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ORIGINAL PAPER

Increased neural activity during overt and continuous semantic verbal fluency in major depression: mainly a failure to deactivate

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Abstract Major depression is associated with impairments in semantic verbal fluency (VF). However, the neural correlates underlying dysfunctional cognitive processing in depressed subjects during the production of semantic category members still remain unclear. In the current study, an overt and continuous semantic VF paradigm was used to examine these mechanisms in a representative sample of 33 patients diagnosed with a current episode of unipolar depression and 33 statistically matched healthy controls. Subjects articulated words in response to semantic category cues while brain activity was measured with functional magnetic resonance imaging (fMRI). Compared to controls, patients showed poorer task performance. On the neural level, a group by condition interaction analysis, corrected for task performance, revealed a reduced task-related deactivation in patients in the right parahippocampal gyrus, the right fusiform gyrus, and the right supplementary motor area. An additional and an increased task-related activation in patients were observed in the right precentral gyrus and the left cerebellum, respectively. These results indicate that a failure to suppress potentially interfering activity from inferior temporal regions involved in default-mode network functions and visual imagery, accompanied by an enhanced recruitment of areas implicated in speech initiation and higher-order language processes, may underlie dysfunctional cognitive processing during semantic VF in depression. The finding that patients with depression demonstrated both decreased performance and aberrant brain activation during the current semantic VF task demonstrates that this paradigm is a sensitive tool for assessing brain dysfunctions in clinical populations.

Keywords Semantic verbal fluency · Major depression · fMRI · Increased neural activity · Failure to deactivate

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Introduction

Major depressive disorder (MDD) is one of the most common psychiatric disorders, affecting about 16 % of the population at some time in their lives [50]. According to present knowledge, MDD is related to dysfunctions within extended networks of cortical, subcortical, and limbic regions, including, for example, prefrontal cortex (PFC), anterior cingulate cortex (ACC), insula, amygdala, basal ganglia, thalamus, cerebellum as well as temporal regions (superior temporal gyrus and (para-)hippocampus), which may cause emotional and cognitive disturbances observed in this disorder (for reviews and meta-analyses see [18–20, 25, 75, 92, 102, 124]). Cognitive dysfunction is a prominent and persistent aspect of MDD, which has been demonstrated on a range of neuropsychological measures (for meta-analyses see [61, 109, 128, 138]). Impaired cognition severely deteriorates social and occupational functioning as well as quality of life, even in apparently remitted patients [6, 45, 74]. Deficits in the verbal fluency (VF) domain, which are among those with the largest effect sizes [138], have been shown to contribute independently of mood symptoms to poor functional outcome in depression [45]. Characterising the neural mechanisms underlying these dysfunctions is not only an important step towards a comprehensive understanding of this disorder but also

relevant for the development of new treatment options [75].

Verbal fluency, which is assessed by the quantity of words produced in response to a stimulus (typically within 1 min), represents one of the most sensitive measures for detecting brain dysfunction [65]. As opposed to phonemic (lexical/letter/phonological) VF (PVF) tasks, which require subjects to generate as many words as possible that begin with a specific letter (e.g. initial letter P), semantic (category) VF (SVF) tasks afford to produce words that belong to a specific semantic category (e.g. animals). SVF is supposed to tap multiple cognitive processes including access to and retrieval from semantic memory, verbal working memory (WM), articulation of the output, sustained attention, and several executive processes such as efficient task initiation and flexibility [11, 41, 42, 48, 100, 126], yet it forms a distinct cognitive domain that is separable from other executive functions [24, 109]. Most behavioural studies that examined SVF in MDD reported poorer performance in patients as compared to healthy controls [30, 59, 80, 81, 96, 103, 117, 136]; comparatively, few did not find significant differences between groups [17, 35, 38]. Moreover, the findings of several meta-analyses of cognitive impairments in depression point to a substantially larger deficit in SVF as compared to PVF [109, 128, 138].

Neuroimaging studies using functional magnetic resonance imaging (fMRI) have recently shed light on the neural correlates underlying SVF in healthy subjects. Overt SVF as compared to rest produces robust activation in a widespread bilateral language network encompassing mainly (pre-)frontal and temporal cortical areas as well as the cerebellum [11, 40, 52, 78]. Regarding the neural correlates of VF in depression, a large number of neuroimaging studies examined PVF by means of near-infrared spectroscopy (NIRS) [43, 47, 71, 72, 82, 85, 93, 94, 121], fMRI [86, 87, 123], positron emission tomography (PET) [127], or single photon (computed) emission tomography (SPET/SPECT) [5, 89]. In these studies, aberrant brain activation, particularly hypoactivation in PFC, was frequently revealed in patients when compared to controls (for review see [53]).

By contrast, little has been done to determine the effect of depression on the neural correlates of SVF. To date, two neuroimaging studies exist on this subject, which yielded inconsistent results and examined small patient samples with specific characteristics [5, 89]. In a pilot SPET investigation, Philpot et al. [89] measured regional cerebral blood flow (rCBF) in 10 elderly (over the age of 65 years) depressed patients at rest and during a mixed semantic and phonemic VF paradigm with a time limit of 1 min per item. Patients' performance was not significantly impaired, and during task execution, only right parietal rCBF was significantly lower in patients as compared to controls. Frontal lobe deficits were not found. For the evaluation of brain activations, however, the authors conducted region-of-interest (ROI)-based analyses and did not differentiate between PVF and SVF. Moreover, group comparisons of rCBF were carried out separately for rest and VF. Audenaert et al. [5] used a similar task with a new baseline condition to examine the functional neuroanatomy of SVF by means of SPECT in 10 depressed patients with a recent suicide attempt. In contrast to the results of Philpot et al. [89], the depressed group displayed significantly poorer SVF performance. SPECT results demonstrated blunted perfusion in the depressed group in the left inferior frontal gyrus (IFG), the right inferior parietal gyrus, and the bilateral ACC. However, patients in this study were significantly older than control subjects, and the group analysis was not corrected for task performance, raising the possibility that decreased prefrontal perfusion in patients reflected poorer task performance in these subjects. Therefore, the pathophysiological mechanisms during SVF performance that are related to depression per se still remain unclear. Further studies are required that examine the neural correlates of SVF in sufficiently large and representative patient samples and well-matched control groups by means of whole-brain analyses corrected for task performance.

