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Neural correlates of generation and inhibition of verbal association patterns in mood disorders

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Objectives: Thought disorders such as rumination or flight of ideas are frequent in patients with mood disorders, and not systematically linked to mood state. These symptoms point to anomalies in cognitive processes mediating the generation and control of thoughts; for example, associative thinking and inhibition. However, their neural substrates are not known. Method: To obtain an ecological measure of neural processes underlying the generation and suppression of spontaneous thoughts, we designed a free word association task during fMRI allowing us to explore verbal associative patterns in patients with mood disorders and matched controls. Participants were presented with emotionally negative, positive or neutral words, and asked to produce two words either related or unrelated to these stimuli. Results: Relative to controls, patients produced a reverse pattern of answer typicality for the related *vs* unrelated conditions. Controls activated larger semantic and executive control networks, as well as basal ganglia, precuneus and middle frontal gyrus. Unlike controls, patients activated fusiform gyrus, parahippocampal gyrus and medial prefrontal cortex for emotional stimuli. Conclusions: Mood disorder patients are impaired in automated associative processes, but prone to produce more unique/personal associations through activation of memory and self-related areas.

Keywords: thoughts; free word association; inhibition; mood disorders; fMRI

INTRODUCTION

Thought processes are often impaired in mood disorders, ranging from racing thoughts to ruminations and thought inhibition (Goodwin and Jamison, 2007). This phenomenology might reflect an impairment in more basic cognitive functions leading to abnormal patterns of associations in the flow of mental processes that generate spontaneous thoughts (Bar *et al.*, 2007; Bar, 2009). Both positive and negative mood states have often been related to distinct associative patterns in cognitive operations, broad or narrow, respectively (Fredrickson, 2001; Pronin and Jacobs, 2008; Mason and Bar, 2012). However, these correlations are not absolute because, in some cases, low mood is accompanied with subjective complaints of numerous and racing thoughts (Akiskal and Benazzi, 2004; Piguet *et al.*, 2010; Desseilles *et al.*, 2012; Keizer *et al.*, 2013).

Given these observations, we postulated that patterns of thought associations might be disrupted in mood disorders. In a recent model of thought disorders (Piguet *et al.*, 2010), we proposed that distinct cognitive abilities underlying mental flexibility and inhibition may constitute core processes whose dysfunction may underlie the phenomenology of thought disorders. Specifically, crowded or racing thoughts might stem from an imbalance between mechanisms responsible for the production (on the one hand) and suppression (on the other hand) of associative thoughts. Anomalies in these processes may represent a common deficit in the spectrum of mood disorders, shared across different diagnostic subcategories (e.g. Major Depressive Disorder [MDD] or Bipolar Disorder [BD]) (Marvel and Paradiso, 2004). Here, we therefore aimed at investigating these traits in a dimensional approach framework (Narrow and Kuhl, 2011; Vieta and Valentí, 2013), across a group of patients suffering from mood disorders with various clinical presentations.

In order to test both production and inhibition components of associative thought processes in the same protocol, we designed a free word association task with two conditions. The first 'close' condition asked participants to generate spontaneous/intuitive associations with a word cue, whereas the second 'remote' condition asked them to produce responses unrelated to the word cue. We used positive, negative and neutral word cues in order to also examine whether emotional meaning had an influence on activated representations and associations. This task thus allowed us to probe for generation and inhibition processes in associative thinking within the same paradigm. To the best of our knowledge, these processes have not previously been investigated in mood disorders.

The 'close' condition in our task resembles verbal fluency tests commonly used in neuropsychology, which assess the initiation of word production and strength of semantic associations (Schwartz *et al.*, 2003). However, compared with the traditional cued word fluency (e.g. phonology- or category-based), free word association tasks are closer to natural thought processes. We also labeled this condition as 'automatic' based on the theory of automatic spreading of activation in semantic networks (Manschreck *et al.*, 1988; Spitzer, 1997). Thus, the production of close associates was postulated to reflect a 'pure' diffusion of activation through conceptual associations. The 'remote' condition in our paradigm was based on the Hayling Sentence Completion Test (Burgess and Shallice, 1996) that requires participants to generate either usual or unusual words in response to a sentence stem, and is used to study both verbal semantic associations and cognitive control. Contrarily to the close condition, producing remote associations requires the retrieval of words that are not linked through direct, automatic associations (e.g. table-giraffe instead of table-chair). This process is effortful and depends on executive control function; therefore, we also labeled this condition as 'inhibition' (Noël *et al.*,

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2012). This process is mediated by the prefrontal cortex, in particular the right inferior frontal gyrus (Volle *et al.*, 2012), that has been implicated in inhibition of automatisms and prepotent responses across many modalities, motor, verbal and other (e.g. Konishi *et al.*, 1999; Xue *et al.*, 2008). Deficits in this task have been found in bipolar (Drysdale *et al.*, 2013; Wang *et al.*, 2013a) and unipolar patients (Gohier *et al.*, 2009); therefore, we predicted that patients would perform worse than controls for the 'remote' condition.

