BRIEF REPORT

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

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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 increase 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

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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 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, that is, 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 dur-
ing 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 {1} the hypothesized negative affect generated by delay for this population and (2) 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 with escapable delay (Lemiere et al., 2012). Although 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 because of some limitations in this study. In particular, there was no examination of the “dose-response,” that is, 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 assess 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 (1) psychophysiological responses (pulse rate, skin conductance), (2) self-reported measures of DAv, and (3) 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, and 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, Rez-Junginger et al., 2003). All patients were free of any current comorbid disorder on axis 1, and five patients had at least one comorbid lifetime diagnosis as determined by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) interview (SCID, First & Pincus, 2002: 3 depression, 2 eating disorder, 2 substance dependence/abuse). Exclusion criteria were schizophrenia, bipolar, and 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 possible 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). Before the task, participants performed a 5-minute 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 duration of the experiment was actually about 20 minutes and variance was low (due to the adaptation of thresholds, see above).

**Behavioral DAv measures.** Three additional tasks were administered during the same experimental session to acquire auxiliary behavioral DAv measures (additional information on these tasks is in the supplemental 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 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 ks indicate stronger delay discounting, that is, a stronger loss of subjective value of money with increasing delay.

In the continuous DAv test (Müller, 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 DAvs 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, Anrop, Wiersema, & Sonuga-Barke, 2006), participants experienced several unexpected delays while performing a simple visual discrimination task. Unknown to the participants, the re-
response box was deactivated during 15 predefined pseudo random-
ized 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 supplemental 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 as a result of technical problems. Finger pulse data are reported as overall pulse rate (in beats per minutes). Psychophysiological measures were combined to provide a composite score (Cronbach’s 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 supplemental 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.

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

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). Preprocessing comprised slice timing, realignment, coregistration, spatial normalization, and smoothing (8 mm 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 1-sec 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 modula-

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) to avoid subsequent extra delays of varying length. RT, reaction time; ISI, interstimulus interval.
tion of neural activity by the length of anticipated delay was calculated for each participant. Group analyses (one- and two-sample t tests) were done on these images. Because of a specific focus on negative emotional states, regions of interest (ROIs) were selected from the literature (Carretié, Albert, Lopez-Martin, & Tapia, 2009; Sehlmeier 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 small volume correction (SVC) was applied with a family-wise error (FWE) correction of 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 in self-report, behavioral and physiological data 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 with 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 Cohen’s d ≤ .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 with 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 ps > .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, that is, 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, the 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 group analysis remained significant for the right amygdala ROI when covarying for lifetime comorbid disorders, depressive or anxiety symptoms (all ps[FWE] < .05).

The whole brain analysis revealed one hyper-modulated cluster within the orbitofrontal cortex for ADHD patients compared with control subjects (MNI\[x/y/z\] = [12/38/−17], t = 4.47). This effect was inversely correlated with self-reported trait anxiety (ADHD

Discussion

ADHD patients exhibited an abnormal pattern of delay-related activity in the right amygdala which, though only trend-wise 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, because 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
of physiological measures (especially pulse rate) would require a closer matching of groups on variables such as physical fitness and body mass index to rule out possible confounds. Lastly, alternative ways of conceptualizing DAv in ADHD, for example, 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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