Brain imaging

Obsessive Compulsive Disorder (OCD) is a condition characterized by recurrent intrusive, often repugnant, and alwaysanxiety-ridden thoughts and images and by sets of ritualized behaviors performed compulsively by the sufferer in an attempt to allay the anxiety. The compulsive behaviors typically provide little relief, however, and the sufferer remains relegated to an anxious and painful daily experience.

Thus, the patient who drives over the same speed bump each morning may find it impossible to relieve oneself of the concern that one may have, on a particular morning, driven over a pedestrian instead, and one is compelled to circle the block in a ritualized fashion searching for a crushed body in the street. While the sufferer is able to acknowledge the perverse and senseless nature of the rituals, this insight alone fails to relieve the experience of helplessness (Pauls et al. , 1995).

As has been true of most psychiatric disorders, traditional etiologic explanations have been based on psychoanalytic findings and constructs. Formulations of the illness based on cognitive processing models represent a more recent development. Still more recently, a significant reconceptualization of obsessive-compulsive symptomatology has followed the development of modern functional imaging technologies, and a biologically-oriented and brain-centered view of OCD has emerged in light of the substantial findings from the last decades.

The most popular brain theory to date explains the pathogenesis of OCD as an imbalance in the action of a pair of interrelated neural circuits which, under normal circumstances, maintain one another in a state of functionally balanced tone. It may be parenthetically added that, to the extent these

brain data are themselves understood, it has become possible to evaluate psychological theories of OCD in functional terms (Robinson et al. , 1991). The neurobiology of OCD has been a subject of research interest for several decades, with the disorder having become increasingly formulated as a neuropsychiatric illness.

Modern neuropsychiatric hypotheses have been guided by data having its origins in data derived from the direct study of OCD patients using newly developed non-invasive brain imaging techniques. Significant findings from this area of inquiry are summarized in the following pages. Background to OCD OCD symptomatology has been reported among patients with closed head trauma to the basal gangliar structures and among those with basal ganglia lesions demonstrable subsequent to carbon monoxide poisoning and to wasp sting (McKeon, 1984).

Symptoms have additionally presented as a clinical feature both of striatal necrosis and frontal lobe lesion (Siebyl et al, 1989). Thus, the initial background of data around OCD has implicated the basal gangliar structures, particularly the striatum, and, to a lesser extent, the frontal lobe. Imaging studies of the living brain are generally divisible into two distinct categories, those representing morphologic or structural abnormality, on the one hand, and those representing disturbance of function at the cellular or metabolic levels, possibly with only very small or wholly undetectable changes in morphology, on the other.

The distinction is important: while investigation at the level of structure and morphology will reveal atrophic change or gross pathology (eg. , tumor, trauma, etc. ,) investigation at the metabolic level provides a window directly

into what has been termed, in traditional discourse, " functional mental illness. " That is, structures which have retained their morphologic integrity may nonetheless be shown to be functioning in metabolically hyperactive or hypoactive state relative to normal. In the interest of maintaining this important distinction, studies deriving from the two imaging modality groups are reviewed here separately.

Structural brain imaging studies Luxenberg, Swedo, Flament et al. (1989) used quantitative Computed Tomography (qCT) to analyze the morphologic volumes of various brain structures believed key in OCD. Clinical subjects withchildhood-onset OCD were selected on the basis of active and unabated symptomatology of at least one year during their illness. While depressive symptomatology with onset after obsessional illness was not an exclusion criterion, none of the patients was depressed at the time of the qCT examination.

The researchers found that mean caudate nucleus volume in the patients was significantly less than that of control subjects. No other significant brain abnormalities were found. Behar, Rapoport and Berg, et al (1984), report on the administration of CT scans and neuropsychological test measures to 16 adolescents with OCD and 16 matched controls. Patients were found to have significantly increased ventricular size (relative to whole-brain volume) and to show spatial-perceptual deficits on theMoneyRoad Map Test of Directional Sense.

The Money Map Test uses a simulated street map with a route indicated by a dotted line. The subject traverses the route and indicates a right or left turn at each choice point. Near the midpoint of the examination the subject is

required to mentally rotate himself in order to reverse his own right-left reference. Patients with frontal lobe lesions have been reported to do poorly on this task. Subjects' ventricular size and neuropsychological test findings were not significantly correlated, however, and the researchers suggest that significant co-morbidity within the patient sample led to unexpected results.

