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Functional connectivity in cortico-subcortical brain networks underlying reward processing in attention-deficit/hyperactivity disorder

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ABSTRACT

Background: Many patients with attention-deficit/hyperactivity disorder (ADHD) display aberrant reward-related behavior. Task-based fMRI studies have related atypical reward processing in ADHD to altered BOLD activity in regions underlying reward processing such as ventral striatum and orbitofrontal cortex. However, it remains unclear whether the observed effects are region-specific or related to changes in functional connectivity of networks supporting reward processing. Here we use resting-state fMRI to comprehensively delineate the functional connectivity architecture underlying aberrant reward processing in ADHD.

Methods: We assessed resting-state functional connectivity of four networks that support reward processing. These networks showed high spatial overlap with the default mode, fronto-parietal, lateral visual, and salience networks, yet only activity within the salience network was effectively sensitive to reward value. We parcelled these networks into their functional cortical and subcortical subregions and obtained functional connectivity matrices by computing Pearson correlations between the regional time series. We compared functional connectivity within each of the four networks between participants with ADHD and controls, and related functional connectivity to dimensional ADHD symptom scores across all participants ($N = 444$; age range: 8.5–30.5; mean age: 17.7).

Results: We did not observe significant ADHD-related alterations in functional connectivity of the salience network, which included key reward regions. Instead, levels of inattention symptoms modulated functional connectivity of the default-mode and fronto-parietal networks, which supported general task processing.

Conclusions: The present study does not corroborate previous childhood evidence for functional connectivity alterations between key reward processing regions in adolescents and young adults with ADHD. Our findings could point to developmental normalization or indicate that reward-processing deficits result from functional connectivity alterations in general task-related networks.

1. Introduction

Aberrant reward processing is considered to be a key feature of attention-deficit/hyperactivity disorder (ADHD; Luman et al. 2005; Sonuga-Barke 2005). Compared to healthy controls, both youth and adults with ADHD show a preference for small immediate rewards over larger delayed rewards (Bitsakou et al. 2009; Marco et al. 2009), make more risky decisions to obtain rewards (Groen et al. 2013), and are more sensitive to the positive effects of rewards while performing cognitive tasks (Luman et al. 2010; Uebel et al. 2010).

Several task-based functional magnetic resonance imaging (fMRI) studies have invested in mapping the neurobiological basis of reward processing in the brain using a variety of reward-probing paradigms. Key structures identified include the dopaminergic midbrain, ventral striatum (including the nucleus accumbens (NAcc)), anterior cingulate cortex (ACC), and orbitofrontal cortex (OFC; Haber and Knutson 2010). Furthermore, several other brain regions such as dorsolateral prefrontal cortex (DLFPC), insula, cerebellum, thalamus, hippocampus, and amygdala, are thought to be important in regulating the reward network (Haber and Knutson 2010; Liu et al. 2011). In the context of

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both childhood and adulthood ADHD, studies have shown decreased BOLD responses in ventral striatum, precuneus, posterior cingulate cortex (PCC) and medial prefrontal cortex (PFC) during reward anticipation (Chantiluke et al. 2014; Hauser et al. 2014; Plichta and Scheres 2014; Rubia et al. 2009; Scheres et al. 2007), increased BOLD responses in ACC and cerebellum during reward anticipation (von Rhein et al. 2015), as well as increased BOLD responses in OFC and occipital cortex during reward receipt (von Rhein et al. 2015).

As neuroimaging is shifting its focus from localizing functions in individual regions to investigating the integration of functionally related areas into larger networks, it becomes increasingly clear that ADHD is not related to dysfunction in isolated brain areas (Oldehinkel et al. 2013). Accordingly, dysfunctional integration within and between reward-related regions may underlie deficient reward processing in ADHD. Initial evidence comes from studies that used resting-state fMRI (R-fMRI) to investigate functional integration within the reward-network in children with ADHD. One of these studies reported *decreased* functional connectivity of ventral striatum with OFC, hippocampus, and anterior PFC in ADHD (Posner et al. 2013; age range: 7–12 years, 22 ADHD participants; 20 controls). Yet, others revealed *increased* functional connectivity of OFC with NAcc and ACC (Tomasi and Volkow 2012; mean age 10.8 ± 1.8 SD; 247 ADHD participants, 309 controls), and of NAcc with ventromedial and anterior PFC in ADHD (Costa Dias et al. 2012; age range: 7–12 years; 35 ADHD participants, 64 controls). Furthermore, these three studies were all conducted in children, while ADHD is known to persist into adolescence and adulthood in many patients (Faraone et al. 2006).

Accordingly, building on these initial studies, we aimed to comprehensively delineate the functional neural architecture underlying aberrant reward processing in ADHD. To this end, we investigated ADHD-related changes in resting-state functional connectivity of networks that support reward processing using a large ADHD cohort ($N = 444$) with a wide age range (8.5–30.5 years). We made use of large-scale functional networks derived during reward processing (von Rhein et al., in revision), thereby extending our focus beyond the reward regions typically identified using highly specific task contrasts. To be able to investigate connectivity within each network, we identified the functional cortical subregions within each network and also assessed each network's cortico-subcortical integration by examining its connectivity with cerebellum, thalamus, and striatum. Next, using diagnostic categories as well as dimensional ADHD symptom measures, we determined the impact of ADHD on these functional connectivity patterns.