Few neuroimaging studies have used a free word association task, probably because these are less constrained than verbal fluency tasks (where participants have to produce words starting by a specific letter or belonging to a specific semantic category). For example, a study comparing free word association and word generation in healthy volunteers showed that both tasks recruited an overlapping semantic network, predominantly located in fronto-temporal areas of the left hemisphere (Wende *et al.*, 2012), in line with current knowledge on semantic systems (e.g. Binder *et al.*, 2009). Among critical brain regions allowing these flexible binding operations between semantic representations, the hippocampus and parahippocampal cortex (known for their role in autobiographical encoding and retrieval in memory) might also play an important role and appear differentially recruited during free verbal association, in comparison to semantic verbal fluency (Bar *et al.*, 2007; Kircher *et al.*, 2008; Whitney *et al.*, 2009). A few studies used the Hayling task in mood disorders, and found greater activity during sentence completion in limbic areas, such as ventromedial prefrontal cortex and ventral striatum for bipolar patients (McIntosh *et al.*, 2008), or amygdala for their healthy relatives (Whalley *et al.*, 2011). To our knowledge, only one pioneer study has performed this task, including the inhibition condition, in bipolar patients, and has found a negative correlation between error scores and cortical volume of right parietal areas, interpreted as failure of inhibition (Haldane *et al.*, 2008). This condition has been found to differentially activate the precuneus and middle/superior frontal gyrus in healthy participants (HPs) (Collette *et al.*, 2001; Allen *et al.*, 2008). However, little is known about the brain systems underlying the production and inhibition of spontaneous associations in this task, and how these cognitive functions are modified in mood disorders.

Here, by using a free word association task with both close (automatic) and remote (inhibition) conditions in mood disorder patients, we tested for any systematic change in verbal associative patterns that might represent dimensional marker of mood disorders, and for any influence of the emotional meaning of word cues. We predicted that both associative patterns and inhibition processes might be altered in mood disorders, across diagnostic boundaries. We also predicted that fMRI should reveal distinct patterns of activations in semantic network during close and remote conditions, with further differences in patients relative to HPs that should reflect their enhanced self-focus, and/or reduced inhibition abilities.

MATERIALS AND METHODS

Participants

Sixty-four participants speaking French for more than 20 years participated in this study, 32 mood disorder patients and 32 HP matched for age, gender, laterality and level of education. Because behavioral data from one HP could not be analyzed due to recording problems, the final sample included 32 patients and 31 HP. All participants gave informed written consent in accordance with procedures approved by the Ethics Committee of the Geneva University Hospital, in accordance with the Helsinki Declaration of 1975. Participants got modest financial compensation for their participation. Patients were recruited from the department of adult psychiatry of the Geneva University Hospital, as well as through advertising on classified advertisements websites. HPs were also recruited from a local database or through web advertising.

Inclusion criteria for patients were: a diagnostic of MDD or BD, age between 18 and 56 years old, stable medication for at least 4 weeks, with no usual contraindication for MRI. Exclusion criteria for HP were: a past or present history of neurological or psychiatric problem, use of medication and contraindication for MRI. The Mini International Neuropsychiatric Interview (MINI [Sheehan *et al.*, 1998]) and the Structured Clinical Interview for the DSM-IV, Mood Disorders section (SCID-II [First *et al.*, 1997]) were administered to patients and HP (during a separate visit for the patients, maximum 1 week apart). Patients were included regardless of their current mood state. As well as meeting criteria for MDD ($N=9$), BD type I (BD-I, $N=7$), type II (BD-II, $N=13$) or BD-Not Otherwise Specified ($N=3$), some patients also met criteria for anxiety disorder ($N=15$), borderline personality disorder ($N=10$), and Attention Deficit/Hyperactivity Disorder ($N=2$), reflecting the high prevalence of comorbid anxiety and personality disorders expected in this population. Laterality was measured by the Edinburgh handedness inventory (Oldfield, 1971). Just before scanning, the current mood state was assessed by the Montgomery–Asberg Depression Rating Scale (MADRS [Montgomery and Asberg, 1979; French version: Pellet *et al.*, 1980]), Young Mania Rating Scale (French version: Young *et al.*, 1978; Favre *et al.*, 2003) through medical interview by trained clinicians. The Hamilton Anxiety Scale (Hamilton, 1959; French version: Pichot *et al.*, 1981) was also rated for both the patients and HP.

Stimuli

Words were selected after a cross-match of (i) existing norms of associations in French in a standard corpus (Ferrand and Alario, 1998; Ferrand, 2001), for both concrete and abstract words, and ii) ratings for emotional valence in the database 'valemo' (available on www.lexique.org). We chose French words that had a first word associate representing 30–60% of total answers (medium-size associative sets). We selected a list of 72 words and divided them in three sets of negative, neutral and positive words (see Supplementary Table). Words with a different valence were counterbalanced for gender, frequency in French (movies), length of the word and number of orthographic neighbors. Due to the multiple constraints for carefully counterbalancing this material across conditions, we also added 11 words (three negatives, two neutrals and six positives) coming from the valence database (valemo) that had no norms for associations, but were judged to be similar in other respect (see Supplementary Table, italic type words). Each word appeared only once in each condition (close or remote). The final experimental conditions were: close-positive words, close-negative words, close-neutral words, remote-positive words, remote-negative words and remote-neutral words.

