeführt: In einer ersten Studie wurde der Zusammenhang zwischen 4-CSRTT Verhaltensmaßen, ihren neuronalen Korrelaten und den ADHS Kern-Symptomen, *Unaufmerksamkeit* (IA) und *Hyperaktivität/Impulsivität* (H/I), überprüft. Es wurden 90 Kinder und Jugendliche mit (*n*=44) und ohne (*n*=46) ADHS-Diagnose untersucht. Erwartungsgemäß war IA, auf funktioneller und struktureller Ebene, mit dorsolateralen präfrontalen Hirnregionen assoziiert, die für Exekutivfunktionen und die Aufmerksamkeitskontrolle zuständig sind. Stärkere Ausprägungen von IA und H/I gingen mit verringerter Aktivität im rechten ventrolateralen präfrontalen Cortex (PFC), einer zentralen Struktur für die Inhibition von Antworten, einher. Moderationsanalysen ergaben, dass diese H/I-assoziierte geringere Aktivität nicht direkt mit Einschränkungen auf Verhaltensebene zusammenhing: Die Hirnaktivierung war nur in Abwesenheit von H/I Symptomen ein signifikanter Prädiktor der Sorgfaltsleistung, was bei stärkerer ADHS-Symptomatik nicht der Fall war. Darüber hinaus wiesen die Ergebnisse auf einen Zusammenhang zwischen H/I und dysfunktionaler Belohnungsverarbeitung hin. Beide Symptombereiche korrelierten während der Belohnungserwartung positiv mit Aktivität im Hippocampus (HC). Zusätzlich zeigte sich, dass bei stark ausgeprägten H/I-Symptomen eine höhere HC-Aktivierung mit höherer Motivation auf Verhaltensebene einher ging. Dies deutet darauf hin, dass Lernprozesse und ein Bewusstsein für Kontingenz bei der Verarbeitung von Belohnungen bei ADHS eine Rolle spielen könnten.

In einer zweiten Studie wurde eine mögliche serotonerge Modulation von WI und dem WI-ADHS Zusammenhang betrachtet. Eine Teilstichprobe von 86 Probanden aus Studie I wurde untersucht. Eine funktionelle Genvariante des Enzyms, welches den entscheidenden Schritt in der Serotonin-Synthese im Gehirn katalysiert, wurde bezüglich seiner Effekte auf WI-Verhalten sowie Struktur und Funktion des WI-Netzwerks getestet. Moderationsanalysen zeigten, dass auf Verhaltensebene eine negative Korrelation zwischen IA und der Sorgfaltsleistung bei GG-Homozygoten, aber kein signifikanter Zusammenhang für Träger des T-Allels bestand. Unterschiedliche Effekte von serotonerger Modulation auf die Aufmerksamkeitsleistung in Abhängigkeit von ADHS-Symptomatik wurden bereits in der Literatur berichtet. Ein Trend-Effekt für die Interaktion zwischen Genotyp und IA und dem Volumen des rechten Gyrus frontalis medius wurde als Hinweis auf eine Beteiligung des PFC in diesem Zusammenhang interpretiert. Auf Grund möglicher Entwicklungseffekte, ist aber ein komplexeres Zusammenspiel der verschiedenen Faktoren anzunehmen. Interaktionseffekte von Genotyp und IA für Aktivität der Amygdala (AMY) und dem HC sowie für H/I und Genotyp bezüglich des Volumens der rechten AMY könnten auf eine serotonerge Modulation der emotionalen Bewertung von Belohnung hindeuten, die je nach ADHS-Symptomatik unterschiedlich ausfällt.

Zusammenfassend zeigte sich, dass mittels des 4-CSRTT ADHS-relevante Aspekte von Impulsivität untersucht werden können: Schwierigkeiten der Antwortinhibition im Kontext von Belohnungserwartung. Sowohl IA als auch H/I hatten unterschiedlichen Einfluss auf WI. Sie sollten in der ADHS-Forschung differenziert betrachtet werden. Die Ergebnisse der zweiten Studie verdeutlichen, dass die serotonerge Transmission bei ADHS besonders bei Aufmerksamkeitsprozessen und emotionaler Verarbeitung eine Rolle spielt. Die vorliegenden Befunde sollten in homogeneren Alterskohorten überprüft werden. Sie machen jedoch Hoffnung, dass mittels des 4-CSRTT und dimensionaler Forschungsansätze psychiatrische Störungen der Impulskontrolle besser verstanden werden können.

I. INTRODUCTION

1.1 Attention-Deficit/Hyperactivity Disorder

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common neuropsychiatric disorders observed in childhood and adolescence (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014). Its phenotypical manifestation is very heterogeneous depending on the extent of two key symptom dimensions: developmentally inappropriate levels of *inattention* (IA) and/or *hyperactivity/impulsivity* (H/I) that have repeatedly been shown to be distinct factors within the disorder (Willcutt et al., 2012). The clinical picture is further complicated by high rates of co-morbid psychopathologies such as oppositional defiant, conduct, substance use or mood disorders (Spencer, Biederman, & Mick, 2007). ADHD also affects adults (estimated prevalence: 2.5%) and persists through the lifespan (Faraone, Biederman, & Mick, 2006; Simon, Czobor, Balint, Meszaros, & Bitter, 2009). Despite a partial remission of symptoms (mainly H/I) in adulthood, ADHD adversely impacts e.g. academic or professional performance (Biederman & Faraone, 2006; Biederman et al., 2004) and reduces overall health-related quality of life (Danckaerts et al., 2010).

A high heritability of ADHD (over 70%) is documented in twin, adoption and other family studies, with a polygenic inheritance pattern, where each risk variant is assumed to have a small effect on the susceptibility to the disease (Faraone et al., 2005). It was shown that the two main symptom dimensions, IA and H/I, share a considerable amount of genetic components, while there are also domain-specific genetic influences (Kuntsi et al., 2014). Identification of specific genes that determine ADHD diagnosis has appeared to be challenging. Beyond the complex genetic background, environmental or psychosocial factors (e.g. maternal smoking during pregnancy or deprivation) as well as gene x environment interactions (reviewed by T. D. Banerjee, Middleton, & Faraone, 2007) complete the

multifactorial aetiology of ADHD and are assumed to further account for the heterogeneity in the disorder.

Concerning the pathophysiology, this heterogeneity is observed not only in terms of variable psychopathology on the behavioral, but also on the cognitive level. Deficits in a variety of neuropsychological domains such as executive functions (e.g. inhibitory control, working memory), temporal processing, decision making and response variability, just as problems with emotional regulation or delay aversion in anticipation of reward, have been identified (Sjowall, Roth, Lindqvist, & Thorell, 2013; Sonuga-Barke, Bitsakou, & Thompson, 2010). Notably, none of the reported deficits is present in all subjects with ADHD and there are also patients that do not show impairment on any of the mentioned cognitive domains (Coghill, Seth, & Matthews, 2014).

Despite the diverse aetiology and pathophysiology, ADHD is still considered a categorical diagnosis, i.e. it is treated as if it represents a homogenous syndrome. In the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) by the American Psychiatric Association, the diagnosis is operationalized by means of 18 symptom criteria (see table 1). They include nine symptoms of IA, six symptoms of hyperactivity and three symptoms of impulsivity, which are combined to the H/I domain (American Psychiatric Association, 2013). The diagnostic process is based on taking the case's history and thorough assessment of presence and quality of symptoms via diagnostic interviews with parents and patients as well as via rating scales. Other features such as assessment of neuropsychological deficits are not mandatory. The DSM-V delineates three categorical presentations: a predominantly inattentive (ADHD-I, at least six criteria on the IA domain fulfilled), a predominantly hyperactive/impulsive (ADHD-HI, at least six criteria on the H/I domain fulfilled) and a combined type of ADHD (ADHD-C, at least six criteria on both domains fulfilled), aimed to capture sub-forms of the disorder that differ in quality and severity of symptoms (Fair, Nigg, et al., 2012; Nikolas & Nigg, 2013).

Table 1: DSM-V criteria for ADHD (abbreviated).

Inattention	**Hyperactivity/Impulsivity**
a) Failure to give close attention	a) Fidgeting/squirming
b) Difficulty of sustained attention	b) Leaving one's seat
c) Not listening	c) Excessive running/climbing
d) Failure to finish tasks	d) Difficulty of quiet play
e) Organizational difficulties	e) Restlessness/appearing "on the go"
f) Dislike/avoidance of tasks of mental effort	f) Excessive talking
g) Loss of necessary things	g) Blurting out answers
h) Increased distractibility	h) Difficulty awaiting turn
i) Forgetfulness	i) Interruption/intrusion on others

In the last decades, a huge amount of research has been conducted trying to unravel the neurobiological underpinnings of this impairing disorder. Yet, results have been mixed concerning its causes and nature (Nigg, 2013). Most of the existing ADHD literature is based on case-control designs. Categorical diagnoses are still indispensable to identify those, who need assistance and/or treatment, but there is increasing consensus, that dimensional research approaches are better suited to identify the complex neurobiology of heterogeneous psychopathologies (Coghill & Sonuga-Barke, 2012). Special emphasis has been placed on dimensional behavioral and biological phenotypes that underlie multiple overlapping disorders as suggested by the research domain criteria (RDoC) initiative (Insel et al., 2010). The initiative was launched aiming to unite neuroscientific research and clinical applicability for mental disorders by investigating the range of behavior and related neural/biological correlates from normal to clinically relevant, instead of dichotomizing it in "healthy" vs "diagnosis" (Cuthbert & Insel, 2013). Evidence that this approach is especially valid for ADHD comes from genetic (Larsson, Anckarsater, Rastam, Chang,

& Lichtenstein, 2012), brain structural (Shaw et al., 2011) or functional studies (Fair, Bathula, Nikolas, & Nigg, 2012). It supports the notion that what is termed 'ADHD' is at the extreme end of dimensional variation in IA and/or H/I that is based on genetic and environmental influences. For this kind of research, it is necessary to use tasks that elicit behavioral or cognitive processes that are "associated with discrete deficits in defined neural systems" (Robbins, Gillan, Smith, de Wit, & Ersche, 2012).

Trait impulsivity is a very suitable example in this context: it is of diagnostic relevance for ADHD (and for other psychiatric disorders) and has also been characterized as "neurocognitive endophenotype" in terms of specific cognitive processes related to distinct dysfunction in neural systems (Beauchaine, Zisner, & Sauder, 2017). Furthermore, it is a dimensional personality trait covering a continuum from adaptive forms, e.g. in situations where rapid decision making is beneficial (Burnett Heyes et al., 2012), to more excessive presentations related to psychiatric disorders (Dalley & Robbins, 2017; Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001). Although impulsive behavior can be broadly defined as acting 'on a whim' and without deliberation, it is a multifaceted construct that contains several different sub-forms (Evenden, 1999). These are sometimes related but also appear to have distinct neural substrates (Dalley, Everitt, & Robbins, 2011).

The focus of the present work is a specific form of impulsivity, i.e. waiting impulsivity (WI), which can be assessed via the 4-choice serial reaction time task (4-CSRTT), a visuospatial test of impulsive action and sustained attention mediated by motivational aspects (Voon et al., 2014). Its behavioral measures, an associated functional neural network and their modulation by serotonin have been well characterized in animals (animal version 5-CSRTT: Robbins, 2002) and were confirmed by functional magnetic resonance imaging (fMRI) in humans (Neufang et al., 2016). The behavioral parameters overlap with cognitive domains that have been implicated in the pathophysiology of ADHD, while abnormalities in structure and function of the regions comprised in the WI-network have also been

associated with the disorder. Evidence from tryptophan depletion and genetic studies implicates an influence of serotonin in the aetiology of ADHD. However, the relationship between WI behavioral measures, neural function and the IA and H/I symptoms used to determine diagnosis in the clinic as well as the contribution of serotonergic genetic variants to this relationship, has not been examined yet.

1.2 Objectives and organization of the thesis

The overall objective of this thesis is to address whether and how WI as measured by the 4-CSRTT may contribute to our understanding of ADHD and its neurobiological underpinnings. To do so, the biological substrates of WI are investigated regarding their relevance to the phenotype of ADHD in children and adolescents. Using different levels of analysis, i.e. behavioral, neural, genetic, it is aimed to better account for the complexity of the disorder. Instead of comparing diagnostic groups, dimensional analyses of the two symptom domains, IA and H/I, are carried out in a pooled sample of ADHD patients and typically developing control subjects (TDC). Two studies are presented: study I focuses on the relationship between 4-CSRTT behavioral measures, neural correlates and ADHD phenotypes. In study II, serotonergic modulation of WI on the behavioral level as well as on structure and function of the WI-network is addressed. Importantly, the interaction of genetic variation and ADHD symptoms on these measures is considered as well.

1.3 Introduction to study I

1.3.1 Behavioral and neural correlates of WI in general

In the 4-CSRTT, WI is operationalized via the tendency to premature responding. It requires the capacity to postpone a response to a reward-related cue, while anticipating reinforcement. Thus, it combines the need for (motor) response inhibition (selecting the appropriate response to the target) with (decisional) reflection impulsivity (tendency to

rapid decision making without enough contextual information) in the context of reward (Dalley & Robbins, 2017). At the beginning of a trial, subjects are presented with 4 choices on a screen (cue). After a certain waiting period (cue-target interval), a target appears in one of the choices and the subject is instructed to respond as fast as possible to the target in order to earn monetary reward. The magnitude of the rewarded outcome is dependent on the individual mean reaction time (M_{RT}). Main behavioral outcome is 'the number of premature responses' (PR), thus any response before onset of the target, which is thought to reflect WI as failure of inhibitory motor processes in combination with impulsive choice or delay aversion in the context of reward. While 'accuracy' (Acc), i.e. the amount of correct responses within the average RT window, is related to attentional performance, the speeding and variability of responses can be assessed as RT on rewarded trials (RT_rew) and RT variability (RTV). A 'motivation index' (Mot_Ind) measures sensitivity to reinforcement by assessing differences in RT while responding to the target without reward feedback, once before and once after the target has been conditioned to the reward (Voon, 2014).

Based on converging evidence from animal studies as well as from fMRI data in humans, a neural network concerning WI has been established: it includes frontal regions such as the ventromedial and dorsolateral prefrontal cortex (vmPFC, dlPFC) and the anterior cingulate cortex (ACC), which are interacting with the mediotemporal structures hippocampus (HC) and amygdala (AMY), as well as with the nucleus accumbens (NAcc) (Dalley et al. 2011; Neufang et al. 2016). In the first task-based fMRI study on WI in humans, dlPFC and vmPFC activation was especially related to processing of the 'target' and during reward receipt, most probably reflecting increasing top-down control demands over the course of the waiting period as well as the need for action selection in the presence of reward (Neufang et al., 2016). Frontal regions, such as the dlPFC and ACC are crucial structures in the neural networks that enable and maintain goal-directed behavior (Buschman & Miller, 2014; Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008).

Furthermore, the ACC has been implicated in reward-guided learning and decision making by integrating error and performance information (Fassbender et al., 2004; Rushworth, Noonan, Boorman, Walton, & Behrens, 2011; Wallis & Kennerley, 2011). In decision making contexts, the vmPFC (together with the NAcc) has been attributed to be responsible for coding of reward value (Levy & Glimcher, 2012; Liu, Hairston, Schrier, & Fan, 2011) and to impulsive preference for immediate rewards (McClure, Ericson, Laibson, Loewenstein, & Cohen, 2007; McClure, Laibson, Loewenstein, & Cohen, 2004). The NAcc, key structure of the ventral striatum, is a central component implicated in impulsive behavior and reward processing (reviewed by Basar et al., 2010). Many studies have shown that the ventral striatum is commonly activated in anticipation of reward (e.g. Knutson, Adams, Fong, & Hommer, 2001; Zink, Pagnoni, Martin-Skurski, Chappelow, & Berns, 2004). In addition, the magnitude of response in this structure towards monetary reward feedback has been found to correlate positively with individual delay discounting functions (Hariri et al., 2006). Furthermore, effective connectivity analyses showed that during WI processing, excitatory modulatory input emerging from the NAcc on vmPFC was highest during receipt of reward, whereas inhibitory modulation by the vmPFC on the NAcc was highest before target presentation (Neufang et al., 2016). So, the interplay of top-down influence by the vmPFC and reward coding in the NAcc is important for behavioral performance on the 4-CSRTT. Finally, mediotemporal regions such as HC and AMY are implicated in decisional forms of impulsivity in terms of their involvement in prospection of future outcomes and coding of emotional value of immediate reinforcement (Peters & Buchel, 2011). In summary, the WI-network comprises inhibition-related frontal regions such as the vmPFC, dlPFC and ACC, which are interacting with HC and AMY, as well as with the NAcc that are associated with reward-related learning and behavior.

1.3.2 Relevance of WI for ADHD

Recent studies already linked WI with impulse control disorders such as substance use disorders (Morris et al., 2016; Voon et al., 2014) and one study reported that the number of PR was a significant predictor of ADHD diagnosis in a case-control comparison (Van Dessel, Morsink, et al., 2019). Premature responding furthermore correlated with parent-reported symptoms of IA and H/I as well as of oppositional defiant and conduct disorder and self-reported delay aversion in the ADHD group (Van Dessel, Morsink, et al., 2019). Concerning cognitive domains covered by the 4-CSRTT, patients have been found to show impairments in e.g. response inhibition, which has been interpreted to reflect a general deficit of executive functions. This has been proposed to be responsible for both the symptoms of IA as well as of impulsivity on the behavioral level (Barkley, 1997). Others have argued that impulsive behavior in ADHD is explained by a strong aversion of delay of reward reinforcement (Sagvolden, Aase, Zeiner, & Berger, 1998; Sagvolden, Johansen, Aase, & Russell, 2005). Finally, both accounts were combined in the "dual pathway model" of ADHD: it was proposed that the executive functions deficits were based on dysregulation of dorsal frontostriatal circuits, while aberrations in the interaction of more ventral frontal regions with striatal reward processing structures (e.g. NAcc) would lead to delay aversion. But both mechanisms would ultimately result in the IA and H/I symptoms characterizing ADHD (Sonuga-Barke, 2003). As mentioned before, IA and H/I are regarded as distinct (also genetically determined, Kuntsi et al., 2014), yet substantially correlated dimensions within the disorder that are also used to describe ADHD-I, ADHD-HI and ADHD-C presentations (Willcutt et al., 2012). Scores of both IA and H/I have been found to correlate negatively with e.g. response inhibition (reflected by longer and more variable RTs) and delay aversion (reflected by steeper temporal discounting rates) (Crosbie et al., 2013; Willcutt et al., 2012). Elevated levels of both IA and H/I, i.e. in patients with ADHD-C, are related to even greater impairments on response inhibition and variability than in ADHD-I

(Willcutt et al., 2012). Furthermore, increased H/I symptoms were associated with greater temporal discounting of rewards in subclinical (Scheres, Lee, & Sumiya, 2008) and clinical populations (Scheres, Tontsch, Thoeny, & Kaczkurkin, 2010).

On the neural level, ADHD patients have been linked to aberrations in structures that were also highlighted in the WI-network. An overall lag of cortical maturation, especially in prefrontal regions, as found by Shaw et al. (2007) was recently extended to subcortical structures, as a mega-analysis by Hoogman et al. (2017) also reported delayed maturation in e.g. NAcc, HC and AMY. In addition to that, structural MRI (sMRI) studies reported negative correlations between H/I symptoms and regional volume of the ventral striatum as well as of the right AMY (Carmona et al., 2009; Frodl et al., 2010). Interestingly, greater AMY volumes were related with lower levels of IA (Frodl et al., 2010), which again highlights the distinctive nature of the two symptom domains. Furthermore, associations between ADHD-I and pathways relevant for goal-directed attention as well as between ADHC-C and ADHD-HI and reward- and impulse control associated circuits have been reported: Meta-analyses of task based fMRI studies reported decreased activation in e.g. right inferior frontal gyrus (IFG), ACC, and basal ganglia during response inhibition and in the dorsal attention network, including dlPFC and dorsal striatum, during attention tasks (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; Rubia, Alegria, & Brinson, 2014). Furthermore, ADHD-I has been linked to aberrant activity in attentional and working memory related prefrontal regions (Orinstein & Stevens, 2014; Solanto, Schulz, Fan, Tang, & Newcorn, 2009), while symptoms of IA were negatively associated with activity in several regions implicated in executive control (e.g. vmPFC, dlPFC, NAcc) during performance of an attentionally demanding task (Depue et al., 2010). Concerning reward processing, adult ADHD-C patients showed weakened orbitofrontal/vmPFC activation when responding to reward feedback, while ADHD-I showed weaker activation in the ventral striatum during reward anticipation (Edel et al., 2013). Conversely, others have found enhanced activity

in the orbitofrontal cortex/vmPFC to covary with higher levels of H/I symptoms in anticipation of high magnitude rewards in an adolescent sample of ADHD patients (Tegelbeckers et al., 2018). Interestingly, in the ventral striatum (incl. NAcc) contrasting findings have been found for patient and control samples: ADHD patients showed ventral striatal hyporesponsiveness in anticipation of reward, while the opposite relationship was found in healthy subjects (meta-analysis by Plichta & Scheres, 2014).

1.4 Introduction to study II

1.4.1 Serotonergic modulation of WI

The WI-network has been described to be modulated by several neurotransmitter systems. Highlighted are the influence of midbrain dopaminergic neurons, of noradrenergic neurons and of serotonergic neurons originating in the raphe nuclei (Dalley et al., 2011). Although a large body of research has focused on the role of dopamine in the context of impulsivity (see e.g. review by Dalley & Roiser, 2012), relevant for the current work will be the influence of serotonin.

