Structural and functional abnormalities in the caudate nucleus of schizophrenic patients with and without obsessive symptoms

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Background
Obsessive–compulsive symptoms (OCS) have been frequently described in schizophrenic populations. There is a controversy on whether this co-occurrence is more than just comorbidity or represents a distinct subgroup in schizophrenia.
Aim
The aim of this study was to investigate whether there are possible underlying structural and functional differences between schizophrenic patients with and those without OCS.
Patients and methods
Participants in this study were divided into three groups: 20 patients having schizophrenia with OCS; 20 patients having schizophrenia without OCS (both were diagnosed according to DSM-IV-TR); and 20 matching controls. All participants underwent an MRI for volumetric measurement of the caudate nucleus and a magnetic resonance spectroscopy to measure choline (Cho), creatine, and *N*-acetyl aspartate (NAA) in the caudate nucleus.
Results
Caudate volume was found to be reduced in schizophrenic patients with or without OCS ($P \leq 0.05$). Magnetic resonance spectroscopy findings showed that schizophrenic patients without OCS had significant increase in Cho concentration ($P \leq 0.05$), but average NAA concentration. In contrast, schizophrenic patients with OCS had significant reduction in NAA concentration ($P \leq 0.05$) with average Cho concentration.
Conclusion
Schizophrenic patients with OCS may have an atypical set of neuroradiological characteristics that would specifically categorize it within the schizophrenia spectrum.

Keywords:
caudate volume, magnetic resonance spectroscopy, obsessive-compulsive symptoms, schizophrenia

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Introduction

Obsessive–compulsive symptoms (OCS) have been frequently described in schizophrenic populations [1]. The prevalence of OCS in schizophrenia varies widely across studies (10–64%) [2]. Several studies have suggested increased rates of OCS and obsessive–compulsive disorder (OCD) among schizophrenic patients to the point of proposing the existence of a distinct diagnostic subgroup of schizo-obsessive disorder [3]. Whether this co-occurrence is more than just comorbidity and represents a distinct subgroup still remains controversial [4].

The presence of disrupted corticostriatothalamocortical circuits in schizophrenic patients [5,6] and in OCD patients [7,8] has been described. MRI and magnetic resonance spectroscopy (MRS) are noninvasive in-vivo methods that allow the study of these functional circuits.

MRI allows a volumetric measurement of the basal ganglion structures including the caudate nucleus [9], whereas MRS provides useful information on brain metabolites [10] such as *N*-acetyl aspartate (NAA) [11], choline [12], and creatine [13]. Several studies have shown disturbance in these metabolites in the caudate of schizophrenic patients [14–16] and in OCD patients [17,18].

Despite the early discovery of this comorbidity, little attention has been paid to it. Consequently, studies on the precise underlying potential neurobiological mechanisms of this comorbid condition have been limited [3].

The aim of our study was to investigate whether there are possible underlying structural and functional differences between schizophrenic patients with and those without OCS.

Patients and methods

Our case–control study was conducted from January 2013 to January 2014 in the Outpatient Clinic of Mansoura University Hospitals. We included schizophrenic patients

with and without OCS and a control group of healthy persons. The study was approved by the medical ethical committee of Mansoura University and all participants accepted to take part after giving either oral or written consent.

Clinical assessment

All patients underwent a neuropsychiatric clinical interview including thorough history taking and examination by a psychiatrist and a neurologist. The diagnosis and further subclassification for the presence or absence of OCS were performed according to the *Diagnostic and statistical manual of mental disorders*, 4th ed., text revised (DSM-IV-TR) criteria [19]. Reconfirmation of the diagnosis was made by two blinded psychiatrists. We included all schizophrenic patients ranging in age from 15 to 50 years from both sexes who were drug naive (if on medication, it had to be stopped for at least 4 weeks). We excluded patients with comorbid mental retardation, organic brain disorders (such as ischemic vascular diseases, brain tumors, trauma, and degenerative disorders), substance use disorders, and language or hearing difficulties.

The patients were divided into group A, comprising 20 schizophrenic patients with OCS, and group B, comprising 20 schizophrenic patients without OCS; group C comprised 20 control participants selected from among nonpsychiatric patients who came to Mansoura University Hospital Outpatient Clinic and some workers in the hospitals. The control group was matched in age and sex with the patient groups.

Imaging studies

Magnetic resonance imaging

All groups were subjected to an MRI of 1.5 T (Magnetom Symphony, Version VA12A; Siemens, Germany) using a head coil. The MRI protocol included axial T_1-WI, sagittal T_2-WI, and coronal FLAIR images.

The left and right caudate nuclei volumes were measured. The volumes of 10 patients were calculated five times on the same scan by two raters to determine test reliability. All volumes were measured by the raters without knowing the diagnosis or MRS measures. The volume of the caudate was calculated according to the manual tracing technique [20,21].

