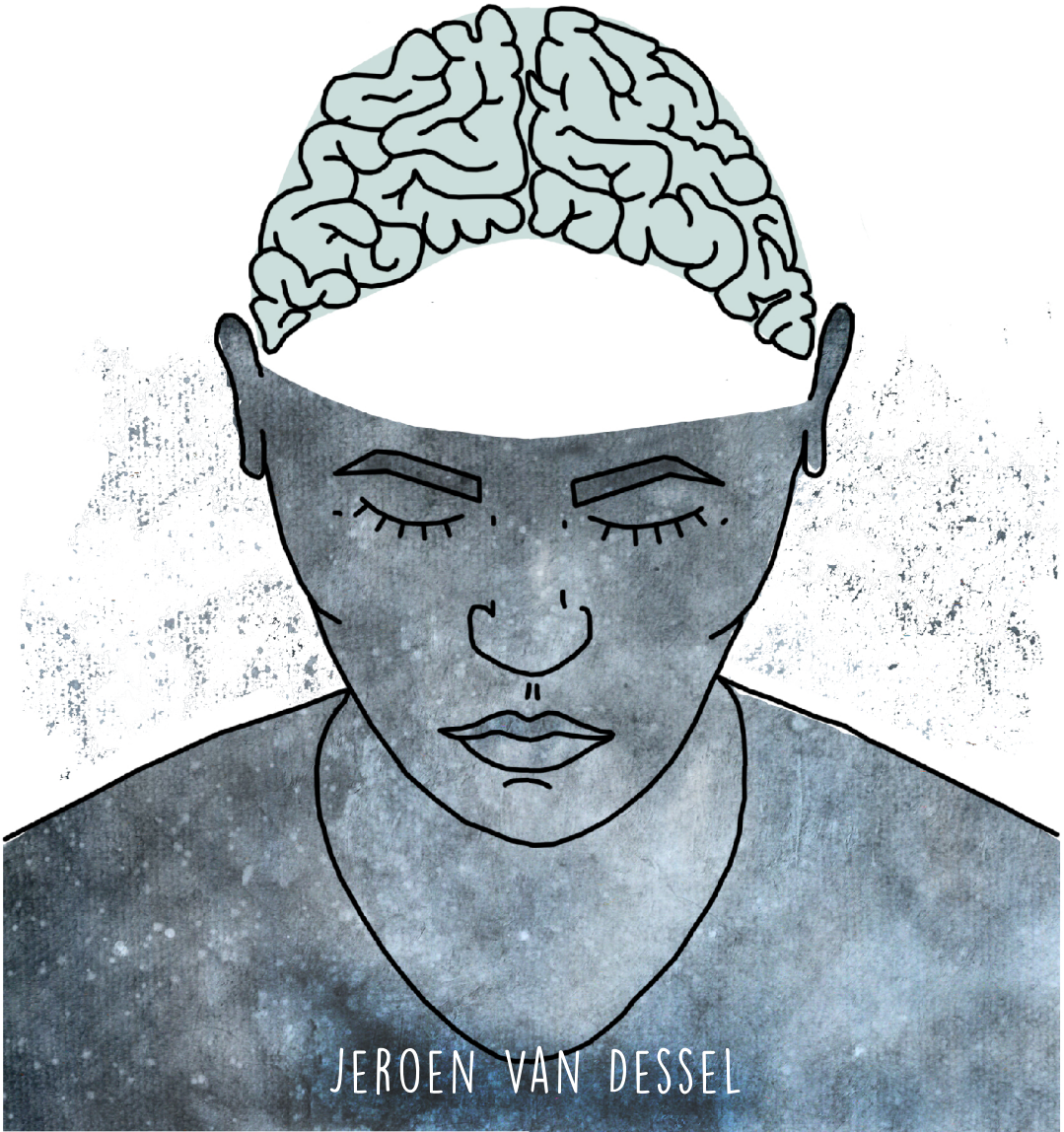
The neural signature of delay aversion in attention-deficit / hyperactivity disorder



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DE NEURALE HANDTEKENING VAN DELAY AVERSION IN AANDACHTSDEFICIËNTIE-HYPERACTIVITEITSSTOORNIS

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Chapter 1 | General Introduction

“Delay always breeds danger; and to protract a great design is often to ruin it”

Miguel De Cervantes (1547-1616), Spanish writer, in “Don Quixote”

Picture this, you are at the grocery store and you just want to go home and make diner, but you are stuck in line and the person in front of you is taking forever to pay with small coins. It is taking ages and the other lines are just as bad. We have all experienced this form of purgatory. Waiting can be so unbearable that many people will pay hundreds of euros to avoid it, whether it is at the airport, for a ride, or at a theme park. But even though we all hate waiting, the frustration is not necessarily about the duration. It is how you experience the waiting that matters – how you think about waiting, and how you spend the time.

According to the influential Delay Aversion model on attention-deficit/hyperactivity disorder (ADHD), developed by Prof. Sonuga-Barke, waiting is hypothesized to be particularly aversive for children and adolescents with ADHD. ADHD-related symptoms could be partially explained by a motivation to escape or avoid the excessive negative effect that individuals with ADHD experience when faced with a delay prior to the delivery of a reward or completion of a task. Even though we have these hypotheses, most of the international research on delay aversion is based on behavioural experiments and neuroscientists do not know much about what the ADHD brain is actually experiencing.

The central aim of this PhD thesis is to provide a coherent validation of one of the main theories of ADHD: the delay aversion theory across brain function, brain structure, psychological testing, and self-rating; with as ultimate aim providing a fundamental basis to the delay aversion dysfunction in ADHD.

In the following sections, I will introduce ADHD and describe the state-of-the-art of research on altered motivational processes in ADHD. In this context, I will outline the concept of Delay Aversion and expand on the response to punishment in children and adolescents with ADHD. The Delay Aversion hypotheses will be clarified by going deeper into negative reinforcement (avoidance of waiting periods) and positive punishment (imposition of delay) processes. In this context, we will focus on the importance of the distinction between neural activity associated with contingency and valence-specific effects. Finally, I will provide a brief outline of each chapter.

Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder (ADHD) is a common developmental psychiatric disorder, characterized by age-inappropriate levels of inattention and/or hyperactivity-impulsivity (American Psychiatric Association, 2013). ADHD typically is diagnosed during childhood, but persists in 50-80% of the cases to adolescence and in 30-50% through to adulthood. During development to adolescence and adulthood hyperactivity symptoms often decline, while impulsivity and attentional deficits mostly persist. If not treated effectively the disorder puts the child at increased risk for substance abuse, poor academic performance, unemployment and antisocial behavior (Shaw et al., 2012). The world-wide prevalence of ADHD in school-aged children is estimated around 5% (Polanczyk, De Lima, Horta, Biederman, & Rohde, 2007) and ADHD seems to be more prevalent in boys compared to girls (Derks, Hudziak, & Boomsma, 2007). Despite being one of the most intensively studied psychiatric disorders in childhood, its underlying etiology still remains a matter of debate.

Motivational Deficits

Contemporary neuropsychological models on ADHD have emphasized the existence of multiple neurodevelopmental pathways from risk to disorder each associated with specific causes (either genetic and/or environmental risk factors) and neuropsychological mediators. Research on ADHD has concentrated for many years on deficiencies in executive functions (Barkley, 1997), in particular inhibition (Alderson, Rapport, & Michael, 2007). However, a growing number of theoretical models have characterized ADHD as a motivational disorder caused by impaired processing of reinforcing events (Sagvolden, Johansen, Aase, & Russell, 2005; Sonuga-barke, Bitsakou, & Thompson, 2010; Sonuga-Barke, 2003, 2005; Tripp & Wickens, 2008).

Reinforcement is used to help increase the likelihood that a behaviour will occur in the future by either delivering or removing a stimulus immediately after a specific behaviour (Shahan, 2010). There are two types of reinforcement: positive and negative (**TABLE 1**). With positive reinforcement, the increase in frequency of behaviour is due to the fact that the behaviour results in the presence of a stimulus (i.e. there is a positive contingency between the behaviour and stimulus), while with negative reinforcement , the increase in behaviour results in the absence of a stimulus (i.e., there is a negative contingency between behaviour and stimulus) (De Houwer & Hughes, 2020). Negative reinforcement should not be confounded with punishment. Punishment is a process by which a consequence immediately follows a behaviour which decreases the future frequency of that behaviour. Like reinforcement, an aversive stimulus can be added (positive punishment) or a rewarding stimulus can be removed (negative punishment) after a particular undesired behaviour is shown (**TABLE 1**).

TABLE 1. Overview of operant conditioning options to learn association between a behaviour and a consequence (whether negative or positive) for that behaviour.

	Administer	Remove
Rewarding stimulus	Positive reinforcement	Negative punishment
Aversive stimulus	Positive punishment	Negative reinforcement

Motivational models on ADHD are mainly supported by research showing an atypical response to positive reinforcement in children with ADHD (for review see Luman, Oosterlaan, & Sergeant, 2005). Three of these motivational models, the Dynamic Developmental Theory (Sagvolden et al., 2005), the Dopamine Transfer Deficit hypothesis (Tripp & Wickens, 2008), and the Dual Pathway model (Sonuga-barke et al., 2010; Sonuga-Barke, 2003, 2005) make specific predictions about the behaviour of children with ADHD in response to positive reinforcement. One of the most consistent findings in this regard is that individuals with ADHD have a characteristic preference for small immediate over larger delayed rewards (Marco et al., 2009). Children and adolescents with ADHD also show a larger cognitive improvement than typically developing controls when performance is positively reinforced (Carlson & Tamm, 2000; Humphreys & Lee, 2011).

Further evidence for altered reward processing deficits comes from functional Magnetic Resonance Imaging (fMRI) studies that have demonstrated a reduced activation in the brain's reward circuit to cues predicting the delivery of future monetary rewards following successful performance on the Monetary Incentive Delay (MID) task (for review see Plichta & Scheres, 2014).

Whether individuals with ADHD also react differently in response to negative reinforcement processes (the avoidance of aversive events) is still unclear, despite recognition that both positive and negative consequences impact behaviour, and potentially differentially in ADHD due to their proposed motivational deficit (Alsop et al., 2016; Luman et al., 2005). While all motivational theories make predictions about the reaction of individuals with ADHD to positive reinforcement, the Dual Pathway model is the only one that makes a prediction for negative reinforcement.

Delay aversion

Within the Dual Pathway model (Sonuga-barke et al., 2010; Sonuga-Barke, 2002, 2003), in addition to the executive function model, a second pathway to ADHD is proposed: the delay aversion theory, which has a clear link with negative reinforcement. This theory is the focus of this thesis. According to the delay aversion theory, delay (e.g., time lapsed during waiting for events or outcomes) represents an extremely aversive state for individuals with ADHD. This can explain why individuals with ADHD often prefer small immediate rewards over large delayed rewards, as they are motivated to sacrifice more valuable future outcomes in order to escape or avoid negative emotions generated by delay. For children with ADHD, waiting and/or delay rewards generates a negative emotional value because it is repeatedly accompanied by disapproval of their environment (e.g., teachers, parents, peers) as they often fail to wait. This, in turn, results in a behaviour that wants to escape from or avoid delay depending on the situation. This characteristic behaviour is retained by negative reinforcement (i.e., escaping from the negative feeling caused by delay).

The delay aversion model has been applied to explain ADHD-related symptoms in terms of their response to delay-rich situations (Sonuga-Barke, 2003; **FIGURE 2**). Individuals with ADHD will try to minimize delay whenever they have the opportunity or choice to escape it. This in turn will lead to impulsive choices. Where delay cannot actually be reduced (cannot be escaped or avoided), it is postulated that delay aversive individuals

allocate their attention to interesting aspects of the environment that alter the perception of the passage of time. Thereby reducing the perceived length of delay, leading to apparent inattention from long and boring tasks. When the background to a task is also boring, the delay aversion theory predicts that individuals act on their environment to create stimulation, leading to hyperactivity in boring and unstimulating environments.

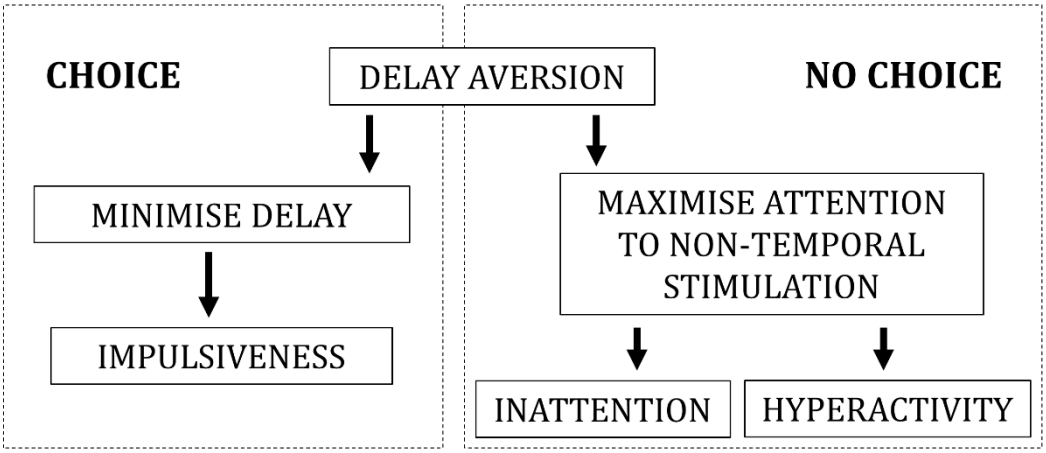

FIGURE 2. Schematic presentation of the delay aversion theory under choice or no choice conditions. Adapted from (Sonuga-Barke, 2003)

There is now a compelling body of behavioural evidence that supports the predictions of the delay aversion hypothesis (for review see Van der Oord & Tripp, 2020). First, cues signaling the imposition of delay appear to capture the automatic attention of children with ADHD in a way similar to that seen when cues of social or physical threat are presented to anxious people (Sonuga-Barke, De Houwer, De Ruiter, Ajzenstzen, & Holland, 2004), while cues signaling their escape elicit an electrophysiological response similar to that shown to rewards (Broyd et al., 2012). Second, ADHD children choose small immediate over large delayed rewards and this effect is exacerbated when such a choice pattern leads to an overall reduction of delay (Marx, Hacker, Yu, Cortese, & Sonuga-Barke, 2018; Patros et al., 2016). Third, ADHD children disengage prematurely from long and difficult tasks (Vile Junod, DuPaul, Jitendra, Volpe, & Cleary, 2006). Fourth, on such tasks, but where disengagement is not possible, ADHD children show higher levels of activity and inattention compared to controls with these effects increasing as a function of time on task (Antrop, Buysse, Roeyers, & Van Oost, 2002; Bitsakou, Antrop, Wiersema, & Sonuga-Barke, 2006; Sonuga-Barke, Saxton, & Hall, 1998) .

At brain level, delay aversion in ADHD is hypothesized to be a two-component developmental process (Sonuga-Barke, 2003). First, early established fundamental alterations in brain reward circuits create a primary drive for immediate reward linked

to hypoactivation in the ventral striatum and related frontal regions in response to reward cues. This impairs the individual's ability to wait for future rewards. Secondly, over time, this results in acquired aversion - where negative affective states are increasingly elicited by delay-rich situations and settings where waiting is required but deficient. Likewise, opportunities to escape delay and the cues that signal them, are predicted to elicit hyperactivation in brain regions linked to the processing of positive and rewarding experiences.

Although the neurobiological predictions of the delay aversion hypothesis were set out more than a decade ago (Sonuga-Barke, 2003), only recently attempts have been made to test these (**FIGURE 3**).

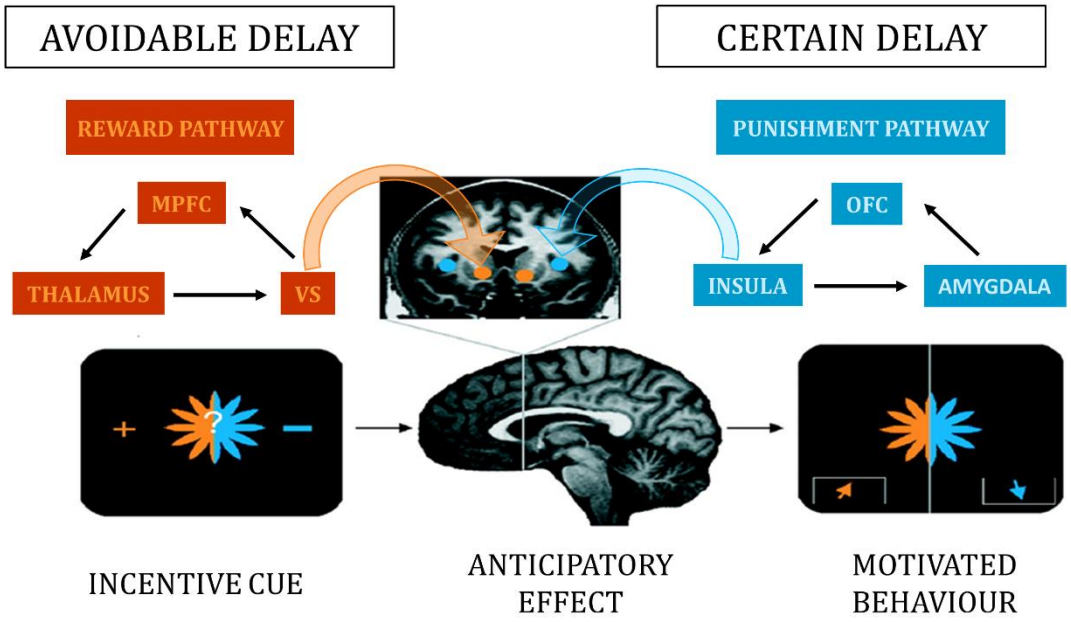

FIGURE 3. Neurobiological predictions of the Delay Aversion hypothesis. Cues signaling the anticipation of the imposition of future delay (CERTAIN DELAY; positive punishment) will result in a hyperactivation of brain regions implicated in the processing of negatively valanced affective stimuli (orbitofrontal cortex, amygdala and insula) in ADHD patients compared to controls. The perspective of the possibility to escape delay (AVOIDABLE DELAY; negative reinforcement) would result in a hyperactivation of reward-related structures (ventral striatum, medial orbitofrontal cortex, ventral striatum), with a delay dose-response relationship in both instances.

The prediction is that delay aversion will be mediated by functional, and possibly structural changes, in brain regions known to be involved in the processing of negative stimuli avoidance (negative reinforcement) and response to aversive outcomes (positive punishment). Neuroimaging studies to date mainly focused on the positive punishment (delay imposition) component and initial evidence comes from two small-scale fMRI studies (Lemiere et al., 2012; Wilbertz et al., 2013), which showed elevated levels of activity within amygdala and insula to cues predicting upcoming future delay. Lemiere and colleagues (2012) compared adolescents with ADHD to age-matched typically developing controls on an adaptation of the MID task (Knutson, Westdorp, Kaiser, & Hommer, 2000) where symbols presented on a screen indicated whether delay would be imposed after a slow response on a simple reaction-time task. They found that ADHD was associated with increased amygdala and insula activation to cues signaling certain,

compared to those signaling avoidable delay (Lemiere et al., 2012). Using a similar task, Wilbertz et al. (2013) compared brain responses to cues signaling different lengths of future delay in adults with ADHD and controls. Again ADHD was associated with a hyperactivation of the amygdala and insula to cues of impending contingent delay with some evidence of a delay-dose response effect apparent in the ADHD group.

However, these studies had significant limitations. First, the studies lacked statistical power because of small sample sizes. Second, the Lemiere et al. study, while being the only study to examine the potential punishing effect of cues signaling certain delay imposition and the potential rewarding effects of conditional delay cues, did not include an appropriate (neutral) control condition that allowed the neural correlates of these two processes to be effectively differentiated. Third, no study included standardized measures of delay aversion to confirm that these brain patterns were related to actual delay averse behaviour in daily life. Furthermore, several important questions have not been answered by these studies: first, it is still unclear whether this proposed aversion to delay is dependent on the dose of delay. A standardized post-response delay could be used to examine a possible dose-response relationship between the length of imposed and conditional delay and brain activity in order to sharpen the specificity of their relationship. Second, it is still unclear whether these functional effects are themselves underpinned by alteration in brain structure, especially with regard to a reduced volume seen in recent studies. Finally, it was never tested whether these fMRI findings are specific for delay aversion or for aversion in general in individuals with ADHD. This specificity of the brain response to delay could be tested by comparing the effect of delay on the brain in individuals with ADHD relative to controls with the effect of a non-delay related aversive event such as loss of monetary reward. In this thesis, these limitations were addressed with as ultimate goal to refine the brain endophenotype of delay aversion in ADHD.

Response to Punishment in ADHD

Compared to rewards, the sensitivity of children and adolescents with ADHD to punishment has received little theoretical and empirical attention (Van der Oord & Tripp, 2020). This is remarkable, certainly, because individuals with ADHD experience more negative events in daily life (Brown et al., 2017), and thus may be especially sensitive to provision of punishment (positive or negative) and may try harder to escape or avoid such negative events (negative reinforcement).

Behavioural and neurocognitive studies have found mixed evidence for negative (removal of positive stimulus) and positive (administration of negative stimulus) punishment. Half of the behavioural studies on negative punishment, also known as response-cost, have shown to enhance the performance of children with ADHD more compared to typically developing controls across a wide range of cognitive tasks (Carlson & Tamm, 2000; Iaboni, Douglas, & Ditto, 1997; Slusarek, Velling, Bunk, & Eggers, 2001). In the other half of the studies no difference was found in the performance of children with ADHD and controls under conditions of response cost (Crone, Jennings, & Van Der Molen, 2003; Cunningham & Knights, 1978; Firestone & Douglas, 1975; Groen, Tucha, Wijers, & Althaus, 2013; Solanto, 1990). Two behavioural studies demonstrated that positive punishment (negative sound) was effective in decreasing off-task behaviour in children with ADHD (Rosén, O'Leary, Joyce, Conway, & Pfiffner, 1984), however, they were more prone to errors under risk of punishment (Worland, 1976). A lack of behavioural persistence to respond and slower responding associated with a higher rate of punishment was shown for children with ADHD when compared to controls (Furukawa, Alsop, Sowerby, Jensen, & Tripp, 2017).

Electrophysiological evidence for punishment sensitivity in ADHD is also mixed. Most studies have described an ADHD-related insensitivity to negative and positive punishment (Potts, George, Martin, & Barratt, 2006; Van Meel, Heslenfeld, Oosterlaan, Luman, & Sergeant, 2011; Van Meel, Oosterlaan, Heslenfeld, & Sergeant, 2005), while others found no group differences (Chronaki, Soltesz, Benikos, & Sonuga-Barke, 2017; Heinrich et al., 2017)

In ADHD studies, the direct evidence of altered brain function to negative stimuli is inconsistent (Shaw, Stringaris, Nigg, & Leibenluft, 2014). Some studies found no alterations (Malisza et al., 2011; Marsh et al., 2008; Schlochtermeier et al., 2011), while others found hyperactivation of brain regions known to be implicated in the processing of aversive events (e.g., amygdala and insula) during both the perception of social (Brotman et al., 2010; Herpertz et al., 2008; Posner et al., 2011) and non-social negative stimuli (Plichta et al., 2009; Wilbertz et al., 2017).

Taken together these results suggest that negative punishment (response-cost) may increase on-task behaviour and reduce unwanted behaviours. Although the use of positive punishment can have unexpected and undesirable side-effects in children with ADHD when used to regulate or shape their behaviour. They may be more focused on avoiding punishment, which in turn can lead to reduced accuracy or effort that would lead to better outcomes. Unfortunately, in contrast to the deviant response to positive reinforcement in ADHD, our understanding of the effects of negative reinforcement in children and adolescent with ADHD remains still unclear. Although avoidance of aversive events has been clearly implicated as central drive to other psychiatric disorders such as anxiety, phobias, posttraumatic stress disorder, major depression and suicide (Servatius, 2016).

Distinguishing Negative from Positive Reinforcement Effects

Most fMRI studies have used the MID task to study impaired reinforcement processing in ADHD (Plichta & Scheres, 2014). Classically, the MID task uses visual stimuli such as a circle to indicate the potential to win money (monetary gain), squares indicating the potential to lose money (monetary loss), and a triangle indicating no money will be won or lost (neutral condition) (Knutson et al., 2000, 2005). This incentive cue is followed by a fixation cross during an anticipation period. After which, a target of variable duration is presented and the participant is instructed to press a button as quickly as possible to either win or avoid losing money. Feedback is shown in which the amount of money won or lost during that trial is displayed and the participant's resulting total amount of money. Monetary amounts to win or lose often vary from €0.10 to €5, and are indicated by horizontal bars inside the visual stimuli.

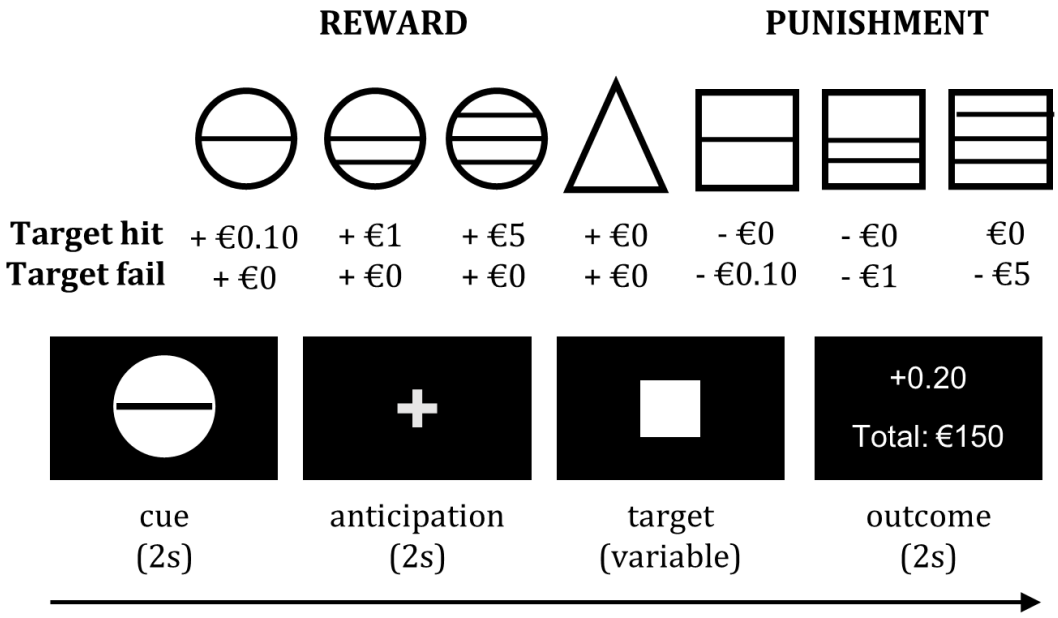

FIGURE 1. Schematic presentation of the monetary incentive delay (MID) task. Adapted from Knutson & Greer, 2008.

In former studies using MID-type tasks, it has been difficult to classify neural activity directly associated with positive (winning money) and negative (avoid losing money) reinforcement, as they were not able to differentiate contingency from valence specific effects (Litt, Plassmann, Shiv, & Rangel, 2011; Maunsell, 2004; Roesch & Olson, 2004). This is because they typically depended on the contrast between monetary gain and monetary loss cues, thereby confounding the analysis of the brain processes involved

in marking the salience of cues predicting a performance-outcome contingency (and the response preparation they motivate) and those predicting the relative valence of the likely outcome. In addition, in MID tasks the relative valence of the conditional monetary loss cues is affected by interspersed monetary gain cues during tasks - so that while relative to immediately preceding monetary gain or neutral cues they are likely to be regarded as negative, whereas in other situations they may be perceived as positive (e.g., if the alternative was certain loss) (Nieuwenhuis et al., 2005).

The valence and salience of predictive cues are important signals for regulating approach-avoidance behavior and attentional processing, respectively (Thorsten Kahnt, Park, Haynes, & Tobler, 2014). However, the two signals are often used interchangeably in reinforcement studies. In order to understand how the brain reacts to opportunities to aversive events, one needs to distinguish the role of two sets of brain processes: (i) the recognition and response to the cue properties signaling contingency (i.e., "this is an important/salient cue - I need to prepare to respond to it") and (ii) those properties coding the valence of the cue (the relative probability of a positive as opposed to a negative outcome). New fMRI paradigms are needed where salience and valence are separable, (i.e. the participant can avoid monetary loss by contingent-performance (contingency effect), always loses money (negative valence) or maintains money irrespective of performance (positive valence)) and that can examine the neural correlates of these two processes to be effectively differentiated.

The small number of fMRI studies that have looked at brain activation to contingent monetary loss in ADHD have limitations in a number of ways and have produced inconsistent results. Most fMRI studies using the MID task have restricted their analysis to predetermined reward-related brain regions (e.g., ventral striatum) (Carmona et al., 2012; Edel et al., 2013; Hoogman et al., 2011; Scheres, Milham, Knutson, & Castellanos, 2007; Ströhle et al., 2008), leaving out some brain network that one might predict would be activated by cues of negative events, such as the amygdala and anterior insula (Lemiere et al., 2012; Wilbertz 2013). Even where individuals with ADHD have been shown to display different activation patterns to cues of performance-contingent monetary gain and loss compared to controls the meaning and significance of these results has been hard to determine since salience and valence had not been separated (Stoy et al., 2011; Wilbertz et al., 2017).

Aim and Outline of the Thesis

The overarching aim of this thesis was to test the hypothesis that Delay Aversion has a distinctive neural signature in ADHD, demonstrated by dose-sensitive functional brain responses (**Chapter 3**), related to behavioral differences in daily life (**Chapter 2 and 3**) and to structural brain differences (**Chapter 4**). A new Escape Monetary Loss Incentive (EMLI) paradigm was developed and validated under the fMRI scanner in typically developing controls (**Chapter 5**). Applying this new paradigm, the specificity of delay-related negative events in ADHD as compared to another aversive event such as monetary loss was investigated, demonstrating that the signature of delay aversion is dissociable from brain responses experienced during other aversive events. (**Chapter 6**).

Overview of the chapters

In **Chapter 2**, we used the 4-choice serial reaction time (4-CSRT) task, a measure of waiting impulsivity, alongside tasks measuring inhibitory control and temporal discounting in children with ADHD and typically developing controls. Questionnaires measuring behavioral disorders symptoms, delay aversion, and various aspects of impulsivity were collected. We examine how the new concept of "waiting impulsivity", adds to our understanding of Delay Aversion in ADHD.

In **Chapter 3**, we further visualized the neural signature of Delay Aversion in ADHD and improved former studies by studying a sample three times larger than previously used, with only right-handed, male adolescents with ADHD and an age-matched control sample. A revised Escape Delay Incentive (rEDI) task was programmed and used, which allowed us to separate activations in relation to contingent delay (possibility to escape delay) and certain delay (imposition of delay) cues in contrast with a control condition with no delay. We specifically tested the hypothesis that in adolescents with ADHD, relative to controls, cues predicting unavoidable delay would elicit stronger activation within brain regions implicated in the processing of negatively valenced affective stimuli, than cues predicting no delay or delay conditional on performance. These effects were expected to be dose dependent and to be related to the ADHD-subjects' delay averse behavior in daily life.

In **Chapter 4**, we extended the analysis of Chapter 3 to test whether these functional effects are underpinned by alterations in amygdala structure. Based on recent studies, we predicted that individuals with ADHD would show reduced amygdala volumes and that these reductions would be correlated with the degree of amygdala hyperactivation to certain delay cues. These structural alterations would statistically mediate the pathway from ADHD to both altered amygdala response and self-reported delay aversion ratings.

In Chapter 5, we designed and validated a new Escape Monetary Loss Incentive (EMLI) paradigm that represents a common aversive event (e.g., monetary loss) that can be compared to specific aversive events in ADHD (e.g., delay). We hoped that this novel fMRI task would not only allow us to study the specific aversive effects of monetary loss (what was not possible in MID paradigms), but would also allow to separate contingency (conditional loss avoidance) from valence-specific effects (certain loss, certain loss avoidance).

In **Chapter 6**, we used the EMLI-task to compare monetary loss processing in ADHD and control children and adolescents. On the basis of prior data from behavioral and neurophysiological studies on ADHD, we expected that cues signalling that monetary loss could be avoided through better performance (conditional loss avoidance) would speed-up reaction time and when contrasted with cues indicating no such contingency (certain loss or certain loss avoidance). This would be marked by an increased activation in the salience and motor response preparation networks in children and adolescents with ADHD to achieve equal brain responses to typically developing controls. We also predicted an exaggerated response in the punishment network including amygdala and anterior insula regions when certain loss cues are contrasted with certain loss avoidance cues (negative-valence contrast). We expected these effects seen at neural level to be mirrored in terms of participants' subjective ratings.

Chapter 7 discusses and integrates the findings of Chapters 2 through 6. In addition, limitations of these studies are addressed and opportunities for future research are presented.

Chapter 2 | Waiting impulsivity: a distinctive feature of ADHD neuropsychology?

Van Dessel, J.*, Morsink, S.*, Van der Oord, S., Lemiere, J., Moerkerke, M., Grandelis, M., Sonuga-Barke, E., & Danckaerts, M. (2019). Waiting impulsivity: a distinctive feature of ADHD neuropsychology?
Child Neuropsychology, *25*(1), 122–129.
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Abstract

Impulsivity is a core feature of attention-deficit hyperactivity disorder (ADHD). It has been conceptualized in a number of different ways. In the current article, we examine how the new concept of "waiting impulsivity", which refers to premature responding before a scheduled target appears, adds to our understanding of impulsivity in ADHD. Sixty children (8–12 years old; 30 ADHD; 30 typically developing controls) completed the 4-choice serial reaction time task, a measure of waiting impulsivity, alongside tasks measuring inhibitory control and temporal discounting and questionnaires measuring behavioral disorder symptoms, delay aversion, and various aspects of impulsivity. A multiple logistic regression model was used to explore the contribution of the primary task outcomes to predict group membership. Children with ADHD displayed more waiting impulsivity and less inhibitory control; they did not differ in temporal discounting. There was no correlation between waiting impulsivity and inhibitory control. Waiting impulsivity was correlated with parent-reported ratings of hyper-activity/impulsivity, inattention, oppositional defiant disorder(ODD), and conduct disorder (CD) and with self-reported delay aversion ratings. Only waiting impulsivity was a significant predictor of ADHD status. In conclusion, waiting impulsivity is distinct from inhibitory control deficits and predicts ADHD status independently of it. Future research needs to examine the relationship with delay aversion and ODD/CD more thoroughly.

Introduction

Impulsivity has been implicated in attention deficit/hyperactivity disorder (ADHD) as both a defining clinical feature (American Psychiatric Association, 2013) and an explanatory neuropsychological mechanism (Bernardi et al., 2012). In this latter case, deficiencies in a range of different, partially distinct, impulsivity-related processes have been identified (Rubia, Smith, & Taylor, 2007). For example, impulsivity in ADHD has been conceptualized as a deficit in inhibitory control, the ability to withhold a dominant or prepotent response when required (Barkley, 1997). It has also been related to a tendency to choose immediate over delayed rewards (i.e., temporal discounting) (Scheres et al., 2006), which is linked to an aversion to the experience of delay (Sonuga-Barke, Bitsakou, & Thompson, 2010) — neuropsychological characteristics that are established correlates of ADHD (Lijffijt, Kenemans, Verbaten, & Van Engeland, 2005; Oosterlaan, Logan, & Sergeant, 1998; Plichta & Scheres, 2014; Verbruggen & Logan, 2009) in a partially independent way (Solanto et al., 2001).

Recently, the concept of waiting impulsivity, derived from animal research (Robinson et al., 2009), has been studied in relation to a range of mental disorders associated with problems of impulse control, for example in binge-eating disorder and addiction (Voon, 2014). Waiting impulsivity is defined experimentally as premature responding during the interval before a scheduled target appears (Voon et al., 2014) and has been shown to be mediated by neural substrates dissociable from inhibitory control and temporal discounting (Dalley, Everitt, & Robbins, 2011). Waiting impulsivity has most often been measured by the "4-choice serial reaction time task" (4-CSRT) (for a review, see Voon, 2014). Although it shares features of the behavioral descriptions of impulsivity in ADHD (blurting out answers before a question is completed, trouble waiting his/her turn), 4-CSRT performance has not been studied in relation to ADHD yet. Therefore, in the present study, to examine the distinctiveness of its contribution to ADHD, we compared waiting impulsivity alongside tasks measuring temporal discounting and inhibitory control in children with ADHD and typically developing individuals and questionnaire measures of delay aversion and other impulsivity-related concepts. We predicted that children with ADHD would have poorer inhibitory control, discount delayed rewards more, be more delay averse, and have more pronounced waiting impulsivity. Furthermore, we predicted that the association between waiting impulsivity and ADHD

would be at least partially independent of those of the other impulsivity constructs. Finally, we explored which concept was the best predictor of group membership using logistic regression.

Materials and Methods

Participants

Thirty children (8–12 years) with a clinical ADHD diagnosis (K-SADS confirmed (Kaufman et al., 1997)) and WISC-III IQ (4 subtest version) greater than 80 (Kort et al., 2005) and 30 age- and gender-matched typically developing individuals were recruited from the Leuven University Child and Adolescent department and from local schools, respectively. The study was approved by the KU Leuven University Hospital ethics committee (S58299). ADHD participants (n= 20) on psychostimulant medication were drug free from 48 h prior to testing. Before the start of the study, participants and their parents gave written informed consent.

