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ADHD and Delay Aversion

Article Title:

Neural and Psychophysiological Markers of Delay Aversion in Attention Deficit Hyperactivity Disorder

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Abstract

Delay aversion (DAv) is thought to be a crucial factor in the manifestation of impulsive behaviors in patients with attention deficit/hyperactivity disorder (ADHD). The imposition of delay is predicted to elicit negative emotional reactions in ADHD. The present study offers a multimodal approach to the investigation of DAv. Twelve adult patients with ADHD and 12 matched healthy controls were tested on a new task with several levels of anticipated delays during functional magnet resonance imaging (fMRI). Behavioral measures of delay discounting, DAv and delay frustration were collected. Skin conductance and finger pulse rate were assessed. Results indicated a group difference in response to changes in delay in the right amygdala: For control participants activity decreased with longer delays, whereas activity tended to increased for ADHD patients. The degree of amygdala increase was correlated with the degree of behavioral DAv within the ADHD group. Patients also exhibited increased emotional arousal on physiological measures. These results support the notion of an exacerbated negative emotional state during the anticipation and processing of delay in ADHD.

Keywords

ADHD; delay; aversion; fMRI; amygdala

Waiting in a queue sooner or later leads to negative emotions and restlessness in most people. Children with attention-deficit/hyperactivity disorder (ADHD) seem to particularly dislike such delay (Marco, et al., 2009; Paloyelis, Asherson, Mehta, Faraone, & Kuntsi, 2010; Solanto, et al., 2001). A number of theoretical models have been developed to explain this (Sonuga-Barke & Fairchild, 2012). First, there are those models that highlight the role of dopamine mediated learning processes. For instance, tonic dopamine deficits leading to steeper delay-of-reinforcement gradients are thought to be responsible for an observed devaluation and reduced effectiveness of delayed rewards in ADHD (Sagvolden, Johansen, Aase, & Russell, 2005). The delay aversion (DAv) model offers an alternative perspective (Sonuga-Barke, 2005). At the core of this account is the notion that impulsive choice in ADHD (the choice of the smaller immediate over the large delayed reward) is motivated by the desire to escape from delay in order to avoid the negative emotional states which waiting for delayed rewards elicits in individuals with ADHD. However, the DAv theory also makes a second distinctive prediction, i.e. that associations between negative emotional reactions and delay develop out of histories of failed waiting experienced by individuals living with ADHD (Sonuga-Barke, 2003). In the DAv theory it is delay per se which is the motivating element rather than the outcome that is delayed (Sonuga-Barke, 2005).

Few fMRI studies have examined delay-related brain activations in ADHD. Plichta and colleagues (2009) found a striatal dissociation in adult ADHD patients between choices of immediate and delayed reward and explicit hyperactivation of the amygdala during the choice of delayed rewards. Indeed increased amygdala response to delayed rewards or cues of delay in ADHD is a core neurobiological prediction of the DAv model given (i) the hypothesized negative affect generated by delay for this population and (ii) the role of this region in processing negative experiences and affective states (e.g. Lanteaume, et al., 2007). Rubia and colleagues (Rubia, Halari, Christakou, & Taylor, 2009) did not report amygdala alterations in delay discounting but found dysfunctions in prefrontal, cingulate, striatal and cerebellar regions in adolescents with ADHD. However, both

paradigms (Plichta, et al., 2009; Rubia, et al., 2009) focused only on decision making about hypothetical future reward, and no actual delays were experienced during these tasks.

A recent study confronted adolescent ADHD patients with real delays and demonstrated a pattern of hyperactivation in limbic structures during the anticipation of inescapable, compared to escapable delay (Lemiere, et al., 2012). While this was interpreted as preliminary evidence for the negative affective element of the DAv motivational style in ADHD, the association of these brain activation patterns with increased DAv in ADHD remains tenuous due to some limitations in this study. In particular, there was no examination of the "dose-response", i.e. parametric relationship between brain activation and delay length. Furthermore no auxiliary assessment of DAv or negative affective reactions to delays besides brain activations (e.g. behavioral and psychophysiological measures) were included, making interpretations of brain activations more difficult.

In the current study, we address these limitations. First, we introduce a new paradigm which takes a parametric approach by using delays of different lengths. Second, we assessed participants' affective response to delay both in terms of their reported experiences/perceptions/reactions and more objectively using physiological measures (i.e. neural activity, skin conductance, heart rate).

Our predictions were as follows: In line with the DAv theory, activity in amygdala and anterior insula (regions involved in the processing of aversive stimuli) will be positively correlated with the length of delay in ADHD patients but not in healthy controls. Furthermore, these group differences in delay-related modulation will be mirrored by increased (a) psychophysiological responses (pulse rate, skin conductance), (b) self-reported measures of DAv, and (c) performance on behavioral DAv tasks.