Magnetic resonance spectroscopy

Single-voxel localization proton MRS was performed using a spin-echo mode sequence. Two voxels ($15 \times 15 \times 15$) were placed on the right and left caudates. The raw data were transferred to an off-line workstation and postprocessed automatically using a spectroscopic analysis package. Three main metabolites were identified: NAA at 2.0 ppm, creatine at 3.0 ppm, and choline at 3.2 ppm. The peak ratios were calculated from the integration of the single peak, including NAA/creatine, NAA/choline, and choline/creatine.

Statistical analysis

The results were computed on an IBM (Chicago, Illinois, USA) compatible personal computer Pentium IV using the statistical software package for the social sciences (SPSS; SPSS Inc., Chicago, Illinois, USA) for Windows 11. Data were summarized using mean, median, and SD for quantitative data. Qualitative data were described as number and percentage.

The χ^2-test with Yates' correction, and relative risks were used to test for association between different categorical variables (qualitative data). The differences between groups were tested using the *t*-test for two-group comparisons and one-way ANOVA for analysis of covariance in more than two groups and the post-hoc multiple comparisons test (Scheffe's test) for within-group paired comparison (quantitative data). The correlation between two continuous groups was assessed using the Pearson correlation test. *P* values were considered significant if less than or equal to 0.05 and highly significant if less than or equal to 0.001 at confidence interval 95%.

Results

Sociodemographic results

All sociodemographic data are presented in Tables 1 and 2. Schizophrenic patients with OCS are more likely to live alone and to have poorer occupational functioning even if they were of higher education level compared with schizophrenic patients without OCS (Table 1).

Eighty-five percent of schizophrenic patients with OCS were right-handed compared with 70% of schizophrenic patients without OCS, with no statistically significant difference ($P = 0.449$) (Table 1).

Regarding the disease duration, the mean duration of illness was higher among schizophrenic patients with OCS (8.65 ± 6.53 years) compared with schizophrenic patients without OCS (6.0 ± 2.22 years), with no statistically significant difference ($P = 0.099$) (Table 1).

Concerning the age at onset, 55% of schizophrenic patients with OCS had onset of the disorder before the age of 15 years in comparison with 25% of schizophrenic patients without OCS. Forty percent of schizophrenic patients with OCS had age at onset between 15 and 30 years in comparison with 50% of schizophrenic patients without OCS. Only 5% of schizophrenic patients with OCS had age at onset from 35 to 45 years compared with 25% of schizophrenic patients without OCS. The difference in overall age at onset is not statistically significant ($P = 0.066$) but χ^2 for trend shows significant difference between the two groups with respect to age at onset before 15 years ($P = 0.043$) (Table 2).

Caudate nucleus volume results

The size of the caudate nucleus on both sides was significantly reduced in schizophrenic patients with OCS compared with schizophrenic patients without OCS and when compared with controls (left, $P = 0.010$; and right, $P = 0.000$) (Table 3).

Table 1 Sociodemographic data of the studied groups

	n (%)				
Variables	Schizophrenia with OCS	Schizophrenia without OCS	χ^2	*P*	RR
Sex					
Male	15 (75)	12 (60)	1.026	0.311	1.444
Female	5 (25)	8 (40)			
Handedness					
Non-right	3 (15)	6 (30)	0.573	0.449	0.722
Right	17 (85)	14 (70)			
Marital status					
Single	15 (75)	11 (55)	4.868	0.088	0.608
Married	5 (25)	6 (30)			
Divorced	0 (0)	3 (15)			
Widow	0 (0)	0 (0)			
Occupation[a]					
Not working	12 (60)	10 (50)	7.141	0.068	1.476
Student	3 (15)	1 (5)			
Semiskilled	3 (15)	8 (40)			
Skilled	2 (10)	1 (5)			
Education (years)[a]					
<6	3 (15)	9 (45)	6.134	0.047*	1.333
6–12	10 (50)	9 (45)			
>12	7 (35)	2 (10)			
Residence					
Rural	16 (80)	14 (70)	0.533	0.465	0.778
Urban	4 (20)	6 (30)			
Duration (mean ± SD)	8.65 ± 6.53	6.00 ± 2.22	1.718	0.099	

An RR of <1 means the event is less likely to occur in the experimental group than in the control group. An RR of >1 means the event is more likely to occur in the experimental group than in the control group. A relative risk of 1 means there is no difference in risk between the two groups.
OCS, obsessive–compulsive symptoms; RR, relative risk.
[a]Classification according to UK National Statistics Socio-Economic Classification [22].
*Statistically significant difference.

