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Aberrant local striatal functional connectivity in attention-deficit/hyperactivity disorder

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Background: Task-based and resting-state functional Magnetic Resonance Imaging (fMRI) studies report attention-deficit/hyperactivity disorder (ADHD)-related alterations in brain regions implicated in cortico-striatal networks. We assessed whether ADHD is associated with changes in the brain's global cortico-striatal functional architecture, or whether ADHD-related alterations are limited to local, intrastriatal functional connections. **Methods:** We included a cohort of adolescents with ADHD ($N = 181$) and healthy controls ($N = 140$) and assessed functional connectivity of nucleus accumbens, caudate nucleus, anterior putamen, and posterior putamen. To assess global cortico-striatal functional architecture we computed whole-brain functional connectivity by including all regions of interest in one multivariate analysis. We assessed local striatal functional connectivity using partial correlations between the time series of the striatal regions. **Results:** Diagnostic status did not influence global cortico-striatal functional architecture. However, compared to controls, participants with ADHD exhibited significantly increased local functional connectivity between anterior and posterior putamen ($p = .0003$; ADHD: $z = .30$, controls: $z = .24$). Results were not affected by medication use or comorbid oppositional defiant disorder and conduct disorder. **Conclusions:** Our results do not support hypotheses that ADHD is associated with alterations in cortico-striatal networks, but suggest changes in local striatal functional connectivity. We interpret our findings as aberrant development of local functional connectivity of the putamen, potentially leading to decreased functional segregation between anterior and posterior putamen in ADHD. **Keywords:** Resting-state fMRI; functional connectivity; attention-deficit/hyperactivity disorder; cortico-striatal networks; striatum; putamen.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) has been associated with deficits in executive functions such as response inhibition, working memory (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005), reward processing (Sonuga-Barke, 2005), and motor function (Stray et al., 2013). Key brain regions associated with these functions are located in the striatum, including three main nuclei: nucleus accumbens (NAcc), caudate nucleus, and putamen. Each striatal structure receives projections from distinct cerebral regions (Alexander, Delong, & Strick, 1986; Di Martino et al., 2008; Helmich et al., 2010). NAcc forms a network with anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC), associated with reward processing and motivational control (Haber & Knutson, 2010). Caudate nucleus regulates cognitive control processes via connections with dorsolateral prefrontal cortex (DLFPC; Levy, Friedman, Davachi, & Goldman-Rakic, 1997). Finally, putamen regulates motor function through connections with motor cortices (Alexander et al., 1986). In addition, it is hypothesized that putamen can be subdivided into a functionally distinct anterior and posterior region (Aramaki, Haruno, Osu, & Sadato, 2011; Tricomi, Balleine, & O'Doherty, 2009). Anterior putamen has been associated with higher order cognitive aspects of motor control including learning and initiating new movements (Aramaki et al., 2011), through connections with presupplementary motor area and ACC (Helmich et al., 2010). Posterior putamen has been related to the execution of well-learnt, skilled movements (Tricomi et al., 2009), via connections to primary and secondary motor areas (Helmich et al., 2010).

As these cortico-striatal networks are implicated in behavior that is often impaired in patients with ADHD, they have been suggested as potential neural underpinnings of ADHD-related deficits (Cubillo, Halari, Smith, Taylor, & Rubia, 2012). Task-based functional Magnetic Resonance Imaging (fMRI) studies support the involvement of cortico-striatal networks in ADHD. Patients with ADHD showed aberrant brain responses in DLPFC, ACC, caudate nucleus, and supplementary motor area during response inhibition and attention, and in

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NAcc and OFC during reward processing (Cortese et al., 2012; Cubillo et al., 2012). Several resting-state fMRI (rs-fMRI) studies have demonstrated aberrant functional connectivity of ACC, frontal cortex, caudate, putamen, NAcc, and motor regions in ADHD (for review, see Oldehinkel, Francx, Beckmann, Buitelaar, & Mennes, 2013). Furthermore, atypical functional connectivity of putamen, OFC, and NAcc, has been associated with severity of symptoms of hyperactivity/impulsivity and inattention (Cao et al., 2009; Costa Dias et al., 2012; Tomasi & Volkow, 2012).

