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ORIGINAL CONTRIBUTION

Caudate volume differences among treatment responders, non-responders and controls in children with obsessive–compulsive disorder

Edoardo F. Q. Vattimo[1] · Vivian B. Barros[2] · Guaraci Requena[3] · João R. Sato[4] · Daniel Fatori[1] · Euripedes C. Miguel[5] · Roseli G. Shavitt[1] · Marcelo Q. Hoexter[5] · Marcelo C. Batistuzzo[5]

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Abstract

Treatment response in obsessive–compulsive disorder (OCD) is heterogeneous and the neurobiological underpinnings of such variability are unknown. To investigate this issue, we looked for differences in brain structures possibly associated with treatment response in children with OCD. 29 children with OCD (7–17 years) and 28 age-matched controls underwent structural magnetic resonance imaging. Patients then received treatment with fluoxetine or group cognitive-behavioral therapy during 14 weeks, and were classified as treatment responders or non-responders. The caudate nucleus, thalamus and orbitofrontal cortex were selected a priori, according to previous evidence of their association with OCD and its treatment. Gray matter (GM) volume comparisons between responders, non-responders and controls were performed, controlling for total GM volume. 17 patients were classified as responders. Differences among responders, non-responders and controls were found in both caudate nuclei (both p-values = 0.041), but after Bonferroni correction for multiple comparisons, these findings were non-significant. However, after excluding the effect of an outlier, findings were significant for the right caudate ($p = 0.004$). Pairwise comparisons showed larger caudate GM volume in responders versus non-responders and controls, bilaterally. The right caudate accounted for 20.2% of the variance in Y-BOCS changes after treatment in a linear regression model, with a positive correlation ($p = 0.016$). We present a possible neural substrate for treatment response in pediatric OCD, which is in line with previous evidence regarding the caudate nucleus. Considering the limitations, further research is needed to replicate this finding and elucidate the heterogeneity of treatment response in children with OCD (National Clinical Trials Registration Number: NCT01148316).

Keywords Obsessive–compulsive disorder · Treatment response · Structural magnetic resonance imaging · Gray matter volume · Caudate nuclei · Selective serotonin reuptake inhibitor · Group cognitive-behavioral therapy

Introduction

Obsessive–compulsive disorder (OCD) is a disabling neuropsychiatric condition with important clinical and epidemiological heterogeneity and complexity. The prevalence of the disorder among children and adolescents is 0.6–2.7% [1, 2] and up to 76% of all OCD cases begin at early ages [3]. Cognitive-behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRI) are well-established treatments [4, 5], albeit clinical response is heterogeneous and only 53% of children present symptomatic remission after combined SSRI and CBT therapy [6].

Clinical variables associated with treatment efficacy have been studied [7]. Yet, little is known about the neurobiological mechanisms that underlie such heterogeneous response.

✉ Edoardo F. Q. Vattimo
edoardo.vattimo@hc.fm.usp.br

1 Department and Institute of Psychiatry, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, R. Dr. Ovídio Pires de Campos 785, Sao Paulo, SP 01060-970, Brazil

2 School of Public Health of the USP, São Paulo, Brazil

3 Department of Statistics, Institute of Mathematics and Statistics, USP, Sao Paulo, Brazil

4 Center of Mathematics, Computing, and Cognition, Universidade Federal do ABC, Santo Andre, Brazil

5 National Institute for Developmental Psychiatry for Children and Adolescents (INPD), Sao Paulo, Brazil

Neuroimaging studies suggest the role of the cortico-striato-thalamo-cortical (CSTC) circuitry in the neurobiology of OCD [8, 9] and large multi-center studies found structural differences in cortical [10] and subcortical [11] regions belonging to this circuit between patients and controls. Particularly, structures of the ventral affective loop of the CSTC, such as the ventral striatum (caudate nucleus and accumbens) and the orbitofrontal cortex (OFC) [12], were associated with symptom severity in functional neuroimaging studies. Moreover, the OFC [13, 14], the caudate nucleus [13–17] and the thalamus [18, 19] are also implicated as key targets for the anti-obsessional effects of both SSRI and CBT, as both treatments produce structural [20, 21], functional [22] and neurochemical changes [19] in these structures that correlate with symptomatic improvement.

In line with these findings, these same structures are associated with treatment response heterogeneity, as functional [23–25] and structural [26, 27] baseline differences have been reported between treatment responders (RS) and non-responders (NR), for either CBT or SSRI. Baseline functional [14, 28–31], structural [27, 32] and neurochemical [33, 34] cerebral correlates of symptomatic improvement after treatment have also been demonstrated. However, most studies analyzed adult patients and their findings should not be generalized to children, as age has a potential confounding effect in neuroimaging studies [35]. In addition, pediatric OCD may be a clinical subtype of the disorder, presenting specific neurobiological underpinnings and a developmental discontinuity with the adult-onset counterpart [3, 9], which also highlights the need for longitudinal studies.