Functional magnetic resonance imaging is ideally suited to assess brain function in depression [20]. However, previous VF studies that used this method, including those examining PVF in depression [86, 87, 123], have typically required silent and experimenter-paced single word generation. Since silent word generation tasks do not provide any performance measures, the results of these studies are difficult to interpret (for details see [7, 11]). Recently, paradigms that allow for overt and self-paced responses have successfully been applied in fMRI [11, 52, 77, 78]. It has been demonstrated that the use of a block design with relatively short task (overt speech) and rest (no speech) periods of about 10 s is suitable for reducing task-related motion artefacts [10, 11]. Moreover, shorter task periods may be important for the study of patients with VF deficits, since in the clinical observation, patients' word production drops off considerably in the course of 1 min [11].

In the current fMRI study, we used such an overt and continuous SVF paradigm with relatively short word production periods to examine the neural correlates of SVF in 33 patients diagnosed with a current episode of unipolar depression and 33 matched healthy controls. To our knowledge, this is the first fMRI study on SVF in depression. In contrast to previous fMRI studies on PVF in depression [86, 87, 123], the present study allowed for overt and self-paced generation of multiple words.

We expected patients to produce fewer words than controls, in line with evidence from studies using standard

behavioural tests [30, 59, 80, 81, 96, 103, 117, 136]. Considering the uncertain and preliminary evidence base regarding the neural correlates of SVF in depression, the current study sought to clarify whether SVF in depressed patients is related to aberrant PFC functioning, which is frequently suggested to underlie executive as well as PVF deficits observed in this disorder [20, 53, 124]. The second aim of the study was to assess whether patients show dysfunctional activation patterns in other brain regions associated with the pathophysiology of MDD, e.g. temporal areas such as superior temporal gyrus and (para-)hippocampus [25]. Based upon results of previous imaging studies on SVF in depression, we anticipated different activation patterns between groups in prefrontal areas, particularly in the left IFG and the ACC [5], as well as in the right parietal cortex [5, 89].

Materials and methods

Subjects

In total, 66 native German speakers were included in this study (for characteristics of study participants see Table 1). We recruited 33 inpatients diagnosed according to ICD-10 criteria with an acute moderate or severe depressive episode at the Department of Psychiatry and Psychotherapy, Philipps-University Marburg. Patients with a history of manic or psychotic episodes were excluded from the study as well as patients with current alcohol or drug abuse, or with a lifetime history of alcohol or drug dependence. Eleven patients had a single diagnosis of depression; fifteen had dysthymia as well. Patients with comorbid somatoform, anxiety, or personality disorders (narcissistic or dependent) were only included in the study, if these comorbidities were not relevant for current hospitalisation. Nine patients (two with "double depression") were additionally diagnosed with one or two of these disorders. Four patients were drug naive; the other patients were treated with either one ($n = 19$) or a combination of two standard antidepressants ($n = 10$). Five patients additionally received one antipsychotic, and four patients were taking one mood stabiliser, respectively. In sum, this patient sample was representative of the population of depressed inpatients.

To minimise the influence of confounding factors, we used the optimal matching algorithm implemented in the MatchIt package [44] for R (version 2.13.1, http://www.r-project.org) to select 33 healthy controls (HC) from a pool of 112 previously recruited local volunteers. The groups were matched for sex, age, and (premorbid) verbal IQ that was assessed with the "Mehrfachwahl-Wortschatz-Intelligenztest" (MWT-B) [62]. In addition, patients and controls did not differ significantly in years of education or lateralisation quotient that was evaluated with the Edinburgh Handedness Inventory [88] (see Table 1).

We applied the Trail Making Test (TMT) parts A and B [97] as a screening instrument for executive dysfunction [65]. Whereas part A is supposed to measure primarily visual search and motor speed skills, part B is presumed to tap also higher cognitive functions such as mental flexibility [12]. We calculated the TMT B/A completion time ratio for each subject, because relative performance on parts B and A provides a measure of executive function that is rather independent of motor and visual scanning

Table 1 Characteristics and behavioural data of study participants

	Patients ($n = 33$)	Controls ($n = 33$)	Statistical difference
Sex (male/female)	13/20	13/20	$\chi^2 = 0$; $p = 1$
Age	35.79 (10.53)	33.15 (12.84)	$t_{64} = 0.91$; $p = 0.365$
Years of education	11.24 (1.66)	11.64 (1.58)	$t_{64} = -0.99$; $p = 0.327$
Lateralisation quotient	0.7 (0.48)	0.86 (0.36)	$t_{64} = -1.49$; $p = 0.142$
Verbal IQ	108.18 (11.06)	109.09 (12.61)	$t_{64} = -0.31$; $p = 0.757$
TMT B/A	2.2 (0.55)	2.43 (0.77)	$t_{64} = -1.4$; $p = 0.166$
BDI	27.27 (8.27)	2.24 (2.18)	$t_{64} = 16.82$; $p < \mathbf{0.001}$
STAI-T	61.36 (8.6)	32.91 (7.09)	$t_{64} = 14.67$; $p < \mathbf{0.001}$
First/recurrent	7/26	–	–
Moderate/severe	17/16	–	–
Words produced	68.1 (12.3)	73.2 (11.1)	$t_{64} = -1.78$; $p = \mathbf{0.04}$
Error rate (%)	7.09 (4.07)	7.22 (4.18)	$t_{64} = -0.13$; $p = 0.447$
Correct responses	63.2 (11.3)	67.9 (10.2)	$t_{64} = -1.74$; $p = \mathbf{0.043}$

Frequencies are reported for sex, episode (first/recurrent), and severity of current episode (moderate/severe); mean values and standard deviations (in brackets) are reported for all other variables. A chi-square test was calculated for sex. One-sided *t* tests were calculated for semantic verbal fluency performance (words produced, error rate, and correct responses); two-sided *t* tests were calculated for the remaining variables.

