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Compensatory hyperactivations as markers of latent working memory dysfunctions in patients with obsessive–compulsive disorder: an fMRI study

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Objective: Behavioural studies have implicated working memory (WM) deficits in obsessive–compulsive disorder (OCD). However, findings are inconsistent, which could be explained by compensation strategies used by a subgroup of OCD patients. To test this hypothesis, we examined patients without a behavioural deficit in WM during performance of different WM tasks using functional magnetic resonance imaging (fMRI). **Methods:** We scaned 11 patients and 11 matched control subjects while they performed 3 verbal and spatial item-recognition tasks. **Results:** Patients and healthy subjects engaged the same set of brain regions. However, in direct comparison, the patients exhibited significantly greater task-related activation in several frontal and parietal brain areas known to underlie WM. **Conclusion:** Patients without manifest WM deficits exhibit increased activation in frontal and parietal brain areas relative to healthy subjects during WM task performance. These hyperactivations may permit them to compensate for reduced efficiency of their WM systems and may thus serve as markers of latent WM dysfunctions.

Objectif : Des études du comportement ont mis en cause des déficits de la mémoire de travail (MT) dans le trouble obsessif-compulsif (TOC). Les résultats manquent toutefois d'uniformité, ce que l'on pourrait expliquer par des stratégies de compensation utilisées par un sous-groupe de patients atteints de TOC. Afin de vérifier cette hypothèse, nous avons examiné des patients sans déficit comportemental de la MT pendant l'exécution de diverses tâches liées à la MT en utilisant l'imagerie par résonance magnétique fonctionnelle (IRMf). **Méthodes :** Nous avons examiné 11 patients et 11 sujets témoins jumelés pendant l'exécution de trois tâches verbales et de reconnaissance d'un objet dans l'espace. **Résultats :** Les patients et les sujets en bonne santé ont mis à contribution le même ensemble de régions cérébrales. Toutefois, lorsqu'on établit une comparaison directe, les patients montrent une activation reliée à la tâche beaucoup plus importante dans plusieurs régions frontales et pariétales du cerveau reconnues pour sous-tendre la MT. **Conclusion :** Les patients sans déficit manifeste de la MT présentent une activation accrue des régions frontales et pariétales du cerveau par rapport aux sujets en bonne santé au cours de l'exécution d'une tâche liée à la MT. Ces hyperactivations peuvent leur permettre de compenser l'efficience réduite de leur système de MT et servir ainsi d'indicateur d'une dysfonction latente de la MT.

Introduction

Obsessive–compulsive disorder (OCD) is characterized by intrusive thoughts and compulsive behaviour that cannot be suppressed. Lifetime prevalence rates for OCD are between 1.5% and 3%.[1] Apart from having these clinical symptoms, it has been suggested that the disorder is associated with cognitive dysfunction wherein disturbances of working memory (WM) seem to be particularly important.[2–5] However, the findings across behavioural studies are inconsistent and the relation between WM disturbances and OCD remains unclear.

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Medical subject headings: obsessive–compulsive disorder; memory; magnetic resonance imaging; cognition.

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One possible explanation for this variation in findings might be that some OCD patients have latent deficits in WM that cannot be detected on the behavioural level. This is suggested by observations of normal WM performance in OCD patients at low task demands but manifest WM deficits at higher task demands.[4,6] These findings have 2 important implications. First, they support the notion that OCD is indeed associated with disturbances of WM. Second, the observation that the patients' WM performance was normal at low task demands and that it dropped significantly below that of control subjects only at higher task demands suggests that OCD patients may be able to compensate for their WM impairments, at least to a certain extent.

Studies with modern imaging techniques could shed light on this issue, but to date, only a few neuroimaging studies have examined WM functions in patients with OCD, most of them focusing on the spatial domain of WM.[6,7] To our knowledge, no study yet has systematically investigated the integrity of the brain circuits underlying different subcomponents of verbal and spatial WM in patients with OCD. Additionally, no study has focused on the question of whether the inconsistencies in previous behavioural experiments might be due to the fact that a subgroup of OCD patients is able to compensate for WM deficits so that they are not detectable by pure neuropsychological assessment.