Results from these fMRI studies suggest dysfunction of cortico-striatal networks in ADHD. However, the observation that one or more regions within a cortico-striatal network show aberrant brain responses does not necessarily imply dysfunction of the entire network. Instead, the observed dysfunctions might be primarily related to impairments in within-striatum cross-talk, based on the assumption that striatal regions modulate each other via striato-nigro-striatal connections (Aarts, van Holstein, & Cools, 2011; Haber, Fudge, & McFarland, 2000). Studies of brain anatomy provide evidence for local striatal abnormalities in ADHD as reduced volume has been reported for caudate nucleus, NAcc, and putamen (Cubillo et al., 2012). Only few studies report on local, intrastriatal functional connectivity and its relation to ADHD. Using regional homogeneity and degree centrality, aberrant local functional connectivity in caudate nucleus (Cao et al., 2009; Di Martino et al., 2013) and putamen was demonstrated using rs-fMRI in ADHD (Di Martino et al., 2013). One of these studies also reported atypical local functional connectivity between putamen and NAcc (Cao et al., 2009). Based on these findings, we hypothesize that aberrant local connectivity between striatal structures is associated with ADHD symptomatology. As different striatal regions can interact with each other via their midbrain connections such local changes of connectivity might also account for changes in associated cortico-striatal networks (Haber et al., 2000).

In the light of this hypothesis we investigate whether ADHD is primarily associated with changes in global cortico-striatal functional architecture or is also evident in changes to local functional connectivity between substructures within striatum. To this end we examine resting-state functional connectivity of NAcc, caudate nucleus, anterior putamen, and posterior putamen in a large sample of participants with ADHD and healthy controls using comprehensive multivariate and partial correlation analyses.

Methods

Participants

All participants were part of the NeuroIMAGE cohort (von Rhein et al., 2014), the Dutch follow-up study of the large-scale International Multicenter ADHD Genetics (IMAGE) study (Muller et al., 2011). The NeuroIMAGE cohort consists of families with children diagnosed with ADHD and control families. Here, we included participants from ADHD families with a DSM-5-based ADHD diagnosis and participants from control families who completed both a structural MRI scan and a rs-fMRI scan ($N = 356$). Diagnoses of ADHD and comorbid disorders, including oppositional defiant disorder (ODD), conduct disorder (CD), anxiety disorders, and depression were assessed by a trained professional 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, Erhardt, & Sparrow, 1999; Conners, Sitarenios, Parker, & Epstein, 1998a). The full diagnostic algorithm and inclusion criteria are described in the Supporting information, further details about the NeuroIMAGE study and its diagnostic and general testing procedures are described elsewhere (von Rhein et al., 2014). Our study was approved by the local ethical committees of the participating centers; written informed consent was obtained from all participants (for participants > 12 years) and their legal guardians (for participants < 18 years).

We excluded participants for head-motion ($N = 22$) as determined by frame-wise displacement (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; cut-off = 0.73 RMS-FD, corresponding to the 5% highest movers in the total sample), and participants with insufficient brain coverage during the rs-fMRI scan ($N = 13$). Our final analyses included 181 participants with ADHD and 140 healthy controls. We tested for significant differences in age, gender, scan site, IQ, comorbid ODD/CD, medication use, and Conners Parent Rating Scale (CPRS) inattentive and CPRS hyperactive/impulsive symptom scores between participants of the included sample ($N = 321$) and participants that were excluded due to excessive motion ($N = 22$). Results for these analyses are presented in the Supporting information. It should be noted that both the ADHD and control group included participants of whom a sibling was present in the same group (ADHD: $n = 35$; controls: $n = 53$). Group characteristics are specified in Table 1 and Table S1. Groups were not balanced with respect to IQ, gender, scan location, and comorbid disorders. Within the ADHD group, 133 participants had used medication prescribed for ADHD during at least 6 months in their lives. All participants were asked to withhold medication use for 48 hr before the day of assessment.

MRI processing

The MRI data were acquired at two scanning sites on 1.5 Tesla Siemens scanners; all participants completed an anatomical scan and an 8-min-long rs-fMRI scan (detailed scan parameters are listed in the Supporting information). The rs-fMRI data were preprocessed using tools from the FMRIB Software Library (FSL version 5.0; http://www.fmrib.ox.ac.uk/fsl) and included removal of the first five volumes to allow for signal equilibration, head movement correction via realignment to the middle volume (MCFLIRT; Jenkinson, Bannister, Brady, & Smith, 2002), grand mean scaling, spatial smoothing using a 6-mm FWHM Gaussian kernel, and high-pass filtering (0.01 Hz). We did not conduct band-pass filtering in an effort to preserve as much signal of interest as possible (Griffanti et al., 2014; Niazy, Xie, Miller, Beckmann, & Smith, 2011). Moreover, in the light of frequency aliasing given our volume TR we believe that respiration or cardiac-related signal would not be adequately removed using the typical 0.1–0.01 Hz band-pass filter. The preprocessed rs-fMRI data were denoised for secondary head motion-related artifacts using automatic noise selection as implemented in ICA-AROMA, a novel method for distinguishing head motion-related components resulting from an ICA decomposition of the preprocessed data (Pruim, Mennes, van Rooij, Llera, Buitelaar, & Beckmann, 2015).