In children with OCD, especifically, magnetic resonance spectroscopy (MRS) and functional neuroimaging studies identified correlates of treatment response, such as lower baseline levels of metabolites in the left thalamus, which were associated with greater post-CBT symptomatic improvement in a sample of five patients [19]. Recently, the same group found that baseline glutamate (glx) levels within the ventral posterior cingulate cortex were negatively associated with symptom improvement after CBT [36]. As for functional neuroimaging, Diller et al. analyzed a sample of 18 children with OCD using Single Photon Emission Computerized Tomography (SPECT) and found a positive correlation between elevated baseline regional cerebral blood flow in the right caudate nucleus and treatment response to paroxetine [37].

Structural neuroimaging studies, in turn, may complement these functional and neurochemical findings, which is of particular interest in children. In this study, we aimed to address this issue, considering the previous evidence of the involvement of the OFC, the caudate nucleus and the thalamus in the neurobiology of OCD and their role as targets for anti-obsessional treatment. Although of great interest, the majority of the aforementioned studies compared pre- and post-treatment neuroimaging data aiming at finding changes elicited by medication or psychotherapy. These findings could represent mediators, or potential mechanisms, by which a certain treatment exerts its effect on the brain, which is clinically manifested as symptom reduction. Baseline studies, on the other hand, are scant in child OCD and provide different information, as they indicate potential predictors of response, rather than mediators. We, thus, aimed to address this gap and hypothesized that baseline gray matter (GM) volumetric findings may differentiate RS, NR and healthy controls (HC). In face of the clinical and demographic complexity of OCD, which is associated with treatment response heterogeneity, we aimed at identifying baseline volumetric differences that could be potential neural substrates for treatment response.

Methods

We analyzed baseline structural neuroimaging and clinical data gathered during a Sequential Multiple Assignment Randomized Trial (SMART) [38], designed to test the efficacy of adaptive treatment strategies for children with OCD. Also, part of this sample was analyzed in a previous functional neuroimaging study [39]. Further details about the clinical trial design can also be found in the supplemental material, available online. The local ethics committee approved the project and children and/or their legal guardians signed consent forms prior to any intervention.

Study participants

Patients were recruited through announcements at the community and mental health facilities. All patients and parents were initially assessed with the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime (KSADS-PL) [40]. Two expert child psychiatrists then confirmed OCD diagnosis under the supervision of a senior psychiatrist (RGS).

The following inclusion criteria were applied: (1) OCD diagnosis according to DSM-IV criteria as the main reason for seeking treatment; (2) age between 7 and 17 years; (3) no limitations for active participation in the treatment protocol due to any physical or mental condition; (4) minimum baseline Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) score of 16 or at least 10 for only obsessions or compulsions; (5) minimum weight percentile of 10. Patients were excluded if any of the following conditions was present: (1) pregnancy; (2) suicidal ideation or symptom severity that required an inpatient treatment regimen; (3) total IQ less than 75; (4) a diagnosis of schizophrenia or psychotic symptoms, bipolar disorder, epilepsy or any other neurological condition; (5) history of substance abuse; (6) any

contraindication for MRI (e.g., pacemaker), the presence of metallic devices or previous history of structural cerebral abnormalities or trauma.

Structural MRI was performed on 32 patients before treatment. All patients were off SSRI or clomipramine for at least 15 days and methylphenidate for at least 24 h prior to the scan. Of these, two patients were excluded from this analysis due to excessive movement artifact. One patient dropped out of the study before any further assessment. Our final sample consisted of 29 OCD patients (for the CONSORT flow diagram, see the online supplemental material).

We also recruited a sample of 28 age-matched HC from the community for neuroimaging analysis and the same demographic and clinical assessments (including the K-SADS) were used in their initial evaluation to exclude OCD and other psychiatric disorders. The other inclusion/exclusion criteria were the same for this group.

Clinical assessment

Prior to randomization, patients were assessed for baseline Y-BOCS [41] score, socio-demographic data, the presence of tics, total IQ, depressive (Children's Depression Rating Scale-Revised—CDRS-R) [42] and anxiety symptoms (Screen for Child Anxiety-Related Disorders (SCARED) [43].

