Brain activation to cues predicting inescapable delay in adolescent Attention Deficit/Hyperactivity Disorder: An fMRI pilot study.

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Abstract

Background: The choice of small immediate over large delayed rewards (i.e., impulsive choice) is a signal marker of motivational style in Attention Deficit/Hyperactivity Disorder (ADHD). The delay aversion model proposes that, in part, this is a conditioned delay avoidance response. Here we test the prediction derived from this model that, in ADHD, cues predicting inescapable delay differentially activate brain regions shown previously to be responsive to motivationally salient, negatively valanced environmental events.

Methods: Ten adolescents with ADHD and 10 age matched controls performed a simple speeded reaction time task under two conditions. On *Escape Delay* trials slow responses only were punished by the imposition of post-response delay periods. On *No Escape Delay* trials post-response delay occurred on all trials irrespective of response speed. Using functional Magnetic Resonance Imaging (fMRI) BOLD responses were acquired to compare anticipatory brain activation following the two cue types. ROI analyses found significant ADHD-related hyperactivation following *No Escape* compared to *Escape Delay* trial cues in the insula, amygdala, ventral striatum and orbito-frontal cortex.

Conclusion: The results of this pilot study provides further evidence for the role of altered motivational systems in ADHD and the most direct evidence for a biological basis of delay aversion.

Keywords; ADHD; Delay Aversion; fMRI; Amygdala; Insula; ventral striatum; orbitofrontal cortex; Escape Delay Incentive task.

1. Introduction

Attention Deficit/Hyperactivity Disorder (ADHD) is a common and debilitating condition marked by persistent and pervasive patterns of inattention, overactivity and impulsiveness that affect individuals across the lifespan (Taylor & Sonuga-Barke, 2008). There is a growing and fairly consistent body of evidence that maladaptive inter-temporal choices (i.e., preference for small earlier over larger later rewards), represent an important marker of ADHD-related impulsiveness (Scheres et al., 2010; Sonuga-Barke et al., 2008). A meta-analysis reported case-control difference of moderate effect size on simple choice delay tasks in 10 studies published up to 2007 (Willcutt et al., 2008). More recent studies have confirmed these effects (Gupta et al., 2011) across the life span: preschoolers (Wilson et al., 2011), adolescents (Marco et al., 2009) and adults (Marx et al., 2010).

A number of models have been proposed to explain impulsive choice in ADHD (Sagvolden et al., 2005; Sonuga-Barke et al., 2010; Tripp & Wickens, 2008). First, there are those accounts that focus on the way that the subjective value of rewards diminishes as they are moved through time into the future; so called temporal reinforcement discounting (Frederick et al., 2002). In normal individuals such discounting is thought to follow a quasi-hyperbolic function so that preference between two rewards reverses as one reward is moved into the future (Killeen, 2011). According to this model, impulsive choice occurs in ADHD because

affected individuals discount the future at a higher rate so that choice performance is characterised by a steeper delay discounting function (Barkley et al., 2001; Scheres et al., 2010). At the neurobiological level steeper discounting in ADHD has been argued to result from attenuation of the dopamine signal to delayed rewards in the brain's reward centres (Sagvolden et al., 2005) or a failure of anticipatory dopamine cell firing (Tripp et al., 2008). ADHD-related ventral striatal hyporesponsiveness during delayed rewards is consistent with this view (Plichta et al., 2009). A second class of accounts proposes that impulsive choice in ADHD is the result of a breakdown in higher order control whereby an affected individual is unable to suppress the drive to respond to the immediate option and so resist temptation (Barkley et al., 2001). According to this model impulsive choice is a specific expression of a general deficit in inhibitory-based executive dysfunction in ADHD which also affects functions such as working memory, planning and set shifting (Barkley & Murphy, 2011). Fronto-striatal circuits (e.g. dorso-lateral prefrontal and dorsal striatum and associated regions) which modulate executive functions and have been shown to be implicated in choices of large delayed rewards (McClure et al., 2004; McClure et al., 2007) are disrupted in ADHD (Durston et al., 2011).

The delay aversion model, offers a third and different perspective on impulsive choice in ADHD. It is based on the idea that, for ADHD patients delay is an aversive experience in and of itself, eliciting a negative affective state, which ADHD children work to

escape or avoid (Sonuga-Barke, 1994; Sonuga-Barke et al., 2004). In this account choice of the small immediate reward is reinforcing because it allows the escape from delay associated with the large delayed outcomes and the subsequent avoidance of the negative affective state. The most recent account sees delay aversion acting in concert with processes such as steeper temporal discounting and an impulsive drive for immediate rewards to exacerbate impulsive choice (Marco et al., 2009; Sonuga-Barke et al., 2010) in ADHD. The delay aversion hypothesis makes predictions about the differential impact of delay on brain function that separates it from the other two accounts of impulsive choice. Most directly, if ADHD children find delay especially aversive they should show a relative hyper-activation of those brain regions implicated in processing of motivationally salient aversive events, when presented with a situation where one cannot escape delay (inescapable delay).