Reductions of serotonergic transmission have been related to increased impulsive behavior. For example, acute tryptophan depletion, a procedure that is thought to reduce central serotonin transmission by consumption of an amino acid cocktail that is lacking the serotonin-precursor tryptophan (Carpenter et al., 1998), has been associated with increased impulsive responding (Walderhaug, Herman, Magnusson, Morgan, & Landro, 2010; Walderhaug et al., 2002), impairments in action restraint (go/no-go) (Eagle, Bari, & Robbins, 2008; Evers et al., 2006) or delay discounting (Schweighofer et al., 2008). Studies on stopping impulsivity in healthy subjects reported no effect of acute tryptophan depletion (Clark et al., 2005; Cools et al., 2005), while others found impairments in action cancellation in subjects with a family history of impulse control disorders (Crean, Richards, & de Wit, 2002). On the neural level, it was shown that after tryptophan depletion, activity

in regions of inhibitory control (e.g. IFG that corresponds to ventrolateral prefrontal cortex, vlPFC) was diminished during performance of go/no-go (Rubia et al., 2005) and interference control tasks (Lamar et al., 2009). One study also examined the effect of the procedure on behavioral measures of the 4-CSRTT: Worbe and colleagues found that in healthy volunteers, tryptophan depletion promoted premature responding, while Acc and Mot_Ind increased, but did not account for differences in impulsive choice as measured by a reward delay-discounting questionnaire (Worbe, Savulich, Voon, Fernandez-Egea, & Robbins, 2014). Serotonergic modulation of impulsivity has also been studied by investigating polymorphisms of the gene coding for tryptophan hydroxylase 2 (*TPH2*). TPH2 is the rate-limiting enzyme in the synthesis of neuronal serotonin (Walther & Bader, 2003), specifically expressed in the raphe nuclei and therewith exclusively responsible for the synthesis of brain serotonin (Gutknecht, Kriegebaum, Waider, Schmitt, & Lesch, 2009). Variants of this gene related to reduced TPH2 function were associated with impaired response inhibition on the stop signal task (Stoltenberg et al., 2006), greater impulsivity on questionnaire-based measures (Oades et al., 2008; Stoltenberg, Christ, & Highland, 2012) and altered probabilistic decision making (Juhasz et al., 2010). Others identified *TPH2* gene variants that significantly explained variance in the regional rate of serotonin synthesis in the vmPFC, which further supports the relevance of this gene for impulse control (Booij et al., 2012).

A commonly investigated single nucleotide polymorphism (SNP) is a G/T substitution in the regulatory promotor region of *TPH2,* which is also noted as *G-703T* (rs4570625). The rare variant is the T-allele that has been shown to alter transcription of *TPH2 in vitro*, which is hypothesized to correspond with lower central serotonin levels, although this was not yet shown *in vivo* (G. L. Chen, Vallender, & Miller, 2008; Lin et al., 2007; but see also Scheuch et al., 2007). Carriers of the T-allele have been associated with impairments in executive control in tasks of goal-directed attention (Enge, Fleischhauer, Lesch, Reif, &

Strobel, 2014; Osinsky et al., 2009; Reuter, Ott, Vaitl, & Hennig, 2007; Strobel et al., 2007). Another study reported reduced no-go anteriorization during response inhibition in GG-homozygotes, which was assumed to reflect diminished prefrontal brain function, while no behavioral differences compared to carriers of the T-allele were found (Baehne et al., 2009). In the context of WI, an interaction effect of the number of PR and the *TPH2 G-703T* variant emerged: high impulsive T-allele carriers exhibited reduced top-down control in the vmPFC before onset of the target, while activity in the NAcc in anticipation of monetary reward was enhanced (Neufang et al., 2016).A recently published study on Estonian birth cohorts found TT-homozygotes to be associated with an “Insatiability by Reward” factor (Pulver, Kiive, & Harro, 2020). This hints towards an association of impaired impulse control and a heightened sensitivity to reward with the T-allele. Thus, findings from tryptophan depletion as well as from genetic studies on *TPH2* variants in the context of executive/impulse control and reward-related processing, emphasize the relevance of serotonergic modulation of impulsivity and WI in specific.

1.4.2 ADHD and serotonin

Due to the beneficial effects of the substances approved for treatment of ADHD, i.e. dopamine- and nor-epinephrine reuptake inhibitors, aberrations in catecholaminergic transmission haven been implicated to be at the core of the disorder (del Campo, Chamberlain, Sahakian, & Robbins, 2011), but others also argue for an involvement of serotonin (E. Banerjee & Nandagopal, 2015). ADHD candidate gene studies yielded significant results for genes involved in serotonergic transmission (Gizer, Ficks, & Waldman, 2009) and some identified variants that contributed significantly to H/I components but not to symptoms of IA (Bralten et al., 2013; Gizer et al., 2009) and vice versa (Smoller et al., 2006). Studies using tryptophan depletion reported increases in lapses of attention and lower Acc in ADHD patients following the procedure (Mette et al., 2013; Zepf et al., 2010) but also described beneficial effects on functional connectivity of the default mode network and

areas responsible for motor planning behavior (Biskup et al., 2016). Concerning impulsivity, tryptophan depletion was shown to modulate response inhibition depending on the level of aggression in children with ADHD (Zepf et al., 2008). Among other variants, several genetic studies have linked variants of *TPH2* to the disorder (Brookes et al., 2006; Sheehan et al., 2005), although replication has appeared difficult (Sheehan, Hawi, Gill, & Kent, 2007). Preferential allele transmission of the *TPH2 G-703T* polymorphism was identified in a family-based association study on ADHD (Walitza et al., 2005). This study found a more frequent transmission of the G-allele to children, who had a diagnosis of ADHD. In a study of adult ADHD, differences in prefrontal function in GG-homozygotes versus T-allele carriers during response inhibition was similar in both patients and controls (Baehne et al., 2009). At the same time, case-control differences on the behavioral level were confirmed in the GG-group only, while no main effect of genotype emerged. Additionally, a candidate gene association study also identified *TPH2* variants that were associated with ADHD but did not replicated the findings for *TPH2 G-703T* by Walitza et al. (Brookes et al., 2006). The latest large GWAS meta-analysis did not report a significant association for *TPH2* with ADHD (Demontis et al., 2019). However, given the already outlined difficulty with case-control designs in heterogenous disorders such as ADHD and the anticipated small effect sizes of single candidate genes on the genome-wide level, this does not rule out the possibility that variation in this gene does contribute to the clinical picture of the disorder. Due to the reasonable associations of *TPH2* variants with neuropsychological and cognitive substrates of ADHD (e.g. response inhibition, top-down control, emotional/reward processing) it remains a relevant locus to investigate in the context of the disorder.

1.5 Aims and hypotheses

STUDY I: ***What are the behavioral and neural correlates of WI in the context of ADHD symptomatology and how do they interact?***

Based on introduced studies that IA and H/I are distinct yet correlated factors within the disorder, shared and differential manifestations of IA and H/I phenotypes were expected.

1) Behavioral correlates

- attention-related parameters, e.g. Acc covary with symptoms of IA
- inhibition- and reward-related parameters (i.e. number of PR, Mot_Ind) covary with H/I

2) Neural correlates

Brain structure

- negative association between volumes of NAcc, AMY and HC with H/I
- negative association of PFC structure with both symptom dimensions

Brain activation

- IA associated with impairments in regions of cognitive control (e.g. dlPFC)
- H/I reflected by atypical reward processing e.g. the ventral striatum (i.e. NAcc) and by reduced top-down control in the vmPFC in anticipation of reward

Because of the heterogeneity of reported findings in TDC and patient groups on reward anticipation, the direction of expected effects concerning NAcc activation was not defined *a priori*.

3) Moderation analyses: interaction of neural correlates and IA or H/I

- differential activation in attentional control regions depending on IA symptoms can explain variance in attention-related behavioral parameters of the 4-CSRTT
- differences in reward processing depending on H/I are associated with impulsivity- and motivation-related measures

STUDY II: ***Is the ADHD-WI relationship moderated by variation in the TPH2 gene?***

Analyses regarding a possible serotonergic modulation, operationalized via variation in the *TPH2 G-703T* polymorphism, were exploratory due to contrasting findings in healthy samples and ADHD patients. In healthy participants, tryptophan depletion as well as T-allele carrier status were associated with enhanced premature responding and impairments of executive control on the behavioral level as well as with aberrant top-down control and reward processing on the neural level. By contrast, in the context of ADHD, homozygosity for the G-allele has been identified as the 'risk constellation'. So, a main effect of genotype was difficult to predict in a combined sample of healthy subjects and ADHD patients. To further explore the relationship between *TPH2 G-703T* genotype, the phenotype of ADHD and WI, moderation analyses were performed to test whether the interaction of *TPH2 G-703T* and IA or H/I would resolve this issue regarding behavioral and neural substrates of the 4-CSRTT.

II. STUDY-OVERLAPPING METHODS

2.1 Participants/Clinical assessment

In total 102 children and adolescents aged 8 to 18 years participated in the project. 46 subjects (5 females) fulfilled diagnostic criteria for ADHD according to DSM-V (American Psychiatric Association, 2013). Patients were recruited from the inpatient and outpatient clinics of the Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy at the University Hospital Würzburg, Germany via the consortium ESCAlife (evidence-based stepped care of ADHD across the life span), funded by the German Federal Ministry of Education and Research (Döpfner et al., 2017; Geissler et al., 2018). A group of 56 TDC, matching the patients in age and sex (6 females), was recruited from the department's control subject pool.

During the recruiting process, interested families were approached and briefly informed about the purpose of the study and relevant inclusion/exclusion criteria. Patients had to fulfill diagnostic criteria for ADHD according to DMS-V, while absence of any psychopathology was mandatory in TDC. Normal intelligence (IQ>75) was an inclusion criterion for both groups. Exclusion criteria were moderate or severe affective disorders, severe developmental disorders, severe somatic or neurologic conditions and fMRI contraindications such as metallic implants/foreign objects in the body or symptoms of claustrophobia. Written informed consent from parents/legal guardians was obtained prior to testing. Every participant received €25 as compensation. All procedures of the present studies are in accordance with the Declaration of Helsinki in its latest version and were approved by the ethics committee of the Faculty of Medicine, University of Würzburg, Germany.

All participants underwent an extensive child psychiatric examination conducted by an experienced child and adolescent psychiatrist/psychologist. ADHD symptom severity was assessed by means of the two scales IA and H/I of the parent-report ADHD-questionnaire

of the "Diagnostic System for Mental Disorders in Children and Adolescents according to ICD-10 and DSM-V" (Döpfner & Görtz-Dorten, 2017). This questionnaire is based on the 18 DSM-V criteria for diagnosis of ADHD, measuring 9 items for IA and 11 items for H/I. Parents rate the frequency of each symptom on a 4-point answer scale ranging from (0) “never” to (1) “sometimes”, (2) “often” or (3) “very often”. Symptoms rated as occurring “often” or “very often” are considered as clinically relevant ADHD-related behavior. For the purpose of the current study, mean item scores were calculated for IA and H/I domains. Additionally, parents rated behavioral and emotional problems by use of the German adaptation of the Child Behavior Checklist (CBCL/6-18R) (Döpfner, Plück, & Kinnen, 2014). Two broad-band scales were calculated, describing internalizing and externalizing behavior. In order to ascertain absence of any psychopathology, all control children were assessed with the "Diagnostic Interview for Mental Disorders for Children and Adolescents" (Schneider, Unnewehr, & Margraf, 2009). This is a structured clinical interview that comprises a child as well as a parent version, in which anxiety disorders, ADHD, conduct disorder, oppositional defiant disorder, tic disorder, enuresis/encopresis, sleep disorders and eating disorders are addressed. Intelligence level was estimated by using the short version of the "Culture Fair Intelligence Test" (Weiss, 2006) and the “Wechsler Nonverbal Scale of Ability” (Wechsler & Naglieri, 2014). For each participant, either venous blood or buccal swabs were collected, which were store at -20°C until DNA isolation.

2.2 Experimental paradigm

The paradigm used in this study was an adapted version of the 4-CSRTT (Voon et al., 2014) suitable for fMRI (Neufang et al., 2016), programmed in Presentation® software (Neurobehavioral systems, Inc., Albany, CA, USA). An experimental trial (see figure 1) started with the presentation of four choices (i.e. four white boxes) as ‘cue’ (200 ms), indicating the beginning of the waiting period. Following this ‘cue-target interval’, a green circle was presented as ‘target’ in one of the choices. Participants were instructed to press a

corresponding button as fast as possible. Subsequently, a reward/punishment feedback was displayed according to the subject's latest performance. To prevent the subjects' distraction due to counting of gains, the total amount of earned money was presented as well. If no response was given 1500 ms after target presentation, the trial was considered a 'miss'. Incorrect responses were not punished, but a reminder to stay attentive was displayed.

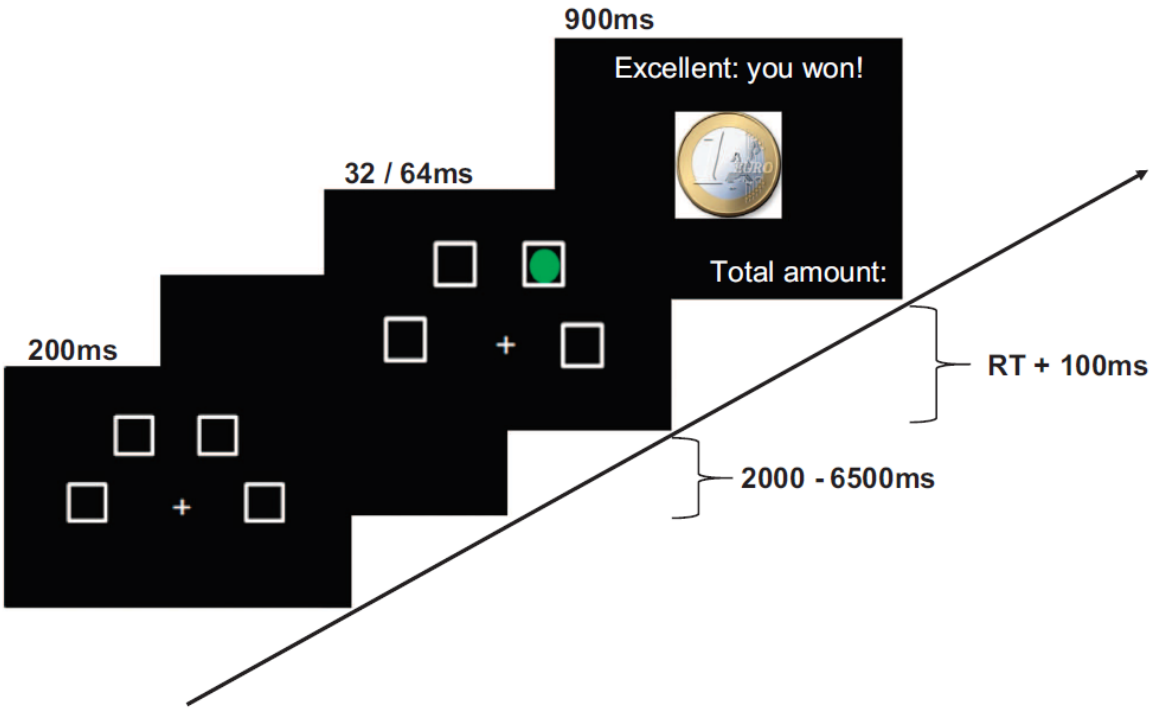

Figure 1: Schematic presentation of a 4-CSRTT trial.
(reprinted from Neufang et al., 2016, under the terms of the Creative Commons CC BY license)

A scanning session included the following steps: outside the scanner, in a first training session (8 trials), subjects were introduced to the "basic task" in front of a computer using a key board as response buttons. The duration of 'cue' (800 ms) and 'target' (200 ms) was prolonged and like the 'cue-target interval' (2000 ms) fixed in order to familiarize participants with the general procedure. Positive verbal feedback was given to reinforce correct and fast answers (<1000 ms), while a reminder to stay attentive followed incorrect or slower responses. In a second training (10 trials), task variations such as monetary

feedback for fast and correct answers (given within 600-1000 ms or faster) and varying waiting periods (2000-6500 ms) or duration of target presentation (64/32 ms) were implemented. To avoid putting the subjects under pressure, it was reassured that the monetary reward was only play money and that the compensation for participation in the study was not affected by task performance. Finally, a first baseline run of 20 trials (fixed duration of 'cue' (200 ms), 'target' (64 ms) and 'cue-target interval' (2000 ms)) was used to determine an individual RT range, while giving no reward feedback. The resulting M_{RT} interval (M_{RT} ±SD) was used for all following experimental runs, if at least 75% of the responses given during the baseline run were correct. Reward criteria for the experimental runs in the scanner were defined as follows: (i) win of 1 Euro for extraordinarily fast (i.e. RT < M_{RT} -SD), correct answers, (ii) win of 10 Cent for averagely speeded (i.e. RT = M_{RT} ±SD), correct answers, or (iii) loss of 1 Euro for any correct response given too slowly (i.e. RT > M_{RT} +SD).

In the scanner, five experimental runs of 20 trials each were conducted. The second of these runs was a second baseline equal to the first one outside the scanner (i.e. without monetary feedback). In the other experimental runs, WI was manipulated by varying task difficulty by the following factors: (a) monetary reward depending on the individually defined reward criteria ('win of 1 Euro/10 Cents' 'loss of 1 Euro'); (b) duration of target presentation: 64 ms in the first and 32 ms in the last three runs; (c) variation of the cue-target interval length: fixed to 2000ms in the first and third or varying between 2000 and 6500 ms in the last two runs; (d) introduction of distractor targets: display of blue and yellow circles (32 ms each) preceding the actual target during the last experimental run (overview of experimental runs in the scanner is given in table 2). Between runs, break periods were included, while showing only a fixation cross on the screen (11 scans each). In total, the completion of the task within the scanner lasted 14 min, while training and the baseline run outside the scanner took approximately 10 min.

Table 2: Increasing difficulty of 4-CSRTT experimental runs in the scanner.

Exp. run	Target presentation		Cue-target interval		Distractors
	long (64ms)	short (32ms)	fixed (2000ms)	variable (2000-6500ms)	
1	x		x		
Baseline 2 ø reward	x		x		
3		x	x		
4		x		x	
5		x		x	x

Behavioral parameters

On the behavioral level, WI was reflected by the number of PR given, i.e. any response that occurred prior to target onset. Attentional performance was indicated by Acc (correct responses/[correct responses + incorrect responses]). The Mot_Ind was calculated as RT difference between the two baseline runs without reward feedback ((M_{RT} baseline 1 - M_{RT} baseline 2)/(M_{RT} baseline 1 + M_{RT} baseline 2)). As suggested by Voon et al. (2014) it was used to quantify 'sensitivity to reward feedback'. RT_rew was determined as indicator of basic task processing speed. Following recommendations to account for both RT speed and variability (Wagenmakers & Brown, 2007), a coefficient of variation in RT_rew (M_{RT} /SD) was calculated as measure of RTV.

2.3 Data acquisition

MRI measurements were performed on a 3 Tesla Siemens MAGNETOM Trio Scanner (Siemens, Erlangen, Germany). During performance of the 4-CSRTT, whole-brain T2*-weighted blood oxygen level-dependent images were recorded with a gradient-echo echo-planar imaging sequence (repetition time = 2000 ms, echo time = 30 ms, 36 slices, 3 mm thickness, field of view = 192 mm, flip angle = 90°, 425 volumes). Afterwards, an isotropic high-resolution T1-weighted three-dimensional structural MR image was acquired using a

magnetization prepared rapid gradient echo sequence (voxel size=1×1×1mm3, repetition time = 2400 ms, echo time = 2.26 ms, field of view = 256 mm, flip angle = 9°, 176 slices).

2.4 Data analysis

sMRI – freesurfer analysis

Data from sMRI were analyzed using the FreeSurfer (version 5.3) software (Fischl et al., 2002). Analysis and quality-control protocols of the ENIGMA consortium were applied including the recon-all stream and the segmentations of 68 (34 left and 34 right) cortical gray matter regions based on the Desikan–Killiany atlas (Desikan et al., 2006). Data of two whole-hemisphere measures were visually inspected and statistically evaluated for outliers following standardized published protocols (http://enigma.ini.usc.edu/protocols/imaging-protocols). After quality control, regional volumes were extracted for WI-network regions (i.e. middle frontal gyrus (MFG), IFG (separately for orbital, triangular and opercular parts), ACC, NAcc, HC and AMY). To correct for confounding effects of individual global brain volume, regional volume measures were calculated as percent of total intracranial volume.

fMRI analysis

Preprocessing

Data from fMRI were analyzed using the Statistical Parametric Mapping Software Package (SPM12, Wellcome Department of Imaging Neuroscience, London, UK, Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/). The first preprocessing step included slice time correction. To correct for differences in image acquisition time between slices, the time series was re-referenced to match the middle slice of the volume (Josephs, Turner, & Friston, 1997). Afterwards, all images were realigned to the first functional image to reduce movement artifacts and unwarped to correct for motion-related distortions of field homogeneity (“susceptibility-by-movement interaction”) (Andersson, Hutton,

Ashburner, Turner, & Friston, 2001; Friston et al., 1995). Estimated realignment parameters were used as regressors in the single-subject's statistical analysis later (see below). Images were then spatially normalized into a standard stereotactic space (Montreal Neurological Institute- MNI space) and resampled to an isotropic voxel size of $2\times2\times2mm^3$ (Ashburner & Friston, 2005). Finally, spatial smoothing with a 3D Gaussian kernel of 8 mm full width at half maximum was performed to reduce between-subject variance and approximate normal distribution of the data (Worsley & Friston, 1995).

fMRI statistical analysis

Statistical analyses of fMRI data were based on the general linear model approach. For every subject, onset regressors for the conditions 'cue', 'target', 'win', 'loss' and 'error' were derived from the log-files. Onsets of 'cue' and 'target' were defined as the time when the corresponding picture appeared, 'win' and 'loss' as one second before presentation of the reward feedback in the respective trials. 'Error' trials were the onsets of target during incorrect trials, break periods between runs were defined as 'baseline' (no. of volumes=55). The design matrix for the single-subject level thus included 4 experimental regressors, while error trials and the movement parameters derived from realignment entered the model as nuisance regressors. Three contrasts of interest were estimated for every subject: First, cue-specific brain activation was determined as 'cue>baseline'. The contrast 'response inhibition' concentrated on behavioral inhibition-related brain activation: 'target > baseline'. To isolate activation associated with the expectation of monetary reward, the contrast 'reward anticipation' was defined as 'win>loss'. Activation maps of the three contrasts of interest were estimated and entered group analyses. All fMRI analyses were performed in a region of interest based approach in WI-network regions (see 1.3.1). A single combined mask was generated using atlases within the Wake Forest University PickAtlas toolbox (Version 3.0.5b; http://fmri.wfubmc.edu/software/pickatlas) comprising the following regions: bilateral superior frontal gyrus, MFG, orbital, triangular and opercular

parts of IFG, ACC, HC and AMY as well as left and right NAcc, caudate nucleus, putamen and medial fronto-orbital gyrus.