Experimental Tasks and Questionnaires

During testing, participants were presented with three tasks counterbalanced in order. A standard stop-signal task (Logan & Cowan, 1984) was used to assess inhibitory control (Lijffijt et al., 2005). Stop-signal reaction time (SSRT), corresponding to the time required to stop the already triggered motor response (for further details, see Logan & Cowan, 1984), was the primary dependent measure and was calculated using the integration method (Verbruggen & Logan, 2009). Second, a temporal discounting task (Scheres et al., 2006) evaluated the extent to which children discounted the value of future large, compared to immediate small rewards. The preference for the delayed reward was plotted as a function of the delay to it and the "area under the curve"(AUC) was the primary outcome; a smaller AUC reflects steeper discounting (for further details, see Scheres et al., 2006). Third, the 4-CSRT (Voon et al., 2014) was used to measure waiting impulsivity. Here, participants are instructed to hold down the space bar with their index finger. When a green target appears in one of the four squares, subjects must release the space bar and touch the screen as quickly as possible. The main outcome is premature response (PR) that is premature release of the spacebar(for a detailed description Voon et al., 2014) (**FIGURE 1**).

A number of questionnaires were also administered: (1) the parent-reported Disruptive Behavior Disorder Rating Scale (Pelham, Gnagy, Greenslade, & Milich, 1992; Dutch translation Oosterlaan et al., 2008) measuring symptoms of ADHD (inattention and hyperactivity/impulsivity), oppositional defiant disorder (ODD), and conduct disorder (CD); (2) the self-reported Barratt Impulsiveness Scale (BIS11) (Patton, Stanford, & Barratt, 1995) assessing attentional (BIS11-A), motoric (BIS11-M), and non-planning (BIS11-NP) aspects of impulsivity; and (3) the self-reported Quick Delay Questionnaire (QDQ; Clare, Helps, & Sonuga-Barke, 2010) which contains five delay aversion and five temporal discounting items.

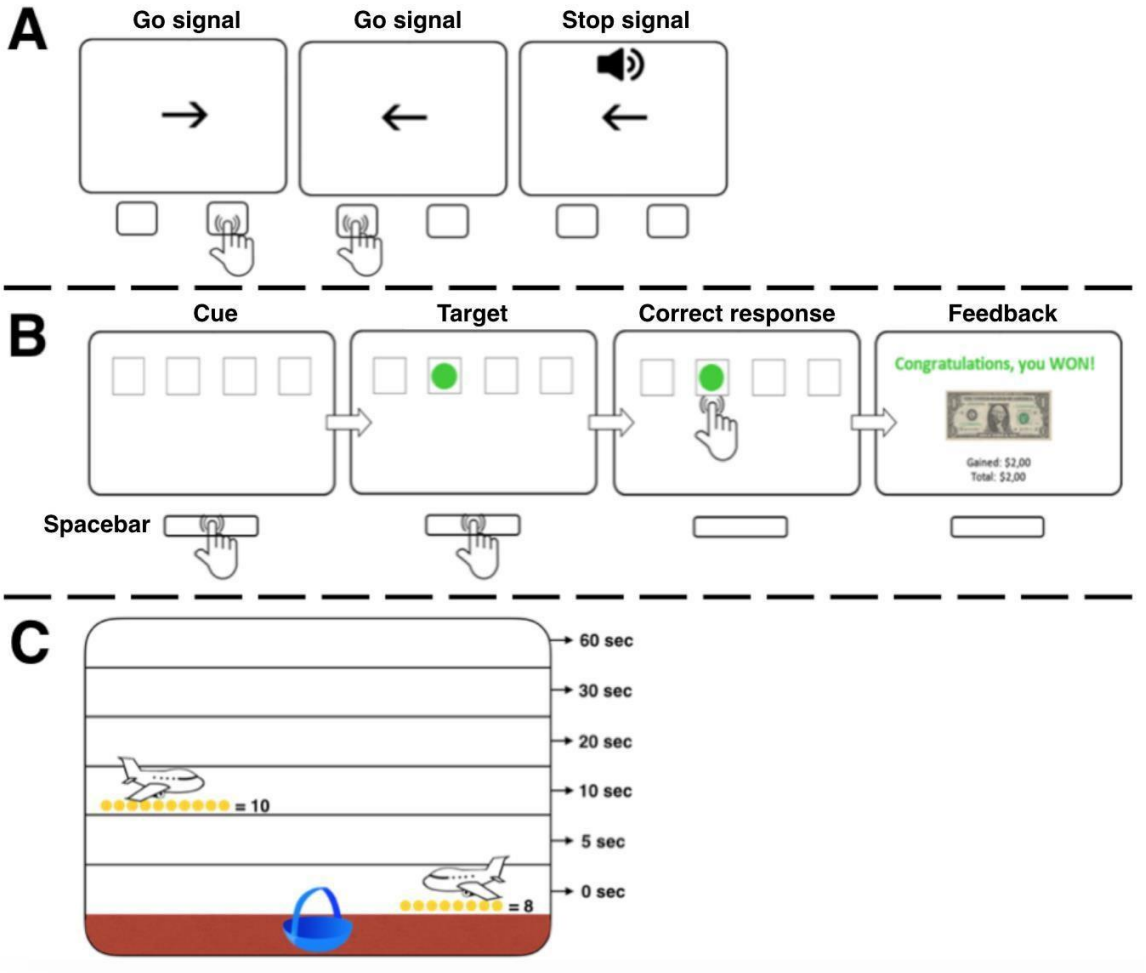

FIGURE 1. Overview of behavioral tasks (A) stop-signal task measuring motor response inhibitory control, (B) 4-choice serial reaction time task assessing waiting impulsivity (C) temporal discounting task evaluating temporal discounting.

Statistical analysis

Primary outcomes with a deviance of more than two standard deviations from the mean were removed from the analysis. As a result, one ADHD participant with a PR of 57 was removed. Statistical assumptions were checked and the Kolmogorov–Smirnov test indicated a non-normal distribution of PR and AUC. Therefore, nonparametric Mann–Whitney tests were conducted for group comparisons. To statistically asses the influence of IQ on the primary out-comes, a first model including the task outcomes and IQ scores was compared with a second nested model containing only task outcomes. Based on the Bayesian information criterion (BIC) and Akaike information criterion (AIC) fit indices, the best fitted model was chosen. The proportion of adolescents with ADHD who met the 90% impairment threshold on each of the impulsivity tasks was calculated. Spearman's correlation coefficients were calculated between performance on the tasks and the rating scales. Finally, a multiple regression model including all constructs was built to assess if the primary task outcomes were able to accurately predict group membership.

Results and Discussion

TABLE 1 summarizes the group characteristics, task performance, and questionnaire measures. There was a significant difference in IQ and on all the DBDRS, Bis-11, and QDQ subscales.

TABLE 1. Demographic, primary task- and questionnaire-related outcomes, denoted as mean (standard deviation).

	ADHD (n=29)	Controls (n=30)	p-value
Background characteristics			
Age	9.9 (1.0)	10.0 (1.3)	0.82
♂ : ♀	19:11	14:16	0.20
IQ	97.8 (10.2)	106.9 (10.3)	< 0.001
Task Performance			
4-Choice Serial Reaction Time Task (waiting impulsivity)			
Number of premature responses	10.4 (6.0)	5.8 (4.8)	0.02
Stop Signal Reaction Time Task (inhibitory control)			
SSRT (ms)	302 (61)	268 (65)	0.04
Temporal Discounting Task (temporal discounting)			
Area under the curve	192.2 (109.5)	217.1 (126.4)	0.29
Questionnaire Measures			
Disruptive Behavior Disorder Rating Scale (Parent-rated behavior problems)			
DBDRS-Inattention	14.9 (1.6)	10.4 (0.8)	< 0.001
DBDRS–Hyperactivity/impulsivity	14.7 (2.1)	10.4 (1.0)	< 0.001
DBDRS–Oppositional defiant disorder	13.2 (2.1)	11.0 (1.4)	< 0.001
DBDRS–Conduct disorder	12.2 (1.8)	10.6 (0.7)	< 0.001
Barratt Impulsiveness Scale 11 (Self-rated impulsivity)			
Attentional	18.3 (4.5)	14.6 (2.7)	< 0.001
Motoric	22.7 (3.4)	20.7 (2.7)	0.02
Non-planning	27.7 (4.5)	24.9 (4.1)	0.02
Quick Delay Questionnaire (Self-rated delay aversion)			
Delay Aversion	18.2 (2.6)	13.3 (3.0)	0.01
Temporal Discounting	14.4 (3.8)	11.2 (3.7)	0.02

The model with only the primary task outcomes fitted the data best (BIC = 1617.8 and AIC = 1601.6) compared to the model that also contained IQ scores(BIC = 1190.4 and AIC = 1178.3). Therefore, IQ was left out in subsequent analyses. Mann–Whitney tests revealed that individuals with ADHD had significantly longer SSRTs(U = 290, p = 0.04) and made significantly more PR (U = 284, p = 0.02) than typically developing individuals. The groups did not differ on AUC (U = 366, p= 0.29) on the temporal discounting task. The three task outcomes were not significantly correlated in either the total or the ADHD sample (**TABLE 2**), suggesting that they are likely dissociable aspects of impulsivity.

Waiting impulsivity was the most prevalent deficit in ADHD (38%; **FIGURE 2**). Comorbid deficits occurred with either inhibitory control (14%) or temporal discounting (3%). This further underlines the heterogeneity of impulsivity in ADHD.

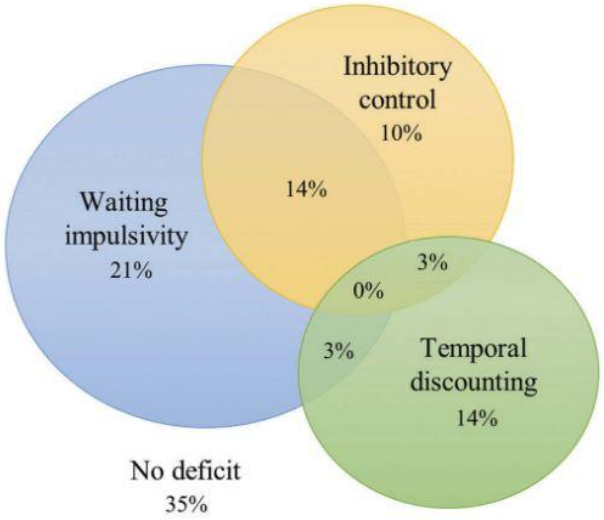

FIGURE 2. Proportion of participants with ADHD (n = 29) with a deficit in waiting impulsivity, inhibitory control or temporal discounting and co-occurrence

Table 2. (A) Spearman's correlation coefficients between the primary task outcomes: premature response (PR), stop signal reaction time (SSRT), area under the curve (AUC) for all participants; (B) for participants with ADHD only; (C) between the primary outcomes and questionnaire scores on Disruptive Behavior Disorder Rating Scale (DBDRS) subscale inattention (I), hyperactivity/impulsivity (HI), oppositional defiant disorder (ODD), and conduct disorder (CD); on Barratt Impulsiveness Scale 11 (BIS11) subscales attentional (A), motor (M), and non-planning (NP); on Quick Delay Questionnaire (QDQ) subscales delay aversion (DA) and temporal discounting (TD).

(A)		**PR**	**SSRT**	**AUC**
PR		1	-	-
SSRT		0.16	1	-
AUC		-0.11	-0.16	1
(B)		**PR**	**SSRT**	**AUC**
PR		1	-	-
SSRT		0.08	1	-
AUC		0.17	-0.15	1
(C)		**PR**	**SSRT**	**AUC**
DBDRS	I	0.35**	0.24	-0.08
	HI	0.38**	0.27*	-0.03
	ODD	0.27*	0.07	0.11
	CD	0.30*	0.08	-0.02
BIS11	A	0.15	0.01	0.02
	M	0.33**	-0.01	-0.21
	NP	0.26*	0.17	-0.14
QDQ	DA	0.40**	0.05	-0.16
	TD	0.01	0.34**	-0.35**

*Significant at the 0.05 level (2-tailed)

**Significant at the 0.01 level (2-tailed)

PR was significantly correlated with both the parent-reported inattention (r_s = 0.35, p = 0.008), hyperactivity/impulsivity (r_s = 0.38,p = 0.004), ODD (r_s = 0.27,p = 0.04), and CD(r_s = 0.30; p = 0.02) measures, with self-reported ratings of motoric (r_s = 0.33, p = 0.01) and non-planning impulsivity (r_s = 0.26,p = 0.04), and with self-ratings of delay aversion (r_s = 0.39, p = 0.001). SSRT was significantly correlated with parent-reported hyperactivity/impulsivity(r_s = 0.27, p = 0.04), and with self-ratings of temporal discounting (r_s = 0.34, p = 0.01). AUC was negatively correlated with self-reported temporal discounting ratings only (r_s= −0.35, p = 0.008) (**TABLE 2**).

In summary, these results show that: (1) in-line with our hypotheses, waiting impulsivity and inhibitory control are associated with parent-reported hyperactivity/impulsivity symptoms. This was not the case for temporal discounting. (2) Waiting impulsivity is associated with self-reported delay aversion, while temporal discounting and inhibitory control are associated with self-ratings of temporal discounting. When SSRT, PR, and AUC were entered as predictors into a multiple logistic regression with ADHD group membership as an outcome, only PR (B = 0.1, Wald = 4.7,p = 0.03, odds ratio = 1.14) made a statistically significant contribution to the model (for AUC: B = 0.01, Wald = 0.21, p = 0.64, odds ratio = 1.00; for SSRT: B = 0.01, Wald = 2.78, p = 0.10, odds ratio = 1.01). The prediction success of the model containing the three task outcomes was 65%, compared to 51% without any predictor variables in the model. Nagelkerke R^2 indicated that 22% of variance was explained by the three predictor variables. PR on its own explained 20% of the model variance, suggesting it to be the best predictor of ADHD group membership. IQ showed not to have a significant predicting value when added in the regression analysis (B = −0.60, Wald = 3.81, p = 0.051, odds ratio = 0.94). The sample characteristics imply some limitations. First, although not uncommon in the ADHD literature, groups differed on IQ, which might reflect inherent difficulties in performance associated with ADHD (Dennis et al., 2009). However, IQ did not seem to have an influence on the primary outcomes. Second, seven participants with ADHD were not of the combined, but of the predominantly inattentive subtype and do not necessarily suffer from impulsivity (American Psychiatric Association, 2013). However, in line with a meta-analysis of Willcutt et al. (2012) showing that ADHD participants of the inattentive versus hyperactive/impulsive subtype did not differ on measures of inhibitory control nor temporal discounting, excluding them did not change any of the results. Third, PR

correlated also with parent-reported ODD and CD ratings. Future research should investigate the role of waiting impulsivity in individuals with ODD and CD.

Conclusion

In conclusion, our results suggest that waiting impulsivity constitutes a potentially important neuropsychological component of ADHD, dissociable from inhibitory control deficits and an independent neuropsychological predictor of ADHD status. Furthermore, these PRs were correlated with parent-reported ADHD symptoms and delay aversion self-ratings. Our results therefore provide further support for the multifaceted and heterogeneous nature of impulsivity in ADHD and highlight the potential importance of tailoring treatments to address different impulsivity-related deficits affecting different individuals. Future research should explore the relationship with delay aversion and ODD/CD more thoroughly.

Chapter 3 | Delay aversion in attention-deficit/hyperactivity disorder is mediated by amygdala and prefrontal cortex hyperactivation

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Van Dessel, J., Sonuga-Barke, E., Mies, G., Lemiere, J., Van der Oord, S., Morsink, S., & Danckaerts, M. (2018). Delay aversion in attention deficit/hyperactivity disorder is mediated by amygdala and prefrontal cortex hyper-activation. *Journal of Child Psychology and Psychiatry*, *59*(8), 888–899. https://doi.org/10.1111/jcpp.12868.

Abstract

Experimental research supports delay aversion as a motivational feature of attention deficit/ hyperactivity disorder (ADHD). To investigate the neurobiology of delay aversion in ADHD, this study examined whether adolescents with ADHD display an unusually strong activation in affective brain regions in response to cues predicting forthcoming delay and whether these effects are (1) delay-dose dependent and (2) statistically mediate the association between ADHD and self-reported delay aversion. Twenty-nine right-handed male adolescents with combined type ADHD and 32 typically developing controls (ages 10–18 years) performed a reaction time task in an MRI scanner. Pretarget cues indicated delay-related response consequences. One indicated that delay would follow the response irrespective of response speed (CERTAIN DELAY), a second that delay would only follow if the response was too slow (CONDITIONAL DELAY), and a third that no delay would follow the response whatever its speed (NO DELAY). Delay levels were 2, 6, or 14 s. Participants also rated their own delay aversion in everyday life. Individuals with ADHD rated themselves as more delay averse than controls. Significantly greater activation to CERTAIN DELAY cues relative to NO DELAY cues was found in participants with ADHD compared to controls (bilaterally) in amygdala, anterior insula, temporal pole, dorsolateral prefrontal cortex (DLPFC), and ventromedial prefrontal cortex. Amygdala and DLPFC activation strength were strongly and delay-dose dependently correlated with delay aversion ratings, and statistically mediated the relationship between ADHD status and delay aversion. When presented with cues predicting impending delay, adolescents with ADHD, relative to controls, displayed a delay-related increase in activation in amygdala and DLPFC, regions known to be implicated in the processing of aversive events. Future studies should examine the specificity of these effects to delay aversion compared to aversive events in general.

Introduction

Attention deficit/hyperactivity disorder (ADHD) implicates multiple brain systems (Sonuga-Barke, Cortese, Fairchild, & Stringaris, 2016). Emotional and cognitive impairments in ADHD are related to both structural (Hoogman et al., 2017; Norman et al., 2016) and functional (Bush, Valera, & Seidman, 2005; Norman et al., 2016; Paloyelis, Mehta, Kuntsi, & Asherson, 2007) brain abnormalities. Findings support a role for atypical brain regions known to mediate the processing of motivationally and emotionally salient stimuli and events (Knutson & Greer, 2008), manifest at a behavioural level as alterations in response to reinforcement (Plichta & Scheres, 2014). One of the most consistent findings in this regard is that individuals with ADHD are unusually sensitive to the imposition of a delay prior to reinforcement (Plichta et al., 2009). This produces a characteristic preference for small immediate over larger delayed rewards, termed impulsive choice (Marco et al., 2009). One theoretical account postulates that impulsive choice in ADHD is the result of a two-component developmental process (Sonuga-Barke, 2005): First, early established fundamental alterations in brain reward circuits create a primary drive for immediate reward, linked to hypo-activation in the ventral striatum and related frontal regions in response to reward cues. This impairs an individual's ability to wait for future rewards. Secondly, over time, this primary drive for immediate reward promotes the acquisition of delay aversion - where negative affective states are increasingly elicited by delay-rich situations and settings where waiting is required. At a behavioural level this in turn motivates delay-averse individuals to avoid such settings – compounding the original primary preference for immediate rewards in choice settings and provoking increases in inattention and hyperactivity in non-choice settings. There is broad support for delay aversion in ADHD from behavioural studies. For instance, Marco et al. (2009) found that linking the choice for a small immediate reward to a reduction in overall delay increased impulsive choice. Furthermore, ADHD is associated with elevated frustration following the imposition of an unexpected delay during task performance (Bitsakou et al., 2006), premature disengagement (Scime & Norvilitis, 2006), and higher levels of activity and inattention during long and boring tasks (Sonuga-Barke, Saxton, & Hall, 1998). In addition, individuals with ADHD show an attentional bias to delay cues, equivalent to the attentional bias to social threat cues seen in anxious individuals (Sonuga-Barke, De Houwer, De Ruiter, Ajzenstzen, & Holland, 2004).

Neurobiological predictions of the delay aversion hypothesis that delay aversion will be mediated by altered functioning of brain regions known to be involved, more generally, in the anticipation and response to aversive outcomes(especially the amygdala and related regions), were set out more than a decade ago (Sonuga-Barke, 2005). Initial support comes from two small-scale functional Magnetic Resonance Imaging (fMRI) studies (Lemiere et al., 2012; Wilbertz et al., 2013) that showed elevated levels of activity within these regions to cues predicting upcoming inescapable delay. Lemiere and colleagues (2012) compared adolescents with ADHD to age-matched typically developing controls on an adaptation of the Monetary Incentive Delay (MID) task (Knutson, Westdorp, Kaiser, & Hommer, 2000), where symbols presented on a screen indicated whether delay would be imposed after a slow response on a simple reaction time task. They found that ADHD was associated with increased amygdala and insula activation to cues signaling inescapable compared to escapable delay (Lemiere et al., 2012). Using a similar task, Wilbertz et al. (2013) compared brain responses to cues signaling delays of different lengths in adults with ADHD and controls. Here also, ADHD was associated with amygdala and insula hyper-activation to cues of impending delay (Wilbertz et al., 2013). The amygdala has been shown to frequently co-activate with the insula during processing of negative emotional stimuli (Hayes & Northoff, 2011; Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012). Consistent with their shared role in affective appraisal, particularly of negative stimuli (Stein et al., 2007), these two brain regions are highly connected anatomically and functionally (Mutschler et al., 2009).

To provide a more definitive examination of the functional neuroanatomy of delay aversion in ADHD, we tested the link between ADHD, delay aversion and brain activity using a task that combines the strengths of those used in the Lemiere et al. (2012) and Wilbertz et al. (2013) studies. We conducted whole brain analyses of neural activation to cues signaling three different delay-related outcomes: One cue signaled that delay was inevitable irrespective of performance, one cue signaled that delay would not occur, and one cue signaled that a delay would occur only if responding was too slow. We predicted that in adolescents with ADHD, relative to controls, cues predicting inevitable delay would elicit stronger activation within amygdala and related affective brain regions than cues predicting no delay or delay conditional on performance. We moreover predicted that these effects would be delay-dose dependent and that they would statistically mediate the relationship between ADHD and self-reported every day delay aversion.

Materials and Methods

The experimental protocol was approved by the ethics committee of the University Hospital Leuven, Leuven, Belgium (S54971). Prior to testing, participants and parents provided written informed consent.

Participants

Thirty-two right-handed male adolescents with combined type ADHD and 36 controls between the age of 10 and 18 years entered the study. Individuals with ADHD were recruited through the Child and Adolescent Psychiatry department of UPC-KU Leuven. All had a pre-existing clinical diagnosis of ADHD based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), as assessed by a child psychiatrist. Presence, pervasiveness and clinical impact of ADHD symptoms across settings (home, school) were confirmed using the parent Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) (Kaufman et al., 1997) (**TABLE 1**). All ADHD participants met the clinical cut-off score on the Achenbach questionnaires for teachers (Teacher Report Form) and parents (Child Behavior Checklist) (Achenbach & Rescorla, 2001) and on the Disruptive Behavior Rating Scale (Pelham et al., 1992; Dutch translation Oosterlaan et al., 2008). The control group was recruited from youth organizations and schools. Controls were excluded if they met DSM-IV criteria for any psychiatric disorder assessed using a K-SADS screening interview with one of the parents. All subjects completed the Dutch adaptation of the Wechsler Intelligence Scale version 3 for Children (short version; Kort et al., 2005) or Adults (Wechsler, 2005), using the vocabulary, similarities, block design and picture arrangement subtests (Sattler, 2001). Participants were excluded if parents reported specific learning disorders (e.g., dyslexia or dyscalculia), drug or substance abuse, neurological abnormalities or MRI contraindications. Twenty-four of the individuals with ADHD were taking psychostimulant medication. Medication was withheld for 72 hours prior to testing and fMRI scanning. **TABLE 1** reports participant characteristics.

TABLE 1. Group characteristics

Characteristic	ADHD (n=29)	Controls (n=30)	p-value
Age (in years)	14.51 (2.14)	14.74 (2.10)	0.68
Full scale intelligence quotient	99.53 (9.56)	111.64 (10.20)	< 0.001
Verbal quotient [a]	97.34 (13.45)	109.53 (10.78)	< 0.001
Performance quotient [b]	101.06 (10.58)	112.78 (12.65)	< 0.001
Total Quick Delay Questionnaire score [c]	25.38 (7.57)	9.02 (5.92)	< 0.001
Delay aversion subscale	14.52 (5.76)	4.62 (3.58)	< 0.001
Task performance (in ms)			
CERTAIN DELAY	294.25 (50.69)	277.64 (35.51)	0.13
CONDITIONAL DELAY	269.03 (31.00)	287.43 (47.10)	0.06
NO DELAY	284.74 (45.45)	270.40 (33.26)	0.13
Comorbidity [d]	Oppositional defiant disorder (n = 3)		

[a] Estimated on basis of vocabulary and similarities subtests

[b] Estimated on basis of block design and picture arrangement subtests

[c] Based on the self-report version of the Quick Delay Questionnaire

[d] Based on the Schedule for Affective Disorders and Schizophrenia for school-age children

Task Design

During fMRI signal acquisition, participants completed a task based on the MID task (Broyd et al., 2012; Knutson et al., 2000; Lemiere et al., 2012). Each trial had five phases: (i) delay cue (250 ms in duration), (ii) variable anticipation period (containing a 3-3.5 s fixation cross), (iii) target stimulus (1.45 s), (iv) outcome (3 s), and (v) delay period (0, 2, 6 or 14 s) (**FIGURE 1**). Participants were instructed to press a button as quickly as possible upon presentation of the target stimulus. The delay cue indicated the delay consequence that would follow after responding to the target. There were three conditions differentiated by delay cue type: (i) in CERTAIN DELAY trials (signaled by a triangle-shaped cue) a post-response delay period was imposed irrespective of the speed of the response to the target; (ii) in CONDITIONAL DELAY trials (signaled by a circle-shaped cue), delay was imposed only if participants responded too slowly (delay frequency was set at one third of the trials); and (iii) in NO DELAY trials (signaled by a diamond-shaped cue) there was no delay regardless of response speed (**FIGURE 1**). Three levels of delay were used (2, 6, and 14 s), indicated by the presence of one, two, or three horizontal lines within the delay cue, respectively. The delay durations were selected based on prior studies and on the need to take account of the exponential nature of time perception (Lemiere et al., 2012; Wilbertz et al., 2013). The length of the anticipation period that followed the delay cue was jittered so that target presentation remained unpredictable. Unbeknown to participants, the threshold for response speed was adapted individually, so that participants would succeed in two thirds of trials across all three cue conditions. At the start of fMRI acquisition, the reaction time (RT) window was derived based on 27 practice trials prior to scanning. The RT was continually adapted throughout the task, based on a staircase tracking algorithm (20-ms increase/decrease). Participants received feedback about their performance - a green "OK" sign (fast enough) or a red cross (too slow). During delay periods the length of the delay was visualized with a white bar. Participants were presented with a total of 189 trials - 63 of each type. Trials were presented in a pseudorandom order in 7 blocks of 27 trials. Participants were told that the task would last for 30 to 45 minutes subdivided in 7 games and that task duration was contingent upon performance. In reality, performance did not affect task duration. Each run lasted 5.5 minutes and total task duration was 38.5 minutes. Participants received €50 upon study completion.

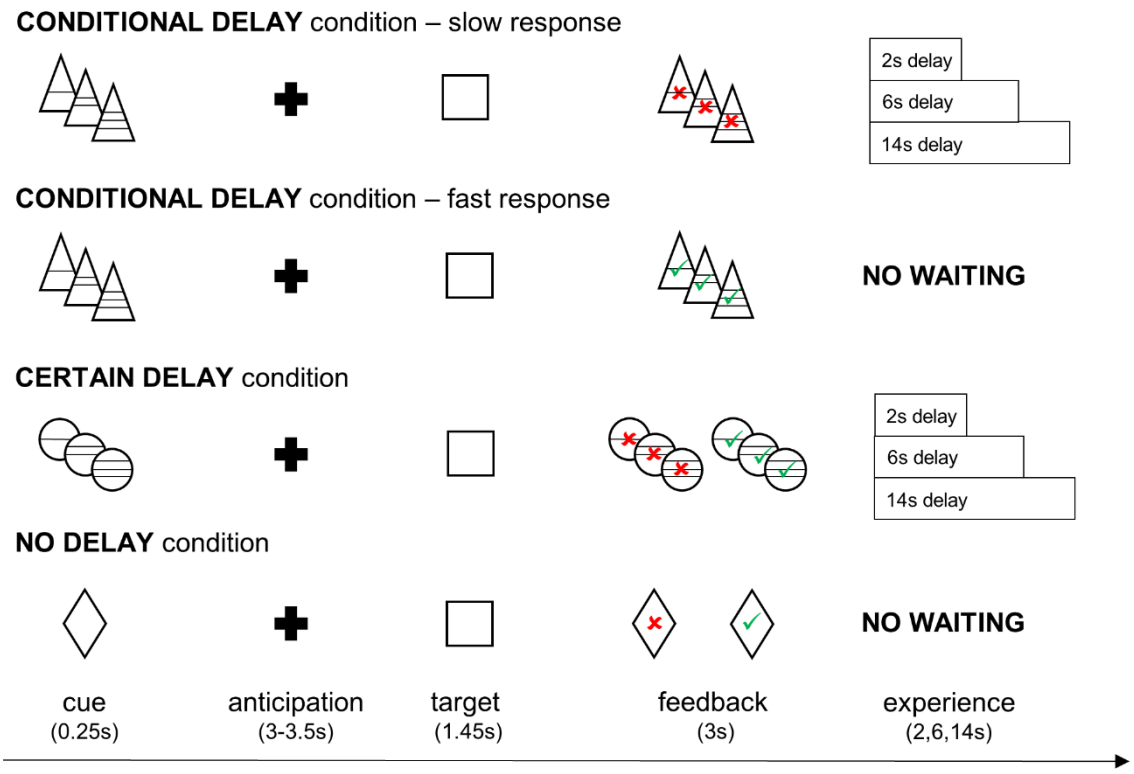

FIGURE 1. Task design. Delay cues indicated different delay-related response consequences. The triangle (CONDITIONAL DELAY) indicated that delay would only follow after slow responses (on 33% of trials). The circle (CERTAIN DELAY) indicated that delay would follow irrespective of response speed. The diamond indicated that no delay would follow, irrespective of response speed (NO DELAY). Delay levels were 2, 6 or 14 s and were indicated by one to three horizontal bars inside the cue. The analysis focused on delay anticipation.

Subjective Ratings of Delay Aversion in Everyday Life

Participants completed the self-report Quick Delay Questionnaire (QDQ), which includes a five-item delay aversion scale: (i) I am usually calm when I have to wait in queues, (ii) I feel relaxed when waiting for things, (iii) I hate waiting for things, (iv) I feel frustrated when I have to wait for someone else to be ready before I can do something, (v) having to wait for things makes me feel stressed and tense. The delay aversion QDQ subscale had good internal and test-retest reliability in a sample of older teenage/young adult students (Clare et al., 2010) and adequate internal reliability in a sample of children with and without ADHD (Hsu, Benikos, & Sonuga-Barke, 2015). Internal reliability of the subscale in the current sample was high (Cronbach's alpha = 0.82).

fMRI Acquisition

Before scanning, participants were familiarized with the scanner and received additional oral instructions on task procedures. Practice trials were performed, accompanied by a description of the task. Cue valence ratings confirmed that all participants had learned the association between delay cue symbols and the nature of the upcoming delay. MR images were acquired at the radiology department, University Hospital Leuven, Belgium, on an Intera© 3T MR scanner (Philips Medical Systems, Best, The Netherlands) using an 8-channel SENSE head coil. Whole brain Blood Oxygen Level Dependent (BOLD) axial Echo Planar Images were obtained using fixed scan parameters: TR = 2000 ms, TE = 30 ms, 90° flip angle, 220 x 220 mm^2 field of view, 80 x 80 matrix, without a slice gap, SENSE reduction factor = 2, 36 sequential bottom-up slices with a slice thickness of 3.5 mm and in plane voxel size of 2.75 mm^2. In the middle of each scanning session, a high-resolution structural scan was acquired using a T1-weighted gradient in order to facilitate localization and co-registration of functional data. Structural scan parameters were: TR = 9.7 ms, TE = 4.6 ms, inversion time = 1100 ms, 12° flip angle, 256 x 256 mm^2 field of view, 256 x 256 matrix and 1 mm^3 voxel size. Stimuli were displayed using Presentation software (version 14.6, Neurobehavioral Systems, Berkeley, USA). Head movement was minimized using a headphone with additional foam fittings.

Image Preprocessing

Prior to statistical analysis, standard preprocessing was performed in Statistical Parametric Mapping 8 (SPM 8) (Wellcome Department of Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm). Data preprocessing included manual reorienting of both structural and functional images to the anterior and posterior commissure line, slice time correction of functional images, realignment of functional images using the middle slice of each run as a reference, co-registration of the structural image to the mean functional image, segmentation of the structural image based on specific adolescent tissue probability maps in Montreal Neurological Institute (MNI) space created with the Template-O-Matic toolbox (Wilke, Holland, Altaye, & Gaser, 2008), spatial normalization of all images, and smoothing of functional images using a 3D Gaussian kernel of 8 mm FWHM.

After realignment, motion correction parameters were inspected and subjects with more than 2 mm translation and 2° rotation were excluded (4 controls and 3 ADHD patients).

Statistical Analysis

Task performance

Repeated-measures ANOVAs examined the effects of condition (CERTAIN DELAY, CONDITIONAL DELAY, NO DELAY) as a within-subject factor and group (ADHD, CONTROL) as a between-subject factor on reaction time (RT). To examine the effect of delay level, further ANOVAs were conducted with delay length (2, 6, 14 s) and task condition (CERTAIN DELAY, CONDITIONAL DELAY) as within-subject factors and group as a between-subject factor. Post-hoc *t*-tests were used to explore significant interaction effects.

Cue-elicited brain activation

For each subject, using SPM 8, a general linear model was estimated using 8 regressors of interest: 3 cue conditions (CERTAIN DELAY, CONDITIONAL DELAY, NO DELAY), 2 possible outcomes (fast enough or too slow response) and 3 possible delay periods (2, 6, and 14 s), and 7 regressors of no interest: 1 for the time period of outcome and delay presentation and 6 motion parameters. Two main T-contrast images CERTAIN DELAY > NO DELAY and CONDITIONAL DELAY > NO DELAY were calculated for each subject. In addition, to examine the delay dose-response curve three additional first-level T-contrast images were created: CERTAIN DELAY 2 s > NO DELAY, CERTAIN DELAY 6 s > NO DELAY, CERTAIN DELAY 14 s > NO DELAY.

Individual contrast images were used in a second-level analysis in a three stage process. First, whole-brain analyses were performed on the main contrasts (CERTAIN DELAY > NO DELAY and CONDITIONAL DELAY > NO DELAY). Whole-brain family wise error (FWE) corrected ($p < 0.05$) significant voxels and clusters were identified based on the peak beta-value and labelled using the SPM12 atlas provided by neuromorphometrics. Second, the effect of delay dose was examined for regions showing FWE-corrected ($p < 0.05$) significant responses to delay cues in the whole brain analysis (CERTAIN DELAY > NO DELAY). For this purpose, contrast estimates were extracted for the individual delay contrasts at the coordinates of significantly activated group peak voxels. Repeated-measures ANOVA using delay length (2, 6, 14 s) as within- and group as between-subject

factors with subsequent contrasts were used to explore delay effects within each group separately. The following bilateral ROIs were defined: ventromedial prefrontal cortex, (VMPFC), dorsolateral prefrontal cortex (DLPFC), anterior insula, amygdala and temporal pole. Significance was determined at $p < 0.01$ to approximate Bonferroni-corrected $p < 0.05$ for the five ROIs. Individual brain activations with a deviance of more than two standard deviations from the mean group activation were excluded from the analysis - seven individual brain activations were removed (1 amygdala 6 s, 2 temporal pole 2 s, 1 VMPFC 2 s, 1 VMPFC 6 s and 2 VMPFC 14 s). Finally, for those regions showing a significant delay dose-response relationship in the ADHD group, a mediational analysis was performed. First, groups were compared on QDQ delay aversion scores using independent *t*-tests. Second, an index of the contrast between CERTAIN DELAY and NO DELAY cue activation was calculated and multiple regression analysis was conducted to test whether this index mediated the relationship between ADHD group membership and QDQ delay aversion scores using a bootstrapping method, in which the indirect effect was evaluated after 5000 bootstrap resamples using a 95% confidence interval (Preacher & Hayes, 2008). Percent mediation and standardized indirect effect confidence intervals were used to indicate the mediation effect size (Preacher & Kelley, 2011).

Results

Task Performance

RTs were shorter on CONDITIONAL DELAY and NO DELAY trials than on CERTAIN DELAY trials (F = 12.60; p < 0.001, η_p^2 = 0.16; Table 1). RT standard deviation was in general higher in the ADHD group (p = 0.04). There was no interaction between cue type and group for RT (F = 0.68; p = 0.55, η_p^2 = 0.009). No main effect of delay length was found (F = 0.85; p = 0.43, η_p^2 = 0.013).

fMRI Data

Whole-brain analyses

SUPPLEMENTARY TABLE 1 and 2 report whole-brain activation as a function of cue type and group. Relative to controls, in ADHD participants there was significantly greater activation averaged over both hemispheres in the temporal pole (t = 4.53; p[FWE] < 0.001), the amygdala (t = 3.60; p[FWE] < 0.01), the anterior insula (t = 3.54; p[FWE] < 0.05], the ventromedial prefrontal cortex (VMPFC) (t = 4.05; p[FWE] < 0.01), and the dorsolateral prefrontal cortex (DLPFC) (t = 3.91; p[FWE] < 0.1) for the CERTAIN DELAY > NO DELAY contrast (**FIGURE 2 and 3**). For the CONDITIONAL DELAY > NO DELAY contrast, similar but smaller differences between ADHD and control participants were seen that did not survive FWE-correction (**FIGURE 2**). Subsequent dose-response analyses therefore only focused on the CERTAIN DELAY > NO DELAY contrast.

