Altered Frontostriatal Resting State Connectivity in Compulsivity-related Neurodevelopmental Disorders

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Obsessive Compulsive Disorder (OCD) and Autism Spectrum Disorder (ASD) share compulsivity-related symptoms and previous research has indicated similar underlying frontostriatal connections. Nevertheless, previous studies have solely focused on one disorder at a time, hampering direct comparison. Furthermore, inconsistent findings might have occurred due to heterogeneity within diagnostic groups and a direct focus on overlapping symptom dimensions might generate more coherent results. Here, we addressed functional connectivity of frontostriatal circuits in OCD and ASD and additionally in relation to compulsive behaviour across groups. Resting state functional magnetic resonance imaging data as well as the Repetitive Behavior Scale-Revised were obtained from children with ASD (N= 25), OCD (N=21) and controls (N=24). A seed-based functional connectivity analysis was conducted by correlating the time series of striatal seed regions to the frontal lobe. Subsequently, we performed group comparisons and analysed cross-disorder associations between connectivity and compulsive behaviour. We detected no significant differences between groups. Across groups, more severe compulsive behaviour was related to lower functional connectivity between the nucleus accumbens and orbitofrontal cortex as well as lower connectivity between the caudate and supplementary motor area. These results show that compulsivity is related to decreased frontostriatal connectivity across disorders, possibly underlying the inability to inhibit behaviour.

Keywords: compulsivity, repetitive behaviour, striatum, frontal cortex, Autism Spectrum Disorder, Obsessive Compulsive Disorder, resting state, functional connectivity, frontostriatal circuit

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Compulsivity is the irresistible urge to perform a certain behaviour repeatedly (Robbins, Gillan, Smith, de Wit, & Ersche, 2012), such as skin picking or excessively washing one's hands. These routines affect the daily functioning of children with Obsessive Compulsive Disorder (OCD), who suffer from an inability to inhibit intrusive repetitive thoughts (obsessions) and behaviours (compulsions). Likewise, Autism Spectrum Disorder (ASD) is characterised by increased repetitive behaviour as well as deficits in communication and social interaction (American Psychiatric Association, 2013). ASD and OCD often coexist, either within the same individual or clustering within a family (Meier et al., 2015). The increased comorbidity rate between the two disorders and the overlapping symptoms of compulsivity suggest shared underlying neural correlates (Naaijen et al., 2017). Accordingly, the disorders ASD and OCD have been related to impairments in functional connectivity between areas in the frontal cortex and the striatum (Bernstein et al., 2016; Chen et al., 2016; Delmonte, Gallagher, O'Hanlon, McGrath, & Balsters, 2013; Di Martino et al., 2011; Harrison et al., 2009; Jung et al., 2013; Vaghi et al., 2017).

The striatum is divided into three nuclei, which form circuits with different areas of the frontal cortex. The nucleus accumbens (NAcc) of the striatum forms the limbic network with the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) and has been related to motivational control and reward processing (Haber & Knutson, 2010; Langen, Durston, Kas, van Engeland, & Staal, 2011). The caudate nucleus of the striatum creates a circuit with the dorsolateral prefrontal cortex (DLPFC), which is involved in cognitive control (Langen et al., 2011; Levy, Friedman, Davachi, & Goldman-Rakic, 1997). The putamen creates a circuit with pre-motor and motor regions. This so-called sensorimotor circuit is involved in motor learning and performance (Alexander & Crutcher., 1990; Langen et al., 2011). Di Martino et al. (2011) replicated these findings on frontostriatal circuits when investigating functional connectivity in resting state functional magnetic resonance imaging (R-fMRI). A benefit of investigating connectivity with R-fMRI is that multiple functionally distinguishable networks can be assessed within a single setting and without giving any demanding task to the participants (Oldehinkel, Francx, Beckmann, Buitleaar, & Mennes, 2013). Therefore, this approach has allowed researchers to study alterations of frontostriatal connectivity in patients with OCD and ASD, who might have difficulties in enduring longer scanning sessions and comprehending demanding tasks.

