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Amygdala Volume Reductions in Pediatric Patients with Obsessive–Compulsive Disorder Treated with Paroxetine: Preliminary Findings

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The amygdala is believed to be highly relevant to the pathophysiology of obsessive–compulsive disorder (OCD) given its prominent role in fear conditioning and because it is an important target of the serotonin reuptake inhibitors (SRIs), the pharmacotherapy of choice for OCD. In the present study, we measured *in vivo* volumetric changes in the amygdala in pediatric patients with OCD following 16 weeks of monotherapy with the selective SRI, paroxetine hydrochloride. Amygdala volumes were computed from contiguous 1.5 mm magnetic resonance (MR) images in 11 psychotropic drug-naive patients with OCD prior to and then following treatment. Eleven healthy pediatric comparison subjects also had baseline and follow-up scans, but none of these subjects received medication. Patients demonstrated significant asymmetry of the amygdala (L > R) prior to pharmacologic intervention in contrast to healthy comparison subjects who showed no asymmetry at the time of their baseline scan. Mixed model analyses using age and total brain volume as time varying covariates indicated that left amygdala volume decreased significantly in patients following treatment. The reduction in left amygdala volume in patients correlated significantly with higher paroxetine dosage at the time of the follow-up scan and total cumulative paroxetine exposure between the scans. No significant changes in either right or left amygdala volume were evident among healthy comparison subjects from the baseline to the follow-up scan. These preliminary findings suggest that abnormal asymmetry of the amygdala may play a role in the pathogenesis of OCD and that paroxetine treatment may be associated with a reduction in amygdala volume.

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INTRODUCTION

Obsessive–compulsive disorder (OCD) is often characterized by chronic functional impairment and is considered the ninth leading cause of all disabilities in the United States and other countries (Murray and Lopez, 1996). The disorder appears to have a bimodal incidence with one peak occurring during childhood and the other in adulthood (Geller *et al*, 1998; Pauls *et al*, 1995). While pediatric and adult-onset OCD share a similar phenomenology and response to behavioral treatment and pharmacotherapy across the lifespan (Swedo *et al*, 1992), there are important differences between these forms of the disorder. In contrast to the adult form of the disorder, childhood OCD appears to have a stronger familial influence, greater male predominance, and higher incidence of tics and developmental disorders (Swedo *et al*, 1992; Geller *et al*, 1998). The investigation of neurobiological mechanisms in OCD may be facilitated by studying the illness in childhood compared to adulthood, which may decrease the likelihood of potentially confounding variables such as illness duration and prior pharmacologic exposure.

Current hypotheses with regard to neurotransmitter system abnormalities in OCD have focused on dysfunction of serotonergic systems (Cartwright and Hollander, 1998). In particular, pharmacologic studies have demonstrated the efficacy and safety of the serotonin reuptake inhibitors (SRIs) in the treatment of OCD (March *et al*, 1998; Rapoport

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et al, 1980). More direct evidence for serotonergic dysfunction in OCD, however, comes from brain imaging studies that have demonstrated reductions in brain activity in patients following the administration of SRIs (Baxter *et al*, 1992; Swedo *et al*, 1989).

The amygdala has been implicated in the pathophysiology of OCD (Szeszko *et al*, 1999; Rosenberg *et al*, 1997a) and hypothesized to represent an important neuroanatomic substrate of the anxiety that maintains compulsive behaviors in OCD (Rauch *et al*, 1998). The amygdala may be particularly relevant to OCD given its role in the emotional appraisal of stimuli (Bechara *et al*, 1995; Ketter *et al*, 1996; Irwin *et al*, 1996) and in acquiring and consolidating conditioned fear responses (Davis, 1997,1992). We suggested previously that a defect involving the ventral 'paleocortical' trend of brain development (Sanides, 1969), involving the amygdala and orbital frontal cortex, may represent an important neurobiological defect in the pathophysiology of OCD (Szeszko *et al*, 1999). Neuropsychological deficits observed on tasks of olfaction (Barnett *et al*, 1999) and response inhibition (Rosenberg *et al*, 1997b, c) are consistent with the hypothesis of a defect involving ventral brain regions.