Method

Participants

Twelve right-handed patients with a current diagnosis of adult ADHD according to the German guidelines (including a retrospective diagnosis of ADHD during childhood; Ebert, Krause, & Roth-Sackenheim, 2003) were recruited from a specialized outpatient clinic. ADHD diagnosis was assessed by experienced clinicians following a detailed psychiatric interview that integrates common psychiatric and somatic differential diagnoses, the patients' medical histories, additional informants and sources (e.g. school reports). ADHD symptoms in childhood were self-rated retrospectively with the validated short-version of the Wender Utah Rating Scale (WURS-k, Retz-Junginger, et al., 2003). All patients were free of any current comorbid disorder on axis 1, five patients had at least one comorbid lifetime diagnosis as determined by the Structured Clinical Interview for DSM-IV-TR interview (SCID, First & Pincus, 2002: 3 depression, 2 eating disorder, 2 substance dependence/ abuse). Exclusion criteria were schizophrenia, bipolar, borderline or antisocial personality disorder. All patients were medication free for >2 months. Twelve right-handed control participants (matched by age, gender, intelligence, and education) were recruited from the general population via newspaper ads, and were free of any lifetime mental disorders as determined by the SCID. All participants gave informed written consent which was approved by the local ethic committee.

Procedure

fMRI DAv Task. In the scanner, participants performed a modified version of the monetary incentive delay task (Knutson, Adams, Fong, & Hommer, 2001, see figure 1). Participants were instructed to respond to a visual target as quickly as possibly by pressing a button. Depending on the trial type, they could expect extra delays of different lengths (10, 20, or 30 seconds, or no delay) which would be added at the end of the trial when they had made a slow response. The length of the potential extra delay was indicated by one of four cues at the beginning of each trial. Feedback for slow and fast responses was based on an adaptive threshold to ensure a predefined hit-rate of

60% per condition (see supplemental material for more detailed information). Prior to the task participants performed a 5 minutes training session and received their financial reimbursement for participation in the study. They were told that the task would last for 15 to 30 minutes and that their performance determined the actual length. However, note that the performance itself did not affect duration of the experiment which was actually about 20 minutes.

Behavioral DAv measures. Three additional tasks were administered during the same experimental session to acquire auxiliary behavioral DAv measures (additional information on these tasks in the supplementary material). During a hypothetical delay discounting task participants chose between a delayed and immediate amount of money. The immediate reward alternative was adjusted up or down after each choice in order to establish the point of indifference with the delayed reward (€200). This procedure was repeated for the delays 1, 3, 9, 24, 60, 120, and 240 months. Points of indifference were used to calculate the fitted parameter *k* which describes the rate of discounting (Rachlin, Raineri, & Cross, 1991). Higher *k*s indicate stronger delay discounting, i.e. a stronger loss of subjective value of money with increasing delay.

In the continuous DAv test (Muller, Sonuga-Barke, Brandeis, & Steinhausen, 2006) participants watched a container slowly filling up with liquid “gold” in each of 40 trials until they decided to go to the next trials. The flow of gold decreased over time according to a logarithmic function so that patients who were DAv were predicted to quit the trial earlier. Proportionately to the amount of gold real money was paid after completion of this task as reimbursement. Total waiting time (in minutes) was used as a measure of DAv.

During a modified version of the delay frustration task (Bitsakou, Antrop, Wiersema, & Sonuga-Barke, 2006) participants experienced several unexpected delays while performing a simple visual discrimination task. Unknown to the participants the response box was deactivated during 15 predefined pseudo randomized *delay periods* (duration 2 to 12 sec) within the *normal task periods*.

The frequency of button presses during delay periods served as behavioral outcome measure, which is suggested to reflect frustration about the undesired delays.

Psychophysiological Assessment. Skin conductance and finger pulse were collected during fMRI and the delay frustration task (see also supplementary material for additional information). In the fMRI task, skin conductance level was assessed as the baseline corrected mean signal (in micro Siemens) during the extra delays. In the delay frustration task, baseline corrected skin conductance level was measured during the unexpected delay periods. Generally, negative values were set to zero and outliers were controlled by the Winsorising technique. Skin conductance data were lost for one patient due to technical problems. Finger pulse data are reported as overall pulse rate (in beats per minutes). Psychophysiological measures were combined to provide a composite score (Cronbachs alpha=.72, cf. Blechert, Michael, Grossman, Lajtman, & Wilhelm, 2007) of physiological DAv via z-standardization of individual outcome measures and averaging over tasks and measures for each participant. Higher scores represented stronger emotional arousal (as indicated by higher skin conductance and faster pulse rate).

Psychometry and self-report measures. Self-reported psychopathology was assessed on various scales as well as potential confounds such as participants' personal financial situation and intelligence (see Table 1). Four self-report measures of DAv were obtained from participants: minutes until they get bored in everyday waiting situations, minutes until they get impatient, average ratings of the online assessed feelings during delays in the fMRI task and retrospective impatience during delays in the delay frustration task (see supplementary material for more details). Z-standardized values were combined to one self-report DAv composite score (Cronbach's alpha .71). Again, higher scores indicated stronger DAv.

Magnetic Resonance Imaging. Imaging was performed on a 3 Tesla Siemens (Erlangen, Germany) Trio MR scanner with a standard 8-channel ^{1}H head coil (T2*-gradient echo planar imaging sequence: TR=2.25sec, TE=30ms, flip angle=90°, 36 axial slices, FOV=192mm, spatial resolution=3×3×3mm; standard T1-weighted pulse sequence: TR=2.2sec, TE=4.11ms, flip angle=12°, FOV=256mm, spatial resolution=1×1×1mm).