2. Material and methods

2.1. Participants

Participants in our study were part of the NeuroIMAGE cohort (von Rhein et al. 2014), consisting of families with one or more children with an ADHD diagnosis as well as control families with children without an ADHD diagnosis. Diagnosis of ADHD and comorbid disorders (including oppositional defiant disorder (ODD), conduct disorder (CD), anxiety disorders, and depression) were assessed by trained psychologists using the Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version (K-SADS; Kaufman et al. 1997), complemented with Conners' ADHD questionnaires (Conners et al. 1998a; Conners et al. 1998b). Participants were diagnosed with ADHD if they displayed six or more DSM-5 ADHD symptoms on at least one domain (inattention or hyperactivity/impulsivity; five or more for participants >18 years). Participants from control families and unaffected siblings of participants with ADHD were allowed to have a maximum of two ADHD symptoms per domain. Participants not belonging to one of these groups were classified as subthreshold ADHD. Next to this categorical classification, we used ADHD symptom scores for inattention and hyperactivity/impulsivity derived from the Conners' Parent Rating Scale (CPRS-RL; Conners et al. 1998a) for our dimensional analyses. The CPRS-RL is an ADHD rating scale from which standardized T-scores ranging from 40 to 90 can be obtained. The full description of the NeuroIMAGE cohort, including inclusion criteria, diagnostic assessment, and general testing procedures can be found in von Rhein et al. (2014). Our study was approved by local ethical committees of the participating centers and conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from all participants (for participants >12 years) and their legal guardians (for participants <18 years).

For the current analysis we selected participants who completed both an anatomical and an 8-minute R-fMRI scan ($N = 507$). We excluded participants with high head-motion ($N = 47$, as determined by calculating the mean root mean square of the frame-wise displacement (RMS-FD > 0.5; Jenkinson et al. 2002) across the R-fMRI scan) and participants with insufficient brain coverage during the R-fMRI scan ($N = 16$). This procedure led to the inclusion of 444 participants in total, including participants with ADHD ($N = 169$), healthy controls ($N = 122$), unaffected siblings of participants with ADHD ($N = 89$), and participants with subthreshold ADHD ($N = 64$). The characteristics of participants included in our analyses are specified in Table 1. Out of the 169 participants with an ADHD diagnosis in our sample, 83 participants had the inattentive presentation, 17 participants had the hyperactivity-impulsive presentation and 69 participants had the combined presentation. In our analyses we chose not to investigate these subgroups separately, given the emphasis of this paper to move towards a more dimensional investigation of ADHD, which (partly) captures this heterogeneity in symptoms. In the ADHD group, 130 participants were on stimulant medication, however, all participants withheld medication starting 48 h before the day of assessment.

2.2. MRI data acquisition and preprocessing

MRI data were acquired at two locations on 1.5 Tesla scanners from Siemens (Siemens AVANTO at the Donders Institute for Brain, Cognition and Behavior in Nijmegen and Siemens SONATA at the VU University Medical Centre in Amsterdam). At both sites identical 8-channel head coils and MRI protocols were employed. Structural images were obtained using an MPRAGE sequence (TR = 2730 ms, TE = 2.95 ms, T1 = 1000 ms, voxel size = 1 × 1 × 1 mm, flip angle = 7, matrix size = 256 × 256, FOV = 256 mm, 176 slices). The R-fMRI data were acquired using a gradient echo-planar imaging sequence (TR = 1960 ms, TE = 40 ms, flip angle = 80, matrix size = 64 × 64, in-plane resolution = 3.5 mm, FOV = 224 mm, 37 axial slices, slice thickness/gap = 3.0 mm/0 mm/0.5 mm, 265 volumes). Participants were instructed to relax and keep their eyes open for the duration of the R-fMRI scan.

The R-fMRI data were preprocessed using a standard preprocessing pipeline incorporating tools from the FMRIB Software Library (FSL version 5.0.6; http://www.fmrib.ox.ac.uk/fsl). Our pipeline included removal of the first five volumes to allow for signal equilibration, primary head movement correction via realignment to the middle volume (MCFLIRT; Jenkinson et al. 2002), grand mean scaling, and spatial smoothing using a 6 mm FWHM Gaussian kernel. Next, ICA-AROMA was applied to the R-fMRI data to select and remove components that represent secondary head motion-related artifacts (Pruim et al. 2015a; Pruim et al., 2015b), followed by nuisance regression to remove signal from white matter and cerebrospinal fluid, and a high-pass filter (0.01 Hz). The R-fMRI images of each participant were co-registered to the participants' anatomical images by means of boundary-based registration implemented in FSL-FLIRT (Greve and Fischl 2009). The T1 images of each participant were registered to MNI152 standard space using 12-parameter affine transformation and refined using non-linear registration with FSL-FNIRT (10 mm warp, 2 mm resampling resolution; Jenkinson et al. 2002). Finally, we brought all R-fMRI images to MNI152 standard space by applying the concatenated R-fMRI to T1 and T1 to MNI152 transformations.