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Assessment of glutamate in striatal subregions in obsessive-compulsive disorder with proton magnetic resonance spectroscopy

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Abstract

Glutamatergic signaling abnormalities in cortico-striatal circuits are hypothesized to lead to the repetitive thoughts and behaviors of obsessive-compulsive disorder (OCD). To test this hypothesis, studies have used proton magnetic resonance spectroscopy (^{1}H MRS) to measure glutamatergic compounds in the striatum of individuals with OCD. However, none has used methods that could measure glutamate minimally contaminated by glutamine and γ-aminobutyric acid (GABA) in striatal subregions. Therefore, in this study, a proton MRS imaging (^{1}H MRSI) technique with relatively high spatial resolution at 3.0 T was used to measure minimally contaminated glutamate levels in three striatal subregions (i.e., dorsal caudate, dorsal putamen, and ventral striatum) in 15 unmedicated adults with OCD and 16 matched healthy control subjects. No significant group differences in glutamate levels were found in any of the three striatal subregions. In contrast, a study in unmedicated pediatric OCD patients that measured glutamatergic compounds in the dorsal caudate by MRS at 1.5T found significant elevations. Further studies are warranted to assess whether these discrepant MRS findings are due to

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differences in subject age or MRS methodology, or potentially are associated with glutamatergic gene variants implicated in OCD.

Keywords

magnetic resonance spectroscopy; OCD; striatum; caudate

1. Introduction

Structural and functional imaging studies indicate that obsessive-compulsive disorder (OCD) is associated with abnormal functioning of brain circuits that include the orbito-frontal cortex (OFC), anterior cingulate cortex (ACC), striatum, and thalamus (Milad and Rauch, 2012). Preclinical and clinical evidence suggests a role for glutamatergic abnormalities in OCD, including reports of associations between OCD and genes related to the glutamate system, of OCD-like behavior in mice following disruption of glutamatergic transmission in cortico-striatal circuits, and of the ability of glutamate-modulating drugs to ameliorate OCD symptoms (reviewed in Insel, 2012; Pittenger et al., 2011). Together, these observations have led to the hypothesis that abnormalities in glutamatergic signaling in OFC-striatal circuits may be implicated in the repetitive thoughts and behaviors that characterize OCD.

Several studies have tested this hypothesis by using proton magnetic resonance spectroscopy (^{1}H MRS) to measure levels of glutamatergic compounds in the striatum of individuals with OCD and healthy control subjects (reviewed in Brennan et al., 2012). The results have been variable, with one study reporting elevations of glutamatergic compounds in the head of the left caudate in unmedicated pediatric patients that decreased with successful treatment (Rosenberg et al., 2000), another study reporting elevated glutamatergic compounds in the left caudate in medicated adult patients (Shekhar et al., 2008), and the majority of studies in both pediatric and adult patients finding no striatal glutamatergic abnormalities (Bartha et al., 1998a; Ebert et al., 1997; Lazaro et al., 2012; O'Neill et al., 2012; Starck et al., 2008; Whiteside et al., 2012; Whiteside et al., 2006). Multiple factors differed across these studies and may explain the discrepant results, including whether OCD subjects were receiving medication at the time of scanning, the magnetic field strength (ranging from 1.5T to 4.0T), the specific MRS methods used to derive the "glutamatergic compound" levels (and thus more or less contaminated with glutamine and γ-aminobutyric acid [GABA]), and the size and location of the striatal voxel of interest.

In the present study, we aimed to minimize or eliminate some of these potential confounds by: (a) studying only unmedicated patients; and (b) taking advantage of the relatively higher detection sensitivity at 3T to implement a MRS imaging (MRSI) method that enables detection of glutamate with minimal glutamine and GABA contamination – as opposed to glutamate that is obtained with approaches that do not attempt to minimize the glutamine and/or GABA contribution, commonly referred to as "Glx" -- from multiple striatal voxels. Based on the glutamatergic theory of OCD and a study at 1.5T that found increased glutamatergic compounds in the left dorsal caudate in unmedicated pediatric OCD patients (Rosenberg et al., 2000), we hypothesized that unmedicated adults with OCD will have

increased glutamate in the left dorsal caudate compared to matched healthy control subjects. We simultaneously measured glutamate levels in the left dorsal putamen and ventral striatum to establish the specificity of the caudate finding, since these striatal subregions receive glutamatergic projections from different cortical regions (Haber and McFarland, 1999).

