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Cognitive control in childhood-onset obsessive–compulsive disorder: a functional MRI study

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ABSTRACT

Background. Failure to resist chronic obsessive–compulsive symptoms may denote an altered state of cognitive control. We searched for the cerebral regions engaged in this dysfunction.

Method. Differences in brain regional activity were examined by event-related functional magnetic regional imaging (fMRI) in a group of adolescents or young adults ($n=12$) with childhood-onset obsessive–compulsive disorder (OCD), relative to healthy subjects. Subjects performed a conflict task involving the presentation of two consecutive and possibly conflicting prime and target numbers. Patients' image dataset was further analysed according to resistance or non-resistance to symptoms during the scans.

Results. Using volume correction based on *a priori* hypotheses, an exploratory analysis revealed that, within the prime-target repetition condition, the OCD subjects activated more than healthy subjects a subregion of the anterior cingulate gyrus and the left parietal lobe. Furthermore, compared with 'resistant' patients, the 'non-resistant' OCD subjects activated a bilateral network including the precuneus, pulvinar and paracentral lobules.

Conclusions. Higher regional activations suggest an abnormal amplification process in OCD subjects during the discrimination of repetitive visual stimuli. The regional distribution of functional changes may vary with the patients' ability to resist obsessions.

INTRODUCTION

Although obsessive thoughts and compulsive rituals may be trivial in nature (counting, checking, washing …), the subject's inability to inhibit their repetition, unless with a conscious effort, warrants their morbid character. One of the diagnostic criteria for obsessive–compulsive disorder (OCD) requires that 'the person has recognized that the obsessions or compulsions are excessive or unreasonable' (DSM-IV; APA, 1994) and the deficit in the ability to inhibit unwanted or conflicting stimuli may be central to the phenomenology of obsessive–compulsive (OC) symptoms. Conscious self-regulation of behaviour, including executive control, mental effort, conflict monitoring, and response inhibition, is probably involved in the emergence of, or resistance to, OC symptoms. Whether one or several of these cognitive functions are

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consistently impaired in OCD remains elusive in the literature. When investigated with cognitive tasks (for review, see Greisberg & McKay, 2003), OCD patients generally perform in the normal range, but they may choose a very cautious approach to task performance, suggesting that such patients are unusually sensitive to conflicts and small variations between stimuli. Altered monitoring of conflicts has been hypothesized (Martinot *et al.* 1990; Bannon *et al.* 2002). Specifically, failure to resist OC symptoms may denote an overactive monitoring system (Van Veen & Carter, 2002). However, the cerebral correlates of the system remain at stake.

Neuroimaging (Martinot *et al.* 1990; Saxena *et al.* 1998), electrophysiological (Johannes *et al.* 2001, 2003) and neurostimulation (Mallet *et al.* 2003) evidence suggests that a rather non-specific dysfunction of the 'frontal-striatal-thalamic-frontal' network is associated with the symptoms of OCD. Nevertheless, there is little agreement regarding the role of regional changes, and it is still unknown whether they vary according to clinical features, such as age of onset of the disorder or subjective resistance to the OC symptoms. Up to 80% of all OCD cases emerge during childhood or adolescence (Rasmussen & Eisen, 1990). Therefore, studies focusing on young patients, close to the onset of their illness, are critical to diminish potential confounds due to chronicity and co-morbidity.

We aimed at studying the differences in brain regional activity detected by event-related functional magnetic regional imaging (fMRI), between a group of adolescents or young adults suffering from childhood-onset OCD, and a healthy group, while performing a cognitive task engaging both priming and interference components. Indeed, priming and interference between stimuli allow an experimental approach of the brain regions that monitor repeated or conflicting information. The task focuses specifically on the comparison of numbers, which elicits activation in the cingulum and parietal cortices (Naccache & Dehaene, 2001), two putative epicenters for attention processes (Small *et al.* 2003) which we hypothesized may be impaired in OCD. In each trial, while the subject performs a constant task, a priming number is presented prior to the target number. The paradigm capitalizes on the logic of psychological priming experiments. By varying the repetition relationship between prime and target, one can detect which brain areas present amplification (or suppression) for certain subsets of trials (Naccache & Dehaene, 2001). We further restricted our analyses on specific coordinates in the cingulate and parietal cortices, according to previous reports in the literature. First, we focused on a area in the anterior cingulate which lies at the centre of the cognitive division cluster, following Bush and co-worker's meta-analysis (Bush *et al.* 2000). This extensive review gathered locations of anterior cingulate local maxima, from selected functional neuroimaging studies, using cognitively demanding tasks involving competing streams of information. Secondly, we focused on a parietal area which correlated positively with task difficulty involving number manipulation (Zago *et al.* 2001).

