



A meta-analysis of functional neuroimaging in obsessive-compulsive disorder

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Received 10 March 2003; received in revised form 21 April 2004; accepted 23 July 2004

Abstract

Recent neurobiological models of obsessive-compulsive disorder (OCD) posit that a dysfunction in orbitofrontal-subcortical circuitry underlies the etiology of this disorder. Much of the empirical support for these theories comes from studies using neuroimaging techniques to compare brain activity in OCD patients with that in non-OCD controls. Qualitative reviews of this literature implicate the orbitofrontal cortex, caudate nuclei, and thalamus. In this study, a meta-analysis was conducted to summarize the results of studies using positron emission tomography (PET) and single photon emission computed tomography (SPECT) to investigate brain activity in OCD. Results suggest that differences in radiotracer uptake between patients with OCD and healthy controls have been found consistently in the orbital gyrus and the head of the caudate nucleus. No other significant differences were found. The implications of these results for theories regarding the etiology of OCD are discussed.

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Keywords: Positron emission tomography; Single photon emission computed tomography; Caudate nucleus; Literature review

1. Introduction

Obsessive-compulsive disorder (OCD) is characterized by intrusive unwanted thoughts, ideas, or images that are distressing (obsessions) and urges to perform ritualistic behaviors or mental acts (com-

pulsions) to reduce this distress. The lifetime prevalence of this anxiety disorder is estimated to be 2–3% around the world (Weissman et al., 1994). OCD is associated with impairment in occupational, academic, and social functioning (Koran et al., 1996), and can sometimes involve self-injury, such as skin damage from excessive hand washing. Although symptoms tend to wax and wane through the course of the disorder, OCD symptoms rarely remit spontaneously. Given the prevalence, course, and functional interference associated with OCD, it

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is important to elucidate variables underlying this disorder.

Recent neurobiological models have postulated that abnormalities in brain activity underlie the etiology of OCD. Specifically, experts implicate dysfunction in the orbitofrontal–subcortical circuits. These circuits are thought to connect regions of the brain that process information involved in the initiation of behavioral responses that are implemented with little conscious awareness (Saxena et al., 2001). The classical conceptualization of this circuitry consists of a direct and an indirect pathway. The direct pathway projects from the cerebral cortex to the striatum to the internal segment of the globus pallidus/substantia nigra, pars reticulata complex, then to the thalamus and back to the cortex. The indirect pathway is similar but projects from the striatum to the external segment of the globus pallidus to the subthalamic nucleus before returning to the common pathway. In patients with OCD, overactivity of the direct circuit purportedly leads to obsessions and compulsions.

Neurobiological theories of OCD are largely derived from results of functional neuroimaging studies. Functional imaging techniques indirectly measure activity levels in specific brain areas and therefore are used to determine whether the structures thought to be involved in OCD are abnormally active in patients with this disorder. Towards this end, researchers have employed positron emission tomography (PET), single photon emission computed tomography (SPECT), and magnetic resonance spectroscopy (MRS) to compare activity levels in multiple brain regions between patients and nonpatients.

¹⁸Fluorodeoxyglucose PET (FDG-PET) is a high-resolution imaging technique that measures cerebral glucose consumption over a period of time (e.g., 30 min) and has been shown to be a highly sensitive indicator of cerebral metabolic rate for glucose (rCMR_{Glu}). Studies utilizing FDG-PET report increased glucose metabolism in the orbitofrontal cortex (OFC), caudate, thalamus, prefrontal cortex, and anterior cingulate among patients with OCD as compared with nonpatients (e.g., Baxter et al., 1987, 1988; Nordahl et al., 1989; Swedo et al., 1989).