Follow-up assessment was provided to patients every two weeks by a psychologist blinded to treatment group, who applied the Y-BOCS and the Clinical Global Impression-Improvement (CGI-I) Scale. As there are no validated Brazilian–Portuguese translations of the Children's Yale–Brown Obsessive–Compulsive Scale (CY-BOCS) [44], we opted to use the Y-BOCS due to the extensive reliability training of our staff with it [45] and good psychometric results in the whole SMART sample [38].

Neuroimaging acquisition and processing

We performed structural MRI before randomization in a 3-Tesla Achieva Phillips scanner with an 8-channel head coil. A T1-weighted high-resolution volumetric sequence was used with a time of repetition (TR) of 7.0 ms, a time of echo (TE) of 3.2 ms and flip angle of 8° within a field of view (FOV): FH 240 mm, AP 240 mm and RL 180 mm. Compressed sampling used was sensitivity encoding (SENSE) with 'P reduction' (AP) = 1, 'P os factor' = 1 and 'S reduction' (RL) = 1.5. Isotropic voxels of 1 mm^3 were acquired using a 240 × 240 matrix. Total scan duration was 5 min and 58 s.

Images were processed using the FreeSurfer software's "recon-all" routine, in which cortical and subcortical structures were segmented, generating output data of GM volume for segmented regions according to the default Desikan/Killiany atlas [46]. We used the FreeSurfer's version 6.0 (http://surfer.nmr.mgh.harvard.edu). For technical details of these procedures please check Fischl et al. [47].

Allocation and treatment

Patients were allocated to one of the two treatment groups, fluoxetine (flexible dose of 10–60 mg depending on treatment response and tolerability) or 14 weekly sessions of Group Cognitive-Behavioral Therapy (GCBT). Allocation was performed by a computerized randomization program, balancing subjects by age, gender, Y-BOCS baseline score and level of education [48]. For further details about treatment, see the online supplemental material.

Statistical analysis

After 14 weeks of treatment, patients were divided in two groups—responders (RS) and non-responders (NR)—defined by a response criterion of both Y-BOCS decrease ≥ 35% and a CGI-I score of 1 or 2 [49]. The outcome for one patient was considered at mid-treatment (7 weeks—only Y-BOCS), as she dropped out of the study afterwards. The two groups were compared for potential clinical confounding factors: baseline Y-BOCS, depressive and anxiety symptoms. Age, sex, the presence of tics and total IQ were compared across RS, NR and HC (see Table 1 and the online supplemental material for further details).

As for our main objective, between-group comparisons were performed to check for volumetric GM differences in a priori selected cerebral structures across RS, NR and HC. We selected the OFC, the caudate nucleus and the thalamus in each hemisphere, which comprise the ventral affective loop of the CSTC circuitry because of its association with symptom severity and treatment response, as described above. We opted to sum the values of medial and lateral OFC provided by the default segmentation atlas, as most studies report findings for the OFC as a whole.

A one-way analysis of covariance (ANCOVA) was performed to compare groups, considering the volume of each region as the dependent variable and total GM volume as covariate. ANCOVA assumptions were checked prior to the analysis. Bonferroni correction for multiple comparisons was applied to determine the significance threshold, set at $p < 0.0083$ (0.05/6 cerebral regions, three per hemisphere).

Post hoc analyses were conducted to further explore group differences across RS, NR and HC using the Tukey honest significant difference method (HSD) for pairwise comparisons. Finally, we also performed a linear regression analysis to verify the influence on treatment response of structures that yielded significant results in the ANCOVA analysis. Treatment response in this model was represented as a linear dependent variable, defined by percentage

Table 1 Clinical and demographic variables in responders, non-responders and healthy controls

	Responders ($n=17$)	Non-responders ($n=12$)	Healthy controls ($n=28$)	p value
Age, years, mean (SD)	12.06 (2.6)	12.3 (2.4)	11.5 (2.3)	0.522[a]
Male sex, *n* (%)	10 (58.8)	7 (58.3)	16 (57.1)	0.993[b]
Total IQ, mean (SD)	106.5 (13.8)	94.8 (13.2)	103.3 (24.0)	0.273[a]
Treatment type: GCBT, *n* (%)	9 (52.9)	8 (66.7)	–	0.703[c]
Baseline Y-BOCS, mean (SD)	25.6 (4.4)	28.5 (5.4)	–	0.122[d]
Post-treatment Y-BOCS, mean (SD)	8 (5.9)	25.6 (4.8)	–	–
CDRS-R, mean (SD)	26.4 (5.9)	32 (13.5)	17.2 (0.8)	0.080[e]
SCARED, mean (SD)	26.2 (12.7)	31.6 (15.6)	6.9 (9.5)	0.471[e]
Any history of tics, *n* (%)	4 (23.52)	3 (25.0)	–	1.0[c]