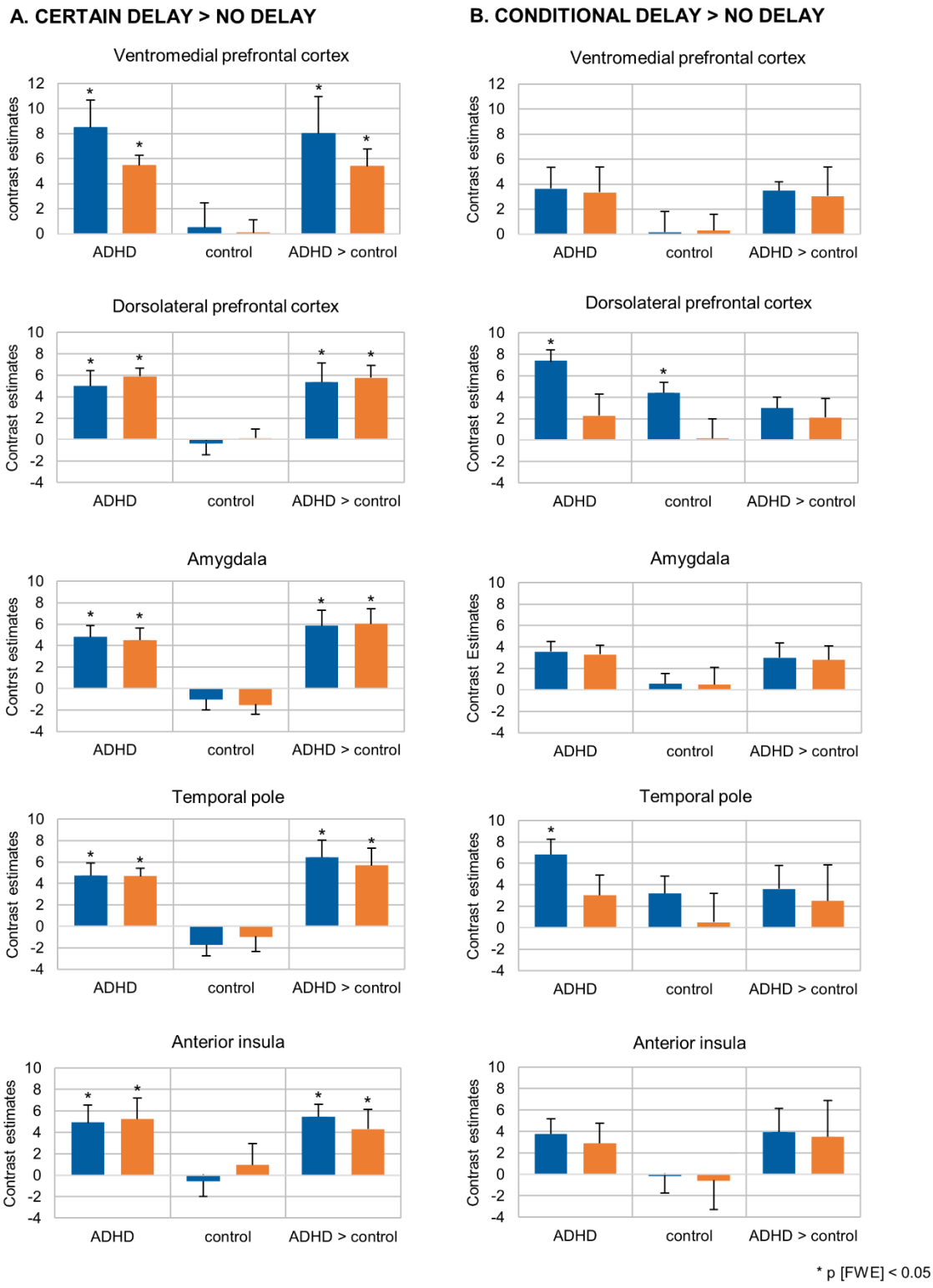

FIGURE 2. Extracted contrast estimates at peak activation clusters for (A) CERTAIN DELAY > NO DELAY and (B) CONDITIONAL DELAY > NO DELAY contrasts in the left (blue) and right (orange) ventromedial prefrontal cortex, dorsolateral prefrontal cortex, amygdala, temporal pole and anterior insula for ADHD, control and group contrast. Error bars display the standard error. Asterisks (*) indicate p[FWE] < 0.05.

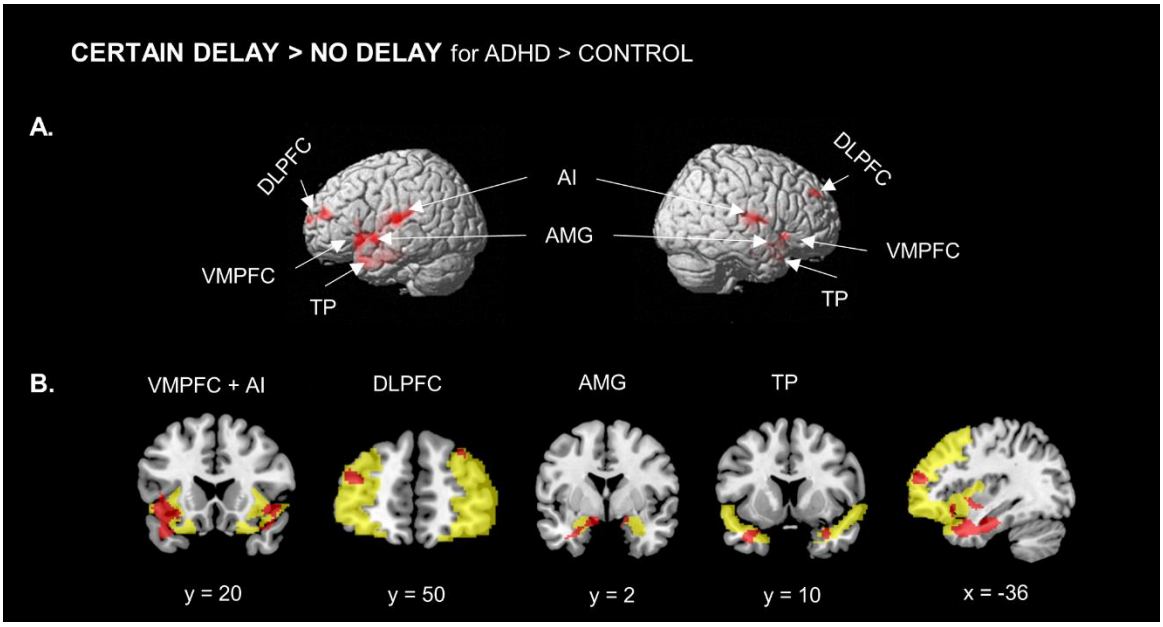

FIGURE 3. (A) Increased activation in the ADHD group compared to the control group was found during anticipation of CERTAIN DELAY > NO DELAY in the ventromedial prefrontal cortex (VMPFC), dorsolateral prefrontal cortex (DLPFC), amygdala (AMG), temporal pole (TP) and anterior insula (AI). (B) The same activations as in A (red), but displayed on cross-sectional coronal slices and one sagittal slice. The anatomical boundaries of these regions are shown in yellow. For visualization purposes, cluster activation is displayed at $p < 0.001$, uncorrected.

The effect of delay length

There was a significant group x dose interaction for amygdala activations ($F = 3.57$; $p = 0.01$; $\eta_p^2 = 0.06$), with increasing activations as a function of delay in the ADHD but not the control group (**FIGURE 4**). Post-hoc tests showed significant differences between delay levels for the ADHD group (2-6 s, $t = 2.78$; 6-14 s, $t = 3.30$; 2-14 s, $t = 4.93$). For DLPFC activations, the differential effect of delay length was not significant overall ($F = 1.25$; $p = 0.29$; $\eta_p^2 = 0.02$). However, when analysis was restricted to the 2 s and 14 s delays, a significant interaction was observed ($F = 4.72$; $p < 0.05$; $\eta_p^2 = 0.14$), with stronger activations to 14 s than 2 s cues in the ADHD group but not the control group ($t = 2.63$). No effect of delay length was seen for temporal pole, anterior insula, or VMPFC ($p > 0.05$) (**FIGURE 4**).

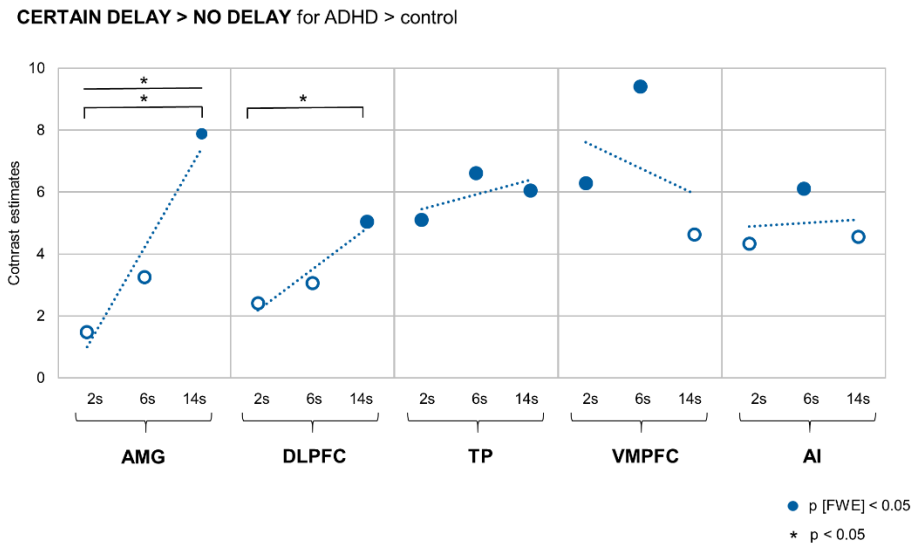

FIGURE 4. Relationship between delay duration (2, 6, 14 s) and brain activation in amygdala (AMG), dorsolateral prefrontal cortex (DLPFC), temporal pole (TP), ventromedial prefrontal cortex (VMPFC), anterior insula (AI) on the CERTAIN DELAY > NO DELAY contrast in ADHD versus control. A significant ($p < 0.05$) dose-response effect was shown for the amygdala for ADHD versus control group. Asterisks (*) indicate significant ($p < 0.05$) post-hoc differences between delay durations. Filled dots indicate significant brain activation ($p < 0.05$) after family wise error [FWE] correction for a given delay duration.

Mediational Analysis

On the basis of the effects of delay length reported above, both amygdala and DLPFC activation were included in the mediational analysis to examine whether the difference in brain activation to CERTAIN DELAY and NO DELAY cues mediates the relationship between ADHD status and self-reported delay aversion. Individuals with ADHD rated themselves as significantly more delay averse than controls on the QDQ delay aversion scale (**TABLE 1)**. Across both groups, these QDQ delay aversion scores were significantly associated with the index of the contrast between CERTAIN DELAY and NO DELAY cue activations in the amygdala for 14 s delay cues ($r = 0.55$; $p < 0.001$), in the DLPFC for 6 s delay cues ($r = 0.27$; $p = 0.02$) and in the DLPFC for 14 s delay cues ($r = 0.47$; $p < 0.001$) (**FIGURE 5A** and **SUPPLEMENTARY FIGURE 1**). The QDQ score was also significantly correlated with delay-related neural activity in the ADHD (amygdala 14 s = 0.39, $p < 0.05$; DLPFC 14 s = 0.38, $p < 0.05$) and control (amygdala 14 s = 0.43, $p < 0.01$; DLPFC 14 s = 0.46, $p < 0.01$) groups separately. The degree of association was larger on trials with longer delays (**FIGURE 5A** and **SUPPLEMENTARY FIGURE 1**). Therefore, the mediational analyses focused on 14 s delay cues (effects were similar if analyses were collapsed across all delay levels). Multiple regression analyses were performed to assess each component

of the proposed mediation model (**FIGURE 5B**). First, it was found that group was positively associated with QDQ delay aversion ratings (β = 0.67, *t* = 7.03, p < 0.001). Second, group was positively associated with CERTAIN DELAY and NO DELAY cue-related differences in amygdala activation (β = 0.43, *t* = 3.68, p < 0.001) and DLPFC activation (β = 0.35, *t* = 2.88, p < 0.001) in response to 14 s delay cues. Third, QDQ delay aversion ratings were positively associated with cue-related differences in amygdala (β = 0.55, *t* = 4.56, p < 0.001) and DLPFC (β = 0.47, *t* = 3.92, p < 0.001) activation. Finally, the group difference in QDQ delay aversion ratings was significantly mediated by amygdala (β = 0.53, *t* = 5.45, p < 0.001) and DLPFC (β = 0.58, *t* = 5.99, p < 0.001) activation differences. The standardized indirect effect for amygdala (95% CI: 0.19 - 0.30) and DLPFC (95% CI: 0.12 - 0.21) activation indicated small to medium effect sizes. The indirect effect accounted for 18% (amygdala) and 24% (DLPFC) of the interaction between group and delay aversion score.

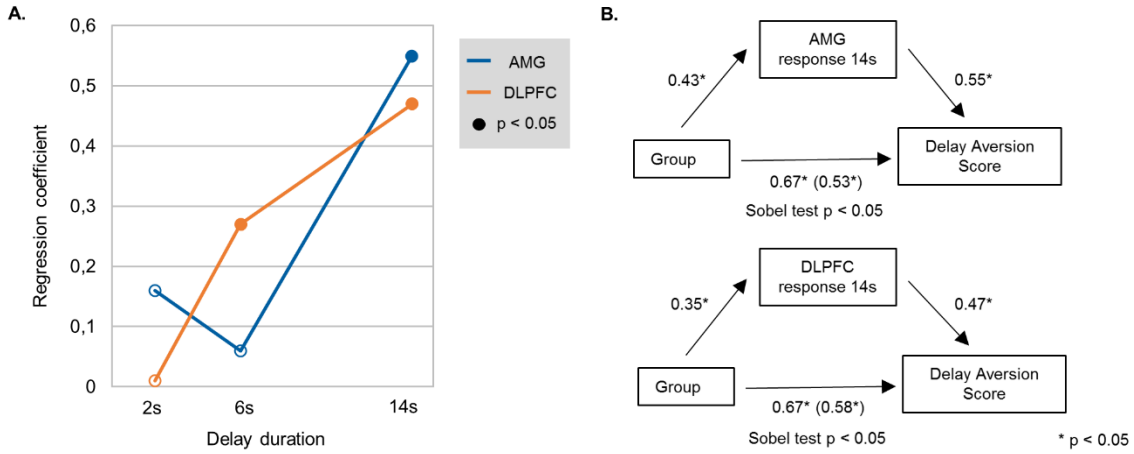

FIGURE 5. (A) Standardized regression coefficients representing the association between QDQ delay aversion scores and individual peak contrast estimates in amygdala (AMG; blue) and dorsolateral prefrontal cortex (DLPFC; orange) at each delay level. The association increases with longer delays. Filled dots indicate significance at p < 0.05. (B) Models illustrating the way that activation to cues signaling 14 s delay in the AMG and DLPFC mediate the association between ADHD and QDQ delay aversion . The mediated effect for the path between ADHD group and QDQ delay aversion is in parentheses. Asterisks (*) indicate p < 0.05.

Discussion

The delay aversion hypothesis of ADHD is based on the idea that symptoms of impulsiveness, inattention and hyperactivity are, in part, determined by a motivation to escape or avoid the excessive negative affect that individuals with ADHD experience when they are confronted with a delay prior to the delivery of a reward or the completion of a task (Sonuga-Barke, 1994). There is empirical evidence that individuals with ADHD do indeed find delay aversive (Clare et al., 2010; Hsu et al., 2015). Our current data from the QDQ provide further support for this notion, in that adolescents with ADHD rate themselves as more delay averse than age-matched controls. At a neurobiological level, this delay-related negative affect should manifest as hyper-activation within those brain regions within the limbic system known to be implicated more generally in the processing of aversive experiences – particularly amygdala and insula (Hayes & Northoff, 2011; Lindquist et al., 2012). The results of two earlier small-scale fMRI studies have provided preliminary evidence to support this prediction of the theory (Lemiere et al., 2012; Wilbertz et al., 2013). The current results, from a much larger sample, confirm and extend these findings in a number of important ways. First, as a group, individuals with ADHD compared to controls displayed an enhanced, dose-dependent neural response to cues that consistently predict an impending delay, in both the amygdala and the DLPFC. Second and most importantly, we were able to link this delay-related activation pattern directly to participants' affective experience of delay in everyday life – providing the first evidence that not only do individuals with ADHD show an altered neural response to impending delay, but also their neural response to impending delay tracks how they subjectively experience delay.

The findings regarding the amygdala were anticipated because of its central role in the processing of delay-related stimuli (Lemiere et al., 2012; Plichta et al., 2009; Wilbertz et al., 2013). Dorsolateral prefrontal cortex hyper-activation to delay cues was not reported in previous studies and was not predicted. However, this region of the prefrontal cortex has shown over-activation to aversive stimuli in a range of other psychiatric disorders such as anxiety (Prater, Hosanagar, Klumpp, Angstadt, & Phan, 2013), depression (Lu et al., 2012), bipolar disorder (Garrett et al., 2012), borderline personality disorder (Dudas et al., 2017) and post-traumatic stress disorder (Aupperle et al., 2012). There are strong interconnections between amygdala and DLPFC, and it is

assumed that these two regions combine to promote the avoidance of aversive stimuli, with a central role of the DLPFC in preparatory and control processes prior to the execution of an avoidant response (Bishop, 2008; Gold, Morey, & McCarthy, 2015). Consistent with such a model, the amygdala-prefrontal circuit plays a role not only in emotion regulation (Banks, Eddy, Angstadt, Nathan, & Phan, 2007) but also in effort-based decision making (Floresco & Ghods-Sharifi, 2007). Combining fMRI with electrophysiological measures, allowing more fine-grained temporal distinctions between cue and response related components, can help test this account (Broyd et al., 2012).

In our study a number of other brain regions, previously implicated in the processing of emotionally charged stimuli, displayed a pattern of enhanced differential activation to CERTAIN versus NO DELAY cues in individuals with ADHD – insula, VMPFC and temporal pole (Hayes & Northoff, 2011; Lindquist et al., 2012). However, these activations did not vary as a function of delay dose. These effects may therefore be driven by the invariance of outcomes predicted by these cues (i.e., circles predict a certain outcome) or their general negative nature (i.e., circles are generally bad news) rather than their delay-related features. Future experimental studies that manipulate certainty and delay independently can test these possibilities.

Our findings raise questions about the role of the amygdala, and the limbic system more generally, in ADHD pathophysiology. There is growing evidence for smaller amygdala volumes in individuals with ADHD (Plessen et al., 2006), a finding confirmed in a recent large-scale mega-analysis (Hoogman et al., 2017). More generally, structural alterations within the limbic system have been observed in individuals with enhanced impulsivity and emotional lability (Tajima-Pozo, Ruiz-Manrique, Yus, Arrazola, & Montañes-Rada, 2015). Altered amygdala connectivity patterns have also been identified in children and adolescents with ADHD (Bebko et al., 2015; Hulvershorn et al., 2014; Posner et al., 2011). Future studies should directly test the relationship between such alterations in amygdala structure and connectivity on the one hand and amygdala activation in response to delay cues on the other.

From a clinical perspective, the enhanced activation patterns in affective brain networks observed here highlight the importance of considering delay when trying to understand what settings and experiences may elicit negative reactions in individuals with ADHD. These negative responses to delay seem to occur irrespective of possible comorbid

patterns of emotional hyper-arousal or dysregulation in ADHD, as only three participants of the ADHD group showed ODD comorbidity. This has implications for assessment, in that ADHD symptoms and related behaviours may be most marked in settings incorporating elements of delay (Morsink et al., 2017). In terms of interventions, our findings suggest a need to modify current settings to limit unnecessary delay where possible, while at the same time also motivating a search for ways to increase delay tolerance in individuals with ADHD, perhaps through shaping and fading procedures or the use of desensitization through gradual exposure (Sonuga-Barke et al., 2004).

The present study has many strengths, especially its relatively large sample and the statistical power this provided, the inclusion of three different delay levels that allowed specific effects of delay to be differentiated from other factors, and the use of FWE-correction of the results. There are however also a number of limitations. First, the design of the study included delay-related cues only. It did not, therefore, allow to discern whether the pattern of neural hyper-reactivity was specific to delay aversion or rather an instantiation of a more general hyper-sensitivity to aversive events. A meta-analysis by Hayes and colleagues (2011) identified a general cross-species aversion-related network that maps onto the same brain regions that were differentially activated by delay cues in the current study. This network was shown to be activated independently of sensory modality and did not related explicitly to cognitive processes (Hayes & Northoff, 2011). Studies have found altered amygdala activations in individuals with ADHD symptoms in response to negatively valenced stimuli other than delay, including fearful faces (Posner et al., 2011; Tye et al., 2014), monetary loss (Wilbertz et al., 2017) and threatening cues (Maier et al., 2014). It also remains possible that this network, and the amygdala in particular, processes stimulus salience rather than aversiveness per se (Librezon, Phan, Decker, & Taylor, 2003). That is, the task used in the current study could be picking up a general affective reactivity in ADHD rather than anything specifically to do with responsiveness to aversive events in general or delay in particular. Although we suspect that each of the regions identified in the current study is involved in basic aversion-related processing, it is probable that some are also specifically involved in modulating emotion processing. Previous studies have already suggested the involvement of frontal cortical regions in the modulation of amygdala reactivity during successful affect regulation (Banks, Eddy, Gold, Morey,& McCarthy, 2015; Morawetz, Bode, Baudewig, & Heekeren, 2017). Further research should compare amygdala and DLPFC responses to delay cues in

individuals with ADHD to responding to cues for other aversive (e.g., monetary loss, fearful faces, etc…) and pleasant experiences and events to address these questions.

Second, the task design did not allow us to fully differentiate between brain responses to delay cues and those to cues of certainty/uncertainty of outcomes. Some researchers have shown that humans have a tendency to prefer predictable over unpredictable aversive outcomes, evident behaviourally as well as in terms of reduced activations in aversion-related networks (Labrenz et al., 2016; Sarinopoulos et al., 2010). For adolescents with ADHD, however, fully predictive delay cues elicited significantly higher activations than the less predictive conditional delay cues. It is possible that not having control over outcomes generally, rather than the delay itself, was the aversive aspect of the certain delay trials in the current experiment (Lemiere et al., 2012). However, this cannot explain the finding of a dose-response relationship for the amygdala and DLPFC activations, a finding that readily agrees with the delay aversion hypothesis.

Finally, the sample in the current study covers a wide age range (10 – 18 years). Future research should further investigate whether developmental factors play a role in the neurobiological signature of delay aversion (Antrop et al., 2006).

Conclusions

We provide evidence of a direct link between hyper-activation in the amygdala and DLPFC to cues of impending delay and the everyday experience of delay aversion in individuals with ADHD. Longitudinal studies are required to examine how this association arises and how it is related to the emerging evidence of ADHD-related structural alterations in sub-cortical brain regions.

Supplementary Material

TABLE S1. Whole brain analysis of estimated brain activations in CERTAIN DELAY > NO DELAY anticipation. Montreal Neurological Institute (MNI) coordinates of peak voxels within these clusters are reported. Asterisks (*) indicate significant brain activation ($p < 0.05$) after family wise error [FWE] correction L = left, R = Right

Brain Region	Side	MNI			T	Cluster
		X	Y	Z	Score	Size
ADHD > CONTROL						
Amygdala	L	-24	-2	-26	3.76*	92
	R	20	6	-17	3.39*	52
Temporal Pole	L	-30	8	-30	3.41*	114
	R	32	10	-30	3.71*	57
Anterior Insula	L	-40	0	-6	3.65*	73
	R	41	12	-2	3.83*	128
Ventromedial Prefrontal Cortex	L	-28	14	-26	3.45*	21
	R	40	32	-2	3.36*	18
Dorsolateral Prefrontal Cortex	L	-36	50	18	3.57*	105
	R	32	46	36	3.90*	27
Cerebellum	L	4	-38	-4	3.95*	138
ADHD						
Amygdala	L	-22	2	-22	3.40*	166
	R	18	4	-17	3.70*	146
Temporal Pole	L	-30	8	-30	3.42*	94
	R	32	10	-30	3.75*	112
Anterior Insula	L	-40	0	-6	3.54*	268
	R	36	8	-16	3.96*	33
Ventromedial Prefrontal Cortex	L	-28	14	-20	3.80*	29
	R	50	18	-8	3.39*	36
Dorsolateral Prefrontal Cortex	L	-28	32	42	4.32*	141
	R	36	10	38	3.87*	33
Occipital Gyrus	L	-24	-82	10	4.66*	157
	R	26	-82	14	5.75*	310
Parietal Cortex	L	-16	-76	44	3.66*	14
	R	32	-46	52	3.72*	27
Cerebellum	L	8	-46	2	3.92*	32
CONTROL						
Occipital Gyrus	L	-26	-82	14	6.12*	75
	R	34	-78	10	6.50*	83
Parietal Cortex	L	-20	-74	46	5.29*	164
	R	30	-58	54	4.89*	138

a

TABLE S2. Whole brain analysis of estimated brain activations in CONDITIONAL DELAY > NO DELAY anticipation. Montreal Neurological Institute (MNI) coordinates of peak voxels within these clusters are reported. Asterisks (*) indicate significant brain activation ($p < 0.05$) after family wise error [FWE] correction. L = left, R = Right

Brain Region	Side	MNI			T Score	Cluster Size
		X	Y	Z		
ADHD > CONTROL						
Amygdala	L	-26	0	-24	2.88	45
	R	18	4	-16	2.85	16
Temporal Pole	L	-36	8	-30	3.14	76
Ventromedial Prefrontal Cortex	L	-28	50	36	3.27	150
Pallidum	L	16	2	2	3.06	102
Occipital gyrus	L	48	-80	8	3.13	15
ADHD						
Amygdala	L	-26	0	-24	3.89	45
	R	18	4	-16	3.82	30
Temporal Pole	L	-26	56	32	3.76*	53
	R	68	-16	8	3.17	114
Ventromedial Prefrontal Cortex	L	-46	24	-8	2.88	166
Dorsolateral Prefrontal Cortex	L	-26	56	32	4.01*	142
Occipital Gyrus	L	-24	-82	10	4.98*	221
	R	38	-78	4	3.89*	275
Parietal Cortex	L	-22	-58	44	3.65*	331
	R	24	-60	48	2.91	75
CONTROL						
Temporal Pole	L	-58	10	-2	2.38	21
Dorsolateral Prefrontal Cortex	L	-40	20	38	3.47*	419
Occipital Gyrus	L	-16	-84	4	5.01*	1693
	R	22	-84	4	3.31	1151
Parietal Cortex	L	-34	-56	50	4.978	1209
	R	26	-54	48	3.63*	310

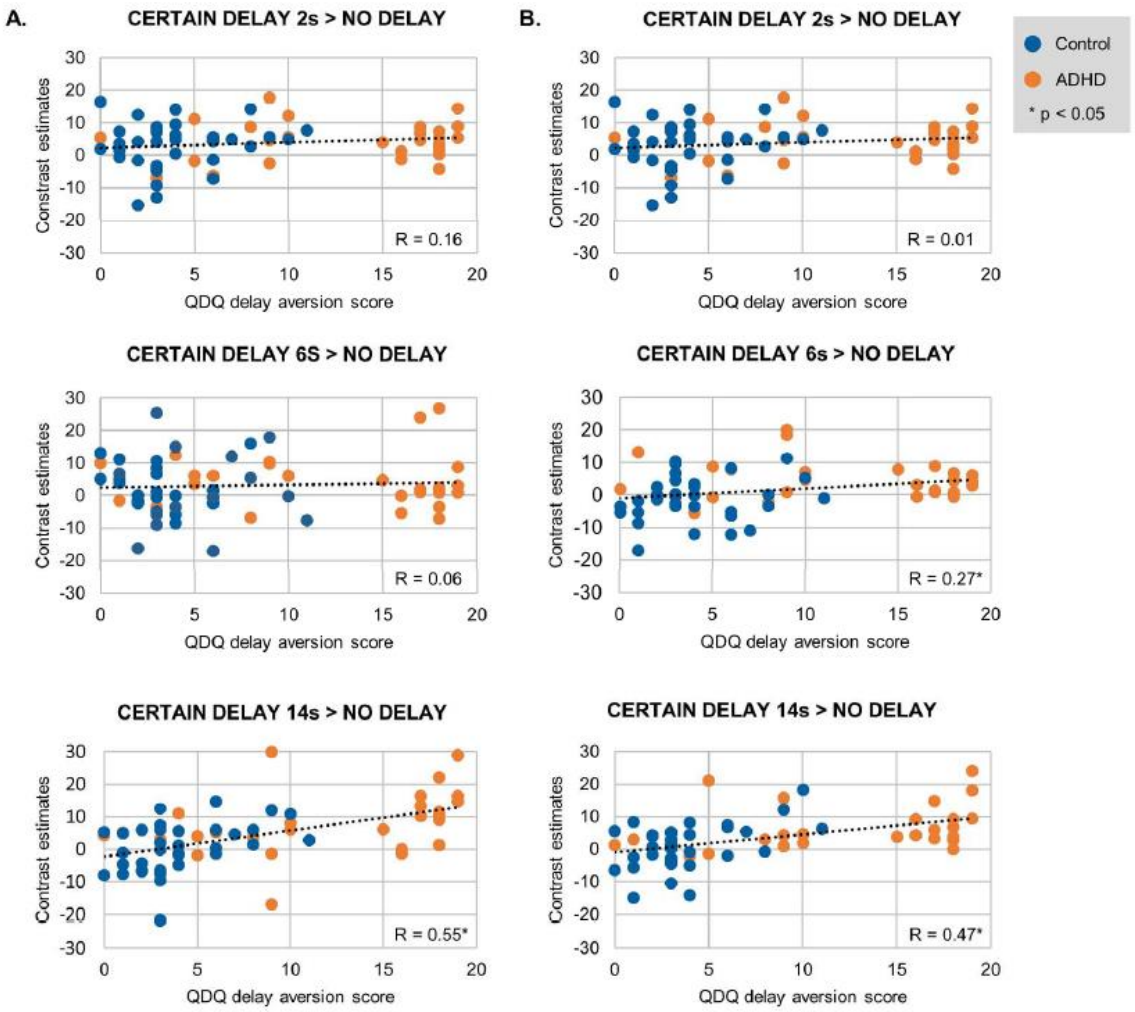

FIGURE S1. Scatter plots for the correlations between Quick Delay Questionnaire (QDQ) delay aversion scores and peak brain activations in (A) the amygdala and (B) the dorsolateral prefrontal cortex for ADHD (orange) and control (blue) participants.

Chapter 4 | The amygdala in attention-deficit/hyperactivity disorder: structural and functional correlates of delay aversion

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Van Dessel, J., Sonuga-Barke, E., Moerkerke, M., Van der Oord, S., Lemiere, J., Morsink, S., & Danckaerts, M. (2019). The amygdala in adolescents with attention-deficit/hyperactivity disorder: Structural and functional correlates of delay aversion. *World Journal of Biological Psychiatry*, *0*(0), 1–12.
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Abstract

Recent magnetic resonance imaging (MRI) studies implicate structural alterations of amygdala, a brain region responsible for processing and experiencing negative emotions, in adolescents with attention deficit/hyperactivity disorder (ADHD). Here we examined ADHD-related structural correlates of amygdala functional activity elicited during a functional MRI task designed to test behavioural and brain responses to the imposition of delay – an event known to both elicit amygdala hyperactivation and aversity in ADHD. Structural MRI scans from 28 right-handed male adolescents with combined type ADHD and 32 age-matched controls were analysed. Regional grey matter volumes of ADHD and control participants ($p[FWE] < 0.05$) were correlated with delay aversion self-ratings and neural activity in response to delay-related cues on the Escape Delay Incentive fMRI task. ADHD was associated with significantly reduced volumes in bilateral amygdala, parahippocampal and temporal gyrus ($p[FWE] < 0.05$), greater basolateral amygdala activation to delay-related cues ($p[FWE] < 0.05$) and higher delay aversion self-ratings. Amygdala volume reductions were significantly correlated with, and statistically mediated the pathway from ADHD to, delay-cue-related amygdala hyperactivity ($p < 0.01$) and self-reported delay aversion ($p < 0.01$). We provide the first evidence of the functional significance of reduced amygdala volumes in adolescents with ADHD by highlighting its relation to delay-induced brain activity that is linked to delay aversion.

Introduction

Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by problems with attention, hyperactivity and impulsivity. Brain imaging studies have found ADHD to be related to widespread, but relatively subtle, structural alterations in cortical brain networks responsible for higher order cognitive functions such as attention control, inhibition and working memory (Bush et al., 2005; Castellanos & Tannock, 2002; Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002; Philip Shaw et al., 2011). Structural alterations have also been found in subcortical regions (Ellison-Wright, Ellison-Wright, & Bullmore, 2008; Frodl & Skokauskas, 2012; Norman et al., 2016; Valera, Faraone, Murray, & Seidman, 2007). A recent mega-analysis, including 1713 patients with ADHD, found the largest volumetric subcortical reductions in amygdala in children and adolescents (up to 15 years old), although not in adults (Hoogman et al., 2017). This confirmed the finding of previous smaller studies (Plessen et al., 2006; Sasayama et al., 2010).

However, the functional significance of these structural effects in adolescents with ADHD remains to be determined. One hypothesis is that ADHD-related alterations in its structure underpin disrupted amygdala activity, which mediate the functional deficits in the processing of both social (e.g., fearful faces; Brotman et al., 2010; Herpertz et al., 2008; Posner et al., 2011) and non-social (e.g., monetary loss; Plichta et al., 2009; Wilbertz et al., 2017) negative affective stimuli. Furthermore, amygdala has been implicated in the regulation and processing of aversive emotional states in adolescents with ADHD (e.g., frustration, anger; Arnsten & Rubia, 2012; Herrmann, Biehl, Jacob, & Deckert, 2010) which are increasingly being championed as important features in a sub-group of patients (Martel, Nigg, & Lucas, 2008). More generally, the pivotal role of the amygdala within a complex network of brain regions governing emotion is increasingly well understood (Hayes & Northoff, 2011; Huang et al., 2018; Pessoa, 2017; Sharp, 2017), whereby it coordinates excitatory signals to brain regions actively involved in emotional processing (anterior insula, orbital frontal cortex, ventromedial prefrontal cortex (PFC) and anterior cingulate cortex), as well as other regions involved in emotional responses (thalamus and hippocampus). Amygdala also receives inhibitory signals from brain regions that are typically involved in emotion regulation (posterior cingulate cortex, precuneus, dorsomedial PFC and dorsolateral PFC).

In ADHD studies, the direct evidence of altered amygdala function is inconsistent (Shaw, Stringaris, Nigg, & Leibenluft, 2014). Some studies found no alterations (Malisza et al., 2011; Marsh et al., 2008; Schlochtermeier et al., 2011), while others found amygdala hyperactivation during both the perception of social (Brotman et al., 2010; Herpertz et al., 2008; Posner et al., 2011) and non-social negative stimuli (Plichta et al., 2009; Wilbertz et al., 2017). Perhaps the clearest and most consistent effect has been found in relation to altered amygdala activation in response to cues of impending delay during task performance when adolescents are obliged to wait for an extended period of time – a prospect which has been both hypothesized (Sonuga-Barke, 1994; Sonuga-Barke, 2005) and then confirmed to be especially aversive for adolescents with ADHD (Bitsakou et al., 2006; Hsu et al., 2015; Van Dessel, Morsink, et al., 2019). Three functional Magnetic Resonance Imaging (fMRI) studies in independent samples using variations of the same task have all shown amygdala hyperactivation to cues indicating that a delay period will be imposed after they have responded to a simple reaction time task (Lemiere et al., 2012; Van Dessel et al., 2018b; Wilbertz et al., 2013) the largest study, contrasted responses to cues predicting NO DELAY, CERTAIN DELAY and CONDITIONAL DELAY (where only slow responses were followed by delay) in 29 adolescents with ADHD and 32 matched controls. It found whole-brain corrected hyperactivation of amygdala to CERTAIN DELAY cues compared with NO DELAY cues which increased linearly with imposed delay duration and more strikingly mediated the relationship between ADHD and the participants' ratings of their levels of delay aversion (Van Dessel et al., 2018b).

In the current paper, we extend this analysis to test whether these functional effects are themselves associated with alterations in amygdala structure – in particular reduced volume seen in other recent studies. To do this we used voxel-based morphometry techniques to investigate anatomical alterations in subcortical and cortical brain regions known to be implicated in emotion processing, including the amygdala. We predicted that: (i) adolescents with ADHD would show reduced amygdala volumes (correcting for total grey and white matter volume); (ii) these reductions would be correlated with the degree of amygdala hyper-activation to certain delay cues and self-ratings of delay aversion and (iii) that they would statistically mediate the pathway from ADHD to both altered amygdala function and ratings of delay aversion.