Technetium-99m (^{99m}Tc)-hexamethylpropylene-amine-oxime SPECT (HMPAO-SPECT) is a measure of regional cerebral blood flow. Studies utilizing this

technique have alternatively found both increased and decreased blood flow to various brain regions including the OFC, caudate, various areas of the cortex, and thalamus in OCD patients as compared with normal controls (Crespo-Facorro et al., 1999; Lucey et al., 1995, 1997). The fact that studies using PET and SPECT sometimes find differences between individuals with OCD and controls in opposite directions is not necessarily contradictory, and could arise because these methods measure different processes. For instance, a region of the brain could have increased glucose metabolism due to increased activation but have reduced blood flow due to constriction of blood vessels. However, increased glucose metabolism paired with decreased blood flow in a single brain region is unusual and, if replicable, could potentially serve as a neuroimaging marker of OCD with great diagnostic utility.

A handful of studies (Bartha et al., 1998; Ebert et al., 1997; Fitzgerald et al., 2000; Ohara et al., 1999; Rosenberg et al., 2000) have used MRS to evaluate the differences in regional brain metabolites between patients with OCD and healthy controls. MRS measures concentrations of brain metabolites, such as *N*-acetyl-L-aspartate (NAA), combined glutamate and glutamine (Glx), *myo*-inositol (mI), choline (Cho), and creatinine (Cr), in brain tissue. Studies comparing OCD patients with healthy controls using MRS methodology have reported that individuals with OCD showed decreased levels of NAA in the left and right striatum and the medial thalamus, as well as increased Glx in the caudate (Bartha et al., 1998; Ebert et al., 1997; Fitzgerald et al., 2000). MRS involves measuring metabolite concentrations in small focal regions of the brain (voxels) rather than throughout the entire brain at once. As such, it is difficult to compare MRS data with imaging data from techniques such as PET and SPECT. Therefore, although we review the results of MRS studies in a narrative fashion, studies employing this technique are not included in the meta-analysis reported below.

Narrative reviews of over a decade's worth of OCD functional neuroimaging studies generally acknowledge variability in findings (Cottraux and Gerard, 1998; Saxena et al., 2001; Saxena and Rauch, 2000). While informative, narrative reviews are largely subjective and do not systematically quantify the differences between patients and con-

trols across studies. In contrast, meta-analysis is an impartial approach to literature review, in which results of multiple studies are aggregated (e.g., averaged) to quantitatively determine effect size magnitude (i.e., the extent of between-group differences) across studies. This is especially important in fields where many studies employ small sample sizes and where the variability in individual study findings is appreciable.

This article presents a comprehensive meta-analytic review of controlled OCD functional neuroimaging studies published through June 2003. To date, only one meta-analysis of this research has been reported; this was a review by *Aylward et al. (1996)* that included nine studies published between 1989 and 1995. These authors did not find empirical support for metabolic or perfusion dysfunction in the caudate in OCD across studies that used PET or SPECT. However, new research has been conducted in the 7 years since this review, including studies on additional brain regions implicated in OCD. Thus, there is a clear need for further meta-analytic studies.

The goal of this meta-analysis was to weigh the currently available evidence regarding abnormalities in brain activity in patients with OCD. The process of quantitatively combining individual studies is necessary to determine which abnormalities have been found with enough reliability to spawn theories about the pathology underlying OCD. Establishing a foundation of reliability would strengthen conclusions regarding the neurobiological etiology of OCD, if it were demonstrated that clear differences between patients with OCD and controls did indeed exist. For instance, the previous meta-analysis (*Aylward et al., 1996*) revealed that current theories regarding dysfunction in the caudate did not accurately reflect the literature. In order to determine if the activity in certain brain regions in OCD patients is unusual, the activity in these patients must be compared to expected levels of activity. As PET and SPECT, in their common usage, do not have standards for average levels of radiotracer uptake in healthy individuals, a comparisons group of individuals without OCD must be included in a study to determine if levels in the OCD group are unusual. Therefore, this meta-analysis only included studies in which a group of OCD patients was compared with a non-OCD control group.