SCARED Screen for Child Anxiety-Related Disorders, *CDRS-R* Children's Depression Rating Scale-Revised, *IQ* intelligence quotient, *Y-BOCS* Yale–Brown Obsessive–Compulsive SCALE, *GCBT* group cognitive-behavioral therapy

[a]One-way Analysis of variance (ANOVA)

[b]Two-Sided Asymptotic Significance, Pearson Chi-Square

[c]Two-Sided Exact Significance, Fisher's Exact Test

[d]Student *t* test for two independent samples (responders and non-responders only)

[e]Exact Significance, Mann–Whitney test for two independent samples (responders and non-responders only, non normal distribution of the data)

decrease in Y-BOCS score after treatment. We also used the stepwise method to force into the regression model the following control variables: age and total GM volume. Non-significant ($p>0.05$) variables were, then, removed from the linear regression model.

All analyses were performed using the software R (version 3.3.3) and the Statistical Package for Social Sciences software (SPSS version 23; IBM, USA).

Results

Baseline clinical and demographic variables and treatment response

Table 1 presents the clinical and demographic characteristics of each group at baseline. The 29 OCD patients presented moderate symptom severity, with a mean pre-treatment Y-BOCS score of 26.8 ± 4.96. After treatment with either GCBT or fluoxetine, 17 patients (58.6%) presented a minimum of 35% Y-BOCS reduction and a CGI-I score of 1 or 2 and were classified as RS, with no significant effect of treatment type on response (8/12 RS in the fluoxetine group with a mean Y-BOCS reduction of 52.7% and 9/17 RS in the GCBT group with 39.0% mean Y-BOCS reduction, p = .30). Baseline Y-BOCS, CDRS-R and SCARED scores were balanced between RS and NR. Mean post-treatment Y-BOCS for RS was 8.0 ± 5.85 (69.7% mean reduction) and 25.6 ± 4.83 for NR (9.2% mean reduction). Treatment RS, NR and HC were balanced for age, sex and total IQ.

In the whole patient sample, 21 presented any comorbidity, the most frequent being Specific Phobia ($N=12$) and ADHD ($N=11$). Sixteen out of 29 patients reported prior history of psychotropic medication use (nine reported any SSRI, three reported methylphenidate, two reported clomipramine and one reported risperidone). In the RS group, four patients presented any history of tics; while, in the NR group, this number was 3, with no significant difference between the two groups (Table 1).

Neuroimaging analysis

The results from the volumetric analysis of the selected regions are presented in Table 2. Before correction for multiple comparisons, a statistically significant ($p<0.05$) difference of GM volume in the left and right caudate nuclei was found between RS, NR and HC: left caudate: $F(2,53)=3.381$, partial $\eta^2=0.113$, $p=0.041$; right caudate: $F(2,53)=3.382$, partial $\eta^2=0.113$, $p=0.041$. These findings, however, are not significant after Bonferroni correction ($p<0.008$). Neither the thalamus nor the OFC, bilaterally, presented significant results in the ANCOVA model. Figure 1 shows boxplots for RS, NR and HC regarding left and right caudate GM volumes. As shown in the boxplot of Fig. 1, the presence of an outlier in the RS group, (the same individual for both caudate—2.2 standard deviations (SD) for left caudate and 2.5 SD for right caudate), may have influenced the results, although the data were normally distributed. Outlier was defined as a value lying more than 1.5 times the Interquartile Range (IQR) away from the 25%

Table 2 Gray matter volumes (in mm^3) in responders, non-responders and healthy controls

Structure	Responders (RS)		Non-responders (NR)		Healthy controls (HC)		*p* value
	Mean	SD	Mean	SD	Mean	SD	
Left caudate	4100.6	(479.8)	3616.6	(445.1)	3661.5	(504.2)	0.041[a]
Right caudate	4264.7	(564.9)	3723.8	(433.4)	3809.9	(514.5)	0.041[a]
Left thalamus	7921.4	(848.5)	7521.4	(681.7)	7436.3	(760.5)	0.428[a]
Right thalamus	7514.1	(748.9)	7090.5	(490.1)	7149.1	(772.8)	0.745[a]
Left orbitofrontal cortex	15,950.1	(1893.1)	15,101.7	(1810.9)	15,834.6	(1987.1)	0.104[a]
Right orbitofrontal cortex	16,430.0	(1847.5)	15,136.9	(1867.8)	16,009.1	(2146.9)	0.142[a]
Total gray matter	746,066.69	(63,682.0)	704,088.6	(73,913.2)	712,317.05	(69,062.4)	0.188[b]