In addition to diagnostic categorization, we divided the OCD subjects into two groups according to presence or absence of subjective resistance to the OC symptoms during the task, hypothesizing that failure to resist may denote an impaired activity in the regions involved in repetition detection.

SUBJECTS AND METHOD

Subjects

Twelve patients with OCD, seven males and five females, were recruited from the Departments of Child and Adolescent Psychiatry of Pitié-Salpétrière and Robert Debré Hospitals in Paris. Inclusion criteria were a DSM-IV diagnosis of OCD, as assessed using the Kiddie-SADS (Kaufman *et al.* 1997), onset of the disorder before 18 years of age, duration of illness of at least one year, and no current co-morbid Axis I or Axis II diagnosis. Exclusion criteria were any neurological or other chronic medical condition, current treatment with a benzodiazepine or a neuroleptic medication, poor visual acuity (not corrected by corneal lenses), native language other than French, and any contraindication to the MRI.

Patients' clinical state at the time of the study was assessed, within a few days prior to the MRI scan, using French versions of: the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman *et al.* 1989*a*, *b*), a clinician-rated 10-item instrument, measuring severity of OC

symptoms (total score, 0–40), including resistance towards obsessions (item score, 0–4) or compulsions (item score, 0–4); the National Institute of Mental Health Obsessive Compulsive scale (NIMH-OC) (Insel *et al.* 1983), a global scale rated by the clinician from 0 (normal) to 15 (most severe OC symptoms); the Leyton Obsessional Inventory–Child Version (LOI-CV), a 44-item self-rated scale measuring the number of symptoms present, as well as the degree of resistance to symptoms and interference with functioning (Cooper, 1970; Berg *et al.* 1986); the 13-item Beck Depression Inventory (BDI; Beck *et al.* 1961); the Spielberger State Trait Anxiety Inventory (STAI; Spielberger *et al.* 1983); and the Clinical Global Impression Severity score (CGI-S; Guy, 1976) for severity of OCD. The Annett (1978) handedness questionnaire was administered to all subjects.

Immediately after the fMRI scan, the patients were instructed to complete the State form of the STAI, in order to describe their mental state during the scan, and they were assessed using a modified version of the Y-BOCS, in which the 10 items were rated according to patient's report on occurrence and characteristics of obsessions and/or compulsions exclusively for the period limited to the time actually spent in the scanner (about 1 h). Two patient subgroups were defined according to the five-level 'resistance' items of the Y-BOCS, i.e. item 4 = resistance to obsessions, and item 9 = resistance to compulsions. Subjects with scores of 0 ('always resist or symptoms so minimal that does not need to resist') on both item 4 and item 9 formed the 'resistant' subgroup; subjects with scores >0 ('partially to completely yield to the symptoms') on either item 4 or item 9 (or both) formed the 'non-resistant' subgroup.

Fifteen normal volunteers, 11 males and 4 females, with no current or past psychiatric diagnosis and no current treatment, were recruited from the local community. Healthy subjects and patients did not significantly differ in age (mean $\pm$ S.D. age was, for patients, 21 ± 5 years and, for healthy subjects, 25 ± 7 years; $t = -1{\cdot}55$, $p = 0{\cdot}13$). All subjects, except one patient and one healthy subject, were right-handed. All healthy subjects were native French speakers, had good visual acuity (or wore corrective lenses), no chronic medical condition, and no contra-indication to the MRI.

The protocol had been approved by the ethics committee of Paris-Hospital Bicêtre, and written consent was obtained from all subjects.

Stimuli

The stimulus set consisted of two sets of 32 randomly intermixed pairs of prime and target numbers, each consisting of the numbers 1, 4, 6 or 9 written in either Arabic or verbal (spelled-out) format. Subjects were asked to compare each target number with number 5 by pressing, as fast as possible, the right-hand key for numbers larger than 5, and the left hand key for numbers smaller than 5. The following factors were manipulated: response congruity (whether or not the prime and target fell on the same side of 5), and repetition (within the congruent trials, whether or not the prime and target were the same number).