When compared to healthy controls, participants with OCD showed higher resting state functional connectivity of the NAcc with the OFC and ACC (Harrison et al., 2009; Vaghi et al., 2017). Additionally, symptom severity was related to higher connectivity of the NAcc with the medial (Jung et al., 2013) and anterior (Harrison et al., 2009) OFC and lower connectivity with the lateral OFC (Jung et al., 2013). Jung et al. (2013) reason that the medial OFC processes emotions and positive rewards, whereas the lateral OFC is related to behavioural inhibition and the processing of punishments. Decreased connectivity with the lateral OFC might therefore underlie the inability to inhibit compulsive behaviour. Other studies report decreased connectivity of the putamen from the sensorimotor circuit, with the OFC, medial- and inferior frontal gyrus (MFG; IFG) in OCD (Bernstein et al., 2016; Harrison et al., 2009; Vaghi et al., 2017). Decreased connectivity of the caudate with the DLPFC (Chen et al., 2016) and the inferior frontal gyrus (Vaghi et al., 2017) has also been found in OCD, pointing to an involvement of the cognitive circuit. Increased connectivity of the caudate with the ventrolateral prefrontal cortex was related to cognitive flexibility in OCD, suggesting that abnormalities in the cognitive circuit underlie the inability to switch flexibly between behavioural alternatives (Vaghi et al., 2017). Additionally, Vaghi et al. (2017) found decreased connectivity between the caudate and an area in the precentral gyrus, which is part of the motor systems. This indicates that also connectivity between the cognitive and sensorimotor circuit is altered in OCD.

Similar to research on OCD, a study reported increased functional connectivity of the NAcc with the right ACC and OFC as well as the MFG in ASD (Delmonte et al., 2013). Additionally, increased connectivity of the caudate with the MFG (Delmonte et al., 2013) and premotor areas was found in ASD (Turner, Frost, Linsenbardt, McIlroy, & Müller, 2006). Especially increased connectivity between the right caudate and the right MFG was related to more severe symptoms of restricted repetitive behaviour (Delmonte et al., 2013). Another study on ASD found elevated connectivity between the putamen and the left precentral gyrus, which contains the primary motor cortex (Di Martino et al., 2011). Overall, alterations within and between the three frontostriatal circuits seem to occur in both OCD and ASD. Yet, in order to identify similarities and differences in

frontostriatal dysfunctioning more specifically and directly, studies comparing both disorders in one set-up together with healthy controls are required. Therefore, the first aim of this study is to explore whether there are group specific and overlapping abnormalities within frontostriatal resting state connectivity in children with OCD and ASD as compared to healthy controls.

Furthermore, previous alterations of frontostriatal connectivity in ASD and OCD have not consistently been found and studies report altered connectivity between the striatum and several different areas in the frontal cortex (Bernstein et al., 2016; Delmonte et al., 2013). This might be due to the diversity of symptoms within a disorder such as ASD or OCD (Langen et al., 2011). Robbins et al. (2012) claim that current diagnostic labels create groups that are too heterogeneous, and a more direct analysis of symptom dimensions should be applied when studying compulsivity related disorders. Additionally, by comparing compulsivity across different disorders, commonalities in the biological mechanisms underlying these disorders might be identified, which could lead to new genetic and therapeutic insights (Robbins et al., 2012). Hence, a second aim of the present study is to assess the relation between resting state connectivity within frontostriatal circuits and compulsive behaviour across diagnostic groups.

Another reason for the diverse findings might have been the age groups of the chosen samples. A study on age-related effects in OCD found that differences in connectivity between the dorsal striatum and the ACC were especially represented in the youngest participants around the age of 11 years (Fitzgerald et al., 2011). Likewise, a study on ASD found that differences between participants with ASD and healthy controls in functional connectivity and interhemispheric correlation decrease with increasing age (Anderson, Locke, Kretzmann, Kasari, & the AIR-B Network, 2011). This might be due to the plasticity of the brain and the development of compensatory mechanisms. In order to improve early diagnosis, prognosis and treatment, more studies on connectivity in childhood are necessary (Hull et al., 2017). Therefore, we focussed the study on children between the ages of 8 and 16 years. We expected to find overlapping abnormalities in frontostriatal connectivity in OCD and ASD groups compared to healthy controls, as well as abnormally connected circuits in relation to compulsive behaviour across disorders.

Method

Participants

The current sample originated from the multicentre study 'Compuls' which was performed at four locations across Europe (Naaijen, 2016). Initially, participants for the ASD group met the criteria for a DSM-IV diagnosis (American Psychiatry Association, 2000). Additionally, patients with ASD were excluded if they had a comorbid diagnosis of OCD or attention-deficit/hyperactivity disorder (ADHD). Participants for the OCD group were included if they had a clinical diagnosis and/or a total score on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS; Scahill et al., 1997) of seven or higher. In this group, participants with any comorbid disorder were included, except for a comorbid diagnosis of ASD. Healthy controls were excluded if they or a first-degree family member had a psychiatric disorder. Additionally, controls were only included if they scored within a normal range on the Child Behavior Checklist and Teacher Report Form (Bordin et al., 2013). All participants were between 8 and 16 years old, of Caucasian descent and did not have any contra-indications for MRI scanning. Only subjects with an IQ above 70 and the ability to communicate fluently in their native language were included in the study. Additionally, they were not allowed to have a major physical illness, past or present head injuries or neurological disorders.