To address these questions, we assessed brain activation patterns in OCD patients while they performed different verbal and spatial WM tasks. Because our primary focus was the question of whether some OCD patients may be able to compensate for impairments in WM, we examined and preselected OCD patients without a behavioural deficit in WM (for details see the Methods section). Another important reason for this preselection was that activation differences between a patient and a control group can only be interpreted unambiguously if the groups are matched for performance. This is a consequence of the complex relation between brain activation and task performance, as outlined by Manoach[8] and Callicott and colleagues.[9] The theoretical model proposed by these authors implies that the hemodynamic response in a task-relevant brain region follows an inverted U-shape as a function of task difficulty. This curve is shifted to the left when the efficiency of a task-relevant brain region is reduced, resulting in characteristic group activation differences when subjects with an impaired system are compared with subjects with an unaffected system (Fig. 1). Such activation differences, however, only reliably reflect a neural dysfunction in one group if both groups present a comparable level of performance because, otherwise, activation differences may simply reflect inattention, poor motivation or the use of an inappropriate strategy in one of the groups.

For these reasons, we used functional magnetic resonance imaging (fMRI) to examine normally performing OCD patients and matched healthy subjects during the performance of different tasks known to specifically activate brain networks supporting core functions of verbal and spatial WM, (i.e., articulatory rehearsal, nonarticulatory phonological maintenance and the maintenance of visuospatial information).

Methods

Participants

We recruited 11 OCD patients and 11 healthy comparison subjects to participate in the study. The patients had a diagnosis of OCD according to the criteria of the *International Classification of Diseases*[10] and the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV)[11] (assessed with the Structured Clinical Interview for DSM-IV) and based on the consensus of several experienced clinicians. Patients were recruited from the psychiatry department at Saarland University Hospital, Homburg, Germany. Exclusion criteria included substance abuse, acute depression, acute suicidal tendency, a history of neurologic illness or brain injury and a diagnosis of psychosis. We included only OCD patients who had shown normal performance in prior behavioural experiments on WM that had taken place in our laboratory a few months before the currently reported fMRI experiments. In this testing, OCD patients and matched healthy control subjects had performed verbal and spatial item-recognition tasks that were highly similar to the tasks employed in the present study. The patients selected to participate in the fMRI experiment presented a task performance in the pretest that was statistically equivalent to the performance of healthy comparison subjects. A further criterion for selection was that the patients showed accuracy scores in each of the WM tasks that were no more than 2 standard deviations (SDs) below the mean of the accuracy scores in the healthy comparison group (most patients showed a much better performance).[12] On the day of the experiment, the clinical state of the patients was assessed by trained physicians using the Beck Depression Inventory[13] and the German version of the semistructured interview of the Yale-Brown Obsessive Compulsive Scale (YBOCS).[14,15] Of the patients, 6 presented mainly washing symptoms, 3 checking symptoms and 2 predominantly aggressive obsessions. Most patients were receiving medication at the time of the study: 8 patients were taking serotonin reuptake inhibitors (SRIs), 1

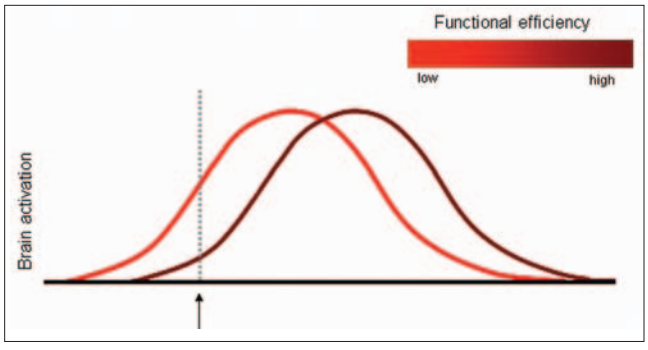

Fig. 1: The relation between brain activation and task performance according to Manoach's model. On the ascending branch of the curves, subjects present normal task performance, whereas task performance declines after the activation maximum is exceeded. The dashed line depicts a given task difficulty. At this level of task difficulty, subjects showing the light red activation curve would present normal task performance but greater brain activation than subjects with the dark red activation curve (modified from Manoach[8]).

patient was taking a tricyclic antidepressant, and 2 patients were medication-free.

