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Striatal structure and its association with N-Acetylaspartate and glutamate in autism spectrum disorder and obsessive compulsive disorder

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Structure

Abstract
Autism spectrum disorders (ASD) and obsessive compulsive disorder (OCD) are often comorbid and are associated with changes in striatal volumes and N-Acetylaspartate (NAA) and glutamate levels. Here, we investigated the relation between dorsal striatal volume and NAA and glutamate levels. We additionally compared striatal volume and shape between ASD, OCD and controls. T1-weighted magnetic resonance (MR) images, proton spectra (1H-MRS) in the left striatum, and phenotypic information were collected from 54 children with ASD, 32 with OCD, and 56 controls (aged 8–13 years) in a four-site study. Dorsal striatal volume and shape were determined using the FMRIB integrated registration and segmentation tool (FIRST). Spectra were processed with Linear Combination Model. The relationship of left striatal volume with NAA and glutamate was investigated, and group comparisons were performed for NAA levels and for bilateral striatal volume and shape. NAA levels were lower in subjects with ASD compared with controls ($t=2.86$, $p=0.005$) and were associated with striatal volume ($\beta=0.37$, $t=2.78$, $p=0.008$). Glutamate levels were also associated with volume in the ASD group ($\beta=0.38$, $t=2.46$, $p=0.018$). No group differences were found for striatal volume or shape, but a post-hoc diagnosis-by-hemisphere interaction ($F_{(2,129)}=3.86$, $p=0.024$) revealed greater asymmetry (right > left) in striatal volume for the disorder-groups compared with controls. Our findings show involvement of NAA and glutamate in striatal volume in ASD and suggest greater asymmetry in paediatric ASD and OCD compared with controls, pointing to overlapping subcortical abnormalities. The lower NAA in ASD reflects reduced neuronal integrity or impaired neuronal functioning.

1. Introduction

Autism spectrum disorders (ASD) and obsessive compulsive disorder (OCD) are neurodevelopmental disorders, which are often comorbid and are both characterized by compulsive behaviors (American Psychiatric Association, 2013). Structural neuroimaging studies investigating these disorders have highlighted alterations in similar brain regions (Hrdlicka, 2008; Radua and Mataix-Cols, 2009). Among the most investigated areas is the dorsal striatum, as are the caudate nucleus and putamen separately. These regions are central to the functioning of the fronto-striatal circuits (e.g. Walhovd et al., 2015; Morris et al., 2016), which have been shown to be affected in ASD and OCD (Langen et al., 2012; Melloni et al., 2012). Several studies found increased caudate volume (Hollander et al., 2005; Voelbel et al., 2006; Qiu et al., 2016) and increased putamen volume (Sato et al., 2014) in participants with ASD compared with controls. However, elevated repetitive behavior has been shown to correlate with decreased bilateral putamen volumes as well in children with ASD (Estes et al., 2011). In a shape study, which is more sensitive to subtle morphological changes, a steeper increase in concavity with age in both caudate and putamen of participants with ASD was found (Schuetze et al., 2016). In OCD, increased putamen (Real et al., 2016) and caudate and putamen volumes (Zarei et al., 2011) have also been reported, but other studies did not show differences in both regions (Szeszko et al., 2004) or decreased left putamen volume (Hoexter et al., 2012). Additionally, positive correlations between putamen volume and obsessive-compulsive symptoms in the healthy population (Kubota et al., 2015), but also negative correlations between contamination/washing symptoms (Van Den Heuvel et al., 2009), total Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS) (Scahill et al., 2006) scores, and caudate volume (Narayanaswamy et al., 2013) have been reported. One shape study found deformity of the caudate in OCD (J. S. Choi et al., 2007). There have also been studies in both disorders reporting regional asymmetries in subcortical volumes (Kang et al., 2008; Dougherty et al., 2016), which may suggest deficits in regional specialization.

Structural abnormalities may be related to neurochemical abnormalities. N-Acetylaspartate (NAA), which is hypothesized to reflect neuronal density and viability, indicating neuronal integrity and functioning (Moffett et al., 2007; Urenjak et al., 1992; Kalra et al., 1998; Rigotti et al., 2007), may be a marker for structural abnormalities. NAA concentrations can be measured with proton magnetic resonance spectroscopy (1H-MRS), and both ASD and OCD have been associated with decreased NAA concentrations in several brain regions, including the striatum (Aoki et al., 2012a, 2012b; Aoki et al., 2012a, 2012b; Ford and Crewther, 2016). NAA is metabolically connected with glutamate, the most abundant excitatory neurotransmitter in the human central nervous system (Pittenger et al., 2011; Mehta et al., 2013); mitochondrial energy production from glutamate is enhanced through NAA, making both viable markers for neuronal health (Moffett et al., 2007; Moffett et al., 2013). Glutamate has also been found altered in OCD and ASD (J Naaijen et al., 2015).

The relation between these metabolites and measures of brain structure has hardly been investigated in ASD or OCD. In ASD, a single study investigated thalamic volume and metabolites (Say et al., 2014); they found increased lateralization in ASD for thalamic volume and no differences in

Table 1 Scan parameters for the structural MRI across the different sites.