Serotonin in the amygdala has been linked with the emotional appraisal of situations (Kawahara *et al*, 1993), modulation of fear (Sommer *et al*, 2001), and conditioned anxiety (Zangrossi *et al*, 1999), factors that seem to play a crucial role in the phenomenology of OCD. Serotonergic receptors have been found to play a role in the inhibition of amygdala neurotransmission (Cheng *et al*, 1998), and the SRIs have been found to exert their effects on receptors in various nuclei within the amygdala (Nagy *et al*, 1979; Hodges *et al*, 1987; Costall *et al*, 1989; Gonzalez *et al*, 1996). Moreover, quantitative autoradiographic studies suggest that there are moderate to high densities of 3[H] paroxetine binding sites in the amygdala (Chen *et al*, 1992; De Souza and Kuyatt, 1987), supporting the idea that this region may be one target of pharmacologic intervention with the SRIs.

In this study, we tested the hypothesis that administration of the SRI, paroxetine hydrochloride, to patients with OCD would result in the alterations of amygdala volume as assessed from structural magnetic resonance (MR) imaging. Patients were studied early in the course of illness and psychotropic drug naive to minimize the possible confounds of illness duration and prior pharmacologic exposure on brain structure volumes.

METHODS

Subjects

In all, 11 dextral psychotropic drug-naive pediatric outpatients with OCD and 11 healthy comparison subjects participated in this study. Sample characteristics are illustrated in Table 1. Patients were ill, on average, for 1.6 years prior to study entry (SD = 1.7 years, range = 0.08–5.2 years). The mean age at onset was 10.2 years (SD = 2.3 years, range = 6.3–12.5 years). This sample does not overlap with a previous sample (Rosenberg and Keshavan, 1998; Rosenberg *et al*, 1997a), but includes 17 subjects reported in a more recent investigation of thalamic volume (Gilbert *et al*, 2000).

Table 1 Sample and Clinical Characteristics

	OCD patients ($N = 11$)	Comparison subjects ($N = 11$)	Statistic	df	*p*-value
Sample characteristic					
Age (years)	11.8 ± 3.0	13.3 ± 2.4	$t = -1.34$	20	0.20
Sex	3M/8F	3M/8F	$\chi^2 = 1.00$	1	0.99
Weight (kg)	41.2 (13.6)	58.6 (18.9)	$t = -2.47$	20	0.02
Height (cm)	58.0 ± 5.6	62.5 ± 5.5	$t = -1.88$	20	0.08
Handedness (R, L)	11R	10R/1L	$\chi^2 = 1.00$	1	0.50
Parental SES[a]	2.6 ± 1.3	2.6 ± 0.5	$\chi^2 = 0.70$	1	0.40
Clinical assessment data[b]					
Total CYBOCS	28.5 ± 6.4	3.0 ± 3.6			
Obsessions	14.5 ± 2.6	1.8 ± 2.7			
Compulsions	14.0 ± 3.9	1.2 ± 1.5			
HAMA	10.4 ± 7.2	1.4 ± 1.4			
HAMD	10.0 ± 5.5	1.1 ± 1.0			
YGTS	0.1 ± 0.3	0.1 ± 0.3			

Data are presented as mean ± SD, unless otherwise indicated.
[a]Parental SES indicates parental socioeconomic status that assesses parental education and occupational functioning on a scale of 1 (highest) to 5 (lowest).
[b]CYBOCS, Children's Yale-Brown Obsessive–Compulsive Scale; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; YGTS, Yale Global Tic Severity Scale.