Bold values indicate significant differences ($p < 0.05$)

speed [4, 12]. Additionally, trait anxiety was assessed in all subjects with the trait version of the State-Trait Anxiety Inventory (STAI-T) [60].

To exclude psychiatric disorders in control subjects, the German version of the Structured Clinical Interview for DSM-IV (SKID-I) [135] was conducted. Furthermore, healthy subjects with psychiatric history in first-degree relatives or Beck-Depression-Inventory (BDI) [39] score $\geq$9 were excluded from the study. Exclusion criteria for all subjects were neurological disorders, serious head injury, mental retardation, severe somatic diseases, or any condition that might have an effect on cerebral metabolism or MR safety. Subjects with head movement exceeding 3 mm or 3° in any direction were also excluded.

After a complete description of the procedure, subjects provided written informed consent to participate in the study. The protocol was approved by the local ethics committee according to the latest version of the Declaration of Helsinki.

fMRI task and procedure

The SVF paradigm applied here has already been used successfully in a previous investigation of ours in healthy subjects [78]. In this paradigm, a block design was employed with 10 blocks for each of the two alternating conditions: word generation (WG) and baseline (BL). At the beginning of each WG block, an instruction slide with a German noun was shown for 3 s, followed by a fixation cross. From then on, subjects had to overtly name, within 12 s, as many members of the category the noun represented, e.g. say "dog", "cat", "eagle" […] after the word "animal" had been shown. The appearance of the word "silence" (presented for 3 s) indicated the beginning of the BL condition, in which the hash mark "#" was presented for 12 s. During this resting phase, participants were required to be silent. Subsequently, a new category name indicated the next WG block. The following 10 categories were applied in fixed order: animals, sports, clothes, professions, fruit, vehicles, furniture, flowers, hobbies, and spices.

In our previous study, analyses with a finite impulse response (FIR) model indicated that the timeframe of 12 s for WG was optimal with regard to the time course of the blood-oxygen-level-dependent (BOLD) signal [78]. Moreover, based on the number of produced words for the 10 WG blocks, a high internal consistency (Cronbach's $\alpha = 0.82$) has been identified for this task [78].

Stimuli were presented in white colour on a black background with Presentation software package (version 14.1.09.21.09, Neurobehavioral Systems Inc.). Subjects' responses were recorded using a scanner-compatible microphone and Audacity software (version 1.2.6, Softonic International S.L.).

To familiarise participants with the task and the rules for WG (see "Behavioural data analysis"), a test session with two exemplary categories was conducted prior to the scanning procedure. These categories were not part of the fMRI investigation.

Behavioural data acquisition

The overt speech production in the scanner was recorded with a 40 dB noise-reducing microphone system (FOMRI-II, Optoacoustics Ltd.) allowing for online speech synchronisation. A dual adaptive filter system (for technical details see, e.g. [112]) subtracted the reference input (MRI noise) from the source input (speech signal) and filtered the speech production instantly while the overt output was recorded. The optic microphone was mounted on the head coil and wired to the sound filter box. The output port was directly wired to the audio in-line plug of the notebook sound card. All audio files were saved and afterwards transcribed into text files.

fMRI data acquisition

Imaging was performed on a 3 Tesla Tim Trio MR scanner (Siemens Medical Systems) at the Department of Psychiatry and Psychotherapy, Philipps-University Marburg. Functional data were acquired with a T2*-weighted echo-planar imaging (EPI) sequence sensitive to BOLD contrast (64 $\times$ 64 matrix, 224 mm $\times$ 224 mm FoV, 40 slices, 3.5 mm slice thickness, TR = 2.5 s, TE = 30 ms, flip angle = 90°). Slices covered the whole brain and were positioned transaxially parallel to the anterior–posterior commissural line (AC–PC). The initial three of the 130 collected functional images were excluded from further analysis to remove the influence of T1 stabilisation effects. To minimise head movements, subjects' heads were fixated with foam pads.

Behavioural data analysis

All transcripts were analysed regarding the number of produced words (including errors) and checked for incorrect responses. The following answers were counted as errors: non-members of the given category, repetitions of words produced during the same block, grammatical variations of the previous word as well as words having the same stem as the preceding one. The total number of generated words, the total number of correctly generated words (correct responses), and the error rate (incorrect responses relative to the total number of generated words) were compared between patients and controls via one-sided independent samples t tests. All behavioural data analyses were carried out with SPSS 15.0 software (SPSS Inc.). A value of $p < 0.05$ (one-sided) was considered to be statistically significant.

fMRI data analysis

Preprocessing

Functional data were analysed using SPM8 (v4290) standard routines and templates (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm) running on MATLAB 7.7.0.471 (R2008b) (The MathWorks, Inc.). After slice-time correction (to the 20th slice), functional images were realigned and normalised to standard MNI (Montreal Neurological Institute) space (resulting voxel size: 2 mm × 2 mm × 2 mm). To increase the signal-to-noise ratio and to compensate for inter-subject anatomical variation, functional scans were spatially smoothed with an 8 mm full-width-at-half-maximum (FWHM) Gaussian kernel.