[a]One-way analysis of covariance (ANCOVA)

[b]One-way analysis of variance (ANOVA)

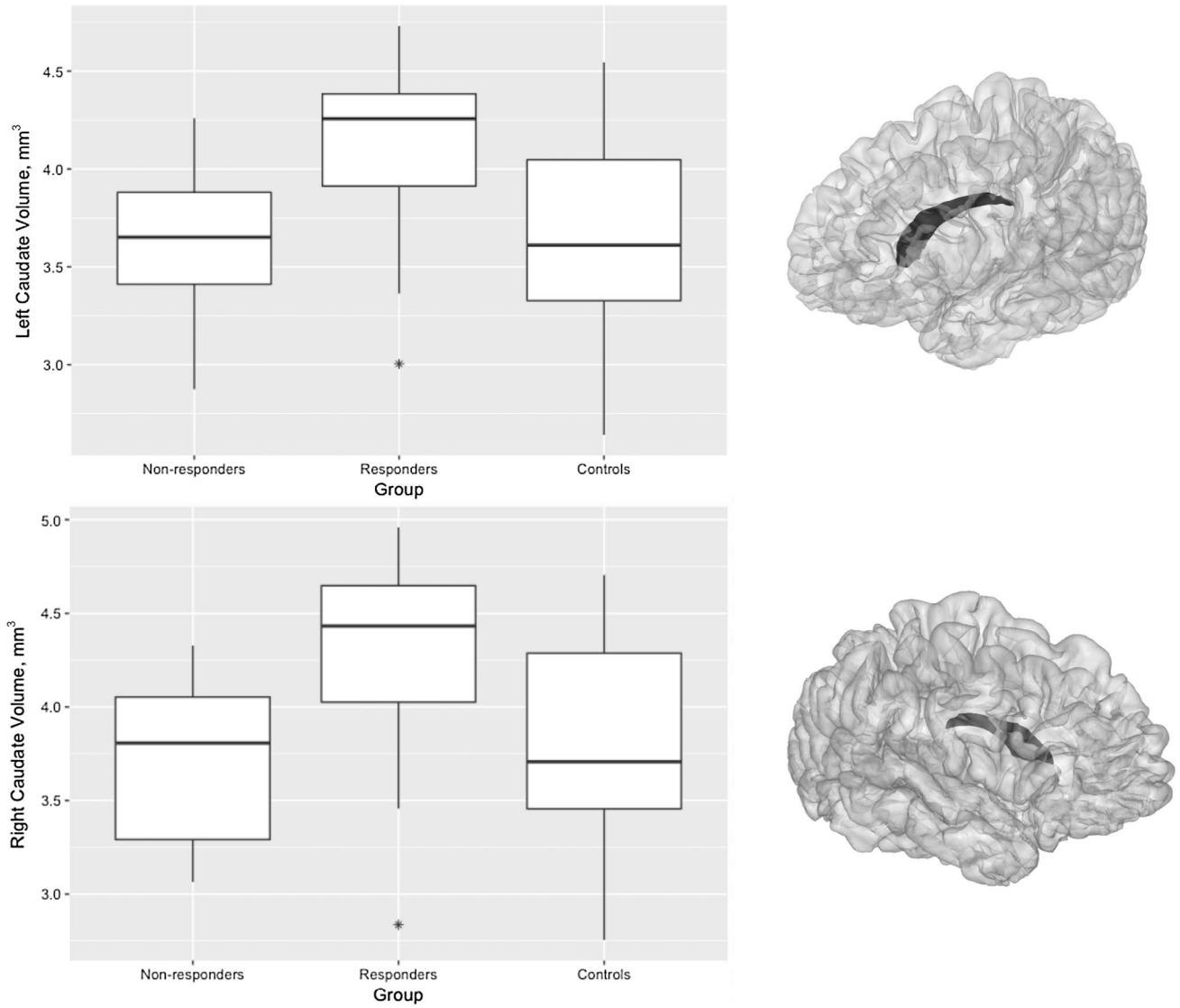

Fig. 1 Boxplots showing the distribution of left and right caudate volumes (mm^3) according to treatment response or control groups. Tridimensional glass brain images highlighting the left and right caudate nuclei from a single patient were inserted for illustration purposes

and 75% quartiles, calculated from Tukey's hinges [50]. We found no errors in the segmentation of the images of this subject. We, thus, decided to re-run the model in the absence of this outlier for both caudate nuclei. Under this condition, one-way ANCOVA showed, before correction for multiple comparisons, significant group differences for both left, $F(2,52) = 5.14$, partial $\eta^2 = 0.165$, $p = 0.009$; and right, $F(2,52) = 6.05$, partial $\eta^2 = 0.189$, $p = 0.004$. The result regarding the right caudate remains significant after Bonferroni correction ($p < 0.008$). The model was again tested for ANCOVA assumptions, which were also met in the absence of the outlier.

