British Journal of Psychiatry (1994), **164**, 459–468

Functional Anatomy of Obsessive–Compulsive Phenomena

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Regional cerebral blood flow was measured with $H_2{}^{15}O$ positron emission tomography in four patients with obsessive–compulsive disorder. Patients were scanned on 12 occasions in the same session, with each scan paired with brief exposure to one of a hierarchy of contaminants that elicited increasingly intense urges to ritualise. The relationship between symptom intensity and regional cerebral blood flow (rCBF; an index of neural activity) was subsequently examined in the group and in individual patients. The group showed significant positive correlations between symptom intensity and blood flow in the right inferior frontal gyrus, caudate nucleus, putamen, globus pallidus and thalamus, and the left hippocampus and posterior cingulate gyrus. Negative correlations were evident in the right superior prefrontal cortex, and the temporo-parietal junction, particularly on the right side. The pattern in single subjects was broadly similar, although individual differences in neural response were also observed. A graded relationship between symptom intensity and regional brain activity can thus be identified in obsessive–compulsive disorder. It is hypothesised that the increases in rCBF in the orbitofrontal cortex, neostriatum, global pallidus and thalamus were related to urges to perform compulsive movements, while those in the hippocampus and posterior cinguiate cortex corresponded to the anxiety that accompanied them.

Although obsessive–compulsive disorder (OCD) has traditionally been regarded as a 'neurotic' condition, accumulating evidence suggests an association with dysfunction in specific brain regions. A large proportion of patients with OCD exhibit 'soft' neurological signs (Hollander *et al*, 1990; Hymas *et al*, 1991). Conversely, several neurological conditions are associated with obsessional phenomena, including post-encephalitic Parkinsonism (Jellife, 1932), Huntington's disease (Rappoport, 1989), Sydenham's chorea (Cummings & Cunningham, 1992) and lesions of the neostriatum (Weilburg *et al*, 1989), globus pallidus (Laplane *et al*, 1989) or frontal lobes (Eslinger & Damasio, 1985).

Studies with positron emission tomography (PET) and single photon emission tomography (SPET) have described alterations in regional cerebral blood flow (rCBF) or metabolism in patients with OCD compared with controls (Baxter *et al*, 1988; Swedo *et al*, 1989; Nordhal, 1989; Martinot *et al*, 1990; Sawle, 1991; Machlin *et al*, 1991; Rubin *et al*, 1992). While there has been some variation in the precise location of differences, the majority have reported increased neuronal activity in prefrontal cortex and/or the neostriatum. As the patients in these studies were scanned at rest, it is unclear whether the findings reflect the presence of obsessive–compulsive symptoms or enduring features of the condition; i.e. abnormalities of state or trait. The resolution of regional changes with treatment (Benkelfat *et al*, 1990; Hoehn-Saric *et al*, 1991; Baxter *et al*, 1992; Swedo *et al*, 1992), suggests an association with obsessive–compulsive symptoms.

We have investigated the relationship between obsessive–compulsive symptoms and regional brain activity in OCD by measuring cerebral blood flow while patients were actually experiencing the urge to ritualise. Regional cerebral blood flow (rCBF) was measured with PET in individual subjects on 12 separate occasions, each scan being paired with a stimulus that elicited a different level of symptom intensity. This enabled the relationship between graded increases in symptom intensity and rCBF to be examined in single subjects, and in the patients as a group. Such a design permits the measurement of changes in cerebral activity (as indicated by rCBF) while the level of symptom intensity is experimentally manipulated.

Method

The subjects were four right-handed males (defined by the Annett scale, 1970) meeting DSM-III-R criteria for OCD (American Psychiatric Association, 1987), with a mean age of 29.5 years (range 23–33) and a mean illness duration of 14 years (range 6–17). At the time of study they were medication free, and were starting behavioural therapy at a specialised unit. Three subjects had previously received pharmacological treatment, without responding. All had predominantly handwashing rituals, related to fears of

contamination with toxic, biological, or sticky substances, although other rituals, such as checking, were also evident. None had generalised anxiety or panic, or a history of serious medical illness or head injury. One subject (subject 2) had previously experienced a single episode of depression in association with obsessive-compulsive symptoms. The study was approved by local ethical committees and by the Administration of Radioactive Substances Advisory Committee (ARSAC) UK.

Evocation of obsessive–compulsive symptoms

Patients were trained to rate the subjective intensity of the urge to ritualise and the intensity of anxiety (0 = no symptom, 10 = most intense possible) as part of a behaviour therapy programme (Marks, 1986). Subjective ratings were used because we were specifically interested in the urge to ritualise and subjective anxiety, which were best assessed by the patients themselves. Potential subjects were tested with a variety of contaminants, from which a set of 12 stimuli that elicited a graded range of urges to ritualise from 0 to 10 were selected. Only patients in whom a full range of urge intensities could be induced were included. The particular contaminants used varied between subjects, as each had their own personal hierarchy of stimuli. For example, subject 1 found that rat poison evoked a maximal desire to handwash, motor oil induced a moderate response, while perfume had a minimal effect. Equivalent stimuli for subject 2 were faeces, tomato ketchup and salt. Each subject was thus presented with a unique set of individually specified contaminants.