In fact, the patient sample had been selected on the basis of its extraordinary psychiatric symptomatology: " It is possible that (the OCD subjects) are atypical in that adult patients commonly report being able to conceal their symptoms after clear onset in childhood" (Behar, Rapoport and Berg, et al. , 1984, p. 365). The results of the Behar study are also inconsistent with those of Insel and associates (1983), who report neither ventricular enlargement on CT brain imaging nor significant neuropsychological deficits on the Halstead-Reitan battery of neuropsychological tests in 18 adult OCD sufferers.

Confirmation for ventricular enlargement is likewise not observed in the present majority of structural brain studies. Garber, Ananth, Chiu, and colleagues (1988) performed Magnetic Resonance Imaging (MRI) scans on 32 patients meeting the DSM-III criteria for OCD in an investigation of the caudate and ventricular findings. Subjects were judged free of psychopathology other than OCD on the basis of psychiatric testing and evaluation, and severity of OCD symptoms was rated at the time of MRI by means of the Yale-Brown Obsessive-Compulsive Scale.

MRI creates highly detailed anatomical images using radiofrequency resonance signals elicited from the hydrogen atoms of tissue under study. The technique produces structural images which are in many respects (eg. ,

spatial resolution) quite superior to those provided by CT (Garber et al. , 1988). Further, a technical routine known as " spin-lattice relaxation time" (or Tl), in which a summary measurement of the time required for protons excited within host molecules to relax to baseline is taken as a direct measurement of the mobility of water protons in membranes and fluids.

In the study with OCD patients, Behar and colleagues discovered significantly lengthier corrected Tl values for clinical subjects relative to controls in the lenticular nuclei and the right frontal lobes white matter. Because of the high degree of heterogeneity in both samples, subgroups within the clinical sample were developed on the basis offamilyhistory and medication status and analyzed against one another. No between group differences were noted based on medication status.

Patients with family histories of OCD differed from those with no such histories in the anterior cingulum, showing significantly briefer Tl values. No gross structural differences were specific to the OCD group. Garber and colleagues (1988) ascribe the altered Tl include to subtle atrophy in the right frontal cortex or diminished blood flow to this region, corresponding to a decline in frontal cortical metabolism. Involvement is also suggested on the parts of the cingulate gyms and lenticular nuclei.

These areas are components of frontal-limbic pathways that may mediate the symptoms of obsessive-compulsive disorder; surgical alteration of the relationships among structures within these pathways have produced symptomatic improvements. Moreover, the authors propose that hereditary influences on the illness may be most directly expressed in the cingulate

region. The implication of the frontal lobes and cingulate gyms in OCD suggests abnormalities in cortical-striatal-thalamic-cortical circuits.

Robinson, Wu, and Munne et al. (1995) used MRI in a structural volumetric analysis of selected brain regions within or adjacent to these circuits in 26 patients with OCD (DSM-VI-R criteria). While subjects were screened for a number of exclusionary criteria, co-morbidity withdepressionwas not among these. Twenty-six screened normal control subjects were matched to the OCD patients. In results which directly contradict those of Scarone, Colombo, and Ambruzzese, et al.

(1992), in which right caudate nucleus size was found by MRI to be increased in patients with OCD, Robinson and colleagues report a significantly diminished morphometic volume for the caudate nuclei bilaterally. These findings are consistent with those of Luxenberg et al. (1988), described above, in which morphometric analysis by CT indicated significantly reduced caudate nucleus volume in patients with OCD. Study by Alyward, Schwartz, and Machlin et al. (1991) report no statistically significant differences between OCD and normal subjects on MRI studies of caudate volume.

Their report demonstrates a direct correlation in patients with OCD between the putamen volume and the Global Severity of psychopathology score developed by the National Institute of MentalHealthas well as between the caudate volume and the Hamilton Depression Rating Scale score, but found no correlations with the Y-BOCS total score or with the obsessions or compulsions subscore on this instrument. Curiously, however, division of the patients with OCD into subgroups based on a history of depression did not demonstrate a significant difference.

Imaging measures were similar between subjects with and without medication histories. There was no evidence of ventricular enlargement in patients with OCD. As a group, studies of brain morphology and structure have returned substantially inconsistent findings in OCD; particularly differing are reports on the caudate nucleus and striatal region. Different study methods and small sample sizes may account partially for these discrepant findings and represent problems which must ultimately be overcome before a valid consensus can be reached.

The significant prevalence of OCD symptomatology within neurologic populations and its high co-morbidity with depression contribute to the potential for heterogeneity in OCD samples (Pauls, 1995). The Alyward finding of increased caudate volume in OCD subjects with higher depression scale scores, but not among OCD subjects at large, not only reveals the heterogeneity of the disorder but illustrates the necessity of rigorously defining sample parameters before meaningful comparison and replication may be undertaken.