Table 2 Distribution of age and age of onset in the studied groups

	n (%)						
	Schizophrenia with OCS	Schizophrenia without OCS	χ^2 for trend	*P*	RR	χ^2	*P*
Age							
<15	0 (0)	0 (0)	0	0	–	2.543	0.280
15–30	10 (50)	6 (30)	1.66	0.197	1.49 0.642		
30–45	7 (35)	12 (60)	2.51	0.113	0.595 1.65		
>45	3 (15)	2 (10)	0.229	0.633	1.23 0.777		
Age of onset							
0–15	11 (55)	5 (25)	3.75	0.043*	1.834 0.5	5.44	0.066
15–30	8 (40)	10 (50)	0.404	0.525	0.814 1.22		
30–45	1 (5)	5 (25)	1.765	0.184	0.298 1.89		
>45	0 (0)	0 (0)					

OCS, obsessive–compulsive symptoms; RR, relative risk.
*Correlation is significant at $P \leq 0.05$ level (2-tailed).

Magnetic resonance spectroscopy results

Choline values are statistically significantly higher in schizophrenic patients with or without OCS compared with controls, on both sides (left, $P = 0.000$; and right, $P = 0.042$). Similar significant choline values were detected in the dominant hemisphere ($P = 0.000$) (Table 4).

The choline/creatine ratio significantly increased in schizophrenic patients with or without OCS compared with controls on the left side ($P = 0.000$); although it increased on the right, the difference was not statistically significant ($P = 0.223$). Similar significant choline/creatine values were detected in the dominant hemisphere ($P = 0.000$) (Table 4).

NAA values were significantly lower in schizophrenic patients with OCS than in schizophrenic patients without OCS and in controls on the left side ($P = 0.040$); although it decreased on the right, the difference was not statistically significant ($P = 0.806$). These differences were also not significant regarding the dominant hemisphere ($P = 0.187$) (Table 4).

Similar results were obtained for the NAA/creatine ratio, which was statistically significantly low in schizophrenic

Table 3 Caudate size in the studied groups

		Overall comparison (one-way ANOVA)				Post-hoc multiple comparisons test (Scheffe's test)					
		Controls	Schizophrenia with OCS	Schizophrenia without OCS	*P*	Controls/ schizophrenia with OCS		Controls/ schizophrenia without OCS		Schizophrenia with OCS/ schizophrenia without OCS	
						Mean differences	*P*	Mean differences	*P*	Mean differences	*P*
Rt caudate	Mean	5.41416	3.91782	4.10193	0.000**	0.880200	0.000**	0.771900	0.000**	−0.10830	0.732
	SD	0.612240	0.398860	0.415288							
Lt caudate	Mean	5.56818	4.21209	3.862791	0.003*	0.797700	0.018*	1.003170**	0.002*	0.205470	0.647
	SD	0.617961	0.918221	0.533191							

Lt, left; OCS, obsessive–compulsive symptoms; Rt, right.
*Correlation is significant at $P \leq 0.05$ level (2-tailed).
**Correlation is highly significant at $P \leq 0.001$ level (2-tailed).

Table 4 Brain metabolites in the studied groups

		Overall comparison (one-way ANOVA)				Post-hoc multiple comparisons test (Scheffe's test)					
MRS parameters		Controls	Schizophrenia with OCS	Schizophrenia without OCS	*P*	Controls/ schizophrenia with OCS		Controls/ schizophrenia without OCS		Schizophrenia with OCS/schizophrenia without OCS	
						Mean differences	*P*	Mean differences	*P*	Mean differences	*P*
Lt Cho	Mean	3.21200	4.06000	5.36150	0.000**	−0.84800	0.292	−2.149	0.001**	−1.3015	0.017*
	SD	0.91146	0.84360	1.89500							
Rt Cho	Mean	3.67800	4.64450	5.12550	0.042*	−0.96650	0.231	−1.447	0.042*	−0.48100	0.574
	SD	0.76405	1.71119	1.37384							
Dominant Cho	Mean	3.24800	4.10250	6.00550	0.000**	−0.85450	0.233	−2.75	0.000**	−1.903	0.000**
	SD	0.73635	0.84126	1.74433							
Lt Cho/Cr	Mean	0.50270	0.53073	0.76535	0.000**	−0.28820	0.910	−0.26260	0.001**	−0.2346	0.000**
	SD	0.18126	0.14036	0.18193							
Rt Cho/Cr	Mean	0.58000	0.72020	0.87966	0.223	−0.14020	0.730	−0.29966	0.246	−0.15946	0.545
	SD	0.13539	0.44703	0.55075							
Dominant Cho/Cr	Mean	0.54470	0.55279	0.88850	0.000**	−0.81803	0.991	−0.3438	0.000**	−0.3357	0.000**
	SD	0.13893	0.14539	0.16895							
Lt NAA	Mean	11.75600	9.53650	11.19250	0.040*	2.21950	0.082	0.56350	0.844	−1.65600	0.121
	SD	2.18776	3.40508	1.23117							
Rt NAA	Mean	10.91100	10.73950	11.41550	0.806	0.17150	0.991	−0.50450	0.926	−0.67600	0.814
	SD	3.10340	3.66938	3.06416							
Dominant NAA	Mean	10.46600	9.53650	11.12550	0.187	0.92950	0.677	−0.65950	0.821	−1.58900	0.189
	SD	3.18195	3.40508	1.30007							

Cho, choline; Cr, creatine; Lt, left; MRS, magnetic resonance spectroscopy; NAA, *N*-acetyl aspartate; OCS, obsessive–compulsive symptoms; Rt, right.
*Correlation is significant at $P \leq 0.05$ level (2-tailed).
**Correlation is highly significant at $P \leq 0.001$ level (2-tailed).

patients with or without OCS compared with controls on the left ($P = 0.000$) and dominant hemisphere ($P = 0.000$), whereas the ratio was statistically insignificantly low on the right side ($P = 0.989$) (Table 5).