Pairwise comparisons were then performed in the sample, again after removal of the outlier, to identify group differences, using the Tukey HSD test. A significant difference was found, with larger caudate GM volume bilaterally in the RS group vs HC (left caudate, mean difference = 406.29 mm^3, t ratio = 3.0, $p = 0.011$; right caudate, mean difference = 425.89 mm^3, t ratio = 3.16, $p = 0.007$) and vs NR (left caudate, mean difference = 426.98 mm^3, t ratio = − 2.58, $p = 0.033$; right caudate, mean difference = 483.66 mm^3, t ratio = − 2.94, $p = 0.013$). No significant differences were found between NR and HC, bilaterally. Figure 2 shows the scatter plot representing group differences of left and right caudate GM volumes, controlling for total GM volume.

A simple linear regression was performed using right caudate GM volume as predictor variable of Y-BOCS change for the 28 patients (outlier excluded), as it yielded significant results on the ANCOVA model after Bonferroni correction. Total GM volume and age were selected as control variables, but were excluded by the stepwise method, as none significantly influenced the results ($p > 0.05$). Right caudate GM volume accounted for 20.2% of the variance of the Y-BOCS change, with larger right caudate correlating to better treatment response [$F(1,26) = 6.58$, $p = 0.016$] (Fig. 3).

Although this was not our main objective, we also analyzed group differences according to treatment type. We found a tendency for significance for the right OFC and both caudate GM volumes, in the GCBT group (outlier excluded), using the same ANCOVA model ($p = 0.09$ for the right OFC and $p = 0.068$ and 0.089 for the right and left caudate nuclei, respectively). In the same group of patients, we also found a difference in the left OFC ($p = 0.029$); however, it was non-significant after Bonferroni correction. In the fluoxetine group, on the other hand, no significant differences were observed in the OFC and only a tendency for significance was shown in both caudate nuclei ($p = 0.05$ and 0.082 for the right and left caudate nuclei, respectively). No significant differences were found in the thalamus, for any group.

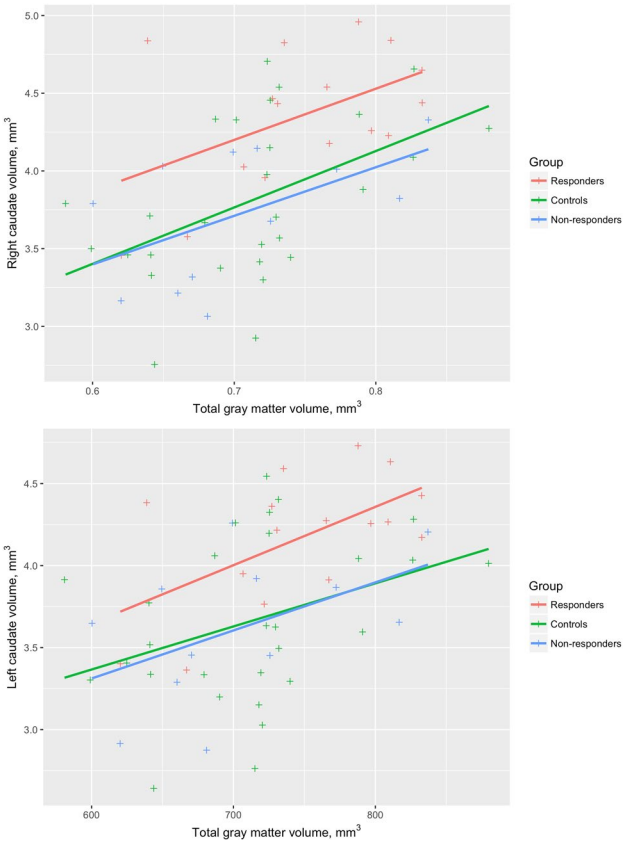

Fig. 2 Scatter plots showing the regression lines for left and right caudate volumes (mm^3) in relation to gray matter volume (mm^3) for responders, non-responders and controls (sample of 28 patients, outlier excluded)