The two brain regions that have been most consistently shown to be activated by the prospect of contingent aversive events in human imaging studies are the amygdala and insula. The amygdala is a core limbic system structure with extensive and reciprocal connections to higher pre-frontal cortex and lower ventral striatum brain centres (Cardinal et al., 2002). In particular the basolateral amygdala is involved in the processing and representation of cue salience and valence that underpin conditioning (Kim et al., 2011). Most studies have focused on its role in processing negative stimuli (Carretie et al., 2009):

including cues signalling aversive events (Iidaka et al., 2010), responses to physical and social threats (Staugaard, 2010), fear-generating stimuli (Sehlmeyer et al., 2009) and punishment (Hahn et al., 2010). Amygdala dysfunction is implicated in accounts of mood disorders where inappropriate perception and response to aversive and threatening stimuli seems core (Elliott et al., 2011). However, the amygdala has also been implicated in the regulation of responses to positive or rewarding stimuli (Bermudez & Schultz, 2010) suggesting a broader role in motivational control (Tye et al., 2008). With regard to ADHD, recent studies have reported smaller amygdala volumes in children (Sasayama et al., 2010; Frodl et al., 2010). There are also reports of altered amygdala functioning during perception of emotional faces (Brotman et al., 2010) and the suggestion that these may be linked to emotional dysregulation (Herrmann et al., 2010). Crucially, for the present study, Plichta et al. (2009) found significant hyper-activation of the amygdala in ADHD individuals when confronted with choices with delayed outcomes. The insula is a cortical structure folded within the lateral sulcus lying between the temporal and the frontal lobe. It plays a key role in the subjective appreciation of physical pain, especially located in the posterior portion of the insula (Isnard et al., 2011) and empathy for pain in others, modulated by the anterior portion (Gu et al., 2010). The anterior insula plays a key role in visceral representation and emotional awareness (Nieuwenhuys, 2012). The insula has also been identified as having a role in punishment

learning (Wachter et al., 2009; Hester et al., 2010) and the regulation of attention to aversive emotional cues (Straube & Miltner, 2011), especially disgust (Deen et al., 2011). Altered insula activation is seen in individuals with anxiety disorders (Shah et al., 2009) and phobias (Rosso et al., 2010). Insula dysfunction has been implicated in ADHD across a number of domains including error processing (Spinelli et al., 2011), loss avoidance (Stoy et al., 2011) and sensori-motor timing (Valera et al., 2010).

The first aim of this study was to employ a region of interest (ROI) approach to *test* the strong prediction that ADHD children will activate the insula and amygdala more than controls when faced with the prospect of inescapable, as opposed to escapable, delay. The second aim of the paper was to *explore* activations to cues of inescapable delay in two other brain regions heavily implicated in the regulation of response to motivationally salient events. The ventral striatum is known to be involved in reward processing and is activated by cues of impending rewards (Knutson et al., 2001). Its role in the anticipation of aversive stimuli remains unresolved with mixed results from imaging studies (Jensen et al., 2003; Knutson & Greer, 2008). The orbito-frontal cortex is involved in coding reinforcer value and guiding decision making between different outcomes (Kennerley & Walton, 2011). A specific role for OFC in relation to aversive events remains uncertain (Ursu & Carter, 2009).

2. Results

The ADHD and control groups did not differ on hit rate while performing the task. For the escape condition the average success rate was 62% and for the no-escape condition 63% ($F(1,18)=0.216$, $p=0.647$). No significant difference between RT escape hits versus RT no-escape hits ($F(1,18)=1.41$, $p=0.251$) or interaction effect (escape versus group) was found ($F(1,18)=0.852$, $p=0.368$).

ROI analysis was performed for the amygdala, insula, ventral striatum and orbito-frontal cortex. In Table 2, the uncorrected, as well as small volume FWE corrected p-values are reported for the comparison - "*No Escape Delay* > *Escape Delay*" for brain activation for ADHD versus controls in these regions. Figure 2 presents bar charts of the most significant voxel to demonstrate the difference in "*No Escape Delay* > *Escape Delay*" brain activation in the control subjects and patients with ADHD in these hypothesized ROIs. For all regions bilaterally the pattern of results was similar with greater increases in activations associated with inescapable delay in ADHD compared to control patients. Most of these effects (except for left amygdala and right orbito-frontal cortex) remained significant after multiple comparison correction for the number of tested regions. Correlations between IQ and activations in the overall group were substantial for two ROIs: left ventral striatum (spearman rho -0.54, $p=0.021$) and left OFC (spearman rho -0.66, $p=0.025$). For these two regions IQ was entered as covariate. This reduced the significance of FWE-corrected case-control differences in

activations which nevertheless remained significant for the left orbito-frontal cortex (FWE-corrected p-value of 0.043).