Choline/NAA ratio was significantly high in schizophrenic patients without OCS compared with schizophrenic patients with OCS and controls on the left ($P = 0.001$) and dominant hemisphere ($P = 0.000$), with higher values in schizophrenic patients with OCS, whereas the ratio was statistically insignificantly low on the right side ($P = 0.059$), again with higher values in schizophrenic patients with OCS (Table 5 and Figs 1–3).

Discussion

In the present study we performed a volumetric assessment and MRS study on the caudate nucleus to investigate whether there are possible underlying structural and functional differences between schizophrenic patients with and those without OCS.

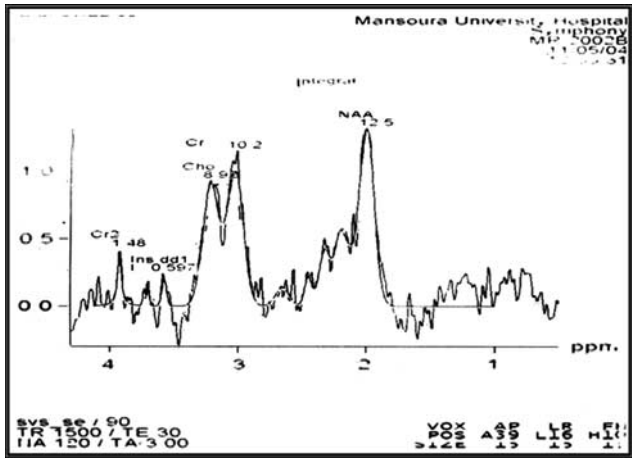
Our results on handedness showed that 85% of schizophrenic patients with OCS were right-handed and 15% were non-right-handed (left-handed or ambidextrous). In contrast, schizophrenic patients without OCS showed more tendencies to be left-handed (70% right-handed and 30% non-right-handed). It is important to note that

Table 5 *N*-acetyl aspartate/creatine and choline/*N*-acetyl aspartate in the studied groups

		Overall comparison (one-way ANOVA)				Post-hoc multiple comparisons test (Scheffe's test)					
		Controls	Schizophrenia with OCS	Schizophrenia without OCS	*P*	Controls/ schizophrenia with OCS		Controls/ schizophrenia without OCS		Schizophrenia with OCS/schizophrenia without OCS	
						Mean differences	*P*	Mean differences	*P*	Mean differences	*P*
NAA/Cr											
Lt	Mean	1.73350	1.04750	1.57950	0.000**	0.59805	0.000**	0.24895	0.217	−0.3491	0.014*
	SD	0.25239	0.10992	0.426702							
Rt	Mean	1.87450	1.67850	1.68900	0.989**	−0.39802	0.994	−0.28803	1	−0.42802	0.990
	SD	0.36182	0.83247	1.21372							
Dominant	Mean	2.03450	1.04750	1.62900	0.000**	1.06015	0.000**	0.67020	0.001**	−0.3899*	0.026*
	SD	0.57927	0.10992	0.62702							
Cho/NAA											
Lt	Mean	0.28580	0.51410	0.49950	0.001**	−0.2283	0.001**	−0.213	0.002*	1.46802	0.953
	SD	8.7092E−02	0.17817	0.14036							
Rt	Mean	0.32543	0.39340	0.42875	0.059	−0.67802	0.282	−0.10332	0.059	−0.353802	0.594
	SD	7.9853E−02	0.11447	0.11488							
Dominant	Mean	0.28403	0.52080	0.55275	0.000**	−0.2367	0.000**	−0.2687	0.000**	−0.32802	0.746
	SD	6.3816E−02	0.17408	0.10298							

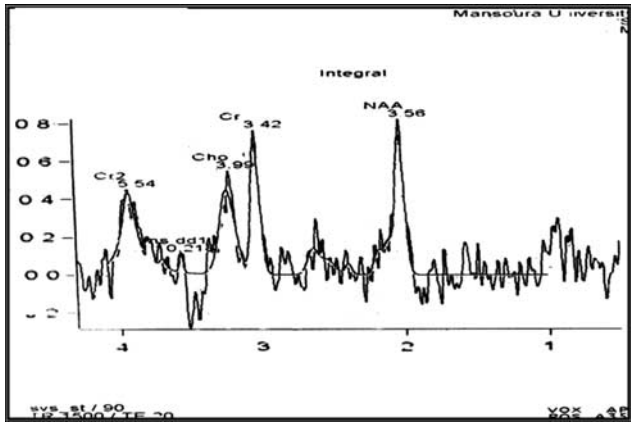
Cho, choline; Cr, creatine; Lt, left; NAA, *N*-acetyl aspartate; OCS, obsessive–compulsive symptoms; Rt, right.
*Correlation is significant at $P \leq 0.05$ level (2-tailed).
**Correlation is highly significant at $P \leq 0.001$ level (2-tailed).