Site	TR/TE/TI (ms)	Flip angle	Field of view (mm)	Matrix RL/AP /slices	Voxel-size (mm)	Parallel Imaging	Coil: # of channels
Nijmegen *(Siemens Prisma)*	2300[a]/2.98/900	9	256	212/256/176	1.0 × 1.0 × 1.2	2	32
Utrecht *(Philips Achieva)*	6.8[a]/3.10/823	9	270	204/252/170	1.1 × 1.1 × 1.2	1.8	8
London *(GE MR750)*	7.31[a]/3.02/400	11	270	256/256/196	1.1 × 1.1 × 1.2	1.75	8
Mannheim *(Siemens Trio)*	2300[a]/2.98/900	9	270	212/254/176	1.1 × 1.1 × 1.2	2	32

MRS sequence parameters were similar across sites and are described in the main text.
[a]As provided by the manufacturer. Philips and GE define a TR as the time between excitation pulses, while Siemens defines TR as the time between inversion recovery pulses.

metabolite concentrations. They did not relate the two measures. An early study in OCD with a limited sample size found no association between caudate volumes and metabolites (Bartha et al., 1998). In another neurodevelopmental disorder, schizophrenia, glutamate-mediated excitotoxicity in subcortical regions (for an overview, see Plitman et al., 2014) as well as decoupling of NAA and glutamate (Coughlin et al., 2015) have been observed. In Huntington's disease, correlations between caudate volume and both NAA and glutamate concentrations have also been found (Padowski et al., 2014). This association between volume and neurochemistry may reflect neuronal integrity and functioning of this region.

In the present study we investigated whether ASD and/or OCD were associated with changes in total NAA (tNAA, consisting of NAA and N-Acetylaspartylglutamate) concentrations and whether these changes and glutamate concentrations were related to striatal volume. We further investigated possible differences between the disorder groups and controls in total striatal volume (to align volumetric analyses with spectroscopy analyses). Post-hoc we investigated caudate and putamen separately including both volume and shape-analysis to see whether observed differences were due to region-specific effects. Based on previous findings, we expected lower striatum tNAA concentrations within the disorder groups compared with controls, and an association of neurochemical concentrations with striatal volume.

2. Experimental procedures

2.1. Participants

We included 68 participants with ASD, 33 with OCD, and 61 healthy controls. Participants (aged 8–13 years) were recruited across four sites in Europe (Radboud University Medical Center and the Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands; Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands; King's College London, London, United Kingdom; Central Institute of Mental Health (CIMH), Mannheim, Germany). The measures used here were part of a larger test battery including questionnaires, neuropsychological testing, and MR scanning, as described in Naaijen et al. (2016). Exclusion criteria for all participants were any contraindications for participating in MRI, IQ<70, and the presence/history of neurological disorders. ASD and OCD participants were not allowed comorbidity of the other disorder of interest. In the healthy comparison group, no DSM axis I disorder was allowed in any relatives up to two generations. Participants both on and off medication were included but they were asked to abstain for 48 hours prior to testing.

2.2. Ethical considerations

Ethical approval for the study was obtained for all sites separately. After description of the study, parents gave written informed consent, children aged 12 years or older gave written informed assent and children younger than 12 gave oral informed assent.

2.3. Phenotypic information

Clinical diagnoses of ASD and OCD were confirmed by structured diagnostic interviews. The Autism Diagnostic Interview Revised (ADI-R (Lord et al., 1994)) and the CY-BOCS (Scahill et al., 2006) were used for ASD and OCD respectively. In addition, all parents were interviewed using the structured Diagnostic Interview Schedule for Children (DISC (Shaffer et al., 2000)), the Development and Well-being Assessment (DAWBA (Goodman et al., 2000)), or the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS (Kaufman et al., 1997)), dependent on site, to assess the presence of possible comorbidities, such as attention deficit hyperactivity disorder (ADHD), a comorbidity very common in both ASD and OCD (van Steensel et al., 2013; Torres et al., 2016). Repetitive behavior was assessed by the Repetitive Behavior Scale (RBS) filled in by parents (Lam and Aman 2007). Full-scale IQ was estimated from four subtests of the Wechsler Intelligence Scale for Children (Wechsler, 2002). Information about use of medication was collected via parental report.

2.4. MR acquisitions

The scanning protocol included a structural MRI and the spectroscopy sequence. The structural T1-weighted sequence was based on the ADNI GO protocols (Jack et al., 2008; Jack et al., 2010) and was matched closely across the different scanning sites (see Table 1 for the T1-weighted scan parameters). Proton spectra were acquired using a point-resolved spectroscopy (PRESS) protocol, similar across sites, with chemically selective suppression (CHESS) water suppression (Haase et al., 1985). One 2 × 2 × 2 cm voxel was placed on the left striatum covering caudate and putamen (TR=3000 ms, TE=30