Each trial included a first blank screen of 71 ms, a prime number for 43 ms, a second blank screen of 71 ms, and a target number of 200 ms. Prior to each trial, a warning signal (a rectangle surrounding the stimulus position) appeared with a lag of 2 s.

Image acquisition

An event-related fMRI design was used. Subjects were presented with training (at least one block of 20 trials) and scanning (two blocks of 32) trials. Stimuli were presented every 14 s through mirror glasses and an active matrix video projector (EGA mode, 70 Hz refresh rate). Stimulus onset was synchronized with the acquisition of the first slice in a series of seven volumes of 18 slices each. We used a gradient-echo echo-planar imaging sequence sensitive to brain oxygen-level-dependent (BOLD) contrast (18 contiguous axial slices, 6 mm thickness, repetition time/echo time = 2000/60 ms, field of view 24 cm, 64×64 matrix, voxel size $3{\cdot}75 \times 3{\cdot}75 \times 6$ mm) on a 1·5 T whole-body system (Signa, General Electrics). High-resolution anatomical images were also acquired using a 3D fast gradient-echo inversion-preparation sequence (124 contiguous axial slices, 1·2 mm thickness, inversion time = 600 ms, TE = 2·2 ms, FOV 24 cm, 256×192 matrix, voxel size $0{\cdot}9375 \times 0{\cdot}9375 \times 1{\cdot}2$ mm).

Statistical analysis

Performance

A first repeated measure analysis of variance (ANOVA) was applied on median response time (RT) with one between-subject factor, i.e. group (healthy, patients), and one within-subject factor, i.e. prime-target congruity (incongruent, congruent trials). A second ANOVA was applied on RT with the factors of group and prime-target repetition congruity (non-repeated-congruent, repeated-congruent trials). A third ANOVA was applied on RT with the factors of subgroup (non-resistant *versus* resistant patients) and prime-target repetition congruity (non-repeated-congruent, repeated-congruent trials). The significance level was set at $p = 0{\cdot}05$, two-tailed.

fMRI data

The first seven images of each block, corresponding to the first trial, were discarded, leaving 224 volumes in each block. Analysis was performed with the Statistical Parametric Mapping (SPM99) software. Images were corrected from subject motion and slice acquisition delays, realigned, normalized into standard stereotaxic space using a linear transform calculated on the anatomical images, and smoothed using a Gaussian spatial filter (full-width at half-maximum = 5 mm).

The signal was modelled as a linear combination of a standard haemodynamic response function and its temporal derivative, thus allowing for different delays across brain regions. Individual analyses were performed with the prime-target relation factor (incongruent, non-repeated-congruent, and repeated-congruent). Afterwards, three random-effect analyses were performed on this factor – random-effect analysis is a conservative procedure that explores the whole normalized fMRI volumes. This procedure is based on the reanalysis of statistical parametric maps obtained from each subject's images (Friston *et al.* 1999). First, an intergroup comparison (OCD *versus* healthy), was performed on the contrast between incongruent *versus* congruent trials. Secondly, an intergroup comparison was performed on the contrast between non-repeated-congruent *versus* repeated-congruent trials. Thirdly, the effect of resistance to obsessions and/or compulsions, as assessed right after the scan, was examined. According to the criteria described above, the patient group was divided into two subgroups of equal size ($n = 6$): non-resistant and resistant. Thus, a subgroup comparison (non-resistant or resistant) was performed on the contrast between non-repeated-congruent *versus* repeated-congruent trials, where OCD *versus* healthy group differences had been detected.

A first analysis was performed on intergroup comparisons, using maps of z statistics showing all voxels significantly activated for voxel threshold $p < 0{\cdot}001$ uncorrected for multiple comparison. Secondly, based on our *a priori* hypotheses, we used statistics corrected for multiple comparison at $p < 0{\cdot}05$ by applying Worsley and co-workers' (1996) small volume correction (SVC) calculation on the cingulate and parietal cortices that were hypothesized impaired in OCD. The approach used in the current study constrained the search volume around a single stereotaxic x, y, z coordinate point taken from previous studies. The first SVC was conducted on the cognitive part of the anterior cingulate gyrus based on a previous report by Bush *et al.* (2000). It was defined by a sphere of 5·0 mm radius centred on the Talairach coordinates 0, 20, 36. In the inferior parietal region, we centred our point on a region previously reported by Zago *et al.* (2001) to be involved in mental calculation. The SVC was defined by a sphere of 20·0 mm radius centred on the Talairach coordinates −30, −52, 50 corresponding to the left intraparietal sulcus. Thirdly, an exploratory analysis was performed on OCD subgroups (non-resistant *versus* resistant to OC symptoms), using maps of z statistics showing all voxels significantly activated for voxel threshold $p < 0{\cdot}001$ uncorrected for multiple comparison.