2. Methods

2.1. Subjects

The institutional review board of the New York State Psychiatric Institute/Columbia University approved the study. Subjects were recruited by advertisements and word of mouth and provided written informed consent.

Subjects had to be between the ages of 18 and 55 and free of any significant medical problems, current or past neurological disorders (other than Tic Disorder), and history of substance or alcohol abuse or dependence (including nicotine). Pregnant, nursing, and postmenopausal women and those using hormonal contraceptives were excluded. OCD subjects had to fulfill the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for OCD for at least one year as their primary psychiatric disorder and not be receiving psychotropic medications (for a minimum of six weeks) or psychotherapy at the time of the study. OCD subjects with other current Axis I disorders (except specific or social phobia) were excluded. Healthy controls had to have no current or past DSM-IV Axis I disorder, no exposure to psychoactive medications, and no family history of OCD as assessed by the Family History Screen (Weissman et al., 2000). Healthy controls were matched to the OCD subjects on age, sex, and ethno-racial categories. All subjects but two (n=1 OCD; n=1 healthy controls) were right-handed.

Diagnoses were determined during a psychiatric evaluation by expert clinicians and confirmed by trained clinical raters using the Structured Clinical Interview for DSM-IV (First et al., 1996). Medical health was established by history and physical examination; a urine drug test and pregnancy test for females were conducted on the day of scanning. OCD and depressive severity were assessed in OCD subjects by trained clinician raters using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al., 1989a; Goodman et al., 1989b) and the 17-item Hamilton Depression Rating Scale (HAM-D, Hamilton, 1960). The Y-BOCS checklist provided current severity scores for each OCD subject along five symptom dimensions (contamination and cleaning, taboo thoughts, doubt and checking, symmetry and ordering, and hoarding) using the approach recommended by Pinto and colleagues (2009). A neuroradiologist confirmed that all MRI scans were free of gross structural abnormalities.

2.2. MR data acquisition procedures

The neuroimaging consisted of a single scanning session lasting approximately 60 min and included structural MRI and MRS acquisitions. It was conducted on a research-dedicated General Electric 3.0T EXCITE MR system at the New York State Psychiatric Institute using a standard quadrature single-channel head coil.

2.2.1. Structural MRI—A three-plane, low-resolution, high-speed scout imaging series was obtained, followed by a series of high-resolution scans, consisting of standardized axial, coronal and sagittal T_1-, T_2-, and spin density-weighted scans that were appropriately obliqued for prescribing the ^{1}H MRS voxels. A T_1-weighted Spoiled Gradient-Recalled echo (SPGR) volumetric scan (TR/TE = 30/8 ms, flip angle 45°, field of view 24 cm, 256 × 256 matrix, 124 coronal slices and a slice thickness of 1.0 mm) was acquired for brain tissue segmentation.

2.2.2 ^{1}H MRSI data acquisition—To obtain the levels of glutamate minimally contaminated by glutamine and GABA from subregions of the striatum, the multi-voxel or ^{1}H MRS imaging (^{1}H MRSI) version of the standard PRESS was implemented with TR 1500 ms, 20×20 phase-encoding steps, a spectroscopic imaging (SI) slice thickness of 2.0 cm, a field-of-view of 16 cm, and TE 80 ms, which was previously established to yield spectra in which the glutamate C-4 resonance at 2.35 ppm is minimally contaminated by the co-resonant glutamine C-4 peak (Mullins et al., 2008). The minimally contaminated glutamate levels thus derived will be referred to herein as simply glutamate. Within the SI slice (positioned coronally anterior to the anterior commissure), three individual voxels (each 0.8×0.8×2.0 cm^3) were then positioned to contain the striatal subregions of interest (i.e., the left dorsal caudate, dorsal putamen, and ventral striatum), with positioning optimized for the dorsal caudate given our hypothesis. The positioning of these MRSI voxels within the PRESS-preselected volume of interest (VOI) is depicted in Figure 1 (panels A&B). The static magnetic field homogeneity within the VOI, which was automatically optimized by the scanner's host computer, was typically 10–15 Hz as measured by the full-width at half maximum (FWHM) of the water resonance.