Procedure

The task consisted of two conditions of free semantic association (with three emotion categories each) plus one control condition where participants had to say aloud the grammatical 'gender' of the stimulus-word (masculine or feminine). The instruction for the 'close' association condition was: 'Please say aloud the first two words that come to your mind when reading the stimulus'. The instruction for the 'remote' association condition was: 'Please say two words as far as possible of the word presented on the screen, try to avoid any link with the stimulus, even the opposite is still a link'. Participants were also told that they should not repeat the same words, and always try to say two words for each trial. Stimuli for the control condition were taken from the list of neutral stimuli that were not used for the other conditions after counterbalancing.

Imaging data were acquired on TRIO 3T whole-body MR unit (Siemens, Germany) equipped with a 32 channel head coil. A sparse temporal acquisition technique (Hall *et al.*, 1999) was used (with a pause between two MRI images), so that the spoken answers could be recorded with an MRI compatible microphone during an interval free of gradient noise. For more details on the procedure and MRI acquisition parameters, see Figure 1 and Supplementary Material.

Analysis of behavioral data

Behavioral data analyses were performed using SPSS Statistics 19.0 (SPSS Inc.). For the number of words produced in the free association task, we calculated a global performance index that could account for missing data (two patients and one HP had only two sessions instead of three due to technical recording problems) and computed a percentage of given verbal responses for each recorded condition (number of words produced/number of possible answers). To obtain a qualitative measure of performance (i.e. response originality), we calculated two indices, one based on the frequency of each word, in response to each cue, across all answers from all participants (FREQ), and one based on the number of 'typical' association as expected by the normative database (TYP).

FREQ was measured by counting the number of time each word appeared relative to the total number of words produced for one cue in our whole sample, and then computing the mean values (per valence and per condition) for words produced by each subject (see Supplementary Material for an example). Thus, performance was associated with high FREQ values when the subject produced answers similar to the rest of the participants, but low FREQ values when the subject produced more 'original' or idiosyncratic answers.

TYP was calculated by computing, for each word cue, how many times the given answer corresponded to one of the five most common 'expected' words according to the association database of French words established by Ferrand and Alario (1998). Thus, like for FREQ, the lower the TYP indices were, the more 'unusual' or idiosyncratic the subject's production was (see Supplementary Material for an example).

Analysis of MRI data

During the free association task in the scanner, verbal answers were recorded in a digital format and then transcribed. We modeled the seven experimental conditions described above in the design matrix (close and remote trials, for negative, neutral and positive words + control condition). In addition, the number of words produced for each trial (0,1,2) was computed and used as a parametric modulator in the first level analysis, in order to control for any global variance between conditions and participants unrelated to the associative and cognitive processes of primary interest. Sparse fMRI data were analyzed using standard procedures (see Supplementary Material). Direct statistical group comparisons were obtained using an exclusive masking procedure to reveal voxels that showed increased response in one population relative to the other population. The map constituting the exclusive mask was thresholded at $P < 0.05$, whereas the contrast to be masked was thresholded at $P < 0.001$, cluster threshold of more than five voxels, unless reported otherwise. Note that the more liberal the threshold of an exclusive mask, the more conservative is the masking procedure. For completeness, besides the main results reported below, auxiliary analyses were performed to compare subgroups with different classes of medication, unipolar and bipolar patients type II, or depressed and euthymic patients, that did not shown any modification of the pattern of results (not reported here).

RESULTS

Participants

The two groups did not differ significantly regarding gender, age, laterality and level of education (Table 1). Among patients, 14 were categorized as euthymic, 10 depressed, 3 hypomanic and 5 in subdepressive/mixed state that did not meet DSM-IV-TR criteria for a Major Depressive Episode. Table 1 summarizes the mean levels of depression, mania and anxiety. Regarding medication, 27 out of 32 patients were taking one or more drugs from one of the class reported in Table 1.

Behavioral results

Number of words

In total, 14 682 words were produced across the six conditions of interest (close_positive, close_negative, close_neutral, remote_positive, remote_negative and remote_neutral) by HP and patients. Results for each condition and each group are summarized in Table 2. A mixed repeated measures 2×3 ANOVA (condition × valence of emotion) with group as between subject factor revealed a main effect of group ($F(1,61) = 9.624$, $P = 0.03$) with patients producing fewer words than HP, a main effect of condition ($F(1,61) = 8.326$, $P = 0.005$) with fewer words produced for the remote condition, and a main effect of emotion ($F(2,60) = 11.348$, $P < 0.001$) with more words produced for the