Healthy comparison subjects were selected to match patients for age, sex and level of education. Exclusion criteria for the healthy comparison subjects were the same as for patients, with the additional criterion of no past or present psychiatric disorder. All participants were right-handed native speakers of German, and all subjects provided written informed consent after study procedures had been explained in detail. The study was approved by the ethics committee of the "Ärztekammer des Saarlandes." Demographic and clinical data of both groups are displayed in Table 1.

Tasks

Subjects performed 3 item-recognition tasks that have been demonstrated in previous imaging studies to consistently activate brain systems underlying domain-specific subcomponents of WM.[16–19] Two of these tasks required the (articulatory or nonarticulatory phonological) maintenance of verbal material, and one required the maintenance of visuospatial material. A letter-case judgment task and a geometric-form judgment task served as control conditions.

The tasks were presented in 3 experimental runs, each comprising 1 variant of the WM task and its corresponding control condition. Within each run, the WM task and the control condition were presented in alternating blocks, with each block consisting of 3 trials of the same task. A cue at the beginning of each block indicated whether a WM task or a judgment task had to be performed in the upcoming block.

Table 1: Clinical, demographic and memory task performance characteristics of patient and control groups

Subject characteristics	Group; mean (and SD)		Group comparison; *p* value
	Patient (*n* = 11)	Control (*n* = 11)	
Age, y	32.64 (7.17)	33.73 (15.29)	0.83
Age at onset, y	18.91 (9.07)	—	—
Education, y	14.09 (2.30)	14.82 (1.47)	0.39
YBOCS score			
Total	21.00 (9.47)	—	—
Obsessions subscale	10.09 (4.53)	—	—
Compulsions subscale	10.91 (5.28)	—	—
BDI score	11.45 (10.93)	—	—
Articulatory rehearsal task			
Accuracy, %	92.6 (5.0)	93.5 (6.1)	0.71
Reaction time, ms	1173 (261)	1174 (213)	0.99
Nonarticulatory phonological maintenance task			
Accuracy, %	88.9 (11.7)	88.4 (5.9)	0.89
Reaction time, ms	1104 (165)	1180 (193)	0.34
Visuospatial maintenance task			
Accuracy, %	92.9 (6.2)	92.5 (7.7)	0.91
Reaction time, ms	1070 (232)	1071 (200)	0.99

BDI = Beck Depression Inventory; SD = standard deviation; YBOCS = Yale-Brown Obsessive Compulsive Scale.

The order of tasks was systematically varied across subjects and balanced across groups.

In both variants of the verbal WM task, each experimental trial started with the 2-second presentation of 4 different letters (randomly chosen from a set of 8 phonologically similar letters), followed by a 4-second delay during which a fixation cross was displayed. The delay was followed by a 1.5-second presentation of a single probe letter (Fig. 2). Subjects had to judge whether this probe letter matched one of the target letters and to respond by pressing a button. Although the general trial structure was similar in both variants of the verbal WM task, subjects were instructed to apply different strategies in each of the 2 task variants. In the first variant, they had to rehearse the presented letters by using inner speech (articulatory rehearsal task), whereas in the second variant, they had to maintain the verbal information in WM without using articulatory rehearsal (nonarticulatory phonological maintenance task). This latter strategy was forced by an articulatory suppression task in which the subjects had to subvocalize "1, 2, 3, 4, 1, 2 …" in a repetitive and rapid manner, paced by tones that were presented throughout the delay interval. Previous studies had demontrated that this procedure prevented subjects from using articulatory rehearsal.[16–18] During the control conditions for the verbal WM tasks, subjects had to merely look at the presented letters without memorizing them and to judge whether the probe letter was uppercase or lowercase. During the control condition for the nonarticulatory phonological WM task (performed under articulatory suppression), they also had to perform the above-mentioned articulatory suppression procedure, which allowed matching of the 2 tasks with respect to the articulation rates. During the spatial WM task, a 5×5 matrix was presented with 4 positions filled by either squares or triangles (Fig. 2). Subjects were instructed to memorize the positions that were filled with geometric forms and to decide whether one of these positions was matched by the position of a probe form presented at the end of the trial. In the corresponding control condition, subjects had to judge whether the probe form was a square or a triangle.