Single-subject analyses

On the first level, we used a block design to model single-subject BOLD responses during the 10 WG and the 10 BL blocks. The instruction periods (initial task instruction and category names) were included as separate condition of no interest to control for neural activations that were caused by reading the instructions. To account for within-subject differences in the amount of speech produced during the 10 WG blocks, the WG condition was modulated with the number of words generated by each subject within each block. Additionally, the six movement parameters of the realignment procedure were entered as regressors of no interest in the first-level analysis. Head movement parameters, which were carefully checked for each participant, were in an acceptable range not exceeding 3 mm or 3° in any direction, similar to previous reports [51, 56, 57, 70, 78]. To remove low-frequency drifts from time series, a high-pass filter with a cut-off period of 128 s was applied.

Group analyses

On the second level, parameter estimates of the WG and the BL condition were entered into an analysis of variance (ANOVA) using a full factorial design with group (MDD vs. HC) as between-subjects factor and condition (WG vs. BL) as within-subjects factor. Furthermore, we included the number of words produced as covariate to account for between-subjects differences in task performance and to exclude that differences in brain activation between groups reflect poorer performance in patients. Common areas of activation in patients and controls were assessed with a group conjunction analysis [(WG MDD > BL MDD) ∩ (WG HC > BL HC)].

Areas of differential activation in patients versus controls were identified with group by condition interaction analyses. An advantage of this procedure is that it takes into account potential differences between groups in BL activity (cf. [37]), which is important since patients with MDD frequently show altered BL activation when compared to HC [25, 58, 130]. This strategy also allows for a more precise analysis of activation patterns compared to subtractive designs (for details see [23, 34, 90]). For example, it provides the opportunity to evaluate whether hyperactivation in one group (e.g. MDD) reflects a greater task-related increase in activation compared to the other group (e.g. HC) or whether it is due to a weaker task-related decrease in activation in this group (here: MDD). We were interested in both, areas with greater activity during WG versus BL in patients as compared to controls, which were revealed by the interaction contrast [(WG MDD > BL MDD) > (WG HC > BL HC)], as well as in areas with greater activity during WG versus BL in controls as opposed to patients, which were assessed with the interaction contrast [(WG HC > BL HC) > (WG MDD > BL MDD)].

To correct for multiple comparisons within a search volume, we employed Monte Carlo simulation (for details see [107, 108, 118]). For a threshold at the voxel level at $p = 0.001$ and spatial properties as present in this study, 10,000 simulations resulted in an extent threshold of 43 resampled voxels. This procedure prevents a false-positive rate above 5 % due to multiple testing. The determined cluster threshold (based on the whole-brain volume) was applied for all contrasts.

For the anatomical localisation, the functional activations were assigned to probabilistic cytoarchitectonic areas with the SPM Anatomy Toolbox (version 1.6) [21]. Brain activations were plotted on the anatomical MRIcron (version 11 Nov. 2011, http://www.mccauslandcenter.sc.edu/mricrogl/) template.

Results

Behavioural results

Behavioural results are listed in Table 1. With a mean total number of 68.1 (SD = 12.3) words, patients produced significantly fewer words (including mistakes) during the 10 WG blocks than control subjects, who generated 73.2 (SD = 11.1) words on average ($t_{64} = -1.78$; $p = 0.04$). A significant difference was also observed for the mean number of correct responses (MDD: $M = 63.2$, SD = 11.3; HC: $M = 67.9$, SD = 10.2; $t_{64} = -1.74$; $p = 0.043$). The error rate of 7.09 % (SD = 4.07) in patients did not differ significantly from the error rate of 7.22 % (SD = 4.18) in controls ($t_{64} = -0.13$; $p = 0.447$).

Regarding the TMT B/A ratio, groups did not differ significantly (see Table 1). To assess the association

Table 2 Results of the conjunction analysis [(WG MDD > BL MDD) ∩ (WG HC > BL HC)] ($p < 0.001$, corrected by Monte Carlo cluster simulations; cluster extent threshold = 43 voxels)

Anatomical region	H	Coordinates			*t* value	Cluster size
		x	*y*	*z*		
Cerebellum	R	22	−60	−22	9.14	5,246
Cerebellum	L	−16	−62	−20	7.76	
Cerebellar vermis	R	6	−82	−20	7.37	
Postcentral gyrus	R	48	−10	36	9.78	3,991
Superior temporal gyrus	R	64	−12	2	7.02	
Superior temporal gyrus	R	64	−26	6	6.56	
Postcentral gyrus	L	−46	−12	36	8.77	2,979
Postcentral gyrus	L	−56	−6	22	7.45	
Superior temporal gyrus	L	−64	−20	2	6.97	
Supplementary motor area	L	−4	6	70	5.99	921
Insula	L	−26	30	12	3.99	266
Cerebellum	L	−20	−64	−50	4.8	217
Cerebellum	L	−28	−58	−50	4.44	
Cuneus	L	0	−88	36	4.88	69
Cuneus	L	−2	−92	28	4.33	
Cuneus	L	−2	−96	20	3.27	

Results refer to grey matter. Coordinates of the peak voxels are listed in MNI (Montreal Neurological Institute) atlas space

H hemisphere, *L* left, *R* right

between executive functioning and performance on the SVF task, we correlated the TMT B/A ratio with the calculated SVF performance measures, separately for patients and controls. Neither in patients nor in controls was the TMT B/A ratio significantly correlated with the number of words produced (MDD: $r = 0.07$, $p = 0.702$; HC: $r = -0.19$, $p = 0.283$), the number of correct responses (MDD: $r = 0.01$, $p = 0.975$; HC: $r = -0.21$, $p = 0.25$), or the error rate (MDD: $r = 0.24$, $p = 0.188$; HC: $r = 0.05$, $p = 0.788$).

fMRI results

The conjunction analysis [(WG MDD > BL MDD) ∩ (WG HC > BL HC)] indicated that common activations of patients and controls were located in the bilateral cerebellum, the bilateral postcentral gyrus, the bilateral superior temporal gyrus, the left supplementary motor area (SMA), the left insula, and the left cuneus (Table 2).