RESULTS

Subjects

For the 12 OCD subjects, the mean (±S.D.) age at onset of the disorder was 8·5 (±3·4) years, with a mean (±S.D.) duration of illness of 13·1 (±6·9) years. Of note, 9 of the 12 patients had obsessions related to numbers or counting compulsions. Eleven of the 12 patients were currently treated with an anti-obsessional medication: five were receiving sertraline, three fluoxetine,

two paroxetine, and one fluoxetine and clomipramine. Clinical assessment regarding the patient's subjective condition while in the scan was as follows: STAI-State score, mean ± S.D. 38·33 ± 7·28, range = 29–45; by definition on the resistance items of the Y-BOCS, the resistant OCD subgroup scored 0, while the non-resistant OCD subgroup had a mean ± S.D. score of 3·0 ± 1·2.

Behavioural results

We first tested the prediction that patients and healthy subjects would differ in their response time for the congruency effect. An ANOVA on median response-time (RT) was conducted with factors of group (healthy, patient), and prime-target congruity (incongruent, congruent). Although patients had higher median RT than healthy subjects whatever the congruity, the difference did not reach statistical significance (patients, 603 ± 132 ms; healthy subjects, 542 ± 94 ms; $F(1, 22) = 1{\cdot}68$, $p = 0{\cdot}20$). Both groups were slower in the incongruent condition compared with the congruent condition (583 ± 113 *versus* 562 ± 123 ms; $F(1, 22) = 10{\cdot}379$, $p = 0{\cdot}003$). However, no interaction was found between group and congruity effects (for incongruent trials, median ± S.D. was 610 ± 134 ms for patients, and 555 ± 86 ms for healthy subjects; for congruent trials, median ± S.D. was 596 ± 136 ms for patients, and 528 ± 103 ms for healthy subjects; $F(1, 22) = 0{\cdot}94$, $p = 0{\cdot}34$).

Secondly, we tested the prediction that patients would be slower than healthy subjects for the number repetition effect, using an ANOVA on median RT, with factors of group and prime-target repetition congruity (non-repeated-congruent, repeated-congruent). Although patients had higher overall median RT, the difference did not reach significance (patients, 596 ± 138 ms; healthy subjects, 528 ± 104 ms; $F(1, 22) = 1{\cdot}86$, $p = 0{\cdot}18$). Also, despite higher medians in patients, the interaction between group and repeating effects only tended towards significance (in the non-repeated-congruent condition, median ± S.D. was 627 ± 147 ms for patients, and 546 ± 104 ms for healthy subjects; in the repeated-congruent condition, median ± S.D. was 564 ± 127 ms for patients, and 510 ± 106 ms for healthy subjects; $F(1, 22) = 3{\cdot}05$, $p = 0{\cdot}09$).

Thirdly, we tested the prediction that, among the OCD subjects, the non-resistant patients would be slower than the resistant patients in the number repetition comparison. An ANOVA on median RT was conducted with factors of subgroup (non-resistant, resistant) and prime-target repetition congruity (non-repeated-congruent, repeated-congruent). Although non-resistant patients had higher median RT, the difference did not reach significance (non-resistant patients, 632 ± 121 ms; resistant patients, 560 ± 150 ms; healthy subjects 528 ± 104 ms; $F(2, 21) = 1{\cdot}47$, $p = 0{\cdot}25$). Also, no interaction was found between subgroups despite higher medians in patients (in the non-repeated-congruent condition, median ± S.D. was 668 ± 125 ms for non-resistant subjects, 586 ± 168 ms for resistant subjects, and 546 ± 104 ms for healthy subjects; in the repeated-congruent condition, median ± S.D. was 627 ± 147 ms for non-resistant subjects, 546 ± 104 ms for resistant subjects, and 510 ± 106 ms for healthy subjects; $F(1, 22) = 1{\cdot}92$, $p = 0{\cdot}17$).

fMRI results

In the incongruent *versus* congruent condition, no significant difference was detected between patients and healthy subjects. However, in the prime-target number repetition condition, when repeated-congruent trials were substracted from non-repeated-congruent trials, the OCD patients showed greater activation than the healthy subjects, in a set of regions located within the left parietal lobe, temporal lobe and right precuneus (Table 1).