The participants of two scan-sites were excluded from the present analysis, because the recruitment numbers of OCD participants were too low. This resulted in 29 included subjects from King's College London, London, United Kingdom and 104 subjects from Radboud University Medical Center and the Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands, with a complete resting state scan. 34 of these participants were diagnosed with ASD, 24 with OCD and 75 children did not have a diagnosis of ASD or OCD respectively. However, one participant from the ASD group was excluded due to comorbid symptoms of OCD and one participant was excluded because he did not have sufficient symptoms for a DSM-IV diagnosis. A participant from the control group was excluded due to too many symptoms of OCD, according to our phenotypic assessment. Additionally, a participant from the OCD group was excluded due to an incidental finding in the structural scan. Another seven subjects were

Table 1.
Demographic information of participants across groups

		Control	ASD	OCD	Test Statistic
N	**Nijmegen**	18	16	12	-
	London	6	9	9	-
% Male		60	58.33	61.91	$\chi^2(2, N = 70) = 0.26, p = .88$
Mean Age in years *(SD)*		11.99 (2.07)	11.64 (2.21)	12.25 (2.16)	$F(2,67) = 0.46, p = .64$
Mean IQ[a] (*SD*)		105.36 (12.27)	104.06 (13.82)	108.32 (17.18)	$F(2,53) = 0.44, p = .65$
RBS-R[b] (*SD*)		1 (1.51)	21.01 (18.07)	26.1 (23.29)	$F(2,65) = 13.97, p < .001$
% left handed		0%	8%	9.52%	-
Medication-use (*N*)		0	2	4	-

Abbreviations: *N* = Number of subjects; *SD* = standard deviation; RBS-R = Repetitive Behavior Scale-Revised; IQ = intelligence quotient

[a]Group mean and SD of estimated IQ based on four subtests of the Wechsler Intelligence Scale for Children-III (Canivez & Watkins, 1998). The estimated IQ was unknown for 13 subjects.
[b]Group mean and SD of total score on RBS-R (Lam & Aman, 2007).

excluded after a quality control procedure as described in the paragraph on pre-processing.

The remaining number of controls in Nijmegen, consisting of 63 subjects, was larger than the OCD group with 12 subjects and ASD group with 11 subjects. Therefore, a smaller healthy control group from Nijmegen was matched to the OCD group from Nijmegen, based on age, IQ and gender, using the full matching procedure of the package MatchIt in R (Ho, Imai, King, & Stuart, 2011; The R Core Team, 2014). The final sample consisted of 25 children with ASD, 21 children with OCD and 24 healthy controls between the ages of 8 and 16 years. Detailed group characteristics are listed in Table 1. Ethical approval for the project was obtained for each site individually. Before the start of participation, the parents filled in a written informed consent and children over the age of 12 filled in an informed assent. From children younger than 12, an oral informed assent was required.

Phenotypic Assessments

The ASD diagnosis and symptom severity was confirmed with a structured interview with the parents using the Autism Diagnostic Interview Revised (ADI-R; Lord, Rutter & Le Couteur, 1994). OCD symptoms were rated with the Children's Yale Brown Obsessive Compulsive Scale (CYBOCS; Scahill et al., 2014), in form of an interview with the parent(s) and child present. In order to assess possible comorbidities, such as conduct disorder, oppositional defiant disorder, anxiety disorder and the presence of tics and Tourette's syndrome, all parents were interviewed with either the structured Diagnostic Interview Schedule for Children (DISC; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) in London or the semi-structured Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman et al., 1997) in Nijmegen.

Compulsive behaviour was defined as the total score on the Repetitive Behavior Scale-Revised (RBS-R; Lam & Aman, 2007). This questionnaire was filled in by the parents and could yield a total score between 0 and 129. Up to two missing items were replaced with the participant's mean score of the respective subscale. As none of the subjects were missing more than two answers, no subjects had to be excluded during this step. The full intelligence quotient (IQ) was estimated by administration of four subtests of the Wechsler Intelligence Scale for Children-III (WISC-III; Canivez & Watkins, 1998): block design, vocabulary, similarities, and picture completion. Past and present use of prescribed medication was assessed with a questionnaire for the parents.