Analysis

The fMRI data were analyzed with SPM8 (Welcome Department of Cognitive Neurology, London) after an automatic online correction for artifacts (Zaitsev, Hennig, & Speck, 2004). Pre-processing comprised slice timing, realignment, co-registration, spatial normalization and smoothing (8mm FWHM). BOLD changes during the DAv task were modeled in a GLM including 6 task regressors as well as 6 movement and 4 slow signal drift regressors (linear, quadratic, cubic and 4th order spline). Three types of events ('cue', 'positive feedback', 'negative feedback') were modeled using a parametric approach. Therefore, onset regressors were weighted by the logarithm of the length of the respective extra-delay in each trial. This resulted in a total of 6 task regressors (3 main effects, 3 parametric modulation effects). Onsets were folded with a 1sec-event canonical hemodynamic response function. Main outcome in this task was the degree by which BOLD was modulated by the length of anticipated delay. Therefore, a single subject contrast image on the parametric modulation of neural activity by the length of anticipated delay was calculated for each participant. Group analysis (one- and two-sample t-tests) were done on these images. Due to a specific focus on negative emotional states regions of interest (ROIs) were selected from the literature (Carretie, Albert, Lopez-Martin, & Tapia, 2009; Sehlmeyer, et al., 2009) and defined according to the automatic anatomical labeling (AAL, Tzourio-Mazoyer, et al., 2002) project: left and right amygdala (39 voxels each) as well as left and right anterior insula (manually separated from posterior parts at y=0, resulting in 358 voxels left, and 311 right). SPM's small volume correction (SVC) was applied with a

family wise error (FWE) correction of $p<.05$. An exploratory whole brain analysis is reported at $p<.001$ uncorrected, and $k>5$.

Because of the small sample size per group Mann-Whitney-U tests were used for the investigation of group differences and Spearman's rank correlation coefficients were used for correlation analyses (correlations were always computed for groups separately). Reported *p* values are two-tailed.

Results

Self-Report, Behavioral and Physiological DAv markers

Results are shown in figure 2A (see also table S3 in the supplemental material for details on individual scales and variables). Patients reported significantly increased impatience, boredom and negative affect during delays compared to controls (self-report DAv composite score: $U=25$, $p=.007$). Self-reported DAv was also positively correlated with ADHD symptoms (CAARS) within the patient group ($r=.69$, $p=.014$), but not with depressive or anxiety symptoms (all ps$>.527$).

Groups did not differ on any of the behavioral DAv measures (all ps$>.56$, all ds$\leq.22$). Neither did behavioral measures correlate with self-reported DAv or psychopathological symptoms. Reaction times in the fMRI task did not differ between groups overall ($p=.419$) and were not correlated with the length of anticipated delay (ADHD: median $R=.40$, $p=.116$, Control: $R=.40$, $p=.968$, group comparison: $p=.395$).

Compared to healthy controls ADHD patients exhibited higher pulse rate and skin conductance level (physiological DAv composite score: $U=30$, $p=.015$). The physiological composite did not

correlate with the other DAv measures or psychopathological symptoms in either group (all *p*s>.106).

Neuroimaging Results

Groups did not differ in terms of averaged BOLD responses during anticipation overall. However, as predicted, significant differences emerged when taking the lengths of anticipated delays into account (parametric approach, see Analysis). Within the ADHD group, levels of anticipated delay significantly modulated BOLD in the anterior insula (MNI[x/y/z]=[45/14/-11], *t*=4.77, *p*[FWE]=.049). There was a statistical trend for the amygdala on the right side (MNI[x/y/z]=27/2/-20, *t*=3.47, *p*[FWE]=.069). This means, BOLD responses within both ROIs were positively correlated with the length of anticipated delay. Within the healthy control group no delay-related positive modulation was found for the amygdala or insula. In contrast, healthy subjects exhibited a reversed modulation effect in the right amygdala, i.e. the longer the delay the lower the activity within the amygdala (MNI[x,y,z]=[27/-1/-23], *t*=4.04, *p*[FWE]=.038). The whole brain analysis revealed one cluster in the left inferior temporal cortex for positive delay modulation in the ADHD group (MNI[x,y,z]=[-42/14/-20], *t*=5.29) as well as three clusters in the control group (dorsomedial prefrontal at MNI[x,y,z]=[-6/50/31], *t*=4.94, and left occipital at MNI[x,y,z]=[-9/-97/19], *t*=5.61, for positive delay modulation; right occipital-temporal for negative delay modulation: MNI[x,y,z]=[48/-70/1], *t*=4.70).

A direct comparison on the parametric contrast between groups revealed significantly different modulation of BOLD in the right amygdala (MNI[x/y/z]=[27/-1/-20], *t*=3.81, *p*[FWE]=.016; see figure 2B). This effect stems from increased recruitment of amygdala with increasing delay in ADHD patients as well as from the inverse effect in control subjects (see above). The group difference in the anterior insula did not reach statistical significance (*p*[FWE]=.252). Within the ADHD group, this degree of parametric modulation in the right amygdala was significantly associated with the number of button presses during unexpected delays in the delay frustration task (r=.63, p=.027) as well as

inversely associated with the self-imposed total waiting time during the continuous DAv test (r=-.59, p=.045; see figure 2C). As a trend it also correlated with ADHD symptom severity during childhood (WURS-k: r=.52, p=.080). It was uncorrelated with depression or anxiety symptoms in the ADHD group (all ps>.40). SPM's group analysis remained significant for the right amygdala ROI when covarying for lifetime comorbid disorders, depressive or anxiety symptoms (p(FWE)<.05).