2.5 Statistical analyses

Statistical analyses of behavioral and sMRI data were performed with IBM SPSS statistics version 25 (IBM Corp., Armonk, NY, USA). Prior to analysis, behavioral data were screened for outliers, i.e. performance +/- 2 SDs of the group mean, who were handled by replacing the extreme values with the second most extreme value, which corresponds to the Winsorizing procedure (L.-A. Chen, Welsh, & Chan, 2001).

III. STUDY I

3.1 Methods

3.1.1 Participants

ADHD-questionnaire data was not available for 10 TDC and two patients were excluded based on excessive movement during fMRI scanning, resulting in a total sample size of *N*=90 (46 TDC and 44 ADHD). Twenty-six patients (all male) were diagnosed as ADHD-I, and 18 (5 girls) met criteria for ADHD-C. Comorbidities observed in the ADHD sample were disruptive behavior (conduct disorder: *n*=3, oppositional defiant disorder: *n*=7), anxiety (*n*=3), dyslexia (*n*=6) and nonorganic enuresis (*n*=1). Patients, who were receiving stimulant medication (*n*=24), underwent a 48h washout phase prior to scanning. Ten patients were medication-naïve, and ten patients were off medication for more than a year.

3.1.2 Statistical analysis

A priori differences between TDC, ADHD-I and ADHD-C were examined using analysis of variance (1x3 ANOVA) with “diagnostic group” (i.e. TDC vs. ADHD-I vs. ADHD-C) as between-subject factor and demographic data as dependent variables. Furthermore, zero-order correlation analyses for all relevant study variables (questionnaire data (parent ratings of ADHD symptoms), 4-CSRTT behavioral data and age) were conducted.

The main hypotheses were assessed via hierarchical multiple regression analyses using parent ratings of IA or H/I as independent factor and 4-CSRTT behavioral measures (i.e. PR, Acc, Mot_Ind, RT_rew, RTV), regional volumes of the 8 WI-network regions (i.e. MFG, IFG pars orbitalis, triangularis and opercularis, ACC, NAcc, HC, AMY) as well as contrast images for the conditions ‘cue’, ‘response inhibition’ and ‘reward anticipation’ as dependent variables. To avoid multicollinearity, both constructs were tested in separate models

as they share a large portion of variance. Covariates (i.e. age and sex) were entered at step 1 and IA or H/I score at step 2 in all models.

After identification of WI brain regions that were significantly related to IA and/or H/I, moderation analyses were performed to explore, how the variation in these regions (activation/regional volume) influenced the relationship between the level of IA or H/I and 4-CSRTT behavior. The SPSS macro PROCESS version 3.3. (Hayes, 2017) was used to set up moderation models based on the “model number 1” as specified in the software. In this model, the influence of one moderator (M) on the effect of an independent variable (X) on a dependent variable (Y) is tested by adding an interaction term of M and X (path b_3) to the simple conditional effects of X (path b_1) and M (path b_2) on Y. A conceptual as well as a statistical path diagram of the model is given in figure 2. The variables X and M were mean-centered prior to analysis. IA or H/I served as independent variable X, behavioral data from the 4-CSRTT as dependent variable Y, while contrast estimates of significantly associated brain activation clusters or regional volume data were included as moderating variable M. As in the multiple regression analyses, age and sex were used as covariates of no interest in all models and separate models were set up for the two ADHD dimensions.

Unless not otherwise indicated, results were corrected for multiple comparisons using the Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995) to control the false discovery rate (FDR) at an alpha-level set to $\alpha<.05$.

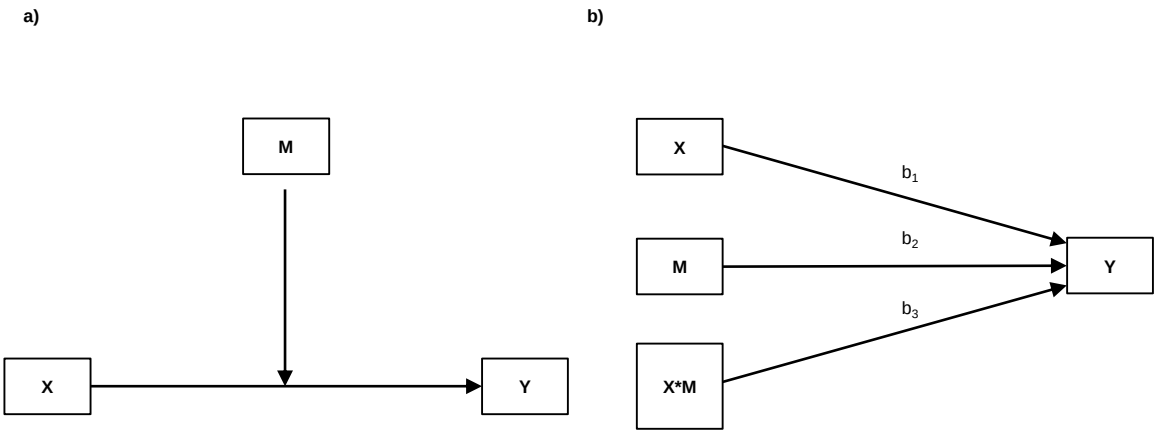

Figure 2: Moderation model with one moderator.
a) Conceptual diagram: M (moderator) moderates the effect of X (independent variable) on Y (dependent) variable. b) Statistical diagram of the moderation model: the path b_1 indicates the conditional effect of X on Y, path b_2 the conditional effect of M on Y and b_3 the effect of the interaction of M and X on Y (i.e. the moderation effect).

3.2 Results

3.2.1 *A priori* differences between ADHD patients and TDC

The three diagnostic groups did not differ regarding age ($F(2,87)=.35$, $p=.707$), see also table 3. IQ-scores differed significantly ($F(2,87)=3.67$, $p=.030$) between TDC ($M_{TDC}=109\pm16$) and ADHD patients ($M_{ADHD\text{-}I}=101\pm11$; $M_{ADHD\text{-}C}=101\pm11$). Concerning parent ratings of ADHD symptoms, patients scored significantly higher in terms of IA ($F(2,87)=51.53$, $p<.001$) and H/I ($F(2,87)=54.19$, $p<.001$) as well as on the scales for internalizing ($F(2,87)=6.63$, $p=.002$) and externalizing problems of the CBCL ($F(2,87)=21.90$, $p<.001$) compared to TDC. Furthermore, post-hoc t-tests revealed that H/I symptoms were rated significantly higher in ADHD-C compared to ADHD-I ($t(42)=4.20$, $p<.001$).

Table 3: Sample characteristics STUDY I.
(presented as M±SD and group differences as revealed by 1x3 ANOVAs)

	TDC [*n*=46]	**ADHD-I [*n*=26]**	**ADHD-C [*n*=18]**	**F-Score**
Age	12.9±.2.5	12.8±2.5	12.4±1.8	0.4
IQ	109±16	101±11	101±11	3.7*
Inattention	0.5±0.6	1.8±0.5	1.7±0.7	51.5**
Hyperactivity/impulsivity	0.2±0.3	0.8±0.6	1.5±0.6	54.2**
CBCL, internalizing	50.7±9.4	57.3±10.3	58.6±6.8	6.6*
CBCL, externalizing	46.3±8.6	55.1±8.9	61.4±8.5	21.9**

Note. *: $p<.05$, **: $p<.001$, uncorrected

Zero-order correlation analyses were performed to explore age effects and interrelatedness of the relevant study variables. Table 4 shows that all behavioral parameters of the 4-CSRTT except for Mot_Ind and RTV significantly correlated with age: PR as well as RT_rew decreased with increasing age (r_{PR} =-0.302, p=.004, r_{RT_rew}=-0.390, p<.001), while Acc measures improved the older subjects were (r_{Acc}=0.405, p<.001). ADHD-questionnaire data did not correlate with age (r_{IA} =-0.094, p=.378, $r_{H/I}$=-0.185, p=.082). The correlation between ratings of IA with those of H/I was high (r=.718, p<.001).

Table 4: Zero-order correlations of questionnaire and 4-CSRTT behavioral data.

	Age	IA	H/I	PR	Acc	Mot_Ind	RT_rew	RTV
Age	1	-	-	-	-	-	-	-
IA	-.094	1	-	-	-	-	-	-
H/I	-.185	.718**	1	-	-	-	-	-
PR	-.302*	-.016	-.018	1	-	-	-	-
Acc	.405**	-.229*	-.241*	-.309*	1	-	-	-
Mot_Ind	-.082	.006	-.124	.226*	-.189	1	-	-
RT_rew	-.390**	.223*	.420**	-.084	-.325*	-.369**	1	-
RTV	-.150	.202	.302*	.313*	-.499**	.014	.371**	1

Note. *: $p<.05$, **: $p<.001$, uncorrected

3.2.2 Behavioral correlates of WI

As depicted in table 4, zero-order correlations between ADHD-symptoms and behavioral parameters of the 4-CSRTT revealed that both symptom domains were negatively correlated with Acc (r_{IA}=-.229, p=.030; $r_{H/I}$=-.241, p=.022) and positively correlated with RT_rew (r_{IA}=.223, p=.034; $r_{H/I}$=.420, $p<.001$), while there was no relation to the number of PR or the Mot_Ind. In addition, only H/I covaried with greater RTV (r=.302, p=.004). Furthermore, PR correlated negatively with Acc (r=-.309, p=.003) and positively with Mot_Ind (r=.226, p=.032) and RTV (r=.313, p=.003), while RT_rew correlated negatively with Acc (r=-.325, p=.002) and Mot_Ind (r=-.369, $p<.001$). Greater RTV was associated with less Acc (r=-.499, $p<.001$) and longer RT_rew (r=.371, $p<.001$).

After including age and sex as covariates into hierarchical multiple regression models with either H/I or IA as predictors and behavioral parameters as dependent variables (see table 5), only the positive correlations of H/I with RT_rew (b=.37, $t(87)$=3.93, $p<.001$) and RTV (b=.29, $t(87)$=2.80, p=.006) remained significant ($p<q^*$; q^*=.02, FDR-corrected for 5 comparisons). After controlling for effects of age and sex, H/I accounted for 13% of the

variance in RT_rew (R^2_{change}=.13, $F_{change}(1,86)$=15.5, p<.001) and for 8% of the variance in RTV (R^2_{change}=.08, $F_{change}(1,86)$=7.8, p=.006). Thus, the greater the subjects' levels of H/I were, the longer and more variable their RT_rew. The relationship between RT_rew and H/I as well as with RTV is shown in the scatterplots in figure 3.

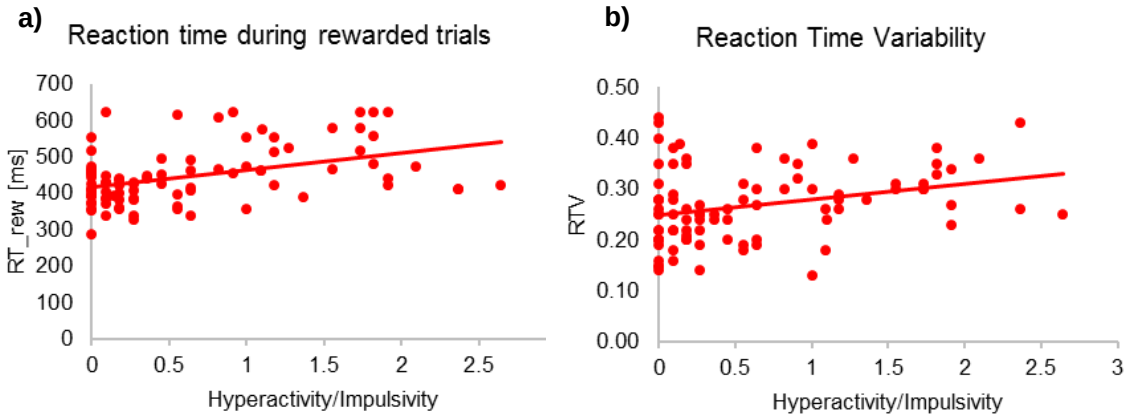

Figure 3: Behavioral correlates of H/I.
Scatterplots of the correlation of a) RT_rew and b) RTV with H/I.

Table 5: Multiple regression analyses of IA and H/I phenotypes with 4-CSRTT behavioral data.

	Inattention[a]				**Hyperactivity/Impulsivity**[b]			
	F_{model}	**R^2**	**β**	***t***	**F_{model}**	**R^2**	**β**	***t***
PR	3.1	0.1	-0.04	-0.4	3.3	0.10	-0.1	-0.8
Acc	9.9	0.3	-0.20	-1.7	10.4	0.27	-0.2	-2.0
Mot_Ind	0.3	0.01	-0.01	-0.1	0.9	0.03	-0.1	-1.3
RT_rew	6.6	0.2	0.20	1.9	11.4	0.29	0.4	3.9*
RTV	1.9	0.06	0.20	1.7	3.6	0.11	0.3	2.8*

Note. [a]: IA entered at last step in model, after entering age and sex as covariates; [b]: H/I entered at last step in model, after entering age and sex as covariates; *p<q*; q*=.02, FDR-corrected for 5 comparisons

3.2.3 Neural correlates of WI

fMRI Data

Condition-specific activation patterns were established across all subjects using one-sample t-tests with contrast-images for ‘cue’, ‘response inhibition’ and ‘reward anticipation’ as dependent variables (see supplementary information, figure S1 and table S1 in the appendix). Phenotype specific multiple regression analyses using contrast images of the three conditions were performed (significant results summarized in table 6) to identify ADHD specific functional correlates in the WI neural network. For the ‘cue’ contrast one positive correlation between activity in the left dlPFC (t=3.2, p<.05) and IA was revealed (figure 4a). There was no significant relationship found for the H/I phenotype. During processing of the target in the ‘response inhibition’ contrast, ADHD symptoms covaried negatively with brain activity in the PFC (figure 4b). Higher levels of hyperactive/impulsive behavior were related to reduced activity in the vmPFC (t=4.2, p<.05) and in the ACC (t=3.5, p<.05) and right vlPFC (t=3.4, p<.05). The inattentive phenotype was significantly negatively related to activity in a cluster in the vlPFC (t=3.8, p<.05) overlapping with the one related to H/I (figure 4c). Additionally, during anticipation of the reward, both phenotypes were related to stronger activity in the left HC (figure 4c), although the relationship was stronger with H/I behavior (t=4.2, p<.05) than with IA (t=3.1, p<.05).

Table 6: Significant influences of IA and H/I phenotypes on brain activity during 4-CSRTT performance as revealed by multiple regression analyses.

Contrast	**Region**		**k**	**x**	**y**	**z**	**Z**	**T**
'cue'								
IA**:** pos. effect	dlPFC	L	239	-26	56	12	3.1	3.2
'response inhibition'								
H/I: neg. effect	vmPFC	R	31	10	52	-10	4.0	4.2
	vlPFC	R	64	44	36	-2	3.3	3.4
	ACC	L	18	-4	38	-8	3.4	3.5
				0	48	-4	3.3	3.4
IA: neg. effect	vlPFC	R	28	44	38	-2	3.6	3.8
			32	48	26	8	3.5	3.6
'reward anticipation'								
H/I: pos. effect	HC	L	61	-12	-34	10	4.0	4.2
IA: pos. effect	HC	L	50	-14	-36	10	3.1	3.2

Note. L: left hemisphere, R: right hemisphere, k: cluster size in no. of voxels, all results significant at $p<0.05$ FDR corrected on voxel level.

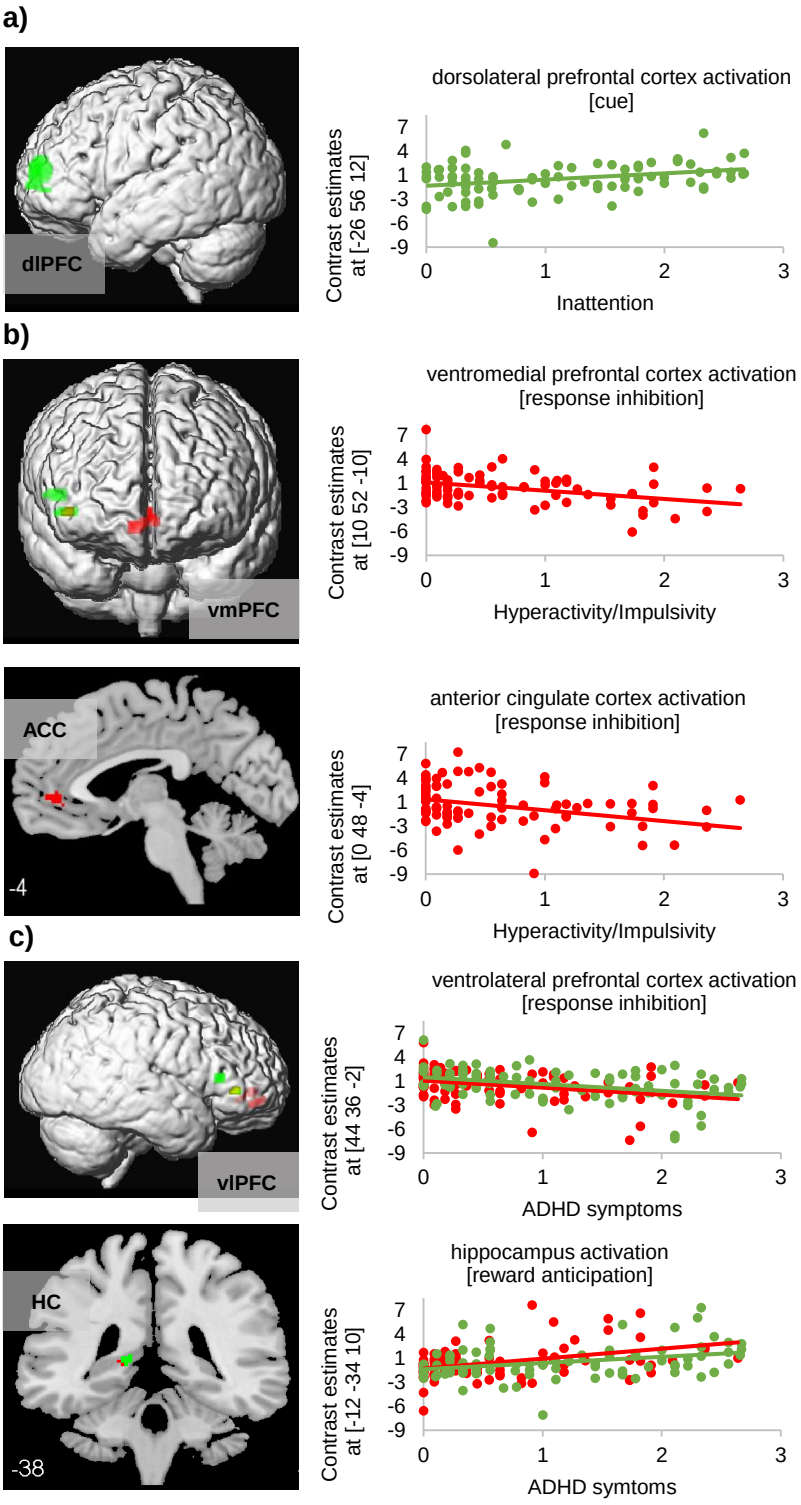

Figure 4: Functional neural correlates of H/I and IA during 4-CSRTT performance.
Cluster activations were plotted on an individual brain surface, scatterplots show the corresponding correlations for a) IA-specific (green) positive correlation in the left dlPFC during 'cue-processing', b) H/I-specific (red) negative correlation in the right vmPFC and left ACC during 'response inhibition': and c) domain-overlapping negative correlation with activity in the right vlPFC during 'response inhibition' and positive correlation with HC activation during 'reward anticipation'.

sMRI Data

Brain structural correlates of ADHD phenotypes were identified by phenotype-specific regression analyses on regional gray matter volumes (bilateral, corrected for individual intracranial volume) of eight a priori defined WI regions as dependent variables: MFG, IFG (orbital/triangular/opercular parts), ACC, NAcc, HC and AMY (summarized in table 7). The analyses showed, that IA was negatively associated with volume of the MFG, but only the relation with the left MFG (*b*=-.33, *t*(87)=3.14, *p*<=002) remained significant after correction for multiple comparisons (see table 7). After controlling for the effects of age and sex, IA accounted for 10% of the variance in left MFG volume (R^2_{change}=.1, F_{change}(1,86)=9.9, *p*=.006). The H/I phenotype correlated negatively with volume of the right NAcc, but the relationship did not survive correction for multiple comparisons.

Table 7: Multiple regression analyses of IA and H/I phenotypes on sMRI data.

		Inattention[a]				**Hyperactivity/Impulsivity[b]**			
		F_{model}	R^2	β	*t*	F_{model}	R^2	β	*t*
MFG	L	4.0	0.12	-0.33	-3.14*	1.9	0.06	-0.21	-1.91
	R	2.2	0.07	-0.27	-2.51	1.4	0.05	-0.22	-2.0
IFG p. orb.	L	1.9	0.06	-0.07	-0.66	1.8	0.06	0.04	0.32
	R	1.4	0.05	0.01	0.10	1.4	0.05	-0.03	-0.25
IFG p. tri.	L	2.1	0.04	-0.12	-1.15	1.7	0.06	-0.53	-0.49
	R	3.0	0.06	-0.17	-1.57	3.4	0.11	-0.20	-1.89
IFG p. op.	L	4.4	0.14	-0.07	-0.71	4.9	0.15	-0.14	-1.32
	R	1.0	0.03	-0.15	-1.36	0.7	0.02	-0.12	-1.05
ACC	L	0.5	0.02	-0.13	-1.22	0.4	0.02	-0.12	-1.11
	R	1.5	0.05	-0.09	-0.82	1.4	0.05	-0.07	-0.66
NAcc	L	3.7	0.12	-0.08	-0.73	4.6	0.14	-0.18	-1.69
	R	4.9	0.15	-0.15	-1.42	6.3	0.18	-0.24	-2.36
HC	L	0.2	0.01	0.03	0.30	0.4	0.01	0.09	0.82
	R	0.6	0.02	0.001	0.007	0.6	0.02	0.02	0.14
AMY	L	1.1	0.04	-0.08	-0.76	1.2	0.04	-0.11	-0.99
	R	0.3	0.01	-0.02	-0.22	0.4	0.01	-0.07	-0.67

Note. [a]: IA entered at last step in model, after including age and sex as covariates; [b]: H/I entered at last step in model, after including age and sex as covariates; *$p<q$*; q*=.003, FDR-corrected for 16 comparisons

3.2.4 Moderation analyses

In total 25 moderation models were tested for each dimension (5 independent variables x 5 dependent variables). Table 8 gives an overview of the results of the interaction effects of IA or H/I and the neural correlates identified in 3.1.3 on 4-CSRTT behavior. For a

complete summary of the moderation analyses please refer to tables S2 (H/I) and S3 (IA) in the appendix.