All stimuli were generated with the use of ERTS software (Experimental run time system, Version 3.11, BeriSoft, Frankfurt am Main, Germany). Responses had to be given by pressing a button with the index or the middle finger of the right hand. Prior to the experiment, subjects were given the necessary training for the completion of the task, outside the scanner, for about 30 minutes.

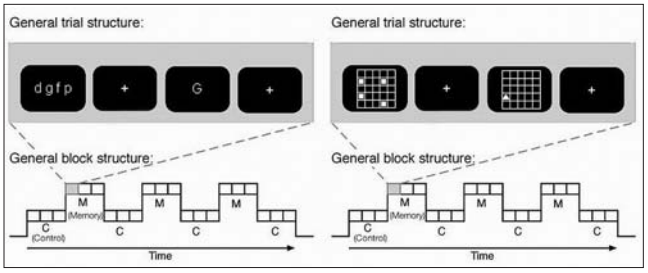

Fig. 2: Experimental design of the verbal (**left**) and spatial (**right**) working memory tasks and the block structure of the experiment. M stands for blocks comprising working memory trials and C for blocks comprising control trials.

Image acquisition

All stimuli were visually presented on a screen as white stimuli on black ground, except for the task cues, which were presented in yellow. Imaging was performed on a 1.5-T scanner (Siemens Sonata, München, Germany), with the following parameters: voxel size $3.6 \times 3.6 \times 4$ mm^3, interscan interval 2500 milliseconds, echo time 50 milliseconds, distance factor 12%, flip angle 90°, field of view 230 mm, 64×64 matrix. There were 3 experimental runs; during each, a total of 271 functional image volumes were acquired, each consisting of 26 axial slices parallel to the AC-PC plane. Functional imaging was synchronized with stimulus presentation by means of ERTS. Additionally, a high-resolution 3D anatomical set (T_1-weighted) was collected for each subject.

Data processing

Behavioural data were analyzed with SPSS (version 13.0). The analyses of between-group differences in error rates and reaction times were conducted by means of 2-sample *t* tests (2-tailed). Reaction time analysis was carried out for correct answers only. fMRI data were processed with SPM2 software (www.fil.ion.ucl.ac.uk/spm/spm2.html). The first 5 volumes of each run were discarded. Preprocessing comprised coregistration, corrections for motion artifacts and slice time acquisition differences, normalization into standard stereotactic space and spatial smoothing with a Gaussian kernel (full width at half maximum = 12 mm). After preprocessing, we calculated individual *t* maps for the contrasts of each variant of the WM task versus its corresponding control condition, using the general linear model. The vectors for analyses of the fMRI data were time-locked to the beginning of the first trial (the presentation of the target letters or positions) in each WM and control block, respectively. For group statistics, we performed random effects analyses on the single subject contrast images (using 1-sample Student´s *t* tests). Results are reported at a statistical threshold of $p_{\text{uncorrected}} < 0.001$. Differences in activation between groups were tested for significance with 2-sample *t* tests, and we report only those results that reached a statistical threshold of $p_{\text{uncorrected}} < 0.005$. For group comparisons, we calculated for each of the task variants the contrast (WM task – control task)$_{\text{controls}}$ > (WM task – control task)$_{\text{patients}}$ and vice versa. We further applied a conjunction analysis to determine common activations in all comparisons between patients and healthy subjects, using the SPM tool provided by Tom Nichols (www.sph.umich.edu/~nichols/Conj). Results of this analysis are reported at a threshold of $p_{\text{uncorrected}} < 0.005$. To determine whether the patients' current psychopathology was associated with imaging findings, we additionally regressed their YBOCS scores on their imaging data. Because we were particularly interested in those regions found to be hyperactivated in the patients, we used small volume corrections (SVC) to correct the search volume to these anatomical regions. Statistical significance is reported at $p < 0.05$, familywise error (FWE) corrected.