Figure 2

Figure 3

Table 2

3. Discussion

Impulsive choice is a core characteristic of ADHD (Marco et al., 2009). The delay aversion model proposes that the choice of immediate over delay rewards characteristic of ADHD inter-temporal choice is driven in part by the desire to escape delay in order to avoid the negative affective states which it elicits (Sonuga-Barke et al., 2010). Our goal in the current study was to begin to test a number of predictions about the neuro-biological mediators of this aversion to delay in ADHD using fMRI. On the basis of the literature on neural correlates of the processing of aversive stimuli we identified the amygdala and insula as our primary ROIs. More specifically we predicted hyper-activation in these regions in response to cues of inescapable delay in ADHD patients compared to controls. These predictions were confirmed by our pilot findings with patients showing greater activation to cues of inescapable delay compared to escapable delay in the insula and

amygdala, while in general controls showed a pattern in the opposite direction.

These results are significant in a number of ways. First, they provide a preliminary neuro-biological perspective to the large and growing behavioural literature supporting a hypersensitivity to delay across different tasks and settings as a core characteristic of ADHD (Bitsakou et al., 2009). While research often focuses on inter-temporal choice settings (where ADHD individuals can choose the more immediate reward to reduce delay) for evidence in this regard (Willcutt et al., 2008) delay has been shown to impact on performance in non-choice settings as well (Bitsakou et al., 2009). For instance, ADHD children seem unusually sensitive to changes in inter-stimulus-interval on information processing tasks with differentially poorer performance on slow event rate tasks (Andreou et al., 2007). The current research provides an interesting perspective on these event rate effects suggesting, for instance, the interesting hypothesis that the RT performance of ADHD patients may deteriorate on trials with longer ISIs, because of competing patterns of activation in emotion centres elicited by an aversion to the delay associated with the longer event rates.

Second, they provide further initial evidence implicating the emotion centres of the brain in core psychological features of ADHD pathophysiology. The vast majority of functional imaging studies to date have focused on tasks designed to tap, so called, cool cognitive control mechanisms (Konrad & Eickhoff, 2010). These

studies have provided convincing evidence of deficits in broad-based brain networks involved in cognitive control mechanisms (Bush, 2011). The current study can be seen as part of a movement to focus on brain circuits involved in so called "hot" emotion and reward processing mechanisms (Castellanos et al., 2005; Durston et al., 2011). There are two strands to this work. First, there are those studies that focus on reward processing deficits in ADHD which seek to extend our understanding of reinforcement learning deficits in ADHD (Luman et al., 2011). So for instance, a number of studies have identified patterns of hypo-activation in the ventral striatum during the anticipation of rewards (Scheres et al., 2007; Strohle et al., 2008). Interestingly we also found evidence of ADHD-related alterations in activation in both the ventral striatum and the orbito-frontal cortex in the current study. We found delay-cue related hyperactivation while the studies of Scheres et al. (2007) and Strohle et al. (2008) found reward-cue related hypoactivation in these structures. Such findings would be consistent with the view that these brain regions are involved in processing stimulus salience rather than positive or negative valence per se (Horvitz, 2000; Zink et al., 2003; Nitschke et al., 2006).

From this perspective the current results favour the notion that altered reinforcement processing in ADHD in part may implicate qualitative difference in what constitutes reinforcement and punishment to individual children (i.e., the outcomes they will work to gain or to avoid) as well as quantitative deficits in

sensitivity to reinforcement more generally (Sonuga-Barke, 2011). A parsimonious account of the results of this study and that of the reward anticipation studies, if replicated (e.g. (Scheres et al., 2007) is that children with ADHD differentially process the anticipation of monetary incentives or delay exposure than control children. In this regard it would be interesting to include a direct comparison of the punishing effects of monetary loss and delay imposition in future studies.

The second strand of research, is linked to a renewed interest in emotional dysregulation (Sobanski et al., 2010) as a clinical feature of ADHD and the overlap between ADHD and paediatric severe mood disorders (Donfrancesco et al., 2011). This has focused interest on amygdala and insula dysfunction in ADHD with recent studies reporting structural (Sasayama et al., 2010) and functional alterations in the amygdala (Brotman et al., 2010; Herrmann et al., 2010). Additionally, a PET study with adults with ADHD demonstrated some preliminary evidence that dopamine abnormalities are present in the amygdala (Volkow et al., 2007). The finding closest to that of the current study were reported by Plichta et al. (2009), who found that ADHD was associated with an increased amygdala activation in the face of delayed outcomes. Functional alterations associated with ADHD in the insula have also been identified (Valera et al., 2010). The current study in a sense straddle this reward and emotion regulation literature by linking hypothesized alterations in the emotional valance of delay to motivated responding in ADHD.

