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ORIGINAL PAPER

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Regional cerebral blood flow in obsessive-compulsive patients with and without a chronic tic disorder. A SPECT study.

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Abstract The main goal of the present study was to explore whether regional cerebral blood flow (rCBF) differs between obsessive-compulsive disorder (OCD) patients without chronic motor tic disorder and those OCD patients with a comorbid chronic tic disorder. Twenty-seven patients suffering from OCD (DSM-IV criteria), including 7 OCD patients who met DSM-IV criteria for simple chronic motor dic disorder, and 16 healthy volunteers were examined at rest using a high resolution SPECT. Seven regions of interest (ROIs) were manually traced and quantified as a percentage of the mean cerebellar uptake. Severity of obsessive-compulsive symptoms (OCS), anxiety and depressive symptoms and presence of motor tics were assessed with the Y-BOCS, HRS-A, HRS-D, MADRS, and Yale Global Tics Severity Scale, respectively. We found a significant relative decrease in rCBF in OCD patients without motor tics compared to healthy volunteers in the right orbitofrontal cortex (OCD without tics = 0.87; healthy volunteers = 0.94; p = 0.02). No significant differences in rCBF were seen when OCD patients with and without chronic tics were directly compared. A lower severity of OCS in OCD patients with chronic tics was found. These results are consistent with previous functional neuroimaging studies at rest that have widely involved the orbitofrontal cortex in the pathophysiology of the OCD. However, our results do not support the idea that OCD patients with chronic tics may constitute a biological subgroup within the OCD.

Key words Obsessive-compulsive disorder · Tic disorder · Orbitofrontal cortex · Single photon emission computed tomography

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Introduction

A relevant increase of OCD diagnosis over the last few years (Stoll et al. 1992) and its heterogeneous clinical presentation, have highlighted the need to define clinical subtypes within OCD (Leckman et al. 1997). In addition to a high lifetime history of tic symptoms in the OCD population, epidemiological studies have also reported a high comorbility between OCD and tic disorders (Lenane et al. 1990; Pauls et al. 1995; Pitman et al. 1987). OCD patients with a history of motor tics may be distinguished based upon their clinical features, and might constitute a distinctive subtype of OCD (Holzer et al. 1994; McDougle et al. 1993; Miguel et al. 1997; Zohar et al. 1997). Consistently, treatment response data have also demonstrated that OCD patients with a comorbid chronic tic disorder may require a combined serotonin-uptake inhibitor plus neuroleptic therapy (McDougle et al. 1994).

Motor tic disorders and obsessive-compulsive symptoms (OCS) have been described in several primarily basal ganglia illnesses (Tourette's syndrome, Huntington's disease, Sydenhan's chorea, and postencephalitic Parkinsonism), basal ganglia calcification (López-Villegas et al. 1996), and autoimmune neuropsychiatric disorders affecting basal ganglia (Swedo et al. 1994). Disturbances in fronto-basal ganglia circuits have been reported in both obsessive-compulsive symptoms (Insel 1992; Laplane et al. 1989) and tic disorders (Cummings and Frankel 1985). Likewise, anatomical and lesion studies have pointed out

that different parts of caudate nucleus make specific contributions to cognitive processes, because of their connections to specific subregions of the frontal lobe (Divac et al. 1967; Goldman-Rakic et al. 1987). The dorsolateral part of head and the ventromedial portion of caudate nucleus are connected to the dorsolateral prefrontal and the orbitofrontal cortex, respectively (Alexander et al. 1986; Goldman-Rakic and Nauta 1977).

However, previous functional neuroimaging studies at rest have led to controversial results regarding brain activity in OCD patients. Although some of them have shown higher metabolic rates in the head of caudate nucleus and orbitofrontal cortex (Baxter et al. 1988; Swedo et al. 1989), several others have described a relative decrease in rCBF in the orbitofrontal cortex and striatum (Edmonstone et al. 1994; Lucey et al. 1995; Martinot et al. 1990) in OCD patients compared to healthy volunteers. Lack of consistent results might be due to comorbid clinical entities in OCD that might determine differences in cerebral blood flow (Lopez-Ibor et al. 1995).