All patients were recruited through the child psychiatry outpatient clinic at Wayne State University School of Medicine in Detroit, Michigan. Patients were diagnosed using DSM-IV criteria (American Psychiatric Association, 1994) and the Schedule for Affective Disorders and Schizophrenia for School Age Children—Present and Lifetime (K-SADS-PL) versions (Kaufman *et al*, 1997). A board-certified child and adolescent psychiatrist (DRR) interviewed all subjects and their parents. The exclusion criteria for patients and healthy comparison subjects included lifetime history of unipolar or bipolar disorder, psychosis, eating disorders, substance abuse or dependence, Sydenham's chorea, Tourette syndrome, and other tic-related conditions, conduct disorder, significantly debilitating medical or neurological conditions, pervasive developmental disorders, mental retardation, or learning disorders. There was no history of psychiatric illness in healthy comparison subjects as determined from the K-SADS-PL or in any of their first-degree relatives. The child's parents served as informants. Legal guardians provided written informed consent and all subjects provided written assent.

Clinical Assessments

All subjects were administered the Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS; Goodman *et al*, 1989; Wolff and Wolff, 1991) to assess OCD symptom severity. The 17-item Hamilton Depression Rating Scale (Hamilton, 1967) measured the severity of depression and the Hamilton Anxiety Rating Scale (Hamilton, 1959)

measured the severity of anxiety. Tic severity was measured with the Yale-Global Tic Severity Scale (Leckman *et al*, 1989). Clinical assessment data are presented in Table 1.

MR Imaging Procedures

MR imaging exams were conducted at the Children's Hospital of Michigan Imaging Center; the image acquisition methods have been described previously (Gilbert *et al*, 2000). Briefly, MR images were acquired in the coronal plane using a 3D spoiled gradient echo pulse sequence with a 40° flip angle, 25 ms repetition time, and 5 ms echo time on a 1.5 T whole body superconducting imaging system (General Electric, Milwaukee, WI). This sequence produced 124 contiguous coronal slices (slice thickness = 1.5 mm) through the whole head with nominal in-plane resolution of $0.94 \times 0.94\ mm^2$ in a 256×256 matrix. Axial proton density and T2-weighted images were obtained to exclude structural abnormalities on MR imaging scans.

Intracranial volume. National Institutes of Health image software (v1.61) (Rasband, 1996) was used to compute intracranial volume in a manner described previously (Rosenberg *et al*, 1997a). This technique yields valid and reliable neuroanatomical measurements using a semiautomated segmentation approach (Rasband, 1996). Inter-rater reliability between two raters (as assessed by intraclass correlations (ICCs)) in 12 cases was 0.99.

Amygdala measurement. Neuroanatomical boundaries for the amygdala were based on operational criteria from postmortem histological work (Bogerts *et al*, 1985) and prior published studies (Watson *et al*, 1992; Szeszko *et al*, 2003). An illustration of the amygdala boundaries is provided in Figure 1. The amygdala was measured from the slice where it first became visible posteriorly. The medial aspect of the posterior part of the amygdala was guided by the crural cistern into the transverse cerebral fissure. The superior border was defined by a straight line drawn laterally from the superiolateral aspect of the optic tract to the fundus of the circular sulcus of the insula. At its most posterior limit care was taken to exclude the tail of the caudate nucleus, globus pallidus, putamen, and the lateral geniculate body from the measurement. The medial border of the amygdala was a thin strip of white matter called the angular bundle, which separates it from the entorhinal cortex. A straight line was drawn on the angular bundle to separate the amygdala laterally from entorhinal cortex medially. The inferior and lateral borders of the amygdala were formed from the temporal horn or adjacent white matter. More anteriorly, the superior border of the amygdala was defined by drawing a straight line from the inferior portion of the circular sulcus of the insula to the endorhinal sulcus. The anterior boundary was the slice where the amygdala no longer appeared to have an ovoid shape, which was either at or posterior to the slice where the closure of the lateral sulcus formed the endorhinal sulcus.