The whole brain analysis revealed one hyper-modulated cluster within the orbitofrontal cortex for ADHD patients compared to control subjects (MNI[x,y,z]=[12/38/-17], t=4.47). This effect was inversely correlated with self-reported trait anxiety (ADHD r=-.71, p=.010, Control r=-.65, p=.023). No other correlations were found.

Discussion

ADHD patients exhibited an abnormal pattern of delay-related activity in the right amygdala which, though only trendwise significant in the ADHD group alone, tended to increase with longer delays. Additionally, they exhibited accelerated pulse rate and higher skin conductance level. These results were consistent with the patients' self-reports revealing more negative emotional reactions (e.g. boredom, impatience) during the experimentally induced delays as well as during waiting situations in their everyday life.

Two prior studies reported amygdala hyperactivity for ADHD patients in delay associated tasks (Lemiere, et al., 2012; Plichta, et al., 2009). It is important to note, however, that the results from the parametric approach in the present study go beyond these findings, since here neural activity was correlated with the length of the delay and this delay was immediately experienced during the task. Because the applied delay task covered delays of 4, 10, 20 and 30 seconds duration it was

possible to concentrate the analysis on brain regions which show this specific modulation effect as a function of delay length. Moreover, whereas evidence for differential effort between delay conditions was not found for ADHD patients (overall steady reaction times for short and long delays), the degree of amygdala modulation was correlated with the degree of behavioral DAv demonstrated in supplemental tasks. Thus, increased amygdala recruitment with increasing delay is unlikely to reflect changes in effort (e.g. to avoid longer delays) but rather to reflect delay-specific anticipation effects. In contrast, the interpretation of the additional group effect found in the medial orbitofrontal cortex remains unclear, since no correlations were found with measures of DAv.

Increased arousal during periods of delay as measured by skin conductance as well as overall accelerated pulse rate in this study are in line with psychophysiological manifestations of negative affective reactions (Kreibig, 2010). To our knowledge, the present study is the first investigation of psychophysiological responses to delay in ADHD. Traditionally, abnormalities in arousal of children with ADHD were found to take the opposite direction to those seen here, linking less demanding task periods with reduced arousal and/or effort and in turn with higher task variability or error production (e.g. Barry, Clarke, Johnstone, McCarthy, & Selikowitz, 2009; Johnstone, Watt, & Dimoska, 2010). Assuming that those task periods were comparable with the imposed delays in the present study these results are inconsistent with ours. It is possible however that those periods were not aversive to participants with ADHD and therefore these results reflected different processes. The present finding of increased psychophysiological arousal in response to delays in ADHD patients needs further replication in larger studies.

Contrary to the findings of neural, psychophysiological and self-reported DAv, the behavioral results from the laboratory tests do not support the DAv model. Several possible explanations have to be considered: First, lack of statistical power might have caused the null effect since group differences, though marginal, ran in the expected direction. Second, one might argue that the DAv tasks used were not appropriate for adult populations. Third, adult patients could have successfully

learned to override disadvantageous behavioral patterns during their lifetime so learning how to cope with the imposition of delays on the level of behavioral output. This view would correspond to the observation of general maturational effects (e.g. increasing self-control) in normal ontogenesis (Green, Fry, & Myerson, 1994) relating to coping with delay (but see also Marx, et al., 2010 who found larger effect sizes in adults than children). Again, larger studies are needed to clarify the issue of behavioral manifestation of DAv in adult ADHD.

The following potential limitations need to be considered: First, sample size in this study is small. Therefore, statistical tests were conducted non-parametrically in order to minimize the influence of individual cases in group analyses. However, absence of significant effects (e.g. in the insula) might be a type II error, whereas positive findings could be artifacts of undetected sampling effects. Second, the amygdala effect was inverse among controls which could have driven the group effect. Third, the associations between different DAv measures were not significant in all cases as predicted (e.g. no correlation between psychophysiology and neural activation). This could be due to the poor reliability or yet unknown aspects of these measures. Fourth, detailed examination of physiological measures (especially pulse rate) would require a closer matching of groups on variables such as physical fitness and body mass index in order to rule out possible confounds. Lastly, alternative ways of conceptualizing DAv in ADHD, e.g. as a result from different time perception (Rubia, et al., 2009) or generally deficient regulation of negative emotions (Musser, et al., 2011), were not addressed with the current study. These alternative explanations therefore cannot be ruled out.

In conclusion, this study describes a new method for investigating DAv in ADHD. The results provide preliminary neural and psychophysiological evidence of DAv in adult patients with ADHD. Future studies should build on this multimodal approach and replicate the results with larger samples. Clinical practice could benefit from a deeper understanding of DAv as a potential driver for impulsivity in adulthood.

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Table 1: Sample characteristics and psychopathology.