Figure 1



Magnetic resonance spectroscopy of a schizophrenic patient without obsessive–compulsive symptoms showing marked increase in choline concentration (8.92 ppm), whereas the *N*-acetyl aspartate (NAA) concentration is of average range (12.5 ppm).

Figure 2



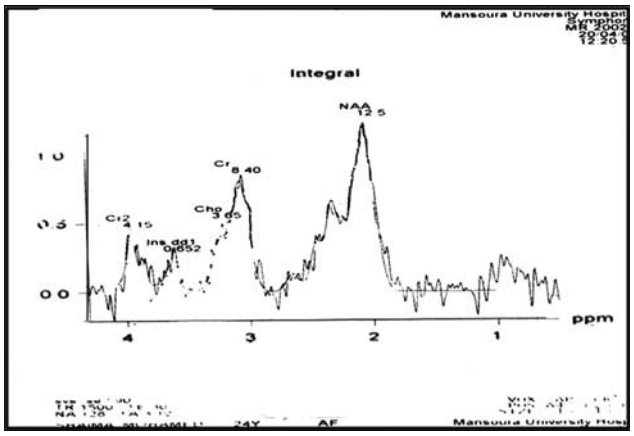
Magnetic resonance spectroscopy of a schizophrenic patient with obsessive–compulsive symptoms showing marked decrease in *N*-acetyl aspartate (NAA) concentration (3.56 ppm), whereas choline concentration is of average range (3.99 ppm).

right-handedness, left cerebral dominance for language, and normal cerebral asymmetry are considered to be secondary to a dominant allele, the 'right-shift factor' [23]. Several studies on schizophrenia have reported an excess of non-right-handedness, decreased language lateralization on the dichotic listening paradigm [24], and decreased anatomical asymmetry [25]. It has been postulated that the genetic mechanism underlying normal left hemispheric dominance is altered in schizophrenia. The discovery of the 'right-shift factor' might identify a locus in which genetic aberrations predispose for schizophrenia [26]. The difference between both groups of schizophrenic patients either with or without OCS as regards handedness may support the idea of being different disorders with different genetic predisposition.

Concerning the age group, our results showed that the age of about half of all schizophrenic patients with OCS was below 30 years in comparison with one-third of schizophrenic patients without OCS. This can be justified by the earlier onset of symptoms: 55% of schizophrenic patients with OCS had an age of onset below 15 years in comparison with 25% of schizophrenic patients without OCS, with a statistically significant difference.

The age of onset in 95% of schizophrenic patients with OCS was below 30 years in comparison with 75% of schizophrenic patients without OCS. This may be explained by the denial of affliction of the illness by family and friends and decreased knowledge about psychiatric illness, resulting in late discovery of the

Figure 3



Magnetic resonance spectroscopy of a control participant showing average concentration of choline (3.65 ppm) and *N*-acetyl aspartate (NAA) (12.5 ppm).

disease. In contrast, the distressing effect of OCS in schizophrenia may trigger the need to seek help and treatment early.

Regarding the volumetric assessment of the caudate nucleus, it was reduced in both schizophrenic groups compared with controls on both sides. This result is consistent with those of McClure *et al*. [5] and Keshavan *et al*. [21], whereas Brandt and Bonelli [9] described an increase in caudate volume in chronic schizophrenic patients. Data from longitudinal studies suggest that neuroleptics may change the brain morphology and these changes are dynamic and might be reversible. Nevertheless, several longitudinal studies have described a greater decrease in brain tissue volumes in the early stage of the illness, but others have failed to confirm these findings [27]. Thus, it remains unclear to what extent the observed structural changes reflect the ongoing illness process and to what extent the type and duration of antipsychotic medication can modify the neuroimaging measures.

When we studied the caudate volume in OCD patients, we found only one study that described an increase in gray matter volume in the head of the left caudate [28]; another study failed to show significant differences in caudate volumes between OCD patients and controls [8]. In contrast, many studies showed reduction in caudate volume in OCD patients [20,29]. On the basis of this confluent data, we can say that our caudate volume results need further studies on larger groups of schizophrenic and OCD patients under different types of medication for better evaluation of the results.