How can we reconcile the numerous studies that highlight dysregulation in brain circuits controlling higher order executive processes with those, such as the current one, implicating "bottom up" processes mediated by circuits regulating emotional and motivational processes within models of ADHD? There are a number of possibilities. First, there are those models that highlight the links between these two aspects of brain function (Nigg & Casey, 2005) – indeed it is clear that there is a dynamic interplay between executive and reward circuits which have intimate structural and functional links through cascading circuits within key regions interconnected in the basal ganglia (Haber & Calzavara, 2009). At the same time, it is becoming increasingly clear that ADHD is a neuropsychologically heterogeneous disorder where not all children are affected to the same degree by deficits in motivational and cognitive circuits (Durston et al., 2011). For instance, for some patients deficits in executive circuits may predominate (ADHD will be essentially a disorder of top-down control) while for others deficits in reward and/or emotion processing circuits may be more characteristic. Recently, two similar models suggested three proto-type deficit ADHD subgroups may exist, characterised by altered processes linked to executive function, a reward-related processing and timing (Sonuga-Barke et al., 2010).

Focusing attention on the amygdala's response to the aversive properties of delay for children with ADHD highlights the putative role of serotonin, a key regulator of amygdala function, in the

pathophysiology of emotional regulation and impulsiveness in ADHD (Novkovic et al., 2009; Novkovic et al., 2009). In this regard there has been an increasing focus on the role of the 5HT transporter gene, encoded by genetic locus *SLC6A4* (chromosome 17q11.2), a key regulator of serotonin function in the amygdala, in ADHD. This gene has been especially closely linked to impulsiveness and aggression in ADHD and related conditions (Aluja et al., 2009; Oades et al., 2008). Our own recent study showed that variations in this gene also predicted variations in impulsive choice in ADHD patients (Sonuga-Barke, 2011). The results of Zepf et al. (2010) - demonstrating that ADHD children with comorbid anxious-depression and/or aggression were sensitive to tryptophan depletion - highlights the possibility that a delay averse sub-group might be more likely to have these comorbidities.

There is growing evidence that the insula plays a crucial role in the interoceptive representation of one's affective state and the conscious perception of affective feelings (Craig, 2003; Craig, 2009; Critchley et al., 2004). An ascending sensory pathway of interoceptive signals, such as heart beat, vasomotor flush and pain terminates in the insula and activation of the insula correlates with subjective feelings from the body. Interestingly the involvement of the insula during decision making has been demonstrated in a PET-study in adult ADHD patients (Ernst et al., 2003). Neuroimaging studies of the last decade have consistently demonstrated that the insula is an important neural focus for aversive anticipation (Nitschke et al., 2006; Phelps et al., 2001;

Simmons et al., 2004; Simmons et al., 2006; Dalton et al., 2005; Onoda et al., 2008; Waugh et al., 2008). Some recent studies provide evidence for an amygdalo-insular network involved in the anticipation of aversive events (Jones et al., 2011; Carlson et al., 2011). During the anticipation of an aversive event the amygdala may initiate physiological changes. These interoceptive modulations are then represented within the insula and contribute to a negative feeling state of aversive anticipation. Our pilot results demonstrated that the anticipation of delay results in a hyperactivation of this amygdalo-insular network. These findings are consistent with the evidence that this network codes for negative events, but a measurement of perceived aversiveness for delay is needed to fully address the link between amygdalo-insular network activation and aversiveness for delay in ADHD.

The current study had a number of limitations that should be addressed in future research. First, the sample size in this pilot study was small and related to that the primary analyses were limited to ROIs. However, the selection of ROIs was explicitly hypothesis-driven. Studies with much larger samples using whole-brain analysis are required to replicate the current findings. Second, the task did not have a control condition which would have allowed a direct comparison between the punishing effects of the imposition of inescapable delay and other forms of punishment such as response cost. This means that we cannot rule out the possibility that the heightened response to cues predicting inescapable delay represented a generalised impairment towards

cues predicting aversive outcomes rather than an effect specific to delay. Additionally, it is possible that not having control over outcomes generally, rather than delay levels specifically, might be the aversive aspect of the no-escape trials and future studies need to control for this possibility. Third, there was no opportunity to compare children with ADHD with and without anxiety and mood disorder which are highly prevalent in the ADHD samples and also likely to implicate the sorts of accentuated emotional responses seen here. Fourth, there was no direct measure of whether patients with ADHD perceived delay to be more aversive then controls. Finally, our groups were not matched on IQ. This represents a significant confound given some significant correlations between significant activations and IQ in the current study. Future samples with groups matched for IQ will be needed to rule out the possibility that the effects seen in the current study are not driven by IQ rather ADHD because of limitations in interpreting anaylses with IQ as a covariate (Miller & Chapman, 2001).

In summary, we found that children with ADHD displayed a specific pattern of hyper-activation of the amygdala and the insula, brain regions shown in the past to be aversive-event sensitive, in response to cues of inescapable delay, as well as the ventral striatum and the orbito-frontal cortex. This data builds on growing evidence of the role of brain-based alterations in bottom up emotional and motivational alterations in the pathophysiology in at least a sub-group of ADHD children.