Materials and Methods

Participants

Thirty-two right-handed male adolescents with ADHD, combined presentation and 36 typically developing male controls that took part in (Van Dessel et al., 2018b) were included (age-range: 10 - 18 years, ADHD mean (SD) = 14.5 (2.1), control mean (SD) = 14.7 (2.1), p = 0.68). All had a pre-existing clinical diagnosis of combined-type ADHD based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) assessed by a child psychiatrist. Presence, pervasiveness and clinical impact of ADHD symptoms across different settings were reassessed using a parent interview with the Schedule for Affective Disorders and Schizophrenia for school-age children (K-SADS) and adolescents were also screened for conduct disorder (n=0) or oppositional defiant disorder comorbidities (n=3) with the K-SADS (Kaufman et al., 1997). Controls were excluded if they met the DSM-IV criteria for any psychiatric disorder assessed using a K-SADS screening interview with one of the parents. Participants were further excluded if parents reported specific learning disorders (e.g., dyslexia or dyscalculia), drug or substance abuse, smoking, neurological abnormalities or MRI contraindications. All subjects completed the short version of the Dutch adaptation of the Wechsler Intelligence Scale version 3 for children (Kort et al., 2005) or adults (Wechsler, 2005), to check for the inclusion criterion of an IQ > 80 (mean total IQ ADHD group (SD) = 99.5 (9.6) and mean total IQ control group (SD) = 111.6 (10.2), $P < 0.001$). ADHD medicated patients (n=24) were taken off psychostimulant medication 72 hours prior to testing and fMRI scanning. The experimental protocol was approved by the ethics committee of the University Hospital Leuven, Belgium (S54971). Prior to testing participants and parents provided informed written consent. In an MRI scanner, participants performed an Escape Delay Incentive (EDI) task to elicit anticipatory brain activation in a delay-related context (Van Dessel et al., 2018b). In the middle of each scanning session, high-resolution structural images were acquired.

Procedure

MRI protocol

Scanning was performed on a 3 Tesla Philips Intera MR scanner (Best, The Netherlands) with an 8-channel head coil. Functional scans were acquired using a Blood Oxygen Level Dependent (BOLD) sensitive echo planar imaging sequence. Scan parameters were fixed at: TR = 2000 ms, TE = 30 ms, flip angle = 90°, field of view = 220 x 220 mm^2, 36 axial slices with 3.5 mm thickness and in plane voxel size of 2.75 mm^2. Structural scans were acquired using a standard T1-weighted pulse sequence with the following scan parameters: TR = 9.7ms, TE = 4.6 ms, flip angle = 12°, field of view = 256 x 256 mm^2 and 1 mm^3 voxel size.

Brain structure

FIGURE 1 shows an overview of the consecutive structural pre-processing steps that were performed in the Computational Anatomy Toolbox 12 (CAT 12, Department of Psychiatry, Jena, Germany) implemented in Statistical Parametric Mapping 12 (SPM 12, Wellcome Trust Centre for Neuroimaging, London, UK). Structural images were manually reoriented to the anterior and posterior commissure line and automatically segmented based on group specific adolescent tissue probability maps created with Template-O-Matic toolbox (Wilke et al., 2008). Spatial normalisation parameters in Montreal Neurological Institute (MNI) space were applied to the structural scans and were smoothed using a 3D Gaussian kernel of 8 mm full width at half maximum (FWHM). In the next step axial slices were visually inspected and quality parameters (amount of noise, bias and weighted overall image quality) were calculated to ensure an accurate segmentation and normalization procedure. Four adolescents with ADHD and four controls were excluded based on these quality measures (28 and 32 participants, respectively, remained). A voxel-based morphometry approach was used to calculate the local concentration of grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) volumes. Total intracranial volumes (TIV) were calculated as the sum of GM, WM and CSF volumes. Subcortical brain regions were defined by the SPM 12 atlas provided by Neuromorphometrics Inc (Bakker, Tiesinga, & Kötter, 2015). Global GM, WM and TIV brain volumes were compared using a One-Way ANOVA in SPSS (IBM Corp, Armonk, NY, USA). Smoothed GM volumes differences between both groups were assessed using a general linear model (GLM) in CAT 12. TIV and age were included as covariates in order

to correct for differences in brain size. Total intelligence quotients were not included in the model according to recommendations of Dennis et al. (2009). Whole–brain analyses were performed for two T-contrasts (ADHD > control and ADHD < control) and whole-brain family wise error (FWE) corrected ($p < 0.05$) significant voxels were identified based on the peak contrast value. Cohen's d indices were calculated to estimate the effect size of volumetric alterations between ADHD and controls. Binary peak cluster were extracted through SPM12 and 3D rendered in Paraview (Ahrens, Geveci, & Law, 2005). Structural and functional amygdala peak coordinates were labelled in the hippocampal module of FreeSurfer 6.0 (Saygin et al., 2017).

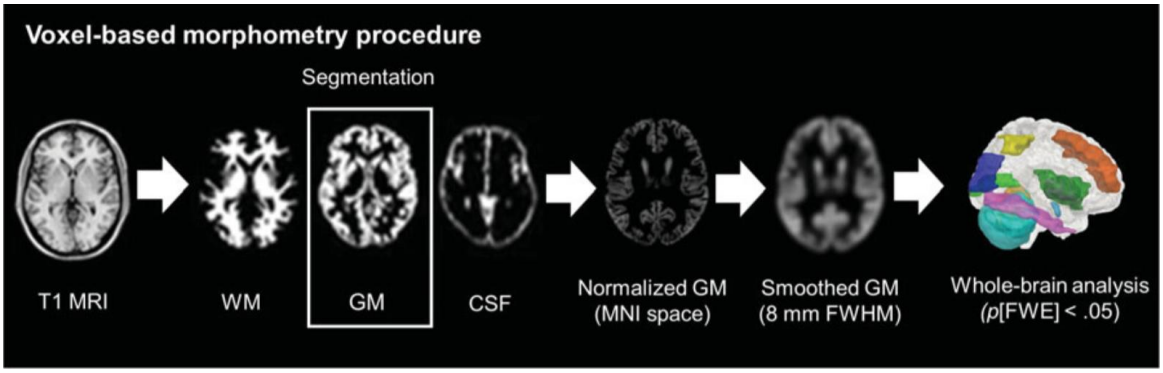

FIGURE 1. Voxel-based morphometry analysis workflow. Structural T1-weighted magnetic resonance imaging (MRI) scans were segmented based on adolescent specific tissue probability maps into white matter (WM), grey matter and cerebrospinal fluid (CSF).These images were normalised in Montreal Neurological Institute (MNI) space, modulated and smoothed with 8 mm full width at half maximum (FWHM). Quality parameters were calculated to ensure an accurate procedure. Whole-brain analyses were used to compare the smoothed GM volumes between both groups.

Brain activity in response to impending delay

During fMRI signal acquisition, participants completed the EDI reaction-time task (for more details see Van Dessel et al., 2018b and **FIGURE 2**). They were instructed to press a button as quickly as possible when a target stimulus (signalled by a square-shaped cue) was presented in the center of the screen. Subjects were presented with three different geometrical cues indicating different outcomes in terms of delay conditions in counterbalanced order: (i) On the CONDITIONAL DELAY trials (signalled by a triangle-shaped cue), a post-response delay period could be escaped with a timely response (delay imposition was set at one third of trials); (ii) On the CERTAIN DELAY trials (signalled by a circle-shaped cue), a post-response delay period was imposed irrespective of the response speed to the target; and (iii) On the NO DELAY trials (signalled by a diamond-shaped cue) there was no delay on any of the trials regardless of response speed. The

length of the anticipation period was jittered so target presentation remained unpredictable. Unknown to the participants, thresholds for "correct" reaction time responses were set so that participants could succeed in two thirds of trials across all three cue conditions. Participants received feedback about their performance in the form of a green "OK" sign (fast enough) or a red cross (too slow), depending on the condition they were in they either needed to wait (2, 6 or 14 s) or they could immediately continue with the next trial. The EDI task trial structure allows direct comparison of cues with different delay-related consequences, while controlling for potential confounds related to sensory input, motor output, arousal and performance. For the present analysis we focused on delay anticipation of the CERTAIN DELAY > NO DELAY contrast collapsed across all delay times, as this contrast was shown to give the largest emotional brain response (Van Dessel et al., 2018b).

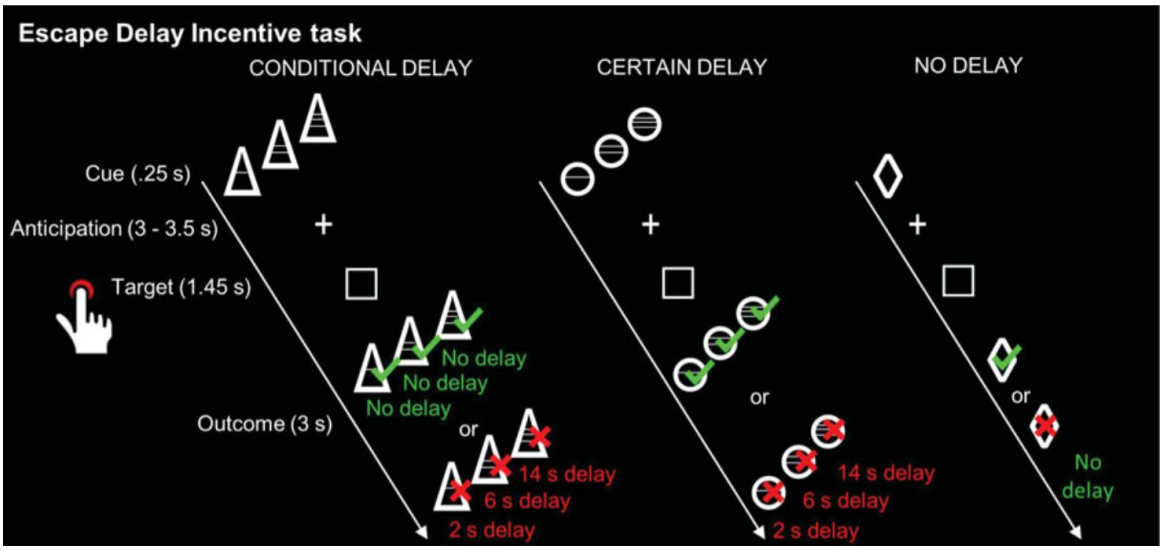

FIGURE 2. Escape Delay Incentive task. Cues indicated different delay-related response consequences. The triangle (CONDITIONALDELAY) indicated that delay would only follow after slow responses (on 33% of trials). The circle (CERTAIN DELAY) indicated that delay would follow irrespective of response speed. The diamond (NO DELAY) indicated that no delay would follow, irrespective of response speed. Delay levels were 2, 6 or 14 s and were indicated by one to three horizontal bars inside the cue. The analysis focused on delay anticipation of the CERTAIN>NO DELAY contrast collapsed across all delay times.

Standard pre-processing steps were conducted in SPM 8 (Wellcome Trust Centre for Neuroimaging, London, UK). Slice timing correction was applied to correct for slice acquisition delay. Next, all slices were realigned to the middle slice from each run to correct for head movement. Motion correction parameters were inspected and no significant difference ($p > 0.05$) in overall movement was observed between both groups. During the realignment procedure a mean image was created and functional images were realigned using this mean image as optimum reference. Then the structural image was co-registered with the mean functional image and normalized in Montreal Neurological Institute (MNI) space. Finally, all functional images were resampled to a voxel size of 2 x 2 x 2 mm^3 and smoothed using a 3D Gaussian kernel with 8 mm FWHM. The CERTAIN DELAY > NO DELAY T-contrast images were calculated for each participant. Contrast estimates for CERTAIN DELAY > NO DELAY at second level were extracted at peak voxel and cluster FWE-corrected ($p[FWE] < 0.05$) within the brain regions showing significant volumetric group differences.

Self-reported Delay Aversion.

Participants answered five questions of the quick delay questionnaire (QDQ) on how they experience delay waiting in everyday life: (i) I am usually calm when I have to wait in queues, (ii) I feel relaxed when waiting for things, (iii) I hate waiting for things, (iv) I feel frustrated when I have to wait for someone else to be ready before I can do something, (v) Having to wait makes me feel stressed and tense (Clare et al., 2010). The delay aversion QDQ subscale had good internal and test-retest reliability in children and adolescents (Clare et al., 2010; Hsu et al., 2015; Van Dessel et al., 2018b).

Analysis integrating brain structure and function

Grey matter volumes of brain regions displaying significant group differences ($p[FWE] < 0.05$) were correlated with their neural activity difference measured between the CERTAIN DELAY and NO DELAY contrast, and with QDQ delay aversion scores using two-tailed Pearson correlations ($p < 0.05$). Multiple regression analysis was conducted to test whether structural brain differences mediated the relationship between ADHD group membership and brain activation during the EDI task, and self-reported delay aversion The Preacher and Hayes bootstrapping method was performed to investigate the indirect effect after 5000 bootstrap resamples using a 95% confidence interval and the

standardized indirect effect were used to indicate the mediation effect size (Preacher & Hayes, 2008).

Results

Brain Structure

No significant group differences were observed in total grey or white matter volumes, or TIV (**TABLE 1**). A whole-brain analysis revealed that adolescents with ADHD had significantly (p[FWE] < 0.05) reduced volumes of the bilateral amygdala, medial temporal gyrus extending anteriorly to temporal pole and parahippocampus (**TABLE 1**). The largest effect size was found for the temporal pole area (Cohen's d left / right side = -1.00 and -1.01), followed by amygdala (d = -0.64 and -0.75) and parahippocampus (d = -0.53 and -0.61). Spatial information on volumetric reduction is depicted in **FIGURE 3**. No enlarged brain volumes were found for adolescents with ADHD.

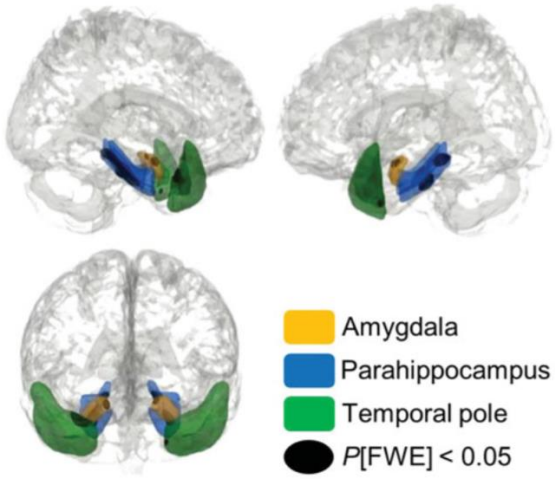

FIGURE 3. Voxel-based morphometry analysis for control > ADHD subjects display an ADHD-related volumetric reduction for bilateral amygdala (orange), temporal pole (green) and parahippocampus blue). Significant (p[FWE] < 0.05) peak clusters within the subcortical regions (black) indicate the specific location of volumetric differences.

TABLE 1. Overview of brain volume comparisons.

Total brain volumes (in cm^3)	Side	ADHD (n=28) Mean (SD)	Control (n=32) Mean (SD)	% reduction in ADHD	Effect size Cohen's d	Peak coordinates Control>ADHD in MNI space	p-value
Total intracranial	-	1600 (152)	1648 (118)	3%			0.13
Total grey matter	-	720 (87)	738 (84)	2%			0.41
Total white matter	-	486 (63)	506 (51)	4%			0.18
Temporal Gyrus	L	14.39 (2.06)	16.32 (1.78)	12%	-1.00	-66/-53/-13	< 0.001
	R	14.57 (1.81)	16.33 (1.61)	11%	-1.01	57/-66/2	< 0.001
Amygdala	L	1.01 (0.15)	1.11 (0.16)	9%	-0.64	-15/-5/-15	0.017
	R	0.92 (0.13)	1.03 (0.18)	11%	-0.75	14/-5/ -17	0.005
Parahippocampal Gyrus	L	3.22 (0.46)	3.44 (0.39)	7%	-0.53	-24/-26/-29	0.046
	R	3.07 (0.38)	3.30 (0.38)	7%	-0.61	24/-23/-29	0.021

Brain Function

The group differences in functional activity within the amygdala for CERTAIN DELAY versus NO DELAY contrast have been reported in detail previously, as have the group differences in QDQ delay aversion self-ratings (Van Dessel et al., 2018b). In brief, adolescents with ADHD (delay aversion score = 12.8 ± 6.1) rated themselves significantly more delay averse in everyday life than controls (delay aversion score = 3.9 ± 2.8, $p < 0.001$). As a group, adolescents with ADHD displayed selective hyper-activation by cues of impending CERTAIN DELAY, and to a lesser extent by cues of impending CONDITIONAL DELAY, in regions previously shown to be involved in processing of negatively valanced emotional stimuli and experiences (amygdala, anterior insula, temporal pole, dorsolateral PFC and ventromedial PFC). For amygdala and dorsolateral PFC these effects were more pronounced for longer delay cues. Amygdala and dorsolateral PFC activations were significantly associated with self-ratings of delay aversion. Finally, the amygdala and dorsolateral PFC activations significantly mediated the relationship between ADHD and self-ratings of delay aversion.

Association Between Brain Structure and Function

Of the regions demonstrating volume reductions in adolescents with ADHD, only the amygdala was significantly ($p < 0.01$) correlated across both groups with the neural activity difference (MNI [-24/-2/-26] and [20/6/-17]) between the CERTAIN DELAY and NO DELAY condition (Pearson correlation left / right r = -0.35 and -0.32) (**FIGURE 4A**); and to self-ratings of delay aversion (r = -0.43 and -0.45) (**FIGURE 4B**). Results did not change when use of psychostimulant medication, TIV or age were added as covariates.

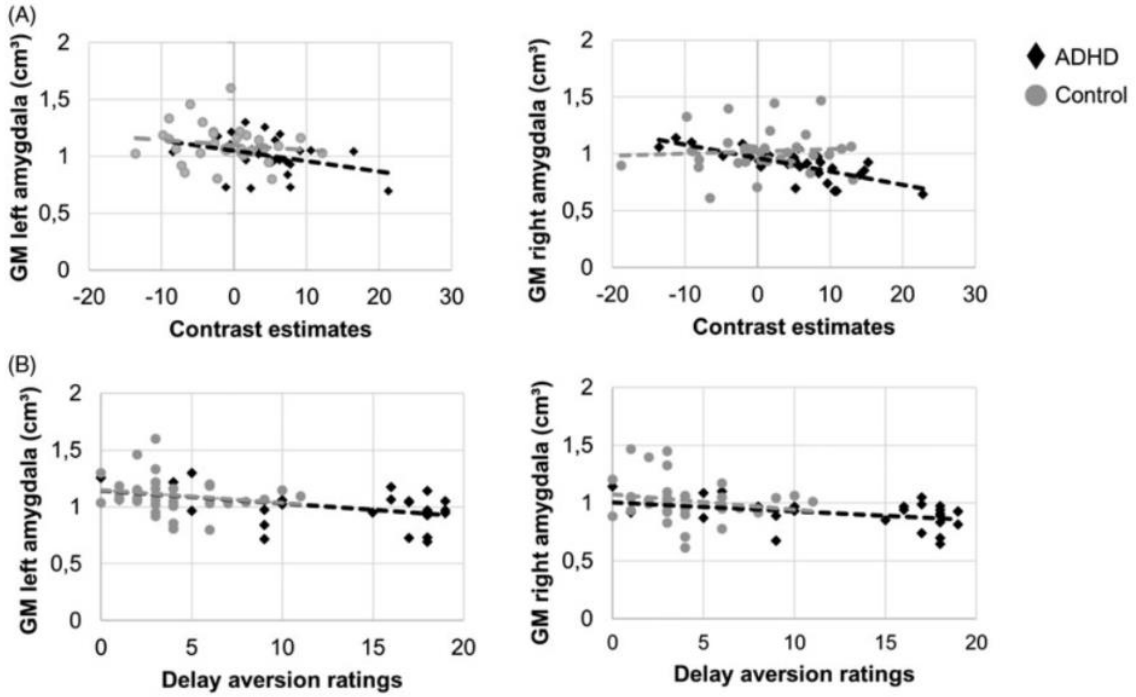

FIGURE 4.(A) Correlation between total left (left graph) and right (right graph) amygdala grey matter (GM), and functional activity within the amygdala during the Escape Delay Incentive task for the CERTAIN DELAY versus NO DELAY contrast. (B) Correlation between left (left graph) and right (right graph) amygdala GM with self-reported delay averse behaviour on the Quick Delay Questionnaire

The QDQ score was also significantly correlated with delay-related neural activity in the ADHD. Amygdala volume reductions statistically mediated the pathway from ADHD to altered amygdala function and self-ratings of delay aversion. Multiple regression analyses were performed on each component of the proposed mediation model (**FIGURE 5**)

First, group was positively associated with amygdala function (β = 0.42; t = 3.60; p < 0.001) and QDQ delay aversion ratings (β = 0.67; t = 7.03; p < 0.001). Second, group was negatively associated with amygdala structure (β = -0.34; t = 2.75; p < 0.01). Third, amygdala structure was negatively associated with amygdala function (β = -0.32; t = 2.70; p < 0.01) and QDQ delay aversion ratings (β = -0.24; t = 2.50; p < 0.01) when correcting for group in the model. Finally, the group difference in amygdala function (β = 0.31; t = 2.67; p < 0.01) and QDQ delay aversion ratings (β = 0.59; t = 6.11; p < 0.001) were significantly mediated by structural amygdala differences. The indirect effect for amygdala structure accounted for 11% and 8% of the association between group and amygdala function and between group and QDQ delay aversion rating, respectively.

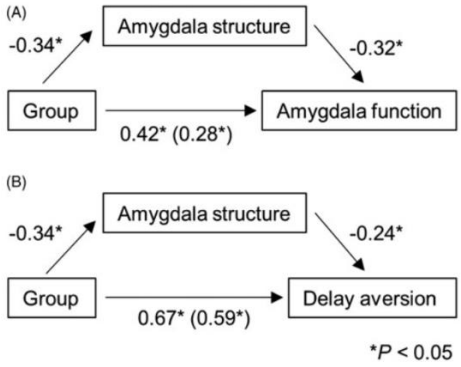

FIGURE 5. Models illustrating the way that amygdala structure mediates the association between ADHD and amygdala function (A) and delay aversion ratings (B). The mediated effect for the path between ADHD group and QDQ delay aversion is in parentheses. Asterisks (*) indicate p < 0.05.

The specific location of structural reductions in the amygdala and related neural hyper-activation did not overlap (**FIGURE 6**). For the right amygdala, functional activity to delay-related cues was found in two distinct clusters (MNI [24/-2/-26] and [25/0/-26], **FIGURE 6A**). A detailed analysis of structural and functional peak coordinates in the amygdala and hippocampus sub-regions shows that reductions in amygdala volume were explicit for the cortex-amygdala transition area, while the functional hyperactivity was the most prominent in the basolateral amygdala (**FIGURE 6B**).

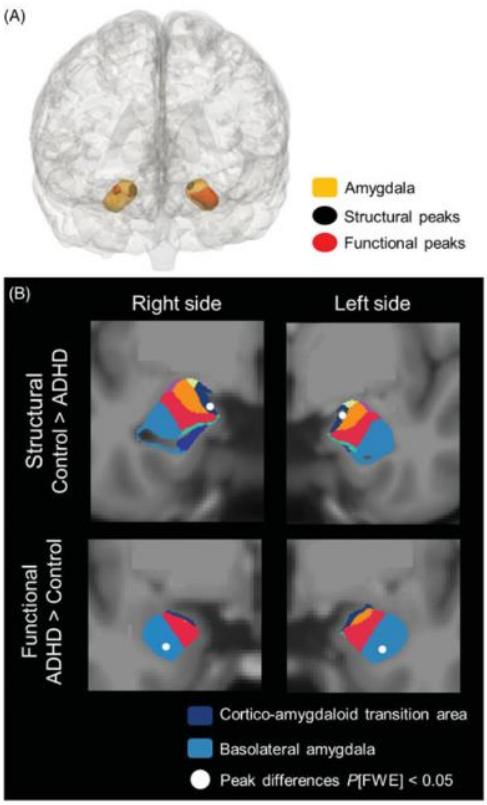

FIGURE 6. (A) Location in the amygdala (orange) of significant (p[FWE] < 0.05) peak clusters for ADHD-related volumetric reductions (black) and neural activity difference between CERTAIN DELAY and NO DELAY (red) on the Escape Delay Incentive task. (B) Analysis of the amygdala and hippocampus subregions highlighted that amygdala volume reductions were explicit for the cortex–amygdala transition area (dark blue), while the functional hyperactivation occurred in the basolateral amygdala (light blue).

Discussion

Previous studies in children and adolescents with ADHD have reported smaller amygdala volumes (Ellison-Wright et al., 2008; Frodl & Skokauskas, 2012; Hoogman et al., 2017; Norman et al., 2016), increased amygdala activity to delay-related cues (Lemiere et al., 2012; Van Dessel et al., 2018b) and negative valence ratings towards pending delay on self-reported questionnaires (Clare et al., 2010; Hsu et al., 2015; Van Dessel, Morsink, et al., 2019; Van Dessel et al., 2018b). The present study employed a multimodal approach to investigate structure-function relationship of brain regions implicated in delay aversion. Three findings were of particular interest. First, confirming recent findings from a large-scale mega-analysis (Hoogman et al., 2017), ADHD-related grey matter reductions were found for bilateral amygdala, parahippocampal and temporal gyrus. Second, of these subcortical regions, only the amygdala volumes were significantly correlated with ADHD-related hyper-activation to EDI-task cues for the CERTAIN DELAY versus NO DELAY contrast and elevated levels of self-rated delay aversion. Third, amygdala structure significantly mediated the relationship between ADHD and brain responses on the delay related task and between ADHD and self-report of delay aversion. Thus, our study,

combining functional and structural data, provides further validation of the role of amygdala in delay aversion for children and adolescents with ADHD.

Neuroimaging studies have identified both widespread structural and functional brain abnormalities in adolescents with ADHD. The interrelationship between function and structure, however, remains poorly understood. In particular, it is not known whether ADHD-related structural and functional deficits are in any way linked by, for example, in terms of spatial overlap (Cortese et al., 2012; Kessler, Angstadt, Welsh, & ipada, 2014) or co-occurrence in functionally related neural networks (Makris et al., 2007; Overmeyer et al., 2001; Pironti et al., 2014). While a number of studies in ADHD have found a clear association between brain structure and task performance (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Casey et al., 1997; McAlonan et al., 2009), far fewer studies have investigated this interrelationship on brain level using task-based fMRI (Kobel et al., 2010; Roman-Urrestarazu et al., 2016). Kobel and colleagues (2010) found a relation between temporal pole hyperactivity during an N-back task and smaller temporal gyrus volumes in 14 adolescents with ADHD compared to 12 matched controls. Roman-Urrestarzu et al. (2016) found that reduced caudate volumes of 21 ADHD adults compared to 23 controls were associated with hypoactivation of the caudate during an fMRI working memory task. The present results suggest for the first time a pathophysiological link between amygdala structure and activity during a delay-related reaction time task in adolescents with ADHD. The pathophysiological mechanisms that may contribute to this amygdala dysregulation cannot be determined based on this study.

The amygdala is a heterogeneous structure that can be subdivided in 13 nuclei and has a variety of different neural cell types (Sah, Faber, De Armentia, & Power, 2003). Our detailed analysis of the amygdala subregions indicated that volume reductions were specific for the cortex-amygdala transition area, while the functional hyper-activity to delay-related cues was most prominent in the basolateral amygdala. Each of these regions has a unique function within the amygdala. The cortex-amygdala transition area plays a role in behavioural responses to emotionally arousing circumstances and has substantial projections to the basal nuclei, whereas the basolateral amygdala stimulates the stress response and receives sensory information directly from the temporal lobe and hippocampus (Cádiz-Moretti, Abellan-Álvaro, Pardo-Bellver, Martinez-Garcia, & Lanuza, 2016; Cho, Ernst, & Fudge, 2013). Interestingly, also these two brain regions showed significantly smaller grey matter volumes for adolescents with ADHD compared to

matched controls. Animal models will need to be developed to provide insight into the neural systems of cellular dysregulation that underlie the behavioral alterations associated with ADHD.

The human brain undergoes significant changes in both its structural and functional organisation during development across the life span. Chronic exposure to stressful events, especially during childhood and old age, may have enduring effects on the brain shaping its development. Animal and human studies suggest that chronic or repeated exposure to stress has the highest impact on the amygdala, hippocampus and prefrontal brain regions, structures that are still in development during childhood and adolescence (Lupien, McEwen, Gunnar, & Heim, 2009; McEwen, Nasca, & Gray, 2016; Tyborowska et al., 2018; Vyas, Mitra, Shankaranarayana Rao, & Chattarji, 2002). Decreased brain volumes could be a consequence of stress-induced structural remodeling, more specifically by dendrite shrinking leading to neuronal loss (McEwen, 2007). Given its cross-sectional nature the current study leaves unanswered key questions about the causal significance of amygdala reductions in ADHD generally or resulting from delay aversion more specifically. There are a number of possibilities. One hypothesis is that early emerging structural differences, perhaps genetically determined, drive the aberrant patterns of brain activation to particular environmental stimuli (such as delay cues) which in turn prime the affected individual to respond disordered to the environment (Francis, Caldji, Champagne, Plotsky, & Meaney, 1999; Ladd et al., 2000). Alternatively, it may be that exposure in general to elevated levels of environmental stressors during early development (e.g. difficulty with school work, feeling pressured to perform or behave beyond their ability, higher amount of daily-failures, parental or social stress), which is expected in the lives of children with ADHD, leads to a persistent state of excitability in the amygdala. This state of excitability shapes its structure which leads to altered amygdala function which in turn creates the context for the emerging hypersensitivity to aversive environmental events (Fareri & Tottenham, 2016; Mitra, Jadhav, McEwen, Vyas, & Chattarji, 2005; Sharp, 2017). Future studies should investigate whether other psychiatric disorders with infantile recurrent trauma also exhibit amygdala hyper-activity to aversive events. A third possibility is that the ADHD child's sensitivity to specific environmental events (e.g., the imposition of delay) is the result of conditioning over development and that this leads to altered brain function, which over time leads to changes in structure (Lupien et al., 2009; McEwen et al., 2016). Such a model

is consistent with the model that sees delay aversion as emerging as a product of the negative interactions between the ADHD child and their social environment when they fail to deal effectively with delay (Sonuga-Barke, 1994; Sonuga-Barke, 2005). A fourth theoretical hypothesis is that brain structure and function alterations are the result of a third common risk factor. For example, the same genetic variant should lead to a deviating amygdala function and structure. So far there is no empirical evidence from genome-wide association studies that supports this hypothesis. Longitudinal studies starting early in life will be essential to test these hypotheses.

Whatever the direction of causation, the finding that altered amygdala structure is linked to altered amygdala function raises important questions about the specificity of effects. On the face of it, it seems unlikely that amygdala volume reductions are due specifically to experiences around delay, rather than other negative experiences, or have their functional impact exclusively in relation to delay. A substantial subset of children with ADHD also have emotional lability problems (Anastopoulos et al., 2011). Higher emotional liability scores in children and adolescents with ADHD have been associated with a weaker amygdala subregion-based connectivity (Hulvershorn et al., 2014; Yu et al., 2016). Because ADHD has been associated with heightened levels of frustration during long and boring tasks (Bitsakou et al., 2006) and with hyperactivity in the amygdala when anticipating delay periods (Lemiere et al., 2012; Van Dessel et al., 2018b; Wilbertz et al., 2013), children and adolescents with ADHD and emotional lability symptoms might be characterized by a particularly strong negative emotional response during delay. Hyperactivation of the basolateral amygdala is also associated with other behavioural disorders characterized by excessive anxiety or emotional problems (Prager, Bergstrom, Wynn, & Braga, 2016; Sharp, 2017). In which the relationship between amygdala volume and activity during emotional information processing tasks has been repeatedly shown (Kalmar et al., 2009; Siegle, Konecky, Thase, & Carter, 2006). The role of ADHD-related amygdala alteration in other potentially aversive emotional experiences needs to be investigated, as does the role of these brain effects in the emergence of later emotional disorders, common in adolescent and adults with ADHD (Van Liefferinge et al., 2018).

This is the first study demonstrating a link between amygdala structure and function in adolescents with ADHD. However, the results need to be considered in the light of a number of limitations. First, these results focus on a specific subgroup of ADHD, more specifically right-handed boys with ADHD, combined presentation and may therefore not

be generalised to the overall ADHD population. Second, our sample included a wide age range (age 10-18), and thus developmental effects could be confounding the study findings. However, such an effect is unlikely because the groups were matched on age and gender. Third, replication is needed in a larger sample, as contradictory structural findings have been reported in the ADHD domain, possibly due to the lack of statistical power from small sample sizes (Schmaal et al., 2016) and the heterogeneity within ADHD (Heidbreder, 2015). The aim of the current study, however, was not to investigate structural differences per se, but to focus on the link between structure and function. It is not always feasible for task-based functional studies to include sufficient numbers of patients deemed necessary for voxel-based morphometry studies. Multicentre collaborations with large samples, standardised data acquisition and analysis procedures, like the ENIGMA consortium, can help to elucidate ADHD specific brain alterations in the near future (Lugo-Candelas & Posner, 2017).

Conclusion

In summary, this study provides further evidence for the role of amygdala in delay aversion. Adolescents with ADHD were characterized by a significant inverse association between amygdala volume, and amygdala response to delay-related stimuli and delay aversion self-ratings. Longitudinal studies are required to test whether structural alterations in amygdala are a cause or consequence of the aversive experience of delay.

Chapter 5 | Dissociating brain systems that respond to contingency and valence during monetary loss avoidance in adolescence

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Abstract

Negative reinforcement processes allow individuals to avoid negative and/or harmful outcomes. They depend on the brain's ability to differentiate; (i) contingency from non-contingency, separately from (ii) judgements about positive and negative valence. Thirty-three males (8-18 years) performed a cued reaction-time task during fMRI scanning to differentiate the brain's responses to contingency and valence during loss avoidance. In two conditions, cues indicated no contingency between participants' responses and monetary loss – (i) CERTAIN LOSS (negative valence) of €0.20, €1 or €5 or (ii) CERTAIN LOSS AVOIDANCE (positive valence). In a third condition, cues indicated a contingency between short reaction times and avoidance of monetary loss. As expected participants had shorter reaction times in this latter condition where CONDITIONAL LOSS AVOIDANCE cues activated salience and motor-response-preparation brain networks - independent of the relative valence of the contrast (CERTAIN LOSS or CERTAIN LOSS AVOIDANCE). Effects of valence were seen toward the session's end where CERTAIN LOSS AVOIDANCE cues activated ventral striatum, medial-orbitofrontal cortex and medial-temporal areas more than CERTAIN LOSS. CONDITIONAL LOSS AVOIDANCE trials with feedback indicating "success" activated ventral striatum more than "failure feedback". The findings support the hypothesis that brain networks controlling contingency and valence processes during negative reinforcement are dissociable.

Introduction

Consequences shape actions as individuals work to increase the likelihood of positive and reduce the likelihood of negative experiences and outcomes. From this perspective, the positive impact of establishing a contingency between an individual's poor task performance and negative outcomes (described as punishment in daily language) is explained, at one level, in terms of negative reinforcement processes - whereby the avoidance of aversive events and experiences reinforces those actions that allow their escape. However, our understanding of the neural mediators of the effects of negative reinforcement on human task performance is currently limited.

Monetary incentive paradigms have been used to study these processes in human subjects (Knutson et al., 2000). In these tasks preparatory cues signal whether "good" (with criteria individually tailored on a trial-by-trial basis) performance on an up-coming reaction time task will be reinforced. Tasks typically include performance-contingent monetary-gain cues but some have included cues indicating that monetary loss can be avoided (Dugré et al., 2018, Knutson and Greer, 2008, Oldham et al., 2018). On both trial types, participants receive feedback telling them how they have performed. Prior meta-analyses suggest that monetary loss avoidance cues speed reaction times (highlighting their motivational value). These cues activate ventral striatum, insula, thalamus, amygdala, premotor cortex, occipital cortex, cerebellum, lingual gyrus, supplementary motor area, middle frontal gyrus, anterior- and mid-cingulate cortex (Dugré et al., 2018, Knutson and Greer, 2008, Oldham et al., 2018). Successful avoidance of monetary loss as signaled by feedback activates bilateral ventral striatum, amygdala, anterior cingulate cortex and medial prefrontal cortex (Dugré et al., 2018; Knutson and Greer, 2008, Oldham et al., 2018). These regions overlap with those activated on reward anticipation rather than loss avoidance trials (Liu, Hairston, Schrier, & Fan, 2011).

In order to understand how the brain reacts to opportunities to avoid punishment (i.e., monetary loss) one needs to distinguish the role of two sets of brain processes: (i) the recognition and response to the cue properties signaling contingency (i.e., "this is an important cue - I need to prepare to respond to it") and (ii) those properties coding valence (the relative probability of a positive as opposed to a negative outcome). The way that monetary incentive tasks are designed and analysed currently precludes this distinction being effectively made. This is because they typically rely on the contrast

between monetary gain and monetary loss cues - so confounding the study of the brain processes implicated in marking the salience of cues predicting a performance-outcome contingency (and the response preparation they motivate) and those predicting the relative valence of the likely outcome. Furthermore, in these tasks the relative valence of the monetary loss cues is colored by being interspersed with monetary gain cues during the task - so that relative to monetary gain or neutral cues they are likely to be regarded as negative - in other situations they are likely to be seen as positive (e.g., if the alternative was certain loss).

In the current paper, we used a variant of the monetary incentive task to address these issues by distinguishing contingency and valence in relation to monetary loss. More specifically, all participants were given an initial stake of €150. They were then presented with three trial types. One in which cues signaled that they can avoid loss of money if they respond sufficiently quickly on a reaction time task (CONDITIONAL LOSS AVOIDANCE); one in which the cues signaled that loss would be imposed irrespective of performance (CERTAIN LOSS) and one where cues signaled that no loss would occur irrespective of performance (CERTAIN LOSS AVOIDANCE).