Results

Demographic measures

The patient and comparison groups did not differ significantly on any demographic variable (see Table 1).

Behavioural results

The overall mean percentage of correct responses was 91.5% (SD 8.1%) for the OCD patients and 91.6% (SD 6.8%) for the comparison subjects (For more details, see Table 1 and Fig. 3). There were no significant group differences in response accuracy or response latencies between the patient and comparison groups in the verbal and spatial WM tasks (accuracy, articulatory rehearsal task, $t_{20} = 0.38$, $p = 0.71$; nonarticulatory phonological maintenance task, $t_{19} = -0.14$, $p = 0.89$; visuospatial maintenance task, $t_{20} = -0.11$, $p = 0.91$; reaction times, articulatory rehearsal task, $t_{20} = 0.01$, $p = 0.99$; nonarticulatory phonological maintenance task, $t_{19} = 0.97$, $p = 0.34$; and visuospatial maintenance task, $t_{20} = 0.02$, $p = 0.99$).

Group average activation

The analysis of fMRI data revealed that both groups activated similar brain regions in each of the 3 WM tasks (Fig. 4). During the verbal rehearsal task, significant memory-related activity showed up in the left precentral gyrus, left inferior frontal gyrus (IFG) (Broca's Area 44), bilateral inferior frontal sulcus (IFS), bilateral fronto-opercular cortex adjacent to the anterior insula, left intraparietal cortex and cerebellum. During nonarticulatory phonological maintenance of verbal information, task-related activity was observed in the left precentral gyrus, bilateral inferior frontal sulcus, left inferior frontal gyrus, bilateral middle frontal gyrus, bilateral frontoopercular cortex, bilateral intraparietal cortex and cerebellum. Activations associated with the maintenance of visuospatial information were detected bilaterally in the cortices along the posterior parts of the superior frontal sulcus as well as along the intraparietal sulcus (IPS), in superior parietal and occipital cortices, in the precentral gyrus and the insula,

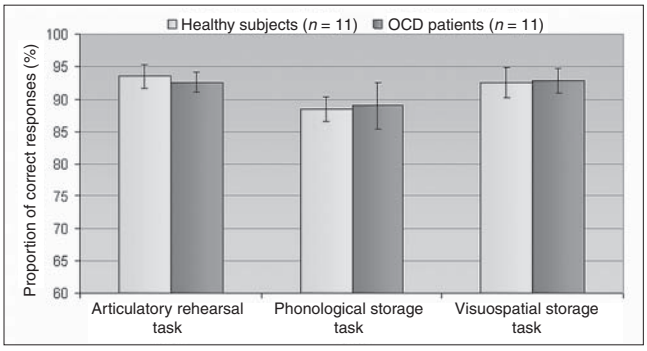

Fig. 3: Working memory task performance of OCD patients and healthy control subjects (mean and standard error). There were no significant differences in task performance between OCD patients and healthy comparison subjects. OCD = obsessive–compulsive disorder.

and in the right middle frontal gyrus, right posterior inferior temporal gyrus and cerebellum.