2.3. ^{1}H MRS data processing and quantification

One objective of this study was to use the multivoxel or MRSI technique with a relatively high spatial resolution to measure glutamate levels simultaneously in striatal subregions (i.e., dorsal caudate, dorsal putamen, and ventral striatum). Using 20 × 20 phase-encoding steps, a field of view 16 cm and a slice thickness of 2 cm yielded 2D MRSI data in a "nominal" voxel size of 0.8 × 0.8 × 2.0 or 1.28 cm^3, which was sufficiently small to fit within each of the striatal subregions as depicted in Figure 1 (panel A). There is a caveat, however. Rather than being perfectly rectangular, voxels obtained by phase-encoding have the shape of the point-spread function (PSF) illustrated in Figure 2 (Barker and Lin, 2006). Due to the limited or truncated number of phase-encoding steps, necessary to minimize scan time, the PSF is a sin(x)/x or sinc(x) function, with decaying sidebands (Figure 2a, b) that lead to contamination of signals inside the voxels with those from outside the voxel. While applying a smoothing filter (e.g., a Gaussian or Hamming function) to the PSF greatly reduces the sidebands (Figure 2c), this leads to a broadening of the voxel by ~40% (Barker and Lin, 2006). In this study, we opted to process all of our raw MRSI data without spatial filtering or PSF smoothing because levels of glutamate, the metabolite of interest, were relatively low and comparable across the three striatal subregions (Figure 1, panel C), and, under these conditions, cross-contamination would be negligible compared to what it would be if we broadened the voxels by ~40% with a spatial filter. To ensure optimal extraction of

spectra from the three voxels of interest for post-processing, the MRSI grid was spatially shifted (Derby et al., 1989) as necessary.

Details of the MRS data quality assessment criteria and procedures used in this study to retain or reject spectra for inclusion in group analyses are provided in the online supplement. For all the cases that fulfilled our quality assessment criteria, metabolite peak areas in each voxel were obtained using a robust and highly optimized public-domain Levenberg-Marquardt nonlinear least-squares IDL minimization routine (Markwardt, 2009) to model the resonances in the frequency domain as a linear combination of pseudo-Voigt functions, which enables more precise analysis of lineshapes that consist of mixtures of Lorentzian and Gaussian functions. The IDL fitting procedure automatically reports the covariance matrix for the estimated set of MRS parameters, from which the parameter correlation matrix, statistical errors at one standard deviation, and uncertainties are computed as measures of goodness of fit (Markwardt, 2009); we also assessed visually for each fit by examining the residual of the difference between the measured and best-fit spectra (Figure 1, panel C).

The spectral data were automatically corrected for susceptibility shifts due to slight variations in magnetic field strength across the brain, and then fitted in the frequency domain as described to obtain the peak area for glutamate. For normalization of levels across subjects, the glutamate peak areas were expressed in institutional units (i.u.) as ratios relative to the root-mean-square (rms) of the background noise in each voxel (i.e., as signal-to-noise ratios) – an approach that we have used previously in a number of publications (Kaufmann et al., 2004; Mathew et al., 2009; Weiduschat et al., 2014; Weiduschat et al., 2013).

2.4. Assessment of voxel tissue heterogeneity

Volumetric MRI-based tissue segmentation was performed to compare the proportions of gray matter (GM), white matter (WM), or CSF contained in the VOI. Segmentation and classification was based on the signal-intensity histogram obtained using the commercial software MEDx (Medical Numerics, Sterling, VA) from each subject's volumetric (SPGR) MRI. From the histogram, a segmentation mask of each voxel was generated and the proportions of GM, WM, and CSF computed.