2. Methods

2.1. Retrieval and selection of studies

Published functional neuroimaging (PET and SPECT) studies comparing OCD patients with non-patient (healthy) control groups were identified through searches of electronic databases and reference lists from publications. Studies containing only a single group (i.e., pre-post treatment) were excluded, because they did not contain an adequate comparison group. This pursuit yielded an initial sample of 23 reports published between 1987 and 2003. From this sample, we excluded four studies because they included previously published data (*Benkelfat et al., 1990; Harris et al., 1993; Horwitz et al., 1991; Mallet et al., 1998*). Six additional studies were excluded for methodological reasons: one (*Adams et al., 1993*) that presented the results in a qualitative format only; one (*Sawle et al., 1991*) that used 15 oxygen PET, which is not directly comparable to FDG-PET studies; and one (*Martinot et al., 1990*), that defined brain regions of interest by functional areas, which is incompatible with the rest of studies that defined regions anatomically. Three studies (*Busatto et al., 2000; Hansen et al., 2002; Kwon et al., 2003*) were not included because they did not report raw data or statistical tests that could be used to calculate effect sizes. Thus, 13 studies remained and were included in the analyses (*Table 1*).

2.2. Variables recorded and coded from studies

The following general information was recorded from the 13 studies: (a) year of publication, (b) lead researcher's affiliation, (c) imaging technique (FDG-PET, HMPAO-SPECT), and (d) type of control group(s) used (healthy controls, patients with psychiatric disorders). Characteristics of participants in each study were recorded as follows: (a) sample/group size, (b) mean age, (c) percent of males in the sample/group, (d) OCD and depression symptom severity as measured by a valid and reliable instrument [e.g., Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), Hamilton Rating Scale for Depression (HAM-D)], (e) duration of symptoms in the OCD group; and (f) length of medication washout period if applicable. Characteristics of the participants in the 13

Table 1
 Characteristics of functional neuroimaging studies of OCD patients and effect sizes by region

Authors	N ^a	Comparison	Imaging technique	Effect size ^b										
				Cortex		OFC	Orb. gyr	Occ. gry	Caudate	HOCN	Parietal	Temporal	Cingulate	Thalamus
				L/R	L/R	L/R	L/R	L/R	L/R	L/R	L/R	L/R	L/R	
Baxter et al., 1987	28	Control, Depressed	FDG-PET	–	–	1.06/0.86	–	–	0.76/0.87	–	–/–	–	–	
Baxter et al., 1988	20	Control	FDG-PET	–	–	1.23/1.21	–	–	1.12/1.05	–	–/–	–	–	
Nordahl et al., 1989	38	Control	FDG-PET	–0.18	1.00	–	–0.39	0.23	–/–	–0.50	–0.14/0.24	–0.42	0.29	
Swedo et al., 1989	36	Control	FDG-PET	0.15	0.30	–	0.30	–0.03	–/–	0.35	0.35/0.51	0.56	–	
Perani et al., 1995	26	Control	FDG-PET	–0.49	–	–	–	–0.02	–/–	–0.49	–/–	1.24	0.60	
Machlin et al., 1991	18	Control	SPECT	1.86	–0.09	–	–	–	–/–	–	–/–	–	–	
Rubin et al., 1992	20	Control	SPECT	1.75	1.87	–	–	–	–0.86/–0.95	1.41	–/–	–	–	
Lucey et al., 1995	60	Control	SPECT	0.37	–	–	0.00	0.31	–/–	0.30	0.61/0.00	–	0.36	
Lucey et al., 1997	30	Control, PTSD, Panic	SPECT	–0.55	–	–	–0.29	–1.03	–/–	–0.37	–0.37/–0.35	–	–0.57	
Crespo-Facorro et al., 1999	36	Control	SPECT	–0.19	–0.82	–	–	–0.66	–/–	0.08	0.17/–0.30	–0.57	–0.83	
Alptekin et al., 2001	15	Control	SPECT	0.26	0.82	–	–0.06	0.38	–/–	–0.01	0.37/0.08	0.95	0.54	
Saxena et al., 2001	44	Control, MDD, OCD+MDD	FDG-PET	0.43	–0.22	–	–	0.30	–/–	–	–/–	–0.13	0.75	
Lacerda et al., 2003	33	Control	SPECT	0.67	0.75	–	0.17	–	–/–	0.05	0.17/0.17	0.41	1.37	

OFC: orbitofrontal cortex; orb. gyr: orbital gyrus; occ. gry: occipital gray matter; HOCN: head of caudate nucleus; b/l/r: bilateral/left/right; SPECT: HMPAO-SPECT.