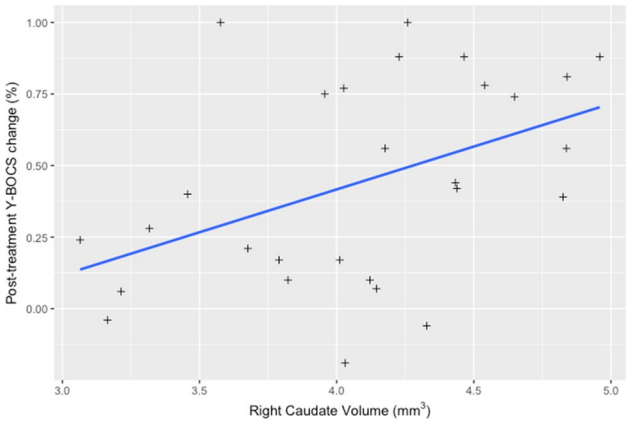

Fig. 3 Simple linear regression showing Y-BOCS post-treatment changes (%) according to right caudate volume (mm^3) in the sample of 28 patients [$F(1,26) = 6.58$, $p = 0.016$, $r^2 = 0.202$]

Discussion

To our knowledge, this is the first study to analyze baseline structural neuroimaging biomarkers of treatment response in children with OCD. The GM volume differences found in both caudate nuclei at baseline between treatment responders (RS), non-responders (NR) and healthy controls (HC) are in line with our *a priori* hypothesis. Our results are controlled for total GM volume, further reinforcing that these cerebral differences are regionally specific. Without the effects of an outlier, this finding survived a rigorous significance threshold after Bonferroni correction for multiple comparisons for the right caudate ($p < 0.008$). Additionally, post hoc pairwise comparisons revealed that RS (without the outlier) presented larger bilateral caudate nuclei compared to HC and NR. It is also noteworthy the positive linear relation found between right caudate GM volume and symptom reduction after treatment. Our findings are consistent with a large body of evidence suggesting the involvement of the caudate nucleus in the neurobiological basis of OCD and also of its treatment. As a possible clinical implication of this study, patients who may probably benefit more from SSRI and CBT treatment could be more precisely identified at baseline. Insights into the mechanistic principles involved in the pathogenesis, pathophysiology and therapeutic effects of treatment in OCD can also be outlined.

The caudate nucleus has been associated with cognitive processes that are altered in OCD patients, such as habit formation [51, 52] and cognitive flexibility [53]. Several studies have found volumetric differences in the caudate of affected individuals compared to HC, although the results are mixed. Two meta-analyses reported conflicting results. While Rotge et al. reported no significant volumetric differences in the caudate of OCD patients [54], Radua et al. reported volume increases in the lenticular nucleus extending to the caudate bilaterally [55]. However, it is also stressed that the studies analyzing children were too few to allow any conclusion in this population.

The phenotypic heterogeneity of OCD [56], however, may be accountable for the conflicting results when patients are compared to HC. Clinical and epidemiological variables such as age of onset and [52] symptom dimensions [57] seem to be associated with distinct neurobiological characteristics, including volumetric abnormalities. For instance, van den Heuvel et al. [57] reported a negative relation between 'contamination/washing' symptoms and volume of the dorsal caudate nucleus bilaterally. Clinical response to SSRI and CBT is also heterogeneous in OCD and may be associated, likewise, with particular cerebral attributes that differentiate patients according to treatment response. Although we found a tendency for significance in the OFC when analyzing only GCBT patients, not present in the SSRI group, in our sample, however, these results do not allow any conclusions. This could be explained by the small sample size of each treatment group, as this study was not design to test this hypothesis.

Caudate volume heterogeneity is also associated with different factors related to the pathogenesis of OCD. For instance, patients with OCD and comorbid Tourette Syndrome (TS) or chronic tics, who have distinct genetic profile [58], present caudate volume reduction compared to OCD patients without tics [59]. On the other hand, larger surface of the caudate was found in OCD patients and their unaffected siblings, compared to HC [60], further suggesting that caudate dimensions are strongly influenced by genetic determinants. Similarly, environmental factors may influence caudate structural abnormalities, such as streptococcal infections associated with OCD and acute caudate enlargement [61], a process that may be mediated by immunological mechanisms [62]. Adverse childhood experiences, another environmental risk factor for OCD [63], have also been associated with larger caudate volumes in OCD patients [64]. It can be, therefore, inferred that environmental and genetic mechanisms of pathogenesis vary among patients and are associated with opposite abnormalities in the structure of the caudate nucleus. This could partially explain the heterogeneity of the structural abnormalities found in OCD patients.