2.5. Statistical analyses

Demographic and clinical characteristics and proportion of tissue composition were compared across diagnostic groups using Fisher's Exact or χ^2 tests for categorical and independent sample *t*-tests for continuous variables. Independent *t*-tests were used to test for differences in total tissue glutamate levels between diagnostic groups. Based on findings from a study in unmedicated pediatric OCD patients (Rosenberg et al., 2000), we hypothesized that glutamate levels in the left dorsal caudate would be increased in adults with OCD compared to controls. Exploratory analyses examined group differences in glutamate levels in the left dorsal putamen and ventral striatum in subjects with viable MRS data in those regions as well. Within the OCD group, the relationship between glutamate levels in the striatal subregions (dorsal caudate, dorsal putamen, and ventral striatum) and OCD severity (measured by the Y-BOCS), age of OCD onset, and each of five OCD

symptom dimensions (current contamination and cleaning, taboo thoughts, doubt and checking, symmetry and ordering, and hoarding) was examined using Pearson's product-moment correlation. All statistical tests were 2-tailed with level of significance $\alpha = .05$.

3. Results

3.1. Sample characteristics

The final sample consisted of 15 OCD and 16 healthy control subjects; an additional three subjects (1 healthy control and 2 OCD subjects) signed consent for the study but did not complete the MRI imaging. The demographic and clinical characteristics of subjects with viable MRS data are provided in Table 1. There were no significant group differences in age ($t = -.24$, $df = 29$, $p = .81$), sex (Fisher's Exact Test, $p = 1.00$), race (Caucasian versus non-Caucasian: $\chi^2 = 0.06$, $df = 1$, $p = .81$), or days since last menstrual period in females ($t = 0.54$, $df = 19$, $p = .59$).

The OCD subjects had clinically significant symptoms, with a mean Y-BOCS score of 26. All five OCD symptom dimensions were represented, with most subjects exhibiting symptoms in more than one domain. Three had symptoms primarily in one domain (contamination and cleaning symptoms, $n = 2$; symmetry and ordering, $n = 1$). As shown in Table 1, 11 of the 15 OCD subjects had never taken any psychotropic medications. Of the four ever exposed to psychotropic medications, all were free of them for at least 18 weeks. Only one OCD subject (one of those exposed to medication) had ever received CBT consisting of exposure and response prevention. None were receiving treatment at the time of MRS scanning.

Measures of tissue segmentation are provided in Table 2 for the three voxels. There were no significant group differences in tissue composition in these three voxels (dorsal caudate: all p-values > .46; dorsal putamen: all p-values > .25; ventral striatum: all p-values > .35).

3.2. Glutamate levels in striatal subregions

In the left dorsal caudate, glutamate levels did not significantly differ by group ($t = -.80$, $df = 29$, $p = .43$). There also were no significant group differences in the left dorsal putamen ($t = .93$, $df = 23$, $p = .36$) or the left ventral striatum ($t = .70$, $df = 25$, $p = .49$). The observed mean values and 95% confidence intervals of the difference in the means by diagnostic group are provided in Table 3. Glutamate levels across the three striatal regions were not significantly correlated with each other (p-values > .47).

The rms of the background noise used for glutamate normalization was found to have outlier values (more than three standard deviations from the mean) for several subjects. To assess the sensitivity of the results to these outliers, subjects meeting this criterion were removed and the analyses rerun on the remaining 10 healthy controls and 13 OCD subjects. This re-analysis did not alter the results: glutamate levels did not significantly differ by group (dorsal caudate: $t = -.49$, $df = 21$, $p = .62$; dorsal putamen: $t = 1.94$, $df = 20$, $p = .07$; ventral striatum: $t = 1.39$, $df = 21$, $p = .18$).

3.3. Clinical correlations

In the OCD sample, glutamate levels in left striatal subregions were not significantly correlated with OCD severity (*p*-values: dorsal caudate > .54; dorsal putamen > .29; ventral striatum > .48), age of OCD onset (*p*-values: dorsal caudate > .38; dorsal putamen > .60; ventral striatum > .09), or any of the five symptom dimensions (all *p*-values: dorsal caudate > .13; dorsal putamen >.16; ventral striatum >.24; except for symmetry and ordering [r=−.51, p=.07]).

4. Discussion

We compared glutamate levels in striatal subregions in unmedicated adults with OCD with those in matched healthy controls using MRS methods designed to measure glutamate with minimal glutamine and GABA contamination. Contrary to our hypothesis, we did not find glutamate abnormalities in the left dorsal caudate in unmedicated adults with OCD; there were no significant associations between glutamate levels and OCD severity, age of OCD onset, or OCD symptom dimensions. There also were no significant group differences in glutamate levels in the left dorsal putamen or ventral striatum.