In our previous study we demonstrated that OCD patients with major depression show a decreased cortical and subcortical activity compared to nondepressed OCD (Lopez-Ibor et al. 1995). Nevertheless, it remains still unclear whether some other comorbid clinical features in OCD migh be associated to specific rCBF patterns and might constitute distinctive pathophysiological entities within the OCD spectrum.

Our main purpose is to extend the investigations of neural mechanisms involved in the pathophysiology of the OCD by exploring the patterns of brain activity at rest of OCD with and without chronic motor tics, and compared them to healthy volunteers. We hypothesize that the presence of a motor tic disorder in OCD patients will lead to differences in blood flow in the basal ganglia and the orbitofrontal cortex. If this hypothesis proves to be correct, it would provide strong support for clinical and pharmacological data suggesting that OCD patients with motor tics might constitute a meaningful subtype of OCD.

Methods

Subjects

Subjects were 16 healthy volunteers (10 males, 6 females) recruited from the community and 29 patients (21 males, 8 females) suffering from OCD (DSM-IV and ICD-10 criteria) and were evaluated at the San Carlos Hospital in Madrid. Healthy volunteers were selected following a similar sex, age, and handedness distribution as the OCD patients and were screened to rule out current or past personal history of psychiatric, neurological illness or alcohol/substance abuse and use of any psychotropic medication using a structured interview (SCID) (Spitzer et al. 1987). Seven out of 29 OCD patients had a comorbid simple chronic motor tic disorder. Obsessive-compulsive symptoms rather than tics were the predominant presenting complaint. Patients were either withdrawn from all medication for a two-week period, a four-week period if they were under flouxetine, prior to study (n = 16) or had never been treated before. Diagnosis was established by a consensus of at least two psychiatrists (BCF, BPG, JJL) involved in this study. The Yale Global Tic Severity Scale was used to screen and to confirm the existence of motor tics. Information gathered from next-of-kin confirmed the presence of chronic motor tics. The SCID was used to confirm the diagnosis. Subjects were screened to rule out current or past history of Gilles de la Tourette syndrome (GTS). None of the patients met DSM-IV diagnosis criteria for GTS. Tics and compulsions were differentiated as follows. Tics were defined as sudden, purposeless, rapid, repetitive involuntary movements occurring irregularly, whereas compulsions were defined as deliberate, complex motor acts preceded by a specific thought (obsession). Only patients with moderate or severe OCS, as defined by the Clinical Global Impressions (CGI) scale, were included in the study. Severity of OCS was measured by the Spanish version of Yale-Brown Obsessive Compulsive Scale (Y-BOCS) that includes two symptom subscales (obsessive and compulsive symptom subscales). Depressive symptoms were rated by 17 items version of Hamilton Rating Scale for Depression (HRS-D) and Montgomery-Åsberg Depression Rating Scale (MADRS). Anxiety symptoms were assessed by the Hamilton Rating Scale for Anxiety (HRS-A). Approval was granted by the local Ethics Committee and procedures were fully explained to all subjects. Written informed consent was obtained before enrollment in the study.

Measurement of rCBF

Regional cerebral blood flow (rCBF) images were obtained by SPECT using technetium-99m-labeled hexamethyl-propyleneamine-oxime ($^{99}Tc^{m}$-HMPAO) (Ceretec, Amersham International). Because of its initial lipophilic state, $^{99}Tc^{m}$-HMPAO rapidly crosses the blood-brain barrier and is delivered into brain cells in proportion to the rCBF. Once in the brain cells, it is converted to a lipophobic state remaining stable for hours. The rCBF of 27 OCD patients, 7 of them with a comorbid chronic tic disorder, and 16 healthy volunteers were analyzed (2 of the 29 OCD patients, who had been clinically evaluated, refused SPECT scan). Prior to the injection, patients stayed in a quiet and dimly lit room for at least 15 minutes. At the time of the administration of 740 Mbq (20 mci) $^{99}Tc^{m}$-HMPAO i.v., the patients were resting in a quiet room in a supine position with their eyes closed, and remained in this position for 10 more minutes. Motor tics were not reported during this time.