Table 1 Participant characteristics

	ADHD (N = 181)		Controls (N = 140)			
	Mean	*SD*	Mean	*SD*	Test statistic	p-value
Age (years)	17.73	3.10	17.07	3.35	$t(319) = 1.814$	.07
Estimated IQ[a]	96.13	15.43	106.20	13.86	$t(315) = -6.019$	**
Inattentive symptoms[b]	7.36	1.52	0.44	1.31	$t(319) = 42.91$	**
Hyperactive/Impulsive symptoms[b]	5.79	2.42	0.37	0.88	$t(319) = 25.28$	**
Medication use (years)	5.44	4.55	–	–	–	–
SES[c]	12.98	1.90	13.95	1.70	$t(312) = 4.678$	**
	N	%	*N*	%		
Number of males	133	73.48	64	45.71	$\chi^2 = 25.67$	**
Scan site Nijmegen	98	54.14	50	35.46	$\chi^2 = 10.79$	**
ODD diagnosis[d]	49	27.07	1	0.71	$\chi^2 = 41.70$	**
CD diagnosis[e]	7	3.87	–	–	–	–
Lifetime medication use[f]	133	74.48	–	–	–	–

ADHD, attention-deficit/hyperactivity disorder; SES, socioeconomic status; ODD, oppositional defiant disorder, CD, conduct disorder.
[a]Estimated IQ based on Wechsler Intelligence Scale for Children or Wechsler Adult Intelligence Scale–III Vocabulary and block design.
[b]Symptom count based on K-SADS interview (Kaufman et al., 1997) and Conners' questionnaires (Conners et al., 1998a,b; Conners et al., 1999); Maximum of nine symptoms per dimension (≥6 is clinical threshold).
[c]Socioeconomic status (parental years of education; average of both parents).
[d]Oppositional defiant disorder.
[e]Conduct disorder.
[f]Participants that used medication prescribed for ADHD during at least 6 months in their lives.
**$p \leq .001$.

Importantly, the selection of components made by ICA-AROMA preserves reproducibility and identifiability of resting-state signal of interest (Pruim, Mennes, Buitelaar, & Beckmann, 2015). Finally, nuisance regression was conducted to remove signal associated with white matter and cerebrospinal fluid.

The rs-fMRI images were coregistered to the participant-level high-resolution anatomical images using boundary-based registration (Greve & Fischl, 2009) implemented in FSL FLIRT. For each participant we calculated the nonlinear transform from the high-resolution anatomical image to a custom study template using FSL FNIRT (Jenkinson et al., 2002). The custom group template (voxel size 2 × 2×2 mm) was generated by averaging across T1-scans (after nonlinear normalization to MNI152 standard space) of all participants in the NeuroIMAGE study (N = 787).

Global striatal functional connectivity analyses

We used the structurally defined seed masks for NAcc, caudate nucleus, and anterior and posterior putamen (see Supporting information for details on seed definition). We extracted the timeseries from the rs-fMRI data for all voxels within each mask, applied singular value decomposition and used the timeseries of the first eigenvariate from this decomposition for further analyses.

Based on these time series, we obtained participant-level whole-brain voxel-wise functional connectivity estimates for all seed-regions by means of multiple regression. By applying a multiple regression approach (instead of a univariate analysis for each striatal seed separately), variance that is shared between striatal seed regions is not attributed to any of the striatal regions. The multiple regression approach thus resulted in unique whole-brain voxel-wise functional connectivity maps for each striatal seed unconfounded by contributions of the other seeds. In addition to whole-brain connectivity maps for each seed, we computed connectivity difference maps for anterior versus posterior putamen to test the hypothesis of a functional distinction between these two regions. Resulting connectivity maps were transformed to the study template for group analysis.

We compared participants with ADHD to healthy controls in a group level analysis for each of the obtained regression maps using permutation testing (1,000 permutations) as implemented in FSL Randomise. Covariates were included for age, gender, IQ, scan-site, and comorbid diagnosis (ODD and/or CD). We applied threshold-free cluster enhancement as implemented in FSL (Smith & Nichols, 2009) and statistical significance was determined by means of a family-wise error threshold of $p < .05$.