Although it is clear that OCD presents heterogeneous cerebral abnormalities, their relation to treatment response is poorly understood. A few functional neuroimaging studies report decreases in caudate metabolism after both pharmacological treatment (SSRI and clomipramine) and CBT [14, 15, 37, 65, 66]. This finding was more consistently observed in RS compared to NR [13–16, 37] and correlated with symptomatic improvement [16], suggesting that the attenuation of caudate baseline metabolic abnormalities in patients with OCD is a mechanism that seems to be necessary for the effect of both CBT and serotonin reuptake inhibitors (SRI). Additionally, Magnetic Resonance Spectroscopy (MRS) studies found higher concentrations of glx in the caudate of OCD patients, which decreased to similar levels observed in HC after treatment with paroxetine [17, 67]. Glx decreases also correlated with symptomatic improvement [17] and endured after paroxetine discontinuation in a patient that persisted in remission [68].

These functional effects of treatment parallel structural brain changes. Benedetti et al., for instance, observed that treatment counteracted the increased caudate volume associated with adverse childhood experiences [64], while Valente et al. found a negative correlation between the duration of SSRI treatment exposure and GM volume of the head of the caudate, bilaterally [69]. Notwithstanding the limitations of these studies, such as the small number of participants and smaller MRI resolution, they suggest that pediatric OCD is associated with potentially reversible brain abnormalities,

which may correspond to neural substrates for the SSRI anti-obsessional effects [17, 68].

Although we do not provide post-treatment neuroimaging data to test this hypothesis, our findings may reflect an underlying baseline neurobiological characteristic present in RS, which is successfully targeted by treatment. Conversely, NR did not present significant differences compared to HC, which could indicate that the cerebral abnormalities of this group lie in other areas than the ones we analyzed. This hypothesis is also supported by a study which identified differential baseline patterns of cerebral activation following symptom provocation in treatment RS, that presented higher baseline metabolic activity in the right caudate compared to NR [24]. Likewise, the authors hypothesize that NR may lack the substrate necessary for SSRI anti-obsessional effect, which seems to be specific to the effect of SSRI in OCD, compared to other disorders [70]. We could, thus, hypothesize that, considering the multiple mechanisms of pathogenesis proposed for OCD and the different cerebral abnormalities associated with them, some patients may present other neural substrates rather than those targeted by the anti-obsessional effects of both SSRI and CBT. Treatment response, thus, may depend on the underlying neurobiology present at baseline, which seems to vary among OCD patients.

It is also important to comment our results regarding the thalamus. The ENIGMA worldwide meta- and mega-analysis reported larger thalamus in unmedicated pediatric OCD patients, which the authors considered to be a key and specific finding in children [10]. In light of this finding, our negative thalamic findings could be explained by a different study design, which compared not only patients versus controls, but also considered treatment response. The ENIGMA study, as expected for a mega-analysis, presents a much more robust statistical power that may have been capable of detecting this finding, not present in our sample, although our data were included in the ENIGMA study. However, this is important to discuss, considering previous findings of volumetric reduction after treatment observed in the thalamus [18].

Our study presents some limitations. First, the small sample size reduces the statistical power of our model and makes it prone to the effects of outliers. However, all studies with similar design, so far, have relatively small sample sizes, which are even more evident for samples with children, subject to greater technical difficulties. We acknowledge that our findings need replication, but we also believe that they could pave the way for future multi-center, collaborative studies, which may overcome the technical obstacles that limit sample size. Second, we recruited not only treatment-naïve patients, but also patients who were exposed previously to psychotropic medications, which can produce cerebral changes that may last after treatment discontinuation. However, we also point that all patients were off SSRI for 15 days before neuroimaging acquisition, although these changes could last longer than this period of time. Third, we could not disentangle potential specificities of CBT and fluoxetine, which are complex and presents several non-shared mechanisms. However, our findings in the caudate nuclei are consistent with previous reports of shared neural effects of both treatments, especially in decreasing caudate metabolism in responders. Fourth, we did not use a specific pediatric segmentation atlas in the neuroimaging analysis. However, the mean age of all subjects in this sample is 11.82 years and previous studies have demonstrated that regional anatomical differences among brains of children and adults may be an issue only for younger children [71]. Finally, we report findings that could be related to developmental abnormalities, as some evidence point to an inverted U-shaped trajectory of caudate volume [72], that could be affected by the onset of the disorder and previous exposure to successful treatment [64, 69, 73].

In summary, considering the limitations, our findings of larger GM volumes of the caudate nucleus in children with OCD who responded to treatment, compared to NR and HC, are in line with previous research implicating this subcortical structure on the pathophysiology of the disorder and treatment response. We hypothesize that this finding may reflect the heterogeneity of neural mechanisms involved in OCD and could shed light into our understanding of the neurobiology of the disorder.

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Compliance with ethical standards

Conflict of interest All authors report no potential conflicts of interest. Dr. Vattimo confirms he had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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