PET scanning

Subjects were blindfolded and scanned in the presence of low background noise. Immediately prior to each scan, a contaminant in a sealed test tube was placed in the subject's folded hands and he was informed of its contents (Fig. 1). Twelve stimuli were presented in random order with respect to the strength of the associated urge to ritualise, each paired with a different scan. Immediately after each scan, subjects reported the intensity of the elicited urges and anxiety, and described any other phenomena they experienced during scanning, such as mental imagery. Subjects were permitted to handwash between scans (while remaining in the scanner), in order to reduce their symptoms to baseline levels before the next stimulus presentation (Fig. 1).

Regional cerebral blood flow (rBCF) was measured by recording the distribution of radioactivity in the brain after the intravenous infusion of $H_2{}^{15}O$, using a CTI model 953B PET scanner. $H_2{}^{15}O$ at a concentration of 55 MBq/ml was infused through an antecubital vein at 10 ml/min. Correction for attenuation was made by performing a transmission scan with an exposed $^{68}Ge/^{68}Ga$ external ring source at the beginning of each scanning session. Images were reconstructed by three-dimensional filtered back projection, with a Hanning filter of cut-off 0.5. The resolution of the resulting images was $8.5 \times 8.5 \times 4.3$ mm full width at half maximum. The integrated counts per pixel

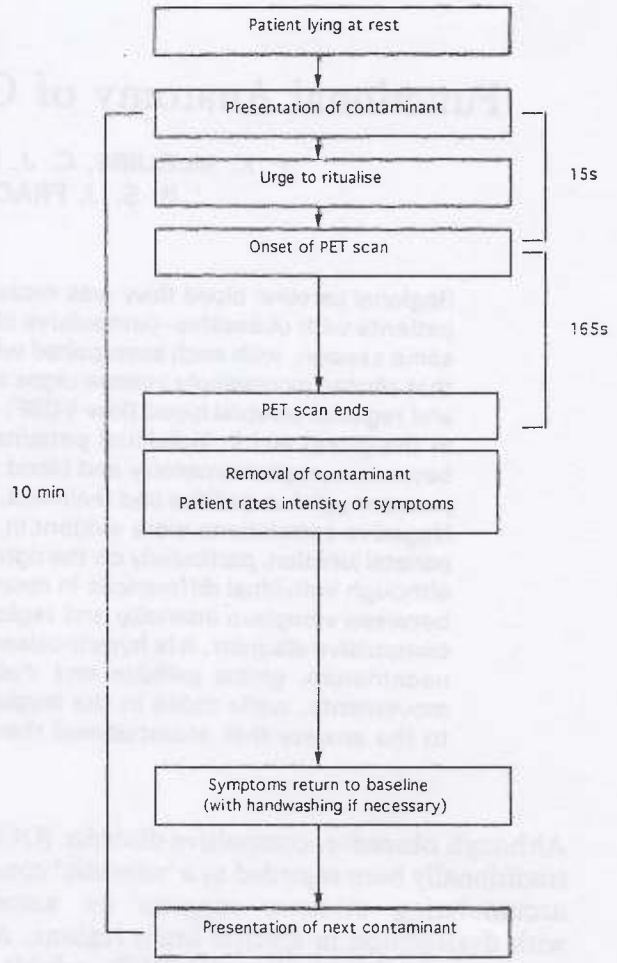

Fig. 1 Measurement of rCBF with PET following brief exposure to contaminants. Flow diagram outlining the sequence of events during a single scanning run. The sequence was performed 12 times in each subject, with each scan following brief exposure to a contaminant that elicited a different intensity of symptoms.

for the 165 seconds build up of ^{15}O in the brain were used as an index of rCBF.

Data analysis

Data analysis was performed on a SPARC 1 workstation (Sun Microsystems Europe Inc., Surrey, UK) using ANALYZE (Biodynamic Research Unit, Mayo Clinic) and PRO MATLAB (Mathworks Inc., New York). The 31 original scan slices were interpolated to 43 planes in order to render the voxels approximately cubic. The images from each subject were automatically realigned to correct for any changes in head position between scans (Woods *et al*, 1992), then resized into a standard stereotactic space, using the intercommisural line as the reference plane for the transformation (Friston *et al*, 1989). The 43 planes of data were resliced into 26 planes in the stereotactic space, with each new plane corresponding to a horizontal section in the atlas of Talairach & Tournoux (1988). In this space, one pixel represents 2 mm in the x and y dimensions, with an

inter-plane distance of 4 mm. In order to increase signal to noise ratio and accommodate normal variability in functional and gyral anatomy, each image was smoothed with a Gaussian filter 10 pixels wide.

In order to optimally display areas where there were correlations between rCBF and symptom intensity in relation to the brain anatomy of an individual patient, a magnetic resonance image was obtained from one subject (subject 2) and co-registered with his PET image, using methods described elsewhere (Watson *et al*, 1993).