Local striatal functional connectivity analyses

Local functional connectivity between the striatal seeds was assessed by calculating full (Pearson) correlations and partial correlations between the eigenvariate time series for every combination of seeds (six pairs). By using partial correlations, variance that is shared between striatal regions is not attributed to any of the striatal regions. Partial correlations thus reflect unique local functional connectivity between each pair of striatal regions. Computing partial correlations between the different striatal seeds can hence be interpreted as the local functional connectivity equivalent of using a multiple regression analysis to compute whole-brain functional connectivity of the striatal seed regions.

Both full and partial correlations were transformed into normally distributed values using Fisher's r-to-Z-transformation. Significant differences in correlation strength between the ADHD and control group were tested using permutation testing with 5,000 permutations for each seed-pair. p-Values were obtained by calculating the proportion of permuted samples that yielded a difference between the ADHD and control group higher than the observed difference. Correction for multiple comparisons was implemented using Bonferroni correction. Differences were considered statistically significant if $p < .008$ (=0.05/6 seeds pairs).

Relationship with symptom severity

For regions that showed significant ADHD versus control differences in the global or local striatal analyses we examined in ADHD patients whether results were related to ADHD symptom severity. We calculated partial correlations (i.e., corrected for effects of age, site, gender, IQ, and ODD/CD

comorbidity) between functional connectivity and symptom count as well as ADHD scores derived from the CPRS (Conners, Sitarenios, Parker, & Epstein, 1998b). ADHD symptom count was assessed by the K-SADS diagnostic interview complemented with Conners' ADHD rating scales. The DSM-Inattentive behavior scale (0–9 symptoms), the DSM-Hyperactivity/Impulsive behavior scale (0–9 symptoms) and DSM-Total symptom scale (0–18 symptoms) were used. In addition, we investigated associations with CPRS inattention scores (scale: 40–90), CPRS hyperactivity/impulsivity scores (scale: 40–90), and CPRS total ADHD scores (scale: 40–90).

Relationship with DRD4 and DAT1 genotypes

We also related observed group differences to available genotyping for two main dopaminergic genes, DRD4 and DAT1, which are thought to play a pivotal role in fronto-striatal signaling (Aarts et al., 2011). Methods and results for this analysis are presented in the Supporting information.

Sensitivity analyses

Finally, we ensured that observed group differences in connectivity were not influenced by ADHD subtype, medication history, IQ, socioeconomic status (SES), gender, scan site, and comorbid ODD/CD (see Supporting information for methods and results).

Results

Global functional connectivity of four striatal regions

Group connectivity maps of NAcc, caudate, anterior putamen, and posterior putamen in both the ADHD and control group replicated the major cortico-striatal networks (Alexander et al., 1986; Di Martino et al., 2008; Helmich et al., 2010). Figure 1 displays regions exhibiting functional connectivity with the four striatal seed regions in both groups. For a description of connectivity patterns see the Supporting information.

We did not observe significant differences between the ADHD and control group in the whole-brain functional connectivity maps. To replicate previous studies we also investigated cortico-striatal connectivity with one seed at a time (as opposed to our multivariate model). Similar to the multivariate analyses, these univariate analyses did not yield differences between our ADHD and control group (see Figure S2).

Local striatal functional connectivity

Local connectivity assessed using full correlations (i.e., uncorrected for global striatal effects) revealed significant group differences in four of the six striatal seed-pair combinations (see Figure 2). Significantly increased intrastriatal correlations were observed in participants with ADHD compared to healthy controls for the seed pairs: NAcc – anterior putamen ($p = .004$; ADHD: $z = .25$, controls: $z = .20$); caudate – anterior putamen ($p = .004$; ADHD: $z = .41$, controls: $z = .34$); caudate – posterior putamen ($p = .008$; ADHD: $z = .26$, controls: $z = .20$); and anterior putamen – posterior putamen ($p = .00006$; ADHD: $z = .39$, controls: $z = .31$).

When controlling for global striatal effects using partial correlations, we observed that local functional connectivity between anterior putamen and posterior putamen was significantly increased in the ADHD group compared to the control group (see Figure 2; $p = .0003$; ADHD: $z = .30$, $SD = .15$, controls: $z = .24$, $SD = .13$). Post hoc analyses revealed that this finding was independent of ADHD subtype and not influenced by medication use, imaging site, gender, IQ, SES, or ODD/CD comorbidity (Figures S3, S4, S5, and S6).