Between-group comparisons of activation

Several areas of abnormally increased brain activation in OCD patients were revealed through direct comparison between the groups during WM task performance (Table 2 and Fig. 5). During performance of the 2 verbal WM tasks, the patients showed significantly increased activity in the left inferior frontal junction area (IFJ), the left inferior frontal gyrus, the middle part of the left inferior frontal sulcus, and in small areas within the left (during articulatory maintenance) and the right (during nonarticulatory phonological maintenance) intraparietal cortex, compared with healthy subjects. During performance of the spatial WM task, abnormally enhanced activity was observed in OCD patients in the left IFJ. The conjunction analysis showed, further, that the left IFJ was the only region that was commonly hyperactivated in patients, compared with healthy subjects, during performance of all WM tasks. Conversely, the healthy control subjects did not show significantly greater brain activation during WM task performance in any brain region, compared with the patients.

Correlations between brain activation and symptom severity

The results of the correlation analyses between clinical ratings and brain activity measures suggest that the amount of activation in some of the hyperactivated brain regions seen in patients was related to symptom severity. We found positive correlations between the total YBOCS score and the amount of activation in the left frontal and the left parietal cortex during performance of the articulatory rehearsal task (IFG –40 24 8, $p_{\text{fwe-corrected}} = 0.023$, $t = 2.32$; IFJ –36 0 32, $p_{\text{fwe-corrected}} = 0.40$, $t = 1.76$; IPS –24 –60 48, $p_{\text{fwe-corrected}} = 0.041$, $t = 1.96$), as well as between the total YBOCS score and the amount of activation in the left IFS during the nonarticulatory maintenance task (IFS –40 20 20, $p_{\text{fwe-corrected}} = 0.033$, $t = 2.10$). During the spatial maintenance task, there was further a positive correlation between the amount of activation in the left IFJ and the total YBOCS score (IFJ –28 –4 32, $p_{\text{fwe-corrected}} = 0.045$, $t = 1.90$).

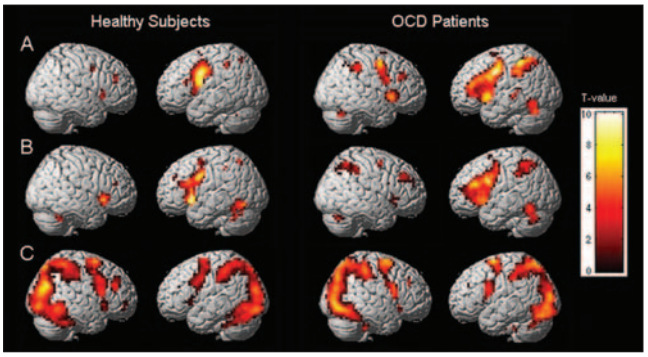

Fig. 4: Group activation maps for OCD patients and healthy control subjects for the contrasts (**A**) articulatory rehearsal task versus letter case judgment task, (**B**) phonological maintenance task versus letter case judgment task (with articulatory suppression procedure), (**C**) visuospatial maintenance task versus geometric form judgment task. All contrasts $p_{\text{uncorrected}} < 0.001$. OCD = obsessive–compulsive disorder.

Discussion

The objective of this study was to compare patterns of brain activation in OCD patients and healthy control subjects during performance of tasks especially targeting different subcomponents of verbal and spatial WM at a controlled level of performance. Following this approach, we wanted to clarify whether some patients with OCD might have latent deficits in WM that are not manifest on the behavioural level.

Our analyses revealed that in each of the WM tasks OCD patients and healthy subjects activated a comparable set of brain regions, a finding consistent with repeated observations in healthy subjects in previous studies using similar experimental paradigms.[16–18] On direct comparison between groups, however, the patients showed abnormal activity in some of these brain regions. The most prominent activation differences occurred during performance of the 2 verbal WM tasks. During

Table 2: Areas of increased activation in OCD patients compared with healthy control subjects during verbal and spatial WM tasks