4. Experimental procedure

4.1. Participants

Twelve adolescents with combined type ADHD who met DSM-IV diagnostic criteria and 12 age matched controls took part in the study. Patients were recruited from the outpatient clinic of the university hospital. The control group comprised 12 children that were recruited from several regular primary and secondary schools. None of the control children had a history of prematurity (PML < 36 weeks), head trauma or any neurological and/or psychiatric disorder. All subjects presented a Full Scale Intelligence Quotient (FSIQ) above 80, as measured with the Dutch adaptation of the *Wechsler Intelligence Scale for Children* (WISC-III (Kort et al., 2005). The diagnosis was based on a clinical history and a semi-structured interview with parents (*Schedule for Affective Disorders and Schizophrenia for School-Age Children,* KSADS; (Kaufman et al., 1997)). Parent ratings on behavioural questionnaires measuring ADHD and other childhood problems were obtained for all subjects (Achenbach & Rescorla, 2001). Handedness was assessed with the Edinburgh Handedness Questionnaire (Oldfield, 1971). Due to motion artifacts 2 adolescents with ADHD and 2 control subjects were removed from further analyses. Therefore, analyses were conducted with 20 participants (10 ADHD and 10 controls). For these subjects movement parameters were found to be low (on average translations less than 2 mm and rotations less than 2 degrees) and no

significant difference of movement parameters between control subjects and patients was observed. Table 1 displays descriptive statistics of the ADHD and the control group. Significant differences were observed for IQ [$t(18) = -4,95$, $p=0.0001$]. All ADHD-children were off medication at least 48 hours prior to testing.

All participants and their parents gave informed consent prior to testing. The study was approved by the ethics committee of KU Leuven University Hospital.

Table 1

4.2. Task Design

The Escape Delay Incentive (EDI) task (Broyd et al., 2011) was based on the Monetary Incentive Delay (MID) task (Knutson et al., 2001). The EDI was presented to the subjects as a RT-task. Subjects were instructed to press a button as quickly as possible with their dominant hand when a target (white square) was presented on the screen. Following the response participants received feedback about whether their responses were fast enough. The response window was between 150-msec and 600-msec and the time the target was presented varied from trial to trial in 20-msec steps. This tracking procedure was used in order to obtain an average of approximately 66% target hits across both conditions and was implemented during performance of the task. There were two types of trial. On *Escape Delay* trials a triangle-shape cue presented on the computer screen signaled that if responses were too slow they would be followed by a period of post-response delay, while if they responded quickly

enough the next trial would follow immediately and they could escape the delay. In the *No Escape Delay* trials a circular-shape cue signaled that no matter how quick a response would be it would always be followed by a post-response delay period – in this trial the delay would be inescapable. In both trial types delays varied pseudo-randomly between 8 to 17 seconds. An auditory signal was presented to alert the participants when the next trial was about to start. There were 30 *Escape Delay* and 30 *No Escape Delay* trials. These trials were presented in random order over four blocks of 15 trials. Figure 1 presents a schematic representation of the structure of the task. Prior to the scanning session all subjects performed the EDI outside the scanner. All subjects received a fixed monetary reward for their participation, but this reward (in contrast with the MID) was not associated with the performance of the subject.

Figure 1

4.3. Image acquisition and statistical analysis

FMRI images were acquired with a 3-T Intera MR scanner (Philips, Best, The Netherlands), using an 8 element SENSE head coil (In Vivo, Waukesha, WI, USA). Whole brain blood oxygen level dependent (BOLD) Field echo planar images (EPI) were obtained with TR/TE = 2000/30 ms, SENSE reduction factor = 2, consisting of 36 sequential bottom-up slices with a slice thickness of 3.75 mm and without a slice gap and in plain voxel size of 2.75 mm. At the end of each scanning session a three-dimensional high resolution T1-

weighted anatomical image, TR/TE = 9.68/4.6 ms, inversion time = 1100 ms, with a resolution of 1x1x1.2 mm^3 was acquired. Stimuli were presented using the presentation software (version 14.6, Neurobehavioral systems).

Imaging data were analyzed with Statistical Parametric Mapping 8 (SPM8) (Wellcome Department of Imaging Neuroscience, London, UK) implemented in MatLab 7 (The MathWorks Inc.). The functional images were realigned to the first volume of the time series to correct for head movements and slice timing was applied to correct for differences in acquisition time during scanning. Thereafter all images were realigned to the mean image that was created in the first realignment step. After co-registering the functional images to the anatomic image, they were spatially normalized to the standard space of the Montreal Neurological Institute (MNI) brain. All functional images were subsampled to a voxel size of 2 x 2 x 2 mm^3 and smoothed with a Gaussian kernel of 8 mm full width at half maximum.