Finally, we confirmed that the obtained ADHD-related result was restricted to local connectivity by directly comparing the whole-brain connectivity maps obtained for anterior and posterior putamen. We observed no significant differences between ADHD and controls in this analysis (see Figure S8).

Relationship with symptom severity

We did not observe significant relationships between anterior–posterior putamen connectivity and inattentive symptoms (symptom count: $r = -.078$, $p = .306$; CPRS inattention: $r = .097$, $p = .087$) hyperactive/impulsive symptoms (symptom count: $r = -.028$, $p = .714$; CRPS hyperactivity/impulsivity: $r = .026$, $p = .649$), or total ADHD symptoms (symptom count: $r = -.065$, $p = .398$; CPRS total score: $r = .072$, $p = .205$).

Discussion

We investigated local and global cortico-striatal connectivity in a large sample of youth with ADHD and healthy controls. Contrasting previous work, we did not replicate ADHD-related alterations in the major cortico-striatal networks. Conversely, ADHD was associated with aberrant local functional connectivity between the anterior and posterior division of putamen.

Consistent with existing theories, we identified the four major cortico-striatal networks in both participants with ADHD and healthy controls (Alexander et al., 1986; Di Martino et al., 2008; Helmich et al., 2010). However, the whole-brain functional networks of NAcc, caudate, anterior putamen, and posterior putamen did not yield differences between the ADHD and control group. As such, our results do not replicate previous task-based fMRI (see Cortese et al., 2012; Cubillo et al., 2012) and rs-fMRI studies (Cao et al., 2009; Costa Dias et al., 2012; Mennes et al., 2011; Tomasi & Volkow, 2012) that reported ADHD-related global dysfunction and atypical functional connectivity in cortico-striatal networks. For example, task-based studies have reported