Task and region	OCD patients > control subjects			Statistical effects; *t* value
	MNI coordinates			
	x	y	z	
Articulatory rehearsal task				
Left precentral sulcus/IFJ	–36/–52	0/8	32/32	3.79*/3.26†
Left intraparietal cortex	–24	–56	52	3.78*
Left inferior frontal gyrus	–44	24	8	3.38*
Left inferior frontal sulcus, middle third	–40	36	20	3.33†
Nonarticulatory phonological maintenance task				
Left precentral sulcus/IFJ	–36/–48	4/4	32/28	4.06*/3.99*
Left inferior frontal sulcus, middle third	–40	24	24	3.88*
Right intraparietal cortex	24	–56	56	3.32†
Left inferior frontal gyrus	–48	24	8	3.02†
Visuospatial maintenance task				
Left precentral sulcus/IFJ	–32	–4	32	2.95†
Common activation				
Left precentral sulcus/IFJ	–32	0	32	2.83†

IFJ = inferior frontal junction; MNI = Montreal Neurological Institute; OCD = obsessive–compulsive disorder; WM = working memory.
*$p = 0.001$.
†$p = 0.005$.

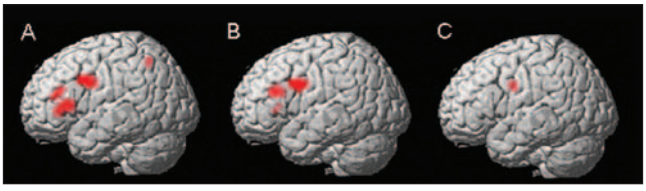

Fig. 5: Brain regions with significantly enhanced activity in OCD patients compared with healthy control subjects during (**A**) the articulatory rehearsal task, (**B**) the phonological maintenance task, (**C**) the visuospatial maintenance task. All contrasts $p_{\text{uncorrected}} < 0.005$. OCD = obsessive–compulsive disorder.

the articulatory rehearsal task and the task requiring the phonological maintenance of verbal information, significant hyperactivation was observed in OCD patients in the left inferior frontal cortex, the middle part of the left inferior frontal sulcus, the left IFJ area and the intraparietal cortex. As repeatedly demonstrated by earlier studies, activation of these brain regions is related to articulatory rehearsal and the phonological maintenance of verbal information in healthy subjects.[17,18] In line with these results, we found the brain areas to be significantly activated in both patients and healthy subjects during WM task performance, indicating a quantitative instead of a qualitative activation difference. In view of the theoretical model proposed by Manoach[8] and Callicott and colleagues,[9] the abnormally increased activity in brain regions supporting WM functions in the investigated patients can be assumed to reflect a shift of the patients' activation curve to the left (Fig. 1). In other words, the patients were required to activate WM-related brain regions to a greater extent than healthy subjects to achieve the same level of performance. Because both groups did not differ in task performance, we could further rule out that the observed group activation differences were simply caused by motivational aspects. Thus the findings of the present study should provide functional neuroanatomical evidence that normally performing OCD patients may have latent deficits in WM that are not reflected in behavioural performance.

The IFJ was hyperactivated in OCD patients, compared with healthy subjects, during performance of the spatial WM task. As well, in earlier studies, the IFJ has also been found to be activated during different WM tasks,[16–18,20] suggesting that this region may underlie domain-independent processes during WM performance. Apart from that, significant activation in the IFJ has been reported across various other cognitive tasks, among them task-switching and set-shifting paradigms[20–22] as well as the Stroop task.[23,24] Taken together, these findings indicate that the IFJ may be linked to processes of cognitive control.[21,25–28] Consequently, the IFJ hyperactivation that the patients exhibited during WM task performance could reflect enhanced recruitment of cognitive control processes. Because the IFJ overactivation occurred together with hyperactivity in brain regions subserving WM functions, one may assume that it also served a compensatory function: cognitive control processes might have been activated more intensely by the patients to achieve normal WM performance in the face of dysfunctions in their WM systems.