Statistical analysis

Differences in global cerebral activity between scans were removed using an ANCOVA (Friston *et al*, 1990). A statistical parametric map (SPM) was generated showing pixels in which significant differences in rCBF across scans within each subject were displayed. The relationship between this regional variance and the symptoms experienced during scanning was examined by correlating the rCBF during each scan with the corresponding ratings for the urge to ritualise and for anxiety, respectively. Transformation of the correlation coefficient to a Z score permitted examination of these correlations in both single subjects and the group as a whole. Pixels showing significant positive and negative correlations were plotted on SPMs illustrating the magnitude of the Z score for the pixels in each plane. The omnibus significance of these SPMs was assessed by comparing the expected and observed number of pixels above a significance of $P=0.01$ (Friston *et al*, 1991). The SPMs were displayed as volume images in three orthogonal projections, showing the highest Z score along the line of view. Only Z scores with a significance of $P<0.01$ were displayed.

Table 1
Intensity of the urge to ritualise experienced by subjects during scanning

Scan	Subjective intensity of urge to ritualise (0–10)			
	Subject 1	Subject 2	Subject 3	Subject 4
1	6	6	1	4
2	4	2	3	9
3	10	9	8	1
4	1	4	8	9
5	8	8	7	3
6	3	5	2	9
7	8	3	3	6
8	6	8	5	3
9	10	5	10	10
10	2	7	7	4
11	0	4	6	1
12	8	1	9	7

Table 2
Intensity of anxiety experienced by subjects during scanning

Scan	Subjective intensity of anxiety (0–10)			
	Subject 1	Subject 2	Subject 3	Subject 4
1	6	6	0	4
2	5	2	1	9
3	10	9	4	1
4	3	4	5	8
5	7	8	3	2
6	4	5	1	8
7	8	4	0	5
8	7	8	2	2
9	10	5	6	10
10	3	7	3	2
11	2	4	2	1
12	8	1	4	4

Results

In all subjects the pre-selected contaminants elicited both urges to ritualise and anxiety, with a full range of intensities (Tables 1 and 2). The ratings for the two phenomena were strikingly similar, with high correlations between ratings in all subjects ($r=0.99$, 0.99, 0.95, 0.96, respectively; $P<0.001$). The correlations described below in relation to rCBF patterns were those seen with the intensity of the urge to ritualise, though virtually identical results were evident when rCBF was correlated with anxiety. As it was not possible to distinguish the neural correlates of these phenomena, the results essentially detail the relationship between rCBF and obsessive-compulsive *symptoms*.

Analysis of the data from the group revealed positive correlations between symptom intensity and rCBF ($P<0.01$) in the lower portion of the right inferior frontal gyrus (BA 47 and 45), an obliquely oriented swathe which spanned the ventral part of the right putamen and the tail of the caudate nucleus, and in the right thalamus. Further positive correlations were evident in left hippocampus, left posterior cingulate gyrus (BA 31), and the left cuneus (BA 18) (Figs 2, 3). Negative correlations between rCBF and symptom intensity were evident in a zone around the right temporo-parietal junction which extended from the right angular (BA 39) gyrus superiorly, to the posterior portion of the middle temporal gyrus (BA 39) inferiorly (Fig. 2). Similar, but less extensive correlations were seen in the left hemisphere, centred around the supramarginal gyrus (BA 40), and there was an additional focus in the inferior part of the left middle temporal gyrus (BA 37). Anteriorly, negative correlations were evident in a region focused on the right middle frontal gyrus (BA 8), and extending into the adjacent superior frontal gyrus (BA 8; Fig. 2). The stereotactic coordinates of the maximal foci for these positive and negative correlations are shown in Tables 3 and 4, respectively.

When the threshold for statistical significance was lowered to $P<0.05$, there were additional positive correlations in the right globus pallidus and the precuneus