First-level statistical analysis was performed for all subjects in the context of the general linear model (GLM). Each of the experimental conditions (*Escape Delay* and *No Escape Delay*) was modeled by multiple stick functions with duration 0 convolved with a hemodynamic response function with its time derivatives in the GLM. Time derivatives were added to account for small variances in the onset time, which might affect the results, especially in event-related fMRI experiments. The use of these derivatives,

however, can lead to fitting implausible shapes (Calhoun et al., 2004) and decreased power (Lindquist et al., 2009).

Given the relatively small sample size in this study, non-parametric tests were applied. To this end, the contrast images of all subjects, masked by the different ROIs, were used as input for the non-parametric statistical toolbox SnPM (Nichols & Holmes, 2002). Pseudo T-contrasts for "*No Escape Delay* > *Escape Delay*" were calculated for each subject. The individual contrast images were used in a second-level random effects analysis to account for subject-to-subject variability and to determine stimuli-specific regional responses for within- and between-group statistical comparisons. In order to examine the differential effects of inescapable versus escapable delay for ADHD versus control participants we adopted a ROI approach comparing the difference in amygdala (50 voxels), insula (410 voxels), ventral striatum (30 voxels) and orbito-frontal cortex (160 voxels) activation on *Escape Delay* and *No Escape Delay* trials in the two groups.

The ROIs were defined based on the BrainMap database (Fox et al., 1994). Only voxels that were present in all data sets were included in this ROI. Especially in the amygdala and the orbitofrontal cortex, some voxels were not included in the ROI, as there was no signal due to susceptibility related artifacts. For these structures, uncorrected p-values, as well as small volume Family Wise Error (FWE) corrected p-values are reported.

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FIGURE LEGEND

Figure 1: A schematic representation of the structure of the Escape Delay Incentive (EDI): Escape Delay and No Escape Delay trials.

Figure 2: Bar charts and 90% confidence intervals showing the differences between Escape delay and No-Escape Delay conditions for the most significant voxel in theright and left amygdala, insula, ventral striatum and orbito-frontal cortex.

Figure 3: Brain activations for No-escape Delay>Escape Delay comparisons in Controls, ADHD patients and ADHD Patients>Controls.

TABLE LEGEND

Table 1: Differences between ADHD and control groups in terms of background and clinical characteristics (Pair wise comparisons between ADHD-C and controls: $p<0.05$ (*); FSIQ: full scale intelligence quotient, VIQ: verbal intelligence quotient, PIQ: performance intelligence quotient)

Table 2: Uncorrected and small volume FWE corrected p-values for the comparison - "*No Escape Delay* > *Escape Delay*" brain activation for ADHD versus controls for amygdala, insula, ventral striatum and orbito-frontal cortex.

Figure 1: A schematic representation of the structure of the Escape Delay Incentive (EDI): Escape Delay and No Escape Delay trials.

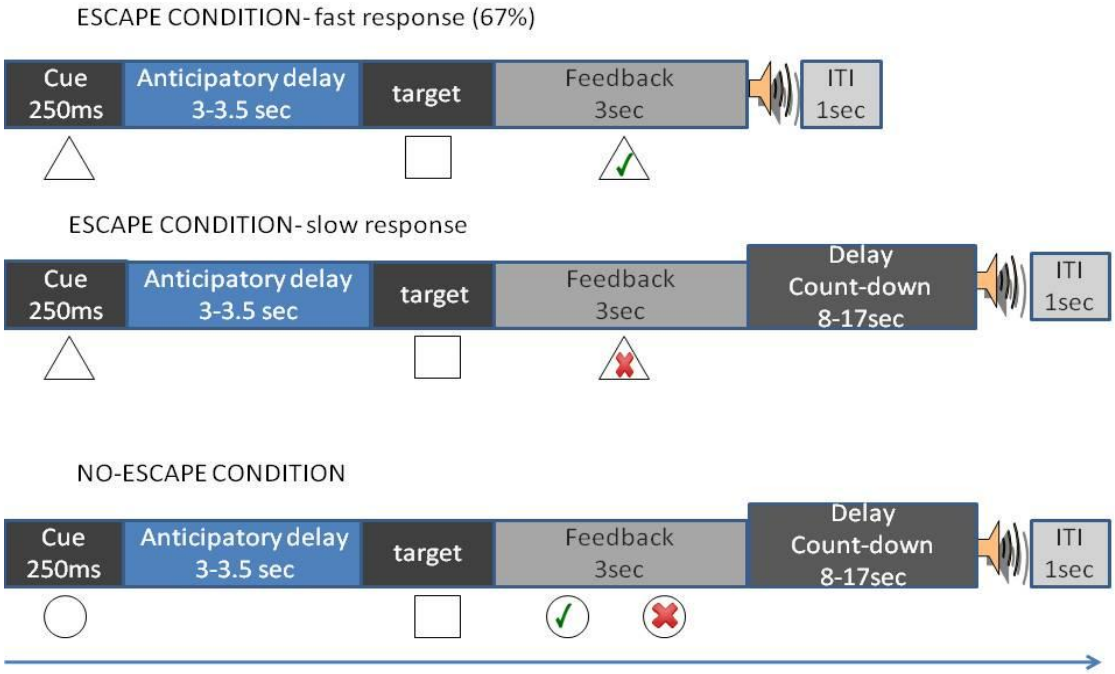

Figure 2:

Bar charts and 90% confidence intervals showing No-Escape Delay>Escape Delay contrasts for the most significant voxel in the right and left amygdala, insula, ventral striatum and orbito-frontal cortex.