The lack of evidence for striatal glutamate abnormalities in OCD agrees with two prior studies in unmedicated patients, including one in 11 treatment-naïve pediatric patients using a 1.5T instrument (Lazaro et al., 2012) and another in 13 unmedicated adults using a 4.0T instrument (Bartha et al., 1998b). However, the voxel in both studies straddled the caudate, putamen, and internal capsule. In contrast, our study measured minimally contaminated glutamate simultaneously in three striatal subregions (i.e., dorsal caudate, dorsal putamen, ventral striatum) in unmedicated adults with OCD; this is important since these striatal subregions receive glutamatergic projections from different cortical regions (Haber and McFarland, 1999), and since medications can change MRS glutamatergic findings (Rosenberg et al., 2000). On the other hand, our results disagree with a single-voxel MRS study in 11 psychotropic drug-naïve pediatric OCD patients (Rosenberg et al., 2000) that also achieved a relatively high spatial resolution and found increased glutamatergic compound levels in the left caudate compared to matched controls at baseline; in their study, these abnormalities normalized with successful treatment, supporting the glutamatergic hypothesis of OCD.

Several factors could explain the discrepancy with this study and ours, even though both sampled striatal subregions. First, we examined subjects 19 years and older, whereas the other study examined subjects ages 8 to 17. Thus, the discrepancy could reflect age-dependence in glutamate abnormalities in OCD. Second, the prior ^{1}H MRS study was conducted on a 1.5 T instrument, which did not enable the discrimination of glutamate from glutamine and GABA; this could yield confounding glutamatergic compound levels if GABA levels were altered, as we previously found in another brain region (Simpson et al., 2012). Finally, the samples could have differed in important clinical characteristics, such as symptom dimensions, comorbidity, or genetic variation that might influence brain glutamatergic systems (Arnold et al., 2009).

This is the first study targeting unmedicated adults with OCD to use a MRSI method designed specifically to measure minimally contaminated glutamate and to examine three different striatal subregions (dorsal caudate, dorsal putamen, ventral striatum). However, the relatively small sample size and the inherent inability of MRS to directly measure glutamatergic neurotransmission are significant limitations. Moreover, while the MRSI method implemented in this study minimized the contamination of glutamate by glutamine and GABA, it did not completely eliminate it (Mullins et al., 2008).

In summary, this study found no evidence of significant striatal glutamatergic abnormalities in unmedicated adults with OCD. If replicated, this would require revisions to the glutamatergic hypothesis of OCD. Future studies in larger samples are warranted to confirm the present findings in adult OCD patients and to determine whether glutamatergic abnormalities in OCD occur only in pediatric OCD or in subjects with gene variants that might influence brain glutamatergic systems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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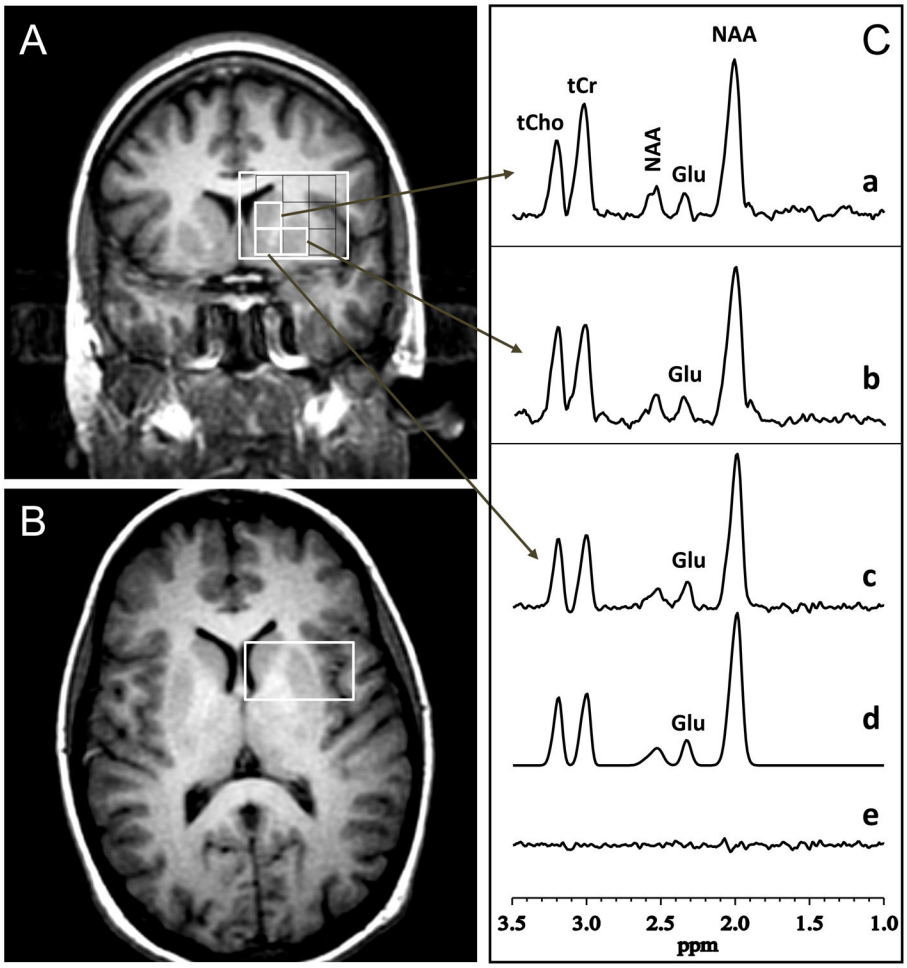