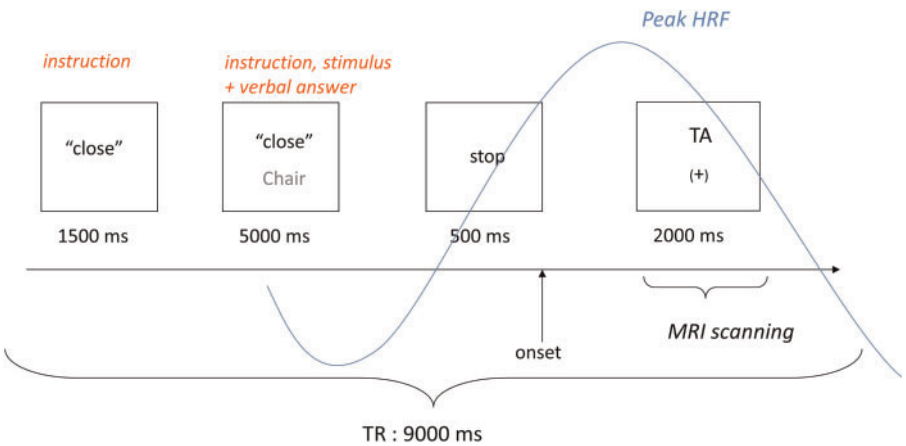

Fig. 1 Free Word Association task. Participants were instructed to respond to the word-cue in two different conditions: they had either to 'say two related words that first come to your mind' (Close condition) or to 'say two words as far and unrelated as possible' (Remote condition). MRI, magnetic resonance imaging; HRF, hemodynamic response function (only drawn for illustrative purpose, not calculated); TA, time of acquisition; TR, time of repetition.

Table 1 Demographic and clinical variables

Characteristics	Patients *M* (s.d.)	Healthy participants *M* (s.d.)
N (males)	32 (14)	31 (14)
Age	40.25 (8.8)	39.6 (8.7)
Level of education	13.3 (3.2)	14 (3)
Edinburgh handedness inventory	10.6 (13.6)	13.4 (13.7)
MADRS	13.75 (9.3)	2 (1.8)*
YMRS	2.4 (2.9)	0.4 (0.8)*
Hamilton anxiety	13.2 (8.2)	3.3 (2.3)*
No. taking antipsychotic (reserve)	12 (11)	–
No. taking antidepressant	17	–
No. taking mood stabilizer	13	–
No. taking benzodiazepine	7 (8)	–
No. Lifetime episodes 1–4	10	–
No. Lifetime episodes 5–9	11	–
No. Lifetime episodes >10	11	–
Mean duration of disease (years)	14.3 (9.4)	–

Notes: *$P < 0.001$ independent samples *t*-test. (M, mean; s.d., standard deviation; MADRS, Montgomery-Asberg Depression Rating Scale; YMRS, Young Mania Rating Scale).

Table 2 Percentage of words produced per condition

Number of words produced % (s.d.)	Patients	Healthy participants
Close condition	79.3 (16.8)	88.4 (9.7)
Remote condition	74.8 (16.5)	86.9 (11.8)
Positive stimuli	76.6 (16.3)	86.8 (10.3)
Negative stimuli	75.5 (16.9)	87.1 (10.5)
Neutral stimuli	77.9 (15)	87 (10.7)
Close_positive	78.6 (17.2)	86.8 (10)
Close_negative	76.2 (18.6)	87 (10)
Close_neutral	83.2 (16.5)	91.4 (10.8)
Remote_positive	74.5 (17.2)	86.7 (12.1)
Remote_negative	74.8 (17.2)	87.3 (12.5)
Remote_neutral	75.2 (17)	86.6 (12.3)
Total	77.1 (15.9)	87.6 (10.4)

neutral stimuli. There was also a condition by emotion interaction ($F(2,60 = 9.534$, $P < 0.001$). No interaction of group × emotion or group × condition was encountered. Post hoc *t*-tests showed that the close_neutral condition was easier (i.e. resulting in more words) than the other conditions for both groups.

Finally, the overall performance correlated negatively with the level of depression (MADRS score, $r(63) = -0.67$, $P < 0.001$) and in both groups individually as well (patients: $r(32) = -0.657$, $P < 0.001$; HP: $r(31) = -0.675$, $P < 0.001$), but not with other clinical questionnaires (e.g. Hamilton Anxiety Scale). As expected, it also correlated positively with level of education ($r(63) = 0.275$, $P = 0.029$), but education levels were matched between groups (independent sample *t*-test: $P = 0.365$).