We made a number of predictions. First, cues indicating that loss could be avoided by fast responding (CONDITIONAL LOSS AVOIDANCE) would (i) be more motivationally salient, (ii) increase mobilization of cognitive resources in preparation for responding and (iii) lead to faster reaction times than both the conditions where there was no contingency between performance and outcome (CERTAIN LOSS and CERTAIN LOSS AVOIDANCE) irrespective of the relative valence of cues (i.e. the negative reinforcement effect). At the neural level, this should lead to activation of two broad networks (Bressler and Menon, 2010, Kahnt et al., 2014, Seeley et al., 2007). First, those regions associated with salience processing (i.e., anterior insula, mid-cingulate cortex, primary visual cortex, inferior parietal cortex, and hippocampus). Second, those associated with motor preparation (i.e., posterior parietal cortex, dorsolateral prefrontal cortex, supplementary motor area, and thalamus).

Our second prediction was that more positively valenced cues would activate what has been called the reward network (i.e., ventral striatum, medial orbitofrontal cortex) while negatively valenced cues would activate what has been called the punishment network (i.e. amygdala, insula) (Chávez et al., 2015). With reward centers more activated in the CERTAIN LOSS AVOIDANCE versus CERTAIN LOSS contrast, while the punishment centers more activated in the CERTAIN LOSS versus CERTAIN LOSS AVOIDANCE contrast.

Third, in terms of outcome processing we predicted that on CONDITIONAL LOSS AVOIDANCE trials (where outcome reflects performance i.e. successfully avoiding loss or failure to avoid loss) feedback indicating success would activate reward centers compared to feedback indicating failure. For all of these effects we predicted that greater effects would be seen when cues signaled the loss or potential loss of larger amounts of money. Given that the design of the task meant that the amount of money lost accumulated over time across trials within a session we predicted that the magnitude of predicted neural activations would increase as a function of time on task.

Materials and Methods

Participants

Thirty-three typically developing, right-handed, male adolescents between 8 and 18 years (13.7 ± 2.6 years) participated in this study. All were recruited from local youth organizations and schools. Participants had no psychiatric or neurologic disorders, nor a first-degree relative with these disorders, were currently not taking any psychotropic medication, had no history of alcohol or substance abuse, or MRI contraindications. To exclude subjects suffering from psychiatric disorders in general, including attention-deficit/hyperactivity disorder (ADHD), we interviewed one of the parents using a semi-structured clinical screening interview based on Diagnostic and Statistical Manual of Mental Disorders 5 criteria (Schedule for Affective Disorders and Schizophrenia for school-age children; Kaufman et al., 1997). Additionally, they did not score in the clinical range on the Dutch version of the parent-rated Disruptive Behaviour Disorders Rating Scale (inattention: 10.8 ± 1.9; hyperactivity/impulsivity 10.5 ± 0.76) and Child Behavioural Checklist (ADHD problems: 52.6 ± 6.0). All subjects completed the short version of the Dutch adaptation of the Wechsler Intelligence Scale for children (version 3; Kort et al., 2005) or adults (version 4; Wechsler, 2005) (total IQ: 106.7 ± 11.7) and were

excluded if their total IQ was below 80. Written informed consent was obtained from parents and participants after detailed explanation of the study protocol. The study was approved by the Ethics Committee of the University Hospital Leuven, Leuven, Belgium (S59637).

Escape Monetary Loss Incentive Task and Training

Participants performed a newly developed reaction time task, the Escape Monetary Loss Incentive (EMLI) task, while their brain responses were measured using fMRI. The trials had five phases: cue presentation, a variable anticipatory delay period, a response phase with target presentation, feedback on performance, and outcome (**FIGURE 1**). Participants started with a €150 stake and were told that they could take home what money remained on completion of the task. All participants, however, received €50 upon study completion irrespective of their performance. Three cues indicated the monetary outcome (2 s): triangle-shaped cues signalled the possibility of avoiding monetary loss (CONDITIONAL LOSS AVOIDANCE) by responding fast during target presentation, circle-shaped cues signalled that monetary loss would be imposed regardless of performance (CERTAIN LOSS) and diamond-shaped cues signalled that monetary loss would always be avoided regardless of performance (CERTAIN LOSS AVOIDANCE). Triangle- and circle-shaped cues both had horizontal lines that indicated how much money was at stake: 3 lines corresponded to €5, 2 lines to €1 and 1 line to €0.20. This was followed by an anticipation interval varying in length (3 - 3.5 s). During the response phase, participants were instructed to press a button as quickly as possible while a target was presented on the screen. In order to achieve correct responses in ± 66 % of all trials for each participant, the reaction time thresholds were adjusted to the participants' performance using a staircase tracking procedure (+20ms at fail / -20ms at success). Feedback informed participants whether they had responded fast enough to meet the specific threshold operating on the current trial. At the end of the trial both the amount of money lost in the current trial and the total amount of money left were indicated.

The EMLI task consisted of 135 counter-balanced trials, 45 for each cue type, and had a total duration of 25 mins. Data were acquired in 5 runs. Before scanning, participants had extensive training to make sure that they learned the cue-related contingencies. Afterwards, they completed 27 practice trials to calculate the initial reaction time threshold. Pre-training ensured stable performances during imaging and eliminated possible confounds associated with instrumental conditioning.

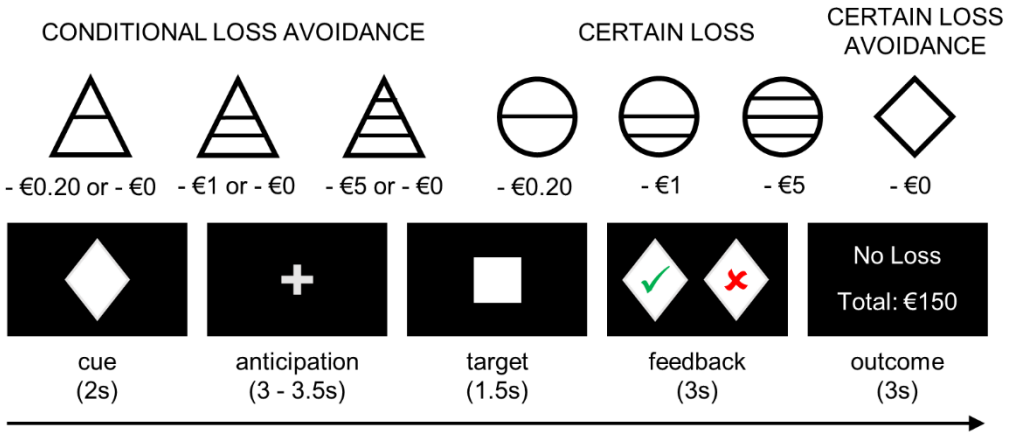

FIGURE 1. Escape Monetary Loss Incentive task design. Cues indicate different money-related response consequences. The triangle (CONDITIONAL LOSS AVOIDANCE) signals monetary loss can be avoided (on 66% of trials) if reaction times meet performance thresholds. The circle (CERTAIN LOSS) demonstrates that monetary loss always occurs, regardless of reaction time. The diamond (CERTAIN LOSS AVOIDANCE) indicates that monetary loss will not occur, regardless of response speed. Monetary amounts were €0.20, €1 or €5 and were indicated by one to three horizontal bars inside the cue. The analysis focused on cue presentation and feedback on performance.

Subjective Valence Ratings of Experimental Cues

After task completion, subjects rated the valence they attached to the experimental cues on a 7-point Likert scale (-3 aversive, 0 neutral, +3 happy) and ranked the different cue types according to the extent they would be likely to invest effort on the upcoming reaction time task. Participants were also asked to describe in one word the emotion the different cue types elicited ranging from negative (disappointed, frustrated, agitated), to neutral (indifferent, normal), attentive (attentive, concentrated, focused) and positive feelings (satisfied, I liked this, happy). Participants were asked to indicate from which run they started to feel the monetary loss particularly aversive.

Statistical Analysis Behavioural Measurements

Two separate repeated-measures ANOVAs examined the effects of condition (CONDITIONAL LOSS AVOIDANCE, CERTAIN LOSS, CERTAIN LOSS AVOIDANCE) on reaction time and subjective cue-valence ratings. To investigate the effect of time-on-task and monetary amount, further separate ANOVA's were performed with run (1, 2, 3, 4, 5) and condition (CONDITIONAL LOSS AVOIDANCE, CERTAIN LOSS, CERTAIN LOSS AVOIDANCE); and money (€0.20, €1, €5) and condition (CONDITIONAL LOSS AVOIDANCE, CERTAIN LOSS) as within-subject factors. Statistical analyses were conducted in SPSS (version 22, IBM, New York, USA) at a significance level of 0.05. Post-hoc *t*-tests were used to explore significant interaction effects, when appropriate.

MRI Acquisition

Before scanning, participants were familiarized with the MRI scanner and received additional oral instructions on the scanning procedure and task. Imaging was performed using an Ingenia 3T MRI scanner (Philips Medical Systems, Best, The Netherlands) equipped with a 32-channel head coil. In a single session, 36 interleaved bottom-up slices with a slice thickness of 3.75 mm and in plan voxel size of 2.75 mm^2 were acquired using a T2*-sensitive echoplanar imaging sequence with the following parameters: repetition time 1100 ms, echo time 30 ms, flip angle 90°, SENSE reduction factor 2, 80 x 80 matrix and 220 x 220 mm^2 field of view without slice gap, resulting in a total of 320 volumes. At the end of each scanning session, a high-resolution structural scan was acquired using a T1-weighted gradient to facilitate localization and co-registration of functional data. Structural scan parameters were repetition time 9.6 ms, echo time 4.6 ms, 8° flip angle, 256 x 256 mm^2 field of view with 1 mm^3 isotropic voxel size. Stimuli were presented on a screen using Presentation (Neurobehavioral Systems, http://www.neurobs.com).

Image Pre-processing

Data were pre-processed and analyzed using Statistical Parametric Mapping software (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK) implemented in Matlab 7 (Math Works, Natick, Massacussetts, USA). Children and adolescents have far more abrupt motions that may bias results. The ArtRepair SPM toolbox was used to improve the fMRI analysis by automatically detecting and removing noisy volumes. The recommended ArtRepair preprocessing pipeline was followed, which included slice-time correction of functional images, functional image realignment to the middle slice of each run, smoothing of functional images using a 3D Gaussian kernel of 4 mm FWHM, motion adjustment by removing volumes with >0.5 mm/TR, artefact repair, spatial normalization of all images, and smoothing of functional images using a 7 mm FWHM kernel (P.K. Mazaika, Hoeft, Glover, & Reiss, 2009). The last EMLI run of four participants was excluded from analyses because of excessive head motion (>25% of volumes repaired).

Neuroimaging Analysis

For each subject, two general linear models were defined, one for the cue onset and one for feedback, using 14 regressors: three cue types (CONDITIONAL LOSS AVOIDANCE, CERTAIN LOSS, CERTAIN LOSS AVOIDANCE), three monetary loss amounts (€0.20, €1, €5) and for the feedback model, two additional regressors on performance outcome (success, fail). Beta weights of each regressor were estimated with reaction time and movement parameters in the 3 directions of motion and 3 degrees of rotation included as covariates. First, six main T-contrast images were calculated for each subject to investigate effects of contingency (CONDITIONAL LOSS AVOIDANCE > CERTAIN LOSS, CONDITIONAL LOSS AVOIDANCE > CERTAIN LOSS AVOIDANCE), valence (CERTAIN LOSS > CERTAIN LOSS AVOIDANCE, CERTAIN LOSS AVOIDANCE > CERTAIN LOSS), and feedback (CONDITIONAL LOSS AVOIDANCE success > CONDITIONAL LOSS AVOIDANCE fail, CERTAIN LOSS success > CERTAIN LOSS fail). Secondly, to examine the influence of monetary loss amounts on contingency, three supplementary T-contrasts were created CONDITIONAL LOSS AVOIDANCE €0.20 > CERTAIN LOSS AVOIDANCE, CONDITIONAL LOSS AVOIDANCE €1 > CERTAIN LOSS AVOIDANCE, CONDITIONAL LOSS AVOIDANCE €5 > CERTAIN LOSS AVOIDANCE. These specific monetary level contrasts were not created for the contingent CONDITIONAL LOSS AVOIDANCE > CERTAIN LOSS contrast, as CERTAIN LOSS also contains separate monetary levels and is therefore underpowered to

explore dose-response influences. Finally, to check the potential influence of time-on-task, the brain activity during run 4-5 (only €50 remaining) was directly contrasted with run 1-3 for the main contingency and valence contrasts. Individual T-contrast images were used in a second-level analysis on whole-brain level for contingency, valence and feedback contrasts with age as a covariate of no interest. In all whole-brain analyses, statistical tests were considered significant having a voxel level *p*-value < 0.05 family wise error (FWE) corrected and a cluster size of > 5 voxels based on the peak beta-value and labelled using the automated anatomical labelling atlas (Tzourio-Mazoyer et al., 2002). Region of interest (ROI) analyses further explored the influence of monetary loss amount on the brain regions found in the whole-brain analyses. To explore the time on task, whole-brain analyses were corrected using small volume correction p[FWE] < 0.05 to account for the limited amount of trials. For the monetary effects, individual contrast estimates were extracted for the individual monetary amounts at the coordinates of significantly activated group peak voxels. Repeated-measures ANOVAs using monetary amount (€0.20, €1, €5) were used to explore monetary effects on brain activation. In ROI analyses, significant statistical tests were considered having a p-value < 0.05 corrected for multiple comparisons (Bonferroni correction) when multiple ROIs were tested.

Results

Behavioral Performance

Participants responded significantly faster ($F = 18.3$; $p < 0.001$; $\eta_p^2 = 0.008$) on CONDITIONAL LOSS AVOIDANCE (375.5 ± 110.5 ms) trials compared to both CERTAIN LOSS 401.7 ± 134.6 ms) and CERTAIN LOSS AVOIDANCE (395.7 ± 121.7 ms) trials. A main effect of time-on-task was found ($F = 5.9$; $p < 0.001$; $\eta_p^2 = 0.004$) as shorter reaction times were observed towards the end of the session. No interaction between condition and time-on-task was found ($F = 1.3$; $p = 0.26$; $\eta_p^2 = 0.002$). There was no overall effect of monetary amount ($F = 0.5$; $p < 0.62$; $\eta_p^2 = 0.0001$). An interaction between monetary amount and condition ($F = 3.5$; $p < 0.03$; $\eta_p^2 = 0.002$) was observed - shorter reaction times ($t = 4.3$, $p < 0.01$) were recorded with increasing monetary amounts in the CONDITIONAL LOSS AVOIDANCE condition relative to the CERTAIN LOSS condition.

Subjective Cue-Valence Ratings

There was a significant main effect of condition ($F = 149.2$; $p < 0.001$; $\eta_p^2 = 0.57$). CERTAIN LOSS cues were rated significantly negatively (-1.6 ± 1.1), CONDITIONAL LOSS AVOIDANCE cues were rated neutral (-0.1 ± 1.4) and CERTAIN LOSS AVOIDANCE cues were rated significantly positively (2.5 ± 1.0). There was a significant effect of amount of money ($F = 55.2$; $p < 0.001$; $\eta_p^2 = 0.37$). The higher the amount of money that could be lost the more negatively the symbols were rated. The interaction between condition and amount was not significant ($F = 1.1$; $p < 0.32$; $\eta_p^2 = 0.01$). All participants indicated that they were more likely to put effort in the CONDITIONAL LOSS AVOIDANCE condition. Participants used predominantly positive words to describe CERTAIN LOSS AVOIDANCE (for 92% of the participants) and negative words for CERTAIN LOSS cues (91%). For CONDITIONAL LOSS AVOIDANCE they used words suggesting attentiveness to cues (86%). Participants reported CERTAIN LOSS was especially aversive from €50 downwards (run 4).

Neuroimaging

Contingency effects

CONDITIONAL LOSS AVOIDANCE cues elicited significant whole-brain corrected hyper-activation (p[FWE] < 0.05) of the bilateral anterior insula, midcingulate cortex, inferior parietal cortex, primary visual cortex, supplementary motor area, posterior parietal cortex, thalamus, dorsolateral prefrontal cortex, and ventral striatum relative to both CERTAIN LOSS and CERTAIN LOSS AVOIDANCE cues (**FIGURE 2** and **TABLE 1**).

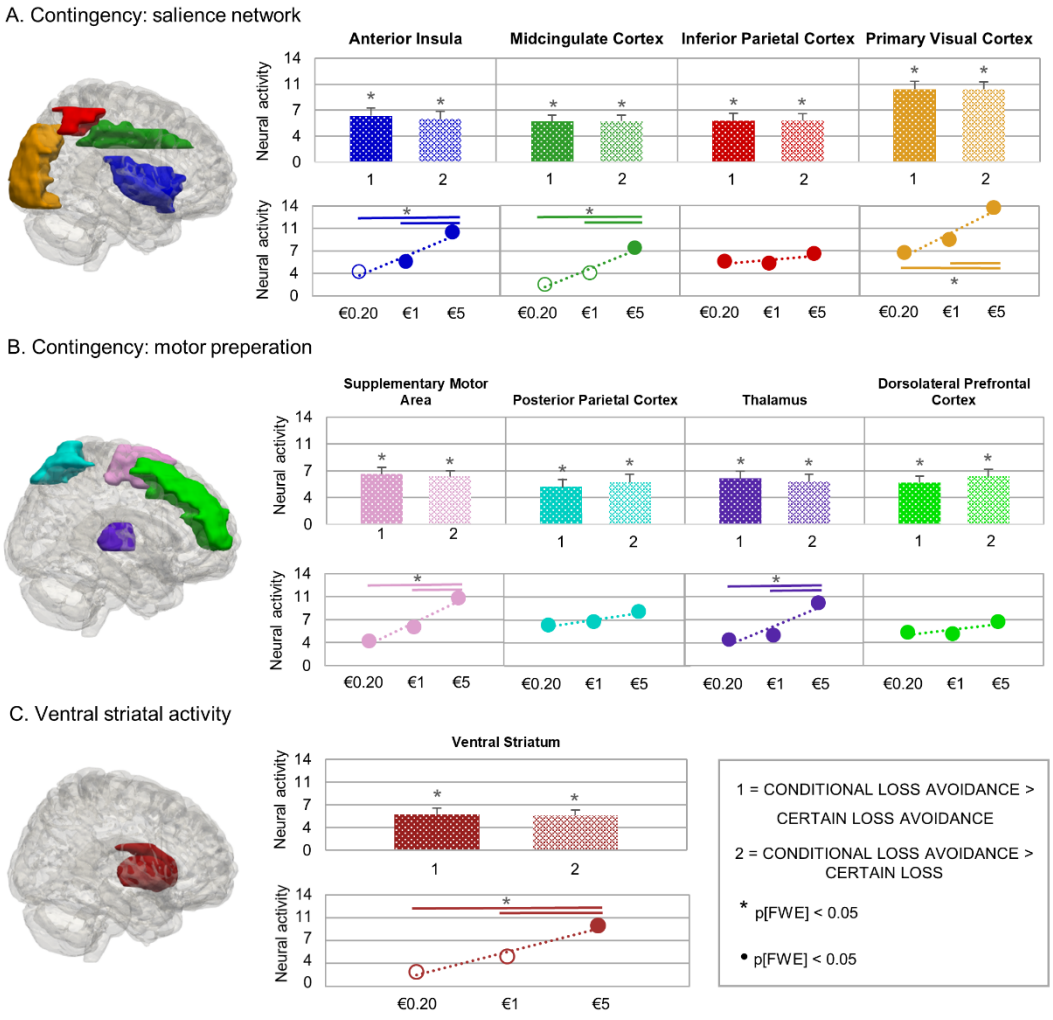

FIGURE 2. Whole-brain activated regions and dose-response relationships for (A) the salience network, (B) the motor preparation network and (C) the ventral striatal activity. Contrast estimates were extracted at peak activation clusters for the CONDITIONAL LOSS AVOIDANCE versus CERTAIN LOSS AVOIDANCE (1) and CONDITIONAL LOSS AVOIDANCE versus CERTAIN LOSS (2) contrast. Neural activation was averaged across both hemispheres. Error bars display the standard error. Asterisks (*) indicate p [family-wise error corrected] < 0.05. Filled dots indicate significant brain activation after FWE for a given monetary amount.

Time-on-task analysis showed that the activation within these brain regions were consistent across the session. Adding age as a covariate did not change the brain response pattern. Region-of-interest analyses were conducted within whole-brain activated regions for both contingent contrasts to assess whether increasing functional activation was associated with larger monetary loss amounts. There was a significant interaction with monetary amount for anterior insula ($F = 9.3$; $p < 0.001$; $\eta_p^2 = 0.23$), midcingulate cortex ($F = 12.6$; $p < 0.001$; $\eta_p^2 = 0.28$), primary visual cortex ($F = 7.1$; $p < 0.01$; $\eta_p^2 = 0.18$), supplementary motor area ($F = 14.1$; $p < 0.001$; $\eta_p^2 = 0.31$), thalamus ($F = 11.6$; $p < 0.001$; $\eta_p^2 = 0.27$) and ventral striatum ($F = 11.8$; $p < 0.001$; $\eta_p^2 = 0.27$) (**FIGURE 2**). No effect of monetary amount was seen for dorsolateral prefrontal cortex, inferior and posterior parietal cortex ($p > 0.05$) (**FIGURE 2**).

TABLE 1. Whole-brain results of estimated brain activation for main contingency contrasts

Brain Region	Side	MNI			T Score	p [FWE]	Cluster Size
		X	Y	Z			
CONTINGENCY EFFECTS							
CONDITIONAL LOSS AVOIDANCE > CERTAIN LOSS AVOIDANCE							
Anterior Insula	L	-42	2	0	5.86	0.02	17
	R	32	20	8	5.96	0.01	15
Midcingulate Cortex	L	-4	24	24	5.62	0.03	214
	R	6	8	28	5.56	0.04	193
Ventral striatum	L	-14	18	-2	6.03	0.01	188
	R	12	14	-4	5.64	0.01	9
Thalamus	L	-6	-16	-2	6.48	0.004	129
	R	6	-18	0	6.18	0.01	56
Posterior Parietal Cortex	L	-22	-68	48	5.54	0.04	5
	R	30	-62	51	6.08	0.01	20
Inferior Parietal Cortex	L	-46	-44	52	5.58	0.04	13
	R	32	-48	46	6.28	0.01	16
Dorsolateral Prefrontal Cortex	L	-36	34	18	6.20	0.01	121
	R	44	44	24	6.28	0.01	72
Supplementary Motor Area	L	-4	-12	62	7.29	0.001	403
	R	12	8	46	7.17	0.001	524
Primary Visual Cortex	L	-32	-90	-12	8.93	< 0.001	1052
	R	38	-82	10	9.79	< 0.001	799
CONDITIONAL LOSS AVOIDANCE> CERTAIN LOSS							
Anterior Insula	L	-32	20	9	5.61	0.03	22
	R	32	16	10	5.92	0.02	34
Midcingulate Cortex	L	-12	4	44	8.39	< 0.001	364
	R	12	4	42	8.17	< 0.001	391
Ventral striatum	L	-16	4	-8	7.44	< 0.001	402
	R	12	16	-6	6.61	0.003	206
Thalamus	L	-16	-8	-2	6.94	< 0.001	489
	R	14	-20	16	6.65	0.003	183
Posterior Parietal Cortex	L	-34	-54	64	5.97	0.01	27
	R	16	-58	50	6.15	0.009	40
Inferior Parietal Cortex	L	-32	-36	42	5.88	0.02	24
	R	-	-	-	-	-	-
Dorsolateral Prefrontal Cortex	L	-28	20	38	5.81	0.02	14
	R	38	44	36	6.78	0.002	33
Supplementary Motor Area	L	-10	2	46	8.11	< 0.001	698
	R	12	2	46	7.76	< 0.001	780
Primary Visual Cortex	L	-40	-80	-6	7.86	< 0.001	395
	R	38	-84	0	8.44	< 0.001	606

Valence effects

No voxels survived FWE-corrected threshold for positive valence in CERTAIN LOSS AVOIDANCE > CERTAIN LOSS contrast and for negative valence in CERTAIN LOSS > CERTAIN LOSS AVOIDANCE contrast. However, there was an effect of time-on-task with bilateral ventral striatum, middle temporal gyrus and medial orbitofrontal cortex activation for CERTAIN LOSS AVOIDANCE cues compared to CERTAIN LOSS emerging towards the end of the session (**TABLE 2**).

TABLE 2. Time-on-task effects for whole-brain activations of the two last runs for main valence contrasts

Brain Region	Side	MNI			T Score	p [FWE]	Cluster Size
		X	Y	Z			
TIME-ON-TASK EFFECTS							
CERTAIN LOSS AVOIDANCE > CERTAIN LOSS							
Ventral Striatum	L	-24	6	8	4.81	0.005	122
	R	26	2	10	4.15	0.03	60
Medial Orbitofrontal Cortex	L	-12	48	-6	3.73	0.03	12
	R	14	52	6	5.56	0.01	86
Middle Temporal Gyrus	L	-54	-10	-8	4.55	< 0.001	107
	R	46	-66	2	5.64	< 0.001	347
CERTAIN LOSS > CERTAIN LOSS AVOIDANCE							
No suprathreshold voxels							

Feedback effects

Feedback indicating successful avoidance of loss on the CONDITIONAL LOSS AVOIDANCE condition resulted in a significant hyper-activation of the bilateral ventral striatum (**TABLE 3**) compared with feedback of failure to avoid loss. No voxels survived the threshold for the feedback in the CERTAIN LOSS condition.

TABLE 3. Whole-brain results of estimated brain activation for main feedback contrasts.

Brain Region	Side	MNI			T Score	p [FWE]	Cluster Size
		X	Y	Z			
FEEDBACK EFFECTS							
CONDITIONAL LOSS AVOIDANCE Success > Failure							
Ventral Striatum	L	-18	8	-4	5.90	0.02	18
	R	22	14	-6	5.70	0.03	8
CONDTIONAL LOSS AVOIDANCE Failure > Success							
No suprathreshold voxels							
CERTAIN LOSS Success > Failure							
No suprathreshold voxels							
CERTAIN LOSS Failure > Success							
No suprathreshold voxels							

Discussion

In the current study, we set out to distinguish brain regions implicated in contingency-related and valence-related cue processing in a monetary loss anticipation negative reinforcement paradigm. All participants were given an initial stake of €150, they then had to perform a cued reaction time task where cues indicated whether they would lose money at the end of each trial and whether the speed of response to a target could change the probability of that loss. There were a number of findings of note.

First, cues signalling the opportunity to avoid loss were negatively reinforcing in that they speeded up responses to the target: reaction times were faster on CONDITIONAL LOSS AVOIDANCE trials than the two "CERTAIN" trial types. These findings were in line with decades of research on negative reinforcement which repeatedly demonstrated that individuals shape their behaviour to avoid negative events (Langthorne, McGill, & Oliver, 2014). In fact much of this research has shown that the avoidance of a potential loss is a greater motivator than the potential gain of an equivalent sized reward (Barkley-Levenson, Van Leijenhorst, & Galván, 2013) - a behavioural phenomenon known as loss aversion (Kahneman & Tversky, 1979). Avoidance of aversive events has also been implicated as central drive to multiple psychiatric disorders, such as anxiety, phobias, posttraumatic stress disorder, major depression and suicide (Servatius, 2016).

Second, participants' subjective evaluations confirmed that they understood what the cues signified - specifically whether they indicated that outcome was contingent upon performance or not. The three cues varied widely in terms of the value they were assigned, with CERTAIN LOSS being rated negatively, CERTAIN LOSS AVOIDANCE being rated positively and CONDITIONAL LOSS AVOIDANCE being rated indifferently. Participants also reported that they applied more effort in this latter condition. This suggested that participants were aware of the distinctive valence and salience properties of the cues, confirming that the EMLI behaviourally engaged participants' negative reinforcement processes. However, a direct association between subjective cue-valence scores and cue-reactivity in brain networks was not clearly present. This may be explained by the truncated range of cue-rating scores with little intra-cue variability. Revising the Likert-scale to include more points and combining it with more objective psychophysiological and eye-tracking measures may produce a more sensitive measure with greater variance in future studies.

Third, in line with our predictions that CONDITIONAL LOSS AVOIDANCE cues would be especially motivationally salient and lead to the mobilization of brain resources in preparation for responding - especially if the amount of money at stake was large - we found that they activated a widespread set of functionally related regions previously linked to salience processing and motor response preparation. In former studies using MID type tasks, identifying neural activity specifically associated with motivational salience has been challenging, as they were not able to distinguish contingency from valence specific effects (Litt et al., 2011; Maunsell, 2004; Roesch & Olson, 2004). However, it is well established that the brain directs an individual's attention towards stimuli of motivational relevance – in this case avoiding monetary loss (Theeuwes, 2010). Consequently, contingent stimuli are more likely to be selected for attentive processing (Becker, Folk, & Remington, 2010; Töllner, Zehetleitner, Gramann, & Müller, 2010). Previous studies that dissociated neural correlates of valence and salience showed that the valence-specific network was associated with the medial orbitofrontal cortex, anterior and posterior cingulate cortex, the salience-specific network with the midcingulate cortex, anterior insula and inferior parietal cortex, while both networks include the ventral striatum (Cooper and Knutson, 2008; Jensen et al., 2007, Kahnt et al., 2014, Litt et al. 2011). It has been frequently shown that when executive task performance is required, the salience network co-activates with a distinct motor preparation network that consist

of the supplementary motor area, posterior parietal cortex, thalamus and dorsolateral prefrontal cortex (FitzGerald, Friston, & Dolan, 2012; Lau, Rogers, Ramnani, & Passingham, 2004; Seeley et al., 2007). In line with previous investigations, we found that higher monetary amounts seemed to induce a larger brain activity in the salience network, while brain regions such as dorsolateral prefrontal cortex and parietal cortex showed to be insensitive to monetary value (Kahnt and Tobler 2013; Kahnt et al. 2014; Ogawa et al. 2013). Furthermore, it is important to note that contingency effects may be defined not only through magnitude but also through probability (Mackintosh, 1975; Yacubian et al., 2006). Unfortunately, direct comparisons between different probability levels were outside the scope of the current study. Future studies, with different contingent probabilities (instead of only 66%) will allow us to discriminate between magnitude- and probability effects.

Fourth, the brain contrasts between the "conditional" and the two "certain" conditions revealed the same activation patterns - despite one of the certain cues (CERTAIN LOSS AVOIDANCE) being designed and clearly experienced by participants as positively valenced in absolute terms and the other (CERTAIN LOSS) experience and recognised as negatively valenced. Maybe the most important finding in this regard relates to the role of the ventral striatum. In both animal and human research, the striatum's response has been primarily linked to anticipation of positively valenced incentives and considered the key region in distinguishing positive from negative valence (Knutson et al. 2001; Lutz and Widmer 2014; Schultz et al. 2008). Yet activity in the ventral striatum has only been observed by those tasks in which there exists both a perceived connection between action and outcome, and where some uncertainty exists about whether the action will lead to the desired outcome (Tricomi, Delgado, & Fiez, 2004; Walton et al., 2009). In accordance with these latter findings our results implicate activity within this region in coding of salience of the cue, rather than the valence itself (Cooper & Knutson, 2008; Jensen et al., 2007; Litt et al., 2011). In rodent models, the ventral striatum, and the nucleus accumbens in particular, can be cytochemically subdivided in two distinct regions, the core and shell, that have shown to contribute in different ways to negative reinforcing effects (Heimer, Zahm, Churchill, Kalivas, & Wohltmann, 1991). The shell is an important site for enhancing motivational effects of responding, whereas the core is involved in the control of motivational salience induced by reinforcing stimuli (Ito, Robbins, & Everitt, 2004; Parkinson, Olmstead, Burns, Robbins, & Everitt, 1999).

Unfortunately, the ventral striatum cannot be subdivided in subregions based on MRI images, as the resolution is not sufficient, but it is possible that these separate regions are responsible for the ventral striatum effects associated with salience and valence contrasts. Nevertheless, the sensitivity of the ventral striatum to contingency between action and outcome gives it a central role in the neurobiology of learning. If the ventral striatum is mostly involved in the prediction of salience, the coding of valence needs to be done elsewhere. The medial orbitofrontal cortex has been widely suggested to guide behaviour based on the anticipated valence (Anderson et al., 2003; Rolls, Kringelbach, & De Araujo, 2003; Small et al., 2003). In the present study, medial orbitofrontal activity was indeed seen to positively valenced cues towards the end of the sessions.

Fifth, unexpectedly, when taking the session as a whole there were no differences in brain activation patterns signifying positive (CERTAIN LOSS AVOIDANCE) as opposed to negative valence (CERTAIN LOSS) - a contrast that we assumed would identify regions normally implicated in valence processing - despite the fact that "success" feedback cues activated the ventral striatum. However, we did find an increase in ventral striatum, middle temporal gyrus and medial orbitofrontal cortex activations to positively valenced cues towards the end of the session, when remaining money was low and the relative size of each individual loss was thus very large. These effects were mirrored in the fact that participants subjectively reported finding cues especially motivating (one way or another) when reaching the €50 threshold. From this point onwards, preservation of the remaining money seemed to become more important, which resulted in acquiring more positive valence of CERTAIN LOSS AVOIDANCE characterized by significant hyper-activation in the reward regions of the brain (Haber, Kim, Mailly, & Calzavara, 2006). Previous research has also shown that individuals adapt responses to take account of depleting resources (Freund, 1997).

Sixth, against expectation, brain networks typically involved in the processing of negatively valenced cues (CERTAIN LOSS) were not activated during the anticipation of certain negative outcomes – even towards the end of the session and despite the fact that participants perceived them as negative in their subjective ratings. Previous studies using instrumental coding designs have highlighted the role of brain regions such as the amygdala, in monetary loss avoidance in the processing of negative events (Mobbs et al., 2009; Schlund & Cataldo, 2010). The amygdala's role in loss avoidance has, however, been hypothesized to be limited to the learning process (Cain & LeDoux, 2008; Jensen et al.,

2007). In our task design, the avoidance behavior was learned through extensive pretraining outside the scanner. Absence of amygdala activation in our study may therefore reflect the fact that the avoidance cue–outcome relations were already learnt before the scanning session started (Andrzejewski, Spencer, & Kelley, 2005; Jensen et al., 2007) or may be explained by the fact that brain responses towards cues are largely determined by automatic rather than conscious processes (De Houwer, Vandorpe, & Beckers, 2005; Töllner et al., 2010). It may however also have depended on the start amount, where a lower start amount would have proportionally higher losses per trial if the same monetary levels are used and therefore have a more punishing effect (Hahn, 2010). Future studies that vary the start amount and amount of loss per trial can provide more insight.

The study had some limitations that need to be taken into account when interpreting its findings. First, in order to ensure equivalent performance of participants, the cue-related contingencies were trained before the start of the experiment. This meant that the process of learning could not be studied. Future research may examine the effects of contingency during learning. Second, different task designs may modulate processes that promote avoidance. In line with prior human neuroimaging studies, a partial avoidance contingency was used in the CONDITIONAL LOSS AVOIDANCE condition in which participants could avoid monetary loss in 66% of the time (Jensen et al., 2007, Kim et al., 2006, Mobbs et al., 2009) or could avoid monetary loss on every trial like in the CERTAIN LOSS AVOIDANCE condition (Schlund & Cataldo, 2010). Varying avoidance probabilities and subsequent beliefs are likely to modulate brain responses. Third, a large developmentally diverse sample was included. Attitudes and feelings about avoiding monetary loss are likely to change over time and be different across generations, as well as in other sociodemographic groups (de Bruin, van Putten, van Emden, & Strough, 2018). An additional age-specific analysis was performed by contrasting the 18 adolescents (ages 13-18) and 15 children (ages 8-12) for both contingent, valence and feedback contrasts. No FWE-corrected significant differences in brain activation were found.

Conclusion

In summary, we were able to distinguish brain networks linked to contingency-related and valence-related cue processing during adolescence. Cues signaling loss avoidance contingency were more motivationally salient, improved performance and activated anterior insula, midcingulate cortex, ventral striatum, thalamus, posterior parietal cortex, inferior parietal cortex, dorsolateral prefrontal cortex, supplementary motor area and primary visual cortex. Brain regions specifically linked to differences in cue valence were less apparent but positively valenced cues were associated with hyper-activation of ventral striatum, middle temporal gyrus and medial orbitofrontal cortex towards the end of the session. Brain networks shown previously to be activated by "punishment" cues were not implicated – even when loss of money was certain. The EMLI can provide a useful way of distinguishing the role of different processes and underlying brain systems in negative reinforcement processing deficits in psychopathological conditions.

Chapter 6 | The limits of motivational influence in ADHD: no evidence for an altered reaction to negative reinforcement by monetary loss avoidance

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Van Dessel, J., Sonuga-Barke, E., Moerkerke, M., Van der Oord, S., Morsink, S., Lemiere, J., & Danckaerts, M. (2020). The limits of motivational influence in ADHD: no evidence for an altered reaction to negative reinforcement by monetary loss avoidance. *Submitted & under review.*

Abstract

Functional Magnetic Resonance Imaging (fMRI) studies have reported a diminished response in the brain's reward circuits to contingent cues predicting future monetary gain in adolescents with attention-deficit/hyperactivity disorder (ADHD). The situation with regard to monetary loss is less clear, despite recognition that both positive and negative consequences impact ADHD behaviour. Here, we employ a new Escape Monetary Loss Incentive task in the MRI scanner, which allows the differentiation of contingency and valence effects during loss avoidance, to examine ADHD-related alterations in monetary loss processing. There was no evidence of atypical processing of contingent or non-contingent monetary loss cues in ADHD - either in terms of ratings of emotional and motivational significance or brain responses. This suggests that the ability to process contingencies between performance and negative outcomes is intact in ADHD and that individuals with ADHD are no more (or less) sensitive to negative outcomes than controls. This latter finding stands in stark contrast to recent evidence from a similar task of atypical emotion network recruitment (e.g., amygdala) in ADHD individuals to cues predicting another negative event: the imposition of delay, which suggests marked specificity in the way they respond to negative events.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) has been characterised as a motivational disorder caused by impaired processing of reinforcing events (Castellanos & Tannock, 2002; Nigg, 2005; Posner, Polanczyk, & Sonuga-Barke, 2020; Sonuga-Barke, 2002; Tripp & Wickens, 2008). These theoretical models are supported by evidence of a diminished ventral-striatal activation to cues predicting the delivery of future monetary rewards following successful performance on the Monetary Incentive Delay (MID) task (for review, see Plichta and Scheres, 2014). The questions as to whether these neural effects extend to negative reinforcement processes (the avoidance of negative outcomes, such as monetary loss) has not been answered definitively (Luman, Tripp, & Scheres, 2010).