Data Acquisition

Prior to the fMRI scan, a practice session was

Table 2.
Scan parameters for the structural and resting state MRI across sites

Scan	Site	TR/TE/ TI (ms)	Flip angle	FOV	Matrix RL/AP/ slices	Voxel-size (mm)	Gap (%)	Parallel Imaging
T1	Nijmegen (Siemens)	2300[a]/ 2.98/ 900	9	256	212/256/ 176	1.0 x 1.0 x 1.2	NA	2
	London (GE)	7.31[a]/ 3.02/ 400	11	270	256/256/ 196	1.1 x 1.1 x 1.2	NA	1.75
R-fMRI[b]	Both	2300/ 12 Nijmegen 13 London/ -	80	240	240/240/ 33	3.8 x 3.8 x 3.8	11	2

[a]The manufacturer of GE defines a TR as the time an excitation pulses, while Siemens defines a TR as the time between inversion recovery pulses
[b]R-fMRI: In London TE2 was 31ms and TE3 was 48ms; in Nijmegen TE2 was 28.41ms and TE3 was 44.82ms

held in a simulator in order to familiarise the participants with the scanning environment. The data acquisition was performed with comparable 3 Tesla MR scanners. In London a General Electric MR750 (GE Medical Systems, Milwaukee, WI, USA) was used with an 8-channel head coil and in Nijmegen a Siemens Prisma scanner (Siemens, Erlangen, Germany) was used with a 32-channel head coil. An anatomical T1-weighted scan and T2-weighted R-fMRI scans were acquired from each participant (see parameters in Table 2). Reference T1-weighted anatomical scans were obtained with an MPRAGE parallel imaging sequence. For the R-fMRI scan a multi-echo sequence was used. During the R-fMRI scan, the light was dimmed and participants were instructed to look at a fixation cross and to avoid falling asleep during the scan.

Preprocessing

A standard preprocessing pipeline was applied on the data using the FMRIB Software Library (FSL version 5.0). The first five volumes of the resting state scan were removed in order to allow for signal equilibration. Head motion correction was applied via realignment to the middle volume with MCFLIRT (Jenkinson, Bannister, Brady, & Smith., 2002). Then, grand mean scaling was performed as well as spatial smoothing with a 6mm FWHM Gaussian kernel. Subsequently, signal components corresponding to secondary head motion artifacts were removed with ICA-AROMA (Pruim, Mennes, Buitelaar, & Beckmann, 2015; Pruim et al., 2015). Nuisance regression was used to remove signal from white matter and cerebrospinal fluid. Additionally, high-pass filtering (100 s) was applied. The images were co-registered to the anatomical image of the respective participant with boundary-based registration in FSL-FLIRT (Greve & Fischl, 2009; Jenkinson et al., 2002; Jenkinson & Smith, 2001). The T1-images of the participants were then registered to the MNI152 standard space with 12-parameter affine transformations and refined using non-linear registration with FSL-FNIRT (Andersson, Jenkinson, & Smith, 2010). By applying the resulting warp fields to the concatenated functional image, this image was also brought into standard space. In total seven participants (ASD: N = 1, OCD: N = 0, Control: N = 6) were excluded based on fMRI quality. This included participants with less than 80% of volumes acquired. Additionally, the root mean square of the frame-wise displacement across functional scans (RMS-FD; Jenkinson, 1999) was computed for each participant as an indicator of head motion and the participants belonging to the 5% with on average the most head motion (highest mean RMS-FD scores) were excluded from the analysis (RMS-FD > 0.80).

Seed Definition

In the present study, a seed-based approach

was applied, using subject specific anatomically defined regions of the striatum: NAcc, caudate and putamen (Langen et al., 2011). Due to the functional differences between the anterior and posterior putamen, it was divided into two seeds (Oldehinkel et al., 2016). Left and right volumes were analysed separately yielding eight seed masks in total (see Fig 1). The masks were created by first segmenting all subcortical structures for each participant with FSL-FIRST (Patenaude, Smith, Kennedy, & Jenkinson, 2011). Each subcortical volume was retrieved separately and warped into MNI152 space. The volumes were then binarised in order to create masks. The putamen was divided into anterior and posterior parts by multiplying its volume with a binarised anterior and posterior mask, based on the coordinates of the anterior commissure, leaving a space of 4 mm (2 voxels) between the anterior and posterior regions to minimise signal overlap.

Participant Level Analysis

From these subcortical seed masks, we extracted the first eigenvariate of the timeseries of the R-fMRI activity in MNI152 standard space. Using these timeseries, General Linear Model (GLM) analyses were performed within FSL (FSL version 5.0). In this approach, voxel-wise correlations of the timeseries of each seed region with the voxels in the whole brain were computed, resulting in connectivity maps for subsequent group analysis.