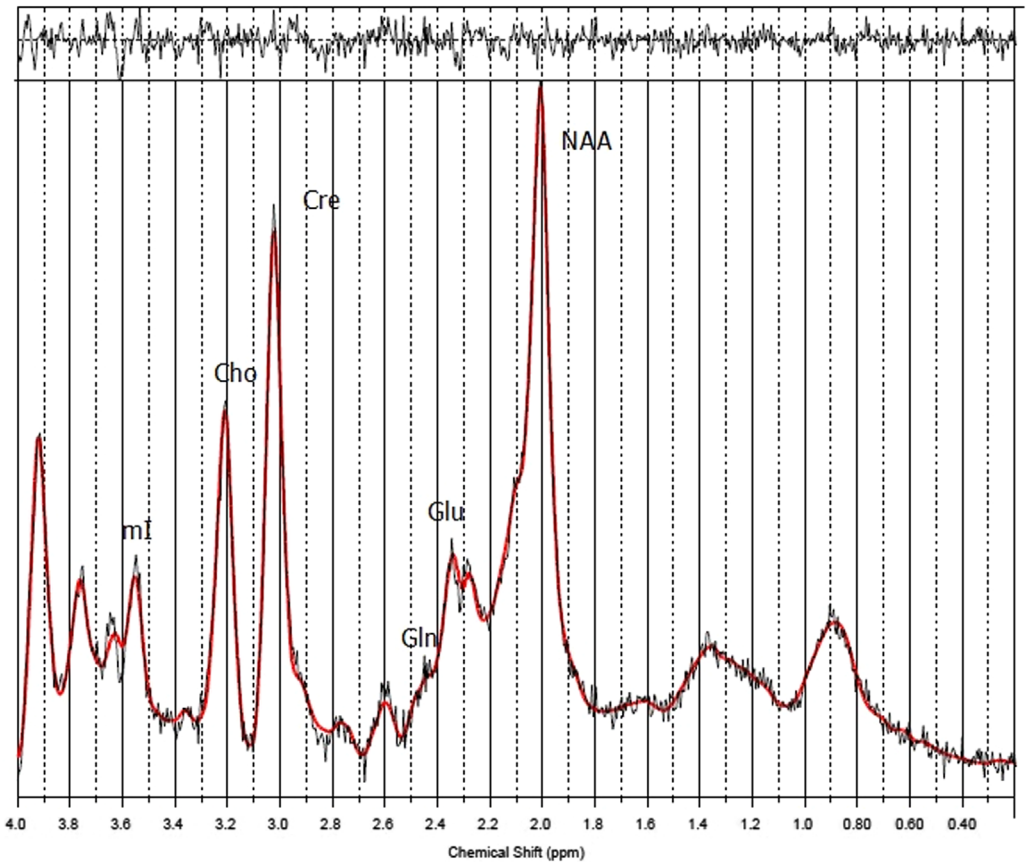

Fig. 1 Representative example spectrum of a 3 T proton magnetic resonance spectroscopy (1H-MRS) Linear Combination Model (LCModel) spectral fit of the striatum. The thin black line represents the frequency-domain data, the red line is the LCModel fit. In the top panel, the residuals are plotted (the data minus the fit).

ms, number of averages =96, bandwidth=5 kHz, number of points = 4096). Additional unsuppressed water reference spectra (16 averages) were acquired. The voxel location was adjusted to maximize its gray matter content. T1-weighted images were used for voxel placement and tissue segmentation. We only measured metabolites in the left striatum, due to time-constraints of the scan-protocol, which was part of a larger study protocol. An example spectrum is shown in Fig. 1 and voxel location of the striatum across the different sites is presented in Fig. 2B, showing consistent placement.

2.5. MR processing and modelling

T1-weighted images were processed with the FMRIB Software Library (FSL) (Woolrich et al., 2009; Smith et al., 2004). Segmentation was performed with the automated FMRIB integrated registration and segmentation tool (FIRST) (Patenaude et al., 2011). The FIRST procedure included affine registration to MNI space (MNI152, $1 \times 1 \times 1$ mm template) followed by a segmentation procedure that integrates both shape and intensity information for accurate segmentation of subcortical structures, including the striatal structures (caudate nucleus and putamen bilaterally). FIRST generated volumetric data and surface meshes for each structure. Volumes of these respective nuclei were extracted for statistical analysis.

First_utils was used to reconstruct the caudate nucleus and putamen in native space (useReconNative). We applied commands to align each structure to the average shape for the cohort (useRigidAlign) and to remove global scaling to account for differences in size (useScale). Vertex-wise statistical analyses of the structure shapes were then conducted. Statistical analyses are further described below in Section 2.6.

The unified segmentation procedure within the VBM8 toolbox of SPM8 (Statistical Parametric Mapping release 8, London, UK) was used to process the T1 images and produce gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) probability maps in conjunction with non-linear transformations to the MNI152 template space. Total brain volume was calculated as the voxel-wise sum of the GM and WM maps.

