The principal features of obsessive-compulsive disorder are obsessions, recurrent intrusive thoughts or images, and compulsions, recurrent stereotyped behaviours which result from obsessions. Patients usually try to resist these phenomena and recognise that they are self-generated. Freud1 saw them as manifestations of repressed sexual and aggressive impulses, whereas rituals were subsequently regarded as learned behaviours that served to reduce anxiety.2 In recent years, data from a diversity of sources have also made it possible to consider obsessive-compulsive phenomena in terms of the anatomy and chemistry of the brain.

Clues to the location of brain regions which might be involved in the pathophysiology of obsessive-compulsive disorder first emerged from independent descriptions of the mental state in several neurological diseases. Thus obsessions and compulsions have been noted in post-encephalitic parkinsonism,3 Huntington's disease,4 Sydenham's chorea,5 Gilles de la Tourette's syndrome,6 and lesions of the neostriatum,7 globus pallidus,8 and frontal lobes.9 A common feature of these conditions is that all are thought to involve pathological changes in the basal ganglia, or the inferior prefrontal cortex, or both.

Just as certain conditions with a probable “organic” basis can be associated with obsessional features, detailed clinical examination in obsessive-compulsive disorder can disclose a variety of “soft” neurological signs. This is particularly evident in patients with the syndrome of obsessional slowness, who show hesitancy in movement initiation, a loss of motor fluency, and abnormalities of gait,10 but even patients with typical obsessive-compulsive disorder may exhibit involuntary movements, mirror movements, and disturbed fine motor coordination.11

Soft signs seem to be commoner on the left side,12 a finding consistent with data from neuropsychological studies, which have identified deficits of non-verbal functions, thus implicating the non-dominant hemisphere. The most common findings have been of impaired visuospatial performance11-14 and difficulties with shifting of cognitive set15; impaired performance on non-verbal memory tasks has also been described.14,15

Obsessive-compulsive disorder is one of the few psychiatric conditions for which neurosurgery is still considered, albeit rarely, in severe cases resistant to behavioural and pharmacological treatment. As double blind trials are difficult to justify on ethical grounds, evaluation of the effectiveness of neurosurgical intervention depends on data from uncontrolled follow up studies. Stereotactic subcaudate tractotomy, with yttrium implants, is the main technique employed in the United Kingdom, and results in “recovery” in 50–60% of patients.16,17 “Limbic leucotomy,” combining lesions of subcortical prefrontal connections and of the cingulate fasciuli, is less often used, but has been associated with success rates of 70–89%.16,17 Thermocagulation of the cingulate fasciculi alone (cingulotomy) is employed in the United States, and leads to improvement in 25–30% of patients.18 Although the total number of psychosurgical operations performed annually in the United Kingdom (for any condition) has fallen from 70 in 1979 to around 20,16,19 the apparent effectiveness of these procedures provides clues to the location of brain areas which may mediate obsessional symptoms: all involve interruption of fibres from the inferior prefrontal or cingulate cortex, implicating these regions in the pathophysiology of obsessive-compulsive disorder.

Surprisingly, obsessive-compulsive disorder is one of the psychiatric conditions which has been most studied with functional neuroimaging techniques (SPECT and PET). This partly reflects the striking and relatively consistent results that emerged from early studies, in contrast with initial work in other psychiatric disorders. Another factor may be that patients with obsessive-compulsive disorder are relatively cooperative, and tend to be more willing and able to tolerate lengthy scanning procedures than, for example, patients who are psychotic.

Positron emission tomography and SPECT were initially used to examine regional cerebral metabolism or blood flow in the resting state, and, whereas there has been some variation in the precise location and laterality of differences, most studies have reported increased activity in the inferior prefrontal (orbitofrontal) or anterior cingulate cortex, or the neostriatum, compared with controls.20-27 Because many of these investigations involved euthymic, drug free patients, the differences are unlikely to reflect confounding effects of concurrent depression or medication. However, as the patients were scanned at rest, it is unclear whether the findings reflect the presence of obsessive-compulsive symptoms or enduring features of the condition—that is, abnormalities of state or trait. Subsequent work involved scanning before and after treatment, and found that symptomatic
improvement was associated with a reduction in metabolism (depending on the study) in inferior prefrontal, cingulate, or striatal regions—are areas where activity had initially been increased. This raised the possibility that the increased activity before treatment was associated with the presence of obsessive-compulsive phenomena, especially in the diagnosis itself.

The relation between symptoms and activity has been explicitly examined in studies which involve the provocation of obsessive-compulsive phenomena by exposing patients to feared stimuli, such as “contaminated” objects in those prone to hand washing rituals. One study compared regional cerebral blood flow during provoked and neutral states, and another used a correlational design, with symptom intensity experimentally manipulated in a graded fashion across a series of scans. Both found that obsessive-compulsive phenomena were associated with increased activity in the inferior prefrontal and cingulate cortex and in the striatum. However, obsessions and compulsions are invariably accompanied by the patient’s attempts to resist them, and by anxiety. The finding that activity in the inferior prefrontal and anterior cingulate cortex is also increased during phobic anxiety, and in association with severe (and distressing) somatic and visceral pain, suggests that at least some of the changes heretofore associated with obsessive-compulsive disorder may be related to anxiety. Resistance to obsessional urges has received less attention, but has also been associated with inferior prefrontal activity. Dissection of the neural correlates of these different phenomena requires examination of obsessive symptoms which are not always accompanied by resistance or anxiety (such as ruminations, or obsessive-compulsive phenomena in Tourette’s syndrome), and further studies of anxiety in the absence of obsessive phenomena.