Analyses of intragroup effects showed no regions activated in the control group while in the patient group the same set of cerebral regions previously detected was activated (data not shown). Thus, the intergroup differences arose from a greater activation in the OCD group and not from regional deactivations in the control group.

The SVC procedure in SPM99, *a priori* centred on the 'cognitive' anterior cingulate gyrus (Bush *et al.* 2000), detected a significant peak activation (cluster-level $P_{corrected} = 0{\cdot}041$, voxel-level $P_{corrected} = 0{\cdot}042$, $Z = 2{\cdot}58$ $(x, y, z) = 0, 20, 32$) in the OCD group compared with the control group. The second SVC, conducted on a parietal region (Zago *et al.* 2001), detected a significant peak activation (cluster-level

Table 1. *Cerebral regions more activated in obsessive–compulsive disorder patients compared with healthy subjects for the non-repeated versus repeated trials*

Region	BA	Cluster volume (mm^3)†	Voxel *Z* score	Talairach coordinates*		
				x	*y*	*z*
L superior frontal gyrus	10	576	3·85	−28	60	4
L superior temporal gyrus	22	576	3·63	−64	−40	16
R paracentral lobule	7	256	3·36	8	−48	64
L intraparietal sulcus	40	128	3·74	−28	−44	56
R cuneus	19	128	3·68	12	−84	28
R inferior frontal gyrus	47	128	3·34	28	24	−12
L inferior parietal gyrus	40	128	3·25	−48	−52	32
L paracentral lobule	7	64	3·23	−16	−48	64
R precuneus	7	64	3·11	24	−56	32

BA, Brodmann area; L, left; R, right.
* Talairach & Tournoux (1988).
† Voxel size = (4·0, 4·0, 4·0) mm.

$P_{corrected} = 0{\cdot}041$, voxel-level $P_{corrected} = 0{\cdot}043$, $Z = 3{\cdot}74$, $(x, y, z) = -28, -44, 56$) in the OCD group compared with the control group.

In the reverse comparison, that is, for repeated *minus* non-repeated trials, no significant activations were detected, either for the control or for the patient groups.

Complementary exploratory analyses determined whether the resistance to OC symptoms accounted for fMRI results during non-repeated trials. When repeated-congruent trials were substracted from non-repeated-congruent trials, the non-resistant patients activated, bilaterally, three distinct posterior clusters of voxels: pulvinar, precuneus and adjacent posterior cingulate, paracentral lobules (Table 2, Figs. 1 and 2). Compared with healthy subjects, the non-resistant patients showed greater activation, bilaterally, in the precuneus, paracentral lobules and inferior parietal lobe. The resistant patients showed a cerebral activation comparable to that of the healthy subjects for the same condition.

Analyses of intragroup effects showed no regions activated in the resistant to OC symptoms subgroup, while in the non-resistant subgroup, the same set of cerebral regions detected above was activated (data not shown). Thus, the inter-group differences arose from a greater activation in the non-resistant subgroup and not from regional deactivations in the resistant subgroup.

Table 2. *Cerebral regions activated in non-resistant compared with resistant patients for the non-repeated versus repeated trials*

Region	BA	Cluster volume (mm^3)†	Voxel *Z* score	Talairach coordinates*		
				x	*y*	*z*
R precuneus	7	5760	4·38	12	−44	32
L precuneus	7		4·25	−8	−44	32
L precuneus	31		3·91	−20	−44	36
L posterior cingulate gyrus	30		3·98	−8	−48	12
R posterior cingulate gyrus	23		3·47	4	−40	24
R pulvinar		1984	4·31	20	−32	8
R thalamus			3·28	12	−24	4
L pulvinar		1344	4·11	−16	−32	8
L postcentral gyrus	4	1024	3·95	−20	−32	60
L paracentral lobule	7		3·22	−8	−24	56
R postcentral gyrus	3	1024	3·91	12	−36	64
R paracentral lobule	6		3·77	8	−32	60
R paracentral lobule	7		3·76	12	−24	56
R superior frontal gyrus	10	640	3·81	12	64	−4
L superior frontal gyrus	10	640	3·63	−16	60	20
L inferior frontal gyrus	45	576	4·35	−52	28	4

BA, Brodmann area; R, right; L, left.
* Talairach & Tournoux (1988).
† Voxel size = (4·0, 4·0, 4·0) mm.