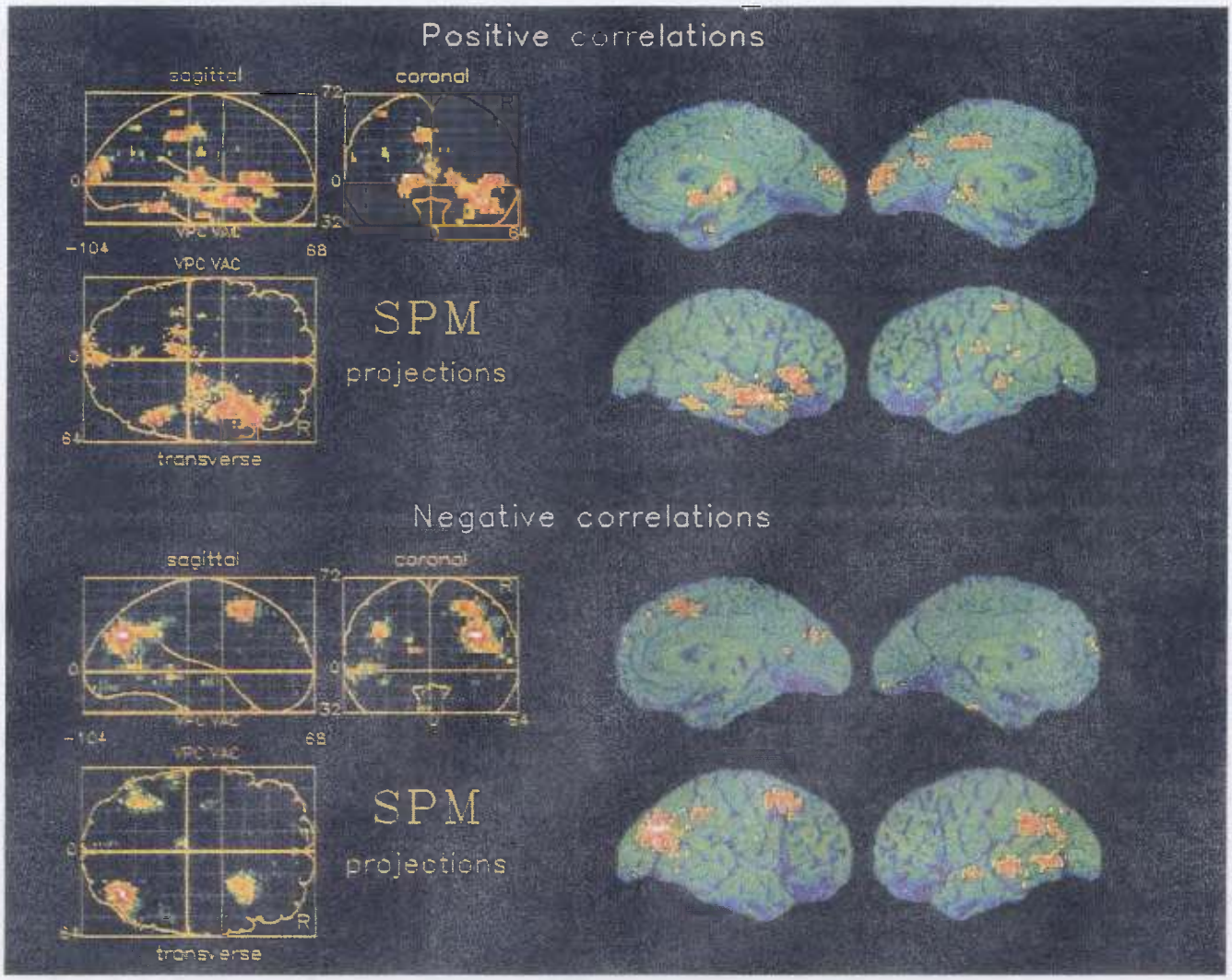

Fig. 2 Positive and negative correlations between symptom intensity and rCBF. Areas where there were significant correlations ($P<0.01$) between symptom intensity and rCBF in the group of patients are shown in orthogonal and surface projections. Positive correlations are evident in the right inferior frontal gyrus (BA 45,47), right neostriatum, right thalamus, left hippocampus, left posterior cingulate cortex (BA 31) and the left cuneus (BA 18). Negative correlations can be seen in the temporo-parietal region (BA 39,40), particularly on the right side, and in the right superior frontal cortex (BA 8).

(BA 7), and further negative correlations in the right supramarginal gyrus (BA 40), left posterior middle temporal gyrus (BA 39), and the left anterior middle temporal gyrus (BA 21).

The areas where there were positive and negative correlations between symptom intensity and rCBF in individual subjects are shown in Table 5. While there were differences between subjects at a statistical threshold of $P<0.01$, the distribution of areas showing significant correlations was broadly similar, and the similarities became more evident when the threshold was lowered to $P<0.05$. The pattern of significant changes in one patient is illustrated in Fig. 4.

Discussion

By demonstrating a graded relationship between the intensity of induced urges to ritualise and rCBF, this study provides strong evidence that at least some of the features described in functional imaging studies of OCD are related to the presence of obsessive–compulsive phenomena. This observation is consistent with the reported resolution of prefrontal and striatal increases in resting state activity following clinical improvement with drug or behaviour therapy (Benkelfat *et al*, 1990; Hoehn-Saric *et al*, 1991;