Group Level Analysis

The second level analysis on group level was performed with FSL Randomise (Winkler, Ridgway, Webster, Smith, & Nichols, 2014). Voxel-wise regression of the eigenvariate timeseries of the individual seed regions with the frontal cortex was computed, correcting for gender, age and scan-site. ASD, OCD, and healthy control groups were compared using a group level analysis on the connectivity maps obtained in the previous step. Permutation testing (5000 permutations) was applied using FSL Randomise (Winkler et al., 2014), including covariates for age, sex, and scan-site. Voxel-wise testing was limited to the voxels within a frontal lobe mask, including the insular cortex. An F-contrast was applied on the full model of each seed in order to test if there were any differences between the groups. In T-contrasts, the functional connectivity of each diagnostic group was compared to the control group and the ASD and OCD groups were compared to each other.

The association of compulsive behaviour with functional connectivity was investigated across groups (ASD, OCD and control groups), using a similar approach as described above. Two participants were excluded from these analyses because their parents had not filled in the RBS-R questionnaire. T-contrasts were used to do voxel-wise tests of either positive or negative associations between compulsive behaviour and connectivity of the respective seed region. In order to assess whether the relation of compulsivity with frontostriatal connectivity differed between the diagnostic groups, the analysis was repeated, including the interaction of compulsivity and diagnosis. For every analysis, threshold-free cluster enhancement (TFCE) was used as implemented in FSL Randomise (Winkler et al., 2014). Significance was defined with a threshold of familywise error (FWE) corrected $p < .05$.

Sensitivity Analysis

In order to check whether IQ or average head motion (RMS-FD) influenced functional connectivity of the significant clusters, nonparametric Spearman correlations were computed between IQ or RMS-FD and the z-statistic extracted from clusters showing significant functional connectivity group differences or associations with compulsive behaviour. The influence of medication was not assessed, as only four subjects in the OCD group and two subjects in the ASD group were using medication regularly (see Table 1).

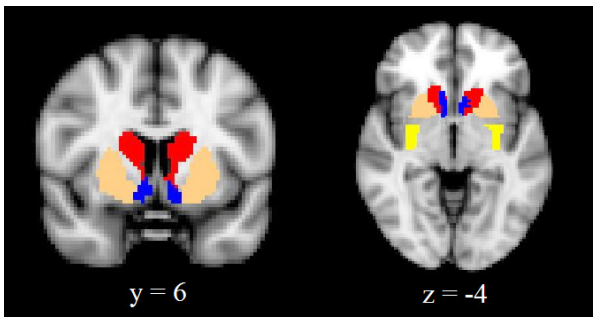

Fig. 1. Seed Regions in the Striatum. An example of the seed regions of a participant, used for connectivity analyses in MNI152 standard space: caudate (red), nucleus accumbens (blue), anterior putamen (orange) and posterior putamen (yellow).

Results

Whole-Brain Functional Connectivity of the Striatal Seed Regions

The whole-brain functional connectivity in the control group roughly corresponded to the frontostriatal circuits described in previous literature (Di Martino et al., 2011). The NAcc was connected with the OFC, ACC and paracingulate gyrus. The network of the caudate included the SMA and the prefrontal cortex as well as the putamen, NAcc and thalamus. The anterior and posterior putamen were both connected with the other striatal seeds, the ACC, the supplementary motor area (SMA) as well as the precentral and postcentral gyrus. Furthermore, they showed connectivity with smaller clusters in the parietal and temporal lobe. Also, the posterior putamen was connected with the thalamus, and smaller clusters in the occipital cortex and the cerebellum. An example of functional connectivity of the right striatal seed regions in controls is displayed in Figure 2.