Originality

The two indices of originality, FREQ (frequency of the word in the whole dataset) and TYP (typicality compared with norms of associations in the French language), are reported in Table 3 and correlated with each other (close condition: $r(63) = 0.906$, $P < 0.001$; remote condition: $r(63) = 0.377$, $P = 0.002$). A similar mixed repeated measures (3 emotions × 2 groups) ANOVA was conducted for both indices, for each task condition separately. The frequency of words given per cue (FREQ) for the close condition revealed a main effect of emotion

Table 3 Index of frequency (FREQ) and typicality (TYP) for each condition

Unusualness (s.d.)	Patients	Healthy participants
FREQ_close	9.3 (1.88)	9.96 (1.57)
FREQ_remote	1.32 (0.18)	1.23 (0.11)
FREQ_close_positive	7.66 (2.03)	8.25 (1.96)
FREQ_close_negative	7.93 (2.66)	9 (1.5)
FREQ_close_neutral	12.17 (1.93)	12.54 (2.4)
FREQ_remote_positive	1.24 (0.16)	1.18 (0.11)
FREQ_remote_negative	1.41 (0.35)	1.27 (0.19)
FREQ_remote_neutral	1.31 (0.15)	1.24 (0.11)
TYP_close	1.7 (0.4)	1.9 (0.3)
TYP_remote	0.14 (0.26)	.03 (.05)
TYP_close_positive	1.5 (0.5)	1.7 (0.4)
TYP_close_negative	1.5 (0.5)	1.7 (0.3)
TYP_close_neutral	2 (0.4)	2.2 (0.4)
TYP_remote_positive	0.11 (0.22)	0.02 (0.04)
TYP_remote_negative	0.15 (0.25)	0.03 (0.10)
TYP_remote_neutral	0.16 (0.39)	0.04 (0.06)

($F(2,60) = 132.72$, $P < 0.001$): participants produced more unusual responses to positive, then negative, then neutral stimuli ($P = 0.04$ and $P < 0.001$ for each paired comparison, respectively). Although the group × emotion interaction did not reach significance, there was a tendency for more unusual responses with negative cues in patients compared with controls ($P = 0.056$, independent sample *t*-test), but no difference in other emotion conditions.

For the number of typical associations (TYP) in the close condition, we also found a main effect of emotion ($F(2,60) = 43.675$, $P < 0.001$): responses were more unusual for both positive and negative than neutral stimuli. Although the group × emotion interaction did not reach significance, there was a tendency for more unusual responses with negative cues in patients compared with HP ($P = 0.062$, independent sample *t*-test, Figure 2). Thus, both indices converged to suggest that patients tended to produce less common/more unique responses than HP for negative cues. Emotion meaning also increased word uniqueness in both groups.

In the remote condition, the FREQ index also showed a main effect of group: now patients were more usual ($F(1,61) = 5.740$, $P = 0.02$, Figure 2), unlike for the close condition. There was again a main effect of emotion ($F(2,60) = 8.574$, $P = 0.001$): responses were more unusual for positive, then neutral, then negative stimuli ($P = 0.02$ and $P = 0.043$, respectively). For the TYP index in the remote condition, a main effect of group ($F(1,61) = 5.55$, $P = 0.022$) also indicated more usual responses in patients than HP in all three emotions (Figure 2).

fMRI results

Main effect of associative tasks

When we compared the two conditions involving semantic-associative processing (close and remote conditions) with the control condition, the whole brain analysis revealed widespread activations within the expected semantic network. Among all participants, activations were found not only in the left middle frontal gyrus, the medial superior frontal cortex, the left operculum, the left superior parietal cortex and the left superior temporal gyrus, but also in the right premotor cortex and the bilateral cerebellum (Figure 3A and Table 4). We then tested for differences between patients and HP, by masking exclusively activations for HP by the same contrast for patients (at $P < 0.05$). This comparison revealed effects in the left superior frontal cortex, left frontal operculum, bilateral postcentral gyri, as well as supplementary

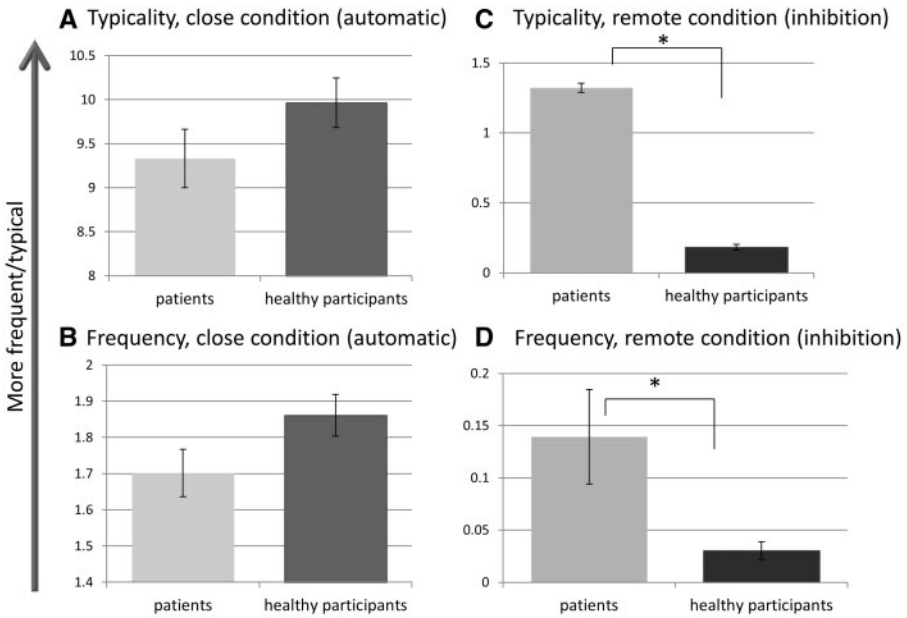

Fig. 2 Behavioral results for indices of originality. (**A**) close 'automatic' condition, TYP index; (**B**) close 'automatic' condition, FREQ index. (**C**) remote 'inhibition' condition, TYP index; (**D**) remote 'inhibition' condition, FREQ index. Group differences. $^*P < 0.05$.

motor area (SMA) and pre-SMA (Table 4), that all were more activated for HP than for patients. The reverse masking procedure yielded no activation.