For the group by condition interaction contrast [(WG HC > BL HC) > (WG MDD > BL MDD)], no suprathreshold voxels were found. The opposite contrast [(WG MDD > BL MDD) > (WG HC > BL HC)] revealed five areas with greater activation during WG versus BL in patients as opposed to controls: the right precentral gyrus (PCG), the left cerebellum (Cb), the right SMA, the right fusiform gyrus (FG), and the right parahippocampal gyrus (PHG) (Table 3; Fig. 1). Including the TMT B/A ratio as additional covariate to control for variance due to individual differences in executive functioning did not alter the results.

Table 3 Results of the group by condition interaction analysis [(WG MDD > BL MDD) > (WG HC > BL HC)] ($p < 0.001$, corrected by Monte Carlo cluster simulations; cluster extent threshold = 43 voxels)

Anatomical region	H	Coordinates			*t* value	Cluster size
		x	*y*	*z*		
Precentral gyrus	R	46	−10	56	4.04	354
Precentral gyrus	R	40	−22	54	3.62	
Precentral gyrus	R	38	−18	64	3.51	
Cerebellum	L	−16	−48	−24	3.7	144
Cerebellum	L	−26	−50	−28	3.23	
Supplementary motor area	R	6	−10	56	3.81	122
Fusiform gyrus	R	28	−42	−10	3.9	90
Parahippocampal gyrus	R	28	0	−34	3.66	81

Coordinates of the peak voxels are listed in MNI (Montreal Neurological Institute) atlas space

H hemisphere, *L* left, *R* right

To examine whether the significant clusters were part of the common SVF network and/or the SVF network of patients and/or controls, the interaction contrast was inclusively masked ($p < 0.001$) separately with the following contrasts: [(WG MDD > BL MDD) ∩ (WG HC > BL HC)], (WG MDD > BL MDD), and (WG HC > BL HC). From the clusters with significant group by condition interaction effect, only 61 voxels of the Cb cluster ($x = -18$, $y = -54$, $z = -20$) overlapped with the commonly activated SVF network and the SVF network of controls. However, 272 voxels of the PCG cluster ($x = 46$, $y = -10$, $z = 56$), 144 voxels of the Cb cluster ($x = -16$, $y = -48$, $z = -24$), 8 voxels of the SMA cluster ($x = 6$, $y = -6$, $z = 58$), and 3 voxels of the PHG cluster ($x = 30$, $y = -6$, $z = -38$) were part of the network activated during WG versus BL in patients.

To examine whether the significant clusters were part of the common BL network and/or the BL network of patients and/or controls, the interaction contrast was inclusively masked ($p < 0.001$) separately with the following contrasts: [(BL MDD > WG MDD) ∩ (BL HC > WG HC)], (BL MDD > WG MDD), and (BL HC > WG HC). These analyses revealed that the clusters with significant group by condition interaction effect did not overlap with the common BL network and the BL network of patients. However, 79 voxels of the SMA cluster ($x = 6$, $y = -10$, $z = 56$), 52 voxels of the FG cluster ($x = 28$, $y = -42$, $z = -10$), and 32 voxels of the PHG cluster ($x = 28$, $y = 0$, $z = -34$)