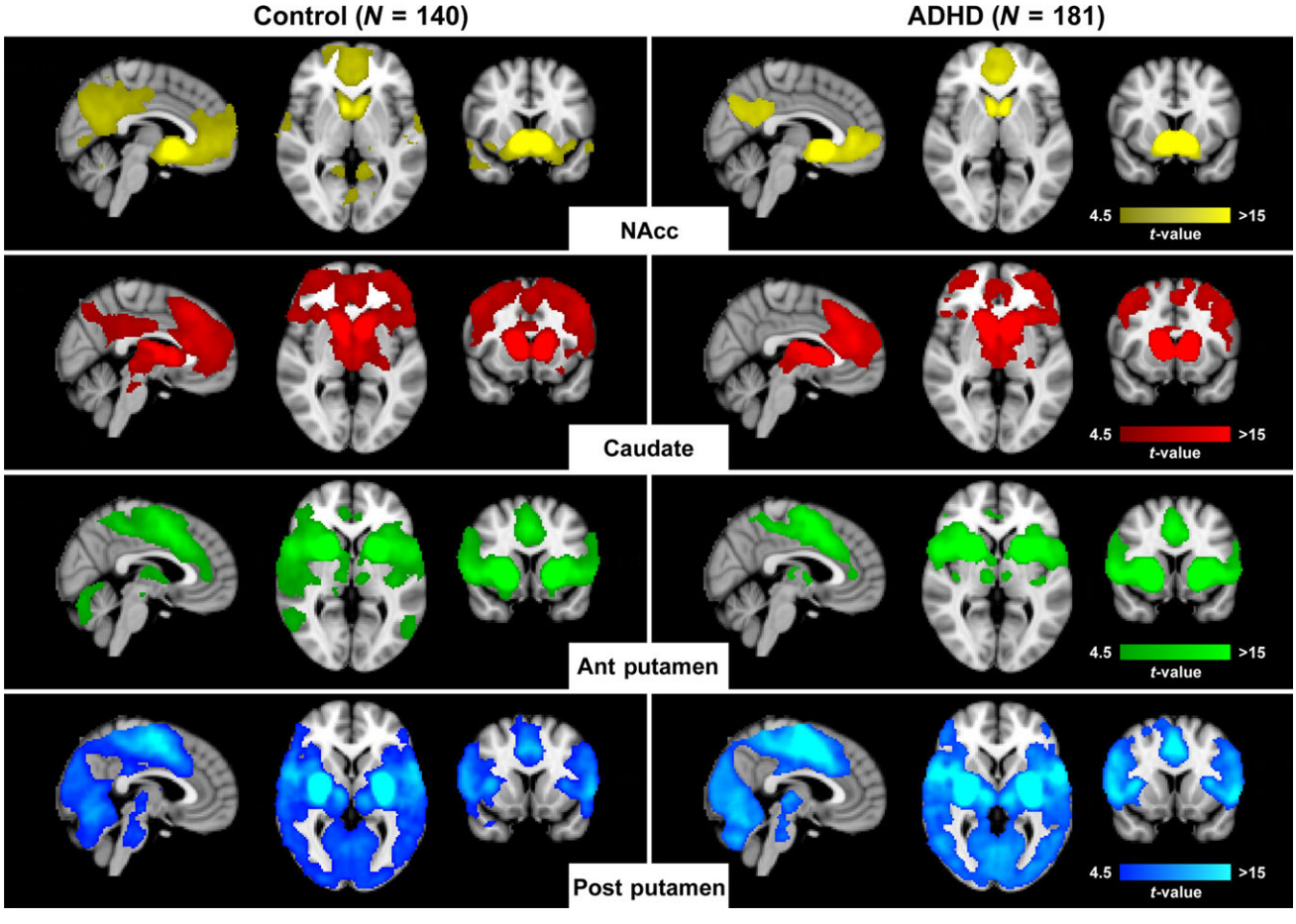

Figure 1 Global striatal connectivity. Whole-brain functional connectivity maps for nucleus accumbens, caudate nucleus, anterior putamen, and posterior putamen in the control (left) and attention-deficit/hyperactivity disorder (ADHD) group (right). Significant activation is shown (FWE-corrected, $p < .05$). We observed no difference between the ADHD and control group

increased activation in NAcc and OFC during reward processing (von Rhein et al., 2015), and decreased activation in putamen, caudate, ACC, and DLPFC during response inhibition and attention tasks in ADHD (Cubillo et al., 2012). Furthermore, reduced functional connectivity of putamen with frontal cortex, temporal cortex, and precuneus (Cao et al., 2009) as well as increased functional connectivity between caudate and ACC has previously been demonstrated (Mennes et al., 2011). In addition, decreased functional connectivity between NAcc and frontal cortex was found to correlate with increased impulsivity scores (Costa Dias et al., 2012).

One explanation for differences with results from task-related studies might be that rs-fMRI, as used in this study, measures the brain when cognitive load is low. When cognitive load increases, as typically induced in task-based fMRI measurements, deficits might become evident in aberrant recruitment of brain regions. This hypothesis corresponds with effort-related deficits in ADHD as proposed by the cognitive-energetic model (Sergeant, 2000). Further, differences between previous rs-fMRI studies and our study might be related to differences in methodology. Previous studies reporting atypical global connectivity of striatal regions applied univariate analysis (Cao et al., 2009; Costa Dias et al., 2012; Mennes et al., 2011; Tomasi & Volkow, 2012). Yet, when implementing this type of analyses we also failed to reveal significant group differences (see Figure S2). However, we can for instance not exclude variability in earlier findings related to insufficient control for head motion artifacts (Pruim, Mennes, van Rooij et al., 2015; Pruim, Mennes, Buitelaar et al., 2015; Van Dijk, Sabuncu, & Buckner, 2012), which was rigorously implemented in the current study (Pruim, Mennes, Buitelaar et al., 2015, Pruim, Mennes, van Rooij et al., 2015,).

The absence of ADHD versus control differences in whole-brain connectivity could also be related to heterogeneity within our sample. Heterogeneity in terms of phenotypic (Sonuga-Barke, 2002) as well as cognitive characteristics (Fair, Bathula, Nikolas, & Nigg, 2012) is a common observation in ADHD as well as healthy populations. This problem is partially mitigated by recruiting participants with similar demographic characteristics. Indeed, previous studies have specifically selected participants without stimulant treatment (Cao et al., 2009), or only participants with combined (Costa Dias et al., 2012) or nonhyperactive subtype (Mennes et al., 2011). Moreover, these studies focused on participants within a small age range. In contrast, our population