Spectral analysis was conducted using the Linear Combination (LC) Model, version V6.03-0I (Provencher, 2001). The MRS processing has been described in detail in Naaijen et al. (2016); briefly, it included eddy current correction and calculation of water-referenced concentrations in institutional units (i.u.). The striatal voxel was subsequently mapped on the above described probability maps as well as on the MNI152 template to provide partial volumes of GM, WM and CSF within the voxel. Total NAA (tNAA) and glutamate concentrations were corrected for these partial volume effects and for water-levels in the different tissue-types using the following formula:

$$Metabolite_{corrected} = Metabolite_{raw}\tilde{n} \times \left(\frac{43300\tilde{n}GMfraction + 35880\tilde{n}WMfraction + 55556\tilde{n}CSFfraction}{35880}\right) \times \left(\frac{1}{1-CSFfraction}\right)$$

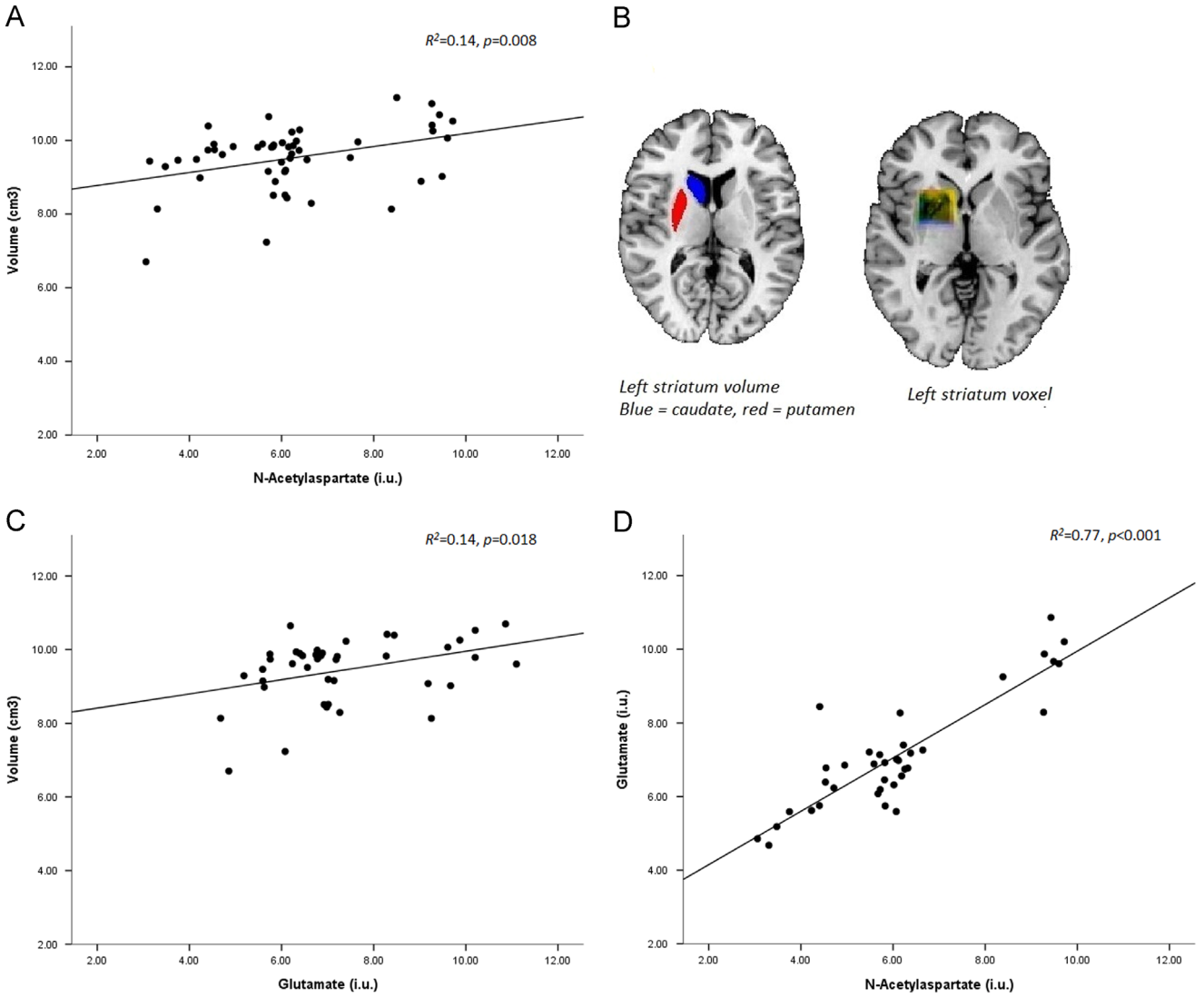

Fig. 2 Association between striatal N-Acetylaspartate and volume (A), glutamate levels and volume (C) and between the two metabolites (D) in the autism spectrum disorder (ASD) group. Panel B shows the anatomically defined caudate and putamen regions used in the volume and shape analyses and the striatum voxel (superposition of all participants' voxels separately per site on the MNI152 template; note the consistent placement). Note, the associations involving glutamate have a smaller sample due to lesser quality than the tNAA measures.

where 43,300, 35,880 and 55,556 are the water concentrations (in millimolar) for GM, WM and CSF, respectively.