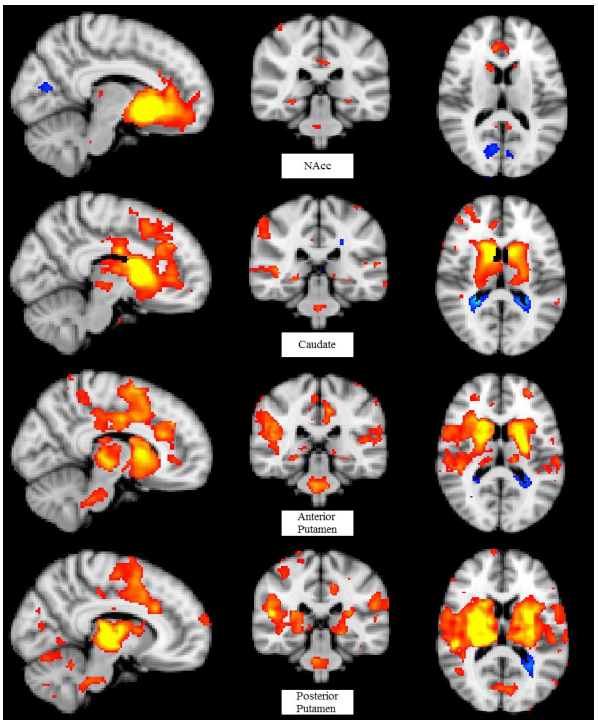

Fig. 2. Global striatal connectivity. Whole-brain functional connectivity of the right striatal seed-regions, nucleus accumbens (NAcc), caudate, anterior and posterior putamen in the control group (N= 24). The figures show T-maps (threshold: $|t| \geq 4$) with MNI 152 coordinates: x= 20, z = 8 and y = 10. Positive connectivity is displayed with a red colour gradient and negative connectivity is displayed with a blue colour gradient.

Group Comparison of Functional Connectivity

When comparing the voxel-wise functional connectivity (within the frontal lobe) of the eight striatal seed regions between groups, none of the F-tests for the overall models yielded significant results. Likewise, the T-contrasts comparing each diagnostic group to the control group and the ASD to the OCD group were not significant.

Association Between Compulsive Behaviour and Functional Connectivity

The analysis on the association between compulsive behaviour (RBS-R total scores) across ASD and OCD groups, and seed-based functional connectivity yielded two significant clusters (results are displayed in Figure 3). Functional connectivity decreased with increasing RBS-R scores between the right NAcc and the left lateral OFC and between the right caudate and the left SMA. The analysis of the interaction effects between compulsivity and diagnosis on the functional connectivity did not reveal any significant clusters. For illustrative purposes, the correlation of the RBS-R with the z-statistic of the significant clusters is displayed group-wise in Figure 4.

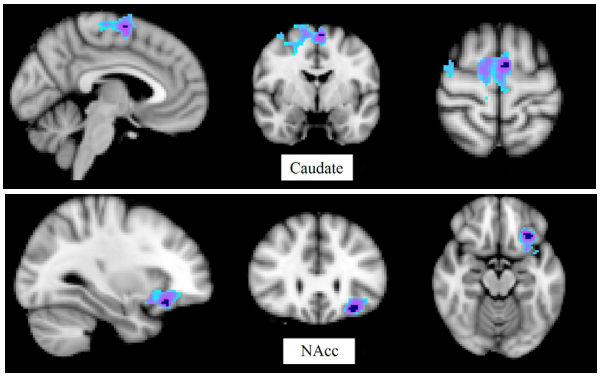

Fig. 3. Compulsivity-related (defined as the total score on the Repetitive Behavior Scale – Revised) hypoconnectivity between striatal seed regions and frontal areas. **A.** Right caudate and left supplementary motor area (p = .045, coordinates: x= -4, y= -4, z= 64). **B.** Right nucleus Accumbens (NAcc) and left OFC (p = .0418; coordinates: x= -30, y= 28, z= -60) The left side in the figures corresponds to the right side of the brain and vice versa. Significant voxels (family-wise error corrected; $p < .05$) are displayed in dark blue. X, y and z are MNI 152 coordinates and correspond to the voxels with the lowest p-values. For illustrative purposes, subthreshold results ($p < .20$) are displayed in a gradient from purple to light blue.

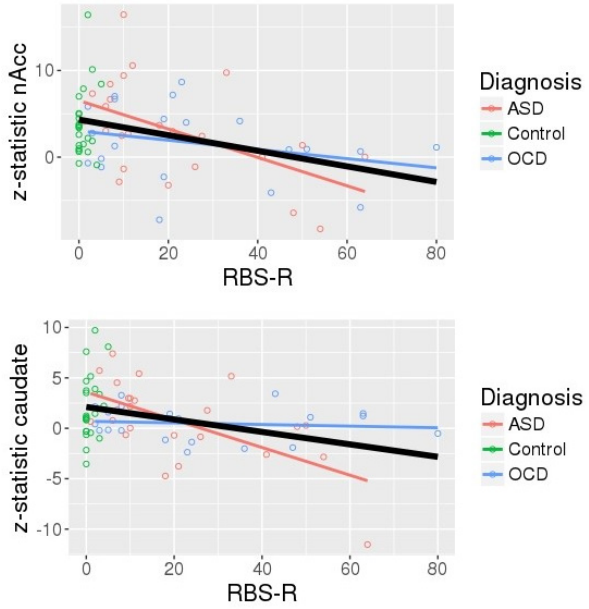

Fig. 4. Correlation of compulsivity with the z-statistic of significant clusters in diagnostic groups. The figures display the correlation of compulsivity (defined as the total score on the Repetitive Behavior Scale – Revised; RBS-R) with the z-statistic of the significant clusters per diagnostic group. The correlation of compulsivity with the z-statistic of the nucleus accumbens (NAcc) and orbitofrontal cortex is displayed on the left and the z-statistic of the caudate and supplementary motor area (SMA) is displayed on the right. The red line shows the correlation in Autism Spectrum Disorder (ASD) and the blue line shows the correlation in Obsessive Compulsive Disorder (OCD). The black line represents the overall correlation across groups.