This question is of interest for a number of reasons. First, individuals with ADHD experience more negative events in daily life (Brown et al., 2017). Second, a number of studies have shown that punishment (response-cost) enhances the performance short-term, while on the long run it leads to more negative effects (e.g. higher error rate) in children and adolescents with ADHD across a wide range of cognitive tasks (Carlson, Mann, & Alexander, 2000; Carlson & Tamm, 2000; Furukawa et al., 2017; Laboni, Douglas, & Baker, 1995; Slusarek et al., 2001). In one study the performance was even related to amount of punishment (Slusarek et al., 2001). Third, behavioural studies have suggested that children with ADHD are more sensitive to monetary loss than monetary gain (Carlson et al., 2000; Carlson & Tamm, 2000). However, electrophysiological evidence for this effect is mixed. Some event-related potential studies have found that individuals with ADHD, compared to typically developing controls, show a hypersensitivity to negative reinforcement (Fosco, Hawk, Rosch, & Bubnik, 2015). Others have described an ADHD-related insensitivity to the negative reinforcement (Potts et al., 2006; Van Meel et al., 2011, 2005), while most studies found no group differences to contingent punishment (Chronaki et al., 2017; Heinrich et al., 2017). The small number of functional magnetic resonance (fMRI) studies that have looked at brain activation to contingent monetary loss in ADHD have been limited in a number of ways and produced inconsistent results. Most fMRI studies using the MID task have restricted their analysis to predetermined reward-related brain regions (e.g., ventral striatum) (Carmona et al., 2012; Edel et al., 2013; Hoogman et al., 2011; Scheres et al., 2007; Ströhle et al., 2008), leaving out some brain

network that one might predict would be activated by cues of negative events, such as the amygdala and anterior insula (Lemiere et al., 2012; Van Dessel et al., 2018a). Even where individuals with ADHD have been shown to display different activation patterns to cues of performance-contingent monetary gain and loss compared to controls the meaning and significance of these results has been hard to determine (Stoy et al., 2011; Wilbertz et al., 2017). This is because how the brain reacts to opportunities to avoid negative events depends on its ability to distinguish both contingent from non-contingent, and positive from negative cues. In the MID task the relative valence of the monetary loss cues is influenced by interspersed monetary gain cues during tasks - so that while relative to immediately preceding monetary gain or neutral cues they are likely to be regarded as negative whereas in other situations they may be perceived as positive (e.g., if the alternative was certain loss) (Nieuwenhuis et al., 2005).

We were recently able to distinguish brain networks activated by contingency-related and valence-related (positive and negative) cues using a modified version of the MID task, the Escape Monetary Loss Incentive (EMLI) task which contrasts cues predicting either certain monetary loss or certain loss avoidance (no contingency) with a cue predicting conditional loss where monetary loss was determined by performance (Van Dessel et al., 2020). Contingency processing, revealed by contrasting the conditional loss condition with the certain loss and certain avoidance conditions, was associated with activation of the salience (i.e., anterior insula, midcingulate cortex, ventral striatum, inferior parietal cortex, primary visual cortex) and motor preparation regions (i.e., dorsolateral prefrontal cortex, posterior parietal cortex, thalamus, supplementary motor area). In contrast, valence processing (contrast between certain loss and certain loss avoidance conditions) was associated with activation in reward-related brain regions such as the ventral striatum, medial orbito-frontal cortex and temporal areas towards the end of sessions.

In the current paper, we used the EMLI task to compare monetary loss processing in ADHD and control children and adolescents. We made a number of predictions. On the basis of prior data from behavioural and neurophysiological studies on ADHD, we expected that cues signalling that monetary loss could be avoided trough better performance (conditional loss avoidance) will speed-up reaction time and when contrasted with cues indicating no such contingency (certain loss or certain loss avoidance) will lead to increased activation in the salience and motor response

preparation networks in children and adolescents with ADHD to achieve equal brain response as in typically developing controls. Based on prior studies showing a heightened sensitivity to aversive events, we also predicted an exaggerated response in the punishment network including amygdala and anterior insula regions (Lemiere et al., 2012; Van Dessel et al., 2018a; Van Dessel, Sonuga-Barke, et al., 2019; Wilbertz et al., 2017) when certain loss cues are contrasted with certain loss avoidance cues (negative-valence contrast). We also expected these effects seen at a neural level to be mirrored in terms of participant's subjective ratings of the cues. With the certain loss cues being rated more negatively than the conditional loss and this being rated more negatively than the certain loss avoidance cues. Although our main focus was on cue processing we also looked at how participants responded to positive and negative feedback. We predicted a diminished response in the brain's reward circuits (i.e. ventral striatum) during positive feedback (successful monetary loss avoidance) and an increased response in emotional brain networks (i.e. amygdala and anterior insula) for negative feedback (monetary loss avoidance failure) when comparing ADHD subjects with controls. Finally, we explored the effect of age on these effects. Little is known about developmental changes in the neural underpinnings of negative reinforcement and so we made no predictions on this matter.

Materials and Methods

Participants

Eighteen right-handed male children (8-12 years) and 20 adolescents (13-18 years) with a clinical diagnosis of ADHD based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) were recruited through the Child and Adolescent Psychiatry department of UPC-KU Leuven (**TABLE 1**). The reassessment procedure of ADHD diagnosis consisted of a Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime (KSADS-PL; Kaufman et al., 1997) interview with one of the parents. Twenty-nine participants met the ADHD combined criteria and 9 met criteria for the inattentive presentation. Nine ADHD participants fulfilled the criteria for an additional diagnosis of a learning disorder, one had comorbid autism spectrum disorder and one comorbid oppositional defiant disorder. Twenty-four of the children and adolescents with ADHD were taking psychostimulant medication (methylphenidate). Medication was withheld 48 hours prior to testing. The Dutch version of the Disruptive Behaviour

Disorders Rating Scale (Pelham *et al.*, 1992; Dutch translation Oosterlaan et al., 2008) was administered to the parent(s) to assess dimensional symptom severity. Fifteen right-handed male typically developing children (8-12 years) and 18 adolescents (13-18 years) were included and were free of any current or lifetime psychiatric disorder as determined by the KSADS-PL interview. Groups were matched based on age and parental monthly allowance (Table 1). The full scale IQ for each subject was estimated using four subtests (vocabulary, similarities, block design and picture arrangement (Sattler, 2001) of the Dutch adaptation of the Wechsler Intelligence Scale for Children (version 3; Kort et al., 2005) or adults (version 4; Wechsler, 2005).

TABLE 1. Demographic data, group characteristics (Disruptive Behaviour Disorders Rating Scale, Quick Delay Questionnaire) and task performance (Escape Monetary Loss Incentive task) are presented as mean (standard deviation).

	ADHD (n = 33) Mean (SD)	**Control (n = 33) Mean (SD)**	**p-value**
Background Characteristics			
Age (years)	13.3 (2.9)	13.7 (2.6)	p = 0.53
IQ	98.1 (9.9)	106.7 (11.7)	p < 0.001
Allowance (€ per week)	4.9 (6.5)	4.6 (5.1)	p = 0.85
Questionnaire Measures			
Disruptive Behavior Disorder Rating Scale (Parent-rated behavior problems)			
DBDRS - Inattention	15.0 (1.7)	10.8 (1.7)	p < 0.001
DBDRS – Hyperactivity/impulsivity	14.3 (2.4)	10.5 (1.3)	p < 0.001
DBDRS – Oppositional defiant disorder	13.9 (2.6)	10.8 (1.4)	p < 0.001
DBDRS – Conduct disorder	12.4 (2.0)	10.7 (1.0)	p < 0.001
Quick Delay Questionnaire (Self-rated delay aversion and discounting)			
Delay aversion	16.8 (5.0)	13.9 (3.1)	p < 0.01
Delay discounting	12.5 (2.7)	11.7 (3.1)	p = 0.32
Task Performance (in ms)			
Escape Monetary Loss Incentive Task			
CONDITIONAL LOSS AVOIDANCE	400.6 (123.9)	375.5 (110.5)	p < 0.001
CERTAIN LOSS AVOIDANCE	424.2 (146.7)	395.7 (121.7)	p < 0.001
CERTAIN LOSS	423.4 (151.8)	401.7 (134.6)	p < 0.001

Experimental Paradigm and Training

Participants performed the Escape Monetary Loss Incentive task (EMLI, Van Dessel et al., 2020), while their brain responses were acquired under fMRI (**FIGURE 1**). At the start of each trial, one of three possible geometrical cues (2s) predicted a contingent or non-contingent monetary outcome. Triangle-shaped cues signalled the possibility of avoiding monetary loss (CONDITIONAL LOSS AVOIDANCE) by responding fast during target presentation, circle-shaped cues signalled that monetary loss would be imposed regardless of performance (CERTAIN LOSS) and diamond-shaped cues signalled that monetary loss would always be avoided regardless of performance (CERTAIN LOSS AVOIDANCE). Triangle- and circle-shaped cues both had horizontal lines that indicated how much money was at stake: 3 lines corresponded to €5, 2 lines to €1 and 1 line to €0.20. After an anticipation interval of between 3 and 3.5s, a square target was briefly presented on the screen (0.25s). Participants were instructed to respond as quickly as possible via a button box. Feedback was given after responses - a green tick for "fast enough" and a red cross for "too slow". This paradigm used a trial-by-trial staircase tracking procedure (+20ms at fail / -20ms at success) that adjusts the response window to obtain "fast enough" responses in 66% of all trials for each participant. This also ensured that all participants lost the same amount of money (± €25 per run). Participants started with a €150 stake and were told that they could take home what money remained on completion of the task. All participants, however, received €50 upon study completion irrespective of their performance and were debriefed on the study purpose. Before scanning, participants received extensive training to ensure that they learned the cue-related contingencies. A practice run of 27 trials was completed to determine the initial response threshold and to confirm the association between each cue and experimental condition. Participants completed five experimental runs of 27 trials with a short break between each run and with a total duration of 25 mins.

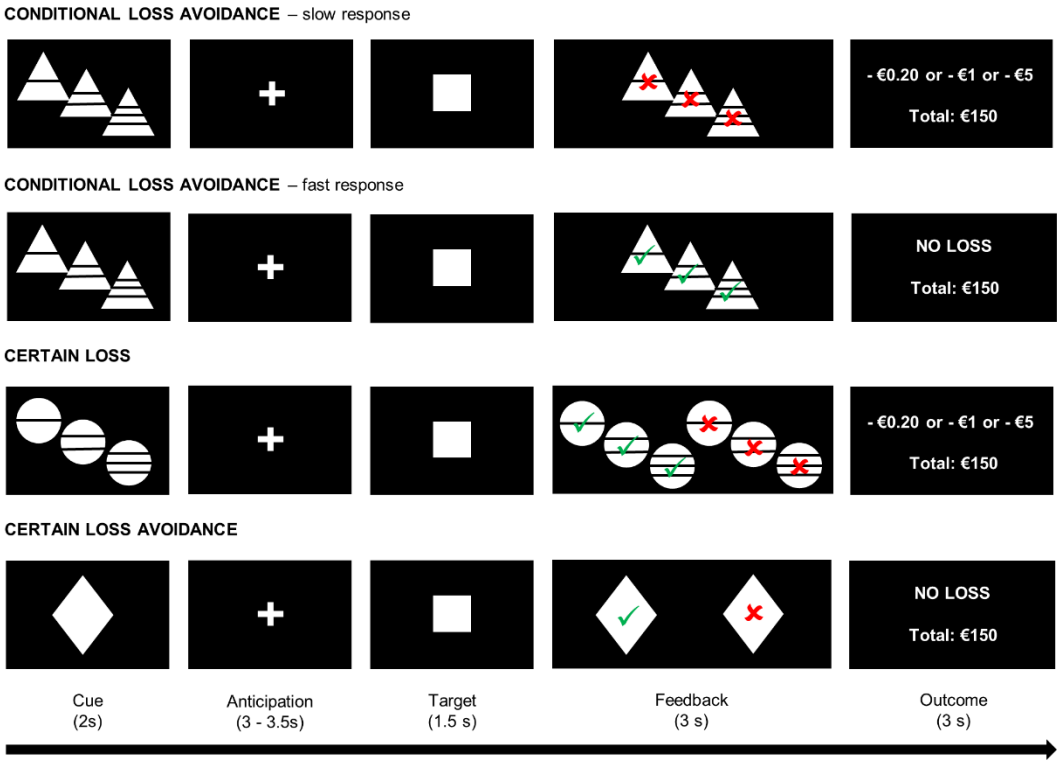

FIGURE 1. Escape Monetary Loss Incentive task design. Cues indicate different money-related response consequences. The triangle (CONDITIONAL LOSS AVOIDANCE) signals monetary loss can be avoided (on 66% of trials) if reaction times meet performance thresholds (contingency). The circle (CERTAIN LOSS) demonstrates that monetary loss always occurs, regardless of reaction time (no contingency). The diamond (CERTAIN LOSS AVOIDANCE) indicates that monetary loss will not occur, regardless of response speed (no contingency). Monetary amounts were €0.20, €1 or €5 and were indicated by one to three horizontal bars inside the cue. The analysis focused on cue presentation and feedback on performance.

Subjective Valence Ratings of Experimental Cues

After task completion, subjects rated the valence they attached to the experimental cues used in the EMLI on a 7-point Likert scale (-3 negative, 0 neutral, +3 positive) and ranked the different cue types according to the extent they would be likely to invest effort on the upcoming reaction time task after their presentation. Participants were also asked to describe in words the emotions the different cue types elicited on four dimensions - negative (disappointed, frustrated, agitated), neutral (indifferent, normal), attentive (attentive, concentrated, focused) and positive (satisfied, I liked this, happy).

MRI Acquisition and Image Preprocessing

Imaging was performed on a 3 Tesla Philips Ingenia MR scanner (Philips Medical Systems, Best, The Netherlands) with a 32-channel head coil at the Department of Radiology of the University Hospital in Leuven. Functional scans were acquired using a blood-oxygen-level depended (BOLD) sensitive T2* echo imaging sequence with the following parameters: TR = 1100 ms, TE = 30 ms, flip angle = 90°, SENSE reduction factor = 2, field of view = 220 x 220 mm^2 without slice gap , 36 interleaved bottom-up slices with a spatial resolution of 2.75 x 2.75 x 3.75 mm. At the end of each scanning session, a high-resolution structural image was acquired using a standard T1-weighted pulse sequence with the following parameters: TR = 9.6 ms, TE = 4.6 ms, flip angle = 8°, field of view = 256 x 256 mm^2, spatial resolution of 1 x 1 x 1 mm. Stimuli were presented on a screen using Presentation (Neurobehavioral Systems, http://www.neurobs.com).

For preprocessing and statistical analyses, Statistical Parametric Mapping software (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK) implemented in Matlab 7 (Math Works, Natick, Massacussetts, USA) was used. Children and adolescents with ADHD often struggle with lying still under the scanner and therefore their MRI images are more susceptible to motion artefacts. The ArtRepair SPM toolbox was used to prevent a decrease in data quality by detecting and removing scans with excessive motion. The recommended ArtRepair preprocessing steps were followed, which included slice-time correction of functional images, functional image realignment to the middle slice of each run, smoothing of functional images using a 3D Gaussian kernel of 4 mm FWHM, motion adjustment by removing volumes with > 0.5 mm/TR, artefact repair, spatial normalization of all images, and smoothing of functional images using a 7 mm FWHM kernel (Paul K Mazaika, Hoeft, Glover, & Reiss, 2009). Runs with more than 25% of volumes repaired and participants with less than half of the runs remaining were excluded from image analyses. These criteria led to the removal of three children and two adolescents with ADHD, resulting in a final sample of 33 ADHD participants and 33 matched controls (each consisting of 15 children and 18 adolescents).

Statistical Analyses

Behavioural Measurements

Two separate repeated-measures ANOVAs examined the effects of group (ADHD, control), condition (CONDITIONAL LOSS AVOIDANCE, CERTAIN LOSS, CERTAIN LOSS AVOIDANCE), age (8-12, 13-18 years) and run (1, 2, 3, 4, 5) on reaction time and subjective cue-valence ratings. To further investigate the effect of monetary amount (€0.20, €1, €5), additional ANOVA's were made with condition (CONDITIONAL LOSS AVOIDANCE, CERTAIN LOSS), group, monetary amount, run and age as within-subject factors. Post-hoc Bonferroni-corrected *t*-tests were used to explore significant interaction effects, when appropriate. Statistical analyses were conducted in SPSS (version 22, IBM, New York, USA) at a significance level of 0.05.

fMRI

A general linear model (GLM) was made with three regressors of interest for each session: cue type (CONDITIONAL LOSS AVOIDANCE, CERTAIN LOSS, CERTAIN LOSS AVOIDANCE), monetary loss amount (€0.20, €1, €5) and performance outcome (success, fail). Realignment parameters and reaction times were included as regressors of no interest to account for variability in movement and response speed. First, six t-contrast images were calculated for each subject to investigate effects of contingency (CONDITIONAL LOSS AVOIDANCE > CERTAIN LOSS, CONDITIONAL LOSS AVOIDANCE > CERTAIN LOSS AVOIDANCE), valence (CERTAIN LOSS > CERTAIN LOSS AVOIDANCE, CERTAIN LOSS AVOIDANCE > CERTAIN LOSS), and feedback (CONDITIONAL LOSS AVOIDANCE success > CONDITIONAL LOSS AVOIDANCE fail, CERTAIN LOSS success > CERTAIN LOSS fail). Secondly, three supplementary contrast images were created to examine the influence of monetary loss amounts on contingency (CONDITIONAL LOSS AVOIDANCE €0.20 > CERTAIN LOSS AVOIDANCE, CONDITIONAL LOSS AVOIDANCE €1 > CERTAIN LOSS AVOIDANCE, CONDITIONAL LOSS AVOIDANCE €5 > CERTAIN LOSS AVOIDANCE). These specific monetary level contrasts were not created for the contingent CONDITIONAL LOSS AVOIDANCE > CERTAIN LOSS contrast, as CERTAIN LOSS also contains separate monetary levels and is therefore underpowered to explore dose-response influences. Thirdly, to check the potential influence of time-on-task, a specific analysis was performed for run 4-5 only (€50 remaining) for the main contingency and valence contrasts.

All individual t-contrast images were then used in second-level analysis. We first conducted a 2 x 2 factorial ANOVA with group (ADHD, control) and age (8–12y, 13-18y) as factors to test the main effects of group and age as well as the potential interaction of the two factors on whole-brain activation for contingency, valence and feedback contrasts. In all whole-brain analyses, statistical tests were considered significant having a voxel level P-value < 0.05 family wise error (FWE) corrected and a cluster size of > 5 voxels based on the peak beta-value and labelled using the automated anatomical labelling atlas (Tzourio-Mazoyer et al., 2002).

Results

Behavioural Results

Performance EMLI task

Individuals with ADHD responded slower ($F = 50.496$; $p < 0.001$; $\eta_p^2 = 0.006$) than typically developing controls, and children slower ($F = 50.496$; $p < 0.001$; $\eta_p^2 = 0.006$) than adolescents. There was an interaction between group and age ($F = 6.2$; $p = 0.001$; $\eta_p^2 = 0.001$) with the largest group difference occurring for children (**FIGURE 2A**). Correlation analysis revealed no significant relation between IQ and performance on the EMLI task ($\rho = 0.15$, $p = 0.53$). Participants responded significantly faster ($F = 36.8$; $p < 0.001$; $\eta_p^2 = 0.008$) on CONDITIONAL LOSS AVOIDANCE trials compared to both CERTAIN LOSS and CERTAIN LOSS AVOIDANCE trials. A main effect of time-on-task was found ($F = 5.4$; $p < 0.001$; $\eta_p^2 = 0.002$) with shorter reaction times observed towards the end of a session. An interaction between condition and time-on-task was found ($F = 3.3$; $p < 0.001$; $\eta_p^2 = 0.003$; **FIGURE 2B**). Shorter reaction times were observed mainly for CONDITIONAL LOSS AVOIDANCE towards task end relative to the CERTAIN conditions.

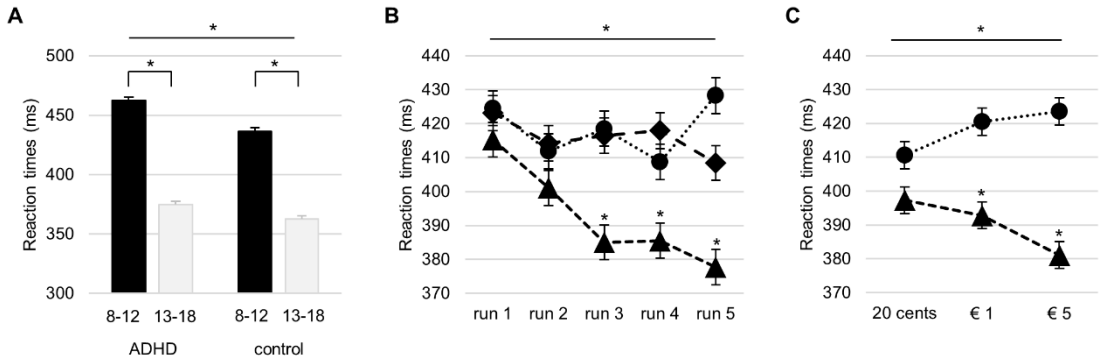

FIGURE 2. Performance on Escape Monetary Loss Incentive task. (A) For children (8-12 years) and adolescents (13-18 years) with attention deficit/hyperactivity disorder (ADHD) and typically developing controls (B) For the contingent CONDITIONAL LOSS AVOIDANCE cue (triangle), and non-contingent CERTAIN LOSS (circle) and CERTAIN LOSS AVOIDANCE (diamond) cues for each task session (C) For CONDITIONAL LOSS AVOIDANCE (triangle) and CERTAIN LOSS (circle) for different monetary amounts. Depicted are means and standard error of the mean in milliseconds. Asterisks (*) indicate $P < 0.05$.

There was no overall effect of monetary amount ($F = 0.7$; $p = 0.52$; $\eta_p^2 < 0.0001$), but an interaction between monetary amount and condition ($F = 4.8$; $p < 0.01$; $\eta_p^2 = 0.002$) was seen. Shorter reaction times were recorded with increasing monetary amounts in the CONDITIONAL LOSS AVOIDANCE condition relative to the CERTAIN LOSS condition (**FIGURE 2C**). No interaction between monetary amount and group was seen ($F = 2.8$; $p = 0.06$; $\eta_p^2 = 0.001$).

Subjective cue ratings

There was a main effect of condition ($F = 149.2$; $p < 0.001$; $\eta_p^2 = 0.57$). CERTAIN LOSS cues were rated significantly negatively (-1.9 ± 0.9), CONDITIONAL LOSS AVOIDANCE cues were rated as neutral (-0.2 ± 0.9) and CERTAIN LOSS AVOIDANCE cues were rated significantly positively (+2.7 ± 0.2). There were no significant interactions between condition and group ($F = 2.63$; $p = 0.07$; $\eta_p^2 = 0.01$), and age ($F = 0.67$; $p = 0.51$; $\eta_p^2 = 0.003$). Individuals with ADHD did not rate the cues significantly differently compared to controls ($F = 50.496$; $p < 0.001$; $\eta_p^2 = 0.006$) nor did children compared to adolescents ($F = 0.67$; $p = 0.51$; $\eta_p^2 = 0.003$).

There was a significant effect of amount of money ($F = 98.8$; $p < 0.001$; $\eta_p^2 = 0.33$). The higher the amount of money that could be lost the more negatively the symbols were rated. The interactions between monetary amount and condition ($F = 0.7$; $p = 0.50$; $\eta_p^2 = 0.003$), and group ($F = 0.2$; $p = 0.84$; $\eta_p^2 = 0.001$) were not significant.

Participants used predominantly positive words to describe CERTAIN LOSS AVOIDANCE (89% ADHD, 92% controls) and negative words for CERTAIN LOSS cues (84% ADHD, 91% controls). For CONDITIONAL LOSS AVOIDANCE the control group used words suggesting attentiveness to cues (88% attentive; 9% negative; 3% neutral), while for the ADHD group it was slightly more negative (70% attentive; 24% negative; 6% neutral). All ADHD participants and controls indicated they wanted to put most effort in the CONDITIONAL LOSS AVOIDANCE condition. Participants reported CERTAIN LOSS was especially aversive from €50 downwards (run 4).

Functional Imaging

Contingency effects

Whole-brain contingency effects were largely the same for the ADHD and control group (**SUPPLEMENTARY TABLE 1** and **SUPPLEMENTARY TABLE 2**) and no group effects were seen for the contingency contrasts (**FIGURE 3**). CONDITIONAL LOSS AVOIDANCE cues elicited significant whole-brain activation ($p[FWE] < 0.05$) in the salience network (bilateral anterior insula, mid-cingulate cortex, inferior parietal cortex, primary visual area), motor preparation network (bilateral thalamus, posterior parietal cortex, dorsolateral prefrontal cortex, supplementary motor area) and ventral striatum compared to both CERTAIN LOSS and CERTAIN LOSS AVOIDANCE cues (**FIGURE 3**).

Time-on task analysis indicated that the activation within these brain regions remained constant across the runs. There was a significant interaction ($p < 0.05$) between monetary amount and brain response in all activated brain regions for each group (**FIGURE 4**).

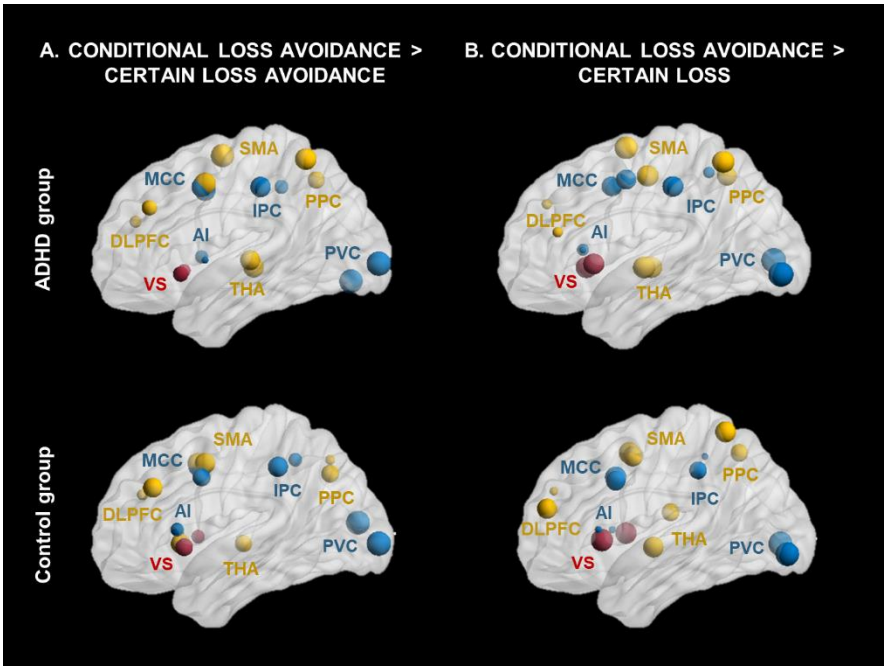

FIGURE 3. Location of significant (p[FWE] < 0.05) whole-brain activation clusters for the contingent CONDITIONAL LOSS AVOIDANCE cue compared to non-contingent (A) CERTAIN LOSS AVOIDANCE and (B) CERTAIN LOSS cues between participants with attention-deficit/hyperactivity disorder (ADHD) and typically developing controls. Similar regions of the salience (anterior insula (AI), midcingulate cortex (MCC), inferior parietal cortex (IPC), primary visual cortex (PVC)) and motor preparation network (dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC), thalamus (THA), supplementary motor area(SMA)), and ventral striatum (VS) were activated for each contingency contrast. The size of the dot corresponds with the cluster size.

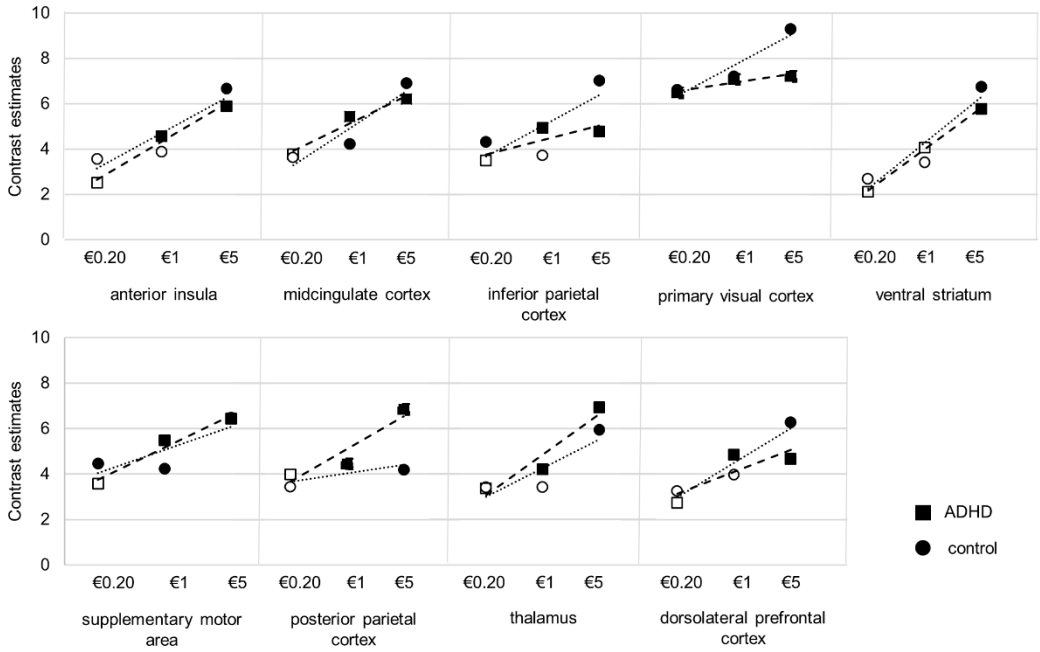

FIGURE 4. Dose-response relationships for brain regions withing the salience and motor preparation network for ADHD (square) and control (circle) participants. Contrast estimates were extracted at peak activation clusters for CONDITIONAL LOSS AVOIDANCE versus CERTAIN LOSS AVOIDANCE. Neural activation was averaged across both hemispheres. Filled dots indicated significant brain activation (p < 0.05) for a given monetary amount.

Valence effects

The ADHD group showed no significant differences (p[FWE] < 0.05) in whole-brain activation for positive (CERTAIN LOSS AVOIDANCE> CERTAIN LOSS) and negative valence (CERTAIN LOSS vs CERTAIN LOSS AVOIDANCE) in comparison with controls.

Feedback processing

Feedback indicating successful avoidance of loss in the CONDITIONAL LOSS AVOIDANCE condition resulted in a significant hypoactivation of the bilateral ventral striatum for the ADHD group compared to controls (**TABLE 2**). Failure feedback in the CERTAIN LOSS condition lead to a significant hyperactivation of the bilateral anterior insula in ADHD participants compared to controls (**TABLE 2**).

Table 2. Whole-brain based differences of estimated brain activations between ADHD and control group for feedback contrasts.

	Side	MNI			T Score	p [FWE]	Cluster Size
		X	Y	Z			
Control > ADHD							
CONDITIONAL LOSS AVOIDANCE success > failure							
Ventral Striatum	L	-28	-18	6	3.86	0.02	185
	R	28	44	6	3.45	0.04	42
CONDITIONAL LOSS AVOIDANCE failure > success							
No suprathreshold voxels							
ADHD > Control							
CERTAIN LOSS success > failure							
No suprathreshold voxels							
CERTAIN LOSS failure > success							
Anterior Insula	L	-30	14	6	4.01	0.007	25
	R	44	0	4	4.07	0.006	50

Age-related differences

Relative to children, in adolescents there was a significant whole-brain hyperactivation (p[FWE] < 0.05) of the salience network (bilateral anterior insula, midcingulate cortex, inferior parietal cortex, primary visual cortex), motor response network (supplementary motor area, posterior parietal cortex, thalamus, dorsolateral prefrontal cortex), and bilateral ventral striatum for CONDITIONAL LOSS AVOIDANCE cues relative to both CERTAIN LOSS AVOIDANCE and in less extend to CERTAIN LOSS cues (**FIGURE 5** and **SUPPLEMENTARY TABLE 3**). No age-related differences were found for feedback processing.

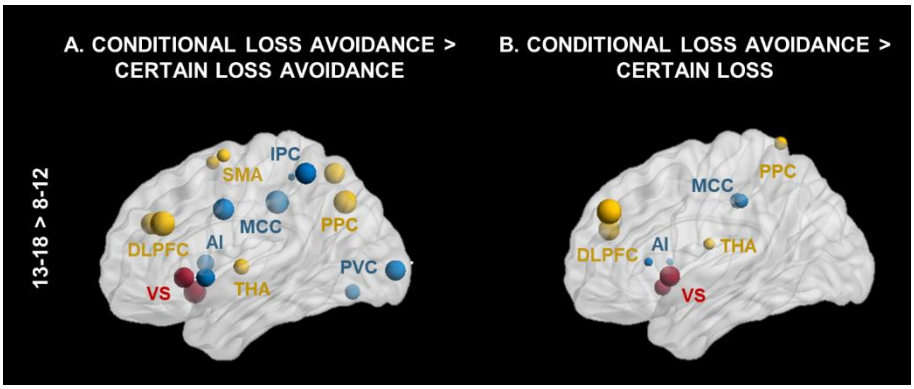

FIGURE. 5. Location of significant (p[FWE] < 0.05) whole-brain activation clusters for the contingent CONDITIONAL LOSS AVOIDANCE cue compared to non-contingent (A) CERTAIN LOSS AVOIDANCE and (B) CERTAIN LOSS cues between adolescents (13-18 years old) and children (8-12 years old). Similar regions of the salience (anterior insula (AI), midcingulate cortex (MCC), inferior parietal cortex (IPC), primary visual cortex (PVC)) and motor preparation network (dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC), thalamus (THA), supplementary motor area(SMA)), and ventral striatum (VS) were activated for each contingency contrast. The size of the dot corresponds with the cluster size.

Discussion

Theoretical models on attention-deficit/hyperactivity disorder (ADHD) suggest that altered processing of reinforcement contingencies contribute to the disorder's symptoms (Luman et al., 2010). Evidence for these motivational deficits in ADHD comes mainly from fMRI studies that have demonstrated a diminished ventral-striatal response during reward anticipation and feedback (Plichta & Scheres, 2014). The question of whether these neural effects extend to negative reinforcement processes (such as monetary loss avoidance) is still unclear, despite recognition that both positive and negative consequences impact ADHD behavior (Alsop et al., 2016; Luman et al., 2005).

This fMRI study investigated ADHD-related alterations in the brain during the processing of monetary loss using a new EMLI task design where pre-target cues predicted either no contingency (CERTAIN LOSS, CERTAIN LOSS AVOIDANCE) or a contingency between performance and outcome (CONDITIONAL LOSS AVOIDANCE). We made three core predictions. First, that contingent stimuli (CONDITIONAL LOSS AVOIDANCE) would increase the performance and would enhance the salience and motor response preparation networks in children and adolescents with ADHD to achieve similar brain responses as in their peers when being contrasted with the non-contingent conditions (CERTAIN LOSS, CERTAIN LOSS AVOIDANCE). Second, that children and adolescents with ADHD would show an exaggerated response to CERTAIN LOSS relative to CERTAIN LOSS AVOIDANCE cues based on the idea that they are more sensitive to the aversive properties of stimuli. Third, that positive feedback (successful monetary loss avoidance) would have a diminished response in the brain's reward circuits (i.e. ventral striatum) and negative feedback (monetary loss avoidance failure) would lead to an increased response in emotional brain networks (i.e. amygdala and anterior insula) when comparing ADHD subjects with controls.

With regard to the first prediction, contrary to fMRI findings for positive reinforcements (Plichta & Scheres, 2014), there was no evidence of an altered response to anticipation of contingent or non-contingent monetary loss at any level. At a behavioural level, cues signalling the opportunity to avoid monetary loss were found equally reinforcing by speeding up responses to the target for ADHD and typically developing controls. Reaction times were faster on CONDITIONAL LOSS AVOIDANCE trials than the two "certain" types. This is in line with behavioural studies that showed

that motivational contingencies do not differentially affect performance of children and adolescence with ADHD when compared to typically developing controls (Liddle et al., 2011; Solanto, 1990; Uebel et al., 2010). Both groups showed a clear distinction of cues in terms of valence and motivation ratings, with CERTAIN LOSS being rated negatively, CERTAIN LOSS AVOIDANCE being rated positively and CONDITIONAL LOSS AVAIDANCE being rated motivational. This suggested that all participants were aware of the distinctive valence and salience properties of the cues, confirming that the EMLI behaviourally engaged participants' negative reinforcement processes.