2.6. Quality control

Structural datasets were visually inspected and evaluated. Segmentation of the striatal structures was also visually examined for processing errors and accuracy of segmentation. Spectra with line-width (full-width at half-maximum) >0.1 ppm, Cramér-Rao lower bounds (CRLB) >20%, signal to noise ratio <5, and concentrations more than 2 standard deviations from the mean were excluded. Thirteen participants with ASD, three participants with OCD, and five healthy controls were excluded due to excessive movement, anxiety in the scanner, or not meeting full diagnostic criteria after inspection of the ADI-R scores. Quality and reliability across sites was assured by making use of so-called travelling heads and phantoms (General Electric MRS phantom; see also (Naaijen et al., 2016). This data showed reliable measures across sites; example spectrums can be found in Fig. S1). Striatum voxel composition did not differ between ASD, OCD, and controls (GM, $F_{(2,138)}$=0.59, p=0.56; WM, $F_{(2,138)}$=0.79, p=0.46; CSF, $F_{(2,138)}$=1.8, p=0.17). Although tNAA CRLBs differed between groups ($F_{(2,129)}$=8.34, p <0.001), all were in a very low range (Mean controls=3.1%, OCD=4.4%, ASD=3.3%). We therefore assumed reliable measurement of tNAA levels.(Kreis, 2015) Differences in scanners (because of the multi-center nature of this study) did not differentially affect the tNAA levels across the three groups (p-value >0.05).

2.7. Statistical analysis

Statistical analyses were performed with SPSS release 21 (SPSS, Inc., Chicago, Illinois). First, demographic information was compared across groups. Group distributions in sex were tested with Pearson's chi-squared test. Group differences in continuous measures (age, IQ, and compulsivity score) were assessed with one-way analyses of variance (ANOVAs) if assumptions of homogeneity of variance and normality of distributions were met (p>0.05 in

Levene's test of homogeneity of variance and Shapiro-Wilk normality test). If these assumptions were violated a non-parametric Kruskal-Wallis rank sum test was used instead. Results were considered statistically significant at $p<0.05$, two-sided. Group differences in tNAA concentrations were analyzed using an ANCOVA with scanner-site, current medication use, sex and age as covariates; total brain volume was not included in this analysis because metabolite concentrations were corrected for partial volume effects. Covariates were removed from analysis if they did not significantly contribute to the explained variance of the model. Additionally, we investigated whether striatal tNAA and glutamate concentrations were associated with left striatal volume using regression analysis.

2.7.1. Volume analysis

A repeated measures analysis of co-variance (ANCOVA) was used to investigate the effect of diagnostic group on dorsal striatal volume (combination of caudate and putamen volumes). We first investigated total volume to allow for direct comparison with the MRS data, which included a region of interest covering both striatal regions. Hemisphere was included as the repeated measures factor, and total brain volume, sex, age, IQ, current medication-use and scanner-site were included as covariates. Secondary, post-hoc analyses were performed for the caudate and putamen separately to establish, whether the observed group differences were due to regional effects.

When asymmetry differences between groups were observed in the main analysis, we calculated an asymmetry index with the following formula:

$$AsymmetryIndex(AI) = \frac{Right_{volume} - Left_{volume}}{Right_{volume} + Left_{volume}}$$

This AI was used in Spearman's rank-correlation analysis to investigate association with phenotypic measures separately for the groups and with a continuous measure of compulsivity across the two disorder groups.

Table 2 Demographic characteristics (n=141).

	ASD (n=54)		OCD (n=31)		Control (n=56)		Test statistic	*p*-value
	N		*N*		*N*			
Sex, m/f	43/11		15/16		38/18		χ^2 =8.85	0.012[*]
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*		
Age	10.72	1.33	10.87	1.62	10.44	1.20	F =1.15	0.318
IQ	108.75	14.59	104.72	15.37	111.51	11.01	K-Wχ^2=4.32	0.115
ADI-Revised								
- Reciprocal interaction	17.28	6.97	-	-	-	-	-	-
- Communication	12.96	4.96	-	-	-	-	-	-
- Repetitive behavior	3.60	2.72	-	-	-	-	-	-
CYBOCS Total score	-	-	18.65	7.26	-	-	-	-
- Obsessions	-	-	9.25	4.53	-	-	-	-
- Compulsions	-	-	10.63	3.55	-	-	-	-
RBS								
Stereotypes	3.15	3.11	2.58	2.74	0.21	0.76	U=908.5	0.414[b]
Self-harm	1.58	2.29	2.00	2.85	0.18	0.54	U=745.5	0.454[b]
Compulsions	2.91	2.71	3.55	3.56	1.30	2.74	U=762.5	0.580[b]
Rituals	4.38	4.92	3.94	4.31	0.07	0.26	U=850.5	0.785[b]
Insisting on sameness	8.34	7.16	6.10	6.45	0.23	0.83	U=991.0	0.114[b]
Limited interests	2.92	2.78	1.42	1.75	0.16	0.37	U=1084	0.013[b,*]
Total score	23.58	20.79	21.29	19.20	1.09	2.28	U=883.5	0.565[b]
	N		*N*					
Medication use								
- Stimulant	7		3				-	-
- Atomoxetine	2		1				-	-
- Antipsychotic	3		4				-	-
- Antidepressant	0		4				-	-
- Other	1		0				-	-

ADI, Autism Diagnostic Interview (Lord et al., 1994); ASD, autism spectrum disorder; CYBOCS, children's Yale-Brown Obsessive Compulsive scale (Scahill et al. 1997); HC, healthy controls; m/f, male/female; OCD, obsessive compulsive disorder; RBS, Repetitive Behavior Scale (Lam and Aman, 2007); SD, standard deviation.