Variable	Patients (N = 12)	Healthy Controls (N = 12)	*p*
Age	38.42 (9.41)	37.67 (10.71)	>.999
Gender (m/f)*	5/7	5/7	>.999
Educational Level (low/medium/high/college)*	2/6/3/1	1/8/2/1	.845
Intelligence (MWT-B)	112.00 (17.31)	107.45 (10.90)	.969
Financial Situation (€ remain monthly)	149.00 (176.79)	115.00 (232.63)	.695
Unemployed*	1	2	.427
Smoker*	4	2	.346
Sleep (h per night)	6.96 (0.99)	7.13 (0.86)	.559
Inventory of Depressive Symptoms (IDS) [1]	16.28 (11.11)	6.97 (5.53)	.010
State Trait Anxiety Inventory (STAI) – State[1]	34.42 (5.71)	29.25 (4.35)	.020
State Trait Anxiety Inventory (STAI) – Trait[1]	44.42 (9.56)	29.67 (5.85)	<.001
Conners' Adult ADHD Rating Scale (CAARS) [1]	85.21 (24.64)	24.71 (11.34)	<.001
Wender Utah Rating Scale short (WURS-k)	34.38 (8.76)	-	-
Barratt's Impulsivity Scale (BIS)	72.50 (9.70)	54.46 (9.31)	<.001

Note: *absolute counts, *p* values refer to χ^2-tests for group comparisons. For all other variables means and standard deviations are reported as well as *p* values of the Mann-Whitney-*U* tests. MWT-B (a German vocabulary test, Lehrl, 1977), IDS (Rush, Gullion, Basco, Jarrett, & Trivedi, 1996), STAI (Spielberger, Gorusch, & Lushene, 1970), CAARS (Christiansen, et al., 2011), BIS-11 (Patton, Stanford, & Barratt, 1995). [1]variables of psychopathological symptoms.

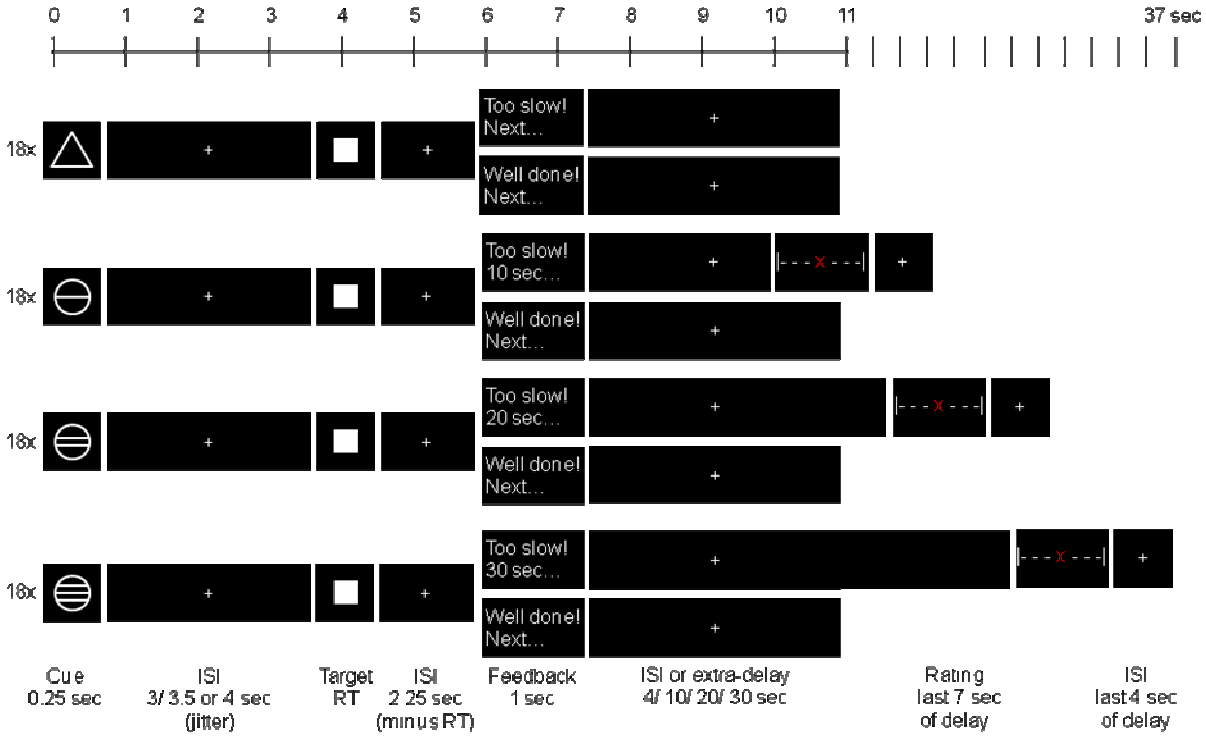

Figure 1: The fMRI delay aversion task consisted of 1 run with 72 trials of 4 different types. Participants had to respond as fast as possible to a target (white square) in order to avoid subsequent extra delays of varying length. Note: RT= reaction time, ISI = Inter stimulus interval.