Effect of closeness (close vs remote associations)

Contrasting the close condition with the remote condition (across the two groups), we found activation in the bilateral inferior occipital cortices, left SMA, left inferior frontal gyrus, left middle temporal gyrus and left superior frontal gyrus (Figure 3B, Table 5). The effect of close *vs* remote associations among HP, masked by the same contrast among patients ($P < 0.05$), revealed differential activations in left frontal operculum, and also left and right pallidum/putamen, and right caudate nucleus. The latter cortico-subcortical regions were therefore more recruited in HP than patients during the production of more 'automatic' associations. The reverse masking procedure yielded no activation.

Effect of inhibition (remote vs close associations)

The comparison between the remote and the close conditions across groups revealed extensive activations in visual areas including bilateral occipital cortex, the left cuneus and right precuneus, as well as the right orbitofrontal cortex and the right middle/superior frontal gyrus (Table 5). When masking the map for remote > close conditions in HP by the same map for the patients (exclusively at $P < 0.05$), we found selective increases in the right inferior and middle frontal gyrus, and also in several visual areas (Figure 3C). This suggests that patients were less efficient at recruiting brain regions normally contributing to inhibit automatic responses and generate unusual responses. The reverse masking procedure yielded no activation.

For completeness, we also tested for any correlation of brain activation patterns with the FREQ and TYP indices derived from the participants' performance, for the close and remote association conditions relative to the control condition. These subsidiary analyses also showed differential recruitment of both occipital and right prefrontal areas in HP and patients (see Supplementary Material), in neighboring but non-overlapping peaks compared with main group differences above.

Effect of emotional stimuli

Finally, in keeping with behavioral effects observed in both controls and patients, we tested whether the emotional content of word cues modulated brain activations during the association task. When contrasting all conditions with emotional stimuli, positive or negative, relative to conditions with neutral stimuli (regardless of the type of association and across both groups), we observed greater activation in widespread regions including visual areas, frontal areas, limbic areas and posterior cingulate cortex (Table 6).

Unlike other conditions, the group comparison now showed greater responses to emotion in patients relative to controls (i.e. by exclusively masking the activation maps for patients by those for HP, at $P < 0.05$). These differential increases were predominantly observed in left fusiform gyrus and bilateral parahippocampal gyrus (PHG) (Figure 4 and Table 6), plus left superior and medial frontal gyrus. The inverse group comparison yielded no activation. These effects suggest that the emotional meaning of word cues enhanced the recruitment of regions associated with imagery and memory in patients.

DISCUSSION

Using a free word association task with positive, negative and neutral cues, we showed that people with mood disorders produced fewer words than HP, and that their global performance correlated negatively with the level of depression. Overall, emotional stimuli elicited fewer and more 'atypical' answers than neutral stimuli in both groups. However, relative to HP, patients tended to produce less typical (i.e. more original or idiosyncratic) words for the close (automatic) condition, but more typical words for the remote (controlled) condition, with a tendency for this pattern to be stronger for negative material. These findings suggest differences in the retrieval of semantic associations in mood disorder patients, partly modulated by the affective valence of word cues.

Accordingly, at the neural level, our associative task was found to activate a distributed semantic network but these effects were more extensive in HP. Critically, during the close condition, HP activated the basal ganglia (putamen, caudate) and left inferior frontal gyrus, which was not the case for patients. During the remote condition, HP