[*]significant at $p<0.05$.

[b]difference between the two diagnostic groups only.

2.7.2. Shape analysis

Shape analysis of the caudate and putamen structures was performed using FSL randomise (Winkler et al., 2014) with 5000 random permutations. Threshold-free cluster enhancement (TFCE (Smith and Nichols, 2009)) was used to detect spatially adjacent areas. Sex, age, IQ and scanner-site were used as covariates. Contrasts to investigate shape difference between the three diagnostic groups were used. Separate models were included for possible associations with the continuous measure of compulsivity (RBS) as well as associations with tNAA and glutamate levels including the same covariates. Statistical significance was determined by means of a family-wise error (FWE) threshold of $p<0.05$.

3. Results

3.1. Demographics

Table 2 shows a summary of the demographic information; Table S1 provides demographic information across the four sites separately. Of the original 162 participants, 141 had MR data-sets available for analysis. Sex differed between the three groups with a male/female imbalance in the ASD and control group compared with the OCD group.

Due to spectral or segmentation quality concerns, 29 and 10 participants were excluded for association analyses of glutamate and NAA concentrations and of brain structure, leaving n=112 and n=131 participants, respectively. The exclusion of these participants did not influence demographic distributions in the group regarding sex ($\chi^2=8.4$, $p=0.015$), IQ (K-Wχ^2 =4.74, $p=0.09$), age ($F=0.652$, $p=0.52$), and RBS-scores (Stereotypes: U=570.0, $p=0.205$; Self-harm: U=469.5, $p=0.877$; Compulsions: U= 481.5, $p=0.983$; Rituals: U=510.0, $p=0.674$; Insisting on sameness: U=588.5, $p=0.129$; Limited interests: U=655.5, $p=0.012$; Total: U=559.5, $p=0.270$). Several comorbidities were present in the disorder groups. ASD participants showed comorbid ADHD (n=15), ODD (n=9), CD (n=1), and tic disorder (n=5). In the OCD group, the following comorbidities were present: ADHD (n=11), oppositional defiant disorder (ODD; n=2), conduct disorder (CD; n=3), tic disorder (n=3), social anxiety disorder (n=1), generalized anxiety disorder (n=4), major depression (n=2), and dysthymia (n=1).

3.2. N-Acetylaspartate

A group difference was found in tNAA levels in the left striatum, while including scanner site as covariate ($F_{(2,124)}=4.29$, $p=0.016$). Medication use, sex and age did not influence the ANCOVA model and were therefore excluded. Post-hoc between-group comparisons revealed lower tNAA levels in the ASD group compared with controls ($t=2.84$, $p=0.005$). No significant differences were found in other group comparisons. Highest CRLB values were found for the OCD group, and ASD and controls did not differ on this measure. We are therefore confident that our results are not driven by differences in spectral quality. Fig. S2 shows group differences in tNAA overall and separately per site.

3.3. Association between striatal volume and metabolite concentrations

We have shown earlier in an overlapping sample (n=114) that glutamate was not significantly different across ASD, OCD and controls (Naaijen et al., 2016). Since tNAA concentrations differed between groups, we investigated associations between metabolite concentrations and striatal volume separately for each group. We found a significant relationship of both tNAA ($\beta=0.37$, $t=2.78$, $p=0.008$; Fig. 2A) and glutamate ($\beta=0.38$, $t=2.46$, $p=0.018$; Fig. 2C) with striatal volume for children with ASD, which were still (trend)-significant after correcting for total brain volume ($\beta_{tNAA}=0.25$, $t=2.28$, $p=0.027$ and $\beta_{glutamate}=0.22$, $t=1.92$, $p=0.06$, respectively) or for site ($\beta_{tNAA}=0.37$, $t=2.61$, $p=0.012$ and $\beta_{glutamate}=0.39$, $t=2.66$, $p=0.011$, respectively). The tNAA and glutamate concentrations were associated with each other as well ($\beta=0.88$, $t=10.84$, $p<0.001$; Fig. 2D). Graphically (as apparent from Fig. 2D), the ASD group is divided in two groups. This is due to the relatively higher neurochemical concentrations for GE scanners (one of the sites) than Siemens and Philips. After removal of this group (n=7), a significant association between the metabolites was still found ($\beta=0.6$, $t=4.06$, $p<0.001$). No significant associations between neurochemicals and striatal volumes were found for the OCD or control groups (see Fig. S5).