Nevertheless, many neurodegenerative disorders such as Parkinson's disease and Huntington's disease are associated with neuropsychiatric symptoms such as OCS, impulse control, depression [30], and psychotic symptoms [31]. Interestingly, a recent study showed that premanifest Huntington's disease reveals the presence of small volume of the caudate nucleus [32,33]. These recent studies highlight the need for further research on the functional circuit dysfunction described in many neuropsychiatric disorders for better evaluation and early management.

The MRS results in our study showed an increase in choline concentration in schizophrenia with or without OCS in comparison with controls. The choline concentration is higher in the absence of OCS. This is in agreement with Buckley and colleagues [13–15], who found significantly higher levels of choline compared with comparison patients. Similar results were found in choline/creatine ratio, which is in agreement with the results of Liu *et al*. [34], who found that the NAA/creatine and choline/creatine ratios were lower in the frontal cortex bilaterally among patients with schizophrenia, the NAA/creatine ratio was higher in the left frontal lobe, and the choline/creatine ratio was higher in the right caudate. The latter finding was observed in our study but in the left caudate.

The NAA concentration is markedly reduced among schizophrenic patients with OCS than among controls and schizophrenic patients without OCS. This is consistent with older results [16,17,35]. Meanwhile, Grošić *et al*. [36] revealed a significant increase in the NAA/creatine level in the studied group that stayed on the same antipsychotic treatment and a significant drop in NAA/creatine in the studied group that switched the antipsychotics. In our study we did not address the effect of medications as all of our patients were drug naive.

Schizophrenic patients without OCS showed relative increase in NAA concentration either in the left or in the dominant caudate nucleus, but showed more or less similar NAA concentration as controls in the right hemisphere, which is in agreement with Buckley *et al*. [37].

The NAA/creatine ratio is markedly reduced among schizophrenic patients with OCS and to less extent in schizophrenic patients without OCS than in controls, which is congruent with the results of other researchers [16,17,37,38]. The increase in the choline to NAA ratio in patients with or without OCS in comparison with controls is in agreement with different studies [13,37,39].

NAA is considered to reflect both, neuronal density and integrity of neuronal mitochondria. Thus, reduction of NAA may represent diminished neuronal integrity [39] or an altered functional (metabolic) state of neurons [40]. This functional finding has been described in other psychiatric disorders, and recent studies have reported reversal of decreased NAA concentration with treatment, reflecting a functional restoration [40].

Deicken *et al*. [41] stated that the most consistently replicated findings in schizophrenia are reduced NAA measures in the hippocampal regions, although this finding is less consistent in the frontal cortex, basal ganglia, cingulate region, and thalamus in schizophrenia. Furthermore, there are no consistently replicated findings for choline or creatine alterations in any of the brain regions examined in schizophrenia.

Recently, Liu *et al*. [34] found a decreased NAA/creatine ratio in the prefrontal cortex among schizophrenic patients. However, most studies have found no significant changes in the choline/creatine ratio. These findings support the hypothesis of the early damage of neurons in the frontal cortex and frontostriatal connection in individuals with schizophrenia.

Choline has been proposed as a marker for neuronal astrocytosis associated with neurodegenerative diseases and other types of brain injury [42]. Elevated creatine suggests abnormal local cell-energy demand and elevated choline suggests a phospholipid membrane disturbance in patients with early age-of-onset schizophrenia [39].

Schizophrenic patients with OCS may have a disorder with two pathologies [schizophrenia with normal NAA level and OCD with decreased NAA level, as postulated by Ebert and colleagues [17,18,43]]. The greater reduction of NAA in the caudate nucleus in schizophrenic patients with OCS compared with schizophrenic patients without OCS could be attributed to the theory that schizophrenic patients without OCS constitute a distinct group with one disorder and one pathology, as put forth by Bustillo *et al*. [35], who showed that schizophrenia alone is associated with normal level of NAA.

Conclusion

Schizophrenic patients with OCS may have an atypical set of neuroradiological characteristics that are reflected in the clinical presentation and perhaps it constitutes a subgroup within the schizophrenia spectrum. More research on a larger group of patients is warranted for optimal categorization of those patients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Tibbo P, Kroetsch M, Chue P, Warneke L. Obsessive–compulsive disorder in schizophrenia. J Psychiatr Res 2000; 34:139–146.

2 Buckley PF, Miller BJ, Lehrer DS, Castle DJ. Psychiatric comorbidities and schizophrenia. Schizophr Bull 2009; 35:383–402.

3 Oulis P, Konstantakopoulos G, Lykouras L, Michalopoulou PG. Differential diagnosis of obsessive–compulsive symptoms from delusions in schizophrenia: a phenomenological approach. World J Psychiatry 2013; 3:50–56.

4 Devi S, Rao NP, Badamath S, Chandrashekhar CR, Janardhan Reddy YC. Prevalence and clinical correlates of obsessive–compulsive disorder in schizophrenia. Compr Psychiatry 2015; 56:141–148.

5 McClure RK, Styner M, Maltbie E, Lieberman JA, Gouttard S, Gerig G, *et al*. Localized differences in caudate and hippocampal shape are associated with schizophrenia but not antipsychotic type. Psychiatry Res 2013; 211:1–10.