In the reverse comparison, that is, for repeated *minus* non-repeated trials, no significant activations were detected, either for the non-resistant or for the resistant subgroups.

DISCUSSION

Using event-related fMRI and number-priming method in young OCD patients we did not detect abnormal activities in anterior brain regions classically involved in the monitoring of incongruity between stimuli. However, abnormal activations were detected in the OCD group compared with the healthy group, in parietal, temporal and precuneus regions for the repetition factor within trials. Moreover, using SVC, anterior cingulate and left parietal subregions were also found to hyperactivate in OCD patients. In the same comparison, the dichotomization of patients according to their resistance to OC symptoms during scanning, revealed a hyperactive posterior network in the non-resistant subgroup only, including bilaterally,

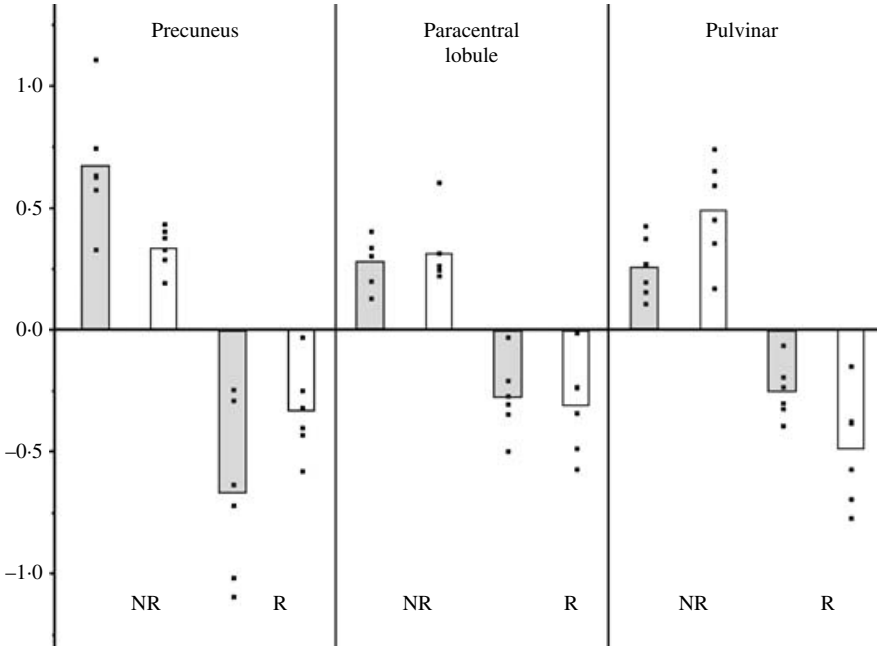
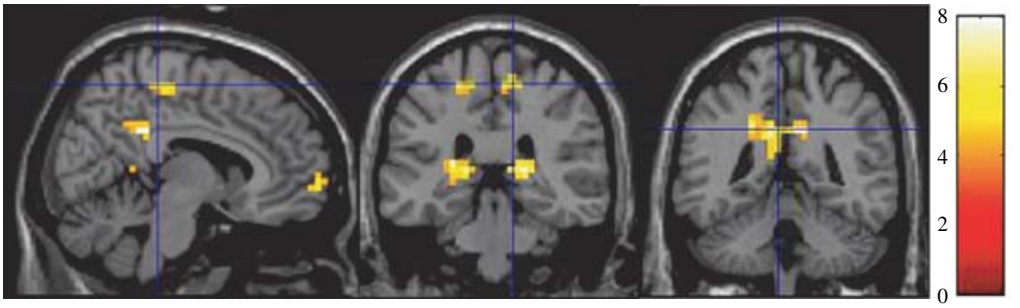


FIG. 1. Adjusted functional magnetic resonance imaging values obtained with SPM99 software in non-resistant compared with resistant patients with obsessive–compulsive disorder, for the non-repeated-congruent *versus* repeated-congruent trials, in three bilateral regions (Talairach's coordinates *x*, *y*, *z*); pulvinar: R (20, −32, 8), L (−16, −32, 8); paracentral lobules: R (12, −36, 64), L (−20, −32, 60); precuneus: R (12, −44, 32), L (−8, −44, 32). (Bar charts show means. NR, non-resistant patients; R, resistant patients; grey, right; white, left.)