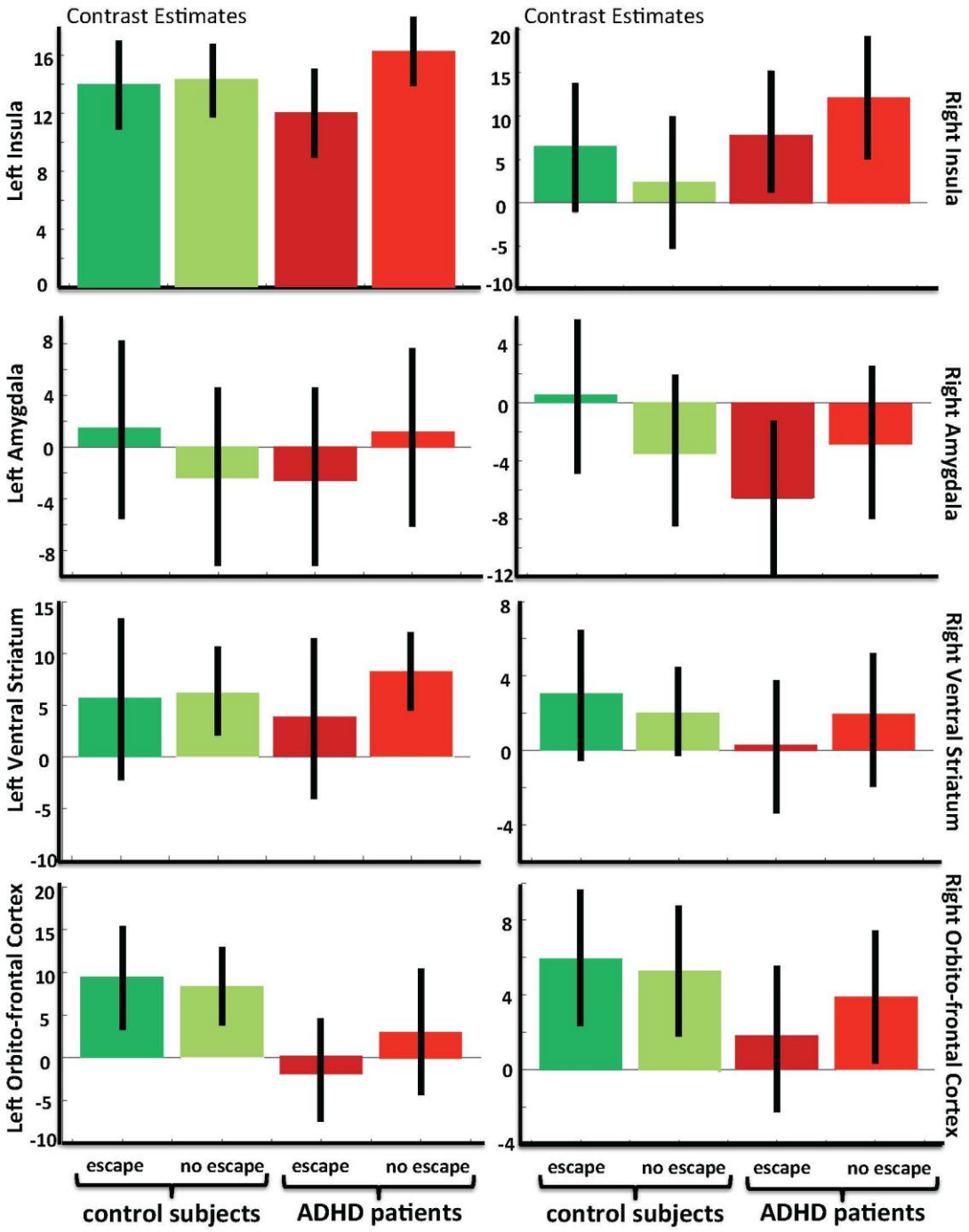

Figure 3: Brain activations for No-escape Delay>Escape Delay comparisons in Controls, ADHD patients and ADHD Patients>Controls.