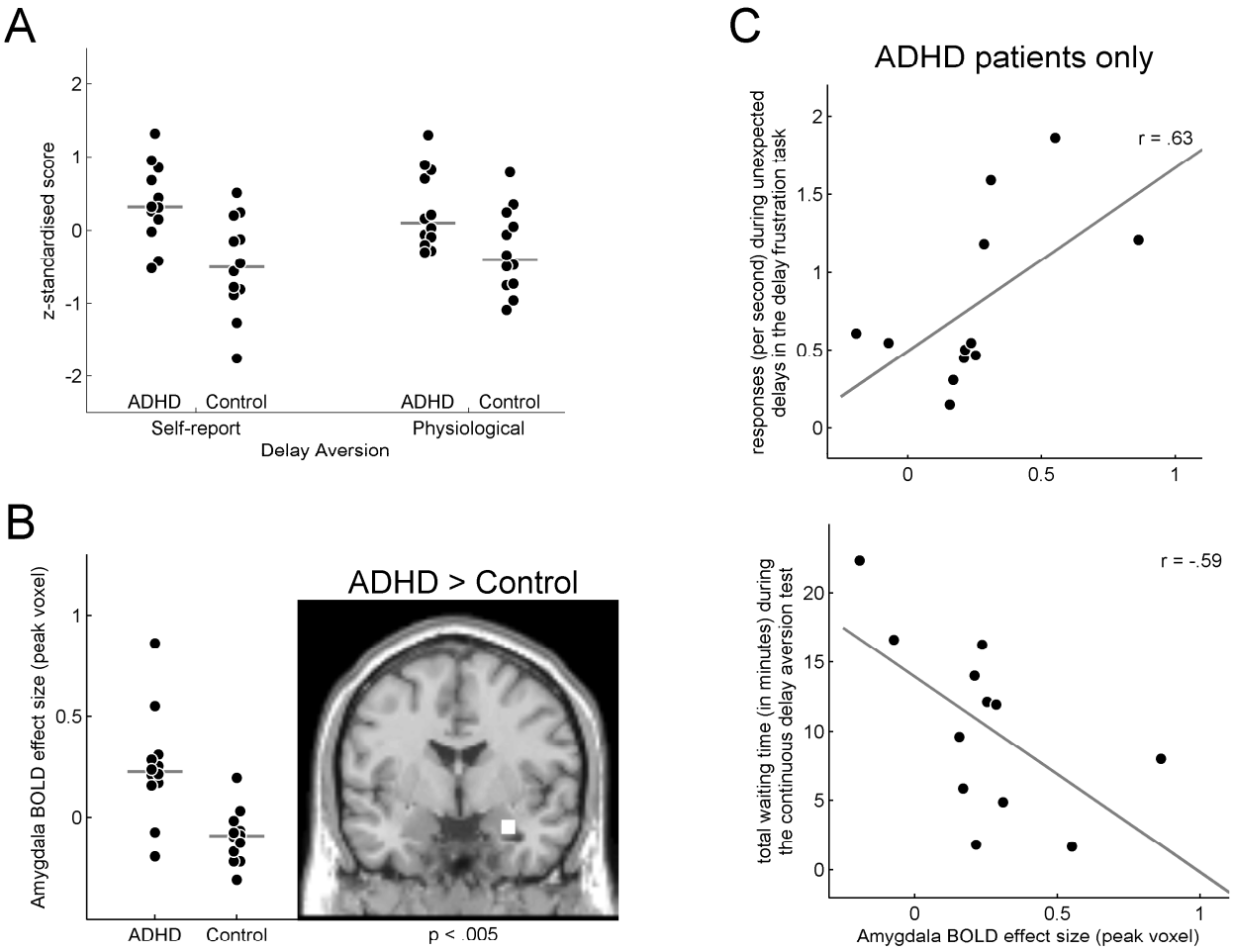

Figure 2: Significant group differences in (A) delay aversion composite scores, and (B) parametric modulation of brain activity by length of delays during the anticipation of delay. Note: depicted are single cases and group medians. (C) Correlations within ADHD patients between right amygdala BOLD response in the parametric delay modulation contrast and two behavioral measures of delay aversion.

Supplementary Material

Methods

fMRI DAv task.

A circle with one line cued a possible time-out of 10 seconds, a circle with two lines 20 seconds and a circle with three lines 30 seconds. In trials of the neutral condition (cued by a triangle) no time-out was to be expected irrespective of performance.

Subsequent to the cue (0.25 seconds) and a jittered inter stimulus interval (3, 3.5 or 4 seconds) a target appeared (white square) to which the participants were instructed to respond as fast as possible. The target disappeared after the participants' response. This was followed by a second interval of 2.25 seconds minus the reaction time (RT). The response window was limited to 0.5 seconds.

Visual feedback was provided in writing (1 second) indicating no extra delay in case of a performance below the acceptable RT threshold ('*Well done! Next trial will start in 4 seconds'*, printed in green letters) or indicating the length of an extra delay in case of a performance above the acceptable RT threshold (*'Too slow! Next trial will start in X seconds'* printed in red letters, with X depending on the trial type, see above). Potential extra delays were added to the minimum delay of 4 sec. During this time participants were instructed to lie still and fixate on a cross in the centre of the screen. At the end of the imposed delay, participants were asked to indicate the valence and strength of their current feelings about the task by moving a red cross on a visual analogues scale with two buttons for both directions ('*How much do you enjoy the task?*' anchors '*not at all*' and '*very much*'). The opportunity for rating began 7 seconds before the regular end of the delay (jittered with +/-0.5 seconds) and terminated after 3 seconds. The interval between the

disappearance of the last stimulus (i.e. rating or feedback) of one trial and beginning of the next trial was always 4 seconds. Each condition appeared 18 times in a pseudo randomized trial order giving a total of 72 trials which were presented in one functional run. The total number of remaining trials was indicated during the task by a continuous display on the computer screen.

Unknown to the participants, thresholds for slow and fast responses were adjusted continuously during the task in order to ensure a predefined hit-rate of 60% per condition as well as a roughly equal distribution of time-outs over the course of the experiment.