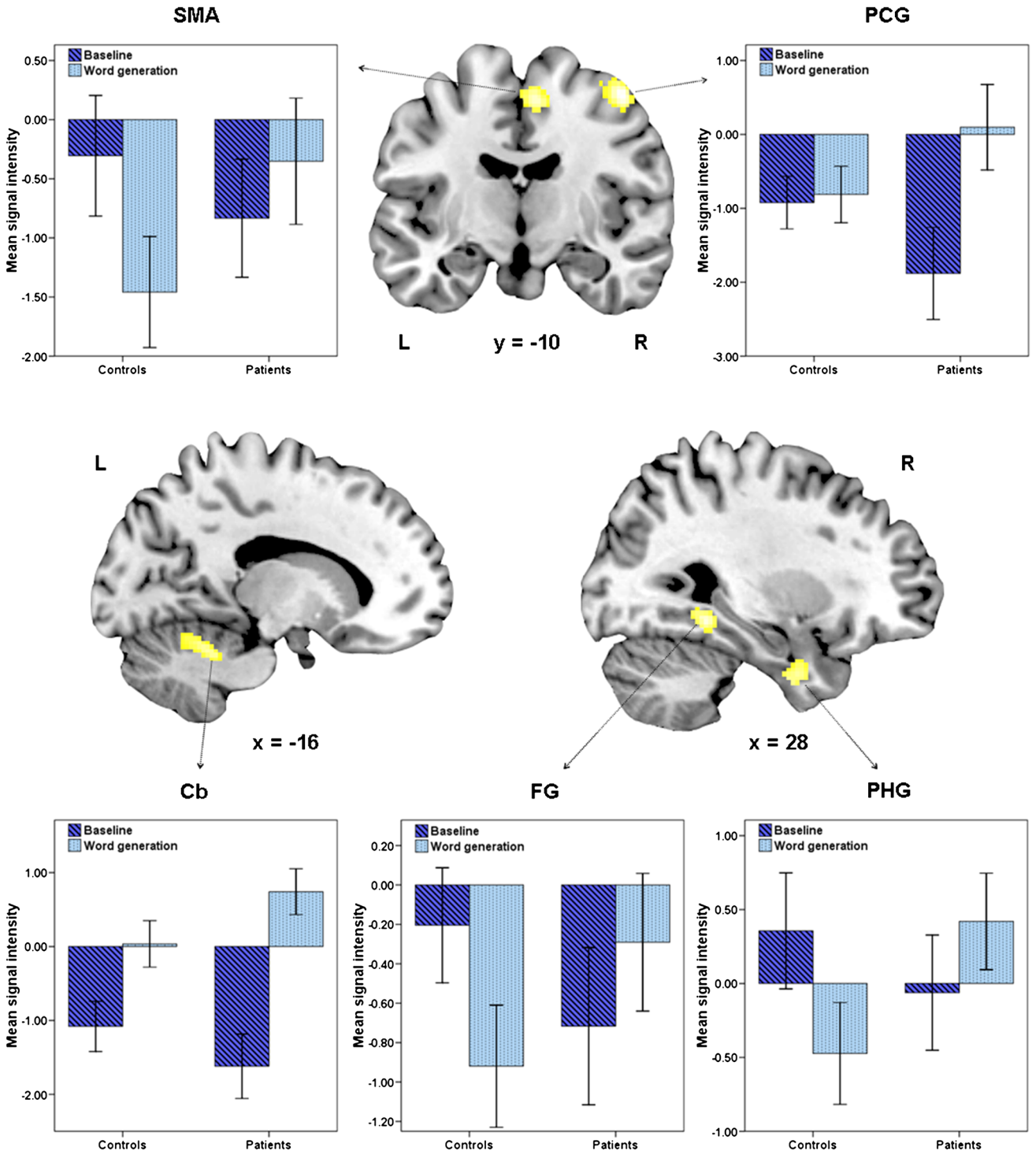

Fig. 1 Brain areas with significant group by condition interaction effect [(WG MDD > BL MDD) > (WG HC > BL HC)] ($p < 0.001$, corrected by Monte Carlo cluster simulations; cluster extent threshold = 43 voxels). Compared to controls, patients showed greater activity during word generation versus baseline in the right precentral gyrus (PCG), the left cerebellum (Cb), the right supplementary motor area (SMA), the right fusiform gyrus (FG), and the right parahippocampal gyrus (PHG). *Bar graphs* display the mean signal intensity during baseline and word generation for the whole PCG, Cb, SMA, FG, and PHG clusters in controls and patients. Values of the *y* axis differ between the graphs. *L* left, *R* right

were part of the network activated during BL versus WG in healthy subjects.

To further explore brain activation in the five areas with significant interaction effect (PCG, Cb, SMA, FG, and PHG), fMRI data were extracted as the first eigenvariate of the respective entire clusters. Post hoc paired t tests (two-tailed) revealed that in both groups, activity in the left Cb increased significantly during WG versus BL (MDD: $t_{32} = -8.04$, $p < 0.001$; HC: $t_{32} = -4.12$, $p < 0.001$). Activity in the right PCG did not change from BL to WG in controls ($t_{32} = -0.37$, $p = 0.713$), but increased significantly in patients ($t_{32} = -4.11$, $p < 0.001$). While activity in the right SMA, the right FG, and the right PHG decreased significantly from BL to WG in controls (SMA: $t_{32} = 3.41$, $p = 0.002$; FG: $t_{32} = 2.88$, $p = 0.007$; PHG: $t_{32} = 3$, $p = 0.005$), activity in these areas did not change significantly in patients (SMA: $t_{32} = -1.5$, $p = 0.143$; FG: $t_{32} = -1.84$, $p = 0.075$; PHG: $t_{32} = -1.95$, $p = 0.06$).

Discussion

This is, to our knowledge, the first fMRI study investigating the effect of depression on the neural mechanisms underlying the production of *semantic* category members. For this purpose, brain activity during an overt and continuous SVF paradigm was compared between 33 depressed patients and 33 well-matched controls. In line with previous imaging studies that contrasted overt word production with a resting condition [40, 52, 78], both groups engaged a widespread network of brain areas encompassing fronto-temporal regions, the cerebellum as well as the insular cortex, and the cuneus. In contrast to previous neuroimaging studies on VF in depression (e.g. [5, 86, 87, 127]), which used within-subject subtraction of BL from WG, we entered both conditions into a full factorial design to explore differential brain activation patterns in patients versus controls via group by condition interaction analyses. This strategy accounts for potential differences between groups in BL activity [25, 37] and, in contrast to subtractive designs in which for example hyperactivation in patients versus controls can also reflect a failure to deactivate (for details see [23, 34, 90]), enables a more precise analysis of activation patterns.

Behavioural results

As hypothesised, patients produced significantly fewer words during the 10 WG blocks (inclusive and exclusive errors) than control subjects. Since the error rate did not differ significantly between groups, depressed patients' performance was affected with respect to the quantity but not regarding the quality of generated words. The finding of reduced word production confirms that unipolar depression is associated with impairments in SVF and is in line with much previous work in the field [5, 30, 59, 80, 81, 96, 103, 117, 136].

Furthermore, performance on the current SVF task was not associated with executive functioning as assessed with the TMT B/A ratio [4, 65], neither in patients nor in controls, which is in line with an understanding of SVF as a distinct cognitive domain that is separable from other executive functions [24, 109].

fMRI results

One aim of this study was to examine whether SVF performance in patients with MDD is related to PFC dysfunctions as suggested in an earlier study [5]. Particularly, aberrant activation was expected in PFC (IFG, ACC) [5] and right parietal cortex [5, 89]. However, the current results do not provide any evidence for dysfunctional activation of these regions in patients. Although the present study could not confirm these earlier reports, the absence of prefrontal deficits accords with the finding of Philpot et al. [89]. It might be speculated that attenuated activity in PFC may be eliminated when analyses are controlled for potential differences in SVF performance between groups, as in the current study, or when patients and controls are equally able to perform the task (cf. [89]). Moreover, previous studies examined only patients with suicidal tendency [5] or old age [89]. Results of these investigations may therefore be related to these specific patient characteristics, as acknowledged by the authors themselves [5].