Concerning the IA domain, interaction effects for left MFG regional gray matter volume on Acc and for vlPFC activity on RT_rew were found, but these did not survive correction for multiple comparisons (see table 8). Analyses for H/I revealed a significant differential effect of response inhibition-related vlPFC activation (b_3=-.033, t(89)=-3.1, p=.003) on Acc on the 4-CSRTT (statistical path diagram is shown in figure 5a). The overall model explained 34% variance in Acc (R^2=.34, F(5,84)=8.4, p<.001), while inclusion of the interaction term accounted for 7% of the variance (R^2_{change}=.07, F(1,84)=9.7, p=.003). To follow up on this interaction, conditional effects of vlPFC activity on Acc at low (mean-1SD), for moderate (mean) and high values (mean+1SD) of H/I were estimated. As depicted in figure 5a, the analyses showed that the more hyperactive/impulsive the subjects were, the smaller the influence of vlPFC activity on the relationship with Acc was. For low H/I symptoms, higher vlPFC activity was significantly associated with greater Acc (b=.034, t(89)=3.0, p=.003), while this effect was only trend-wise significant at moderate levels of H/I (b=.014, t(89)=1.8, p=.075) and reversed but not significant at high levels of H/I (b=-.008, t(89)=-.87, p=.388).

Anticipatory processing of reward in the HC was significantly associated with motivation and varied as a function of H/I (b_3=-.009, t(89)=-2.7, p=.009). A complete statistical path diagram is shown in figure 5b. The overall model explained 14% variance in the Mot_Ind (R^2=.14, F(5,84)=2.8, p=.024), while inclusion of the interaction term accounted for 7% of the variance (R^2_{change}=.07, F(1,84)=7.2, p=.009). Follow-up analyses revealed that for high H/I symptoms, the Mot_Ind was higher the greater the reward-related activation in the HC was (b=.008, t(89)=3.0, p=.003), while the effect was not significant at low (b=-.004, t(89)=-1.0, p=.346) and moderate (b=.002, t(89)=.6, p=.554) levels of H/I (see figure 5b).

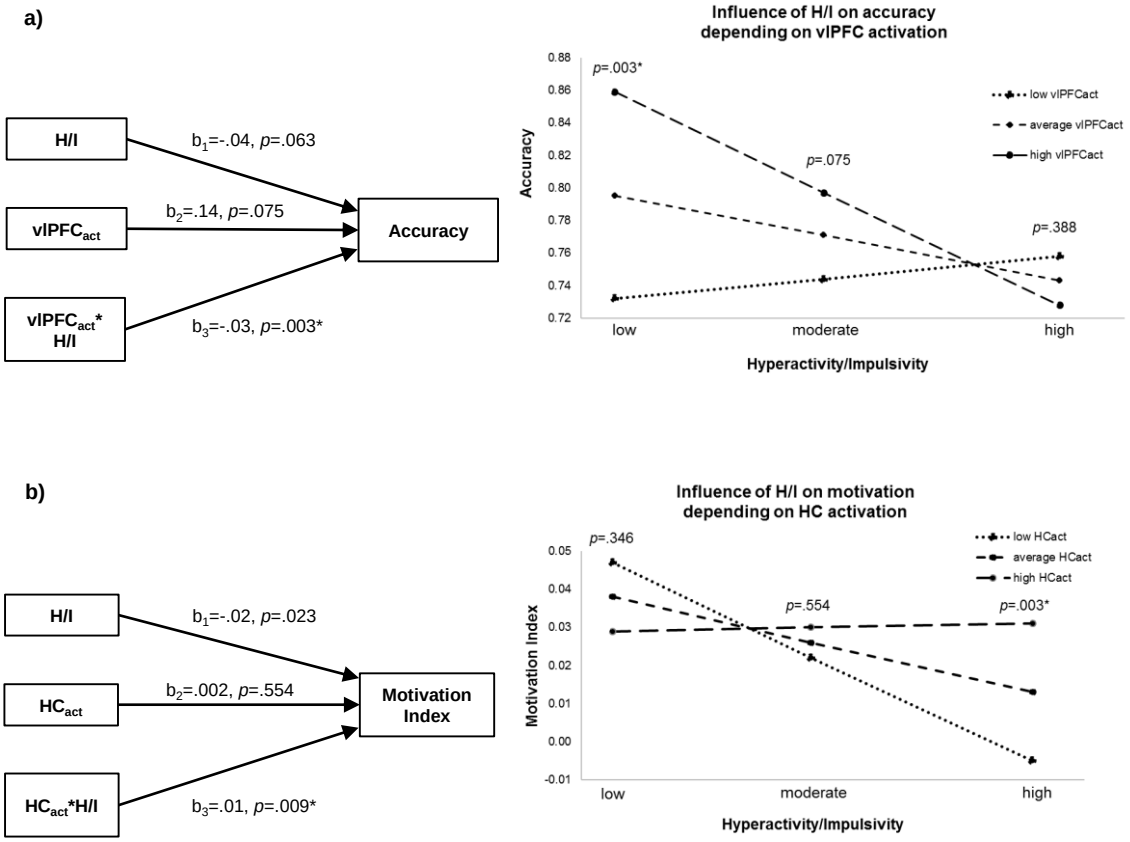

Figure 5: Significant moderation models of brain activation on the relationship between H/I and 4-CSRTT behavioral parameters.
The influence of H/I on a) Acc depends on vlPFC activation during response inhibition and b) on Mot_Ind depends on HC activity during reward anticipation. Statistical path diagrams on the left show the conditional effect of brain activation and H/I as well as their interaction effect on the behavioral parameters. For visualization, the conditional effect of brain activation on behavior was plotted for different values of H/I. *p<q*, q*=.01 FDR-corrected for 5 comparisons

Table 8: Interaction effects of IA or H/I and neural correlates on 4-CSRTT behavior.

Inattention				**Hyperactivity/Impulsivity**			
Premature responses							
Interaction	**Coeff.**	***t***	***p***	**Interaction**	**Coeff.**	***t***	***p***
IA*vlPFC1$_{act}$	.083	.811	.420	H/I*vmPFC$_{act}$	-.006	-.044	.965
IA*vlPFC2$_{act}$	.049	.478	.634	H/I*ACC1$_{act}$	.053	.481	.632
IA*HC$_{act}$	.030	.288	.774	H/I*ACC2$_{act}$	.082	.939	.350
IA*MFG$_{struct}$	-.749	-.497	.621	H/I*vlPFC$_{act}$	.180	1.388	.169
IA*dlPFC$_{act}$	.144	1.312	.193	H/I*HC$_{act}$	.069	.609	.544
Accuracy							
Interaction	**Coeff.**	***t***	***p***	**Interaction**	**Coeff.**	***t***	***p***
IA*vlPFC1$_{act}$	-.015	-1.758	.083	H/I*vmPFC$_{act}$	-.012	-1.122	.265
IA*vlPFC2$_{act}$	-.003	-.306	.760	H/I*ACC1$_{act}$	-.021	-2.351	.021
IA*HC$_{act}$	-.010	-1.131	.261	H/I*ACC2$_{act}$	-.014	-1.971	.052
IA*MFG$_{struct}$	-.311	-2.532	.013	H/I*vlPFC$_{act}$	-.033	-3.112	.003*
IA*dlPFC$_{act}$	-.008	-.821	.414	H/I*HC$_{act}$	-.011	-1.109	.271
Motivation Index							
Interaction	**Coeff.**	***t***	***p***	**Interaction**	**Coeff.**	***t***	***p***
IA*vlPFC1$_{act}$	.007	2.262	.026	H/I*vmPFC$_{act}$	-.001	-.151	.880
IA*vlPFC2$_{act}$	.005	1.385	.170	H/I*ACC1$_{act}$	.003	.778	.439
IA*HC$_{act}$	.004	1.150	.254	H/I*ACC2$_{act}$	.001	.250	.803
IA*MFG$_{struct}$	-.023	-.464	.644	H/I*vlPFC$_{act}$	.008	1.958	.054
IA*dlPFC$_{act}$	.004	1.062	.291	H/I*HC$_{act}$	.009	2.679	.009*
Reaction time reward							
Interaction	**Coeff.**	***t***	***p***	**Interaction**	**Coeff.**	***t***	***p***
IA*vlPFC1$_{act}$	-4.973	-1.077	.285	H/I*vmPFC$_{act}$	5.354	1.008	.316
IA*vlPFC2$_{act}$	-10.76	-2.453	.016	H/I*ACC1$_{act}$	-2.351	-.510	.611
IA*HC$_{act}$	3.750	.797	.428	H/I*ACC2$_{act}$	-1.641	-.444	.658
IA*MFG$_{struct}$	57.792	.840	.403	H/I*vlPFC$_{act}$	-4.162	-.751	.455
IA*dlPFC$_{act}$	4.472	.930	.355	H/I*HC$_{act}$	-6.011	-1.246	.216
Reaction time variability							
Interaction	**Coeff.**	***t***	***p***	**Interaction**	**Coeff.**	***t***	***p***
IA*vlPFC1$_{act}$	.004	.891	.375	H/I*vmPFC$_{act}$	-.010	-1.862	.066
IA*vlPFC2$_{act}$	-.002	-.487	.627	H/I*ACC1$_{act}$	-.005	-.947	.346
IA*HC$_{act}$	.007	1.498	.138	H/I*ACC2$_{act}$	-.002	-.417	.678
IA*MFG$_{struct}$	.084	1.267	.209	H/I*vlPFC$_{act}$	.001	.240	.811
IA*dlPFC$_{act}$	.004	.707	.481	H/I*HC$_{act}$	.008	1.651	.102

Note: *p<q*; q*=.01, FDR-corrected for 5 comparisons, act=activity, struct=regional volume

3.3 Discussion

As hypothesized, symptoms of IA were specifically related with the dlPFC, however, in distinct ways. On the structural level, regional volume of the left MFG correlated negatively with IA. This is in line with previous findings, as smaller volumes in the MFG have been reported in ADHD patients before and were also shown to correlate with greater symptom severity (Castellanos et al., 2002; Villemonteix et al., 2015). During 'cue'-processing, activity in the left dlPFC increased with greater IA. A positive relation between a personality trait and brain activation often hints towards a compensatory increase of a crucial brain region to be able to perform a certain task (Pliszka et al., 2006) or "to compensate for under-activity in the 'appropriate' network" (Fassbender & Schweitzer, 2006). Typically, executive functions are attributed to the right PFC, which is a key structure for selective attention and especially activated in response inhibition paradigms with increased working memory load (Arnsten, 2009; Mostofsky et al., 2003). The dlPFC has been shown to be active during processing of task cues (Swann, Tandon, Pieters, & Aron, 2013) and it has been attributed to be responsible for continuously monitoring the task goals and hence a subject's performance (Garavan, Ross, Murphy, Roche, & Stein, 2002; MacDonald, Cohen, Stenger, & Carter, 2000). Interestingly, Solanto et al. (2009) reported that in contrast to ADHD-C, patients with ADHD-I activated the dlPFC bilaterally in a go/no-go task of inhibitory control, while behavioral performance was comparable between the two subgroups. It was speculated that insufficient recruitment of higher-order executive control regions may account for some of the phenotypic differences between ADHD-I and ADHD-C (Solanto et al., 2009). The positive correlation of left dlPFC activity and symptoms of IA but not with H/I points towards a similar direction and confirms phenotypic differences between the two domains.

Specific effects for both IA and H/I phenotypes were mainly related to the target condition. The need to withhold the response over the course of the waiting period accumulates up

to this time point, i.e. the highest amount of response inhibition is required. Impaired response inhibition in relation with impulsivity and with ADHD-C has been documented in numerous studies regarding behavioral performance (Huang-Pollock, Nigg, & Halperin, 2006), brain activation (Nagashima et al., 2014) and functional connectivity from resting-state fMRI (Wang et al., 2016). Consequently, higher levels of both domains of ADHD symptoms covaried with decreased activity in the right vlPFC, a central structure for response inhibition (Aron, Robbins, & Poldrack, 2004) and recently defined more precisely as a "brake" able to "stop" and to "pause" responses depending on the individual task demands (Aron, Robbins, & Poldrack, 2014). Dysfunction of this region has been related to impulsive behavior in healthy subjects and ADHD patients before (Casey et al., 2007), while Solanto et al. (2009) reported similar activation of vlPFC regions in a go/no-go task on inhibitory control in both ADHD-I and ADHD-C. Moderation analyses revealed that the relationship between H/I and Acc varied as a function of right vlPFC activity during response inhibition. For low and trend-wise for moderate levels of H/I, the amount of vlPFC activation predicted higher Acc on the behavioral level, whereas there was no influence of activity in this structure on task performance in subjects with high H/I. This is in line with previous literature that reported activity in the vlPFC to be related to successful inhibitory behavioral performance in healthy control subjects but not in ADHD patients (Durston, Mulder, Casey, Ziermans, & van Engeland, 2006). Thus, although often described as dysfunctional in ADHD patients, the right vlPFC appears not to be the sole structure responsible for the inhibitory deficits.

Consistent with expectations, symptoms of H/I covaried significantly with activity in the vmPFC and furthermore with ACC, both crucial structures in the modulation and top-down control of executive functions. Several neuroimaging studies have implicated the vmPFC (together with striatal regions) in reward-based decision making (see e.g. meta-analysis by Liu et al., 2011), with vmPFC activation reflecting the control of the NAcc to regulate

the response to reward (i.e. the winning pleasure; e.g. van Duijvenvoorde, Achterberg, Braams, Peters, & Crone, 2016) and to code for reward value (Wilbertz et al., 2012). For example, Wilbertz et al. (2012) reported, that neural signals in the vmPFC were dysregulated in adult ADHD patients based on overvaluing low-incentive rewards and undervaluing high-incentive rewards. In healthy young adults, activity in the vmPFC varied as a function of WI during trials of high but not low reward expectancy (Mechelmans et al., 2017). The ACC has been implicated in error detection and processing as well as with evaluation of reward (Fassbender et al., 2004) making it "particularly relevant to reward/motivation and cognitive theories of ADHD" (Bush, 2011). Hypoactivation of ACC in ADHD patients has been shown on a variety of response inhibition (e.g. Pliszka et al., 2006), time discrimination (e.g. Durston et al., 2007) or attentional tasks (e.g. Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006). On the structural level, cortical thinning in the ACC has been found to be a significant predictor of parent- and teacher-rated ADHD symptomatology (Bledsoe, Semrud-Clikeman, & Pliszka, 2013). The fact that the linear relationship between activity in these regions was found with H/I but not with IA, supports the notion that impulsivity in the context of ADHD is related to dysfunctional executive control in relation to rewards (Umemoto, Lukie, Kerns, Muller, & Holroyd, 2014).

There was no significant relationship between structure of or activity in the NAcc and symptoms of H/I. As introduced, studies on ventral striatal activity during reward anticipation have found opposing relationships for adolescent and adult control and patient samples (Plichta & Scheres, 2014). One study corroborated ADHD-related hypoactivity also in younger children (van Hulst et al., 2017), while another did not (Kappel et al., 2015). Notably, van Hulst and colleagues did not find a linear relationship between parent-rated ADHD symptoms and ventral striatal hypoactivity, neither in the patient, nor in the TDC group (van Hulst et al., 2017). Thus, our findings line up with evidence, that attempts to explain altered ventral striatal anticipatory processing of rewards in the context of ADHD

with (simple) linear models are not very well suited. Plichta and Scheres (2014) proposed three theoretical integrative approaches to resolve this issue: the possibility of an inverted u-shaped relationship between ventral striatal responsiveness and impulsivity, the presence of an e.g. genetically determined moderator, or an alternative model that assumes that ventral striatal hypo-responsiveness is not related to trait impulsivity in specific but to other ADHD-related factors (Plichta & Scheres, 2014). However, another important point to note is the possibility that the reward magnitude in the 4-CSRTT may not have been high enough. Usually, studies on reward processing using e.g. the money incentive delay task apply 5$ as high magnitude reward condition and this has been reported to be crucial for test-retest reliability of ventral striatal response (Plichta & Scheres, 2015). Furthermore, ADHD patients have been shown to be especially sensitive to higher incentives, which has been interpreted as reflecting a greater motivational threshold (Liddle et al., 2011). Thus, it is possible that application of 1€ as high reward condition was not sufficient to elicit differential activation in the ventral striatum depending on the level of ADHD symptoms. By contrast, both IA and H/I phenotypes were found to be significantly related to increases in HC activity during reward anticipation. An increase in hippocampal activity during reward processing was also found in healthy young adults, while performing the fMRI version of 4-CSRTT, interpreted as reflecting reward prediction and evaluation of future outcomes (Neufang et al., 2016). This indicates that within the WI-network, ADHD symptomatology may not map linearly on altered reward processing per se but might be associated with reward-related learning.

On the behavioral level, H/I symptoms were associated with greater task-related impairment in terms of longer RTs during successful trials. This is in line with previous reports of slower response latencies in individuals with higher levels of ADHD trait scores during response inhibition paradigms such as the stop signal task (Lipszyc & Schachar, 2010). In this context, slower RTs in patients with ADHD have been interpreted as reflecting

deficient response inhibition processes (Schachar, Mota, Logan, Tannock, & Klim, 2000) and reductions of attention (Weissman, Warner, & Woldorff, 2009). In addition, higher levels of H/I were also related to greater RTV, which has been proposed to reflect a more precise behavioral correlate of attentional lapses on response inhibition paradigms (see e.g. Epstein et al., 2011; review by Tamm et al., 2012). Contrary to the hypotheses, H/I was not found to be related to increased WI on the behavioral level, as there was no correlation between the number of PR and parent ratings of ADHD symptoms. Until now, there is only one other study investigating WI in terms of premature responding in patients with ADHD. Premature responding was found to be a significant predictor of ADHD diagnosis and correlated positively with parent ratings of ADHD, conduct and oppositional defiant disorder as well as with self-report ratings of motoric and non-planning aspects of impulsivity and delay aversion (Van Dessel, Morsink, et al., 2019). However, the sample investigated in that study consisted of children aged 8-12 years, thus a considerably narrower age range than in this study. Premature responding was negatively associated with age in the current sample, consistent with the decline of impulsivity in adolescence (Steinberg et al., 2008). It is possible, that these strong age effects covered a potential relation between WI and parent-rated ADHD symptoms in this study or that the relationship between WI and ADHD behavioral domains is stronger in or specific to younger subjects. Further, age was not used as a covariate in van Dessel et al. (2019) and no correlation analysis with behavioral parameters was reported, so a possible influence of age on the case-control comparison remains unknown.

It was also hypothesized that H/I would positively correlate with the Mot_Ind. This was partly confirmed as moderation analyses revealed that the relationship between H/I and motivation varied as a function of HC activity in anticipation of reward. For high hyperactive/impulsive subjects and trend-wise for moderate levels of H/I, greater activation in the HC predicted motivation on the behavioral level. As outlined before, HC activity in reward

processing has been implicated in prospection and evaluation of outcomes (Peters & Buchel, 2011). According to the developers of the 4-CSRTT paradigm, the Mot_Ind allows "testing either differences [in RT] in responding to over-learned instrumental goal-directed behavior tested in extinction, or if the target becomes conditioned to the reward, then testing responding to the conditioned stimulus in extinction" (Voon, 2014). So, it is possible that those subjects with high H/I, who adequately processed the outcome of the response-reward relationship, improved their responding in order to earn reward. At the same time, it might be that those high H/I subjects, who did not realize this contingency, even negative motivation indices on average, which probably reflects frustration or fatigue. While this could be due to the already mentioned heightened motivational threshold according to the magnitude of reward in ADHD patients, this also implies that altered reward processing may at least to some extent depend on awareness. It is interesting to note that across all subjects, the Mot_Ind covaried significantly with the number of PR, which supports the notion that this specific form of impulsivity arises as a consequence of heightened reward sensitivity (Mechelmans et al., 2017).

IV. STUDY II

4.1 Methods

4.1.1 Genotyping

DNA was extracted from whole blood or buccal swabs. Standard PCR (polymerase chain reaction)-protocols were applied to amplify a 309 bp fragment containing the *TPH2 G-703T* (rs4570625) SNP at nucleotide position -703 upstream of the transcription start site of *TPH2.* For amplification the forward primer SNP25 5'-TTTCCATGATTTCCAGTAGA-GAG-3´ and a modified reverse primer SNP25 5'-AAGCTTTTTCTGACTTGACAAAT-3´ were used. The PCR mix (25 µl total) included 18 µl double-distilled water, 15 mM magnesium chloride (2.5 µl), 1 µl of each of the primers, 2.5 mM of each nucleotide (1 µl), 0.5 µl Taq polymerase and 1 µl genomic DNA. PCR reaction started with an initial denaturation step at 95°C for 5 minutes, which was followed by 40 cycles of denaturation at 95°C for 45 seconds, annealing at 55°C for 45 seconds and extension at 72°C for 45 seconds and a final elongation at 72°C for 3 minutes. The PCR products were digested for 16 hours at 37°C using the restriction endonuclease Xap1 and separated on a 4% agarose gel. Distinct DNA fragments were obtained that differed in size according to the respective genotype. The undigested fragment (309 bp) carried the T-allele and characterized TT-homozygotes. Digested products yielded two fragments of 24 and 285 bp, which identified GG-homozygotes. Accordingly, presence of three fragments (309, 24 and 285 bp) indicated G/T heterozygosity. Visualization was done by ethidium bromide staining using ultraviolet light.