Measurement of the amygdala was completed in MEDx (Medx, 1998) following alignment along the anterior and posterior commissures for purposes of standardization. Prior to measurements, scans of patients and comparison subjects were flipped randomly in the right–left axis and mixed together. No identifying information was available from the scan. All measurements were thus completed by a single well-trained and reliable operator (SM) who was blind to group membership, hemisphere, and scan time point. Right amygdala volume could not be computed for one healthy volunteer at the time of the baseline scan due to scan artifact. ICCs for the right and left amygdala were 0.85 and 0.93, respectively.

Paroxetine Treatment

Paroxetine treatment began at 10 mg/day for all patients and was titrated to a maximum dosage of 60 mg/day based on response (mean (SD) = 38 mg/day; SD = 16; range = 10–60 mg/day). Patients with OCD had follow-up clinical assessments and MR imaging exams after receiving paroxetine hydrochloride for an average of 16 weeks (SD = 3.8). Patients were monitored for medication side effects and adverse experiences during the treatment trial. All patients received paroxetine only and were not receiving cognitive-behavioral therapy or psychotherapy other than supportive therapy. Patients did not participate in this part of the study if: (1) they were unable to be maintained on paroxetine monotherapy; (2) there was a contraindication to paroxetine therapy; (3) there was a need for additional behavioral or psychosocial interventions, or (4) the patient's parents refused to consent to their child taking psychotropic medications, MR imaging procedures, and/or the treating psychiatrist determined that alternative treatment was warranted.

Data Analysis

Group differences in clinical assessments and intracranial volume were examined using independent groups *t*-tests. χ^2 tests were used to examine group differences in sex, handedness, and social class. Paired *t*-tests were used to compare pretreatment and post-treatment intracranial volume, CYBOCS, Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, and Yale Global Tic Severity Scale scores in the patient group. Tests of association between continuous variables were examined using Pearson's product moment correlations.

Mixed models analyses (SAS, 2001) were used to examine group differences in amygdala volume using age and total intracranial volume as time-dependent covariates. Thus, changes in amygdala volume were examined while controlling for changes in age and intracranial volume between the scans. Age was included as a statistical covariate given that patients tended to be younger than healthy comparison subjects. Intracranial volume was included as a statistical covariate to control for nonspecific changes in amygdala volume over time. In addition, given group differences in height and weight, we investigated the potential effects of these variables on amygdala volumes by including them as statistical covariates in subsequent analyses. The group (patient *vs* healthy comparison subject) was a between-subject factor and time (initial *vs* follow-up scan) and hemisphere were within-subject factors. Right and left hemisphere volumes could not be pooled in the analyses because preliminary analyses revealed a significant

hemisphere-by-time interaction for the patient group. To examine whether changes in brain structure volumes were associated with changes in symptoms or medication dosage, we computed percent change scores relative to baseline scores [((Post-test−pretest)/(pretest)) × 100]. All analyses were two-tailed with alpha set to 0.05.

RESULTS

Sample characteristics for patients and healthy volunteers are provided in Table 1. Patients did not differ significantly from healthy comparison subjects in distributions of age, height, sex, or parental social class ($ps > 0.05$). Patients, however, weighed significantly less compared to healthy volunteers. Patients did not differ significantly from healthy volunteers in intracranial volume either at the time of the baseline or follow-up scans ($ps > 0.05$).

Following treatment with paroxetine, patients showed significant reductions in symptom severity as reflected by their lower CYBOCS ($t_{1,10} = 4.37$, $p = 0.001$; pre-treatment = 28.5; SD = 6.4 and post-treatment = 18.2; SD = 7.9), Hamilton Depression ($t_{1,10} = 2.71$, $p = 0.02$; pre-treatment = 10.0; SD = 5.5 and post-treatment = 3.9; SD = 3.5) and Hamilton Anxiety ($t_{1,10} = 2.63$, $p = 0.03$; pretreatment = 10.4; SD = 7.2 and post-treatment = 4.0; SD = 2.3) scores. Illness duration was not significantly correlated with either right or left amygdala volumes at the time of the baseline scan ($ps > 0.05$).