An alternative explanation for IFJ hyperactivation in OCD patients could be that this activity represents a general pathophysiological marker of the disorder that is not specifically related to WM performance. This explanation seems plausible because the patients exhibited abnormally increased activity in the IFJ during performance of all WM tasks. However, if this interpretation is true, one would also have expected similar hyperactivations to be observed in OCD patients in other neuroimaging studies using different paradigms. The absence of such findings[6,29] suggests that the IFJ hyperactivation found in the present study was indeed most likely related to compensatory processing that enabled the patients to perform normally during WM tasks.

In contrast to the findings in the verbal domain of WM, brain regions that are known to selectively underlie spatial WM were activated normally in the OCD patients during performance of the spatial WM task. This finding is consistent with data from a previous fMRI study (using a spatial N-back task) in which OCD patients did not present any abnormalities in brain regions subserving spatial WM.[6] However, it may seem difficult to reconcile these results with findings from previous neuropsychological studies demonstrating behavioural deficits in OCD patients during tests of spatial WM.[2–5] One explanation for this discrepancy may be that, at least in some of these studies, impaired task performance was attributable to other factors, rather than being a reflection of a specific dysfunction of the spatial WM system. Recent findings indicate, for instance, that deficits in spatial WM may be state-dependent in OCD.[30] Because our patients were all clinically stable, it might be that they only had slight disturbances of spatial WM and that these deficits were not detectable in our analyses. Future work is needed to test this hypothesis.

The same is true for the relation between disturbances of WM and the symptoms of OCD. As described above, we found positive correlations between the severity of OCD symptoms and the amount of activation in several frontal and parietal brain areas during WM task performance. Although these correlations were weak, they suggest a connection between disturbances of WM and OCD symptoms. A recent imaging study added support to this notion by providing evidence that there are dynamic interactions between brain regions implicated in the processing of OCD-related stimuli and brain regions underlying WM functions in patients with OCD.[31] In this study, it was observed that after symptom provocation the WM-related connectivity between subcortical, frontal and parietal regions, which had been present during task performance in the unprovoked state, was disrupted. In light of this finding, one may hypothesize that the WM impairments in OCD patients are secondary to interfering influences from regions supporting OCD-related processing. Conversely, it might also be that disturbances of WM functions contribute to the expression of the typical behaviours of OCD patients. Several studies have shown that OCD patients present reduced "memory confidence."[32–34] One may therefore speculate that disturbances of WM might contribute to uncertainty and doubt as a clinical feature of OCD. These hypotheses, however, are highly speculative and need further exploration.

Limitations

The findings of the current study are preliminary and could have benefited from the selection of a more homogenous patient group. However, the study was planned to have an exploratory character, and the fact that we observed abnormal brain activation patterns even in a mixed sample of OCD patients highlights the general significance of WM impairments for this disorder. On the basis of this work, it will be possible to investigate homogenous subgroups of OCD patients in future studies. A further limitation of the study may be the inclusion of medicated patients. However, the great majority of patients were on a stable dosage of SRIs at the time of the study. It has been demonstrated that SRI-medicated patients do not

differ from medication-free patients during neuropsychological testing of WM[35] and that escitalopram (an SRI) has no significant effects on performance or on the hemodynamic response during WM tasks.[36] Therefore, it is not likely that the observed group activation differences between patients and healthy subjects are due to effects brought on with medication.

Conclusions

In the present study, we used fMRI to investigate the brain circuits underlying different subcomponents of human WM in patients with OCD and in matched healthy control subjects. Compared with healthy subjects, the investigated OCD patients exhibited significantly increased activity in several brain regions known to play a critical role for WM. Because the patient and control groups were matched for behavioural performance, these hyperactivations presumably reflect compensatory processing that was required because of deficiencies in the patients' WM systems. The findings of the present study thus indicate that fMRI is in some cases a more sensitive method than neuropsychological testing to detect WM dysfunctions in patients with OCD.

Competing interests: None declared.

Contributors: Drs. Henseler, Gruber and Kraft designed the sudy. All authors acquired the data, which Drs. Henseler and Gruber analyzed. Drs. Henseler and Gruber wrote the article, and all authors revised it. All authors gave final approval for the article to be published.

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