Figure 1.

Striatal Subregions and Associated Sample ^{1}H MR Spectral Data. [A] Coronal and [B] axial localizer images showing the size and location of the volume of interest (large white box) pre-localized with the PRESS method. The spectroscopic imaging (SI) slice thickness was 20 mm, field of view 16 cm, with the slice positioned coronally anterior to the anterior commissure. The coronal view, [A], is overlaid with a grid of voxels that cover the striatum and its subregions. Within this grid, three individual voxels (0.8 × 0.8 × 2.0 cm^3) were positioned to contain the dorsal caudate, dorsal putamen, and ventral striatum. The multi-voxel PRESS data set was acquired in 20 min using TE/TR 80/1500 ms, 20×20 phase-encoding (PE) steps, 2 excitations per PE. The arrows point to sample ^{1}H spectra recorded from these three striatal voxels, labeled as follows in panel [C]: (a) dorsal caudate; (b) dorsal putamen; and (c) ventral striatum; Shown left-to-right in each spectrum are the resonances for total choline (tCho), total creatine (tCr), N-acetyl-L-aspartate (NAA, methylene), uncontaminated glutamate (Glu), and NAA (methyl); (d) A nonlinear least-squares best-fit spectrum obtained by fitting the experimental spectrum in (c) to a sum of pseudo-Voigt lineshape functions in the frequency domain; (e) The residuals of the difference between (d) and (e). The fitting procedure yields areas under the metabolite resonances, which are proportional to concentrations.

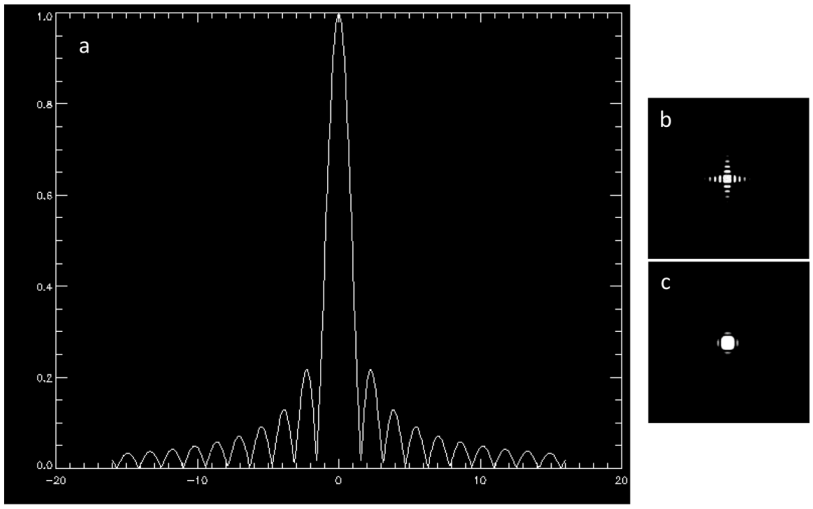

Figure 2.