Such rigor has not yet been sufficiently applied in structural imaging studies. Notwithstanding these issues, the question of a chronic degenerative process with resultant caudate diminution over time is suggested by certain of the data, in particular light of the fact that most of the OCD patients studied by the Robinson and Luxenberg groups were longtime sufferers. Longitudinal follow-up studies would be needed to determine whether caudate volume changes in OCD are progressive.

Additionally, because structural brain imaging modalities are sensitive only to pathology which has resulted in physical change in tissue, they omit

consideration of metabolic or functional change. The following section offers a discussion of imaging findings based on functional processes of the brain; modalities of this type substantially enlarge the data available from structural imaging alone. Functional brain imaging studies

Functional brain imaging refers collectively to that set of techniques used to derive images reflecting biochemical, physiologic, or electrical properties of the central nervous system (Devous, 1995). The most developed of these techniques have in common the registration of such data in digitized maps which thus represent visually to the diagnostician or researcher the relative metabolic activations among brain structures of interest (provided that the dimensions of these lay within the spatial resolution capability of the particular technique).

The maps can typically be rendered in any standard anatomical plane for the sake of further clarifying these metabolic relationships. Positron Emission Tomography (PET), so named for the species of radioactive decay on which it depends, and the more economical and widely available modality of Single Photon Emission Computed Tomography (SPECT) each registers in a digitized functional map relative regional metabolic activations for any given brain state (eg. , under challenge, during active symptomatology, at rest, and so forth).

SPECT maps the distribution of a radioactively labeled pharmaceutical administered intravenously administered to a subject and typically designed to integrate itself into brain blood flow processes in a manner correspondent to the relative activations of the latter (Devous, 1995). The emission of gamma radiation from the agent after it has been allowed to incorporate

itself into brain tissue enables the subsequent mapping of blood perfusion densities across cortical regions with the use of SPECT imaging hardware.

Blood flow and metabolism are tightly coupled within the brain under most normal and pathologic circumstances, and therefore inferences about neurometabolism are accurately informed by measures of relative blood flow (Devous, 1995). One of the more popular radiopharmaceuticals for such blood flow mapping is referred to generically as " HMPAO," an acronym for the chemical structure of the agent. Bound to this chemical structure is the radioactive element Technetium-99m, which is favored as an imaging isotope because of its half-life and energy characteristics (Devous, 1995).

Two facts of brain function are pertinent to any review of imaging studies in this area. The first of these requires the reader to keep in mind that an activated cortical region may be inhibitory or excitatory. In the basal ganglia system, for example, excitatory and inhibitory input sf contribute mutually to a functionally balanced neural tone. The second fact is closely related: A system which lies efferent to the hypermetabolic one will correspond to the nature of this input: Inhibitory or excitatory.

Notwithstanding the complexities connected to image interpretation, the functional modalities have permitted the development of a more conclusive body of evidence regarding brain function in OCD than has been the case with structural imaging modalities. A consensus has emerged around increased activity in the right orbitofrontal cortex (OFC). Less agreement exists withrespectto the role of the striatum and associated basal gangliar structures. Rubin, Villanueva-Meyer, and Ananth et al.

(1995) studied ten adult male patients with OCD and ten age-matched adult male normal controls using SPECT Patients with OCD had significantly increased uptake of the metabolic tracer radionuclide in the high dorsal parietal cortex bilaterally, in the left posterofrontal cortex, and in the orbital frontal cortex bilaterally The patients also had significantly reduced tracer uptake in the head of the caudate nucleus bilaterally, but not in the putamen or thalamus, consistent with the hypothesized reduction of caudate nucleus activity in OCD. Baxter, Schwartz, Maziotta et al.

(1992) reports findings which conflict with those of Rubin and co-workers on the activation of the caudate nuclei. In the Baxter study, ten non-depressed OCD patients were compared with ten age- and gender-matched normals using PET scans. Subjects were screened for current co-morbidity with major depression, bipolar disorder, cyclothymic disorder and dysthymia. All but two subjects had suffered from depressive disorders in the past. Comparison of the scans indicated that patients with OCD had significantly higher overall glucose metabolic rate values than normal controls.

Orbital gyri were significantly higher in metabolic activation bilaterally, as were the bilateral heads of the caudate nuclei. As described, Rubin et al. (1995) report diminished metabolic activity in the head of the caudate nuclei bilaterally. Machlin, Harris, and Pearlson, el al. (1991) found elevated blood flow in the prefrontal cortex and cingulate (termed the medial-frontal region) in ten OCD patients studied with SPECT relative to a matched sample of eight normals.