Whereas obsessive-compulsive disorder has primarily been associated with increases in regional brain activity, obsessional symptoms have also been correlated with a pronounced reduction in blood flow in the right inferior parietal lobule. As this region is concerned with attention to extrapersonal space, and lesions in this area produce visuospatial neglect, these functional changes may be related to the deficits in visuospatial function evident in patients with obsessive-compulsive disorder on neuropsychological testing.

By contrast, with functional imaging, there have been few studies of brain structure in obsessive-compulsive disorder, and the results have been inconsistent. A bilateral reduction in the volume of the caudate nuclei was reported from an early investigation with CT, but this has not been replicated in studies with MRI. In fact, one study found the opposite result, and two others failed to find differences between patients and controls in any region.

By contrast, functional imaging studies have identified reduction in transcranial magnetic stimulation of the head, and reduced activity in the striatum.

Perspectives on the pathophysiology of obsessive-compulsive disorder have also been altered by the recent discovery that antidepressants with a principle action at serotonergic synapses—such as clomipramine, fluoxetine, and fluvoxamine—have an ameliorating effect on obsessional symptoms. This is not merely secondary to their effect on mood, and these drugs are more effective than non-serotonergic antidepressants. Whether the extent of their impact on obsessive-compulsive phenomena depends on the inhibition of transmitter reuptake or effects on receptor densities is unclear, but their effectiveness suggests that obsessive-compulsive disorder involves an abnormality of serotonergic transmission. This is consistent with data from neuroendocrine studies, which indicate that patients with obsessive-compulsive disorder show reduced hypothalamic sensitivity to serotonergic probes such as D-fenfluramine. Serotoninergic antidepressants are now an established part of the management of obsessive-compulsive disorder, although they usually lead to less improvement in the condition rather than complete remission, and the benefits of their use in the long term have yet to be fully evaluated.

Although pharmacotherapy has emerged as a valuable tool in the management of obsessive-compulsive disorder, behaviour therapy (typically involving graded exposure to feared stimuli and prevention of subsequent avoidance and rituals), remains arguably the most effective means of treatment, although it is critically dependent on patient motivation. Little is known of how it may affect brain function, but a recent study found that successful behaviour therapy, like successful treatment with serotoninergic antidepressants, was associated with a reduction in striatal hypermetabolism. This suggests that both forms of treatment may act on a common neural substrate, an intriguing hypothesis which merits further exploration with neuroimaging.

One reason why the data from functional neuroimaging studies in obsessive-compulsive disorder have generated such interest is that they are broadly consistent with the clinical findings which implicate frontocingulate and striatal regions in its pathophysiology. Moreover, these areas are anatomically connected in a corticothalamic striatal loop, comprising a neural network which may normally be involved in switching between patterns of behaviour. Dysfunction in this network could thus underlie obsessive-compulsive phenomena.

At present the evidence linking this network with a disturbance in serotonergic dysfunction in obsessive-compulsive disorder is largely indirect. Serotonergic neurons in the Raphe nuclei project to the relevant cortical and striatal areas, but also send axons to most other telencephalic regions. Depletion of serotonin in experimental animals leads to increased expression of normally suppressed behaviours, whereas treatment of obsessive compulsions with serotoninergic antidepressants seems to reduce metabolic overactivity in frontocingulate and striatal regions, suggesting a serotonergic effect on activity at these sites. In the absence of suitable PET or SPECT animal studies, it has not yet been possible to examine the distribution of serotonin receptors in obsessive-compulsive disorder, but such compounds should soon be available. The interaction between serotonergic inputs and corticostriatal areas could be explored more directly by investigating the modulatory effects of serotonergic agents on neural responses to symptom provocation, using a combined behavioural and pharmacological challenge. This strategy has been successfully employed in other contexts.

In summary, there is now much evidence pointing to the importance of frontocingulate and striatal areas and serotoninergic transmission in obsessive-compulsive disorder, and this has greatly advanced our understanding of the condition. These findings challenge traditional perspectives on obsessive-compulsive disorder, which has generally been regarded as a “neurotic” condition, with the tacit implication that biological factors play a minor role in its pathogenesis. At the same time, this should not divert attention from the importance of psychological processes in obsessive-compulsive disorder, as underlined by the effectiveness of behaviour therapy, and the striking finding that it may lead to similar changes in regional brain activity as does pharmacological treatment. Nevertheless, recognition of the role of biological factors in obsessive-compulsive disorder has profoundly increased public awareness about a condition which was,
until recently, considered uncommon and difficult to treat. This is of particular relevance in obsessive-compulsive disorder, as, on average, patients do not seek help until 10 years after its onset, yet the condition can be as disabling as a chronic psychosis.

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