Brain SPECT was performed using a Siemens ORBITER rotating single-head gamma camera with high-resolution collimators and routine protocols. During a 360° rotation in 64×64 matrix, 60 $\times$ 20 s frames were collected and a 6×6 pixel size was obtained. Reconstruction in the transverse, coronal, and sagittal planes was performed with filtered back-projection using Shepp-Logan-Hanning prefilter (1.0 cycles/cm cut-off frequency), a Ramp filter, and attenuation correction coefficient of 0.12. Total acquisition time for each individual was 20 minutes. Seven manually-traced ROIs were drawn. Thus, regional indices were measured in the following ROIs: dorsolateral prefrontal cortex, orbitofrontal cortex, thalamus, caudate nucleus, temporal cortex, parietal cortex, and anterior cingulate. All regions were represented in both hemispheres, except for the anterior cingulate that was considered as a single bilateral region. Transaxial, coronal, and sagittal slices were selected with a neuroanatomical atlas being used for reference, in order to encompass the different ROIs. Uptakes of radioligand in these regions were calculated and expressed as within-subject ratios to the cerebellar blood flow. The cerebellum seems not to be affected either in OCD or in tic disorders and has not been demonstrated to be involved in the pathophysiology of OCD. No attempt was made to directly compare counts in ROIs. Three transaxial slices parallel to the orbito-meatal line were selected. The cerebellum was analyzed as a unique region at the level where inferior pole of temporal lobe was seen. The head of caudate nuclei was drawn in the second transaxial slice from the bottom in which the caudate head was seen. The transaxial slice immediately above the superior-most edge of the thalamus showed the anterior cingulate, the dorsolateral prefrontal, and the parietal cortex. Two coronal slices were selected: first, the orbitofrontal cortex was identified in the first coronal slice rostral to the anterior horns of the lateral ventricles; second, the temporal cortex was traced in the slice containing the

largest size of the temporal lobe (including superior, middle, and inferior temporal gyri). Bilaterally, the most medial sagittal images were selected to assess the rCBF in the thalamus. The rCBF was automatically calculated blind to clinical status and diagnosis.

Statistical analysis

Group means of rCBF ratios were compared in OCD with tics, OCD without tics, and the control subjects for ROIs selected, using analysis of variance (ANOVA). Corrections for multiple comparisons were made by Bonferroni's test. The rCBF ratios were calculated by comparing uptake in the region under evaluation with uptake in the cerebellar area. Cerebellar rCBF did not show statistically significant differences between groups. Differences in rCBF ratios between groups were evaluated for each particular ROI. Results were presented as a mean (SD) and were reported as significant when $P < 0.05$ (two tailed).

Results

Clinical results

OCD patients with a comorbid tic disorder had statistically significant lower scores on the global Y-BOCS and on the subscale of obsessions (Table 1). OCD patients with a comorbid chronic tic disorder, compared to OCD patients without tics, did not differ in terms of sociodemographic features, depression, and anxiety rating scores.

Semiquantitative analysis

The comparison of the OCD patients without chronic tic disorder and the healthy volunteer groups revealed a relative decrease in rCBF in the right OFC in the OCD group (OCD without tics: mean = 0.87 (0.08); Healthy volun-

Table 1 Clinical and demographic characteristics of OCD patients and healthy volunteers