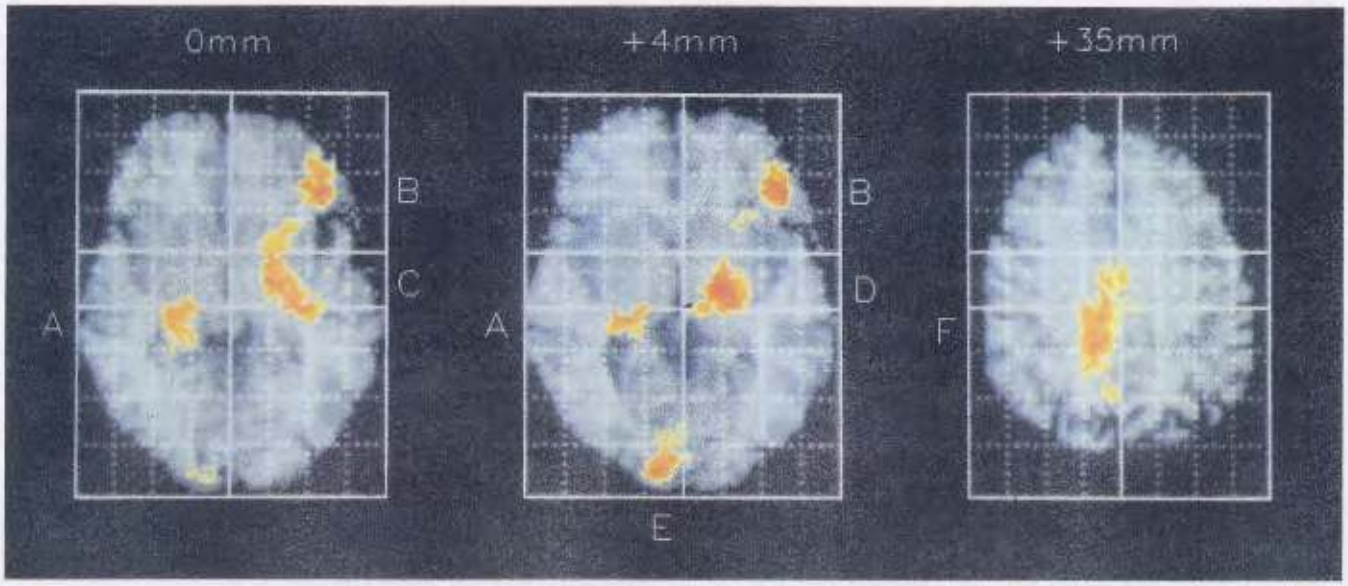

Fig. 3 Positive correlations between symptom intensity and rCBF. Three transverse planes showing areas where there were significant positive correlations between symptom intensity and rCBF in the patient group. The PET data have been superimposed on an MRI scan from one of the patients which has been transformed into the stereotactic space of the Talairach & Tournoux atlas, to serve as an anatomical reference. The level of each plane relative to the AC–PC line is shown above each slice. In the 0 mm plane, positive correlations are evident in the left hippocampus (A), right inferior frontal gyrus (B), and the right putamen and globus pallidus (C). At 4 mm, positive correlations can be seen in the left hippocampus (A), right inferior frontal gyrus (B), right thalamus (D), and the left cuneus (E). In the 35 m plane there are positive correlations in the left posterior cingulate gyrus (F).