4.1.2 Participants

Blood samples were available for 86 out of the 90 participants described in study I. Fulfilment of the Hardy-Weinberg criteria for the *TPH2 G-703T* (rs4570625) polymorphism was

tested using the program DeFinetti (online tool provided by the Institute of Human Genetics, Helmholtz Center Munich, Germany: https://ihg.gsf.de/cgi-bin/hw/hwa1.pl). The observed *TPH2 G-703T* genotype distribution in the whole sample was as follows: GG=46 (53.5%), GT=37 (43.0%) and TT=3 (3.5%). No deviation from the corresponding Hardy-Weinberg equilibrium was found (p(exact)=0.25). The sample was stratified according to subjects homozygous for the G-allele (n=46) as well as to carriers of at least one T-allele (n=40). *A priori* differences between the genotype groups were examined using chi-square tests to describe the distribution of patients/TDC, diagnostic groups or males/females, while two-sample t-tests were used to compare demographic variables.

4.1.3 Statistical Analyses

Main effects of genotype were assessed by multiple analysis of covariance (MANCOVA) with the between-subject factor genotype (GG vs T-allele) and 4-CSRTT behavioral data (i.e. PR, Acc, Mot_Ind, RT_rew, RTV) or regional volumes of the 8 specified WI-networks regions (i.e. MFG, IFG pars orbitalis, triangularis and opercularis, ACC, NAcc, HC, AMY) as dependent variables. In terms of brain function, two-sample t-tests were conducted for contrast images of the conditions ‘cue’, ‘response inhibition’ and ‘reward anticipation’. Age and sex were included as covariates in all analyses.

To test whether the *TPH2 G-307T* genotype in combination with ADHD symptoms would be able to significantly explain variance in 4-CSRTT behavior as well as in related brain data, separate moderation models for the two ADHD dimension were estimated. Again, the model number 1 as specified in the SPSS macro PROCESS was used (see 3.1.2 and figure 2). On the behavioral level, parent-rated ADHD symptoms for either IA or H/I served as independent variable X, 4-CSRTT behavioral parameters as dependent variable Y, while genotype (GG/T-allele) was included as the moderator M. Similar models were tested for brain data, where either regional volume of the WI-network regions or contrast

images for the task conditions served as dependent variable Y, while age and sex were included as nuisance variables. Results were considered significant for an alpha level set at .05, two-tailed, while a *p*-value ≤.08 was considered as trend.

4.2 Results

4.2.1 *A priori* differences between TPH2 G-703T genotypes

A priori differences between *TPH2 G-703T* genotype groups are summarized in table 9. Distribution of patients and TDC subjects was balanced across both genotype groups ($X^2(1)=1.08$, $p=.299$), which was also the case when looking at TDC, ADHD-I and ADHD-C as diagnostic groups ($X^2(2)=2.85$, $p=.241$). The sex ratio was comparable as well (*p*(exact)=.728). Two sample *t*-tests did not reveal any significant differences regarding age ($t(84)=1.6$, $p=.104$) or intelligence level ($t(84)=-.67$, $p=.507$). On trend-level, higher ratings for ADHD symptoms were found for IA ($t(84)=1.8$, $p=.081$) as well as for H/I ($t(84)=1.9$, $p=.064$) in T-allele carriers. Ratings on the CBCL were comparable (internalizing problems: $t(84)=1.7$, $p=.090$, externalizing problems: $t(84)=1.3$, $p=.199$).

Table 9: Sample characteristic STUDY II.
(presented as M±SD and group differences as revealed by chi-square and two-sample t-tests)

	GG-homozygotes [*n* = 46]	**T-allele carriers [*n* = 40]**	**Statistics**
Group			
TDC	27	19	$X^2(1)=1.08$,
ADHD	19	21	$p=.299$
Diagnostic group			
TDC	27	19	$X^2(2)=2.85$,
ADHD-I	13	10	$p=.241$
ADHD-C	6	11	
Sex			
Females	4	5	p(exact)=.728
Males	42	35	
Age	13.2±2.3	12.4±2.3	$t(84)=1.6$, $p=.104$
IQ	104±15	106±13	$t(84)=-.67$, $p=.507$
IA	1.0±0.8	1.3±0.9	$t(84)=1.8$, $p=.081$
H/I	0.5±0.6	0.8±0.8	$t(84)=1.9$, $p=.064$
CBCL, internalizing	52.9±10.9	56.4±8.1	$t(84)=1.7$, $p=.090$
CBCL, externalizing	50.7±11.0	53.7±9.9	$t(84)=1.3$, $p=.199$

4.2.2 Main effect of *TPH2 G-307T* genotype

MANCOVA with the between-subject factor genotype (GG vs T-allele) and 4-CSRTT behavioral data as dependent variables, while covarying for age and sex, was used to identify possible main effects of the *TPH2 G-307T* genotype on WI-related behavior. As summarized in table 10, no significant main effect was found for any of the investigated measures.

Table 10: Comparison of *TPH2 G-703T* genotypes on 4-CSRTT behavioral performance. (presented as M±SD and MANCOVA results with age and sex as covariates)

	GG-homozygotes	**T-allele carriers**	**Statistics**
PR	2.7±.2	2.6±.2	F(1,84)=.03, *p*=.861
Acc	.79±.02	.78±.02	F(1,84)=.03, *p*=.861
Mot_Ind	.031±.01	.033±.01	F(1,84)=.02, *p*=.896
RT_rew	449±11	447±12	F(1,84)=.02, *p*=.875
RTV	.27±.01	.27±.01	F(1,84)=.07, *p*=.785

Regarding brain data, a similar MANCOVA model was set up for regional brain volumes of WI-related structures, while on the brain functional level two sample t-tests (GG vs T-allele) were run using contrast images of 'cue', 'response inhibition' as well as 'reward anticipation' as dependent variables and age and sex as covariates. The MANCOVA did not reveal significant differences of brain structure between the genotypes (see table 11), while in the fMRI analyses no clusters survived correction for multiple comparisons on voxel level.

Table 11: Comparison of regional volume in WI regions of *TPH2 G-703T* genotypes. (presented as M±SD and MANCOVA results with age and sex as covariates)

		GG-homozygotes	T-allele carriers	Statistics
MFG	L	.82±.022	.79 ±.023	F(1,84)=1.0, *p*=.332
	R	.70±.020	.69±.021	F(1,84)=.3, *p*=.616
IFG p. orb.	L	.07±.003	.07±.003	F(1,84)=.6, *p*=.439
	R	.07±.002	.07±.003	F(1,84)=.2, *p*=.631
IFG p. tri.	L	.22±.007	.21±.007	F(1,84)=2.9, *p*=.093
	R	.19±.007	.20±.007	F(1,84)=.3, *p*=.586
IFG p. op.	L	.27±.007	.27±.007	F(1,84)=.2, *p*=.685
	R	.25±.007	.24±.007	F(1,84)=.1, *p*=.725
ACC	L	.36±.008	.36±.008	F(1,84)=.2, *p*=.621
	R	.39±.008	.40±.008	F(1,84)=.3, *p*=.617
NAcc	L	.05±.001	.05±.001	F(1,84)=.1, *p*=.748
	R	.05±.001	.05±.001	F(1,84)=.4, *p*=.510
HC	L	.29±.004	.29±.004	F(1,84)=.5, *p*=.495
	R	.29±.004	.30±.004	F(1,84)=.3, *p*=.569
AMY	L	.12±.002	.12±.002	F(1,84)=2.6, *p*=.108
	R	.12±.002	.12±.002	F(1,84)=.3, *p*=.857

4.2.3 Interaction of *TPH2 G-307T* genotype and ADHD symptomatology

Behavioral data

To test whether the *TPH2 G-307T* genotype in combination with parent ratings of ADHD symptoms would be able to significantly explain variance in 4-CSRTT behavior as well as in related brain data, separate moderation models for the two ADHD dimensions were estimated.

For each dimension 5 moderation models were tested on the behavioral level using ADHD symptoms (either IA or H/I) as independent variable, *TPH2 G-307T* genotype as moderator and PR, Acc, Mot_Ind, RT_rew as well as RTV as dependent variables (covariates: age and sex). Table 12 gives an overview of the results of the interaction effects of IA or H/I and *TPH2 G-307T* genotype on behavioral measures of the 4-CSRTT. For a complete summary of the moderation analyses please refer to tables S4 (H/I) and S5 (IA) in the appendix.

Table 12: Interaction effects *TPH2 G-307T* genotype and IA or H/I on 4-CSRTT behavior.

	IATPH2 G-703T***			**H/I**TPH2 G-703T***		
	Coeff.	***t***	***p***	**Coeff.**	***t***	***p***
PR	-.469	-1.139	.258	-.325	-.620	.537
Acc	.060	1.779	.079	.015	.355	.724
Mot_Ind	-.015	-1.163	.248	.001	.035	.972
RTrew	11.316	.612	.542	-13.728	-.626	.533
RTV	-.013	-.673	.503	-.016	-.687	.494

A trend-level interaction of the genotype and levels of IA was found for the Acc measure (b_3=.060, t(85)=1.8, p=.079). The overall model explained 29% of the variance (R^2=.29, F(5,80)=6.4, p<.001), while inclusion of the interaction term accounted for 3% of the variance (R^2_{change}=.03, F(1,80)=3.2, p=.079). Follow-up of this interaction revealed that IA was negatively correlated with Acc only in GG-homozygotes (b=-.060, t(89)=2.4, p=.021), while the relationship was not significant in T-allele carriers (b<.001, t(89)=-.019, p=.985). To illustrate the interaction, Acc was plotted against IA in figure 6 and the differences between the genotypes are highlighted.

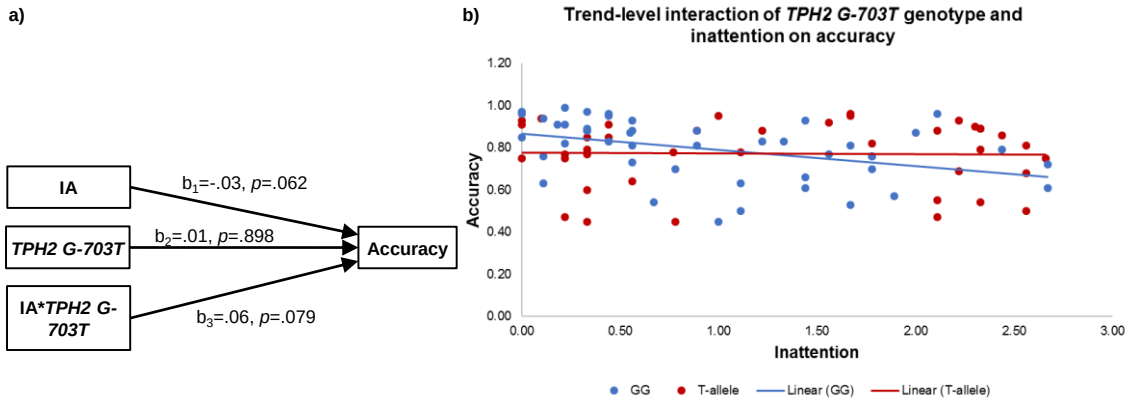

Figure 6: Behavior: Trend-level interaction of *TPH2 G-307T* genotype and IA on the Acc measure. a) Statistical path diagram showing the conditional effects of *TPH2 G-703T* genotype and IA as well as their interaction effect on Acc. b) The negative correlation between IA and Acc is present only in GG-homozygotes (blue), whereas no significant relationship was found for T-allele carriers (red).

fMRI data

On the neural activation level, separate moderation analyses were run using contrast images of either 'cue', 'response inhibition' or 'reward anticipation'. A significant interaction was found for *TPH2 G-703T* genotype and IA during the cue condition for left AMY activity ($F(1,80)=9.06$, $p_{FDR}<.05$). Follow up of this interaction by setting up t-contrasts revealed a significant effect of the interaction term in the AMY (cluster size $k=22$, peak voxel: x=-16, y=-2, z=-12, $t(84)=3.0$, $p_{FDR}<.05$). For illustrative purposes the contrast estimates at the peak voxel were extracted and plotted against IA in a scatterplot. As depicted in figure 7a, AMY activity decreased with greater IA in T-allele carriers, whereas the inverse relationship appeared in GG-homozygotes. Another interaction of *TPH2 G-307T* genotype and IA was found for right HC activity during response inhibition ($F(1,80)=9.04$, $p_{FDR}<.05$). A significant follow up t-contrast was found for the negative effect of the interaction term in the HC cluster (cluster size $k=434$, peak voxel: x=22, y=-24, z=-8, $t(84)=3.1$). Again, contrast estimates from the respective peak voxel were extracted and plotted against IA to illustrate the quality of the effect (see figure 7b).

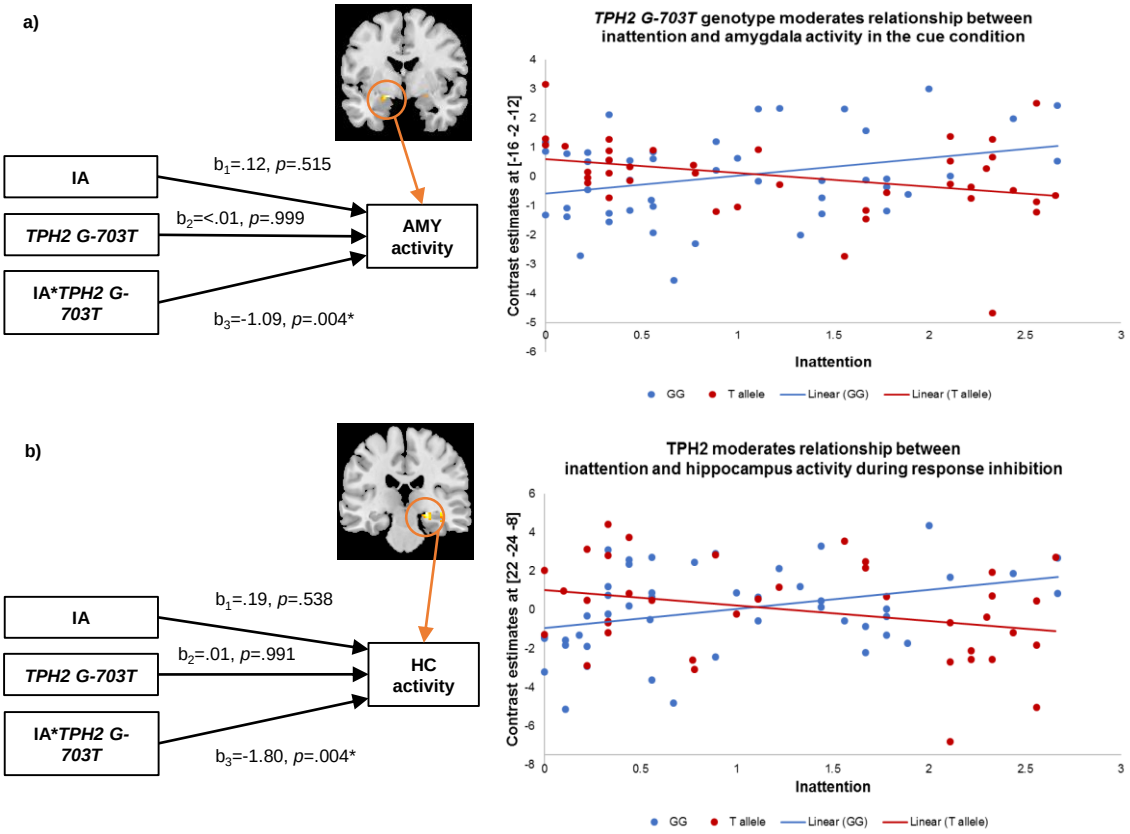

Figure 7: Brain activation: Interaction of *TPH2 G-307T* genotype and IA on AMY and HC activity. Conditional effects of *TPH2 G-703T* genotype and IA as well as their interaction effect on a) AMY activity and b) HC activity are summarized in statistical path diagrams (left), while scatterplots (right) illustrate the relationship of IA and brain activity in GG-homozygotes (blue) and in T-allele carriers (blue). *p<.05 uncorrected

sMRI data

An overview of moderation analyses on brain structural data (16 models per dimension) is given in table 13 (results for the interaction effects of IA or H/I and *TPH2 G-307T* genotype on regional volumes of WI network structures). For a complete summary of the moderation analyses please refer to tables S6 (H/I) and S7 (IA) in the appendix.

Table 13: Interaction effects *TPH2 G-307T* genotype and IA or H/I on WI-network structures.

		IATPH2 G-703T***			**H/I**TPH2 G-703T***		
		Coeff.	***t***	***p***	**Coeff.**	***t***	***p***
MFG	L	-.016	-.452	.653	-.039	-.831	.408
	R	-.062	-1.871	.065	-.058	-1.365	.176
IFG p. orb.	L	-.003	-.565	.574	-.006	-1.129	.262
	R	-.004	-.835	.406	-.005	-.970	.335
IFG p. tri.	L	.006	.503	.616	-.010	-.674	.502
	R	.011	1.005	.318	.004	.265	.792
IFG p. op.	L	-.008	-.673	.503	-.020	-1.423	.159
	R	.005	.517	.607	-.004	-.312	.756
ACC	L	.002	.640	.524	.002	.577	.566
	R	.001	.414	.680	.002	.932	.354
NAcc	L	.017	1.288	.201	.007	.405	.686
	R	.001	.096	.923	-.013	-.767	.445
HC	L	.004	.486	.628	-.011	-1.201	.233
	R	-.002	-.343	.732	-.014	-1.717	.090
AMY	L	-.001	-.139	.890	.000	-1.061	.292
	R	-.002	-.581	.563	-.011	-2.213	.030

Analyses revealed a significant effect of H/I and *TPH2 G-703T* on regional volume of the right AMY (b_3=-.011, t(85)=-2.2, p=.030). The overall model was not significant (F(5,80)=1.2, p=.342), while inclusion of the interaction term accounted for 6% of the variance (R^2_{change}=.06, F(1,80)=4.9, p=.030). Follow-up of this interaction did not reveal a significant relationship between right AMY volume and H/I in GG-homozygotes (b=.006, t(89)=1.5, p=.145), while it was just not in the trend-level range for T-allele carriers (b<-.005, t(89)=-1.7, p=.089). For illustrative purposes, values for right AMY volume of GG-

homozygotes and T-allele carriers were plotted against H/I in figure 8a. A trend-level interaction effect of IA and genotype on right MFG volume emerged (b_3=-.062, t(85)=-1.9, p=.065). The overall model showed a trend and explained 12% of the variance (R^2=.12 F(5,80)=2.0, p=.083), while inclusion of the interaction term accounted for 4% of the variance (R^2_{change}=.04, F(1,80)=3.5, p=.065). Follow-up of this interaction did reveal a significant relationship between right MFG volume and IA in T-allele carriers (b=-.065, t(89)=-3.1, p=.003), while no significant relationship between the two variables was found for GG-homozygotes (b<-.003, t(89)=-.13, p=.897). The interaction effect is shown in figure 8b.

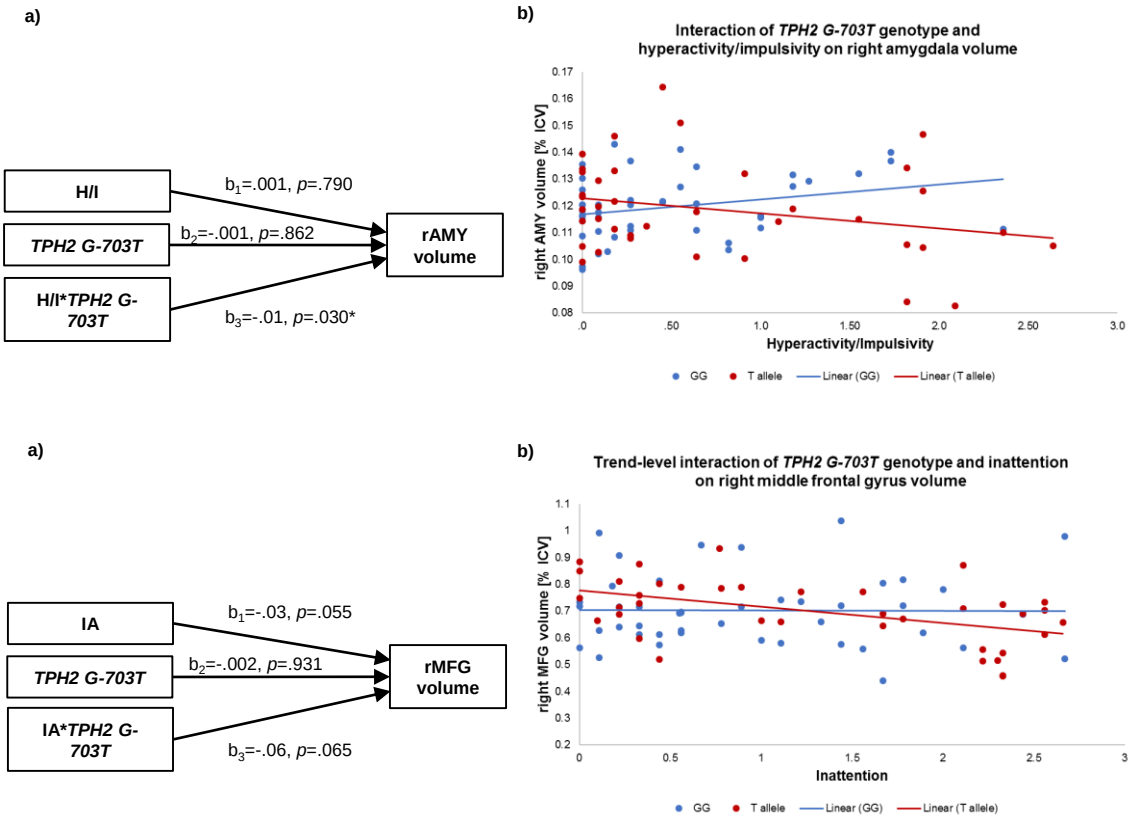

Figure 8: Brain structure: Interaction of *TPH2 G-307T* genotype and H/I on right AMY volume and trend-level interaction of *TPH2 G-307T* genotype and IA on right MFG volume.
Statistical path diagrams (left) showing the conditional effects of a) *TPH2 G-703T* genotype and H/I as well as their interaction effect on right AMY volume and b) of *TPH2 G-703T* genotype and IA as well as their interaction effect on right MFG volume. Scatterplots (right) show the relationship of ADHD symptoms and the respective regional brain volumes in GG-homozygotes (blue) and in T-allele carriers (red). *p<.05 uncorrected

4.3 Discussion

TPH2 G-703T genotype differences were found to depend mainly on levels of IA: On the behavioral level, a negative correlation between Acc and IA appeared to be present only in GG-homozygotes, whereas no significant relationship emerged for carriers of the T-allele. The G-allele of this variant has been associated with attentional performance before. In healthy volunteers, compared to TT-homozygotes, G-allele carriers made less errors and showed greater interference control on the attentional network test as well as faster conflict processing on “cognitive and emotional Stroop paradigms” (Osinsky et al., 2009; Reuter et al., 2007). Additionally, on tasks of goal-directed attention, GG-homozygotes outperformed T-allele carriers in terms of higher Acc measures and less variable or faster responding (Enge et al., 2014; Strobel et al., 2007). The only study that investigated the effects of *TPH2 G-703T* on executive control in adult ADHD found a similar relationship of the GG genotype, impaired task performance and case/control status as the current study: patients in the GG-group showed greater deficits of response control in terms of more errors of commission as well as omission on the continuous performance task than control subjects homozygous for the G-allele, while this effect was not found for carriers of the T-allele (Baehne et al., 2009). Reduced cerebral serotonin as evoked by tryptophan depletion lead to greater premature responding in healthy volunteers but was also associated with increased Acc (Worbe et al., 2014), whereas in ADHD patients more lapses of attention occurred and Acc decreased following the depletion procedure (Mette et al., 2013; Zepf et al., 2010). This also hints towards differential effects of serotonergic modulation on attentional performance depending on the presence or absence of ADHD symptomatology. Similarly, studies on stopping impulsivity in healthy subjects reported no effect of tryptophan depletion (Clark et al., 2005; Cools et al., 2005), while others found impairments in action cancellation in subjects with a family history of impulse control disorders (Crean et al., 2002). Finally, the effect of the *TPH2 G-703T* polymorphism was also

moderated by the extent of WI in healthy male adults in a way that it were only the high impulsive T-allele carriers, who showed aberrant top-down control and enhanced anticipation of reward (Neufang et al., 2016).