COLOUR

FIG. 2. Images showing activation of a bilateral network in non-resistant compared with resistant patients with obsessive–compulsive disorder, for the non-repeated-congruent *versus* repeated-congruent trials. Centre image: the coronal plane shows pulvinar and paracentral lobules (crosshair indicates Talairach's coordinates: $x=8$, $y=-32$, $z=60$). The right image shows the precuneus ($x=-8$, $y=-44$, $z=32$). The left image (sagittal plane: $x=8$, $y=-32$, $z=60$) shows activations both in these posterior structures, and in the left superior/medial frontal gyrus. (Colour scale: voxel *Z*-score values.)

the pulvinar, precuneus and posterior cingulate, and paracentral lobules.

Patient sample characteristics

All patients presented a childhood-onset OCD, with a chronic course of illness. All had pure OCD, with no current co-morbidity. Nine patients had obsessions and/or rituals involving counting or number manipulation. The frequency of such symptoms in a large referred adult OCD population was 36% (Rasmussen & Tsuang, 1986); in series of children and adolescents, counting obsessions are reported by at least 18% of subjects (Swedo *et al*. 1989).

Clinical severity of OCD, as assessed by the Y-BOCS total score, ranged from 20 to 33; a score of 20 is often the cut-off chosen to include subjects with clinically significant OCD in treatment trials, while a score of 33 denotes very severe OCD. Thus, clinical severity of OCD in subjects included in the current study can be considered as moderate to marked.

Behavioural performance

Obsessional slowness has been consistently reported during neuropsychological testing (Hymas *et al.* 1991; Galderisi *et al.* 1995). Inspection of RT medians in our patient sample showed that they were systematically slower than healthy subjects, although no significant differences were detected for congruity or repetition conditions. High within-group variability, and the limited number of subjects, may have precluded the detection of a significant difference. Only the interaction between group and repetition conditions tended towards significance ($p = 0{\cdot}09$). The intergroup RT differences appeared longer in the non-repeated-congruent (mean = 81 ms) than in the repeated-congruent (54 ms) condition. A trend can only be used to generate a hypothesis requiring further confirmation. Thus, we can only speculate that patients' slowness was marked in the non-repeated-congruent condition, that is, when the stimuli were only subtly different. When the differences between stimuli were more straightforward, that is, in the incongruent (55 ms) or in the repeated-congruent conditions, patients appeared less impaired.

Brain imaging

In the incongruent *versus* congruent condition, we did not detect abnormal activity in the cingulate cortex, a region classically involved in situations of conflict or competition between stimuli (MacLeod *et al.* 2000). However, peculiarities in patients' brain functioning were observed when they had to manage small differences between the stimuli, that is, within the congruent-repetition condition. Excessive activations were detected during the condition where the prime and target numbers were congruent, but different (that is, the prime and target numbers are both superior or both inferior to 5, and non-repeated), relative to the condition in which the prime and target numbers were identical. This reflects the increased difficulty in comparing two numbers that are congruent, but non-repeated, than two identical numbers. In other words, OCD patients showed increased activations when more subtle discrimination between stimuli was required. In comparison to healthy subjects, the OCD patients showed greater activation in the left parietal regions (intraparietal sulcus, and inferior and superior parietal lobules). This result mirrors that of Naccache & Dehaene (2001) in healthy subjects, showing that the repetition of the same number reduced activation relative to non-repeated trials, precisely in the intraparietal sulcus, a region thought to encode the quantity meaning of numbers. The same authors hypothesized that the parietal lobe is central to the mental representation of numerical quantities (Cohen & Dehaene, 1995; Dehaene *et al.* 1998). Previous functional imaging studies revealed that parietal lobes play a role in number processing and calculation, such as comparison of two numbers (Rueckert *et al.* 1996; Chochon *et al.* 1999; Dehaene *et al.* 1999; Pinel *et al.* 1999, 2001; Pesenti *et al.* 2000; Dehaene *et al.* 2003).