The second aim of the present study was to detect potential dysfunctional activation patterns in other brain areas associated with the pathophysiology of MDD, e.g. in temporal regions such as superior temporal gyrus and (para-)hippocampus. The group by condition interaction analysis revealed that patients, compared to controls, showed greater activation during WG versus BL in clusters of the right PHG (~Brodmann area (BA) 36/20), the right FG (~BA 37), the right SMA (~BA 6), the right PCG (~BA 6/4), and the left Cb (lobules IV/V and VI), all of which are considered relevant to depression [18, 25, 26, 69, 130, 139]. In particular, patients showed a greater task-related increase in activity in the left Cb and an additional increase in activation in the right PCG when compared to controls. Moreover, while controls demonstrated a task-related suppression of activity in the PHG, FG, and SMA, depressed patients failed to do so. The data indicate that increased brain responses during SVF in patients were mainly due to decreased attenuation of brain regions not expected to be active during task performance. Enhanced and additional recruitment of brain areas likely supporting WG in these subjects also played a role. Note that the different activation patterns between groups did not reflect

differences in task performance or speech output, since we controlled for the number of generated words in the second-level analysis. Therefore, the identified activation differences are supposed to reflect altered cognitive processing related to depression per se. Since the inclusion of TMT B/A ratio as additional covariate did also not alter the results, aberrant activation patterns during SVF in patients might be regarded as relatively independent from the processes that are tapped by this screening instrument for executive dysfunctions.

Functional alterations of PHG (e.g. [29, 120, 132]), FG (e.g. [16, 119, 130]), Cb (e.g. [32, 33, 66, 79]), and motor cortical areas such as SMA (e.g. [26, 129]) have been frequently reported in studies examining brain activity or connectivity in MDD during various tasks as well as at rest. Moreover, there is growing evidence for an involvement of PHG, FG, and Cb in the pathophysiology of this disorder [18, 19, 92, 130]. In the following, regions showing decreased task-related suppression or additional/increased task-related activation in patients are discussed with regard to their potential functional relevance for SVF performance.

Decreased task-related suppression in PHG, FG, and SMA

Activity in PHG and FG may be related to internal cognitive and affective processes in which subjects typically engage during rest such as recall and visual imagery of past experiences. PHG is an important hub of the default-mode network (DMN) [95] and mediates the connectivity between hippocampus and other cortical DMN hubs implicated in the pathophysiology of MDD, e.g. posterior cingulate cortex [13, 131]. The DMN represents a set of brain regions that typically increase activity during spontaneous cognition and task-independent self-referential thought such as autobiographical memory recall, mind wandering, considering social interactions, and thinking about the future [2, 13, 110]. Attenuation of DMN activity during various goal-directed behaviours [34, 95] is interpreted as a mechanism through which self-referential activity can be suppressed to optimise cognitive functioning [3]. In line with the default-mode interference hypothesis [110], reduced DMN suppression during task execution, as it has been reported for depressed subjects (e.g. [31, 105]), may lead to interference of self-referential introspection and internal emotional states with task-specific neural processing [3, 105, 133]. While controls showed a task-related deactivation of PHG in the current study, this was not the case in patients. Increased PHG activity in patients might therefore reflect a failure to suppress activity in an important node of the DMN during task execution, which might have led to detrimental effects on task-related cognitive processing. This assumption is in line with a growing body of evidence that implicates dysfunctions of DMN regions, including PHG, in cognitive impairments and symptoms associated with depression, e.g. in maladaptive depressive rumination, increased self-referential focus, and aberrant autobiographical memory recall [36, 64, 140].

Activity in the PHG has also been related to other processes of internal cognition such as visual mental imagery [27, 54, 55, 141], especially when the imagined scene is emotionally distressing [106]. Previous research suggests that, among other cortical areas, PHG as well as FG, another region in which we found a lack of deactivation in patients, is involved in visual mental imagery in general and especially with regard to scenes and faces, respectively [27, 28, 54, 55, 73, 83, 125, 141]. It has been proposed that PHG and FG may connect visual and long-term memory processes to support imagery of objects retrieved from long-term knowledge [28]. Although these processes likely are not unique to either the right or the left hemisphere, as activation of PHG and FG has been found bilaterally during visual imagery [27, 141], increased activity in the right FG during SVF may reflect, like the enhanced right PHG activity, interference from internal mental processes during task execution in patients. This interpretation is in line with the finding that large parts of the PHG and FG clusters were included within the neural network that was activated during rest as compared to WG in healthy subjects. It might further be speculated that the failure of patients to suppress activity in these areas during SVF reflects an inability to detach themselves from their internal emotional and cognitive states (e.g. ruminative thoughts), which may therefore occupy cognitive resources [109, 133].

The third region in which activity was suppressed during WG versus BL in controls but not in patients was the right SMA (BA 6). The SMA belongs to the supplementary motor complex (SMC), which is supposed to be important for linking action and cognition (for review see [76]). In the context of language, activity in the SMA is frequently related to the planning and execution of overt speech [1, 14, 91]. However, there is evidence that the SMC, especially the right-hemispheric medial BA 6, also contributes to processes that inhibit speech [137] and motor responses in general [76, 122]. In line with this function, the right SMA cluster was not part of the common SVF network in the current study and was even deactivated in controls during WG relative to BL. Moreover, a large part of the right SMA cluster was active during BL versus WG in controls. Greater activity in this area might therefore reflect a failure of depressed patients to reduce the influence of a region potentially involved in processes that inhibit speech during the current SVF task.