Variable	OCD without chronic motor tics (n = 21) Mean (SD)/ Proportion	OCD with chronic motor tics (n = 8) Mean (SD)/ Proportion	Healthy volunteers (n = 16) Mean (SD)/ Proportion	P
Age (years)	32 (9)	26 (6)	28 (5)	ns
Sex (M/F)	14/7	7/1	10/6	ns
Smokers (+/–)	4/17	1/7	6/10	ns
Handedness (R/L)	19/2	8/0	15/1	ns
Y-BOCS (Total score)	26 (5)	20 (7)	–	< 0.05
Obsession Subscale	13 (3)	10 (3)	–	< 0.05
Compulsion Subscale	12 (4)	9 (5)	–	ns
HRS-D	14 (8)	11 (6)	–	ns
MADRS	15 (12)	12 (8)	–	ns
HRS-A	10 (6)	7 (4)	–	ns

Y-BOCS = Yale-Brown Obsessive-Compulsive Scale; HRS-D = Hamilton Rating Scale for Depression; MADRS = Montgomery-Åsberg Depression Rating Scale; HRS-A = Hamilton Rating Scale for Anxiety

Table 2 Regional cerebral blood flow at rest in OCD patients without and with a motor tic disorder and healthy volunteers

Regions	OCD without chronic Tics (n = 20) Mean (SD)	OCD with chronic Tics (n = 7) Mean (SD)	Controls (n = 16) Mean (SD)
Caudate nucleus			
Left	0.91 (0.06)	0.94 (0.06)	0.96 (0.07)
Right	0.92 (0.07)	0.96 (0.02)	0.96 (0.08)
Orbitofrontal cortex			
Left	0.87 (0.06)	0.92 (0.04)	0.91 (0.06)
Right	**0.87 (0.08)***	**0.89 (0.07)**	**0.94 (0.06)**
Dorsolat. prefrontal cortex			
Left	0.85 (0.05)	0.89 (0.08)	0.86 (0.05)
Right	0.87 (0.05)	0.87 (0.07)	0.88 (0.06)
Ant. cingulate	0.85 (0.07)	0.87 (0.05)	0.89 (0.07)
Thalamus			
Left	0.95 (0.06)	0.94 (0.07)	1.01 (0.06)
Right	0.94 (0.08)	0.95 (0.07)	0.99 (0.07)
Temporal cortex			
Left	0.87 (0.06)	0.87 (0.07)	0.86 (0.06)
Right	0.88 (0.07)	0.92 (0.07)	0.90 (0.06)
Parietal cortex			
Left	0.85 (0.07)	0.86 (0.05)	0.84 (0.05)
Right	0.86 (0.05)	0.90 (0.07)	0.86 (0.04)

Note. Regions rCBF were normalized by cerebellum rCBF
*$P < 0.05$, Bonferroni's test

teers: mean = 0.94 (0.06); $P = 0.02$) (Table 2). No differences in flow were found when OCD patients with and without chronic motor tics were compared.

Discussion

The present study has shown that unmedicated OCD patients without a concomitant chronic tic disorder show a relative decrease in flow in the right OFC compared to healthy volunteers, at rest. Conversely to our hypothesis, no differences in rCBF between OCD patients with and without tics were found. However, the clinical evaluation demonstrated that OCD patients with chronic tics had a lower severity of OCS, particularly on the obsessive symptom subscale. Our results provide additional support to the idea that the OFC plays a key role in neural mechanisms underlying the pathophysiology of the OCD. Likewise, they are also consistent with previous studies that have reported clinical differences between adolescent OCD patients with and without tics (Zohar et al. 1997).

Neuroimaging studies at rest, during exposure to triggering stimuli, or exploring the effects of pharmacological and behavioral therapy have consistently implicated the OFC in the neural mechanisms underlying the pathophysiology of the OCD (for review see Zald and Kim 1996). The OFC is a large cytoarchitectonic heterogeneous region of the ventral prefrontal cortex (Carmichael and Price 1994; Hof et al. 1995). It is considered to be a component of the paralimbic cortical "belt" and is involved in higher order association functions, including the integration of emotion, mnemonic functions, and sensory processes (Morecraft et al. 1992; Rolls et al. 1996). Additionally, it has been demonstrated that the OFC is involved in inhibitory control of cognitive processes (Dias et al. 1997; Fuster 1989; Passingham 1972). Interestingly, a basic disturbance of neurobehavioral response inhibition has been described in OCD patients (Rosenberg et al. 1997; Tien et al. 1992).