Further confirmation was provided by using the SVC procedure which detected analogous changes, in the same condition. The analyses centred on the left intraparietal sulcus, an area previously reported to enhance activation in difficult complex calculations relative to easier calculations (Zago *et al.* 2001). Thus, OCD patients, while accomplishing an effortful task, showed greater activation in a region known to process task difficulty.

Moreover, the SVC procedure, performed on the anterior cingulate area reported in Bush and colleagues' (2000) previous meta-analysis, found a significant peak activation in the OCD group compared with the control group for the same condition (that is, non-repeated-congruent relative to the repeated-congruent trials). This analysis was centred on a point located in the cognitive division of the anterior cingulate gyrus, a region belonging to a distributed attentional network and maintaining reciprocal interconnections with the parietal cortex (Bush *et al.* 2000). This region is known to show greater activation during difficult tasks (Barch *et al.* 1997). Correlation of activity in the anterior cingulate

with task difficulty was also found in a vast review of over 100 positron emission tomography studies (Paus *et al*. 1998). Neuroimaging studies on OCD have implicated the anterior cingulate as part of an abnormally functioning fronto-thalamo-basal ganglia circuitry. Extensive evidence is provided by neuroimaging studies of abnormal anterior cingulate hyperactivations in tasks where OCD patients have to deal with conflicting information (van Veen & Carter, 2002; Ursu *et al*. 2003) or with task difficulty (Van der Wee *et al*. 2003). The findings obtained in the present study are congruent with this literature: OCD patients showed greater activation in a region known to process task difficulty.

The patient group activated more the regions solicited by the task's type of stimulus, that is, numbers. It is likely that this higher activation by a distracting number (when it differs from the target that actually has to be processed) is directly related to the patients' inability to control their obsessive behaviour, which often involves complex calculation schemes.

In order to further investigate the impact of patients' clinical features on cerebral activation during the number comparison task, the OCD group was divided in two subgroups. The non-resistant patients showed enhanced activation in a clear-cut bilateral and symmetric posterior network involving the pulvinar, the precuneus and adjacent posterior cingulate, and the paracentral lobules, compared with the resistant subjects. Because of the relatively small number of subjects in each patient subgroup and the absence of corrections for the number of voxels tested, these results are exploratory and must be interpreted with caution.

We speculate that this result denotes the excessive activity of posterior structures involved in the amplification aspect of attention. The pulvinar is an 'associative' thalamic nucleus that plays a central role in attention by intensifying the cortico-cortical connections between areas engaged by a task (LaBerge, 2000). It is involved in visual focal attention (Shipp, 2004). All the stimuli in our study were presented in the visual modality. Precuneus activation was demonstrated in previous imaging studies to reflect an attention shift to visual stimuli, when discriminating stimuli features (Fink *et al*. 1997; Nagahama *et al*. 1999; Brass *et al*. 2001). The posterior cingulate cortex might mediate the anticipatory allocation of spatial attention in a visual task (Small *et al*. 2003). Paracentral lobule (PL) activation can be attention-dependent, particularly in tasks involving the sensorimotor modality (Forss *et al*. 1996). This modality was engaged in the present task during hand responses. Thus, higher activation of the PL in the non-resistant compared with the resistant patients corroborates the excessive recruitment of a posterior attentional network.

Interestingly, the absence of abnormalities in regions such as the orbitofrontal or caudate nuclei, often reported as abnormal in resting-state brain imaging studies (e.g. Saxena *et al*. 1998), suggests that the detection of dysfunction in OCD varies according to the patient samples and experimental conditions. Also, variations in regional activations with OCD symptom dimensions were reported recently. Mataix-Cols *et al*. (2004) investigated the neural correlates of three different symptom dimensions in OCD (washing, checking and hoarding) using fMRI. Their results showed a distinct pattern of activation associated with each symptom dimension. These findings, in line with our results, suggest that different OC symptom dimensions are mediated by distinct components of cortical-subcortical circuits. Consequently, neuroimaging information regarding OCD should be considered together with the specificities of the experimental tasks and patient samples, when used as evidence regarding rationalization for physical treatments such as brain stimulation.

Overall, in a sample of patients with early-onset OC disorder, regional hyperactivations suggest abnormal attentional amplification process in OCD subjects during the discrimination of repetitive visual stimuli. The regional distribution in functional changes may depend on the patients' ability to resist obsessional symptoms.

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