However, alternative explanations for increased SMA, PHG, and FG activity in patients have to be considered.

One possibility regarding FG and PHG is that the activation differences in these areas reflected differences in retrieval strategies between groups. Since elements of the DMN may be differentially suppressed as a function of task demands [110], higher PHG and FG activity in patients might be explained by a retrieval strategy of patients that relied more on autobiographical and spatial information (e.g. visualising themselves in the zoo while producing items for the category "animals") as those employed by controls (cf. [101, 104]). Although we cannot fully exclude this possibility, there seems to be no reason to suppose that groups differed systematically in their WG strategies.

A second alternative explanation for the activation differences would be an insufficient compensatory mechanism, assuming that patients recruited additional processing resources in SMA, FG, and PHG. According to such an interpretation, increased right SMA activity in patients might be interpreted as an additional need for patients to inhibit potentially inappropriate responses. Increased activity in PHG and FG might in this context reflect a supplementary recruitment of brain areas suggested to be involved in semantic processing [9]. These explanations, however, seem highly implausible since these regions did not show a significant task-related increase in activation in patients and even displayed significantly task-related deactivation in controls, implying that all three of these areas were not part of the SVF network in neither of the two groups.

Additional and increased task-related activation in PCG and Cb

The PCG cluster encompassed parts of the primary motor region BA 4 as well as parts of the premotor region BA 6, which both contribute to the initiation and execution of overt speech [46, 67, 91]. Furthermore, previous research has shown that a high rate of speech production is related to increased activity in motor regions such as primary motor cortex and cerebellum [98, 134]. Increased participation of (pre-)motor regions during WG might therefore represent an auxiliary mechanism in patients to maintain a certain level of performance. It also points to potential difficulties in speech initiation in patients, an assumption that is in line with psychomotor disturbances typically observed in depression such as slowed speech [68].

Like the PCG, the Cb typically increases activity during the production of speech [91] and plays an important role in speech motor control [67, 111, 113], specifically under time-critical conditions [134]. However, there is evidence for an important contribution of the Cb not only to articulatory but also to cognitive aspects of language [15, 84, 115]. In general, it has become apparent that beyond the motor domain, the Cb is involved in various higher cognitive functions including higher-order language processes, WM, and executive functions (for reviews and meta-analyses see [15, 49, 84, 113, 114, 116]). In the current study, increased activation in patients was found in left cerebellar lobules IV/V and VI, which are, according to a recent meta-analysis [49], related to language (left lobule VI) and verbal WM (left lobule IV/V). However, preceding research suggested that the anterior lobe including lobule IV is predominantly sensorimotor and engaged in motor control, whereas lobule VI (among others) contributes to higher-level processes [114, 116]. Therefore, the greater increase in left Cb activity during WG in patients might reflect enhanced recruitment of regions supporting higher-order language processes and verbal WM or speech motor control. Both these explanations seem possible since successful SVF performance involves articulatory as well as WM processes. Taken together, the additional and increased task-related responses of depressed patients in the right PCG and the left Cb likely reflect an enhanced need of these subjects to recruit brain areas supporting speech initiation and cognitive aspects of language production during the current SVF task. It might be speculated that the increased responses in these areas represent an insufficient compensatory mechanism for interfering activity in PHG, FG, and SMA.

Limitations

This investigation was limited by the inclusion of patients taking antidepressant medication. Due to the possibility of medication effects (for review see [8]), the generalisability to unmedicated patients is unclear. There are some reports of normalised brain activation, particularly in PFC, in depressed patients after successful antidepressant treatment [22, 63, 75, 99], raising the possibility that antidepressant therapy in the present patient sample led to the absence of activation differences in PFC between groups. However, in a recent meta-analysis, no effect of medication was found on SVF performance [109].

Conclusions

This is the first fMRI study providing evidence for effects of depression on the neural correlates underlying SVF. While healthy subjects down-regulated activity in the right PHG, the right FG, and the right SMA during periods of WG as compared to rest, patients with MDD failed to do so. Furthermore, patients showed additional and increased task-related activation of right PCG and left Cb, respectively. The data point to a failure of depressed patients to deactivate right-hemispheric brain regions involved in DMN-related functions, such as self-referential thought or

visual imagery (PHG and FG), and speech inhibitory processes (SMA) during WG, which may lead to interference with task execution. Results further demonstrate enhanced task-related recruitment of areas supporting speech initiation and articulation (PCG/Cb) as well as higher-order language processes and verbal WM (Cb). Therefore, a failure to reduce potentially distracting activity from task-irrelevant regions combined with an insufficient compensational recruitment of task-relevant areas may underlie poorer SVF in MDD. In general, it might be speculated that depressed subjects are unable to completely detach from internal emotional and cognitive states, which may occupy cognitive resources during task execution and may thus lead to cognitive dysfunctions [109, 133].

The novel findings of the present investigation illustrate that studies examining the neural correlates of cognitive deficits in depression should not only focus on prefrontal brain areas, as was the case in most PVF studies (for review see [53]). We found, for example, dysfunctional activation patterns in PHG, FG, and Cb, which are increasingly recognised as relevant to depression [25, 119, 130]. Taken together, the findings of decreased performance as well as of aberrant brain activation during the current SVF task in patients with depression demonstrate that this paradigm represents a sensitive tool for detecting brain dysfunctions in clinical populations.

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Conflict of interest The authors declare that they have no conflict of interest.

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