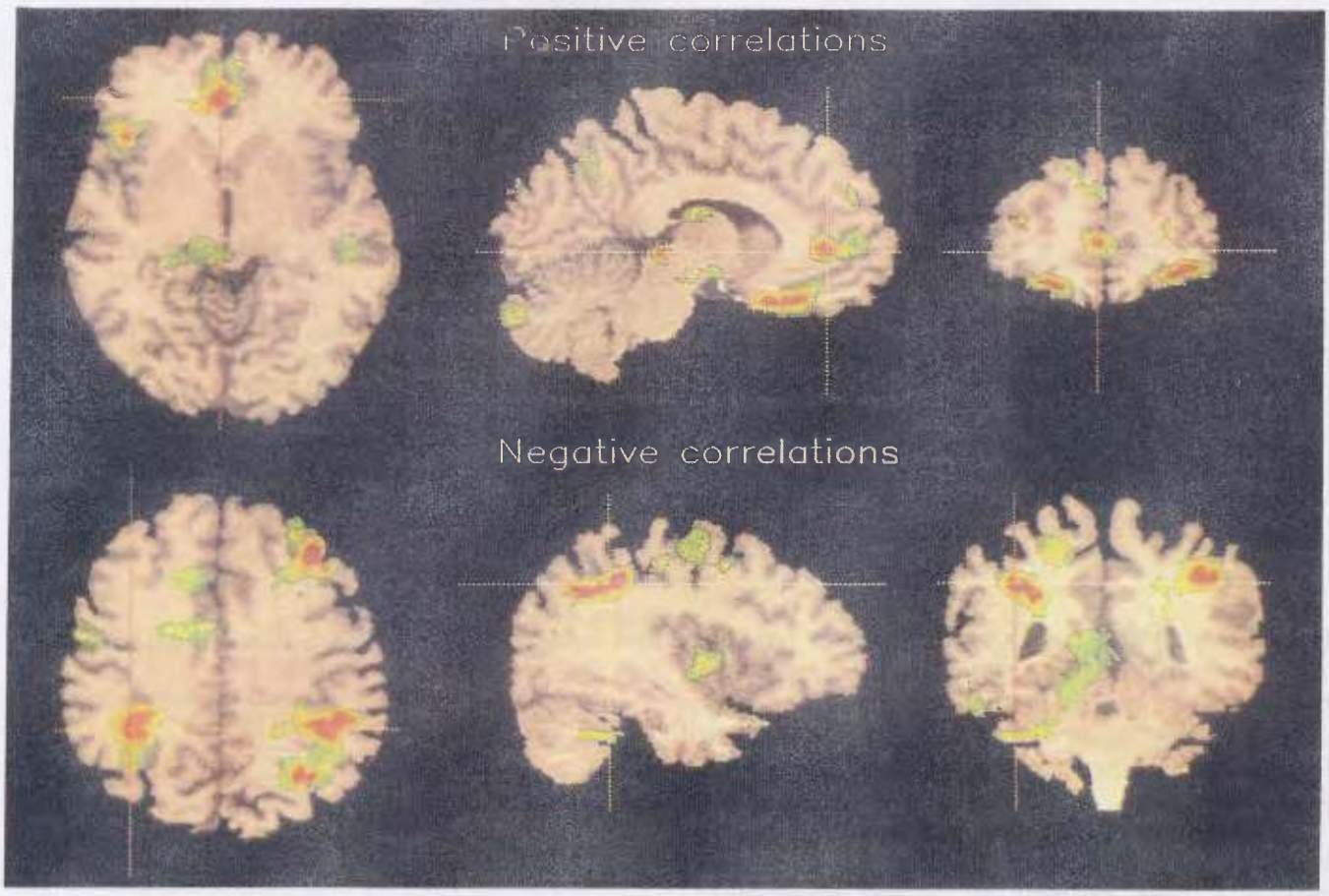

Fig. 4 Areas where rCBF correlated with symptom intensity in a single patient with OCD. Co-registered PET and MRI scans from subject 2. Some of the areas where rCBF correlated with symptom intensity in this particular patient are shown in transverse, saggital and coronal sections through the anterior cingulate gyrus (upper row), and the temporo-parietal region (lower row), at the level of the crossed lines. The upper sections show positive correlations in the left orbital gyri, the inferior frontal gyri, and the anterior cingulate cortex. The lower sections show negative correlations in the right middle frontal gyrus and bilaterally in the temporo-parietal region.

Table 3
Stereotactic coordinates of maximal positive correlations between symptom intensity and rCBF

x	*y*	*z*	*Z* score	Brodmann's area
34	22	−8	3.1	Right inferior frontal gyrus (BA 47)
24	6	−8	3.2	Right putamen
34	−26	−4	3.1	Right caudate nucleus
−20	−30	0	3.1	Left hippocampus
20	−14	0	2.8	Right globus pallidus
46	22	4	3.4	Right inferior frontal gyrus (BA 45)
16	−16	4	3.1	Right thalamus
−18	−100	8	4.0	Left cuneus (BA 18)
−10	−32	40	3.1	Left posterior cingulate gyrus (BA 31)

The coordinates are in millimetres and correspond to the stereotactic atlas of Talairach & Tournoux (1988). The *x* and *z* coordinates indicate the distance from a line between the anterior and posterior commissures, while the *y* coordinate indicates the position relative to the anterior commissure.

Table 4
Stereotactic coordinates of maximal negative correlations between symptom intensity and rCBF

x	*y*	*z*	*Z* score	Brodmann's area
−44	−62	4	3.1	Left anterior middle temporal gyrus (BA 37)
32	−72	28	4.6	Right posterior middle temporal gyrus (BA 39)
38	−72	32	4.0	Right angular gyrus (BA 39)
−38	−58	32	3.1	Left supramarginal gyrus (BA 39/40)
36	20	44	3.5	Right middle frontal gyrus (BA 8)

Baxter *et al*, 1992; Swedo *et al*, 1992). It remains unclear whether intense urges to perform repetetive movements in normal people are associated with similar changes in rCBF, or whether patients can still be distinguished from controls when they are asymptomatic

Although our study involved a small number of subjects, by performing multiple scans in each patient it was possible to obtain statistically significant results. Indeed, the method we used permits the study of individual subjects. This

Table 5
Areas where rCBF significantly correlated with symptom intensity in individual patients ($P<0.01$)

Positive correlations	Negative correlations
Subject 1	
Right putamen	Left frontal pole (10)
Right globus pallidus	Left anterior cingulate (32)
Right caudate nucleus	Right lingual gyrus (18)
Right inferior frontal gyrus (45)	
Left hippocampus	
Left lingual gyrus (17,18)	
Left cuneus (18)	
Left precuneus (7)	
Right anterior middle temporal gyrus (21)	
Left posterior cingulate gyrus (31)	
Right precentral gyrus (6,4)	
Right postcentral gyrus (40,3,1,2)	
Subject 2	
Right uncus (28,36)	Left lingual gyrus (18)
Right cerebellum	**Posterior middle temporal gyrus (39)**
Right fusiform gyrus (37)	**Right angular gyrus (39)**
Left orbital gyri (11,47)	**Right middle frontal gyrus (8,6)**
Left amygdala	
Right temporal pole (38)	
Right inferior frontal gyrus (47)	
Left inferior frontal gyrus (47,45)	
Left hippocampus	
Anterior cingulate gyrus (32,24)	
Left precuneus (7)	
Subject 3	
Left hippocampus	Right temporal pole (22)
Right putamen	**Left anterior middle temporal gyrus (21)**
Right inferior frontal gyrus (47,45)	Left posterior middle temporal gyrus (37)
Left inferior frontal gyrus (47)	Left thalamus
Left temporal pole (22)	**Right posterior middle temporal gyrus (39)**
Frontal pole (10)	**Right angular gyrus (39)**
Left cuneus (18)	Right pre- and postcentral gyrus (4,3,1,2)
Right anterior middle temporal gyrus (21)	
Subject 4	
Right thalamus	**Anterior middle temporal gyrus (21)**
Right globus pallidus	Left posterior middle temporal gyrus (39)
Anterior cingulate gyrus (24)	Left angular gyrus (39)
Left posterior cingulate gyrus (31)	**Left supramarginal gyrus (40)**
Left precuneus (7)	**Right middle frontal gyrus (6)**
Supplementary motor area (6)	Left superior frontal gyrus (8)
Right precentral gyrus (6,4)	