While controlling for changes in age and intracranial volume between scans, the main finding that distinguished patients from healthy comparison subjects for amygdala volume was a significant group-by-hemisphere-by-time interaction ($F_{1,56} = 2.67$, $p = 0.02$). At the time of the initial scan patients had significantly larger left amygdala volume compared to their right amygdala volumes ($t_{1,56} = 3.00$, $p = 0.004$; see Figure 2); this asymmetry was absent among healthy comparison subjects (see Figure 3). Patients did not differ from healthy comparison subjects in either right or left baseline amygdala volumes ($ps > 0.05$). Following the administration of paroxetine patients showed a significant reduction in left amygdala volume ($t_{1,56} = 3.26$, $p = 0.002$; see Figure 2), which decreased, on an average, by 0.25 cm^3 or approximately 15%. The reductions in left amygdala volume occurred in nine of 11 children (see Figure 4). Among healthy comparison subjects there was no significant change in left amygdala volume from the initial scan to the follow-up scan ($p > 0.05$; see Figure 3). The use of height and weight as statistical covariates and the exclusion of the one nondextral participant from analyses did not alter these findings.

Among patients, the reduction in left amygdala volume did not correlate significantly with changes in clinical measures ($ps > 0.05$), but correlated significantly with higher paroxetine dosage at the time of the follow-up scan ($r = -0.65$, $N = 11$, $p = 0.03$) and total cumulative paroxetine exposure received between the scans ($r = -0.71$, $N = 11$, $p = 0.01$).

These correlations remained statistically significant while controlling for changes in clinical symptoms. At the time of the follow-up scan neither patients nor healthy comparison subjects demonstrated significant asymmetry in amygdala

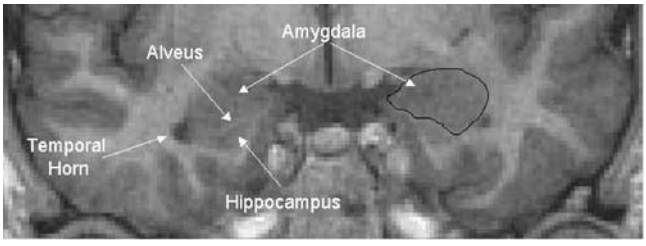

Figure 1 Illustration of the amygdala boundaries.

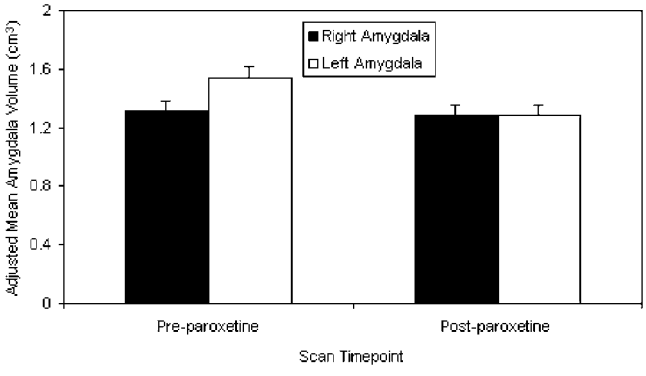

Figure 2 Adjusted mean amygdala volumes with standard errors for patients.

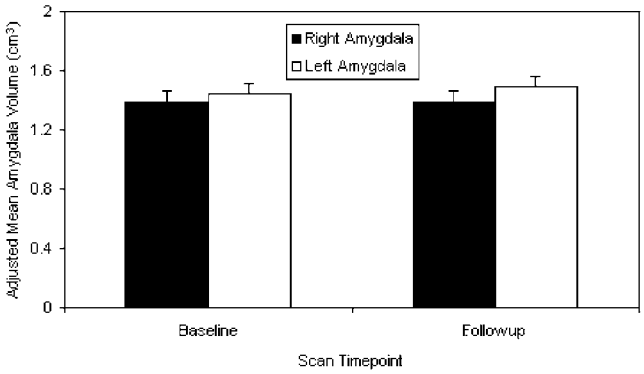

Figure 3 Adjusted mean amygdala volumes with standard errors for healthy volunteers.