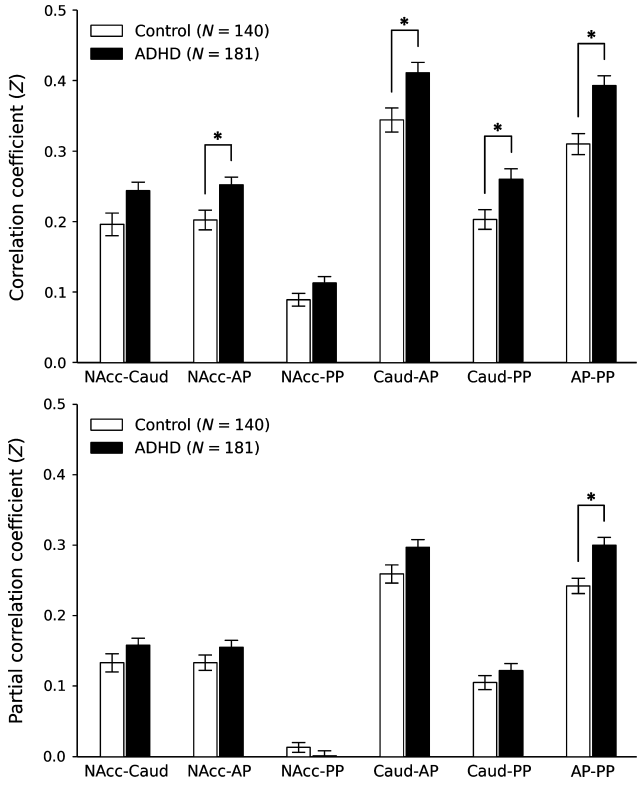

Figure 2 Local striatal connectivity. Mean Fisher-*z* transformed correlation coefficients indexing local, between seed functional connectivity. Full correlations are shown in the top graph. Significantly increased correlations were observed in the attention-deficit/hyperactivity disorder (ADHD) compared to control group for NAcc - anterior putamen (p = .004; ADHD: z = 0.25, SD = 0.15, controls: z = 0.20, SD = 0.16), caudate – anterior putamen (p = .004; ADHD: z = 0.41, SD = 0.21, controls: z = 0.34, SD = 0.20), caudate - posterior putamen (p = .008; ADHD: z = 0.26, SD = 0.20, controls: z = 0.20, SD = 0.17) and anterior putamen–posterior putamen (p = .00006; ADHD: z = 0.39, SD = 0.19, controls: z = 0.31, SD = 0.17) connectivity. Partial correlations are shown in the bottom graph. A significantly increased partial correlation between anterior putamen and posterior putamen connectivity was found in the ADHD group (p = .0003; ADHD: z = 0.300, SD = 0.15, controls: z = 0.242, SD = 0.13). Error bars indicate standard error of the mean. Abbreviations: NAcc = nucleus accumbens, Caud = caudate nucleus, AP = anterior putamen, PP = posterior putamen. Statistical differences were assessed using permutation testing and a Bonferroni-corrected alpha level of $p < .008$ (=0.05/6 seeds pairs). *$p < 0.008$.

study included the broad clinical phenotype with all subtypes, with and without stimulant treatment, and participants within a broad developmental age range. This approach may, however, wash out effects previously reported in smaller, more homogeneous samples. Yet, within our local findings we did not observe differences between the different ADHD subtypes (see Figure S6).

In contrast to the absence of ADHD-related effects on the major cortico-striatal networks, we did observe associations between ADHD diagnosis and functional connectivity locally within the striatum. Local connectivity between several striatal regions was increased in participants with ADHD compared to controls (full correlation results). Subsequent partial correlation analysis suggested that these effects were attributable to a specific increase in functional connectivity between anterior and posterior putamen in participants with ADHD. We interpret this finding as decreased functional segregation of anterior and posterior putamen in ADHD.

Taking into account the cognitive functions attributed to anterior and posterior putamen, our results lead to new, testable hypotheses. Anterior putamen has been associated with higher order cognitive aspects of motor control such as learning and initiating new movements (Aramaki et al., 2011). Posterior putamen on the other hand, has been implicated in the execution of well-learned, skilled movements (Tricomi et al., 2009). In this context, it is possible that decreased functional segregation of the neural correlates for 'learning and initiating new movements' and 'execution of skilled movements' might be related to the various motor skill deficits observed in ADHD, such as delays in gross motor milestones (sitting, crawling, walking), clumsiness, and poor fine motor control (Vasserman, Bender, & Macallister, 2014). Accordingly, our results warrant research into the hypothesis that the difference between 'learning and initiating new movements' and 'execution of skilled movements' is less distinctive in participants with ADHD compared to healthy controls. As a preliminary examination we assessed general motor function using the Developmental Coordination Disorder Questionnaire (DCD-Q; Wilson, Kaplan, Crawford, Campbell, & Dewey, 2000), see Supporting information. Although motor skills were significantly impaired in the ADHD compared to the control group ($p < .002$), motor skills were not related to anterior–posterior putamen connectivity ($-.038 < r > .037$; $p > .52$ for all scales). In the light of our hypothesis this result is not unexpected, as the DCD-Q might not be the best instrument to distinguish 'learning and initiating new movements' from 'execution of skilled movements'.