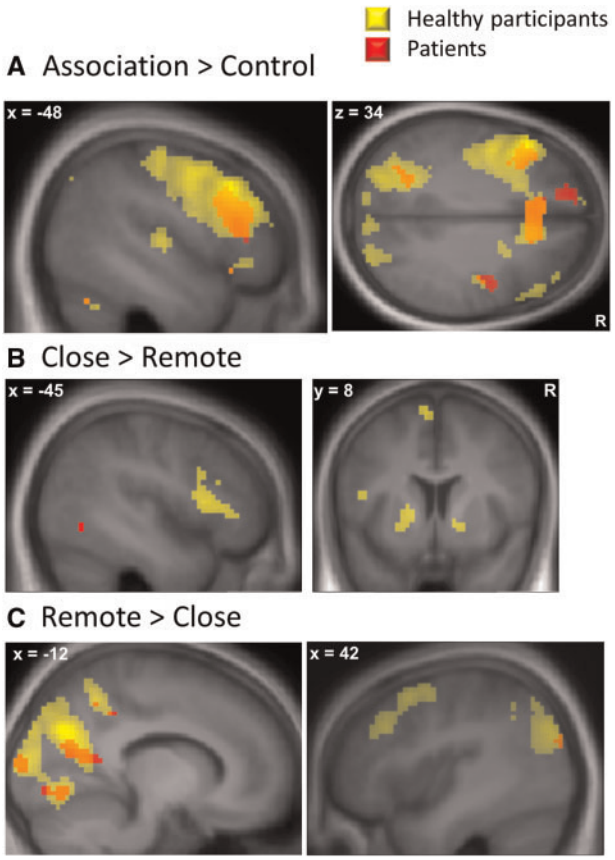

Fig. 3 Regions activated by conditions of interest. (**A**) Associative tasks *vs* control task: left and right frontal gyrus, medial superior frontal gyrus, left superior parietal cortex. (**B**) Close *vs* remote conditions: left inferior frontal gyrus, basal ganglia. (**C**) Remote *vs* close conditions: occipital cortex, right middle/inferior frontal gyrus. Maps with a threshold at $P < 0.001$ uncorrected are overlaid on average T1 structural scan.

Table 4 Brain regions showing activations for associative tasks (MNI coordinates; CS: cluster size in number of voxels; HP, healthy participants)

	x	*y*	*z*	*Z*-score	CS
Association > control task*					
Right middle frontal gyrus	30	11	49	7.15	183
Left middle/inferior frontal gyrus (operculum)	−45	20	34	6.46	1564
Medial superior frontal cortex	0	11	52	6.22	Above
Right precentral gyrus	39	−10	55	5.35	70
Left superior temporal gyrus	−48	−19	4	4.98	17
Left superior parietal cortex	−21	−67	49	5.57	240
Left pallidum	−15	5	4	4.85	10
Brain stem	−3	−34	−8	5.64	85
Left/right cerebellum	−24	−61	−26	6.72	1485
Association > control task, HP masked by patients					
Left superior frontal gyrus	−24	−1	64	5.39	30
Left middle/inferior frontal gyrus (operculum)	−51	23	34	5.37	80
Pre-supplementary motor area	3	26	49	4.18	12
Supplementary motor area	3	2	64	4.44	53
Left postcentral gyrus	−42	−22	52	5.57	658
Right postcentral gyrus	48	−19	55	4.72	129
Left cerebellum/brainstem	−3	−37	−11	4.96	118

Note: $P < 0.001$ uncorrected except $^*P = 0.05$ corrected.

activated the right inferior/middle frontal gyrus, bilateral cuneus/precuneus and visual cortex, again unlike patients. In contrast, only patients activated self-related regions, such as the medial prefrontal cortex (mPFC) and PHG, in response to emotional *vs* neutral stimuli.

Table 5 Brain regions showing activations in close and remote conditions (MNI coordinates; CS, cluster size in number of voxels; HP, healthy participants)

	x	*y*	*z*	*Z*-score	CS
Close > remote					
Left inferior frontal gyrus	−54	20	1	4.33	370
Left superior frontal gyrus	−12	47	43	4.01	23
Left supplementary motor area	−9	17	64	4.57	95
Left middle temporal gyrus	−63	−43	−2	4.08	108
Right postcentral gyrus	63	−7	25	3.96	30
Right inferior occipital cortex (visual)	30	−94	−8	5.78	36
Left inferior occipital cortex	−33	−91	−11	5.46	46
Close > remote, HP masked by patients					
Left inferior frontal gyrus (operculum)	−45	14	7	4.11	186
Right superior temporal gyrus	48	−13	−2	3.39	13
Left pallidum/putamen	−18	8	−2	3.7	38
Right pallidum/putamen	12	8	−8	3.47	10
Right caudate	15	−1	25	3.46	6
Cerebellum	30	−82	−35	3.76	40
Remote > close					
Right orbitofrontal cortex	18	53	−14	4.06	16
Right middle/superior frontal gyrus	30	35	43	3.98	286
Left cuneus	−9	−73	28	6.15	5415
Right precuneus	9	−52	49	6.09	Above
Right occipital cortex	12	−103	13	6.27	Above
Remote > close, HP masked by patients					
Right middle frontal gyrus	42	11	52	4.04	79
Right middle/inferior frontal gyrus	42	26	31	4.02	141
Right cuneus	21	−58	22	4.81	46
Right fusiform gyrus	30	−70	−17	3.86	27
Left superior occipital cortex	−18	−70	28	5.32	496

Note: $P < 0.001$ uncorrected.