[a] Point spread function (PSF) for the spatial response of 16×16 linearly applied phase-encoding, showing the characteristic sin(x)/x or sinc(x) function with decaying sidebands due to the use of a limited or truncated number of phase-encoding steps.

[b] The PSF in [a] displayed as a 2D image scaled to 25% of maximum pixel intensity.

[c] The PSF in [b] shown after application of a Hamming filter. Note that the sidebands have been greatly reduced but at the expense of a ~40% increase in voxel size.

Table 1

Demographic and clinical characteristics

Characteristics	OCD *n*=15	Healthy control *n*=16
Mean age in years (SD)	30 (9)	30 (8)
Number of males/females	10/5	11/5
Race-ethnicity	6AA/5Cau/3His/1O	6AA/6Cau/3His/1O
Mean age of OCD onset in years (SD)	16 (10)	-
OCD in first degree relative (by subject self-report)	4	0
Mean Y-BOCS (SD)	26 (3)	-
Mean HAM-D (SD)	3 (4)	-
DSM-IV axis I psychiatric comorbidity:		
None	10	16
Current specific or social phobia only	2	0
Current specific or social phobia with past	2	0
MDD	0	0
Past MDD only	1	0
History of substance or alcohol abuse/dependence	0	0
Current or past tic disorder	0	0
Treatment history:		
Any prior exposure to psychotropic medications	4	0
SRIs	3	0
Mean wks (SD, range) since last SRI dose	86 (61, 46–156)	0
Other medications (wks since last dose)	1 (18)	0
Prior exposure therapy	1	0

Abbreviations: AA, African-American; Cau, Caucasian; HAM-D, Hamilton Depression Rating Scale (17-item); HIS, Hispanic; MDD, major depressive disorder; O, other; OCD, obsessive-compulsive disorder; SD, standard deviation; SRI, serotonin reuptake inhibitor; wks, weeks; Y-BOCS, Yale-Brown Obsessive Compulsive Scale

Table 2

Tissue segmentation in striatal subregions

	OCD (*n*=15)	Healthy control (*n*=16)	95% CI for difference in means
Tissue composition	***Mean percent (SD)***	***Mean percent (SD)***	
Dorsal caudate			
CSF	6.04 (4.28)	6.36 (5.77)	−3.43, 4.08
Gray matter	62.24 (7.39)	63.99 (5.83)	−3.12, 6.62
White matter	31.70 (9.95)	29.63 (8.62)	−8.91, 4.75
Dorsal putamen			
CSF	0.05 (0.05)	0.15 (0.33)	−0.08, 0.28
Gray matter	62.74 (6.35)	61.84 (5.96)	−5.42, 3.63
White matter	37.20 (6.34)	38.01 (6.02)	−3.74, 5.34
Ventral striatum			
CSF	0.03 (0.04)	0.07 (0.15)	−0.04, 0.12
Gray matter	42.67 (8.29)	42.91 (6.47)	−5.20, 5.68
White matter	57.30 (8.29)	57.02 (6.49)	−5.72, 5.18

Abbreviations: CI, confidence interval; CSF, cerebral spinal fluid; OCD, obsessive-compulsive disorder; SD, standard deviation

Table 3

Striatal levels of glutamate minimally contaminated by glutamine and γ-aminobutyric acid

	OCD (n=15)[a]	Healthy control (n=16)[a]	95% CI for difference in means
Striatal subregions	***Mean (SD), i.u.***	***Mean (SD), i.u.***	
Dorsal caudate	5.30 (1.60)	4.75 (2.20)	−1.98, 0.86
Dorsal putamen	6.22 (2.05)	7.10 (2.63)	−1.08, 2.85
Ventral striatum	4.70 (2.50)	5.35 (2.38)	−1.28, 2.59

Abbreviations: CI, confidence interval; i.u., Institutional units; SD, standard deviation

[a]Samples sizes were smaller for the dorsal putamen (12 OCD, 13 healthy control) and the ventral striatum (13 OCD, 14 healthy control).