A possible mechanism that could mediate the differential influence of *TPH2 G-703T* on cognitive control is serotonergic modulation of the PFC. In the study by Baehne and colleagues, GG-homozygotes were related to an altered topography of go- and no-go centroids in the electroencephalogram during response inhibition on the continuous performance task, which was used as a proxy of prefrontal brain function (Baehne et al., 2009). On the structural level, lower gray matter concentration in the inferior orbitofrontal cortex in healthy GG-homozygotes was reported in a study using voxel-based morphometry (Yoon, Lee, Kim, Lee, & Ham, 2012). Others identified *TPH2* polymorphisms that significantly explained variance in the regional rate of serotonin synthesis in the orbitofrontal PFC as measured by positron emission tomography (Booij et al., 2012). In the present study, a trend-wise interaction effect of IA and *TPH2 G-703T* genotype was found for the structure of the right MFG. A negative correlation between IA and MFG volume was revealed by the follow-up analyses in T-allele carriers only. Interestingly, no significant relationship was found in GG-homozygotes, thus contrasting the results for Acc on the behavioral level in this study as well as the reports mentioned above that related prefrontal abnormalities mainly to the G-allele (Baehne et al., 2009; Yoon et al., 2012). However, in absence of any findings concerning prefrontal activity during performance of the 4-CSRTT, the functional significance of these results remains uncertain. Furthermore, methodological differences, e.g. analysis via freesurfer and the use of a complex behavioral task as well as that the present data was from minors, while the above-mentioned studies were all on adults, should be considered. It might be reasonably assumed that the mechanism underlying serotonergic PFC modulation and its effect on cognitive control is more

complex, especially so in the developing brain. Nevertheless, the current findings emphasize the importance of the PFC as a neural substrate of serotonergic transmission.

In studies on emotion regulation in healthy participants, variation in the *TPH2 G-703T* polymorphism has repeatedly been reported to modulate AMY responsiveness towards stimuli of positive and negative valence (Brown et al., 2005; Canli, Congdon, Gutknecht, Constable, & Lesch, 2005; Canli, Congdon, Todd Constable, & Lesch, 2008; Herrmann et al., 2007). This was also found in the current study as during cue processing, AMY activation differed between genotypes depending on the level of IA. In T-allele carriers, AMY activity decreased with greater IA, whereas the opposite relationship was found in GG-homozygotes. In addition, the *TPH2 G-703T* genotype also modulated activity in the HC. During response inhibition, HC activity decreased with greater IA in T-allele carriers, while the reverse pattern was observed in subjects homozygous for the G-allele. Another way to interpret this, is to propose that AMY/HC activation was greater for T-allele carriers than for GG-homozygotes in absence of ADHD-related symptoms of IA (i.e. in “health”), but lower for high (i.e. clinically relevant) levels of IA. Data from healthy subjects showed that T-allele carriers exhibit enhanced AMY activity towards emotionally arousing stimuli (e.g. Brown et al., 2005; Canli et al., 2005), while in ADHD patients, AMY hyperactivation has been associated with delay aversion of reward (Van Dessel, Sonuga-Barke, et al., 2019). In the context of the present study, this could be interpreted as an enhanced emotional reaction towards a stimulus (i.e. the ‘cue’) that is coding the next chance to win a reward, which is differentially modulated by *TPH2 G-703T* variation in subjects that exhibit greater levels of ADHD IA symptoms. In healthy adults, the T-allele was also associated with enhanced excitatory activity in anticipation of reward during the 4-CSRTT, but this time in the NAcc (Neufang et al., 2016). Others found the polymorphism to be related to a measure of reward sensitivity, which was especially evident in TT-homozygotes (Pulver et al., 2020). Interestingly, a recent study on DNA methylation patterns of ADHD candidate

genes reported that methylation of the *TPH2* gene correlated significantly with improvements in RTV depending on the availability of incentives in a sample of young boys aged 6-8 years (Heinrich et al., 2017). Furthermore, maternal ratings of ADHD behavior, using the same questionnaire as the present study, correlated positively with DNA methylation of *TPH2*. This also hints towards a link between *TPH2*, reward-related processes and the severity of ADHD symptomatology.

The relationship between AMY and HC and variation in *TPH2 G-703T* has also been reported on the structural level. In the present study, a significant interaction effect of symptoms of H/I and genotype were found for regional volume of the right AMY. Others found T-allele carriers to have smaller volumes of AMY and HC compared to GG-homozygotes and to be further associated with greater reward dependence as measured by a personality inventory (Inoue et al., 2010). Additionally, variation in *TPH2 G-703T* has been linked to altered associations between trait anxiety and AMY–HC connectivity (Hahn et al., 2013). Connectivity between the two structures correlated positively with trait anxiety scores in subjects homozygous for the G-allele, while for T-allele carriers a negative relationship was shown. This was interpreted in the context of the reinforcement sensitivity theory as reflecting differential modulation of the behavioral inhibition system responsible for reactions to aversive events (Hahn et al., 2013). So, all in all, the present findings hint towards a serotonergic modulation of coding of the emotional value of reward during performance of the 4-CSRTT that varies depending on the presence or absence of traits associated with psychopathology. In addition, it is interesting to note that the T-allele has been linked to emotional instability as well as to personality disorders and major depression (Harvey et al., 2004; Kataja et al., 2020; Ottenhof, Sild, Levesque, Ruhe, & Booij, 2018). Differences in emotional functioning have been identified as separate contributing factor to ADHD: it was reported that a substantial subgroup of children with ADHD was characterized by emotional dysregulation that was independent of executive function deficits

(Sjowall et al., 2013). Serotonergic modulation of AMY/HC activity and the influence of structural differences in these brain regions might be a reasonable neural substrate for this observation.

Together, the findings of the present study are broadly in line with previous reports of an association of the *TPH2 G-703T* polymorphism and attentional control as well as AMY reactivity to emotionally salient cues. It implicates that in the context of ADHD, serotonergic modulation may play a role especially in affective structures of the WI-network as well as for attentional control on the behavioral level, which is likely mediated by prefrontal brain activity. In accordance with findings from tryptophan depletion studies, this implicates that central nervous availability of serotonin plays a role in attentional processes related with ADHD. However, as the functional consequences of the *TPH2 G-703T* variant concerning brain serotonin levels are still unclear (see 1.4.1), interpretations in terms of either increased serotonin or deprivation thereof remain speculative. Nevertheless, based on differential findings for the two alleles a dual role of both deficit or increase of *TPH2* activity is likely (Kulikova & Kulikov, 2019). This has also been reported for other genetic variants involved in serotonergic transmission such as the serotonin transporter-linked polymorphic region (Homberg & Lesch, 2011). Interestingly, an additive effective of the short variant of this polymorphism and T-allele carrier status for *TPH2 G-703T* was found concerning enhanced neural activity during processing of emotional stimuli (Herrmann et al., 2007).

Nevertheless, as the analyses of the present study were exploratory, the interpretation of the findings should be considered as preliminary and treated with caution. Serotonin synthesis and therewith cerebral serotonin levels do not necessarily predict concentration of the neurotransmitter at the synapse. Thus, other genetic variants coding for pre- and postsynaptic receptors or transporters are likely to further influence the effect of serotonin. As mentioned before, in healthy subjects, additive effects of *TPH2 G-703T* and variation in

the promotor region of the serotonin transporter have been reported (Canli et al., 2008; Herrmann et al., 2007), which were further moderated by environmental factors such as traumatic life events (Hermann et al., 2012). But also interaction effects with e.g. other neurotransmitters such as the noradrenergic system (Enge et al., 2014) or with a well-studied polymorphism in the gene coding for brain-derived neurotrophic factor (BDNF Val^{66}Met) (Latsko et al., 2016) have been investigated. Likewise, ADHD has also been associated with polymorphisms e.g. in the serotonin transporter gene (Sonuga-Barke et al., 2011) and its promotor region (Manor et al., 2001; Seeger, Schloss, & Schmidt, 2001) or in genes coding for serotonin receptors (Hawi et al., 2002; Quist et al., 2000), of which one was specifically related with ADHD-I (Smoller et al., 2006). This again highlights the polygenic nature of ADHD but also shows that some genetic variation contributes differentially to the two diagnostic symptom domains as it was also the case in the present study. It furthermore emphasizes that "whether genetic vulnerability will be expressed behaviorally may depend on other biological and environmental factors" (Booij et al., 2012) that need to be taken into careful consideration.

V. GENERAL DISCUSSION

Focus of this dissertation thesis were the biological substrates of WI and their relation to the two symptom domains of ADHD in children and adolescents with and without diagnosis of the disorder. Using a dimensional research approach, domain-specific as well as overlapping manifestations were identified in the neural network. In study I, symptoms of IA were specifically related with the dlPFC. On the structural level, regional volume of the left MFG correlated negatively with IA, while during 'cue'-processing, activity in the left dlPFC increased with greater IA. H/I was related to decreased activity in several prefrontal top-down control regions such as the vmPFC and vlPFC as well as ACC during 'response inhibition', whereas symptoms of IA were negatively related to vlPFC activity only. Both symptom domains were positively correlated with activity in the HC in anticipation of reward. On the behavioral level H/I was associated with a greater task-related impairment (i.e. longer RTs and greater RTV during rewarded trials). Analyses of interaction effects of neural correlates and ADHD symptoms on WI behavior revealed that the relationship between Acc and H/I was moderated by activation in the right vlPFC during response inhibition. For low/moderate levels of H/I, greater vlPFC activity predicted greater Acc. Furthermore, activity in the left HC significantly moderated the relationship between the Mot_Ind and H/I. For high levels of H/I, greater HC activation was significantly associated with greater motivation.

In the second study, moderation analyses revealed *TPH2 G-703T* genotype differences depending on levels of IA: On the behavioral level, an interaction effect between the two variables was found for the Acc measure. Follow-up analyses revealed a negative correlation between Acc and IA only in GG-homozygotes, whereas no significant relationship emerged for carriers of the T-allele. During the cue condition, AMY activation decreased with greater IA in T-allele carriers, whereas the opposite relationship was found in GG-homozygotes. Similarly, HC activity decreased with greater IA in T-allele carriers during

response inhibition, while the reversed pattern was observed in subjects homozygous for the G-allele. On the brain structural level, a trend-wise interaction effect of *TPH2 G-703T* genotype and IA emerged for regional volume of the right MFG. A negative correlation between MFG volume and IA for T-allele carriers, but no signification relationship between the two variables for GG-homozygotes, was revealed by follow-up analyses. For the H/I domain, an interaction effect with the genotype was found for the volume of the right AMY. Subsequent follow-up analyses did not yield significant results for the relationship of H/I and right AMY volume for any of the two genotype groups.

All in all, in study I, plausible neural correlates of the two symptom domains were identified and associated with WI on the behavioral level. As expected, IA was associated with brain regions linked with executive functions and attentional control. H/I in return, revealed a more profound influence on WI processing that went beyond pure response inhibition deficits and additionally implicated dysfunctional top-down control of reward evaluation. Study II highlighted that variation in *TPH2 G-703T* appears to modulate attentional performance on the behavioral level but also the response in brain regions associated with emotional processing depending on the degree of IA symptoms. Moderation analyses in study I emphasized that H/I-related decreased activation in the vlPFC is not solely responsible for the observed difficulties on the behavioral level, as vlPFC was a significant predictor of Acc only, when H/I symptoms were low/absent. Together with the findings from the multiple regression analyses that activity in other frontal regions (i.e. vmPFC and ACC) was also negatively associated with H/I, this corroborates the conceptualization that ADHD symptomatology is related to weaknesses in widespread neural systems rather than based on single deficient structures (Aron et al., 2014; Whelan et al., 2012). Interestingly, the results from study II additionally hint towards a serotonergic modulation of attentional performance. Only for GG-homozygotes of the *TPH2 G-703T* variant a negative relationship between Acc and IA emerged, which was not found in T-allele carriers. It is probable

that the PFC structures identified in study I are the neural substrate of this serotonergic modulation, which was also indicated by an interaction effect of ADHD symptomatology and *TPH2 G-703T* genotype on structure of the right MFG in study II. As the PFC is still undergoing maturation during adolescence (Fuster, 2002), it is likely that developmental effects additionally influence the gene x PFC brain activity x ADHD symptoms relationship. Due to the characteristics of the sample (large age-range) and limitations of statistical power, the examination of this hypothesis was beyond the scope of the present work.

Furthermore, in study I, HC activation during reward anticipation predicted a greater Mot_Ind only, when H/I levels were high, hinting towards differences in reward-related learning that were associated with motivation on the behavioral level. These results imply that contingency awareness possibly mediates the relationship between altered motivation and sensitivity to reinforcement that is hypothesized to lead up to performance deficits in ADHD patients. In addition to that, moderation analysis of study II further revealed that variation in *TPH2 G-703T* appears to influence coding of the emotional value of reward during performance of the 4-CSRTT depending on the presence or absence of IA symptoms. Both HC and AMY activity were differently related to IA according to *TPH2 G-703T* genotype: in GG-homozygotes, the activity in both regions increased with greater IA, whereas the opposite was observed in T-allele carriers. This provides further evidence that reward-related processing in the context of ADHD does not simply vary as a function of increasing symptoms on the behavioral level but is also influenced by additional, e.g. genetic, factors. Although the effect of one single variant should not be over-interpreted in a polygenic disorder such as ADHD, the present findings fit well with previous reports that identified the *TPH2* gene as a risk locus for psychiatric disorders (Ottenhof et al., 2018). Furthermore, it emphasizes the relevance of serotonergic transmission for attentional and emotional processing in the context of ADHD pathophysiology.

Finally, it is remarkable that whereas in study I the behavioral and neural correlates of WI as well as their interaction effects were mainly related to H/I, the results of study II showed that variation in *TPH2 G-703T* and therewith serotonergic modulation appears to be especially relevant for the IA domain. This is in accordance with the view that although IA and H/I have been shown to be valid characterizations of the clinical phenotype of ADHD (Bidwell et al., 2017; Willcutt et al., 2012), the biological pathways leading to their occurrence are likely diverse (Coghill & Sonuga-Barke, 2012; Sonuga-Barke et al., 2010). In study I, the bias in favor of the H/I phenotype might be due to the fact, that the examined WI-network is one form of impulsivity, and thus, addresses impulsivity-relevant brain regions and cognitive processes more directly than attention-related parameters. The second study was in line with previous reports describing contrasting effects of cerebral availability of serotonin on attentional control in patients and control subjects but indicated that in the present sample this was not related to the diagnosis per se yet depended mainly on the severity of IA symptoms.

The results of the present studies may also have clinical implications. ADHD-related behavioral problems and neurocognitive impairments as described in study I are typically treated with pharmacological and/or cognitive behavioral therapies. Psychological treatments that aim to improve inadequate conduct, often include incentives and are based on reinforcement contingencies (Daley et al., 2014). Obviously, motivation and sensitivity to reward play a great role in the outcome of such approaches. The findings in study I that in subjects with high H/I motivation to earn a reward varied depending on the degree of reinforcement-learning is important to consider, when adapting treatment plans for individual patient needs. In addition, study II highlighted that the emotional value and coding of reward is differentially modulated by serotonin in some patients. Pharmacologic treatment options mainly concentrate on the effects of dopamine and norepinephrine and clinical studies did not find conclusive evidence that e.g. serotonin reuptake inhibitors are effective

therapy options for ADHD in general (Riley & Overton, 2019). However, the current findings implicate that there may be a specific subgroup of patients, who are sensitive to serotonergic modulation and could benefit from such medication. Others also pointed out that interaction effects of dopamine and serotonin should be considered as well (Oades, 2008). The effects of serotonergic modulation identified in study II were especially related to the IA domain. Given the pervasiveness of IA symptoms across the lifetime and the risk of insufficient long-term response to stimulant medication, it is necessary to further exploit such possibilities to increase treatment success.

VI. LIMITATIONS AND CONCLUSION

The presented studies may also include limitations that should be considered when interpreting the results. In line with earlier findings of ADHD subgroups, IA influenced brain activation in regions associated with executive functions and attention-related regions. H/I, in return revealed a more profound influence on WI as significant manifestations were documented on behavioral performance and brain activation. Despite this risk of bias, the 4-CSRTT includes the two crucial cognitions in one paradigm, which have been described to differentiate ADHD-I and ADHD-C: executive functions and impulsivity-related reward processing (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Dosenbach et al., 2008; Musser et al., 2011; for a review see Nigg & Casey, 2005; Sagvolden et al., 2005). The dimensional approach that was used in this study followed the idea of the RDoC to address neuro-psychiatric impairments in terms of a gradual change rather than dichotomizing it in “healthy” and “diagnosis”. To date, however, the number of studies using the same approach in the field of ADHD is very small (but see e.g. Fair, Nigg, et al., 2012; Larsson et al., 2012; Shaw et al., 2011). Therefore, the references used to discuss and interpret the results were mainly to findings from group-comparisons. But also shared manifestations similarly related to both symptom domains were found that may reflect effects of ADHD as a diagnostic entity. This shows a relative strength of the dimensional

approach that is to be able to cover both aspects of contemporary discussion concerning ADHD nosology (Coghill & Sonuga-Barke, 2012). However, for some traits and their neural correlates, e.g. aberrant reward processing and related activity in the ventral striatum, linear models may not be useful as there appear to be some non-linear discontinuities in the ADHD spectrum, which need to be addressed with other statistical approaches (Salum et al., 2014).

Furthermore, the characteristics of the present sample may imply some limitations. Aiming to investigate the complete spectrum of ADHD symptoms by investigating both healthy individuals and patients, a representative sample of ADHD patients with ADHD-I and ADHD-C presentations was included. Unfortunately, it was not possible to recruit a purely "hyperactive/impulsive" subgroup as the ADHD-HI presentation is the least prevalent one (Willcutt, 2012). Comorbidities such as major depression or pervasive developmental disorders were excluded, while conduct or anxiety disorders were not. Of course, this increased the heterogeneity of the investigated sample, but may also better reflect clinical reality. However, in order to increase the cross-categorical relevance of WI beyond variation in health and one DSM-V diagnostic group, future studies should also include subjects with other impulsivity-related (developmental) disorders (see e.g. van Hulst et al., 2017) and investigate the respective qualitative effects in more detail. Finally, the sample covered a broad age range (8-18 years). This was addressed by using age as a covariate in all analyses and robust effects were found that appear independent of developmental changes in this time frame. However, to address developmental changes, which may also follow a non-linear course, higher powered studies, able to form well-defined age-subgroups, are necessary.

Concerning the current paradigm change to replace case-control comparisons with dimensional studies to increase clinical applicability of the results, it was corroborated that some ADHD-related deficits show a dimensional linear course from healthy to clinically relevant

manifestations. The moderation analyses revealed that the relationship between behavioral performance and aberrant brain function is not always straight forward but also depending on other factors related to the disorder. It becomes also clear that looking at only one level of impairment (e.g. behavioral or brain functional) is not likely to significantly improve our understanding of what causes and characterizes ADHD biologically. The dimensional approach is a promising step in this direction, although it does not necessarily resolve the clinical dilemma to define the threshold of where the impairment is severe enough to be in need of treatment (Matte, Rohde, & Grevet, 2012). Nevertheless, it is hoped that it will inform targets for therapeutic interventions as well as the question of who will benefit best from what kind of treatment (Lenet, 2017; Robbins et al., 2012). In the future, the qualitive information from small scale studies such as the present work will probably be relevant in studies that apply e.g. machine learning algorithms to model the complex interplay of different risk profiles in psychiatric disorders (Tai et al., 2019).