The observed increased local functional connectivity between anterior and posterior putamen in the ADHD group can also be interpreted in a developmental context. Typical development or maturation of functional brain networks has been characterized by both a decrease in short-range, local connectivity strength (segregation) and a simultaneous increase in the strength of long-range, global functional connectivity (integration) (Fair et al., 2009; Kelly et al., 2009). According to the delayed maturation hypothesis for ADHD, local connectivity would be increased and global connectivity decreased in youth with ADHD, while connectivity would normalize at a later age. Although not significant, supplementary analyses exploring the effects of age hinted that local anterior–posterior putamen connectivity decreased with age in the control group but not in the ADHD group (see Figure S7). These findings suggest aberrant development of local connectivity in the ADHD group, potentially resulting in local 'overconnectivity' in ADHD.

When comparing our whole-brain functional connectivity results with previous rs-fMRI studies we note that our methodology improved several key aspects. First, we did not investigate functional connectivity of a single region, but included four striatal regions in one analysis. We thereby increased the specificity of our findings: variance that was shared between striatal seeds was not assigned to any of the striatal seeds. As a result, we obtained unique whole-brain functional connectivity maps for each region that were not confounded by possible global alterations in connectivity. This approach echoed in the partial correlation analyses. Second, we did not define seed regions based on an anatomical atlas or standard coordinates. Instead we used subject-specific regions of interest based on an anatomical segmentation of each individual brain. Accounting for interindividual differences in striatal anatomy, we increased the specificity of our analyses. Third, we used an advanced data-driven method for secondary motion denoising resulting in functional connectivity maps that are minimally confounded by motion (Pruim, Mennes, Buitelaar et al., 2015, Pruim, Mennes, van Rooij et al., 2015).

When interpreting our results, limitations have to be considered. Within the ADHD group differences existed regarding dose and type of medication. Stimulant medications are effective in suppressing ADHD symptoms (Swanson, Baler, & Volkow, 2011) and have been demonstrated to have acute effects on brain function (Rubia et al., 2013). All participants in our study were, however, free of medication starting 48 hr before the rs-fMRI scan, which should have eliminated acute effects of medication on brain function. Furthermore, it should be noted that the control group and ADHD group differed significantly in gender, scan site, IQ, SES, and ODD/CD comorbidity. However, sensitivity analyses revealed no influence of these factors on our findings.

Conclusion

We observed increased local functional connectivity between the anterior and posterior region of putamen in participants with ADHD relative to controls. We interpret this finding as a decreased functional segregation of both putamen regions in ADHD, which might be related to motor deficits in ADHD.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Additional participant characteristics (not available for full dataset).

Table S2. Distribution of dopamine genotypes across diagnostic groups.

Figure S1. Head motion, as determined by mean squared displacement (RMS-FD) does not differ between the ADHD and control group.

Figure S2. Whole-brain spatial maps of the control and ADHD group for the different striatal seeds.

Figure S3. Correlations of anterior–posterior putamen connectivity with IQ in the control group and ADHD group.

Figure S4. Correlations of anterior–posterior putamen connectivity with SES in the control group and ADHD group.

Figure S5. Correlations of anterior–posterior putamen connectivity with medication history (in the ADHD group).

Figure S6. The anterior–posterior putamen connectivity in the control group and ADHD group, displayed separately for the two genders, the two scan locations, for the full sample and the sample without participants with ODD/CD comorbidity, and for the different ADHD subtypes.

Figure S7. Correlation with age.

Figure S8. Difference map of whole brain posterior putamen versus anterior putamen connectivity.

Figure S9. Intrastriatal correlation coefficient for anterior putamen (AP) and posterior putamen (PP), stratified by diagnosis and risk-gene variants.

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Key points

- Resting-state fMRI studies report ADHD-related alterations in cortico-striatal networks, however, heterogeneity exists in the exact regions implicated.
- We investigated functional connectivity of nucleus accumbens, caudate, anterior, and posterior putamen in a large ADHD cohort but did not replicate previous findings of ADHD-related alterations in the major cortico-striatal networks.
- We observed increased local functional connectivity between anterior and posterior putamen in participants with ADHD relative to controls.
- We interpret this finding as a decreased functional segregation of both putamen regions in ADHD, potentially related to motor deficits in ADHD.

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