In order to test for possible behavioral effects of DAv in this task individual performance patterns were investigated for correspondence to delay lengths. Therefore, reaction times were averaged per condition for each individual and rank correlated with the four levels of delay length. A correlation coefficient approaching 1 would mean that this person exhibited relatively fast responses after cues indicating longer delays and relatively slow responses after cues indicating no or short delays. A correlation coefficient approaching -1 would mean that this person exhibited the inverse pattern, i.e. relatively slow responses after cues indicating longer delays and relatively fast responses after cues indicating no or short delays. These individual rank correlation coefficients were fisher-z-transformed before entering group analysis. Finally, single group median correlation coefficients (*R*) were tested against zero and compared between groups.

For analysis of fMRI data, a parametric approach was used in this study. Note, that an alternative categorial approach (i.e. including separate task regressors for long, medium, short, and no delay) revealed similar results but leads to several possible contrast images (e.g. long vs. no delay, long vs. short delay, long vs. medium delay, medium vs. no delay medium vs. short delay, short vs. no delay) instead of just one for the parametric approach. Furthermore, analysis in this study was concentrated on the anticipation phase (or cue phase) of the task, i.e. BOLD in response to cues signaling delays of different length. Data from the feedback phase, in contrast, were not the focus of this task/ study.

Behavioral Delay Aversion.

Before entering the scanner participants completed a computerized hypothetical delay discounting task. On each of 42 trials participants chose between €200 (about $270) that would be delayed by the time to delivery (t) and an immediate amount of money that was adaptively decreased or increased in order to reach a subjective indifference point. Every 7 trials t changed (1, 3, 9, 24, 60, 120, 240 months) and the immediate reward option was reset to €100. Indifference points for the 7 delay periods were used to calculate the fitted parameter k which describes the rate of discounting. Task duration was between 1 and 3.5 minutes.

Afterwards participants performed the continuous delay aversion test which was originally designed for use in childhood and adolescence. In analogy to a popular German fairy tale, a cartoons of a donkey spitting gold out of its mouth was presented on every trial until the participant decided to go to the next trial. The amount of gold corresponded to real money that was paid after completion of this task as reimbursement. The money flow slowed down over time according to a logarithmic function so that patients who were DAv were predicted to stop the trial earlier. To test this, several opportunities to terminate the trial were included in each session. The task lasted for 8 to 30 minutes.

During the delay frustration task participants still lay in the scanner (after the fMRI DAv task). The instruction for the visual discrimination task was to indicate via button press '*Which of the three depicted squares is the smallest?'*. Prior to the task the participants were informed about possible malfunction of the response box in which cases they should just press the button again. Total task duration was 6.5 to 8.5 minutes.

Psychophysiological Assessment.

Skin conductance was obtained using 11-mm inner diameter Ag/AgCl electrodes from the middle phalanx of the ring and middle finger of the left hand connected to a BrainAmps ExG MR device (BrainProducts, Gilching, Munich, Germany). During the fMRI DAv task, the skin conductance level measure was obtained by averaging the signal from a time window covering the time-out periods after slow responses (i.e. the first 4, 14 or 24 sec in 10, 20, 30sec time-outs, respectively) and subtracting the baseline, defined as the minimum during the preceding 6 sec (i.e. from cue to feedback). In the delay frustration task, skin conductance level was measured during periods of unexpected delays (i.e. during putative malfunction of the response box). Here, it was baseline corrected using the mean skin conductance signal 1 sec before the delay onset. The applied Winsoring technique for controlling outliers referred to the replacement of all extreme values that are more than 3 standard deviations above the mean by measures equivalent to 3 standard deviations above the mean.

Finger pulse was recorded continuously during both tasks using pulse oximetry in the integrated Siemens physiological monitoring unit (photoplethysmograph with an infra-red emitter at the tip of the left index finger, sampling rate 50 Hz). Due to technical problems the pulse data could not be associated precisely with task events and are therefore reported as overall pulse rate for the whole tasks.

Self-Report.

Participants were asked to rate the time point they usually get bored and impatient in 6 typical everyday waiting or delay situations on a visual analogous scale ranging from 0 to 15 minutes: waiting for green at a traffic light, waiting for a bus, waiting in the checkout line, waiting for someone on a date, waiting in a telephone queue, filling out a questionnaire. Reliability for these

two scales was good (Cronbach's alpha = .88 and .86 for minutes until getting bored and minutes until getting impatient, respectively). Task specific DAv was consecutively collected during the fMRI DAv task via online ratings regarding the current feelings towards the task at the end of each time-out (see above). Finally, retrospective assessment of task-specific DAv in the delay frustration task comprised the question *'Did you get impatient?',* rated on a 5-point Likert type scale with 'not at all' and 'very much' as anchors. Before averaging these different variables for each participant, ratings from the everyday waiting situations as well as the continuously assessed ratings during fMRI were inverted, so that higher values indicate higher degrees of DAv in all variables.

Participants.