Several other well-conceived functional imaging studies implicate the structures of both the Papez circuit and Modell's hypothesized fronto-striatal-

pallido-thalamic-frontal loop. Swedo et al. (1989) compared 18 OCD patients and 18 normals using PET, and while no whole-brain glucose metabolic differences were found between groups, the left orbitofrontal, right sensorimotor, and bilateral prefrontal and anterior cingulate regions were notably higher in adults with childhood-onset OCD. Within this group, a positive correlation emerged between glucose uptake in the prefrontal and orbitofrontal regions and state measures of anxiety.

In addition, responders to treatment with clomipramine were distinguishable from non-responders on the basis of regional changes in the right cingulate and right orbitofrontal regions, with response failures evincing significantly higher pre-therapy activations. Baxter et al. (1992), in a series of studies with a total of 24 adult patients with OCD, found increased FDG uptake in the cerebral hemispheres overall, and in the orbital gyri and caudate nuclei in the OCD group as compared to normal controls.

Rubin, et al (1995) used SPECT imaging and found elevated uptake in the dorsal parietal cortex bilaterally, the left posterofrontal cortex and the OFC bilaterally. The group also found decreased uptake in the heads of the caudate nuclei bilaterally. Two paired comparisons have been made of OCD subjects before and after symptom aggravation. Rauch et al. (1994) used oxygen-15 labeled carbon dioxide PET to study individually tailored provocative stimuli in order to provoke symptoms in eight patients with OCD.

Paired comparisons pre- and post-challenge yielded an increase in regional Cerebral Blood Flow (rCBF) in the right caudate nucleus, left anterior cingulate cortex, and also bilaterally in the OFC subsequent to challenge. McGuire et al. (1992) studied four OCD patients during actual exposure to

contaminants in a pattern tailored individually to produce successively greater degrees of anxiety. rCBF was found to increase in the OFC, neostriatum. globus pallidus, and thalamus in relation to the urge to perform compulsive movements.

These two paired comparisons of patients pre- and post-challenge provide a unique opportunity to examine differences between a resting and an obsessional state in the same patient during a brief period. Further, such an examination sheds light on the manner in which inconsistencies among functional imaging studies may be due to variations in the mental state of obsessional patients at the time of the imaging studies. While the architecture of the anxiety challenge varies considerably between the Rauch and McGuire protocols, it remains nonetheless somewhat disappointing that more consistent findings are not elicited in the paired comparisons.

In these studies, as in the literature more generally, substantial disagreement exists on the response of the cingulate cortex and caudate nuclei. It is noteworthy, however, that the two paired challenge studies concur with respect to the hyperactivated state of the OFC. It is on the issue of striatal, specifically caudate, activation and morphology that most disagreement exists across both the structural and functional brain imaging studies. It is possible to speculate on the cause of this inconsistency: Caudate metabolism may be a state, rather than a trait, marker in OCD.

It may also be that pathology in this region is progressive: Subjects with damaged striatal mechanisms may, for instance, manifest a hypermetabolic condition in the region for some lengthy period before an atrophic process ultimately begins and results in the opposite finding, hypometabolism and

volumetric diminution over a period of time. Uniformity across subject samples in terms both of length and history of illness and co-morbidity with other pathology is therefore essential to further investigation of this region in OCD. Conclusion

The two categories of imaging study at times assume roles along a continuum of pathological severity or etiology. For example, a degenerative change in tissue density or overall size and shape may have developed only after a lengthy period of metabolic dysregulation. An imaging technique sensitive only to morphology would pick up such pathology only at a relatively late stage in its development. Early changes, those occurring at the metabolic level, would be visualized only by means of a functional imaging technique. On the issue of orbital and frontal activation there exists substantial agreement.

Although a great deal of data implicates these structures, it is not yet possible to demonstrate which specific obsessive-compulsive symptoms are related to the observed abnormalities in these neuroanatomic regions or what specific role the region plays in the neuropsychology of the illness. References Alyward E. H, Schwartz J, Machlin S, Pearison G. D. (1991). Bicaudate ratio as a measure of caudate volume on MR images. American Journal ofNeuroradiology, 12, 1217-1222. Baxter L. R. , Schwartz J. M. , Bergman K. S. , Szuba M. P. , Guze B. H. , Mazziotta J C , Alazraki A, Selin C. E. , Phelps ME (1992).

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