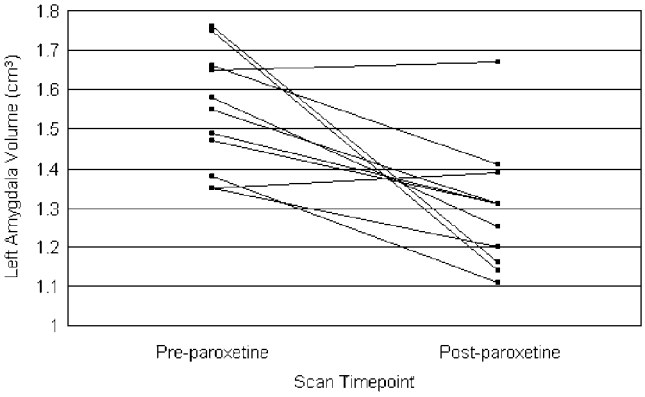

Figure 4 Changes in left amygdala volume in each patient following treatment.

volume ($ps > 0.05$; see Figures 2 and 3), and there were no significant group differences in either right or left amygdala volume ($ps > 0.05$).

DISCUSSION

To our knowledge this study represents the first *in vivo* demonstration of changes in amygdala volume in OCD following SRI pharmacotherapy using structural MR imaging. The main findings were that pediatric psychotropic drug-naïve patients with OCD demonstrate greater left than right amygdala volume compared to healthy volunteers and that the administration of paroxetine to patients was associated with a reduction in left amygdala volume in a dose-dependent manner. The reduction in volume remained significant after controlling for changes in total intracranial volume and age, and was in contrast to the lack of significant change in amygdala volume in untreated healthy comparison children.

The finding of larger left compared to right amygdala volume in our sample of medication-free patients is consistent with the results of Kwon *et al* (2003), who reported significantly larger left amygdala volume in their sample of OCD patients compared to patients with schizophrenia and healthy volunteers. These findings may have relevance for a prior study that reported smaller amygdala volume in previously treated adults with OCD compared to healthy comparison subjects (Szeszko *et al*, 1999). It is possible that in our prior study smaller amygdala volume was associated with treatment. It is difficult to compare these studies directly; however, given differences in the populations, imaging methodology, and methods for measuring the amygdala. For example, in our prior study measurements of the amygdala included the most rostral part of the anterior hippocampus. Nevertheless, our findings do highlight the importance of controlling for prior medication history when examining volumetric measures of the brain anatomy.

There may be several possible mechanisms through which paroxetine could result in amygdala volume reductions in our patient sample. Although disease progression cannot be entirely ruled out, this seems unlikely given the magnitude of the change and brief duration in which these changes occurred. In addition, therapeutic doses of paroxetine appear to lack any important hemodynamic or electrophysiological effects (Warrington and Lewis, 1992), thus arguing against these possibilities. It seems plausible that the reductions in amygdala volume were treatment induced given the significant inverse relationship between these reductions and paroxetine treatment. Specifically, paroxetine treatment in OCD may be associated with a reversal of left amygdala hypertrophy given that right and left amygdala volumes were comparable following treatment. It is possible that SRI administration results in deactivation and consequent hypotrophy of neural components within the amygdala. In addition, downregulation of serotonergic receptors following paroxetine administration has also been reported in young, depressed patients (Meyer *et al*, 2001), and this could also conceivably be associated with a reduction in amygdala volume. Whether such volumetric alterations are plastic over the course of treatment could not be addressed in the present study, but would be an important question for future research.