^a N for combined OCD and healthy control samples, does not include participants in patient control groups.

^b Effect size for the comparison between OCD patients and healthy controls.

imaging studies are presented in Table 2. The majority of the studies excluded patients with a mood disorder (85%). Of the studies included in the analysis, 31% excluded patients with a tic disorder, while 15% included at least one patient with tics.

Regions of interest were chosen for further metaanalysis as follows. Initially, each area examined in each study was coded individually, using the original author's terminology; over 130 separate regions were catalogued in this fashion. Next, a board-certified neuroradiologist and neuroanatomist (JDP) reviewed each article using the available information to create meaningful groupings of these regions that were used for further analysis. This process was quite challenging, as many of the articles only referred to regions by name; later articles displayed diagrams of specific regions, greatly facilitating comparisons and groupings. Groupings included right and left caudate, caudate head, striatum, lentiform nucleus, thalamus, orbital gyrus, orbitofrontal cortex, parietal lobe, frontal lobe, temporal lobe, occipital lobe, amygdala, and hippocampus. Occasionally lateralizing information was not available; in such cases, general groups were created such as "general caudate," "general orbitofrontal cortex,"

"general striatum," and "general thalamus." In addition, inclusive groupings were created that included all measures of an area, such as "caudate inclusive" made up of left + right + bilateral caudate. Measures of specific areas, such as "head of the caudate," were not subsumed into broader regions, such as "caudate." In several studies, the groupings were placed in the midline of the brain, creating groupings such as anterior cingulate cortex, visual cortex, and cerebellar vermis. Finally, "supergroups" were formed by combining the above into groups such as limbic system (anterior cingulate + amygdala + hippocampus) or frontal cortex (left + right frontal lobe + orbital gyrus + orbitofrontal cortex).

As far as technical differences between studies, all SPECT studies were performed under similar experimental conditions, i.e., patients were injected in quiet rooms at rest; half of the studies injected patients with their eyes opened, half with their eyes closed. For PET studies, there was more variability, with most patients injected in quiet rooms during rest. One study had the patient performing a task during injection (Nordahl et al., 1989), and several studies did not specify the injection conditions. Half of the PET studies performed attenuation correction and half did not, or did not specify whether they did. Half of the PET studies performed injections with eyes open; half did not specify or performed injections with eyes closed. Overall, the authors felt that the imaging protocols for each modality (SPECT and PET) were similar enough that valid comparisons could be performed.

2.3. Effect size computation

In each study utilizing PET and SPECT imaging techniques, the dependent variables of interest were the baseline neuroimaging values of the OCD and control groups. Although each technique indirectly measures localized brain functioning, the biological processes that are measured differ across techniques. For example, whereas PET measures cerebral glucose metabolic rates, SPECT measures regional cerebral blood flow. In addition, for a given imaging modality (PET or SPECT), differences in technique can potentially cause considerable variability in numerical results. Moreover, studies utilizing identical imaging techniques might have procedural and/or equipment idiosyncrasies that differ from study to study yet are

Table 2
Characteristics of participants in functional neuroimaging studies of OCD patients

Study characteristic	Number of studies	Mean	S.D.	Range
N of OCD group	13	15.23	6.95	8–30
N of healthy control group	13	15.85	7.30	6–30
Age of OCD group (years)	13	32.89	3.46	26–38
Age of control group (years)	13	32.36	3.86	28–40
Percent males in OCD group	13	56.39	18.28	27–100
Percent males in control group	13	51.02	22.20	5–100
Y-BOCS score of the OCD group	9	24.23	2.07	19.70–26.46
HAM-D score of the OCD group	6	11.40	4.33	7.50–19.00
HAM-D score of the control group	2	0.92	0.31	0.70–1.14
Duration of OCD symptoms (years)	6	14.83	4.44	7.55–19.90
Minimum washout period	10	4.9	6.77	2–24

consistent between groups within a given study. Therefore, we expressed between-group differences on each dependent variable in each study in terms of Cohen's d , which is a standardized measure of effect size (i.e., the difference between the OCD group and the control group). Cohen's d was computed by subtracting the control group's mean from the OCD group's mean and dividing this difference by the standard deviation pooled from both groups. By computing effect size in this manner, we achieved greater statistical control over subtle background variables, because these variables did not differ between groups within the same study.