Animal and lesion studies have widely described connections between the caudate nucleus and the prefrontal cortex (Caplan et al. 1990; Goldman-Rakic 1987). The projections contribute to a pair of segregated loops connecting the OFC, striatum, globus pallidus, and thalamus (Alexander et al. 1986). Different regions in the OFC project toward specific parts of caudate nucleus. Thus, lateral orbitofrontal cortex is connected to the ventromedial strip of the caudate nucleus, whereas the medial orbitofrontal cortex provides projections to the extreme edge of the ventral caudate (Nauta 1979). It has been postulated that the comorbidity of tic disorders in OCD could represent a different biological entity depending on the neuroanatomical location of the pathology within the basal ganglia (Baxter et al. 1988; Baxter 1990a). Based on positron emission tomographic (PET) studies, Baxter and colleagues have hypothesized that both OCD and chronic tic disorders (including GTS) are expressions of abnormalities within the basal ganglia (Baxter et al. 1990b). Contrarily to this hypothesis, our results have failed to show any significant difference in flow between OCD with and without tics. Nevertheless, two limiting factors of our study should be considered. First, the resolution of SPECT scans does not allow us to discriminate between specific subregions of the caudate nucleus and, second, the small sample size.

Previous functional neuroimaging studies have consistently shown specific differences in brain activity in both orbitofrontal cortex and basal ganglia in OCD patients at rest. However, the results of these studies have been inconclusive. Some studies have shown a relative decreased flow in the OFC (Edmonstone et al. 1994; Lucey et al. 1995; Martinot et al. 1990), and in contrast several others have reported either a relative increase or no differences in cerebral metabolic rates or blood flow in the OFC in OCD patients, at rest (Baxter et al. 1988; Machlin et al. 1991; Modell et al. 1989; Nordahl et al. 1989; Rauch et al. 1994; Rubin et al. 1992; Swedo et al. 1989). Regional brain activity in OCD patients depends on levels of obsessionality and anxiety (Lucey et al. 1995). Since only the group of OCD patients without motor tics shows differences in the pattern of brain activity at rest compared to healthy volunteers, it is conceivable to argue that the presence of motor tic might be considered a relevant factor to determine rCBF characteristics of OCD patients.

Structural neuroimaging studies have led to a similar controversy regarding structural abnormalities in OCD across studies. Some studies have shown a significantly reduced volume of the prefrontal cortex, caudate or white-matter (Jenike et al. 1996; Luxenberg et al. 1988; Robinson et al. 1995), whereas other studies have not found such abnormalities (Aylward et al. 1996; Kellner et al. 1991). Magnetic resonance spectroscopy studies have also provided evidence for neuronal loss in the corpus striatum in OCD patients (Bartha et al. 1998; Ebert et al. 1997). Overall, data from clinical, neuropharmacological, neuropsychological, psychosurgical investigations converge to the idea of a dysfunctional prefrontal cortico-striato-thalamic brain system in OCD (Insel 1992; Schwartz et al. 1996; Trivedi 1996).

In summary, the results of our study support the idea that the OCD is a heterogeneous illness in which different pathophysiological mechanisms, involving a cortico-striato-thalamo-cortical loop, are implicated. However, whether there is an increase or a decrease in brain activity in the different nodes of this loop still remains unclear. The comorbility of depression, tic disorder, and the characteristics of the obsessive symptoms may determine differences in the pattern of brain activity in OCD patients. Based on these findings, it is conceivable to speculate the inconsistency of results could be understood in the context of shifts in the rCBF of this common disturbed circuitry due to different clinical features of the sample. Further investigations are needed to explore the normal functional connectivity between these brain regions in patients suffering from OCD.