Areas in bold type showed significant changes in the group analysis ($P<0.01$). Brodmann's areas are shown in parentheses. If laterality is not specified, the changes were bilateral.

approach depends on the administration of small doses of radiation, of short half-life, with each scan, something which is not currently possible with other isotopes. Comparing scans across conditions within individuals allows the subjects to act as their own controls, eliminating the potentially confounding effects of demographic and intellectual differences between separate patient and control groups.

One potential disadvantage of this approach is that inclusion of an atypical subject in a small group could distort the results. This seems unlikely to have occurred in this study, as the patterns of blood flow seen in four different patients were broadly similar. Some of the differences can perhaps be understood in terms of variations in the individual's subjective response to exposure. For example, subject 4 reported focusing on the movements he imagined performing if given the opportunity to handwash, which might explain the increases in the supplementary motor area and precentral gyrus seen in that patient.

We predicted that exposure to contaminants in patients with OCD would elicit both urges to ritualise and anxiety, and therefore obtained separate ratings for these phenomena in an effort to distinguish their respective neural correlates. Although this was precluded by the high correlation between urges to ritualise and anxiety, existing data on the functional anatomy of the regions concerned provides clues as to which of these phenomena activity in a given area might correspond.

The orbitofrontal cortex (including the inferior frontal gyrus), ventral neostriatum, globus pallidus and thalamus are anatomically connected in a 'loop', and are thought to comprise a neural network involved in switching between patterns of behaviour (Alexander *et al*, 1986). Insel (1992) has suggested that dysfunction in this network underlies compulsive phenomena. Consistent with this view are findings that these regions are those most consistently reported as showing increased activity in resting state functional imaging studies of OCD (Baxter *et al*, 1988; Swedo *et al*, 1989; Nordhal, 1989; Martinot *et al*, 1990; Sawle, 1991; Machlin *et al*, 1991; Rubin *et al*, 1992). Moreover, neurological conditions involving the basal ganglia, including Sydenham's chorea (Rappoport, 1989), post-encephalitic Parkinsonism (Jellife, 1932), and Huntington's disease (Cummings & Cunningham, 1992), and lesions in the neostriatum (Weilburg *et al*, 1989), globus pallidus (Laplane *et al*, 1989), and orbitofrontal cortex (Eslinger & Damasio, 1985), are associated with compulsive phenomena, rather than anxiety. Division or ablation of the tracts carrying subcortical projections from the anterior cingulate and orbitofrontal cortex is reported to reduce compulsive behaviour in OCD (Bridges, 1989), although this remains controversial.

In contrast, the posterior cingulate cortex and hippocampus are regarded as part of the 'limbic system', and animal studies implicate these regions in the expression of anxiety (Kaada, 1960; Gray, 1982). PET studies, in the resting state, of patients with panic disorder have identified an asymmetry of activity in the parahippocampal region (Reiman *et al*, 1984; Nordhal *et al*, 1990). However, the results from neuroimaging studies of subjects actually experiencing anxiety have been inconsistent (Curtis, 1991), and the apparently robust finding of temporal polar activation in association with both anticipatory anxiety and with lactate-induced panic (Reiman *et al*, 1989*a*,*b*) has recently been retracted due to inaccurate anatomical localisation (Drevets *et al*, 1992). State anxiety and agitation in patients with depression seems to correlate positively with rCBF in the posterior cingulate cortex (Bench *et al*, 1993).

We propose that the positive correlations in the orbitofrontal cortex, neostriatum, globus pallidus and thalamus may therefore be related to urges to ritualise, while those in the hippocampus and posterior cingulate cortex may correspond to the anxiety that accompanies them. The dissection of the respective neural correlates of compulsive urges and anxiety will require studies of anxiety without the urge to ritualise, or the study of obsessive ruminations which are sometimes not associated with anxiety.