Our findings are consistent with studies demonstrating an inhibitory effect of SRIs on brain structure and function. The SRIs appear to target various amygdaloid nuclei (Costall *et al*, 1989; Gonzalez *et al*, 1996) and inhibition of neurotransmission within the amygdala may be mediated partly by serotonergic receptors (Cheng *et al*, 1998). In addition, animal studies indicate that administration of SRIs is associated with decreased stress-induced Fos-like immunoreactivity in the medial amygdala (Lino-de-Oliveira *et al*, 2001). Functional neuroimaging studies reported decreased cortical and subcortical glucose metabolism in patients with OCD following SRI administration (Baxter *et al*, 1992; Swedo *et al*, 1989) and normalization of left amygdala hyperarousal was identified in patients with major depressive disorder after SRI pharmacotherapy (Sheline *et al*, 2001). The present findings also converge with our prior study demonstrating thalamus volume reductions in OCD following SRI pharmacotherapy (Gilbert *et al*, 2000), suggesting that paroxetine may be exerting similar inhibitory effects on other brain regions implicated in the pathophysiology of OCD. In this regard, it is worth noting that no significant changes in intracranial volume were observed in patients following treatment, suggesting that our findings were not an artifact of global volumetric reductions. The potential inhibitory effects of the SRIs may depend on the underlying pathophysiology of the disorder (Saxena *et al*, 2002) however, and thus, our findings may not be generalizable to other clinical populations. In addition, although prior studies reported neurogenesis in humans (Vermetten *et al*, 2003) and rats (Malberg *et al*, 2000) following SRI pharmacotherapy, these effects were observed in the hippocampus, and thus may not be directly comparable to our findings.

The finding that changes in amygdala volume following paroxetine administration were lateralized to the left hemisphere is consistent with prior studies implicating dysregulation of left hemisphere cortical networks in OCD (Baxter *et al*, 1987; Brody *et al*, 1998). In a study of correlations between normalized regional cerebral metabolic rates for glucose, Horwitz *et al* (1991) found that the left hemisphere anterior medial temporal region (which mainly included the amygdala) was one of the regions that had the largest number of reference ratio correlations that differed significantly between patients with OCD and healthy comparison subjects. Moreover, the left anterior medial temporal region had increased interactions with left frontal structures in OCD relative to healthy individuals. It is also worth noting that the left amygdala has been reported to play a role in anticipatory anxiety (Phelps *et al*, 2001) and responds when individuals are conscious of the aversive nature of a stimulus (Morris *et al*, 1998), factors which appear to be highly relevant to the phenomenology of OCD.

There were several limitations to this study that preclude firm conclusions. The number of participants was small, and thus these findings should be considered preliminary until replicated in a larger sample. Although a double-blind placebo-controlled study may have been superior for delineating treatment *vs* placebo effects, such a study would have required a much larger sample and been more difficult

to justify given the efficacy of the SRIs compared to placebo in treating OCD. Another potential study limitation was that changes in amygdala volume did not correlate significantly with symptom changes. This lack of association might reflect the possibility that symptom changes occurred at a differential rate compared to volumetric changes. Also, given that the amygdala maintains connections with other serotonergic regions implicated in the pathophysiology of OCD such as the thalamus (Price, 2003; Oke *et al*, 1997), it is possible that the observed amygdala volumetric changes are an epiphenomena of the underlying pathophysiology of the disorder and/or a nonspecific correlate of treatment intervention. Moreover, changes in the dopaminergic system could also be related to the observed volumetric alterations given that animal studies have demonstrated that dopamine inhibition may be indirectly affected by serotonin (Korsgaard *et al*, 1985).

In summary, our results suggest that an abnormality involving amygdala asymmetry may play a role in the pathogenesis of OCD and that reductions in amygdala volume are associated with paroxetine treatment. Further studies are needed to assess the potential long-term neuroanatomical changes of the SRIs and mechanisms of response.

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