3.4. Striatal volume

There was no main effect of diagnosis ($F_{(2,129)}=0.97$, $p=0.39$) on striatal volume, and no effects of IQ, sex, age, medication use or scanner-site were found (all p-values >0.1). There was a main effect of total brain volume ($F_{(1,131)}=32.48$, $p<0.001$) on striatal volume, which on itself did not differ between the three diagnostic groups ($F_{(2,132)}=0.51$, $p=0.60$). The effect of hemisphere was at trend level ($F_{(1,129)}=3.49$, $p=0.064$).

A hemisphere by diagnosis interaction ($F_{(2,129)}=3.86$, $p=0.024$) suggested differences in left-right asymmetry in striatal volume across the three groups. Post-hoc, we therefore investigated this interaction more closely, by comparing the three groups with each other in three 2×2-designs, which showed the same diagnosis by hemisphere interactions, when comparing ASD with controls ($F_{(1,99)}=7.95$, $p=0.006$) and OCD with controls ($F_{(1,76)}=3.99$, $p=0.049$), but not ASD with OCD ($F_{(1,74)}=0.03$, $p=0.86$). Fig. 3 shows striatal volumes across the diagnostic groups and hemispheres; Fig. S3 shows these results separately per site. After removal of participants using medication and those with comorbidities, the asymmetry finding remained significant ($F_{(2,111)}=3.507$, $p=0.033$ and $F_{(2,97)}=3.706$, $p=0.028$, respectively). When investigating the caudate nucleus and putamen separately (Fig. S4), likely due to power restrictions, the hemisphere by diagnosis interaction was no longer seen, nor were any main effect of diagnosis or hemisphere (p-values >0.05).

Because of the significant group difference in striatal volume asymmetry, we conducted further analysis using the asymmetry index (AI). Within the ASD group, there were no significant

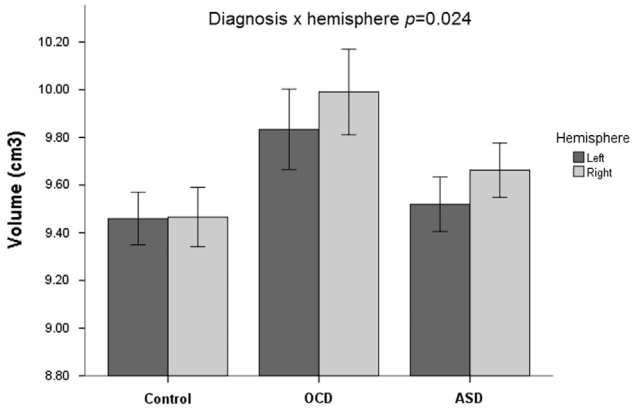

Fig. 3 Left and right striatal volume for each group. There was a significant interaction between diagnosis and hemisphere showing asymmetry in ASD and OCD compared with controls. ASD and OCD did not differ from each other in asymmetry (ASD = autism spectrum disorder, OCD = obsessive compulsive disorder). The error-bars represent the standard-error.

associations between striatal AI and any phenotypic measure of the ADI-R: social interaction (rho=0.10, p=0.47), communication and language (rho=0.04, p=0.76), and restricted and repetitive behaviors (rho=-0.11, p=0.42). For the OCD group we found no significant associations for CYBOCS-obsessions (rho=0.07, p=0.72) or CYBOCS-compulsions (rho=0.08, p=0.66). For the groups pooled together, no associations with any of the subscales as measured with the RBS (all p-values $>$ 0.1) were observed. These were all uncorrected for multiple comparisons.

3.5. Striatal shape

Shape analysis of the caudate and putamen did not reveal any differences related to diagnosis, nor any association with RBS measures, tNAA or glutamate concentrations (all p-values $>$0.05).

4. Discussion

Here we investigated dorsal striatal structure in relation to levels of tNAA and glutamate in ASD and OCD children. In children with ASD only, an association between left striatal volume and both tNAA and glutamate concentrations was found. Volume and shape analyses showed no structural changes of the striatum associated with ASD, OCD, compulsivity, or metabolite concentrations. However, we found hemispheric asymmetry (right$>$left) in striatal volume in ASD and OCD compared with controls, while the two disorder groups did not differ from each other. This asymmetry was not associated with any phenotypic measures in either of the groups nor with total brain volume.

Total NAA concentrations were lower in the left striatum of children with ASD compared with controls. This is in line with previous studies (e.g. see Ford and Crewther, 2016). In the same group, striatal volume positively correlated with tNAA concentrations. Studies of the relation between subcortical volume and NAA in other disorders (Padowski et al., 2014; Coughlin et al., 2015) have suggested NAA to be an underlying measure of neuronal integrity. Since NAA is mainly found in neurons in the brain (Urenjak et al., 1992), reductions in this metabolite may point to decreased neuronal density within the region of interest. Compared with controls, children with ASD may therefore have reduced neuronal integrity in the striatum. However, it has also been suggested that reductions in NAA reflect impaired neuronal functioning rather than a reduced number of neurons per se (Devito et al., 2007). A reduced concentration of NAA may therefore reflect both a decrease in neuronal density as well as impaired functioning.