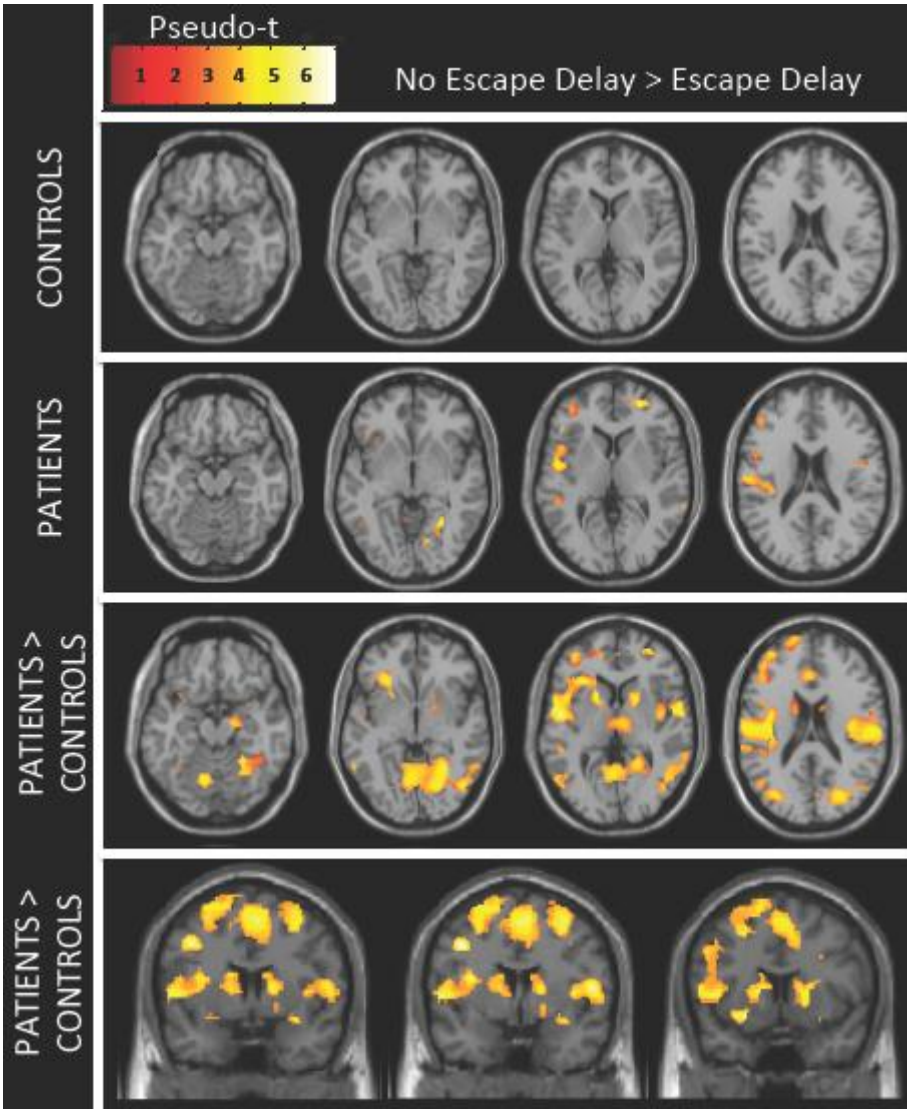

Table 1: Differences between ADHD and control groups in terms of background and clinical characteristics (Pair wise comparisons between ADHD-C and controls: $p<0.05$ (*); FSIQ: full scale intelligence quotient, VIQ: verbal intelligence quotient, PIQ: performance intelligence quotient)

	ADHD (n=10)	CONTROLS (n=10)
Age	14.72 ° 1.49	14.40 °1.33
Sex (M:F)	8:2	7:3
Handedness (R:L)	8:2	7:3
FSIQ*	96.30°6.93	116.50°10.89
VIQ*	99.70°7.33	117.60°9.95
PIQ*	93.30°9.78	110.90°10.70
Comorbidity	Oppositional Defiant Disorder (n=1)	
	Depressive disorder(n=1)	
	Adjustment disorder (n=1)	

Table 2:

Uncorrected and small volume FWE corrected p-values for the comparison - "*No Escape Delay* > *Escape Delay*" brain activation for ADHD versus controls for amygdala, insula, ventral striatum and orbito-frontal cortex. In addition, the MNI coordinates, the number of voxels in the cluster with p<0.05 and the pseudo-T score were added for all regions of interest.

	uncorrected p-value	FWE corrected p-value	MNI coordinates			Cluster size	Z
Insula R	<0.001	0.014	26	18	6	126	3.8
Insula L	<0.001	0.006	-34	18	8	150	3.97
Amygdala R	0.004	0.015	18	-6	-16	23	3.12
Amygdala L	0.024	0.062	-24	-4	-14	17	2.24
Ventral striatum R	0.002	0.009	18	12	-4	15	3.94
Ventral striatum L	0.01	0.023	-20	8	-6	8	2.86
Orbito-frontal cortex R	<0.001	0.152	30	26	0	48	3.38
Orbito-frontal cortex L	<0.001	0.006	-32	28	-2	134	4.38