6 Womer FY, Wang L, Alpert KI, Smith MJ, Csernansky JG, Barch DM, Mamah D. Basal ganglia and thalamic morphology in schizophrenia and bipolar disorder. Psychiatry Res 2014; 223:75–83.

7 Robinson D, Wu H, Munne RA, Ashtari M, Alvir JM, Lerner G, *et al*. Reduced caudate nucleus volume in obsessive–compulsive disorder. Arch Gen Psychiatry 1995; 52:393–398.

8 Narayanaswamy JC, Jose DA, Kalmady SV, Venkatasubramanian G, Janardhana Reddy YC. Clinical correlates of caudate volume in drug-naïve adult patients with obsessive–compulsive disorder. Psychiatry Res 2013; 212:7–13.

9 Brandt GN, Bonelli RM. Structural neuroimaging of the basal ganglia in schizophrenic patients: a review. Wien Med Wochenschr 2008; 158:84–90.

10 Bertolino A, Nawroz S, Mattay VS, Barnett AS, Duyn JH, Moonen CT, *et al*. Regionally specific pattern of neurochemical pathology in schizophrenia as assessed by multislice proton magnetic resonance spectroscopic imaging. Am J Psychiatry 1996; 153:1554–1563.

11 Dautry C, Vaufrey F, Brouillet E, Bizat N, Henry PG, Condé F, *et al*. Early N-acetylaspartate depletion is a marker of neuronal dysfunction in rats and primates chronically treated with the mitochondrial toxin 3-nitropropionic acid. J Cereb Blood Flow Metab 2000; 20:789–799.

12 Simone IL, Tortorella C, Federico F. The contribution of (1)H-magnetic resonance spectroscopy in defining the pathophysiology of multiple sclerosis. Ital J Neurol Sci 1999; 20 (Suppl):S241–S245.

13 Buckley PF, Friedman L. Magnetic resonance spectroscopy. Bridging the neurochemistry and neuroanatomy of schizophrenia. Br J Psychiatry 2000; 176:203–205.

14 Shioiri T, Hamakawa H, Kato T, Murashita J, Fujii K, Inubushi T, Takahashi S. Proton magnetic resonance spectroscopy of the basal ganglia in patients with schizophrenia: a preliminary report. Schizophr Res 1996; 22:19–26.

15 Fujimoto T, Nakano T, Takano T, Takeuchi K, Yamada K, Fukuzako T, Akimoto H. Proton magnetic resonance spectroscopy of basal ganglia in chronic schizophrenia. Biol Psychiatry 1996; 40:14–18.

16 Bustillo JR, Rowland LM, Lauriello J, Petropoulos H, Hammond R, Hart B, Brooks WM. High choline concentrations in the caudate nucleus in antipsychotic-naive patients with schizophrenia. Am J Psychiatry 2002; 159:130–133.

17 Ebert D, Speck O, König A, Berger M, Hennig J, Hohagen F. ^{1}H-Magnetic resonance spectroscopy in obsessive–compulsive disorder: evidence for neuronal loss in the cingulate gyrus and the right striatum. Psychiatry Res 1997; 74:173–176.

18 Bartha R, Stein MB, Williamson PC, Drost DJ, Neufeld RW, Carr TJ, *et al*. A short echo ^{1}H spectroscopy and volumetric MRI study of the corpus striatum in patients with obsessive–compulsive disorder and comparison subjects. Am J Psychiatry 1998; 155:1584–1591.

19 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*, 4th ed., text revision. Washington, DC: American Psychiatric Association; 2000.

20 Rosenberg DR, Keshavan MS, O'Hearn KM, Dick EL, Bagwell WW, Seymour AB, *et al*. Frontostriatal measurement in treatment-naive children with obsessive–compulsive disorder. Arch Gen Psychiatry 1997; 54:824–830.

21 Keshavan MS, Rosenberg D, Sweeney JA, Pettegrew JW. Decreased caudate volume in neuroleptic-naive psychotic patients. Am J Psychiatry 1998; 155:774–778.

22 Chandola T, Jenkinson C. The new UK National Statistics Socio-Economic Classification (NS-SEC); investigating social class differences in self-reported health status. J Public Health Med 2000; 22:182–190.

23 Annett M. Handedness and cerebral dominance: the right shift theory. J Neuropsychiatry Clin Neurosci 1998; 10:459–469.

24 Bruder G, Kayser J, Tenke C, Amador X, Friedman M, Sharif Z, Gorman J. Left temporal lobe dysfunction in schizophrenia: event-related potential and behavioral evidence from phonetic and tonal dichotic listening tasks. Arch Gen Psychiatry 1999; 56:267–276.

25 Barta PE, Pearlson GD, Brill LB II, Royall R, McGilchrist IK, Pulver AE, *et al*. Planum temporale asymmetry reversal in schizophrenia: replication and relationship to gray matter abnormalities. Am J Psychiatry 1997; 154: 661–667.