The 13 studies using PET and SPECT techniques included 17 comparisons between OCD patient groups and control groups. Multiple control groups were utilized when, within the same study, researchers compared OCD patients with healthy individuals as well as a group of patients with another clinical disorder (e.g., depression). Differences between OCD and control groups were usually assessed in multiple brain regions. As described above, we computed effect sizes for each brain region reported in a study. We included all comparisons (significant and non-significant) that were presented in the individual articles. The vast majority of articles, 85%, reported all analyses conducted, including those that were nonsignificant.

With one exception (Alptekin et al., 2001), we calculated effect sizes directly from the means and standard deviations reported in the studies. When this information was not available, results of other statistical tests (e.g., values of t) were used (Ray and Shadish, 1996). If incomplete information for calculation of an effect size was presented for nonsignificant analyses, we conservatively estimated the effect size to be 0 (this was necessary for one study). To reduce the potential for knowledge of a study's results to bias the coding of its characteristics, we calculated effect sizes only after the coding of all studies had been completed. Cohen (1977) suggested that effect size magnitudes of 0.20, 0.50, and 0.80 correspond to small, medium, and large effects, respectively. Table 1 presents the effect sizes derived from each study.

Following the methodology of Aylward et al. (1996), we meta-analytically combined results from PET and SPECT studies in our review. As mentioned above, PET and SPECT measure distinct biological

processes that may or may not be directly related. Specifically, increases in glucose metabolism may be associated with increased, decreased, or unchanged cerebral blood flow. Therefore, simply combining the results of PET and SPECT studies may erroneously obscure consistently meaningful findings. Specifically, if PET studies consistently find *increased* activity in the caudate nucleus of OCD patients (i.e., positive effect sizes) and SPECT studies consistently find *decreased* activity (i.e., negative effect sizes), then a mean effect size derived across studies using both imaging techniques might be close to zero and might be misleading. Therefore, in our review, we first aggregated the results of PET and SPECT studies separately and then combined them in a manner so that sign was not indicative of increased or decreased activity in OCD patients compared with controls but merely of a *difference* in activity level. In this method, the relative signs of the effect sizes *within* each technique (PET or SPECT) were preserved, because removing the signs at this point would clearly artificially reduce the variability in the findings within each technique. Finally, we also analyzed data from PET and SPECT studies independently, which allowed for exploration of how differences between PET and SPECT results may illuminate the pathogenesis of OCD.

3. Results

Our meta-analytic results are presented in the following sequence: first, we examined overall effects by computing the mean effect sizes across all comparisons between OCD and control groups. Second, we calculated effect sizes for different brain regions hypothesized to be involved in OCD. As discussed above, we combined effect sizes from PET and SPECT studies because our aim was to examine the extent of *differences* in brain activity between OCD patients and controls regardless of the direction of these differences. Therefore, the mean effect sizes presented below (Table 3) represent the absolute value of the combined mean effect size derived from PET studies and that derived from SPECT studies. For example, if the effect sizes derived from two SPECT studies were 0.20 and -0.60 (mean = -0.20), the absolute value (0.20) was averaged (weighted by the