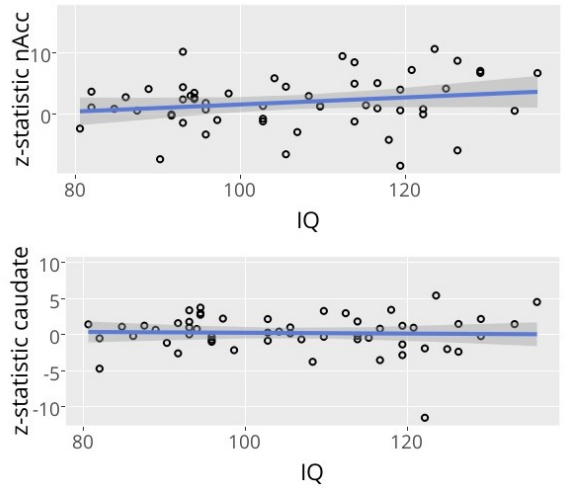

Fig. 5. Correlation of intelligence quotient and head motion with functional connectivity. **A.** Correlation of the estimated intelligence quotient (IQ) based on four subtests of the Wechsler Intelligence Scale for Children-III (Canivez & Watkins, 1998) with the z-statistic of functional connectivity of the nucleus Accumbens (NAcc) with the orbitofrontal cortex. **B.** Correlation of head motion as defined by root mean square of the frame-wise displacement across functional scans (RMS-FD; Jenkinson, 1999) with the z-statistic of functional connectivity of the nucleus accumbens (NAcc) with the orbitofrontal cortex and the caudate with the supplementary motor area.

Sensitivity Analysis

The sensitivity analyses showed no significant correlation of IQ ($\varrho\rho$ = -0.01, p = .92) or RMS-FD ($\varrho\rho$ = -0.14, p = .27) with the connectivity between the right caudate and the left SMA. Likewise, the correlations of IQ ($\varrho\rho$ = 0.21, p = .12) and RMS-FD ($\varrho\rho$ = -0.05, p = .68) with the functional connectivity of the right NAcc and the left OFC were not significant (see Figure 5).

Discussion

The aim of the present study was to investigate overlapping and group-specific abnormalities of resting state frontostriatal connectivity in ASD and OCD. Additionally, we assessed the cross-disorder association between compulsive behaviour and frontostriatal connectivity. We did not detect any abnormalities related to ASD or OCD. More severely compulsive behaviour, on the other hand, was associated with hypoconnectivity between the NAcc and OFC and between the caudate and SMA.

In the present analysis, we could not replicate previous findings on abnormalities related to OCD and ASD in the limbic (Delmonte et al., 2013; Harrison et al., 2009; Jung et al., 2013; Vaghi et al., 2017), cognitive (Chen et al., 2016; Delmonte et al., 2013; Fitzgerald et al., 2011; Vaghi et al., 2017) or sensorimotor (Bernstein et al., 2016; Harrison et al., 2009; Vaghi et al., 2017) frontostriatal circuits. An explanation for the absence of commonalities and differences between groups might be the heterogeneity of symptom representation within the disorders (Robbins et al., 2012). While some patients with ASD, for instance, show increased levels of compulsivity, others might suffer more from symptoms of social deficits. Likewise, children with OCD might differ on the amount of compulsions and obsessions expressed in daily behaviour. When investigating brain circuits underlying the common mechanisms in ASD and OCD, this could have caused a large variance within groups of the present

study. Hence, the hypothesised abnormalities in functional connectivity might be present only in participants with ASD and OCD who show more severe symptoms of compulsivity.

In line with this reasoning, we found that more severely compulsive behaviour was related to decreased connectivity between the NAcc and the lateral OFC. While previous studies on the two disorders mainly reported increased connectivity within the limbic circuit (Delmonte et al., 2013; Harrison et al., 2009; Vaghi et al., 2017), a distinction has to be made between lateral and medial OFC (Jung et al., 2013). Jung and colleagues (2013) found that the NAcc and medial OFC were more connected, whereas the NAcc and the lateral OFC were less connected in relation to symptom severity in OCD. The latter is in line with the present results. Considering the role of the lateral OFC in behavioural inhibition and processing of punishment (Jung et al., 2013), this suggests that compulsivity is related to an inability to inhibit negative repetitive symptoms.