Crucially, for the aims of the current paper, the EMLI task also effectively differentiated the specific brain responses associated with contingency and valence (Van Dessel et al., 2020). In line with our predictions and behavioural findings, CONDITIONAL LOSS AVOIDANCE cues activated brain regions previously associated with the salience network anchored in the midcingulate cortex, anterior insula and inferior parietal cortex and primary visual cortex (Jensen et al., 2007; T. Kahnt et al., 2014) It has been frequently shown that when a directed action is required, the salience network co-activates with a distinct motor preparation network that consist of the supplementary motor area, posterior parietal cortex, thalamus and dorsolateral prefrontal cortex (Lau et al., 2004; Seeley et al., 2007). In line with previous investigations, we found that higher monetary amounts seemed to induce larger brain activity withing these brain regions of the salience and motor preparation network (Lallement et al., 2014).

Our results demonstrate that the brain processes underpinning contingency-related actions are intact in ADHD - at least with regard to monetary loss. This finding is in accordance with electrophysiological research in which event-related potentials associated with attention allocation (cue P3) and cognitive preparation (contingent negative variation) were only attenuated in ADHD on non-incentive trials (Albrecht et al., 2013). Heinrich and colleagues (2017) found no differential effects on reward contingent cues on either cue component between ADHD and controls. This was further confirmed by Chronaki and colleagues (2017) who found that cue P3 and CNV were not differently modulated by contingency between ADHD and controls. Previous fMRI studies using MID tasks were not able to isolate the neural activity specifically associated with motivational salience towards avoidance of monetary loss, as they were not able to distinguish contingency from valence effects (Litt et al., 2011; Maunsell, 2004). This is because MID tasks typically rely on the direct contrast between monetary gain and monetary loss cues,

therefore indistinguishably mixing-up the relative contribution of each valence outcome. Differential brain responses have been found for the same monetary amount during "gain" conditions ($0 is the worst possible outcome) and "lose" conditions ($0 is the best possible outcome) (Nieuwenhuis et al., 2005).

With regard to the second prediction, there was no evidence of a heightened neural sensitivity to the aversiveness of monetary loss anticipation. This despite that one of the certain cues CERTAIN LOSS AVOIDANCE was designed and clearly experienced by participants as positively valenced and the other CERTAIN LOSS experienced and recognized as negatively valanced. This seems to stand in stark contrast to previous fMRI research using a very similar paradigm in which children and adolescents with ADHD displayed amygdala hyperactivation in response to cues predicting the imposition of delay (Lemiere et al., 2012; Van Dessel et al., 2018a; Van Dessel, Sonuga-Barke, et al., 2019; Wilbertz et al., 2013). This indicates that individuals with ADHD are not more sensitive to aversive stimuli in general, but rather to specific aversive stimuli such as delay (Edmund J.S. Sonuga-Barke, 2005; Van Dessel, Morsink, et al., 2019). In contrast to the models predicting neural hypoactivation during reward processing in ADHD, the delay aversion theory postulates hyperactivation toward delayed reward in the emotional network. Future studies testing delayed monetary loss can result in another neural activation pattern.

Despite the fact that the processing of reinforcement contingencies seems to be intact, children and adolescents with ADHD show a different response to performance feedback compared to typically developing controls. A diminished brain response to successful and an increased response to failure feedback was found. This is consistent with the neuroimaging literature on feedback processing, where children and adolescents with ADHD show a hypoactivation of the ventral striatum to positive feedback (Plichta & Scheres, 2014) and hyperactivity of the anterior insula to negative feedback (Wilbertz et al., 2017). Several neuropsychological studies have indicated a dysfunctional processing of positive and negative feedback in ADHD (Groen et al., 2013, 2008; Rosch & Hawk, 2013; Van Meel et al., 2005). The findings for feedback processing raise several intriguing questions, particularly because feedback-related brain activations showed a significant correlation with ADHD and oppositional defiant disorder symptom severity ($\rho = 0.56$, $p < 0.01$). Perhaps they are a sign of emotional dysregulation, an important transdiagnostic feature associated with both disorders.

Of more general interest, there was an age-specific increase in activation of the salience and motor preparation network towards contingent monetary loss cues. Both age groups, however, reported to perform their utmost best when they had the opportunity to avoid monetary loss and no differential brain response was seen for valence-related and feedback-related contrasts. Since the neurocognitive level automatically increases with age, it is difficult to say how specific the age-related effects are for negative reinforcement (Reed, Chan, & Mikels, 2014). A staircase tracking algorithm of the EMLI ensured that brain responses were not linked to differences in performance. Reaction times were included in the GLM to account for variability in response speed. Evidence from neurodevelopmental studies has solely focused on positive reinforcing brain effects, and consistently reported increased activation in the ventral striatum to monetary gain during adolescence (Bjork et al., 2004; Galvan et al., 2006; Van Leijenhorst et al., 2010). Future studies are needed to replicate these findings not only for monetary loss avoidance, but for other aversive stimuli in general.

Despite clear evidence that the task itself worked well in distinguishing contingency and valence-related effects since these were mirrored in terms of performance and subjective ratings of cue valence, there are some limitations that need to be taken into account. First, the design of the study only included monetary loss-related cues. It did, therefore, not allow to conclude that the hypersensitivity to negative reinforcement in ADHD is specifically limited to delay aversion. Future ADHD studies, comparing monetary loss directly to forced waiting times and maybe other aversive cues will allow us to answer the specificity of delay aversion. Second, studying age-related changes is challenging, as there is a large heterogeneity of aging processes especially during puberty. Individual differences in the rate of development might also result in variable functional patterns of activation in children and adolescents (Casey, Giedd, & Thomas, 2000), which could reduce group activation maps. Slower cortical thinning during adolescence has been linked with the presence of ADHD symptoms (Shaw et al., 2011). Unfortunately, we did not control for precise pubertal development using any standardized measures. Third, to guarantee equal performance of participants, the significance of each cue symbol was trained before the start of the experiment. This meant that the process of learning could not be tudied. Future research should examine the effects of contingency during learning.

Conclusion

The current results were clear cut in finding no evidence that children and adolescents with ADHD react to anticipation of monetary loss differently from controls either in terms of contingency-related or valence-related effects. Motivational models of ADHD need to explain the specificity of motivation effects – why they show *a general* hyposensitivity to the positive reinforcement (monetary gain) but not negative reinforcement (monetary loss avoidance) – while the effects related to negative reinforcement seem to have a greater specificity, being related specifically to a heightened aversion to delay.

Supplementary Material

SUPPLEMENTARY TABLE 1. Whole-brain based analyses of estimated brain activations in contingency contrasts for ADHD participants.

Brain Region	Side	MNI			T Score	p [FWE]	Cluster Size
		X	Y	Z			
CONDITIONAL LOSS AVOIDANCE > CERTAIN LOSS AVOIDANCE							
Anterior Insula	L	-42	4	2	5.96	0.001	30
	R	34	6	4	6.33	<0.001	125
Midcingulate Cortex	L	-12	6	44	8.62	<0.001	659
	R	8	4	42	7.29	<0.001	839
Ventral striatum	L	-14	18	-6	5.97	0.001	215
	R	10	16	-4	6.23	0.001	127
Thalamus	L	-14	-22	2	6.14	0.001	681
	R	22	-24	-2	7.62	<0.001	778
Posterior Parietal Cortex	L	-28	-54	60	6.99	<0.001	964
	R	24	-60	48	7.07	<0.001	354
Inferior Parietal Cortex	L	-42	-28	44	6.91	<0.001	724
	R	40	-40	44	5.61	<0.01	158
Dorsolateral Prefrontal Cortex	L	-34	36	32	5.59	<0.01	214
	R	44	44	24	6.92	<0.001	94
Supplementary Motor Area	L	-12	4	46	8.39	<0.001	953
	R	6	-6	62	7.96	<0.001	1434
Primary Visual Cortex	L	-16	-96	0	10.36	< 0.001	1828
	R	34	-80	-10	8.95	< 0.001	1506
CONDITIONAL LOSS AVOIDANCE> CERTAIN LOSS							
Anterior Insula	L	-28	22	8	5.26	0.04	22
	R	30	22	8	5.81	0.002	74
Midcingulate Cortex	L	-4	-2	48	6.84	< 0.001	574
	R	12	6	44	6.86	0.001	556
Ventral striatum	L	-16	16	0	6.63	<0.001	692
	R	12	20	-2	6.74	<0.001	807
Thalamus Prefrontal Cortex	L	-16	-12	-2	8.32	0.001	902
	R	22	-16	-2	8.18	<0.001	786
Posterior Parietal Cortex	L	-28	-56	58	7.63	<0.001	922
	R	16	-58	50	7.12	<0.001	495
Inferior Parietal Cortex	L	-42	-28	44	7.57	<0.001	656
	R	26	48	52	6.37	<0.001	64
Dorsolateral Prefrontal Cortex	L	-28	36	18	5.69	0.003	50
	R	36	42	34	5.44	0.01	51
Supplementary Motor Area	L	-10	-14	50	7.46	< 0.001	803
	R	10	-2	66	7.71	< 0.001	1108
Primary Visual Cortex	L	-40	-88	-6	8.08	< 0.001	1819
	R	36	-84	2	8.72	< 0.001	1702

SUPPLEMENTARY TABLE 2. Whole-brain based analyses of estimated brain activations in contingency contrasts for control participants.

Brain Region	Side	MNI			T Score	p [FWE]	Cluster Size
		X	Y	Z			
CONDITIONAL LOSS AVOIDANCE > CERTAIN LOSS AVOIDANCE							
Anterior Insula	L	-30	20	8	5.74	0.003	132
	R	34	18	6	5.40	0.01	29
Midcingulate Cortex	L	-10	6	38	7.01	<0.001	373
	R	10	8	44	7.07	<0.001	497
Ventral striatum	L	-8	16	-2	6.24	0.001	369
	R	10	8	4	6.33	<0.001	132
Thalamus	L	-4	18	0	6.10	0.001	566
	R	4	-18	0	6.16	0.001	314
Posterior Parietal Cortex	L	-14	-68	40	5.87	0.002	360
	R	26	-68	48	5.8	0.002	60
Inferior Parietal Cortex	L	-44	-38	44	5.91	0.002	633
	R	32	-48	48	5.47	0.01	138
Dorsolateral Prefrontal Cortex	L	-34	34	32	6.88	<0.001	555
	R	42	40	28	5.07	0.02	74
Supplementary Motor Area	L	-4	4	46	6.59	0.001	659
	R	10	8	46	7.15	0.001	773
Primary Visual Cortex	L	-14	-96	0	9.60	< 0.001	1647
	R	34	-84	12	9.10	< 0.001	1496
CONDITIONAL LOSS AVOIDANCE> CERTAIN LOSS							
Anterior Insula	L	-30	22	8	6.01	0.001	80
	R	34	14	8	6.16	0.001	82
Midcingulate Cortex	L	-10	12	36	7.41	< 0.001	680
	R	8	12	38	7.67	< 0.001	932
Ventral striatum	L	-10	20	2	7.76	< 0.001	1077
	R	10	6	6	6.99	< 0.001	913
Thalamus Prefrontal Cortex	L	-16	-10	-2	7.32	< 0.001	809
	R	16	-20	18	6.97	< 0.001	511
Posterior Parietal Cortex	L	-32	-52	64	7.28	< 0.001	842
	R	16	-60	52	6.97	< 0.001	488
Inferior Parietal Cortex	L	-32	-36	42	6.85	< 0.001	490
	R	34	-40	50	5.84	0.002	77
Dorsolateral Prefrontal Cortex	L	-34	52	20	6.71	< 0.001	743
	R	34	48	30	6.66	0.001	102
Supplementary Motor Area	L	-2	2	50	7.45	< 0.001	760
	R	8	4	52	7.83	< 0.001	971
Primary Visual Cortex	L	-40	-88	-6	8.24	< 0.001	1384
	R	38	-84	0	8.70	< 0.001	1494

SUPPLEMENTARY TABLE 3. Whole-brain based differences of estimated brain activations in contingency contracts between adolescents (13-18 years) and children (8-12 years).

	Side	MNI			T Score	p [FWE]	Cluster Size
		X	Y	Z			
CONDITIONAL LOSS AVOIDANCE > CERTAIN LOSS AVOIDANCE							
Anterior Insula	L	-44	12	0	4.19	0.01	188
	R	40	10	8	4.84	0.002	309
Ventral Striatum	L	-12	22	-2	4.14	0.007	249
	R	20	16	-10	4.12	0.008	407
Midcingulate Cortex	L	2	24	28	4.07	0.02	400
	R	-10	0	36	4.68	0.004	492
Dorsolateral Prefrontal Cortex	L	-26	34	28	5.41	0.001	770
	R	26	40	28	4.68	0.008	315
Primary Visual Cortex	L	-14	-96	2	4.39	0.04	229
	R	34	-72	-10	4.56	0.005	61
Posterior Parietal Cortex	L	-14	-68	40	4.69	0.002	478
	R	20	-62	56	4.41	0.004	268
Inferior Parietal Cortex	L	-40	-46	56	3.99	0.02	285
Supplementary Motor Area	L	-26	-12	52	4.04	0.01	209
Thalamus	L	-6	-10	4	3.79	0.01	68
CONDITIONAL LOSS AVOIDANCE> CERTAIN LOSS							
Anterior Insula	L	-28	22	6	3.55	0.02	14
	R	38	10	6	3.72	0.02	10
Ventral Striatum	L	-6	10	-2	3.81	0.02	168
	R	10	14	-8	3.65	0.03	75
Midcingulate Cortex	L	-8	14	28	3.71	0.03	30
	R	12	16	32	3.73	0.04	99
Dorsolateral Prefrontal Cortex	L	-32	44	34	4.63	0.008	419
	R	24	44	24	4.48	0.01	202
Posterior Parietal Cortex	R	26	-52	72	3.98	0.02	35
Thalamus	R	-14	-12	16	3.55	0.02	25

Chapter 7 | General Discussion

Attention-deficit/hyperactivity disorder (ADHD) is a common developmental childhood disorder characterized by problems with attention, hyperactivity and impulsivity. Given the social and psychological costs associated with ADHD it is important to get insight in the underlying neurobiological pathways. This thesis focuses on Delay Aversion, an important altered motivational process in individuals with ADHD. Within contemporary neuropsychological models of ADHD, Delay Aversion may represent one neurobiological pathway, explaining a substantial proportion of symptom variation. We envisaged to study the neural correlates of Delay Aversion in four MRI studies and the collection of neuropsychological data outside the MRI scanner. The overall aim of this PhD project was to test the hypothesis that Delay Aversion has a distinctive neural signature in ADHD, demonstrated by dose-sensitive functional brain responses, related to behavioural differences in daily life and to structural brain differences. The signature then was tested for its specificity, based on its dissociability from brain responses during negative reinforcement of other aversive stimuli such as monetary loss.

In this chapter, a brief summary of the key findings will be presented (**TABLE 1)** after which I reflect on the main findings presented in this thesis in relation to current literature. Subsequently, strengths and shortcomings are discussed together with potential perspectives to explore in future research.

Summary of the main findings

Chapter 2 examined how waiting impulsivity, which refers to premature responding before a scheduled target appears, adds to our understanding of impulsivity in ADHD. Thirty 8 to 12 year old children with ADHD and 30 age-matched typically developing controls completed the 4-choice serial reaction time task, alongside tasks measuring inhibitory control and temporal discounting. Questionnaires measuring behavioral disorder symptoms, delay aversion, and various aspects of impulsivity were collected. A multiple logistic regression model was used to explore the contribution of the primary task outcomes to predict group membership. Children with ADHD displayed more waiting impulsivity and less inhibitory control; they did not differ in temporal discounting. There was no correlation between waiting impulsivity and inhibitory control. Waiting impulsivity was correlated with parent-reported ratings of hyper-activity/impulsivity, inattention, oppositional defiant disorder, and conduct disorder and with self-reported delay aversion ratings. Only waiting impulsivity was a significant predictor of ADHD

status. This indicated that waiting impulsivity is distinct from other neuropsychological deficits and predicts ADHD status independently of it.

In **Chapter 3**, we examined the dose-response brain activations during anticipation of delay-related cues and validated the brain activity patterns against self-reported measures of Delay Aversion. Thirty-two right-handed male adolescents with combined-type ADHD and 36 age-matched controls between 10-18 years completed the rEDI task under the fMRI scanner. Patterns of brain activation within the affective brain network were compared during the anticipation to three different delay-related cues (CERTAIN DELAY, CONDITIONAL DELAY, NO DELAY). The obtained results were strongly supportive for the existence of delay aversion in adolescents with ADHD both at the behavioural and neurobiological level. Our predictions were confirmed in four ways. First, individuals with ADHD rated themselves as more delay averse and rated the valence of delay-related stimuli more negatively than controls. Second, there was a highly significant association between ADHD and delay-related cue-elicited hyperactivation in five brain regions know to mediate the processing of negatively valenced emotional stimuli (amygdala, temporal pole, anterior insula, ventromedial prefrontal cortex and dorsolateral prefrontal cortex). Third, these effects were more pronounced on those trials associated with longer delays. Fourth, delay-related brain responses were strongly correlated to self-ratings of delay aversion.

The results from Chapter 3 were so strikingly coherent that in **Chapter 4** we studied the link between these neurofunctional findings and structural neuro-anatomy. The 60 structural MRI scans, collected in study 2, were preprocessed and structurally analyzed using Voxel-Based Morphometry techniques. A decreased grey matter volume was found for the bilateral amygdala, parahippocampal and temporal gyrus in the ADHD group as compared to controls. Additional region of interest specific analyses for the five activated brain regions during the rEDI task indicated a significant inverse relationship between amygdala and (1) behavioural measures of delay aversion and (2) brain functional response.

In **Chapter 5**, we designed a new EMLI task by analogy with the rEDI task (Chapter 3 and 4), in which anticipation of delay was replaced by anticipation of monetary loss. Thirty-four typically developing adolescents started with €150 and could not gain extra money, but could avoid losing money depending on their performance. The EMLI task was able to distinguish brain networks linked to contingency-related (CONDITIONAL LOSS AVOIDANCE) and valence-related (CERTAIN LOSS, CERTAIN LOSS AVOIDANCE) cue processing. CONDITIONAL LOSS AVOIDANCE cues were motivationally salient, improved performance and activated brain networks known to underpin salience processing and motor response preparation. Effects varied by monetary loss amount in a number of regions. Brain regions linked to differences in cue valence were less apparent, but positively valanced cues (CERTAIN LOSS AVOIDANCE) were associated with a hyperactivation of reward associated brain regions. Successful feedback on CONDITIONAL LOSS AVOIDANCE trials activated ventral striatum more compared to feedback on failure. These findings validate the EMLI for distinguishing the role of different processes and underlying brain systems in negative reinforcement processes.

In Chapter 6, eighteen right-handed male children (8-12 years) and twenty adolescents (12-18 years) with ADHD completed the EMLI task under the fMRI scanner. In contrast to differential cue ratings of the rEDI task (Chapter 3), individuals with ADHD did not rate the EMLI cues significantly different from controls. Cues predicting a contingency between performance and monetary loss activated the brain salience and motor response preparation networks to an equal degree in ADHD and controls independent of whether they were contrasted to a cue indicating positive (CERTAIN LOSS AVOIDANCE) or negative valence (CERTAIN LOSS). The valence effects observed towards the end of the sessions were also equal for ADHD and controls. These results indicate that Delay Aversion has a neural signature that is dissociable from brain responses during other aversive experiences.

TABLE 1. Key findings of research Chapters in this thesis

Chapter 2	• Children with ADHD displayed more waiting impulsivity, less inhibitory control and did not differ in temporal discounting compared to controls. • There was no correlation between neuropsychological concepts. • Waiting impulsivity was correlated with parent-reported ratings of hyper-activity/impulsivity, inattention, oppositional defiant disorder, and conduct disorder and with self-reported delay aversion ratings. • Only waiting impulsivity was a significant predictor of ADHD status.
Chapter 3	• Individuals with ADHD rated themselves as more delay averse than controls. • Cues of upcoming delay elicited an unusually strong pattern of activation within brain regions known to be implicated in the processing of aversive events. • ADHD-related elevation in activation in response to cues predicting certain delay relative to cues predicting no delay, in amygdala and dorsolateral prefrontal cortex, was delay-dose sensitive and statistically mediated the relationship between ADHD and self-rated delay aversion • Future research should explore whether these neural effects are specific to delay aversion or are a marker of a more general sensitivity to aversive events in individuals with ADHD. • Clinical practice could benefit from a more detailed understanding of delay aversion as a potential driver of ADHD-related symptoms and/or comorbidity.
Chapter 4	• ADHD was associated with reduced volumes in bilateral amygdala, parahippocampal and temporal gyrus. • A greater basolateral amygdala activation to delay-related cues was found for individuals with ADHD compared to controls. • Amygdala volume reductions were significantly correlated with, and statistically mediated the pathway from ADHD to, delay-cue-related amygdala hyperactivity and self-reported delay aversion. • We provide the first evidence of the functional significance of reduced amygdala volumes in adolescents with ADHD by highlighting its relation to delay-induced brain activity that is linked to delay aversion.

Chapter 5	• We distinguished brain networks involved in the processing of contingency-related and valence-related information. • Cues signaling a contingency between performance and loss avoidance activated brain networks known to be involved in salience processing and motor response preparation relative to cues signaling either positively or negatively valenced certain outcomes (i.e., no contingency). • Positively valenced cues were associated with hyper-activation of ventral striatum, middle temporal gyrus and medial orbitofrontal cortex towards the end of the session.
Chapter 6	• There was no evidence of atypical processing of contingent or non-contingent monetary loss cues in ADHD. • The ability to process contingencies between performance and negative outcomes is intact in ADHD and that individuals with ADHD are no more (or less) sensitive to monetary loss than controls. • Successful avoidance feedback resulted in an ADHD-related hypoactivation of the reward network, while feedback indicating failure caused a hyperactivation of the bilateral insula compared to controls. • Adolescents showed a hyperactivation of the salience and motor-response network for contingent compared to non-contingent monetary loss cues. • This is in stark contrast to recent evidence from a similar task of atypical emotion network recruitment (e.g., amygdala) in ADHD individuals to cues predicting another negative event the imposition of delay suggesting marked specificity in the way they respond to negative events.

Reflection and Advancing Knowledge

The Delay Aversion Theory

The main achievement of this PhD thesis is the comprehensive validation of the delay-aversion theory across brain function (**Chapter 3**), brain structure (**Chapter 4**), psychological testing (**Chapter 2 and 3**), and self-rating (**Chapter 2 and 3**). This is of great importance to test the Delay Aversion hypothesis in ADHD specifically and to study the pathophysiology of ADHD in general because, while the neurobiological predictions of the delay aversion hypothesis were set out more than a decade ago, only recently attempts have been made to test these. The studies included in this monograph, demonstrated that the relationship between ADHD and suboptimal behavioural test results on a delay aversion paradigm is partially mediated by underlying brain dysfunction.

Based on two previous small-scale fMRI studies (Lemiere et al. 2013, Wilbertz et al. 2013), our initial hypotheses on delay aversion were the following (**FIGURE 3** in general introduction): First, cues signaling the anticipation of the imposition of future delay (CERTAIN DELAY) would result in a hyperactivation of brain regions implicated in the processing of negatively valenced affective stimuli (amygdala and insula) in ADHD patients compared to controls. Second, the perspective of the possibility to escape delay (CONDITIONAL DELAY) would result in a hyperactivation of reward-related structures (ventral striatum and medial orbitofrontal cortex), with a delay
dose-response relationship in both instances.

We have added a control condition (NO DELAY) to the rEDI paradigm in order to be able to identify the brain regions activated by CERTAIN DELAY and CONDITIONAL DELAY cues separately, rather than as relative comparison to one another (e.g., CERTAIN DELAY vs CONDITIONAL DELAY and vice versa). However, from **Chapters 5 and 6**, we have learned that the brain response from the contrast CONDITIONAL DELAY > NO DELAY could be interspersed with contingency-related effects. Nonetheless, we did not find any group-specific or group-related differences in brain regions associated with salience processing or motor preparation (besides for the parietal cortex). In contrast, similar but much smaller differences between ADHD and control participants were seen in brain regions implicated in the processing of aversive stimuli. While we hypothesized the CONDITIONAL DELAY > NO DELAY contrast to be rewarding, subjective cue-ratings showed that CONDITIONAL DELAY was rather perceived as negative, although less

negative than the CERTAIN DELAY condition (**FIGURE 1**). On second thought, this seems only logical because in 33% of the cases participants still have to experience a delay period. The condition that was clearly perceived most rewarding was the NO DELAY condition, as participants were able to escape or avoid delay in 100% of the cases. Unfortunately, our analyses in **Chapter 3** were limited to CERTAIN DELAY and CONDITIONAL DELAY versus NO DELAY. Future full scale analysis of contingency and valence contrasts, by analogy with **Chapters 5 and 6**, can provide more insight in the specific rewarding effects of delay avoidance.

Delay versus Monetary Loss

In order to test the specificity of the delay aversion model it was crucial to look whether the behavioural and neural responses to delay (**Chapter 3**) differ from other aversive events, such as monetary loss (**Chapter 6**). While we predicted both delay and monetary loss to be rated aversive and activate brain regions implicated in the processing of aversive events in general, these effects were expected to be larger in ADHD patients for delay anticipation than monetary loss, relative to the effects seen for controls. Maybe the most convincing evidence for a differential response to delay in ADHD comes from the explorative-analysis combining subjective cue-ratings on the rEDI from **Chapter 3** and cue-ratings on the EMLI paradigm from **Chapter 6** (**FIGURE 1**). After finishing the reaction-time task under the fMRI scanner, participants were asked to rate all anticipatory cues on a 7-point Likert scale (-3 negative, 0 neutral, +3 positive).

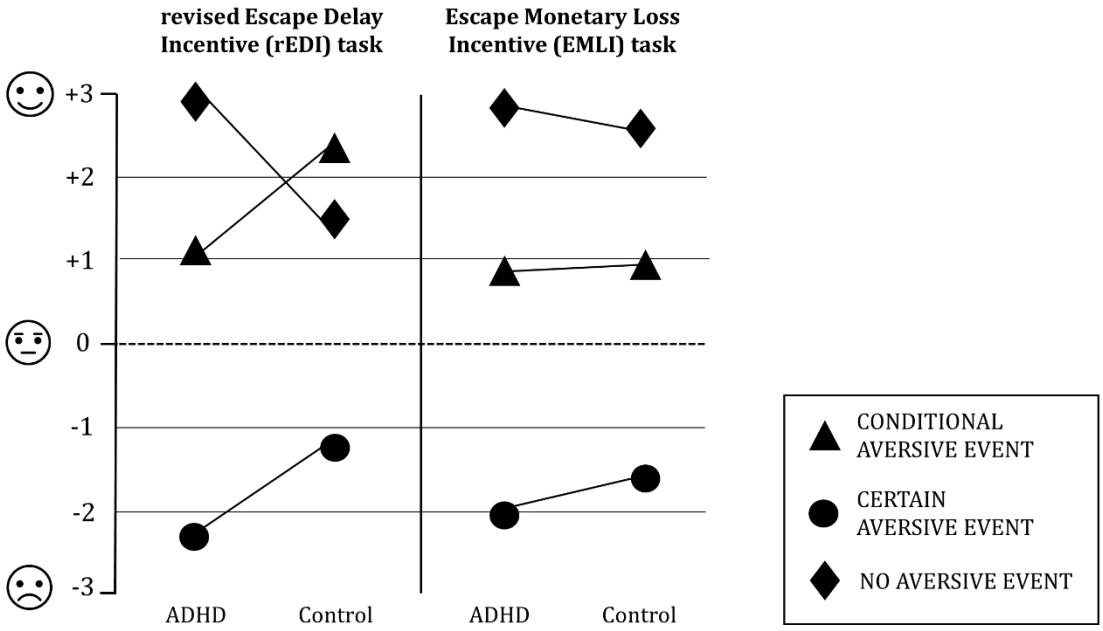

FIGURE 1. Subjective anticipated cue ratings for the revised Escape Delay Incentive (rEDI) task and Escape Monetary Loss Incentive (EMLI) task for ADHD and typically developing controls.

While adolescents with ADHD did not rate the cue-types significantly different compared to controls on the EMLI paradigm, there was a clear difference in ratings for the rEDI paradigm (**FIGURE 1**). The CONDITIONAL DELAY cue was perceived more negative and the NO DELAY cue as most rewarding in ADHD. In contrast, the control group considered the CONDITIONAL DELAY cue as most rewarding cue type. These differences in cue ratings extend to the differences found in the brain response. While no evidence of a heightened neural sensitivity to the aversiveness of monetary loss anticipation was found, on the rEDI a significantly greater activation to CERTAIN DELAY cues relative to NO DELAY cues was found in participants with ADHD compared to controls in amygdala, anterior insula, temporal pole, dorsolateral prefrontal cortex and ventromedial prefrontal cortex, all brain regions known to be implicated in the processing of aversive events. It should be noted that the interpretation of the brain responses only became clear to us after looking at the subjective cue-ratings. It is not because you expect something to be rewarding or punishing that it is perceived in this way by the participant. It is therefore extremely important to collect subjective cue-ratings at the end of the task.

The subjective cue-ratings not only helped us to interpret the brain responses, they also confirmed that our participants clearly understood the distinctive cue properties signaling valence and salience. However, in **Chapter 3**, we noticed towards the paradigm's end that a clear distinction in subjective feeling was made between the anticipated and the feedback cues. CONDITIONAL DELAY cues indicating successful feedback were perceived as the most positive condition, more positive than NO DELAY cues indicating success or failure. In contrast, CONDITIONAL DELAY cues indicating failure were perceived as most negative, more negative than CERTAIN DELAY cues, because here waiting was caused by slow response (i.e. by their own failure). This is why in **Chapters 5 and 6**, we systematically scored the feedback cues as well, in addition to anticipatory cues to facilitate the interpretation of the brain responses during feedback of success or failure.

We have to admit that the currently used design was not the most appropriate to directly compare the brain response between delay-related cues and other aversive events (in casu monetary loss). Future studies are needed to compare the activations of valence-related and contingency-related contrasts in ADHD and adolescent controls using the same subject group twice in a cross-over design. We chose to separately examine both aversive events because combining monetary loss and delay in one design would have been too complex. The multitude of symbols that would be needed in one task paradigm could confound with working memory problems, especially in the ADHD-group. Also carrying out both tasks in the same participants was deemed not feasible because of limited time within the scanner. In order to have sufficient power to study differences in brain response, we calculated that we need at least 5 runs per paradigm (±30 min). This would mean that the participants would have to lie still in the fMRI scanner for about 1 hour, which would be very challenging for individuals with ADHD and/or young children. The longer the time span, the more chance movement artifacts will occur and the less reliable our analyses would be. Based on current results, we would expect to find a main effect for group (ADHD > control) and an interaction between group (ADHD > control) and task (rEDI > EMLI)

Negative Reinforcement

In **Chapter 3, 5 and 6,** two new fMRI-compatible paradigms were developed and validated to test reactions to avoidance of aversive stimuli. The revised Escape Delay Incentive (rEDI) and the Escape Monetary Loss Incentive (EMLI) paradigms are now available for researchers in the field. The rEDI offers the possibility to test contingent-performance, subjective cue valence-ratings and brain response in relation to the anticipation and/or experience of delay periods. The EMLI parallels the former with delay being replaced by monetary loss. Both paradigms can provide a useful way of distinguishing the role of different processes and underlying brain systems in contingency-related and valence-related cue processing, which is not evident to investigate using other fMRI paradigms. This is because they typically rely on the contrast between reward and punishing cues, thereby confounding the study of the brain processes implicated in marking the salience of cues predicting a performance-outcome contingency (and the response preparation they motivate) and those predicting the relative valence of the likely outcome Our newly developed paradigms can help to identify potential negative reinforcement processing deficits in other psychiatric conditions.

Multimodal Brain Analysis

A substantial number of studies are currently collecting multimodal brain imaging data and information from the same participants. Particularly structural MRI scans are always taken in combination with an fMRI sequence, as the resolution of a fMRI scan is too low to accurately represent brain anatomy and pathology. However, only few studies are fully exploiting the rich multimodal information that exists in combining brain imaging data, although this may reveal important relationships that cannot be detected using a single modality. While neuroimaging studies have identified widespread structural and functional brain abnormalities in ADHD, the majority of these studies have separately identified group differences in either structure or function. This is very different from the multimodal approach we used in **Chapter 4** by identifying a specific relevant trait from structural MRI (e.g., amygdala volume) and correlating it with brain voxels on the fMRI scan (e.g., brain response during rEDI task) within the same brain region. The latter can be considered a type of data fusion, because both modalities are used to estimate a joint result. Multimodal fusion can help us to find the missing links in psychiatric disorders, as

it can facilitate differentiation between patients and typically developing controls (Calhoun & Sui, 2016).

Developmental Effects

A carefully matched developmental sample was included in this study series. This allowed us to identify in **Chapter 6** an age-specific hyperactivation of salience processing and motor preparation brain regions towards contingent monetary loss. Considerable evidence supports the idea of developmental changes in attention, response and memory, by which older adolescents and adults tend to pay greater attention, process, and remember more information compared to children (Mather, 2016; Reed et al., 2014). In addition, attitudes and feelings about waiting and money are likely to change during adolescence. Adolescents attach more value to monetary outcomes (Kasser, 2005) and less to waiting when compared to younger children (Montroy, Bowles, Skibbe, McClelland, & Morrison, 2016). This may indicate that age-related differences can occur as a function of differential engagement. However, all participants reported to perform their utmost best when they had the opportunity to avoid an aversive stimuli. Since the neurocognitive level automatically increases with age, it is difficult to say how age-related effects are specific for negative reinforcement. Most neuroimaging studies to date have directly compared positive reinforcing brain effects across development with generally mixed findings (Bjork et al., 2004; Galvan et al., 2006; Van Leijenhorst et al., 2010). Future longitudinal research using these fMRI paradigms can help to investigate whether developmental factors play a role in the neurobiological signature of delay aversion specifically or to negative reinforcement processes in general.

Methodological Limitations and Implications

The following section reflects on the main limitations of the research in this thesis that should be taken into consideration with respect to the generalizability of the presented results.

First, the results in this thesis focus on a specific subgroup of ADHD, more specifically right-handed boys with ADHD, mostly with combined presentation, and may therefore not be generalized to the overall ADHD population. Although there are no indications that girls react differently to aversive stimuli (Lithari et al., 2010), nor that the Delay Aversion theory would imply differently for them (Paloyelis, Asherson, & Kuntsi, 2009). The same applies to the potential implications of left-handedness.

Second, although not uncommon in the ADHD literature, groups differed on IQ, which might result in inherent difficulties in performance associated with ADHD. However, in all our behavioral and fMRI analyses the potential influence of IQ on primary outcomes and brain responses was investigated and no correlation between performance and IQ was found. Furthermore, a staircase tracking algorithm in the fMRI paradigms ensured that performance rates were equal over the groups and thus that the brain responses could not be due to differences in performance. Moreover, reaction times were included in the GLM to account for variability in response speed.

Third, the study sample covers a wide age range (8–18 years), and thus developmental effects could be confounding our study findings. Individual structural differences in the rate of development might result in variable functional patterns of activation in children and adolescents, which could reduce group activation maps. Unfortunately, we did not control for precise pubertal development using any standardized measures. Developmental differences are however unlikely in the current experiments, because the groups were carefully matched on age and gender. Future longitudinal research should further investigate whether developmental factors play a role in the neurobiological signature of delay aversion specifically or in negative reinforcement processes in general.

Fourth, even though a sample three times larger than previously used was included in this study series, replication of our results is still needed. Contradictory findings are often reported in the ADHD domain, possibly due to the lack of statistical power from small sample sizes in fMRI studies and the heterogeneity within ADHD. It is not always feasible for monocentric task-based functional studies to include hundreds of patients.

Multicentre collaborations with large samples, standardized data acquisition and analysis procedures, such as the ENIGMA consortium, can help to elucidate ADHD-specific brain alterations in the near future.

Fifth, different task designs may modulate processes that promote avoidance. In line with prior human neuroimaging studies, a partial avoidance contingency was used in the CONDITIONAL condition in which participants could avoid delay or monetary loss in 66% of the time or could avoid delay or monetary loss on every trial like in the CERTAIN LOSS AVOIDANCE condition. Varying avoidance probabilities and subsequent beliefs are likely to modulate brain responses.

Sixth, in order to ensure equivalent performance of participants, the cue-related contingencies were trained before the start of the experiment. This meant that the process of learning could not be studied. Future research may examine the effects of contingency during the learning period.

Future Directions

Pathophysiological Models of ADHD

The findings described in this thesis have an impact on models of motivation and emotion generally and how these models can be applied to ADHD more specifically. While progress is being made in understanding the separate neural underpinnings of cognitive, motivational and emotional processes in children and adolescents and their relationship to cognitive impairments and mental disorders, there have been very few studies looking at the way that these different brain systems interact in humans. The Dual Pathway model postulates that two separate neural pathways are involved in the pathophysiology of ADHD: delay aversion and executive functioning. However there are few neurobiological studies examining the predictions of this model in the same participants. Future studies should investigate the distinctive and overlapping neural correlates of delay aversion and executive functioning in individuals with ADHD by contrasting the rEDI with a commonly used Stop Signal Task of inhibitory control (used in **Chapter 2**). This is of great importance to support the delay aversion hypothesis in ADHD specifically and to study the pathophysiology of ADHD in general because, while it is now generally accepted that ADHD is a pathophysiologically heterogeneous condition with different individuals showing different patterns of deficits across a wide range of neuropsychological processes, there has been little or no research looking at the extent to which these distinctive patterns of deficits are underpinned by dissociable patterns of functional activity in different brain networks.