Table 3
Regional effect sizes for PET and SPECT studies

Brain region	N	Effect size (<i>d</i>)		
		<i>M</i>	S.D.	95% CI
Frontal cortex	11	0.39	0.80	−0.15, 0.92
OFC	7	0.45	0.84	−0.25, 1.15
Left orbital gyrus	2	1.15*	0.12	0.07, 2.22
Right orbital gyrus	2	1.04	0.25	−1.20, 3.26
Occipital gray	6	0.05	0.26	−0.23, 0.32
Caudate	8	0.18	0.48	−0.22, 0.59
Left head of caudate	3	0.91*	0.19	0.45, 1.38
Right head of caudate	3	0.96**	0.09	0.74, 1.18
Parietal	9	0.22	0.54	−0.18, 0.65
Left temporal	7	0.17	0.33	−0.14, 0.47
Right temporal	7	0.17	0.25	−0.07, 0.40
Anterior cingulate	7	0.29	0.69	−0.35, 0.92
Thalamus	8	0.31	0.71	−0.28, 0.91

* $P < 0.05$.

** $P < 0.01$.

number of observations) along with a similar absolute value derived from PET studies. As is illustrated in this example, the relative effect sizes were maintained when aggregating the results *within* imaging technique. Specifically, the absolute value of the mean from the PET studies was then combined with the absolute value of the mean from the SPECT studies, with each mean being weighted by the number of observations.

Because some studies compared OCD patients with both healthy controls and patients suffering from other psychiatric disorders, we computed separate effect sizes for each type of comparison group. The mean effect size for comparison to health controls was moderate, mean=0.34 (S.D.=0.53), and significantly differed from no effect, $t(12)=2.27$, $P < 0.05$. Comparison to groups with other psychiatric diagnoses was small, mean=0.23 (S.D.=0.43), and not significant. A t -test indicated that these effect sizes did not differ significantly from each other, $t(15) < 1$. As each study that provided a comparison to patients also compared the same OCD group with healthy controls, only the comparisons to healthy controls were included in the following analysis, because including multiple comparisons to the same group would violate the independence of data points.

Table 3 presents the mean effect sizes for each brain region. As can be seen, on average, studies imaging the orbital gyrus found a large difference between OCD patients and controls. More specifi-

cally, although this difference was of similar magnitude in both the left and the right orbital gyrus, only the former differed significantly from no effect. However, with only two studies measuring these areas, these analyses suffered from low power. The mean effect size for the OFC (a larger region that includes the orbital gyrus) was not significantly different from no effect.

Effect sizes derived from studies of the caudate nucleus indicate that the difference in activity for this region between OCD patients and controls was small and not significantly different from no effect. However, three studies that examined the more finely defined head of the caudate nucleus reported a large and significant difference between OCD patients and controls, t 's(2)=8.47 and 18.90 for the left and right, respectively, P 's<0.05. Two of these three studies employed PET and yielded mean effect sizes of 0.94 and 0.96 (S.D.=0.26, 0.13) for the left and right sides, respectively. The remaining study employed SPECT and reported effect sizes of −0.86 and −0.95, respectively. Thus, whereas PET studies found greater activity among OCD patients relative to controls, the SPECT study found greater activity among controls.

No significant mean effect sizes were found for the remaining brain regions. We also analyzed effect sizes derived from studies using PET and SPECT scans separately for those brain regions that had been studied with each technique. These results were generally similar to those reported above, although some differences were no longer significant due to the lack of power. However, when examining the PET studies, the effect size for the right caudate, mean=0.28 (S.D.=0.05), also significantly differed from no effect, $t(2)=9.39$, $P < 0.05$.

4. Discussion

Although the OCD neuroimaging literature has been thoroughly reviewed qualitatively (Saxena et al., 2001), no broadly inclusive quantitative reviews have been conducted. Meta-analysis (i.e., quantitative review) offers the advantage of standardizing the results of studies and then objectively aggregating these results to determine the overall magnitude of differences in brain activity between OCD patients and controls across the published literature.