Taken together, it was shown that the 4-CSRTT taps distinct domains of impulsivity with relevance to ADHD symptomatology: (proactive) response inhibition with anticipation of reward, which may better reflect the nature of impulsivity implicated in the pathophysiology of the disorder than other paradigms that measure “pure” response inhibition. Furthermore, the two symptom domains, IA and H/I, contribute differently to WI, which was evident especially on the neural level. Investigation of the effects of the *TPH2 G-703T* genetic variant highlighted the relevance of serotonergic transmission especially for attentional control and emotional processing. Although the present findings need replication and further refinement in more homogenous age groups, the use of the 4-CSRTT with a dimensional approach is a very promising strategy, which will hopefully extend our understanding of impulsivity-related mental disorders in the future.

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APPENDIX

Supplementary Information

Condition-specific activation patterns were established across all subjects using one-sample t-tests with contrast-images for ‘cue’, ‘response inhibition’ and ‘reward anticipation’ as dependent variables. The ‘cue’ condition was characterized by activity in the bilateral putamen (t_{left}=6.3, t_{right}=5.8). During the 'response inhibition' condition, significantly activated frontal regions were found in the left and right MFG (t_{right}=13.5; t_{left}=14.4), in the left IFG (p. opercular, t=13.3, and p. triangularis, t=11.9) and the dorsal ACC (t_{left}=12.7, t_{right}=11.6). Additionally, mediotemporal regions such as the HC (t_{right}=12.9, t_{left}=13.8) and AMY (t_{right}=7.2, t_{left}=6.6) as well as striatal regions such as the NAcc (t_{right}=8.1, t_{left}=8.0) and right putamen (t=6,1) were involved. 'Reward anticipation' was related to significant activations in the right putamen (t=5.1) and the left HC (t=4.8). For a detailed description of activated network regions during task processing see table S1 in the appendix, while figure S1 gives an overview.

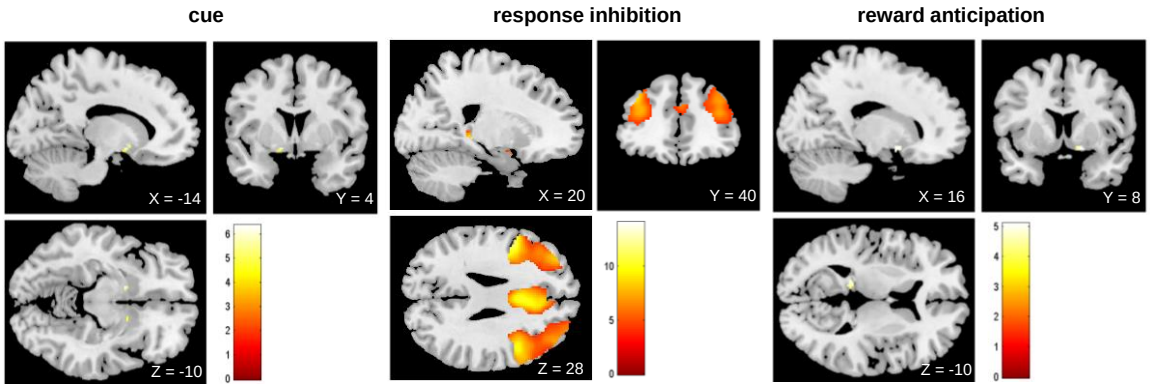

Figure S1. Condition-specific activation patterns for ‘cue’, ‘response inhibition’ and ‘reward anticipation’. target and reward. Color bars represent T-scores (significant at p<0.05 FWE corrected).

Table S1. Condition-specific brain activation, as revealed by one sample t-tests across all subjects.

Region		*k*	x	y	z	Z	T
Positive effect of 'cue'							
Putamen	L	8	-14	4	-10	5.7	6.3
	R	6	14	6	-8	5.3	5.8
Positive effect of 'response inhibition'							
Middle frontal gyrus	R	5427	38	-4	64	>8	13.5
			50	16	-2	>8	10.9
			42	6	38	>8	10.0
		17	32	60	-2	4.6	4.9
	L	284	-30	-6	64	>8	14.4
			-30	-6	52	>8	14.2
			-42	2	52	6.9	8.0
Inferior frontal gyrus (p. operc.)	L	3756	-52	8	28	>8	13.3
			-54	6	6	>8	11.1
Inferior frontal gyrus (p. triang.)			-32	20	10	>8	11.9
Anterior Cingulate Cortex	L	1295	-2	10	30	>8	12.7
	R		4	20	28	>8	11.6
Hippocampus	R	411	24	-28	-6	>8	12.9
			36	-10	-14	4.8	5.1
Amygdala	R		18	2	-16	6.4	7.2
Hippocampus	L	361	-22	-28	-6	>8	13.8
Amygdala	L		-18	0	-14	5.9	6.6
			-16	-10	-12	4.9	5.3
N. Accumbens	R	54	10	8	-8	7.0	8.1
Putamen	R		16	6	-14	5.6	6.1
N. Accumbens	L	30	-10	6	-8	6.9	8.0
Positive effect of 'reward anticipation'							
Putamen	R	21	16	8	-10	4.8	5.1
Hippocampus	L	11	-16	-36	-10	4.5	4.8

Note. p. triang: pars triangularis; p. operc: pars opercularis; L: left hemisphere, R: right hemisphere; k: cluster size in no of voxels; all results significant at $p<0.05$ FWE corrected

Table S2. Moderation models for neural correlates of H/I and H/I on 4-CSRTT behavior.

PREMATURE RESPONSES

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.099	2.567	1.823	5, 83	.117			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→PR	b_1	-.196	.287	-.684	.496	-.766	.374
2 (M→Y)	$vmPFC_{act}$→PR	b_2	.017	.103	.161	.872	-.188	.221
3 (X*M→Y)	H/I*$vmPFC_{act}$→PR	b_3	-.006	.129	-.044	.965	-.262	.250

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.106	2.547	1.969	5, 83	.092			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→PR	b_1	-.246	.269	-.914	.363	-.782	.290
2 (M→Y)	ACC_{act}→PR	b_2	-.063	.081	-.775	.441	-.223	.098
3 (X*M→Y)	H/I*ACC_{act}→PR	b_3	.053	.110	.481	.632	-.166	.272

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.124	2.493	2373	5, 83	.046			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→PR	b_1	-.278	.265	-1.051	.296	-.805	.248
2 (M→Y)	ACC_{act}→PR	b_2	-.093	.063	-1.465	.147	-.219	.033
3 (X*M→Y)	H/I*ACC_{act}→PR	b_3	.082	.087	.939	.350	-.092	.256

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.141	2.449	2.716	5, 83	.025			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→PR	b_1	-.286	.262	-1.094	.277	-.806	.234
2 (M→Y)	$vlPFC_{act}$→PR	b_2	-.173	.099	-1.746	.084	-.370	.024
3 (X*M→Y)	H/I*$vlPFC_{act}$→PR	b_3	.180	.130	1.388	.169	-.078	.438

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.111	2.432	2.072	5, 83	.077			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→PR	b_1	-.037	.265	-.140	.889	-.563	.489
2 (M→Y)	HC_{act} →PR	b_2	-.143	.095	-1.511	.135	-.331	.045
3 (X*M→Y)	H/I*HC_{act}→PR	b_3	.069	.114	.609	.544	-.157	.296

Table S2 (continued). Moderation models for neural correlates of H/I and H/I on 4-CSRTT behavior.

ACCURACY

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.264	.018	5.960	5, 83	<.001			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→Acc	b_1	-.053	.024	-2.212	.030	-.100	-.005
2 (M→Y)	$vmPFC_{act}$→Acc	b_2	-.005	.009	-.568	.571	-.022	.012
3 (X*M→Y)	H/I*$vmPFC_{act}$→Acc	b_3	-.012	.011	-1.122	.265	-.033	.009

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.304	.017	7.236	5, 83	<.001			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→Acc	b_1	-.041	.022	-1.866	.066	-.084	.003
2 (M→Y)	ACC_{act}→Acc	b_2	.010	.007	1.562	.122	-.003	.023
3 (X*M→Y)	H/I*ACC_{act}→Acc	b_3	-.021	.009	-2.351	.021	-.039	-.003

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.288	.017	6.727	5, 83	<.001			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→Acc	b_1	-.040	.022	-1.812	.074	-.083	.004
2 (M→Y)	ACC_{act}→Acc	b_2	.007	.005	1.286	.202	-.004	.017
3 (X*M→Y)	H/I*ACC_{act}→Acc	b_3	-.014	.007	-1.971	.052	-.029	.000

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.336	.016	8.406	5, 83	<.001			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→Acc	b_1	-.040	.021	-1.887	.063	-.082	.002
2 (M→Y)	$vlPFC_{act}$→Acc	b_2	.014	.008	1.806	.075	-.001	.030
3 (X*M→Y)	H/I*$vlPFC_{act}$→Acc	b_3	-.033	.010	-3.112	.003	-.053	-.012

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.271	.017	6.176	5, 83	<.001			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→Acc	b_1	-.050	.022	-2.237	.028	-.094	-.005
2 (M→Y)	HC_{act}→Acc	b_2	.012	.008	1.470	.145	-.004	.027
3 (X*M→Y)	H/I*HC_{act}→Acc	b_3	-.011	.010	-1.109	.271	-.030	.008

Table S2 (continued). Moderation models for neural correlates of H/I and H/I on 4-CSRTT behavior.

MOTIVATION INDEX

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.031	.003	.539	5, 83	.747			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→Mot_Ind	b_1	-.012	.009	-1.280	.204	-.030	.006
2 (M→Y)	$vmPFC_{act}$→Mot_Ind	b_2	.000	.003	.083	.934	-.006	.007
3 (X*M→Y)	H/I*$vmPFC_{act}$→MotInd	b_3	-.001	.004	-.151	.880	-.009	.008

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.038	.003	.658	5, 83	.656			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→Mot_Ind	b_1	-.010	.009	-1.202	.233	-.027	.007
2 (M→Y)	ACC_{act}→Mot_Ind	b_2	-.001	.003	-.216	.829	-.006	.005
3 (X*M→Y)	H/I*ACC_{act}→Mot_Ind	b_3	.003	.004	.778	.439	-.004	.010

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.038	.002	.653	5, 83	.660			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→Mot_Ind	b_1	-.009	.009	-1.074	.286	-.026	.008
2 (M→Y)	ACC_{act}→Mot_Ind	b_2	.001	.002	.637	.526	-.003	.005
3 (X*M→Y)	H/I*ACC_{act}→Mot_Ind	b_3	.001	.003	.250	.803	-.005	.006

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.074	.002	1.324	5, 83	.262			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→Mot_Ind	b_1	-.009	.008	-1.112	.269	-.026	.007
2 (M→Y)	$vlPFC_{act}$→Mot_Ind	b_2	-.001	.003	-.470	.640	-.008	.005
3 (X*M→Y)	H/I*$vlPFC_{act}$→Mot_Ind	b_3	.008	.004	1.958	.054	.000	.016

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.142	.002	2.749	5, 83	.024			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→Mot_Ind	b_1	-.018	.008	-2.315	.023	-.034	-.003
2 (M→Y)	HC_{act}→Mot_Ind	b_2	.002	.003	.594	.554	-.004	.007
3 (X*M→Y)	H/I*HC_{act}→Mot_Ind	b_3	.009	.003	2.679	.009	.002	.016

Table S2 (continued). Moderation models for neural correlates of H/I and H/I on 4-CSRTT behavior.

REACTION TIME REWARD

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.289	4371.549	6.753	5, 83	<.001			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→RT	b_1	34.534	11.823	2.921	.004	11.019	58.048
2 (M→Y)	$vmPFC_{act}$→RT	b_2	-7.346	4.239	-1.733	.087	-15.778	1.085
3 (X*M→Y)	H/I*$vmPFC_{act}$→RT	b_3	5.354	5.312	1.008	.316	-5.210	15.919

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.274	4464.394	6.268	5, 83	<.001			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→RT	b_1	32.426	11.281	2.874	.005	9.988	54.864
2 (M→Y)	ACC_{act}→RT	b_2	-3.804	3.383	-1.124	.264	-.533	2.925
3 (X*M→Y)	H/I*ACC_{act}→RT	b_3	-2.351	4.610	-.510	.611	-11.520	6.817

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.276	4451.513	6.334	5, 83	<.001			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→RT	b_1	32.421	11.185	2.899	.005	1.175	54.667
2 (M→Y)	ACC_{act}→RT	b_2	-3.397	2.683	-1.266	.209	-8.733	1.939
3 (X*M→Y)	H/I*ACC_{act}→RT	b_3	-1.641	3.693	-.444	.658	-8.987	5.704

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.273	4471.794	6.230	5, 83	<.001			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→RT	b_1	33.098	11.181	2.960	.004	10.860	55.336
2 (M→Y)	$vlPFC_{act}$→RT	b_2	-3.848	4.233	-.909	.366	-12.27	4.572
3 (X*M→Y)	H/I*$vlPFC_{act}$→RT	b_3	-4.162	5.546	-.751	.455	-15.193	6.868

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.234	4347.239	7.959	5, 83	<.001			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→RT	b_1	38.334	11.187	3.427	.001	16.084	6.585
2 (M→Y)	HC_{act}→RT	b_2	4.562	4.003	1.140	.258	-3.401	12.525
3 (X*M→Y)	H/I*HC_{act}→RT	b_3	-6.011	4.825	-1.246	.216	-15.608	3.586

Table S2 (continued). Moderation models for neural correlates of H/I and H/I on 4-CSRTT behavior.

REACTION TIME VARIABILITY

Model summary	**R-sq**	**MSE**	**F**		**Df**	***p***			
	.142	.005	2.756		5, 83	.024			
Step	**Variables**		**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
								LL	UL
1 (X→Y)	H/I→RTV		b_1	.019	.012	1.509	.135	-.006	.043
2 (M→Y)	$vmPFC_{act}$→RTV		b_2	-.003	.004	-.622	.536	-.012	.006
3 (X*M→Y)	H/I*$vmPFC_{act}$→RTV		b_3	-.010	.006	-1.862	.066	-.021	.001

Model summary	**R-sq**	**MSE**	**F**		**Df**	***p***			
	.122	.005	2.315		5, 83	.051			
Step	**Variables**		**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
								LL	UL
1 (X→Y)	H/I→RTV		b_1	.023	.012	1.943	.055	-.001	.046
2 (M→Y)	ACC_{act}→RTV		b_2	-.003	.004	-.800	.426	-.010	.004
3 (X*M→Y)	H/I*ACC_{act}→RTV		b_3	-.005	.005	-.947	.346	-.014	.005

Model summary	**R-sq**	**MSE**	**F**		**Df**	***p***			
	.137	.005	2.641		5, 83	.029			
Step	**Variables**		**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
								LL	UL
1 (X→Y)	H/I→RTV		b_1	.021	.012	1.853	.067	-.002	.044
2 (M→Y)	ACC_{act}→RTV		b_2	-.005	.003	-1.679	.097	-.010	.001
3 (X*M→Y)	H/I*ACC_{act}→RTV		b_3	-.002	.004	-.417	.678	-.009	.006

Model summary	**R-sq**	**MSE**	**F**		**Df**	***p***			
	.139	.005	2.671		5, 83	.027			
Step	**Variables**		**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
								LL	UL
1 (X→Y)	H/I→RTV		b_1	.022	.012	1.93	.057	-.001	.045
2 (M→Y)	$vlPFC_{act}$→RTV		b_2	-.008	.004	-1.905	.060	-.017	.000
3 (X*M→Y)	H/I*$vlPFC_{act}$→RTV		b_3	.001	.006	.240	.811	-.010	.013

Model summary	**R-sq**	**MSE**	**F**		**Df**	***p***			
	.156	.005	3.068		5, 83	.014			
Step	**Variables**		**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
								LL	UL
1 (X→Y)	H/I→RTV		b_1	.034	.012	2.934	.004	.011	.057
2 (M→Y)	HC_{act}→RTV		b_2	-.008	.004	-1.960	.053	-.016	.000
3 (X*M→Y)	H/I*HC_{act}→RTV		b_3	.008	.005	1.651	.102	-.002	.018

Table S3. Moderation models for neural correlates of IA and IA on 4-CSRTT behavior.

PREMATURE RESPONSES

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.136	2.462	2.615	5, 84	.030			
Step	**Variables**		**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**
								LL UL
1 (X→Y)	IA→PR		b_1	-.238	.215	-1.108	.271	-.665 .189
2 (M→Y)	$vlPFC_{act}$ →PR		b_2	-.194	.097	-2.013	.047	-.386 -.002
3 (X*M→Y)	IA*$vlPFC_{act}$→PR		b_3	.083	.103	.811	.420	-.121 .288

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.105	2.551	1.945	5, 84	.096			
Step	**Variables**		**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**
								LL UL
1 (X→Y)	IA→PR		b_1	-.159	.217	-.729	.468	-.591 .274
2 (M→Y)	$vlPFC_{act}$ →PR		b_2	-.094	.094	-.997	.322	-.28 .093
3 (X*M→Y)	IA*$vlPFC_{act}$→PR		b_3	.049	.102	.478	.634	-.155 .253

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.100	2.463	1.835	5, 84	.115			
Step	**Variables**		**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**
								LL UL
1 (X→Y)	IA→PR		b_1	-.019	.211	-.089	.929	-.438 .401
2 (M→Y)	HC_{act}→PR		b_2	-.111	.091	-1.217	.227	-.293 .07
3 (X*M→Y)	IA*HC_{act}→PR		b_3	.030	.106	.288	.774	-.180 .241

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.119	2.513	2.205	5, 84	.062			
Step	**Variables**		**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**
								LL UL
1 (X→Y)	IA→PR		b_1	-.132	.212	-.62	.537	-.554 .291
2 (M→Y)	MFG_{struct}→PR		b_2	-1.524	1.303	-1.17	.246	-4.118 1.069
3 (X*M→Y)	IA*MFG_{struct}→PR		b_3	-.749	1.507	-.497	.621	-3.746 2.248

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.121	2.504	2.286	5, 84	.053			
Step	**Variables**		**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**
								LL UL
1 (X→Y)	IA→PR		b_1	-.232	.221	-1.047	.298	-.672 .208
2 (M→Y)	$dlPFC_{act}$ →PR		b_2	.115	.091	1.258	.212	-.067 .296
3 (X*M→Y)	IA*$dlPFC_{act}$→PR		b_3	.144	.109	1.312	.193	-.074 .361

Table S3 (continued). Moderation models for neural correlates of IA and IA on 4-CSRTT behavior.

ACCURACY

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.524	.017	6.294	5, 84	<.001			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→Acc	b_1	-.020	.018	-1.106	.272	-.056	.016
2 (M→Y)	$vlPFC_{act}$ →Acc	b_2	.010	.008	1.290	.201	-.006	.027
3 (X*M→Y)	IA*$vlPFC_{act}$→Acc	b_3	-.015	.009	-1.758	.083	-.032	.002

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.243	.018	5.326	5, 84	.096			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→Acc	b_1	-.029	.018	-1.568	.121	-.065	.008
2 (M→Y)	$vlPFC_{act}$ →Acc	b_2	-.002	.008	-.255	.800	-.018	.014
3 (X*M→Y)	IA*$vlPFC_{act}$→Acc	b_3	-.003	.009	-.306	.760	-.020	.015

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.267	.017	6.047	5, 84	<.001			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→Acc	b_1	-.033	.018	-1.894	.062	-.068	.002
2 (M→Y)	HC_{act}→Acc	b_2	.014	.008	1.788	.077	-.002	.029
3 (X*M→Y)	IA*HC_{act}→Acc	b_3	-.010	.009	-1.131	.261	-.028	.008

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.327	.017	7.962	5, 84	<.001			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→Acc	b_1	-.021	.017	-1.198	.235	-.055	.014
2 (M→Y)	MFG_{struct}→Acc	b_2	.190	.106	1.791	.077	-.021	.402
3 (X*M→Y)	IA*MFG_{struct}→Acc	b_3	-.311	.123	-2.532	.013	-.555	-.067

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.247	.018	5.456	5, 84	<.001			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→Acc	b_1	-.023	.019	-1.207	.231	-.06	.015
2 (M→Y)	$dlPFC_{act}$ →Acc	b_2	-.001	.008	-.165	.869	-.017	.014
3 (X*M→Y)	IA*$dlPFC_{act}$→Acc	b_3	-.008	.009	-.821	.414	-.026	.011

Table S3 (continued). Moderation models for neural correlates of IA and IA on 4-CSRTT behavior.

MOTIVATION INDEX

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.065	.003	1.154	5, 84	.339			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→Mot_Ind	b_1	-.001	.007	-.198	.844	-.015	.012
2 (M→Y)	$vlPFC_{act}$ →Mot_Ind	b_2	-.001	.003	-.431	.668	-.007	.005
3 (X*M→Y)	IA*$vlPFC_{act}$→Mot_Ind	b_3	.007	.003	2.262	.026	.001	.014

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.030	.003	.511	5, 84	.767			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→Mot_Ind	b_1	-.002	.007	-.262	.794	-.016	.012
2 (M→Y)	$vlPFC_{act}$ →Mot_Ind	b_2	-.001	.003	-.344	.731	-.007	.005
3 (X*M→Y)	IA*$vlPFC_{act}$→Mot_Ind	b_3	.005	.003	1.385	.170	-.002	.011

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.038	.002	.658	5, 84	.656			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→Mot_Ind	b_1	-.005	.007	-.788	.433	-.019	.008
2 (M→Y)	HC_{act}→Mot_Ind	b_2	.003	.003	.920	.360	-.003	.008
3 (X*M→Y)	IA*HC_{act}→Mot_Ind	b_3	.004	.003	1.150	.254	-.003	.011

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.031	.003	.519	5, 84	.761			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→Mot_Ind	b_1	-.003	.007	-.494	.623	-.017	.010
2 (M→Y)	MFG_{struct}→Mot_Ind	b_2	-.047	.042	-1.100	.274	-.131	.038
3 (X*M→Y)	IA*MFG_{struct}→Mot_Ind	b_3	-.023	.049	-.464	.644	-.120	.075

Model summary	**R-sq**	**MSE**	**F**	**Df**	***p***			
	.023	.003	.396	5, 84	.850			
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→Mot_Ind	b_1	-.002	.007	-.319	.751	-.017	.012
2 (M→Y)	$dlPFC_{act}$ →Mot_Ind	b_2	-.001	.003	-.226	.822	-.007	.005
3 (X*M→Y)	IA*$dlPFC_{act}$ →MotInd	b_3	.004	.004	1.062	.291	-.003	.011

Table S3 (continued). Moderation models for neural correlates of IA and IA on 4-CSRTT behavior.