26 Crow TJ. Commentary on Annett, Yeo et al., Klar, Saugstad and Orr: cerebral asymmetry, language and psychosis – the case for a Homo sapiens-specific sex-linked gene for brain growth. Schizophr Res 1999; 39: 219–231.

27 Ayesa-Arriola R, Roiz-Santiáñez R, Pérez-Iglesias R, Ferro A, Sainz J, Crespo-Facorro B. Neuroanatomical differences between first-episode psychosis patients with and without neurocognitive deficit: a 3-year longitudinal study. Front Psychiatry 2013; 4:134.

28 Benedetti F, Poletti S, Radaelli D, Pozzi E, Giacosa C, Ruffini C, *et al*. Caudate gray matter volume in obsessive–compulsive disorder is influenced by adverse childhood experiences and ongoing drug treatment. J Clin Psychopharmacol 2012; 32:544–547.

29 Luxenberg JS, Swedo SE, Flament MF, Friedland RP, Rapoport J, Rapoport SI. Neuroanatomical abnormalities in obsessive–compulsive disorder detected with quantitative X-ray computed tomography. Am J Psychiatry 1988; 145:1089–1093.

30 Jaakkola E, Kaasinen V, Siri C, Martikainen K, Cilia R, Niemelä S, Joutsa J. Impulse control disorders are associated with multiple psychiatric symptoms in Parkinson's disease. J Parkinsons Dis 2014; 4:507–515.

31 van Duijn E, Craufurd D, Hubers AA, Giltay EJ, Bonelli R, Rickards H, *et al*. Neuropsychiatric symptoms in a European Huntington's disease cohort (REGISTRY). J Neurol Neurosurg Psychiatry 2014; 85:1411–1418.

32 Apple AC, Possin KL, Satris G, Johnson E, Lupo JM, Jakary A, *et al*. Quantitative 7T phase imaging in premanifest Huntington disease. Am J Neuroradiol 2014; 35:1707–1713.

33 Harrington DL, Liu D, Smith MM, Mills JA, Long JD, Aylward EH, Paulsen JS. Neuroanatomical correlates of cognitive functioning in prodromal Huntington disease. Brain Behav 2014; 4:29–40.

34 Liu D, Xu Y, Jiang K. Advances in neuroimaging research of schizophrenia in China. Shanghai Arch Psychiatry 2014; 26:181–193.

35 Bustillo JR, Rowland LM, Jung R, Brooks WM, Qualls C, Hammond R, *et al*. Proton magnetic resonance spectroscopy during initial treatment with antipsychotic medication in schizophrenia. Neuropsychopharmacology 2008; 33:2456–2466.

36 Grošić V, Grošić PF, Kalember P, Janović MB, Radoš M, Mihanović M, Henigsberg N. The effect of atypical antipsychotics on brain N-acetylaspartate levels in antipsychotic-naïve first-episode patients with schizophrenia: A preliminary study. Neuropsychiatr Dis Treat 2014; 10:1243–1253.

37 Buckley PF, Moore C, Long H, Larkin C, Thompson P, Mulvany F, *et al*. ^{1}H-magnetic resonance spectroscopy of the left temporal and frontal lobes in schizophrenia: clinical, neurodevelopmental, and cognitive correlates. Biol Psychiatry 1994; 36:792–800.

38 Szulc A, Galinska B, Tarasow E, Waszkiewicz N, Konarzewska B, Poplawska R, *et al*. Proton magnetic resonance spectroscopy study of brain metabolite changes after antipsychotic treatment. Pharmacopsychiatry 2011; 44:148–157.

39 O'Neill J, Levitt J, Caplan R, Asarnow R, McCracken JT, Toga AW, Alger JR. ^{1}H MRSI evidence of metabolic abnormalities in childhood-onset schizophrenia. Neuroimage 2004; 21:1781–1789.

40 Paslakis G, Träber F, Roberz J, Block W, Jessen F. N-acetyl-aspartate (NAA) as a correlate of pharmacological treatment in psychiatric disorders: a systematic review. Eur Neuropsychopharmacol 2014; 24:1659–1675.

41 Deicken RF, Johnson C, Pegues M. Proton magnetic resonance spectroscopy of the human brain in schizophrenia. Rev Neurosci 2000; 11:147–158.

42 Bertolino A, Kumra S, Callicott JH, Mattay VS, Lestz RM, Jacobsen L, *et al*. Common pattern of cortical pathology in childhood-onset and adult-onset schizophrenia as identified by proton magnetic resonance spectroscopic imaging. Am J Psychiatry 1998; 155:1376–1383.

43 Choi JS, Kim SH, Yoo SY, Kang DH, Kim CW, Lee JM, *et al*. Shape deformity of the corpus striatum in obsessive–compulsive disorder. Psychiatry Res 2007; 155:257–264.