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References

Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Ann Rev Neurosci 9:357–381

Aylward EH, Harris GJ, Hoehn-Saric R, Barta PE, Machlin SR, Pearlson GD (1996) Normal caudate nucleus in obsessive-compulsive disorder assessed by quantitative neuroimaging. Arch Gen Psychiatry 53:577–584

Bartha R, Stein MB, Williamson PC, Drost DJ, Neufeld RW, Carr TJ, Canaran G, Densmore M, Anderson G, Siddiqui AR (1998) A short echo 1H spectroscopy and volumetric MRI study of the corpus striatum in patients with obsessive-compulsive disorder and comparison subjects. Am J Psychiatry 155:1584–1591

Baxter LR, Schwartz JM, Mazziotta JC, Phelps ME, Pahl JJ, Guze BH, Fairbanks L (1988) Cerebral glucose metabolism rates in nondepressed patients with obsessive-compulsive disorder. Am J Psychiatry 145:1560–1563

Baxter LR (1990a) Brain imaging as a tool in establishing a theory of the brain pathology in obsessive-compulsive disorder. J Clin Psychiatry 51 (2, Suppl):22–25

Baxter LR, Schwartz JM, Guze BH, Bergman K, Szuba MP (1990 b) PET imaging in obsessive compulsive disorder with and without depression. J Clin Psychiatry 51 (4, Suppl):61–69

Caplan LR, Schmahmann JD, Kase CS, Feldmann E, Baquis G, Greenberg JP, Gorelick PB, Helgason C, Hier DB (1990) Caudate infarcts. Arch Neurol 47:133–143

Carmichael ST, Price JL (1994) Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. J Comp Neurol 346:366–402

Cummings JL, Frankel M (1985) Gilles de la Tourette syndrome and the neurological basis of obsessions and compulsions. Biol Psychiatry 20:1117–1126

Dias R, Robbins TW, Roberts AC (1997) Dissociable forms of inhibitory control within prefrontal cortex with an analog of the Wisconsin Card Sort Test: restriction to novel situations and independence from "on-line" processing. J Neurosci 17:9285–9297

Divac I, Rosvold HE, Scwarcbart MK (1967) Behavioural effects of selective ablation of the caudate nucleus. J Comp Physiol Psychol 63:184–190

Ebert D, Speck O, Konig A, Berger M, Hennig J, Hohagen F (1997) 1H-magnetic resonance spectroscopy in obsessive-compulsive disorder: evidence for neuronal loss in the cingulate gyrus and the right striatum. Psychiatry Res 74:173–176

Edmonstone Y, Austin MP, Prentice N, Dougall N, Freeman CP, Ebmeier KP, Goodwin GM (1994) Uptake of 99m Tc-exametazime shown by single photon emission computerized tomography in obsessive-compulsive disorder compared with major depression and normal controls. Acta Psychiat Scand 90:298–303

Fuster JM (1989) The Prefrontal Cortex: Anatomy, Physiology and Neuropsychology of the Frontal Lobe. Raven Press, New York

Goldman-Rakic PS, Nauta WJH (1977) An intricately patterned prefronto-caudate projection in the rhesus monkey. J Comp Neurol 72:369–386

Goldman-Rakic PS (1987) Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: Plum F and Mouncastle U (eds) Handbook of Psychology Vol. 5. The American Physiological Society, Washington DC, pp 373–417

Hof PR, Mufson EJ, Morrison JH (1995) Human orbitofrontal cortex: cytoarchitectural and quantitative immunohistochemical parcellation. J Comp Neurol 359:48–68

Holzer JC, Goodman WK, McDougle CJ, Baer L, Boyarsky BK, Leckman JF, Price LH (1994) Obsessive-compulsive disorder with and without a chronic tic disorder: A comparison of symptoms in 70 patients. Br J Psychiatry 164:469–473

Insel T (1992) Towards the neuroanatomy of obsessive-compulsive disorder. Arch Gen Psychiatry 49:739–744