Our meta-analytic results partially support the conclusions drawn from previous narrative reviews (e.g., Saxena et al., 2001) that point to structures in the OFC, caudate nucleus, and thalamus. In particular, the orbital gyrus and the head of the caudate nucleus emerged as the areas in which reliable differences are present between patients with OCD and controls. However, significant effect sizes were not found in the more inclusive regions of the caudate and the OFC. This pattern of results suggests that there are differences between patients with OCD and control subjects, and that examining small focal regions of interest is necessary to detect these differences. Such differences may be obscured when larger, more global regions, such as the caudate, are imaged, because the activity in the focal region is averaged with nearby brain regions. Other areas postulated to be involved in OCD, such as the thalamus and the anterior cingulate, did not demonstrate reliable differences between patients with OCD and healthy control participants. Finally, in the studies of the head of the caudate, although the PET studies found greater activity in patients with OCD, the SPECT study found decreased activity.

In discussing the implications of our results for neuropsychiatric models of OCD, the state of empirical evidence for such models deserves comment. Saxena et al. (2001) have elucidated direct and indirect pathways hypothesized to be involved in OCD, concluding that “functional neuroimaging data clearly support pathophysiological theories” (p. 93). However, we argue that such a strong assertion is premature. For example, much of the knowledge of the frontal–basal ganglia–thalamo–cortical pathways is derived from animal studies, specifically from primates (Saxena et al., 2001), with little work evaluating these pathways in humans. Although there are similarities with primates, human brains are more complex and have additional cortical areas (see Kandel et al., 2000). Furthermore, Saxena et al. describe how studies using very different imaging techniques support “elevated OFC activity in the untreated state” (p. 91), implying that the *neural activity* (i.e., the number of neuronal action potentials) is increased. However, it cannot be assumed that increases in rCBF are *directly* linked to increased neural activity in a particular region, or to “decreased release of excitatory neurotransmitters such as glutamate” (p. 96), as there is no direct scientific evidence of this in humans. Finally, given that neurobiological

theories of OCD were *derived from* studies finding differences in the caudate and orbital gyrus, replication of these findings should not be construed as adding additional support to these theories. This is especially important given that the significant results of this meta-analysis come primarily from two studies (Baxter et al., 1987, 1992). The studies by Baxter et al. are the only ones to examine the orbital gyrus, and there is only one additional study that examines the head of the caudate nucleus. Therefore, with one exception, the literature following the initial positive findings by Baxter et al. has not found any reliable differences in brain functioning between patients with OCD and healthy controls. This conclusion, of course, is limited to the studies included in this meta-analysis and excludes other promising techniques, such as MRS.

Indeed, our results indicate reliable differences between OCD patients and controls in radiotracer uptake in the head of the caudate nucleus that are suggestive of increased activity in OCD patients. Although these findings indicate that such brain regions are in some sense *involved* in OCD, the designs of existing studies do not permit one to conclude that (a) the differences represent *abnormalities* in functioning or (b) the differences are related to the *cause* of OCD. First, differences found in neuroimaging studies may merely represent different activation levels of intact, normally functioning neural systems, such as those involved in worry, which are engaged to a greater amount in patients with active OCD than in control individuals or those with treated OCD (Salkovskis, 1996). Second, to infer causation, studies would need to be conducted in which brain activity in certain areas was experimentally manipulated, resulting in the development of OCD. In the absence of such prospective experimental manipulations, statements regarding OCD and neuroimaging findings should be limited to the conclusions allowed by correlational data. Specifically, there are three possible explanations for the current findings: (1) alterations in functioning in certain brain regions cause OCD; (2) OCD causes alterations in functioning as observed in certain brain regions; or (3) a third variable causes both phenomena. Presently, the data reviewed above do not support one explanation over another.

An explanation of the apparent discrepancy in the direction of differences in FDG-PET and SPECT findings in the head of the caudate can be found by

examining the details of the tracers employed with each imaging technique. FDG is a glucose analog that is rapidly taken up into neurons and astrocytes using the active glucose transporter. As such, FDG serves as a measure of the regional cerebral metabolic rate of glucose (rCMRglu). HMPAO, used in SPECT, is a lipophilic compound that rapidly crosses the blood–brain barrier, accumulating in neurons and astrocytes in concentrations proportional to regional blood flow (Slosman et al., 2001). As such, HMPAO serves as a measure of regional cerebral blood flow (rCBF).