Implications for Practice

Validation of the Delay Aversion theory in this PhD thesis is relevant to a large proportion of children with ADHD, which often share general clinical characteristics, but based on the Dual Pathway model are made up of subgroups with distinctly different neuropsychological profiles marked by variations in motivational and cognitive deficits (Sonuga-Barke, Sergeant, Nigg, & Willcutt, 2008). By demonstrating that delay is particularly aversive for a large subgroup of children and adolescents with ADHD, one can think about the necessity to incorporate delay aversion in the basic assessment of individuals with ADHD, in order to be able to adapt treatment plans to their specific needs.

Current treatments for ADHD are generic and symptomatic in nature. More specific treatments, aiming at specific dysfunctions may be necessary. So far, delay aversion is hardly addressed in the treatment of ADHD. Based on the results of this thesis, Delay Aversion shows to be an important, specific and fundamental dysfunction and therefore needs to be addressed specifically, since it may underlie specific risk factors associated with ADHD, such as risk taking behaviours.

Emotion Dysregulation

Both behavioural reactions (**Chapter 2**) and neurobiological responses on delay (**Chapter 3 and 6**) showed a significant correlation with ADHD and Oppositional Defiant Disorder symptom severity. Perhaps these are a sign of emotional dysregulation, an important transdiagnostic feature, associated with both disorders. Emotion dysregulation is a common and disabling feature of a number of childhood behavioural and emotional disorders (Banaschewski et al., 2012). In order to understand the neurobiological underpinnings of such dysfunction, scientists have employed a number of different laboratory paradigms. These studies have highlighted how such emotional responses are mediated by activations in key regions of the brain such as the amygdala, insula and ventral medial prefrontal cortex (Roy et. Al.,. 2013; Bertocci et al., 2014; Wolf & Herringa 2016). Most of the time, studies have employed case-control designs, contrasting reactions of a group with a single disorder to a group of typically developing youth. Until recently few studies have directly compared emotional responses in different disorders. This means that the questions of the disorder-specificity of emotional problems have not been properly addressed. More recently, however, trans-diagnostic approaches, involving studies comparing children with different disorders, have started to demonstrate a degree of specificity with responses to emotionally charged events and stimuli being different in different disorders (Brotman et al., 2010). In order to do so, we scanned 24 children and adolescents with a pre-existing diagnosis of anxiety disorder by analogy of the study set-up described in **Chapter 6** and compared with individuals with ADHD and typically developing controls (Van Dessel et al. in preparation, data not part of this thesis).

Individuals with anxiety disorder have shown an increased sensitivity to social (e.g., fearful faces) and non-social (e.g. monetary loss) aversive stimuli. However, few studies have investigated the behavioral and neural correlates associated with avoidance of aversive stimuli, while avoidance behaviour is a specific characteristic of anxiety. The possibility of avoiding an aversive event has shown to be particularly aversive for individuals with anxiety disorder, which has been linked to an increased sensitivity to uncertainty (Salters-Pedneault & Diller, 2013). The EMLI task is the ideal paradigm to specifically test these hypotheses. Our preliminary analysis (Van Dessel et al. in preparation) shows that as a group, children and adolescents with anxiety displayed selective hyperactivation during contingency-related contrasts (CONDITIONAL LOSS AVOIDANCE versus CERTAIN LOSS and CERTAIN LOSS AVOIDANCE) compared to ADHD and controls in regions previously shown to be involved in processing of negatively valenced emotional stimuli and experiences (e.g., amygdala), regions involved in the salience (e.g., anterior insula, midcingulate cortex, ventral striatum, inferior parietal cortex, primary visual cortex) and motor preparation regions (e.g., posterior parietal cortex, thalamus, supplementary motor area). In most of these regions a dose-response relationship was found. These findings indicate that children and adolescents with anxiety react different to contingent performance in comparison to ADHD and controls, and may be more intolerant to the uncertainty of negative events. Future studies are needed to test the potential specificity of brain reactions to these different negative emotional triggers in different disorders, for example in children with conduct disorder for whom could be postulated that they are less sensitive to punishing events.

Environmental factors

Little is known about the role of early environmental factors (such as parenting) on reinforcement deficits in young children, and how their interaction may relate to the development of ADHD. This inconsistency in the literature is remarkable, considering the primary role of parental actions in children's emotional and behavioural development (Masten & Coatsworth, 1998). Negative parenting is a reliable correlate of ADHD and externalizing behaviors in children (Burke, Pardini, & Loeber, 2008; Chamberlain & Patterson, 1995; Kaiser, McBurnett, & Pfiffner, 2011). Parents of children with ADHD are more harsh, critical and less physically involved with their children compared to parents of typically-developing children (Sonuga-Barke & Halperin, 2010).

Previous medication studies have shown that these negative parenting behaviours may be the result of the disruptive behaviours rather than the cause, as the negative parenting diminishes, when the child's symptoms are reduced. However, these behaviors are likely to be reciprocal as well (Harold et al., 2013). In the delay aversion hypothesis, it is postulated that delay aversion develops and exuberates due to negative reactions of parents to the child favoring immediacy of rewards. In this instance, one would expect the aversion to increase, because the children are not able to avoid the behaviour that their parents try to punish and as a result avoidance of delay further develops. Future longitudinal studies are needed to investigate contextual factors (such as parenting) that may influence the processing of reinforcers over development towards negative events such as delay.

Conclusion

This dissertation shows an extensive validation of the Delay Aversion theory with respect to behavioural experiments (**Chapters 2 and 3**), self-assessment of delay aversion (**Chapters 2 and 3**), brain function (**Chapter 3**) and brain structure (**Chapter 4)**. This thesis also provides evidence that the differential aversion of children and adolescents with ADHD compared to typically developing controls is specific to waiting and is not different in reaction to monetary loss (**Chapters 5 and 6**). In addition, it shows that delay aversion is of great importance in ADHD symptomatology and that neurobiological research is essential to study the pathophysiology of ADHD.

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Appendices | Dutch Summary, Personal Contribution, Conflict of Interest, Acknowledgements, About the Author, PhD Portfolio

Dutch Summary

Stel je voor, je bent in de supermarkt en je wil gewoon naar huis om eten te maken, maar je staat in de rij en de persoon voor je doet er erg lang over om met muntstukken te betalen. Het duurt eeuwen en de andere rijen gaan ook maar niet vooruit. We hebben deze hatelijke situatie al allemaal ervaren. Wachten kan soms zo ondraaglijk zijn dat veel mensen honderden euro's willen betalen om wachtrijen te vermijden, of het nu op de luchthaven is, voor een taxirit, of in een pretpark. Ook al hebben we allemaal een hekel aan wachten, deze frustratie gaat niet noodzakelijkerwijs over de *duur* van de wachtperiode. Het is de *manier waarop je het wachten ervaart* die ertoe doet - hoe je denkt over het wachten, en hoe je de tijd doorbrengt.

Volgens het invloedrijke Delay Aversion model ontwikkeld door Prof. Sonuga-Barke, wordt wachten verondersteld bijzonder aversief te zijn voor kinderen en adolescenten met aandachtstekort-hyperactiviteitsstoornis (ADHD), bijvoorbeeld wanneer ze geconfronteerd worden met wachten voorafgaand aan een beloning of bij voltooiing van een taak. ADHD-gerelateerde symptomen zouden gedeeltelijk verklaard kunnen worden door een motivatie om te ontsnappen aan het excessieve negatieve effect dat individuen met ADHD ervaren Hoewel deze hypothesen een decennium geleden werden vooropgesteld is het grootste deel van het internationale onderzoek naar delay aversion voornamelijk gebaseerd op gedragsexperimenten en zijn de neurowetenschappelijke processen zeer zelden bekeken. Het fundamentele doel van dit proefschrift is een coherente validatie van een van de belangrijkste theorieën van ADHD: de “delay aversion” theorie op neurobiologisch niveau (hersenfunctie, hersenstructuur), en op gedragsmatig niveau(psychologische experimenten, en zelfbeoordeling); Met als finaal doel een neurobiologische en gedragsmatige basis te bieden voor de delay aversion dysfunctie bij ADHD.

In **Hoofdstuk 2** werd onderzocht hoe het concept van “waiting impulsivity” bijdraagt aan Delay Aversion theorie bij ADHD. Dertig, 8 tot 12 jaar oude kinderen met ADHD en 30 leeftijd-gekoppelde typisch ontwikkelende kinderen voltooiden de 4-Choice Serial Reaction Time taak, een inhibitie-controletaak en temporele discountingtaak. Vragenlijsten werden afgenomen om de gedragssymptomen, delay aversion en verschillende aspecten van impulsiviteit te evalueren. Een meervoudig logistiek regressiemodel werd gebruikt om de bijdrage van elk van deze individuele

taakparameters te onderzoeken bij het voorspellen van de aanwezigheid van een ADHD diagnose. Kinderen met ADHD vertoonden meer “waiting impulsivity” en minder inhibotorische controle, maar verschilden niet in temporele discountingDe 3 taakparameters waren ongecorreleerd. Waiting impulsivity was gecorreleerd met de door de ouder-gerapporteerde symptomen van hyperactiviteit, impulsiviteit, onoplettendheid, oppositioneel opstandig gedrag, en gedragsstoornis, en met de door het kind zelf-gerapporteerde beoordeling van aversie t.o.v. wachten. Alleen “waiting impulsivity” was een belangrijke voorspeller van de aanwezigheid van een ADHD diagnose. Dit duidt erop dat waiting impulsiviteit verschilt van andere neuropsychologische tekorten en een onafhankelijke bijdrag kan leveren aan de voorspelling van ADHD diagnose

In **Hoofdstuk 3** hebben we de mate van hersenactiviteit (dosis-respons) onderzocht tijdens het anticiperen op wacht-gerelateerde signalen. Hierbij hebben we deze hersenactiviteitspatronen vergeleken met zelf-gerapporteerde delay aversion. Tweeëndertig rechtshandige mannelijke adolescenten met ADHD (gecombineerde beeld) en 36 leeftijd-gekoppelde typisch ontwikkelende kinderen tussen 10 -18 jaar voltooide de revised Escape Delay Incentive-taak onder de fMRI-scanner. Patronen van hersenactivatie binnen het affectieve hersennetwerk werden tijdens de anticipatie vergeleken met drie verschillende wacht-gerelateerde signalen (ZEKER WACHTEN, CONDITIONEEL WACHTEN, NOOIT WACHTEN). De resultaten wezen op het bestaan van delay aversion bij adolescenten met ADHD, zowel op gedragsmatig als op neurobiologisch niveau. Onze voorspellingen werden op vier manieren bevestigd. Ten eerste, individuen met ADHD beoordeelden zichzelf als meer aversief t.o.v. wachten en beoordeelden de waarde van de wacht-gerelateerde stimuli negatiever dan de controles. Ten tweede was er een significante associatie tussen ADHD en wacht-gerelateerde hyperactiviteit in vijf hersengebieden die gekend zijn in de verwerking van emotionele stimuli (amygdala, temporele pool, anterieure insula, ventromediale prefrontale cortex en dorsolaterale prefrontale cortex). Ten derde waren deze effecten meer uitgesproken op trials die gepaard gingen met langere wachttijden (dosis-respons effect). Ten vierde, wacht gerelateerde hersenreacties (neurobiologisch) waren sterk gecorreleerd met zelfratings van de vertragingsafkeer (gedragsmatig).

Teneinde de resultaten van Hoofdstuk 3 optimaal te kunnen interpreteren, hebben we in **Hoofdstuk 4** het verband tussen deze neurofunctionele bevindingen en structurele neuroanatomie bestudeerd. De 60 structurele MRI-scans, verzameld in studie 2, werden structureel geanalyseerd met behulp van Voxel-Based Morphometry technieken. Een verminderde hoeveelheid grijze stof werd gevonden voor de bilaterale amygdala, parahippocampale en temporele gyrus bij de deelnemers met ADHD in vergelijking met de controle deelnemers. Specifieke regio-gebaseerde analyses voor de vijf geactiveerde hersengebieden tijdens de rEDI taak toonde een significante omgekeerde relatie tussen amygdala en delay aversion, en functionele respons.

Om de vraag te beantwoorden of deze aversie geassocieerd met ADHD op gedragsmatig en neurobioloigsch niveau specifiek is voor de negatieve ervaring van wachten, en anders is dan andere negatieve ervaringen hebben we in **Hoofdstuk 5** een nieuwe Escape Monetary Loss Incentive (EMLI)-taak ontworpen naar analogie van de rEDI-taak (hoofdstuk 3 en 4), waarbij het anticiperen op wachten werd vervangen door het anticiperen op mogelijk geld verlies. Vierendertig typisch ontwikkelende adolescenten begonnen met €150 en konden geen extra geld verdienen, maar konden wel voorkomen dat ze geld zouden verliezen, afhankelijk van hun prestaties. De EMLI-taak was in staat om onderscheid te maken tussen hersennetwerken gekoppeld aan prestatie-gerelateerde (CONDITIONEEL VERLIES) en waarde-gerelateerde (ZEKER VERLIES, NOOIT VERLIES) stimulus-verwerking. CONDITIONEEL VERLIES signalen waren motiverend, verbeterden de prestaties en activeerden hersennetwerken gekend voor motivatie en het voorbereiden van een motorische respons. Deze hersenactiviteit was afhankelijk van het bedrag dat mogelijk verloren kon worden (dosisrepons). Stimuli die NOOIT VERLIES signaleerden werden geassocieerd met een hyperactivatie in hersenregio's die de respons op beloningen verwerken ten opzichte van ?. Succesvolle feedback op CONDITIONEEL VERLIES trials activeerden het ventrale striatum meer in vergelijking met feedback bij falen. Dankzij deze bevindingen kan men stellen dat de EMLI taak in staat is om de verschillende processen die belangrijk zijn bij anticipatie en feedback van negatieve bekrachtiging van elkaar te onderscheiden.

In **Hoofdstuk 6** hebben achttien rechtshandige mannelijke kinderen (8-12 jaar) en twintig adolescenten (12-18 jaar) met ADHD de EMLI-taak onder een fMRI-scanner voltooid. In tegenstelling tot de verschillende scores van visuele stimuli in de rEDI-taak (hoofdstuk 3), beoordeelden personen met ADHD de EMLI-cues niet significant anders dan de controles. CONDITIONEEL VERLIES signalen waren opnieuw motiverend, verbeterden de prestaties en activeerden hersennetwerken gekend voor motivatie en het voorbereiden van een motorische respons in gelijke mate bij deelnemers met ADHD en als controle deelnemers. Dit onafhankelijk van de valentie die gepaard gaat met de cue (CERTAIN LOSS AVOIDANCE = positieve valentie;(CERTAIN LOSS = negatieve valentie). Deze resultaten geven aan dat Delay Aversion een neurale handtekening heeft die losstaat van de hersenreacties tijdens andere aversieve ervaringen.

In conclusie toont dit proefschrift een uitgebreide validatie van de Delay Aversion theorie aan met betrekking tot de hersenfunctie (Hoofdstuk 3), hersenstructuur (Hoofdstuk 4), gedragsmatige experimenten (Hoofdstuk 2 en 3), en zelfbeoordeling van aversie ten opzichte van wachten (Hoofdstuk 2 en 3).Tevens geeft deze thesis evidentie dat het aversieve effect van wachten specifiek is voor de activiteit en losstaat van andere negatieve stimuli zoals geld verlies (Hoofdstuk 5 en 6) Daarenboven blijkt uit deze thesis dat delay aversion van groot belang is bij ADHD-symptomatologie en dat neurobiologisch onderzoek essentieel is om de pathofysiologie van ADHD te bestuderen.

Personal Contribution

The work presented in this thesis is the result of several scientific collaborations. Jeroen Van Dessel programmed all fMRI paradigms, scanned all participants, collected all data outside the fMRI scanner, performed all data analyses and manuscript preparation, with several contributors for each chapter as listed below. Prof. dr. Marina Danckaerts, prof. dr. Emund Sonuga-Barke, prof. dr. Saskia Van der Oord and dr. Jurgen Lemiere provided senior mentorship on all articles in this thesis.

Chapter 2:

JVD, SM, SVDO, JL, ESB and MD conceived and designed the study. SM, MM and MG contributed to participant recruitment. JVD, SM, MM and MG collected the data. JVD and SM statistically analysed and interpreted the data. MM and MG contributed to data analysis and all authors discussed the results. JVD and SM drafted the manuscript. SVDO, JL, MM, MG, ESB and MD contributed to the writing of the manuscript, and all authors provided feedback and approved the final version.

Chapter 3:

JVD, SVDO, JL, ESB and MD conceived and designed the study. GM gave additional senior scientific guidance. JVD and JL programmed the paradigm. GM and SM contributed to participant recruitment. JVD, GM, SM collected and preprocessed all data. JVD and GM statistically analysed the data. All authors interpreted and discussed the results. JVD drafted the manuscript. All authors contributed to the writing of the manuscript. All authors provided feedback and approved the final version.

Chapter 4:

JVD, ESB, MM, SVDO, JL, SM and MD conceived and designed the study. MM and SM contributed to participant recruitment. JVD and MM collected and preprocessed all data. JVD and MM statistically analysed the data. All authors interpreted and discussed the results. JVD and MM drafted the manuscript. All authors contributed to the writing of the manuscript. All authors provided feedback and approved the final version.

Chapter 5:

JVD, MD, MM, SVDO, SM, JL and ESB conceived and designed the study. JVD and MM programmed the paradigm. MM and SM contributed to participant recruitment. JVD and MM collected and preprocessed all data. JVD and MM statistically analysed the data. All authors interpreted and discussed the results. JVD and ESB drafted the manuscript. All authors contributed to the writing of the manuscript. All authors provided feedback and approved the final version.

Chapter 6:

JVD, ESB, MM, SVDO, SM, JL and MD conceived and designed the study. MM and SM contributed to participant recruitment. JVD and MM collected and preprocessed all data. JVD and MM statistically analysed the data. All authors interpreted and discussed the results. JVD drafted the manuscript and all authors contributed to the writing of the manuscript. All authors provided feedback and approved the final version.

Conflict of Interest Statement

JVD, MM, GM, SM, MG, JL have no disclosures. SVDO was a paid speaker (Shire, MEDICE) and consultant (Janssen Cilag), co-developer of a cognitive training game "Brain game Brian" and two cognitive-behavioral treatments "Plan my Life" and "Solution Focused Treatment"(non-financial). ESB received speaker fees, research funding, and conference support from and has served as consultant to Shire Pharma and received speaker fees from Janssen-Cilag. He served as consultant to Neurotech Solutions, Aarhus University, Copenhagen University and Berhanderling, Skolerne, Copenhagen and KU Leuven. He has received royalties from Oxford University Press and Jessica Kingsley. MD was a paid member of advisory boards for Shire and Neurotech Solutions, a paid speaker at conferences supported by Shire, Novartis, Medice, and a consultant for Neurotech Solutions.

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Jeroen,
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About the Author

Jeroen Van Dessel was born on November 5th 1988 in Bonheiden, Belgium. His passion for scientific research became clear after completing his Bachelor Biomedical Sciences at the KU Leuven in 2009. Subsequently, he enrolled in the Master's program Biomedical Sciences Research and completed his master thesis "Radiographic analyses on peri-implentair bone subjected to various implant protocols" under the supervision of prof. dr. R. Jacobs in OMFS-IMPATH at KU Leuven, in collaboration with Hasselt University (Hasselt, Belgium) in 2012. During his master thesis, Jeroen was a visiting researcher at the University of São Paulo (Bauru, Brazil) and Pontifical Catholic University of Paraná (Curitiba, Brazil). Thanks to his passion for radiology, he completed the postgraduate Advanced Medical Imaging at the KU Leuven in 2013. He was invited by the University of São Paulo to perform his postgraduate internship titled "A comparative evaluation of cone-beam computed tomography and micro-CT on trabecular bone structures in human mandibles". After graduating, he became ombudsman of the postgraduate Advance Medical Imaging and started teaching in medical imaging-related topics. In 2012, he started a PhD position at the Center for Developmental Psychiatry under supervision of prof. dr. M. Danckaerts, prof. dr. S. Van der Oord, dr. J. Lemiere, and prof. dr. E. Sonuga-Barke, one of the world authorities in ADHD research and founder of Delay Aversion theory. During his PhD, he obtained a personal FWO-doctoral scholarship in 2014, which allowed him to extend his neuroimaging research for two more years. From the start of his PhD, Jeroen committed himself as PhD and post-doc representative in the Department of Neurosciences. His PhD research has been honored with the EUNETHYDIS Sagvolden Award (2015), a FWO travel grant (2018) and ECNP Junior Research Award (2018). Throughout his PhD in the psychiatry domain, he remained active in the oral radiology field as a researcher at the OMFS-IMPATH research group. For this research he received the COB Oral Research award (2013), EADMFR Oral Research Award (2012; 2014), the EADMFR Research Fellowship (2016) and EADMFR Poster Research Award (2018). Thanks to the support of the EADMFR association, he was able to complete a research internship at Karolinska Institute (Stockholm, Sweden). Currently he works as clinical support and research manager at the department of Oral & MaxilloFacial Surgery, UZ Leuven and coordinates the Institute for MaxilloFacial Training and Education (IOMFCOT).

PhD Portfolio

Journal Articles

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Van Dessel, J., Huang, Y., Depypere, M., Rubira-Bullen, I., Maes, F., & Jacobs, R. (2013). A comparative evaluation of cone beam CT and micro-CT on trabecular bone structures in the human mandible. *Dentomaxillofacial Radiology*, 42, 20130145. https://doi.org/10.1259/dmfr.20130145. [IF: 1.15 (2012); ranked 46/83 (dentistry, oral surgery & medicine)]

Huang, Y., **Van Dessel, J.**, Liang, X., Depypere, M., Zhong, W., Ma, G., Lambrichts, I., Maes, F., & Jacobs, R. (2013). Effect of immediate and delayed loading on peri-implant trabecular structures: a cone-beam CT evaluation. *Clinical Implant Dentistry and Related Research*; 16:873-83. https://doi.org/10.1111/cid.12063. [IF: 3.82 (2013); ranked 3/83 (dentistry, oral surgery & medicine)]

Conference abstracts and proceedings (first author only)

Van Dessel, J., Beckers, S., Moerkerke, M., Sonuga-Bark, E., Morsink, S., Van der Oord, S., Lemiere, J., Sijmons, H., & Danckaerts, M. (2020). How the emotional brain responds to impending monetary loss: common and distinct elements between ADHD and anxiety disorder. Neuronus, IBRO Neuroscience, Krakow, Poland. [ORAL PRESENTATION]

Van Dessel, J, Nicolielo, L. F. P., Stratis, A., Ma, H., Benchimol, D., Lambrichts, I., Politis, C., & Jacobs, R. (2019). Does low dose provide sufficient quality? Optimization of CBCT scanning protocols for volumetric analysis of tooth extraction sockets. Swedental, Stockholm, Sweden. [ORAL PRESENTATION]

Van Dessel, J., Moerkerke, M., Sonuga-Barke, E., Van der Oord, S., Lemiere, J., & Danckaerts, M. (2018). Distinctive neural response towards certain and conditional monetary loss in adolescents with attention-deficit hyperactivity disorder. 31st European College of Neuropsychopharmacology Conference, Barcelona, Spain. [INVIDED ORAL PRESENTATION]

Van Dessel, J., Moerkerke, M., Sonuga-Barke; E., Van der Oord, S., Lemiere, J., & Danckaerts, M. (2018). Distinctive neural response towards certain and conditional monetary loss in adolescents with attention-deficit hyperactivity disorder. ECNP Workshop for Junior Scientists in Europe, Nice, France. [WINNER BEST JUNIOR ECNP RESEARCH]

Van Dessel, J., Nicolielo, L. F. P, Stratis, A, Benchimol, D., Lambrichts, I., & Jacobs, R. (2018). Validation and optimization of CBCT scanning protocols for volumetric analysis of extraction sockets. 16th European Congress of DentoMaxilloFacial Radiology, Luzern, Switzerland. [FIRST PLACE POSTER AWARD]

Van Dessel, J., Moerkerke, M., Sonuga-Barke, E., Van der Oord, S., Lemiere, J., & Danckaerts, M. (2018). Developmental changes in affective response towards monetary loss in children and adolescents with attention-deficit/hyperactivity disorder. Neuronus, IBRO Neuroscience Forum, Krakow, Poland. [ORAL PRESENTATION]

Van Dessel, J., Moerkerke, M., Sonuga-Barke, E., Lemiere, J., Van der Oord, S., & Danckaerts, M. (2018). Distinctive neural response towards certain and conditional monetary loss anticipation in adolescents. 46th Annual Meeting of the International Neuropsychological Society, Washington DC, USA. [ORAL PRESENTATION]

Van Dessel, J., Moerkerke, M., Sonuga-Barke E, Lemiere, J., Van der Oord, S., & Danckaerts, M. (2018). Role of the amygdala in ADHD: structural and functional correlates of delay aversion. 46th Annual Meeting of the International Neuropsychological Society, Washington DC, USA. [POSTER PRESENTATION]

Van Dessel, J., Moerkerke, M., Sonuga-Barke, E., Lemiere, J., Van der Oord, S., Danckaerts, M. (2017). Role of the amygdala in ADHD: structural and functional correlates of delay aversion. 10th Donders Discussions of Radboud University, Nijmegen. [POSTER PRESENTATION]

Van Dessel, J., Sonuga-Barke, E., Moerkerke, M., Gabry, M., Van der Oord, S., Lemiere, J., Morsink, S, & Danckaerts, M. (2017). Negative emotions in ADHD: What are you waiting for? 10th Donders Discussions of Radboud University, Nijmegen. [INVITED ORAL PRESENTATION]

Van Dessel, J., Moerkerke, M., Sonuga-Barke, E., Lemiere, J., Van der Oord S, Danckaerts M. (2017). Role of the amygdala in ADHD: structural and functional correlates of delay aversion. 10th Donders Discussions of Radboud University, Nijmegen. [POSTER PRESENTATION]

Van Dessel, J., Moerkerke, M., Sonuga-Barke, E., Lemiere, J., Van der Oord, S., & Danckaerts, M. (2017). Understanding the role of the amygdala in attention-deficit/hyperactivity disorder: association between brain structure, function and delay aversion. 30th European College of Neuropsychopharmacology Congress, Paris, France. [POSTER PRESENTATION]

Van Dessel, J., Temmerman, A., Castro, A. B., Van de Casteele, E., Quirynen, M., & Jacobs, R. (2016). Bone quality evaluation of L-PRF induced bone growth using micro-CT. 1st European Meeting on Enhanced Natural Healing in Dentistry, Leuven, Belgium. [ORAL PRESENTATION]

Van Dessel, J., Nicolielo, L. F. P., El Maharoui, O., van Lenthe, H., & Jacobs, R. (2016). Accuracy of three-dimensional finite element modelling of trabecular and cortical bone structures using cone-beam computed tomography. 15th European Congress of DentoMaxilloFacial Radiology, Cardiff, Wales. [POSTER PRESENTATION]

Van Dessel, J., Morsink, S., Mies, G., Lemiere, J., Van der Oord, S., Sonuga-Barke, E., & Danckaerts, M. (2015). Delay aversion in ADHD is mediated by amygdala hypersensitivity. 24th Network Meeting of the European Network of Hyperkinetic Disorders, Stockholm, Sweden. [WINNER SAGVOLDEN AWARD]

Van Dessel, J., Temmerman, A., Van de Casteele, E., Castro, A. B., Quirynen, M., & Jacobs, R. (2015). Objective 3D quantification of socket preservation treatment strategies using L-PRF: A spit mouth randomized control trail. European Association for Osseointegration congress, Stockholm, Sweden. [POSTER PRESENTATION]

Van Dessel, J., Morsink, S., Mies, G., Tofec, L., Lemiere, J., Van der Oord, S., Sonuga-Barke, E., & Danckaerts, M. (2015). Neural correlates of delay aversion in ADHD. 3rd Annual Flux Congress, Leiden, the Netherlands. [POSTER PRESENTATION]

Van Dessel, J., Morsink, S., Mies, G., Tofec, L., Lemiere, J., Van der Oord, S., Sonuga-Barke, E., & Danckaerts, M. (2015). Neurobiological evidence for delay aversion underlying impulsive choice in ADHD. International Society for Research on Impulsivity, Amsterdam, the Netherlands. [ORAL PRESENTATION]

Van Dessel, J., Morsink, S., Mies, G., Lemiere, J., Van der Oord, S., Sonuga-Barke, E., & Danckaerts, M. (2015). The neural underpinnings of delay aversion in ADHD. Symposium Pick your brain on ADHD, Meeting of the Belgian Association for Psychological Science, Brussels, Belgium. [ORAL PRESENTATION]

Van Dessel, J., Machkour, S., Mies, G., Lemiere, J., Van der Oord, S., Sonuga-Barke, E., & Danckaerts, M. (2015). Altered reward processing in adolescents with ADHD compared to control participants. Meeting of the Belgian Association for Psychological Science, Brussels, Belgium. [POSTER PRESENTATION]

Van Dessel, J., Van de Casteele, E., Temmerman, A., Quirynen, M., & Jacobs, R. (2015). Micro-CT evaluation of PRF induced bone growth. Micro-CT User Meeting, Brugge, Belgium. [ORAL PRESENTATION]

Van Dessel, J. (2014). Automatic image analysis of digital images in the dental practice. 1th Encontro Paranaense de Radiologia Odontológica, Curitiba, Brazil. [KEYNOTE PRESENTATION]

Van Dessel, J. (2014). Post-processing of digital images in the dental practice. 19th Jornada da Associacao Brasileira de Radiologia Odontológica, Vitoria, Brazil. [KEYNOTE PRESENTATION]

Van Dessel, J., Morsink, S., Lemiere, J., Van der Oord, S., Sonuga-Barke, E., & Danckaerts, M. (2014). Altered lymbic system and default mode network response during delay anticipation vs. experience in ADHD. BCNBP-VVP Research in Psychiatry, Duffel, Belgium. [FINALIST HUGO D'HAENEN AWARD]

Van Dessel, J., Huang, Y., Nicolielo, L. F. P., Slagmolen, P., & Jacobs, R. (2014) Accuracy of different cone-beam CT devices for trabecular bone structure analysis: an in vitro study. 14th European Congress of DentoMaxilloFacial Radiology, Cluj-Napoca, Romania. [FIRST PLACE ORAL RESEARCH AWARD]

Van Dessel, J., Morsink, S., Lemiere, J., Van der Oord, S., Sonuga-Barke, E., & Danckaerts, M. (2014) Altered lymbic system and Default Mode Network response during delay anticipation vs. experience in ADHD. Meeting of the Belgian Association for Psychological Science, Leuven, Belgium. [POSTER PRESENTATION]

Van Dessel, J., Lemiere, J., Van der Oord, S., Sonuga-Barke, E., & Danckaerts, M. (2014). Limbic system response during experience of delay. 3rd Junior EUNETHYDIS conference on ADHD, Istanbul, Turkey. [POSTER PRESENTATION]

Van Dessel, J., Huang, Y., Nicolielo, L. F. P., Slagmolen, P., & Jacobs, R. (2014). Accuracy of different cone-beam CT devices for trabecular bone structure analysis: an in vitro study. 1st European Congress of DentoMaxilloFacial Radiology Junior meeting, Umea, Sweden. [ORAL PRESENTATION]

Van Dessel, J., Lemiere, J., Van der Oord, S., Sonuga-Barke, E., & Danckaerts, M. (2013). The neural signature of delay aversion in ADHD. 23rd Network Meeting of the European Network of Hyperkinetic Disorders, Prague, Czech Republic. [POSTER PRESENTATION]

Van Dessel, J., Lemiere, J., Van der Oord, S., Sonuga-Barke, E., & Danckaerts, M. (2013). De neurale handtekening van Delay Aversion: nieuw bewijs vanuit de beeldvorming. 9th Vlaams Congres Kinder- en Jeugdpsychiatrie en –psychotherapie, Antwerpen, Belgium. [ORAL PRESENTATION]

Van Dessel, J., Huang, Y., Depypere, M., Rubira-Bullen, I., Maes, F., & Jacobs R. (2013). A comparative evaluation of cone-beam computed tomography (CBCT) and micro-CT on trabecular bone structures in human mandible. 19th International Congress of DentoMaxilloFacial Radiology, Bergen, Norway. [FINALIST IADMFR MAXILLOFACIAL IMAGING RESEARCH AWARD]

Van Dessel, J., Lemiere, J., Van der Oord, S., Sonuga-Barke, E., & Danckaerts, M. (2013). Delay Aversion in attention deficit hyperactivity disorder: exploring dose-response relationships between amount of delay and amygdala/insula activation. 18th Scientific meeting of the International Society for Research on Child and Adolescent Psychopathology, Leuven, Belgium. [POSTER PRESENTATION]

Van Dessel, J., Huang, Y., Rubira-Bullen, I., Depypere, M., Nicolielo, L. F. P., Maes, F., Duarte, M. A. H., & Jacobs, R. (2013). Clinical applicability of trabecular bone structure evaluation using Cone-Beam Computed Tomography. 26th Congresso Odontológico de Bauru (COB), Bauru, Brazil. [FIRST PRICE IN THE ORAL RESEARCH AWARD]

Van Dessel, J., Huang, Y., Zhong, W., Depypere, M., Kou, N., Ma, G., Liang, X., Lambrichts, I., Maes, F., & Jacobs, R. (2012). Radiographic analysis on peri-implant bone subjected to various implant protocols. 13th European Congress of DentoMaxilloFacial Radiology, Leipzig, Germany. [SECOND PLACE IN ORAL AWARD]

Teaching

- Lecturer in Hot Topics in Medical Imaging II (E05N2A, KU Leuven)
- Lecturer in Topics in Maxillofacial Surgery (E07M2A, KU Leuven)
- Guest lecture “Image analysis for dentomaxillofacial applications” (Chulalongkorn University, Bangkok, Thailand)
- Guest lecture “Image analysis for dentomaxillofacial applications” (University of São Paulo, Bauru, Brazil)
- Guest lecture “Open-source imaging processing software for radiological images” (University of São Paulo, Bauru, Brazil)
- Guest lecture “Processing of digital images in the dental practice” (Federal University of Paraná, Curitiba, Brazil)
- Guest lecture “MRI applications: future in dental research?” (Karolinska Institutet, Stockholm, Sweden)
- Guest lecture “Image analysis for dentomaxillofacial applications” (Karolinska Institutet, Stockholm, Sweden)

Additional Degrees and Education

- Matlab (KU Leuven)
- Technology transfer and exploitation of research (KU Leuven)
- Inter-university program on the use of Cone-Beam CT for DMFR applications (KU Leuven)
- Certificate of handling laboratory animals (KU Leuven)
- Scientific integrity (KU Leuven)
- Practical data analysis and modelling in cognitive and clinical neuroscience (Ghent University)
- Statistical parametric mapping (University of Lausanne, Switzerland)
- Biomedical imaging (University of Queensland, Australia)
- Programming for everybody (Python) (Michigan University, USA)
- Statistical analysis of fMRI data (Johns Hopkins University, USA)
- Medical neuroscience (Dukes University, USA)
- Machine learning (Stanford University, USA)

Supervision of Master Theses

- Biomedical Sciences master thesis: 4
- Psychology master thesis: 1
- Educational Sciences master thesis: 1
- Postgraduate in Advanced Medical Imaging thesis: 1
- Biomechanical Engineering master thesis: 1
- Dentistry master thesis: 6
- Speech Therapy master thesis: 5
- Oral & Maxillofacial residents: 6
- International visiting students: 11

Membership

- Board Member in the European Academy for DMFR (2018- …)
- Ombuds Postgraduate in Advanced Medical Imaging (2013 – …)
- PhD & Post-doc representative in the department of Neuroscience (2013 – 2018)

International Research Stays

- University of São Paulo, Bauru, Brazil, under invitation of Prof. dr. Rubira-Bullen (September 2018)
- Karolinska Institute, Stockholm, Sweden, under invitation of dr. Prof. Benchimol (December 2016 – February 2017)
- Paris Descartes University, Paris, France, under invitation of Prof. dr. Salmon (June 2015)
- Chulalongkorn University, Bangkok, Thailand, under invitation of Prof. dr. Panmekiate and Prof. dr. Pittayapat (Research visit 6/05/2015 – 9/05/2015)
- University of São Paulo, Bauru, Brazil, under invitation of Prof. dr. Rubira-Bullen (October – November 2014)
- University of São Paulo, Bauru, Brazil, under invitation of Prof. dr. Rubira-Bullen (April – May 2013; July – September 2012)
- Pontifical University Catholic of Paraná, Curitiba, Brazil, under invitation of Prof. dr. Couto Souza (November – December 2011)
- University of São Paulo, Bauru, Brazil, under invitation of Prof. dr. Rubira-Bullen (September – October 2011)

Scientific Awards

Personal Doctoral Scholarship, 2014 - 2018

FWO Travel Grant, 2018

Sagvolden Award, 2015

Broaden Your Horizon Conference Grant, 2014

International Cooperation Latin America Fund, 2016

Finalist in Hugo D'Haenen Award, 2014

2th in Oral Research Award, 2012

EADMFR Travel Grant, 2012

1th in Oral Research Award 2014

Finalist Oral Research Award, 2016

1th EADMFR Research Fellowship, 2016

1th in Oral Research Award, 2013

Finalist Basic Research Award, 2012

Finalist Basic Research Award, 2013

Junior EADMFR Representative, 2014

Finalist Maxillofacial Imaging Research Award, 2013

Finalist Best Talk, 2017

Best Article JOE; Clinical Research, 2016

ECNP Junior Research Award, 2018

OMFS-IMPATH Young Talent Award, 2019

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