Jenike MA, Breiter HC, Baer L, Kennedy DN, Savage CR, Olivares MJ, O'Sullivan RL, Shera DM, Rauch SL, Keuthen N, Rosen BR, Caviness VS, Filipek PA (1996) Cerebral structural abnormalities in obsessive-compulsive disorder: a quantitative morphometric magnetic resonance imaging study. Arch Gen Psychiatry 53:625–632

Kellner CH, Jolley RR, Holgate RC, Austin L, Lydiard RB, Laraia M, Ballenger JC (1991) Brain MRI in obsessive-compulsive disorder. Psychiatr Res 36:45–49

Laplane D, Levasseur M, Pillon B, Dubois B, Baulac M, Mazoyer B, Dinh ST, Sette G, Danze F, Baron JC (1989) Obsessive-compulsive and other behavioural changes with bilateral basal ganglia lesions. A neuropsychological, magnetic resonance imaging and positron emisson tomography study. Brain 112:699–725

Leckman JF, Grice DE, Boardman J, Zhang H, Vitale A, Bondi C, Alsobrook J, Peterson BS, Cohen DJ, Rasmussen SA, Goodman WK, McDougle CJ, Pauls DL (1997) Symptoms of obsessive-compulsive disorder. Am J Psychiatry 154:911–917

Lenane MC, Swedo SE, Leonard H, Pauls DL, Sceery W, Rapoport JL (1990) Psychiatric disorders in first degree relatives of children and adolescents with obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry 29:407–412

López-Ibor JJ, Saiz Ruiz J, López-Ibor Alcocer MI, Vinas R (1995) Obsessive-compulsive disorder and depression. Actas Luso Esp Neurol Psiquiat Cienc Afines 23:97–113

López-Villegas D, Kulisevsky J, Deus J, Junque C, Pujol J, Guardia E, Grau JM (1996) Neuropsychological alterations in patients with computed tomography-detected basal ganglia calcification. Arch Neurol 53:251–256

Lucey JV, Costa DC, Blanes T, Bussato GF, Pilowsky LS, Takei N, Marks I, Ell PJ, Kerwin RW (1995) Regional cerebral blood flow in obsessive-compulsive disordered patients at rest. Differential correlates with obsessive-compulsive and anxious-avoidant dimensions. Br J Psychiatry 167:629–634

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

Machlin SR, Harris GJ, Pearlson GD, Hoehn-Saric R, Jeffery P, Camargo EE (1991) Elevated medial-frontal cerebral blood flow in obsessive-compulsive patients: a SPECT study. Am J Psychiatry 148:1240–1242

Martinot JL, Allilaire JF, Mazoyer BM, Hantouche E, Huret JD, Legaut-Demare F, Deslauriers AG, Hardy P, Pappata S, Baron JC, Syrota A (1990) Obsessive-compulsive disorder: clinical, neuropsychological and positron emission tomography study. Acta Psychiat Scand 82:233–242

McDougle CJ, Goodman WK, Leckman JF, Barr LC, Heninger GR, Price LH (1993) The efficacy of fluvoxamine in obsessive-compulsive disorder: Effects of comorbid chronic tic disorder. J Clin Psychopharmacol 13:354–358

McDougle CJ, Goodman WK, Leckman JF, Lee NC, Heninger GR, Price LH (1994) Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder. A double-blind, placebo-controlled study in patients with and without tics. Arch Gen Psychiatry 51:302–308

Miguel EC, Baer L, Coffey BJ, Rauch SL, Savage CR, O'Sullivan RL, Phillips K, Moretti C, Leckman JF, Jenike MA (1997) Phenomenological differences appearing with repetitive behaviours in obsessive-compulsive disorder and Gilles de la Tourette's syndrome. Br J Psychiatry 170:140–145

Modell JG, Mountz JM, Curtis GC, Greden JF (1989) Neurophysiologic dysfunction in basal ganglia/limbic striatal and thalamocortical circuits as a pathogenetic mechanism of obsessive-compulsive disorder. J Neuropsychiatry Clin Neurosci 1:27–36

Morecraft RJ, Geula C, Mesulam MM (1992) Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. J Comp Neurol 323:341–358