REACTION TIME REWARD

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.192	4969.541		3.943	5, 84	.003		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→RT	b_1	10.523	9.640	1.092	.278	-8.651	29.697
2 (M→Y)	$vlPFC_{act}$ →RT	b_2	-4.158	4.338	-.958	.341	-12.786	4.471
3 (X*M→Y)	IA*$vlPFC_{act}$→RT	b_3	-4.973	4.619	-1.077	.285	-14.161	4.214

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.239	4679.391		5.217	5, 84	<.001		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→RT	b_1	10.251	9.315	1.100	.274	-8.277	28.779
2 (M→Y)	$vlPFC_{act}$ →RT	b_2	-4.421	4.020	-1.100	.275	-12.416	3.574
3 (X*M→Y)	IA*$vlPFC_{act}$→RT	b_3	-10.76	4.385	-2.453	.016	-19.479	-2.035

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.242	4873.242		5.309	5, 84	<.001		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→RT	b_1	13.523	9.385	1.441	.153	-5.143	32.189
2 (M→Y)	HC_{act}→RT	b_2	3.879	4.059	.956	.342	-4.194	11.952
3 (X*M→Y)	IA*HC_{act}→RT	b_3	3.750	4.706	.797	.428	-5.611	13.110

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.206	5241.430		4.248	5, 84	.002		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→RT	b_1	19.504	9.701	2.011	.048	.206	38.802
2 (M→Y)	MFG_{struct}→RT	b_2	38.880	59.530	.653	.516	-79.544	157.305
3 (X*M→Y)	IA*MFG_{struct}→RT	b_3	57.792	68.804	.840	.403	-79.081	194.664

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.214	4836.512		4.508	5, 84	.001		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→RT	b_1	5.920	9.725	.609	.544	-13.422	25.262
2 (M→Y)	$dlPFC_{act}$ →RT	b_2	8.901	3.999	2.225	.029	.946	16.855
3 (X*M→Y)	IA*$dlPFC_{act}$→RT	b_3	4.472	4.811	.930	.355	-5.097	14.041

Table S3 (continued). Moderation models for neural correlates of IA and IA on 4-CSRTT behavior.

REACTION TIME VARIABILITY

Model summary	**R-sq**	**MSE**			**F**	**Df**	***p***		
	.101	.005			1.857	5, 84	.111		
Step	**Variables**		**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
								LL	UL
1 (X→Y)	IA→RTV		b_1	.008	.010	.784	.436	-.012	.027
2 (M→Y)	$vlPFC_{act}$ →RTV		b_2	-.009	.004	-2.049	.044	-.017	.000
3 (X*M→Y)	IA*$vlPFC_{act}$→RTV		b_3	.004	.005	.891	.375	-.005	.013

Model summary	**R-sq**	**MSE**			**F**	**Df**	***p***		
	.082	.005			1.477	5, 84	.206		
Step	**Variables**		**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
								LL	UL
1 (X→Y)	IA→RTV		b_1	.009	.010	.958	.341	-.010	.029
2 (M→Y)	$vlPFC_{act}$ →RTV		b_2	-.006	.004	-1.445	.152	-.014	.002
3 (X*M→Y)	IA*$vlPFC_{act}$→RTV		b_3	-.002	.005	-.487	.627	-.011	.007

Model summary	**R-sq**	**MSE**			**F**	**Df**	***p***		
	.093	.005			1.710	5, 84	.141		
Step	**Variables**		**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
								LL	UL
1 (X→Y)	IA→RTV		b_1	.016	.010	1.696	.094	-.003	.035
2 (M→Y)	HC_{act}→RTV		b_2	-.005	.004	-1.134	.260	-.013	.004
3 (X*M→Y)	IA*HC_{act}→RTV		b_3	.007	.005	1.498	.138	-.002	.017

Model summary	**R-sq**	**MSE**			**F**	**Df**	***p***		
	.116	.005			2.146	5, 84	.068		
Step	**Variables**		**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
								LL	UL
1 (X→Y)	IA→RTV		b_1	.011	.009	1.131	.261	-.008	.029
2 (M→Y)	MFG_{struct}→RTV		b_2	-.111	.058	-1.927	.057	-.226	.004
3 (X*M→Y)	IA*MFG_{struct}→RTV		b_3	.084	.067	1.267	.209	-.048	.217

Model summary	**R-sq**	**MSE**			**F**	**Df**	***p***		
	.061	.005			1.075	5, 84	.380		
Step	**Variables**		**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
								LL	UL
1 (X→Y)	IA→RTV		b_1	.011	.010	1.130	.262	-.009	.031
2 (M→Y)	$dlPFC_{act}$ →RTV		b_2	.002	.004	.551	.583	-.006	.011
3 (X*M→Y)	IA*$dlPFC_{act}$→RTV		b_3	.004	.005	.707	.481	-.006	.013

Table S4. Moderation models for *TPH2* genotype and H/I on 4-CSRT behavior.

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.093	2.538		1.637	5, 80	.160		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→PR	b_1	-.075	.269	-.280	.780	-.611	.461
2 (M→Y)	TPH2→PR	b_2	-.036	.356	-.100	.921	-.744	.673
3 (X*M→Y)	H/I*TPH2→PR	b_3	-.325	.524	-.620	.537	-1.367	.718

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.273	.017		6.008	5, 80	<.001		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→Acc	b_1	-.044	.022	-1.991	.050	-.088	.000
2 (M→Y)	TPH2→Acc	b_2	.006	.029	.189	.851	-.053	.064
3 (X*M→Y)	H/I*TPH2→Acc	b_3	.015	.043	.355	.724	-.071	.101

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.022	.003		.357	5, 80	.876		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→Mot_Ind	b_1	-.010	.009	-1.202	.233	-.027	.007
2 (M→Y)	TPH2→Mot_Ind	b_2	.004	.011	.353	.725	-.018	.026
3 (X*M→Y)	H/I*TPH2→Mot_Ind	b_3	.001	.017	.035	.972	-.032	.034

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.329	4444.253		7.860	5, 80	<.000		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→RTrew	b_1	45.695	11.267	4.056	.000	23.273	68.116
2 (M→Y)	TPH2→RTrew	b_2	-13.599	14.899	-.913	.364	-43.250	16.052
3 (X*M→Y)	H/I*TPH2→RTrew	b_3	-13.728	21.914	-.626	.533	-57.339	29.882

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.130	.005		2.399	5, 80	.044		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→RTV	b_1	.034	.012	2.845	.006	.010	.057
2 (M→Y)	TPH2→RTV	b_2	-.004	.016	-.235	.815	-.035	.028
3 (X*M→Y)	H/I*TPH2→RTV	b_3	-.016	.023	-.687	.494	-.062	.030

Table S5. Moderation models for *TPH2* genotype and IA on 4-CSRT behavior.

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.101	2.515		1.797	5, 80	.123		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→PR	b_1	-.012	.210	-.057	.955	-.430	.406
2 (M→Y)	TPH2→PR	b_2	-.043	.355	-.121	.904	-.750	.664
3 (X*M→Y)	IA*TPH2→PR	b_3	-.469	.412	-1.139	.258	-1.288	.350

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.285	.017		6.380	5, 80	<.001		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→Acc	b_1	-.033	.017	-1.890	.062	-.067	.002
2 (M→Y)	TPH2→Acc	b_2	.004	.029	.129	.898	-.054	.062
3 (X*M→Y)	IA*TPH2→Acc	b_3	.060	.034	1.779	.079	-.007	.127

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.020	.003		.321	5, 80	.899		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→Mot_Ind	b_1	.000	.007	-.021	.983	-.013	.013
2 (M→Y)	TPH2→Mot_Ind	b_2	.002	.011	.173	.863	-.021	.024
3 (X*M→Y)	IA*TPH2→Mot_Ind	b_3	-.015	.013	-1.163	.248	-.041	.011

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.235	5067.627		4.920	5, 80	.001		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→RTrew	b_1	18.929	9.428	2.008	.048	.167	37.691
2 (M→Y)	TPH2→RTrew	b_2	-9.072	15.942	-.569	.571	-4.798	22.653
3 (X*M→Y)	IA*TPH2→RTrew	b_3	11.316	18.478	.612	.542	-25.456	48.088

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.080	.005		1.393	5, 80	.236		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→RTV	b_1	.017	.010	1.819	.073	-.002	.036
2 (M→Y)	TPH2→RTV	b_2	-.001	.016	-.059	.953	-.033	.031
3 (X*M→Y)	IA*TPH2→RTV	b_3	-.013	.019	-.673	.503	-.050	.025

Table S6. Moderation models for *TPH2* genotype and H/I on WI-network structures.

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.089	.020		1.524	5, 80	.192		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→lMFG	b_1	-.037	.024	-1.555	.124	-.085	.010
2 (M→Y)	TPH2→lMFG	b_2	-.022	.032	-.692	.491	-.086	.041
3 (X*M→Y)	H/I*TPH2→lMFG	b_3	-.039	.047	-.831	.408	-.132	.054

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.077	.016		1.311	5, 80	.268		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→rMFG	b_1	-.030	.022	-1.393	.168	-.073	.013
2 (M→Y)	TPH2→rMFG	b_2	-.007	.029	-.238	.813	-.065	.051
3 (X*M→Y)	H/I*TPH2→rMFG	b_3	-.058	.042	-1.365	.176	-.143	.027

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.071	.000		1.201	5, 80	.317		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→lIFGorb	b_1	.001	.003	.507	.614	-.004	.007
2 (M→Y)	TPH2→lIFGorb	b_2	.003	.004	.704	.483	-.005	.010
3 (X*M→Y)	H/I*TPH2→lIFGorb	b_3	-.006	.006	-1.129	.262	-.017	.005

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.085	.000		1.453	5, 80	.215		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→rIFGorb	b_1	.000	.003	-.113	.911	-.006	.005
2 (M→Y)	TPH2→rIFGorb	b_2	.002	.004	.515	.608	-.005	.009
3 (X*M→Y)	H/I*TPH2→rIFGorb	b_3	-.005	.005	-.970	.335	-.016	.005

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.135	.002		2.428	5, 80	.042		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→lIFGtri	b_1	-.002	.008	-.218	.828	-.017	.014
2 (M→Y)	TPH2→lIFGtri	b_2	-.017	.010	-1.612	.111	-.037	.004
3 (X*M→Y)	H/I*TPH2→lIFGtri	b_3	-.010	.015	-.674	.502	-.040	.020

Table S6. (continued) Moderation models for *TPH2* genotype and H/I on WI-network structures.

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.149	.002		2.725	5, 80	.025		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→rIFGtri	b_1	-.016	.007	-2.200	.031	-.030	-.001
2 (M→Y)	TPH2→rIFGtri	b_2	.009	.010	.921	.360	-.010	.028
3 (X*M→Y)	H/I*TPH2→rIFGtri	b_3	.004	.014	.265	.792	-.024	.032

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.169	.002		3.183	5, 80	.011		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→lIFGop	b_1	-.005	.007	-.738	.463	-.020	.009
2 (M→Y)	TPH2→lIFGop	b_2	-.002	.010	-.245	.807	-.022	.017
3 (X*M→Y)	H/I*TPH2→lIFGop	b_3	-.020	.014	-1.423	.159	-.048	.008

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.036	.002		.583	5, 80	.713		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→rIFGop	b_1	-.006	.007	-.830	.409	-.019	.008
2 (M→Y)	TPH2→rIFGop	b_2	-.002	.009	-.197	.845	-.020	.016
3 (X*M→Y)	H/I*TPH2→rIFGop	b_3	-.004	.013	-.312	.756	-.031	.022

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.108	.000		1.879	5, 80	.107		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→lNAcc	b_1	-.002	.002	-1.466	.147	-.005	.001
2 (M→Y)	TPH2→lNAcc	b_2	-.001	.002	-.253	.801	-.005	.004
3 (X*M→Y)	H/I*TPH2→lNAcc	b_3	.002	.003	.577	.566	-.004	.008

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.173	.000		3.259	5, 80	.010		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→rNAcc	b_1	-.002	.001	-2.341	.022	-.005	.000
2 (M→Y)	TPH2→rNAcc	b_2	.000	.001	-.127	.900	-.003	.003
3 (X*M→Y)	H/I*TPH2→rNAcc	b_3	.002	.002	.932	.354	-.002	.006

Table S6. (continued) Moderation models for *TPH2* genotype and H/I on WI-network structures.

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.026	.003		.417	5, 80	.836		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→lACC	b_1	-.012	.009	-1.367	.176	-.029	.005
2 (M→Y)	TPH2→lACC	b_2	.006	.012	.542	.589	-.017	.030
3 (X*M→Y)	H/I*TPH2→lACC	b_3	.007	.017	.405	.686	-.027	.041

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.072	.003		1.214	5, 80	.311		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→rACC	b_1	-.006	.009	-.646	.520	-.023	.012
2 (M→Y)	TPH2→rACC	b_2	.009	.012	.779	.438	-.014	.032
3 (X*M→Y)	H/I*TPH2→rACC	b_3	-.013	.017	-.767	.445	-.047	.021

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.036	.001		.581	5, 80	.715		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→lHC	b_1	.005	.005	1.139	.258	-.004	.014
2 (M→Y)	TPH2→lHC	b_2	.003	.006	.509	.612	-.009	.015
3 (X*M→Y)	H/I*TPH2→lHC	b_3	-.011	.009	-1.201	.233	-.029	.007

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.061	.001		1.016	5, 80	.414		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→rHC	b_1	.003	.004	.817	.416	-.005	.012
2 (M→Y)	TPH2→rHC	b_2	.003	.006	.468	.641	-.008	.014
3 (X*M→Y)	H/I*TPH2→rHC	b_3	-.014	.008	-1.717	.090	-.030	.002

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.114	.000		2.000	5, 80	.088		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→lAMY	b_1	-.003	.002	-1.205	.232	-.008	.002
2 (M→Y)	TPH2→lAMY	b_2	.000	.000	.646	.520	.000	.000
3 (X*M→Y)	H/I*TPH2→lAMY	b_3	.000	.000	-1.061	.292	-.001	.000

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.069	.000		1.148	5, 80	.342		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	H/I→rAMY	b_1	.001	.002	.268	.790	-.004	.006
2 (M→Y)	TPH2→rAMY	b_2	-.001	.003	-.175	.862	-.007	.006
3 (X*M→Y)	H/I*TPH2→rAMY	b_3	-.011	.005	-2.213	.030	-.020	-.001

Table S7. Moderation models for *TPH2* genotype and IA on WI-network structures.

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.139	.019		2.514	5, 80	.037		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→lMFG	b_1	-.052	.018	-2.839	.006	-.089	-.016
2 (M→Y)	TPH2→lMFG	b_2	-.014	.031	-.439	.662	-.076	.048
3 (X*M→Y)	IA*TPH2→lMFG	b_3	-.016	.036	-.452	.653	-.088	.056

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.115	.016		2.037	5, 80	.083		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→rMFG	b_1	-.033	.017	-1.950	.055	-.066	.001
2 (M→Y)	TPH2→rMFG	b_2	-.002	.029	-.087	.931	-.059	.054
3 (X*M→Y)	IA*TPH2→rMFG	b_3	-.062	.033	-1.871	.065	-.128	.004

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.074	.000		1.249	5, 80	.294		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→lIFGorb	b_1	-.002	.002	-.944	.348	-.007	.002
2 (M→Y)	TPH2→lIFGorb	b_2	.004	.004	.961	.340	-.004	.011
3 (X*M→Y)	IA*TPH2→lIFGorb	b_3	-.003	.004	-.565	.574	-.011	.006

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.080	.000		1.353	5, 80	.251		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→rIFGorb	b_1	.000	.002	.233	.816	-.004	.005
2 (M→Y)	TPH2→rIFGorb	b_2	.002	.004	.447	.656	-.006	.009
3 (X*M→Y)	IA*TPH2→rIFGorb	b_3	-.004	.004	-.835	.406	-.012	.005

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.139	.002		2.516	5, 80	.036		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→lIFGtri	b_1	-.006	.006	-.991	.325	-.018	.006
2 (M→Y)	TPH2→lIFGtri	b_2	-.015	.010	-1.484	.142	-.036	.005
3 (X*M→Y)	IA*TPH2→lIFGtri	b_3	.006	.012	.503	.616	-.018	.030

Table S7. (continued) Moderation models for *TPH2* genotype and IA on WI-network structures.

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.141	.002		2.559	5, 80	.034		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→rIFGtri	b_1	-.011	.006	-2.004	.049	-.023	.000
2 (M→Y)	TPH2→rIFGtri	b_2	.009	.010	.905	.368	-.010	.028
3 (X*M→Y)	IA*TPH2→rIFGtri	b_3	.011	.011	1.005	.318	-.011	.033

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.139	.002		2.527	5, 80	.036		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→lIFGop	b_1	-.003	.006	-.477	.635	-.014	.009
2 (M→Y)	TPH2→lIFGop	b_2	-.003	.010	-.285	.776	-.023	.017
3 (X*M→Y)	IA*TPH2→lIFGop	b_3	-.008	.011	-.673	.503	-.031	.015

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.043	.002		.708	5. 80	.619		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→rIFGop	b_1	-.007	.005	-1.281	.204	-.018	.004
2 (M→Y)	TPH2→rIFGop	b_2	-.001	.009	-.113	.911	-.019	.017
3 (X*M→Y)	IA*TPH2→rIFGop	b_3	.005	.011	.517	.607	-.016	.026

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.093	.000		1.603	5, 80	.169		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→lNAcc	b_1	-.001	.001	-.816	.417	-.003	.001
2 (M→Y)	TPH2→lNAcc	b_2	-.001	.002	-.344	.732	-.005	.003
3 (X*M→Y)	IA*TPH2→lNAcc	b_3	.002	.002	.640	.524	-.003	.006

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.136	.000		2.445	5, 80	.041		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→rNAcc	b_1	-.001	.001	-1.372	.174	-.003	.001
2 (M→Y)	TPH2→rNAcc	b_2	.000	.001	-.238	.812	-.003	.003
3 (X*M→Y)	IA*TPH2→rNAcc	b_3	.001	.002	.414	.680	-.003	.004

Table S7. (continued) Moderation models for *TPH2* genotype and IA on WI-network structures.

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.045	.003		.737	5, 80	.598		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→lACC	b_1	-.011	.007	-1.596	.115	-.025	.003
2 (M→Y)	TPH2→lACC	b_2	.007	.012	.592	.555	-.016	.030
3 (X*M→Y)	IA*TPH2→lACC	b_3	.017	.013	1.288	.201	-.009	.044

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.066	.003		1.098	5, 80	.368		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→rACC	b_1	-.007	.007	-.980	.330	-.021	.007
2 (M→Y)	TPH2→rACC	b_2	.010	.012	.832	.408	-.014	.033
3 (X*M→Y)	IA*TPH2→rACC	b_3	.001	.014	.096	.923	-.026	.028

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.014	.001		.218	5, 80	.954		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→lHC	b_1	.000	.004	.008	.994	-.007	.007
2 (M→Y)	TPH2→lHC	b_2	.004	.006	.650	.518	-.008	.016
3 (X*M→Y)	IA*TPH2→lHC	b_3	.004	.007	.486	.628	-.011	.018

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.026	.001		.425	5, 80	.830		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→rHC	b_1	.000	.003	-.011	.991	-.007	.007
2 (M→Y)	TPH2→rHC	b_2	.003	.006	.566	.573	-.008	.015
3 (X*M→Y)	IA*TPH2→rHC	b_3	-.002	.007	-.343	.732	-.015	.011

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.083	.000		1.408	5, 80	.230		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→lAMY	b_1	-.002	.002	-1.145	.256	-.006	.002
2 (M→Y)	TPH2→lAMY	b_2	.006	.003	1.817	.073	-.001	.013
3 (X*M→Y)	IA*TPH2→lAMY	b_3	-.001	.004	-.139	.890	-.008	.007

Model summary	**R-sq**	**MSE**		**F**	**Df**	***p***		
	.012	.000		.191	5, 80	.965		
Step	**Variables**	**Path**	**Coeff.**	**SE**	***t***	***p***	**95% CI**	
							LL	UL
1 (X→Y)	IA→rAMY	b_1	.000	.002	-.138	.891	-.004	.004
2 (M→Y)	TPH2→rAMY	b_2	.000	.003	-.133	.895	-.007	.006
3 (X*M→Y)	IA*TPH2→rAMY	b_3	-.002	.004	-.581	.563	-.010	.006

List of publications

PUBLICATIONS

Kneer, K., Reinhard, J., Ziegler, C., Slyschak, A., Schiele, M., Vietz, M., **Peters, K.**, Meisenzahl, E. M., Pauli, P., Reif, A., Deckert, J., Romanos, M., Domschke, K., Neufang, S. (2019). Serotonergic influence on depressive symptoms and trait anxiety is mediated by negative life events and frontal activation in children and adolescents. *European Child & Adolescent Psychiatry*. doi:10.1007/s00787-019-01389-3. IF:3.7

MEETING ABSTRACTS

Peters K, Romanos M, Neufang S (2017). Developmental processes in waiting impulsivity, 6th World Congress on ADHD: From Child to Adult Disorder. *ADHD Atten Def Hyp Disord* 9, 1–55 (2017). https://doi.org/10.1007/s12402-017-0224-y

Peters K, Reinhard J, Romanos M, Neufang S (2017). Waiting impulsivity and anxiety-related traits, Abstracts of the WASAD Conference 2017, 14–16 September, Würzburg, Germany. *J Neural Transm* 124**,** 1277–1328 (2017). https://doi.org/10.1007/s00702-017-1777-9