It has generally been assumed that there is a dynamic coupling of rCMRglu and rCBF; that is, as glucose utilization increases, so too does the blood flow to increase glucose supply and to carry away metabolic waste products. However, recently, examples of rCMRglu–rCBF uncoupling have been documented in the literature (for review, see Conca et al., 2000). Such uncoupling can be seen in Alzheimer’s disease (e.g., Herholz et al., 2002; Slosman et al., 2001), epilepsy (e.g., Gaillard et al., 1995; Lee et al., 2001), chronic fatigue syndrome (e.g., Abu-Judeh et al., 1998), and depression (e.g., Conca et al., 2000). Furthermore, our own clinical observations suggest decreased rCBF and increased rCMRglu in the basal ganglia of patients with Parkinson’s disease. The explanation for such uncoupling may lie in a recent study examining the cellular mechanisms of HMPAO uptake in which Slosman et al. (2001) found that HMPAO retention within cells can be decreased with certain metabolic alterations despite normal blood flow (Ahn et al., 1994; Neirinckx et al., 1988; Slosman et al., 2001). Perhaps, in OCD, such “metabolic alterations” lead to more rapid washout of HMPAO and thus may not reflect actual decreased rCBF when OCD patients were scanned. Finally, it is possible that alterations of the blood–brain barrier could disrupt the trapping of HMPAO, thereby producing the noted discrepancies between SPECT and PET results.

A direction for future study in the imaging of OCD involves the use of MRS, a technique that measures concentrations of brain metabolites. Most MRS studies in OCD have focused on NAA (a marker of neuronal viability) and Glx (which includes compounds that are involved in excitatory neurotransmission). MRS studies comparing OCD patients with healthy controls suggest that OCD is associated with decreased levels of NAA in the left and right striatum

and the medial thalamus, as well as increased Glx in the caudate (Bartha et al., 1998; Ebert et al., 1997; Fitzgerald et al., 2000). While promising, MRS is not an imaging technique and therefore is limited to sampling focal brain regions rather than the entire brain at once (as is done for PET and SPECT). As such, it is prone to sampling errors, i.e., gathering spectra from normal brain areas while missing abnormal brain areas. No studies performed to date with adults have specifically performed spectroscopy in the head of the caudate nucleus and orbitofrontal cortex, areas of abnormality suggested by PET and SPECT data; this is a potential area of future research using the MRS technique.

A relatively new MR technique called magnetic resonance spectroscopic imaging (MRSI) may provide a better alternative to single voxel MRS. This technique acquires spectroscopic data from an entire brain slice at a time; thus, it is a technique better suited to screening the brain when the location of the abnormalities is unknown. In most clinical situations, a single MRSI slice takes longer to acquire than a single MRS voxel and has more artifacts, but newer techniques and very high field magnets (i.e., 3 Tesla or more) make MRSI a more viable alternative to MRS.

Although, meta-analysis is a valuable tool for consolidating results from multiple individual studies, this review has some important limitations, many of which arise from characteristics of the primary studies under review. First, determining the comparability of regions of interest between studies was difficult because most of the studies did not illustrate their exact regions of interest on anatomical images. As such, we cannot be certain that the results we combined from different studies actually measured the same brain region. Moreover, some studies were not included due to their use of valid but incompatible methods to define regions of the brain (Busatto et al., 2000; Hansen et al., 2002; Kwon et al., 2003; Sawle et al., 1991). Attempts to standardize methods or to provide information to facilitate interstudy comparisons would help the field advance. Second, the small number of studies available limited the reliability of our meta-analytic findings. Despite these limitations, meta-analysis is a critical step in the development of a field of research by integrating previous findings and directing future endeavors. In summary, the results of this analysis suggest that differences between patients

with OCD and controls have been found reliably in the orbital gyrus and the head of the caudate nucleus.

Acknowledgments

We thank Brian Mullan, MD, for his insights into the mechanisms of rCBF and rCMRGlucose uncoupling. This study was supported by an Obsessive–Compulsive Foundation grant.

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