Nauta HJ (1979) A proposed conceptual reorganization of the basal ganglia and telencephalon. Neuroscience 4:1875–1881

Nordahl TE, Benkelfat C, Semple SW, Gross M, King AC, Cohen RM (1989) Cerebral metabolic rates in obsessive-compulsive disorder. Neuropsychopharmacology 2:23–28

Passingham RE (1972) Visual discrimination learning after selective prefrontal ablations in monkeys. Neuropsychologia 10: 27–39

Pauls DL, Alsobrook JP, Goodman W, Rasmussen S, Leckman JF (1995) A family study of obsessive-compulsive disorder. Am J Psychiatry 152:76–84

Pitman RK, Green RC, Jenike MA, Mesulam MM (1987) Clinical comparison of Tourette's disorder and obsessive-compulsive disorder. Am J Psychiatry 144:1166–1171

Rauch SL, Jenike MA, Alpert NM, Baer L, Breiter HC, Savage CR, Fischman AJ (1994) Regional cerebral blood flow measured during provocation in obsessive-compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. Arch Gen Psychiatry 51:62–70

Robinson D, Wu H, Munne RA, Ashtari M, Alvir JM, Lerner G, Koreen A, Cole K, Bogerts B (1995) Reduced caudate nucleus volume in obsessive-compulsive disorder. Arch Gen Psychiatry 52:393–398

Rolls ET, Critchley HD, Mason R, Wakeman EA (1996) Orbitofrontal cortex neurons: role in olfactory and visual association learning. J Neurophysiol 75:1970–1981

Rosenberg DR, Dick EL, O'Hearn KM, Sweeney JA (1997) Response-inhibition deficits in obsessive-compulsive disorder: an indicator of dysfunction in frontostriatal circuits. J Psych Neurosci 22:29–38

Rubin RT, Villanueva-Meyer J, Ananth J, Trajmar PG, Mena I (1992) Regional xenon 133 cerebral blood flow and Tc-99m-HMPAO uptake in unmedicated OCD and matched normal controls. Arch Gen Psychiatry 49:695–702

Schwartz JM, Stoessel PW, Baxter LR, Martin KM, Phelps ME (1996) Systematic changes in cerebral glucose metabolic rate after successful behavior modification treatment of obsessive-compulsive disorder. Arch Gen Psychiatry 53:109–113

Spitzer RL, Willians JBW, Gibbon M (1987) Structured Clinical Interview for DSM-III-r (SCID). New York, New York State Psychiatric Institute, Biometric Research

Stoll RL, Tohen M, Baldessarini RJ (1992) Increasing frequency of the diagnosis of obsessive-compulsive disorder. Am J Psychiatry 149:638–640

Swedo SE, Schapiro MB, Grady CL, Cheslow DL, Leonard HL, Kumar A, Friedland R, Rapoport SI, Rapoport JL (1989) Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. Arch Gen Psychiatry 46:518–523

Swedo SE, Leonard HL, Kiessling LS (1994) Speculations on antineuronal antibody-mediated neuropsychiatric disorders of childhood. Pediatrics 93:323–326

Tien AY, Pearlson GD, Machlin SR, Bylsma FW, Hoehn-Saric R (1992) Oculomotor performance in obsessive-compulsive disorder. Am J Psychiatry 149:641–646

Trivedi MH (1996) Functional neuroanatomy of obsessive-compulsive disorder. J Clin Psychiatry 57 (8, Suppl):26–35

Zald DH, Kim SW (1996) Anatomy and function of the orbital frontal cortex II: Function and relevance to obsessive-compulsive disorder. J Neuropsychiatry Clin Neurosci 8:249–261

Zohar AH, Pauls DL, Ratzoni G, Apter A, Dycian A, Binder M, King R, Leckman JF, Kron S, Cohen DJ (1997) Obsessive-compulsive disorder with and without tics in an epidemiological sample of adolescents. Am J Psychiatry 154:274–276