The positive correlations we observed in the cuneus and precuneus are difficult to attribute to either of these phenomena. However, our patients often reported having imagined visual representations of the contaminants which they had held in their hands (but were able to see) during scanning, suggesting that these changes may have been related to visual imagery. Lesions in the posterior part of the left hemisphere are known to impair visual imagery, which appears to involve activity in extra-striate visual areas (reviewed in Farah, 1989). The cuneus and precuneus have been activated in PET studies of visual imagery (Kosslyn *et al*, 1993), and by memory tasks with a visual imagery component (Roland & Seitz, 1989; Grasby *et al*, 1993).

The negative correlations we observed between symptom intensity and rCBF were centred around the temporo-parietal junction and the right superior prefrontal cortex. These are unlikely to reflect hypocapnia in response to anxiety-induced hyperventilation, as differences in global blood flow between scans were covaried out with an ANCOVA, and the correlations were focal rather than global. The region around the temporo-parietal junction is

concerned with attention to extrapersonal space (Andersen, 1987; Musulam, 1981), and lesions in this area produce the neurological syndrome of visuo-spatial neglect (Hier *et al*, 1983; Heilman & Valenstein, 1985), while the superior prefrontal region has recently been found to be active when attention is directed to the visuo-spatial periphery (Corbetta *et al*, 1993). Decreased activity in these regions with increasing symptom intensity might therefore reflect a shift in attention from extrapersonal space, perhaps consequent upon the subject's preoccupation with the essentially 'internal' experience of an urge to ritualise and the associated anxiety. Analogous observations have been made with PET studies of subjects performing visual and somatosensory tasks: during a visual task there is a decrease in perfusion in somatosensory cortex and vice versa (Kawashima, 1993), suggesting that cognitive tasks may be associated with a selective inhibition of activity in areas which do not contribute to a given neural operation. The decreases we observed in areas specialised for visuo-spatial functions may also be related to the impairments in complex spatial and shifting abilities that have been identified in neuropsychological studies of OCD (Hymas *et al*, 1991).

While decreases in activity have not been identified in resting state studies of OCD, a previous study of patients following exposure to obsessive–compulsive stimuli, using the xenon inhalation technique, reported decreases in the parietal and temporal cortex (Zohar *et al*, 1989). Decreased inferior parietal metabolism has also been reported in patients with panic disorder (Nordhal *et al*, 1990), suggesting that the negative correlations we observed in this region may have been more related to anxiety than urges to ritualise. Intriguingly, anxiety in patients with depression has recently been found to correlate *positively* with rCBF in the inferior parietal lobule (Bench *et al*, 1993). However, the anxiety experienced in depression may differ from that in OCD in being externally, rather than internally, directed, and this might account for a difference in the polarity of the relationship with rCBF in this region in the two conditions.

Most of the positive correlations between symptom intensity and rCBF were unilateral, with the majority lateralised to the right hemisphere. While resting state studies of OCD have usually reported bilateral abnormalities (Baxter *et al*, 1988; Nordhal *et al*, 1989; Swedo *et al*, 1989; Sawle *et al*, 1991), regional changes in association with treatment have tended to be right-sided (Benkelfat *et al*, 1990; Baxter *et al*, 1988, 1992; Swedo *et al*, 1992), suggesting that obsessive–compulsive phenomena may be particularly associated with activity in right hemispheric structures. The predominance of negative correlations in the right hemisphere may reflect the tendency for visuo-spatial functions to be lateralised to that side.

Some of the areas we identified as associated with obsessional symptoms (e.g. the globus pallidus, putamen, thalamus, posterior cingulate cortex, and hippocampus) have not been described in imaging studies of OCD before. Increases in activity in previous investigations have largely been restricted to one or two regions, and most studies have not reported any decreases (Baxter *et al*, 1988; Swedo *et al*, 1989; Nordhal, 1989; Martinot *et al*, 1990; Sawle, 1991; Machlin *et al*, 1991; Rubin *et al*, 1992). This may reflect two important methodological differences between this and previous work. Firstly, cerebral activity was examined in the symptomatic rather than the resting state, using patients as their own controls. Secondly, the data were analysed with an approach (statistical parametric mapping; Friston & Frackowiak, 1991) which examines all pixels in the data set, rather than with a region-of-interest analysis, which is limited to a subset of brain areas, and therefore increases the probability of type II errors.

In terms of basic mechanisms, the clinical efficacy of serotonergic reuptake inhibitors points to future avenues of investigation with functional imaging in OCD. *In vivo* neuroimaging studies of 5-HT receptors would be of considerable interest, particularly as suitable PET ligands have recently been developed (Blin *et al*, 1990; Nyberg *et al*, 1993). In addition, the role of serotonergic inputs in modulating brain systems mediating obsessive–compulsive phenomena can be investigated directly. Strategies for such an approach, using combined pharmacological–behavioural challenges, have recently been outlined (Friston *et al*, 1992). Such studies should further extend our understanding of the pathophysiology of OCD, and concurrently provide insights into the normal functions of the neural systems involved in the disorder.

Acknowledgement

PKM was supported by the Wellcome Trust.

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(First received September 1993, final revision November 1993, accepted November 1993)