Additionally, the present results reveal a relationship of compulsive behaviour with underconnectivity between the caudate nucleus and the SMA. The SMA is located within the MFG, anterior to the motor cortex (Nachev, Wydell, O'Neill, Husain, & Kennard, 2007) and is part of the sensorimotor circuit of frontostriatal connectivity (Morris et al., 2015). In line with the results of the current study, Vaghi et al. (2017) also found decreased connectivity in OCD between the caudate and an area in the precentral gyrus, which is also part of the sensorimotor circuit. The present results suggest abnormalities of communication between the caudate of the cognitive circuit and the sensorimotor circuit. More specifically, the SMA plays a role in motoric inhibition of behaviour (Bari & Robbins, 2013; Nachev et al., 2007). Together, the present results on underconnectivity of the NAcc with the lateral OFC and the caudate with the SMA indicate that deficits in the ability to inhibit actions might lead to compulsive behaviour.

In accordance with that, studies found a deficit of inhibitory skills in the Go/No-go task in patients with OCD and ASD (van Velzen, Vriend, de Wit, & van den Heuvel, 2014; Christ, Holt, & White, 2007; Kana, Keller, Minshew, & Just, 2011; Uzefovski, Allison, Smith, & Baron-Cohen, 2016). Next to ASD and OCD, also the trait compulsivity in healthy participants has been related to impaired inhibitory skills in a Go/No-go task (Sánchez-Kuhn et al., 2017). In order to explain the emergence of compulsive symptoms in related disorders, however, the direct link of compulsivity, inhibitory skills and functional connectivity should be investigated across disorders in future studies.

Even though the present results show abnormalities in frontostriatal circuits, they differ from the findings of a previous study on ASD (Delmonte et al., 2013). In the present study, mainly hypoconnectivity between the right caudate and the left SMA in the MFG has been related to compulsive behaviour. However, Delmonte et al. (2013) reported hyperconnectivity between the right caudate and the right MFG in relation to repetitive behaviour in ASD. Though these results seem contradictory at first, they are not necessarily inconsistent with one another. Studies on functional connectivity in ASD found that overconnectivity and underconnectivity often coexist. More specifically, some studies found overconnectivity within the right hemisphere of the brain and underconnectivity between the two hemispheres (Hull et al., 2017; Anderson et al., 2011). Accordingly, Delmonte et al. (2013) reported hyperconnectivity within the right hemisphere, whereas the present results revealed hypoconnectivity between the right striatum and the left frontal cortex. Our results suggest that the distinction between intrahemispheric overconnecitivity and interhemispheric underconnectivity could be an interesting avenue for further investigation and that treating left and right seed regions separately is recommended when investigating functional connectivity.

Another reason for the discrepancies between findings might be the chosen age groups. A study on age-related effects of frontostriatal circuits in ASD found that differences diminish with increasing age and that classification is easier in younger subjects (Anderson et al., 2011). Likewise, Fitzgerald et al. (2011) reported age-related effects on frontostriatal connectivity in OCD. This demonstrates the importance of studies on children, since they are diagnosed earlier and the neural plasticity might still compensate for functional connectivity deficits during development in childhood and adolescence (Anderson et al., 2011).

While the present study did focus on younger participants, there are still limitations that should be considered when interpreting the results. The sample size of the current analysis was not large and might therefore limit the power to detect significant effects. Additionally, the scope of the current study did not allow for an analysis of the sub-scales of the RBS-R (Lam & Aman, 2006). In the present analysis, we have exclusively investigated the total score of compulsive behaviour, and

therefore no conclusions can be made on different types of repetitive behaviour, such as self-harming or stereotyped behaviour. Further analyses on the subtypes of compulsive behaviour would be of great value to elucidate more specific relationships between dysfunction in different frontostriatal circuits and behavioural subtypes. Furthermore, the RBS-R used in the present analysis has especially been designed to investigate ASD (Lam & Aman, 2006). Therefore, it might be less sensitive in measuring repetitive behaviour in OCD and alternative assessment tools should be considered in future studies.

Conclusion

In the present study, we found decreased connectivity of the right NAcc with the left OFC and the right caudate with the left SMA in relation to compulsive behaviour across diagnostic groups. This suggests that compulsivity is linked to abnormalities in connectivity of the right striatum with the left frontal cortex. On the other hand, no group differences between OCD and ASD diagnostic groups and healthy controls were detected. This is in line with recent suggestions in the field that diagnostic labels are heterogeneous and that we should strive towards a more direct investigation of cross-disorder phenotypes in order to identify subtypes of compulsivity-related disorders.

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