Glutamate and striatal volume were associated in ASD as well, but were only trend-significant after correcting for total brain volume. Previous studies, for instance in schizophrenia (Plitman et al., 2014), suggest that neuronal loss in the striatum may be the result of excitotoxicity (Engelsen, 1986; Choi, 1988) caused by increased afferent glutamatergic projections from the prefrontal cortex. Here, we found a positive relation between both glutamate and striatal volume and tNAA and striatal volume in children with ASD, which contradicts this hypothesis of excitotoxicity. Glutamate as measured with MRS, however, does not only reflect glutamate as a neurotransmitter (Govindaraju et al., 2000), which may be responsible for excitotoxicity, but also glial and metabolic concentrations. Glutamate and tNAA concentrations were correlated as well, confirming an earlier report (Devito et al., 2007) and is suggested to be a marker of impairment in neuronal metabolism. Children with ASD thus show possibly impaired neuronal metabolism in the striatum, concomitant with alterations in volume.

Both ASD and OCD have been associated with striatal alterations before, but findings have been inconsistent. In ASD, mainly increased volumes of caudate (Hollander et al., 2005; Voelbel et al., 2006; Qiu et al., 2016) and putamen (Sato et al., 2014) have been found, which we could not replicate here. In OCD, the findings have been less consistent so far, with increased (Real et al., 2016), decreased (Zarei et al., 2011) and no differences (Szeszko et al., 2004) in striatal volumes observed, mainly with a focus on putamen. Asymmetry was reported in controls but not in participants with ASD in one study (Hollander et al., 2005), which is in contrast with our results. The previous study, however, was performed in a small sample of adults, while ours included a paediatric sample with a restricted age-range. Investigation of other regions in ASD (Say et al., 2014) showed asymmetry of the thalamus compared with controls as well. No studies in OCD have shown regional volumetric asymmetry before. The current finding of striatal asymmetry, which was present in both ASD and OCD, has not been reported before and could point to similarities in altered striatal structure in both disorders within children. This cross-disorder finding needs replication in an independent sample but may provide more insight into the underlying neurobiology of both disorders, supporting the approach adopted by the Research Domain Criteria (RDoC (Cuthbert, 2014)).

Strengths of the current study are the use of the complementary analyses of volume and in relation to neuro-metabolites, the combination of the two disorder groups in one relatively large study and additional approaches investigating shape and the relation between the striatal volume asymmetry and phenotypic measures. Additionally, combining volumetric and neuro-metabolite data gave us the opportunity to more specifically investigate underlying mechanisms of volume alterations in ASD and OCD. There were, however, also some limitations. First, the OCD group was smaller than the ASD and control groups due to recruitment difficulties. This resulted in less statistical power. Second, the groups were quite heterogeneous in terms of medication-use and comorbidities, although the results remained stable after removal of these participants. Additionally, the ASD group consisted of only high-functioning ASD patients. Our results are therefore not generalizable to all children with ASD. Third, our striatum voxel contains a significant amount of white matter (from the internal capsule) and some gray matter from the globus pallidus. We corrected for partial volumes to address the WM contribution, however, it was not possible to eliminate the possible slight contribution from the globus pallidus. This is a common limitation across MRS studies given the size and shape restrictions of voxels. Last, we did not measure metabolite concentrations from the striatum bilaterally, which limits us in further investigating the striatal asymmetry we found in relation to the metabolite concentrations. Additionally, the striatal volume and the MRS-voxel location are not perfectly matched, but since both voxel positioning and volumes did not differ between the groups,

this may have had minimal effects. Using multi-centre data was both a strength and a limitation; it allowed us to have a larger study sample but at the same time adds a lot of variance which needed to be accounted for in our analyses.

In conclusion, the current study showed that glutamate concentrations and lower tNAA levels in ASD compared with controls were both positively associated with left striatal volume. In addition, we found asymmetry in striatal volume in children with ASD and OCD compared with controls, which was not region-specific. These results need replication in an independent sample, but nevertheless provide insights in the involvement of NAA and glutamate in striatal volume in ASD and the overlap in asymmetry in striatal volume in paediatric ASD and OCD.

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Conflict of interest

B Franke has received educational speaking fees from Merz and Shire. DJ Lythgoe has acted as a consultant for Ixico PLC. JK Buitelaar has been consultant to/member of advisory board of and/or speaker for Janssen Cilag BV, Eli Lilly, Bristol-Myer Squibb, Shering Plough, UCB, Shire, Novartis and Servier. He is not an employee of any of these companies, nor a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, and royalties. J Naaijen, MP Zwiers, NJ Fotde, SCR Williams, S Durston, D Brandeos and JC Glennon do not report any conflicts of interest.

Author disclosure

JK Buitelaar designed the study and wrote the protocol. J Naaijen managed the literature searches. J Naaijen, MP Zwiers, NJ Forde and DJ Lythgoe managed the analyses. J Naaijen undertook statistical analyses. J Naaijen, MP Zwiers, DJ Lythgoe and JK Buitelaar wrote the first draft of the manuscript. All authors were involved in reviewing and editing of the final manuscript. All authors contributed and have approved the final manuscript.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.euroneuro.2017.11.010.

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