Variable	**Patients (N = 12)**	**Healthy Controls (N = 12)**	***p***
Conners' Adult ADHD Rating Scale (CAARS)			
Subscale Inattention	17.51 (5.40)	4.92 (3.23)	<.001
Subscale Hyperactivity	14.08 (6.49)	5.50 (2.94)	.001
Subscale Impulsivity	15.92 (5.37)	5.37 (3.11)	<.001

Results

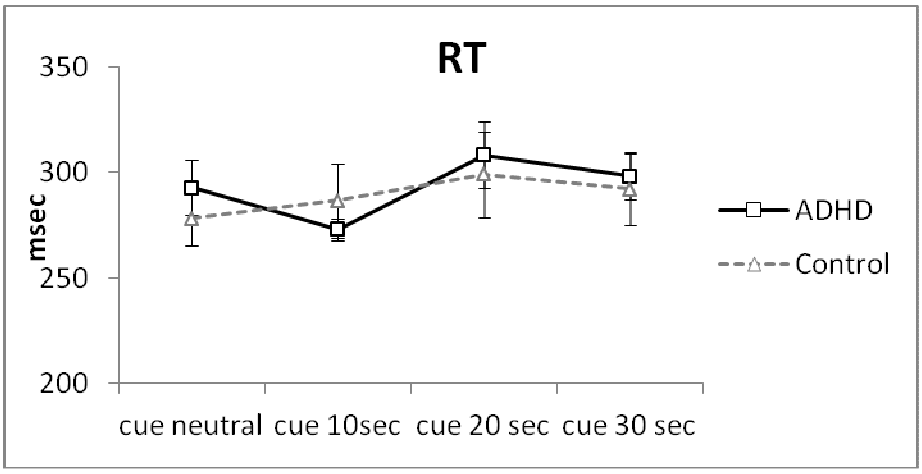

Figure S1: Reaction times after cues indicating different length of possible delays (or no delay=neutral) in the fMRI DAv task. Depicted are means and standard errors of the mean in msec. Group differences were not significant (all *p*s>.10).

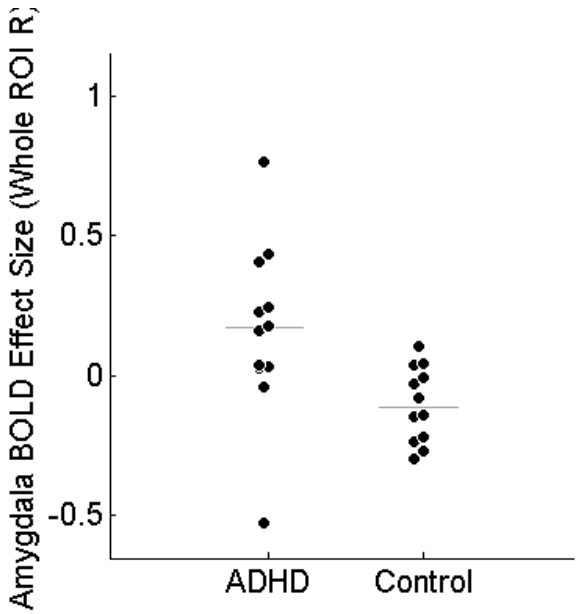

Figure S2: Individual parameter estimates for the modulation-by-delay effect averaged over all voxels within the a priori defined right amygdala ROI for each participant (black dots) as well as group medians (gray lines). Note: ROI = region of interest.

Table S3: Results (mean and standard deviation) of individual scales and outcome variables.

	ADHD *M* (*SD*)	**Control** *M* (*SD*)	Mann-Whitney-U test *p*
Self-Report			
online rating of feelings during fMRI DAv task			
- after 10 sec delay	-0.78 (2.57)	1.34 (5.76)	.119
- after 20 sec delay	-0.54 (2.72)	1.73 (5.04)	.119
- after 30 sec delay	-0.62 (2.45)	1.71 (4.44)	.094
[mean]	-0.64 (2.54)	1.59 (5.09)	.119
retrospective impatience during the delay frustration task	2.56 (1.01)	1.44 (0.73)	.009
everyday waiting situations			
- boredom (in minutes)	5.78 (2.29)	8.94 (3.32)	.017
- impatience (in minutes)	7.67 (3.0)	9.75 (3.52)	.094
Psychophysiological			
fMRI DAv task			
pulse rate (in beats per minute)	54.87 (6.44)	49.31 (6.34)	.065
skin conductance level (in micro Siemens)			
- 10 sec delay	0.19 (0.16)	0.11 (0.11)	.196
- 20 sec delay	0.15 (0.15)	0.06 (0.07)	.196
- 30 sec delay	0.12 (0.12)	0.04 (0.05)	.124
[mean]	0.15 (0.12)	0.07 (0.06)	.065
Delay frustration task			
pulse rate (in beats per minute)	56.16 (5.30)	51.27 (6.60)	.056
skin conductance level during delay periods (in micro Siemens)	0.04 (0.05)	0.02 (0.03)	.065
Behavioral			
Delay discounting *k* parameter	0.35 (0.32)	0.41 (0.62)	.603
Continuous DAv test waiting time (in minutes)	10.42 (6.34)	11.89 (7.66)	.564
fMRI DAv task			
reaction time (in msec)			
- cue neutral	316.24 (39.02)	299.58 (51.28)	.100
- cue 10 sec delay	304.46 (21.50)	314.21 (66.05)	.862
- cue 20 sec delay	332.18 (35.59)	313.48 (65.62)	.356
- cue 30 sec delay	325.16 (34.64)	314.75 (59.57)	.644
[mean]	319.51 (22.91)	310.50 (55.64)	.419
Delay frustration task			
response rate (in button presses per second)			
- normal period	0.46 (0.10)	0.47 (0.08)	.624
- delay period	0.79 (0.54)	0.70 (0.43)	.686
increase from normal to delay (in %)	70.01 (112.07)	45.75 (81.13)	.773

Note: M=mean, SD=standard deviation, DAv=delay aversion.