Table 6 Brain regions showing activations for emotional stimuli (MNI coordinates; CS, cluster size in number of voxels; HP, healthy participants)

	x	*y*	*z*	*Z*-score	CS
Emotion > neutral					
Left medial superior frontal gyrus	−9	62	19	4.99	331
Left inferior frontal gyrus	−54	23	−2	3.9	58
Posterior cingulate cortex	0	−49	28	4.32	170
Left middle temporal gyrus	−54	−37	−2	4.49	70
Right fusiform gyrus	39	−67	−23	3.86	69
Left fusiform gyrus	−27	−67	−17	4.38	760
Left lingual gyrus (visual)	−24	−91	−14	6.18	Above
Right occipital cortex	24	−100	10	5.74	436
Emotion > neutral, patients masked by HP					
Left superior frontal gyrus	−12	65	16	4.46	25
Left inferior frontal gyrus	−51	23	−5	4.26	99
Medial superior PFC	6	59	4	3.94	69
Middle cingulate cortex	12	11	34	4.18	17
Left supplementary motor area	−12	14	64	4.3	38
Right parahippocampal gyrus	18	−22	−8	4.37	81
Left parahippocampal gyrus	−9	−28	−14	4.34	85
Left fusiform gyrus	−27	−64	−17	4.98	222
Right fusiform gyrus	33	−58	−23	4.17	196

Note: $P < 0.001$ uncorrected.

A previous behavioral study using an emotional word association task with depressed college students also reported that more associations were produced in response to neutral words in general, whereas depressed students additionally showed a negative priming bias in word associations (Watkins *et al.*, 1996). These effects might partly be due to the nature of word stimuli. Neutral words more often refer to concrete entities when compared with emotion words, and it

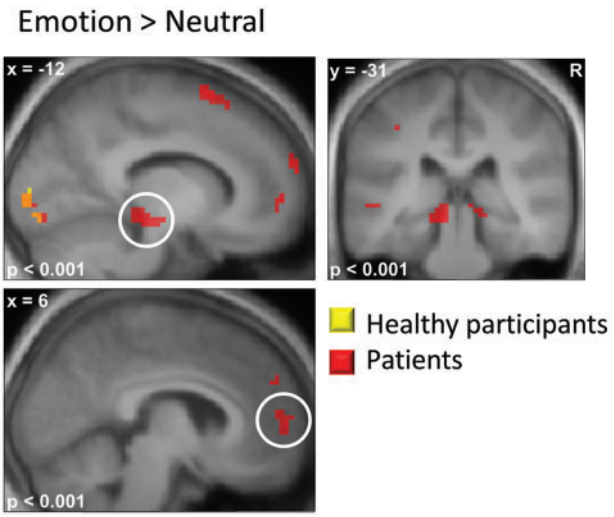

Fig. 4 Effect of emotion *vs* neutral stimuli. Patients activate more the PHG and medial prefrontal gyrus than HPs for emotional stimuli (all conditions pooled together).

is possible that concrete words activate more stereotyped associations, hence the high number and also high typicality of answers to the neutral word cues. Interestingly, here we also found that people with mood disorders tend to produce more unusual words in the close association condition, both for positive and negative cues (a pattern that has been debated; see Isen *et al.*, 1985). We were not able to directly examine the effect of current mood on the pattern of association since our subgroup of patients with hypomania was too small, but the total number of words produced did correlate negatively with depression scores across the whole sample (i.e., in both patients and controls), which is consistent with the idea that positive affect is associated with improved word production (fluency, flexibility) and broader conceptual processing (Fredrickson, 2001).

The reverse pattern of 'originality' found between patients and HP for close and remote associations, respectively, fits well with the idea that when the task is more 'automatic', the patients might tend to retrieve more idiosyncratic, self- or memory-related information when compared with HP. Thus, the observed increase in atypical associations in the close condition might reflect a facilitation of access to self-related thoughts. This would be consistent with the proposal that associative thinking biases in depression are characterized by greater self focus (Watson *et al.*, 2012), and not just narrower contextual associations (Bar, 2009). In contrast, when the task requires an inhibition of spontaneous associative processes, patients appear more stereotyped. Thus, in the remote condition, they produced more 'incorrect' answers (persistence of typical associations), which reflect a relative inability to inhibit the automatic/familiar associations. Again, this may arise either because patients are influenced by personal concerns that were cued by the emotional word meaning and interfered with the task, or because they have less powerful cognitive control. These findings are also consistent with the notion that producing more remote associations takes more time, which might explain why patients produced fewer words in total (Mednick, 1962).

At the brain level, we found that the two associative conditions activated many cortical regions known to be involved in semantic processing and language (Thompson-Schill *et al.*, 1997; Binder *et al.*, 2009). In addition, the close condition (relative to the remote) further activated the left SMA and left inferior frontal cortex, crucially implicated in semantic retrieval (Binder *et al.*, 2009; Wende *et al.*, 2012). Both associative tasks also activated regions of visual cortex, but especially during the remote condition. This is consistent with a contribution of mental imagery during associative processing (Desseilles *et al.*, 2011), either automatically or strategically used by participants in the remote condition, as well as during performance on semantic fluency tasks (Birn *et al.*, 2010).

Both the left inferior frontal cortex and the basal ganglia were activated significantly less (or even not at all) in patients when compared with HP in the close association condition. Basal ganglia are known to contribute to word generation, and the caudate nucleus is involved in lexical retrieval through a left SMA-dorsal caudate-ventral anterior thalamic loop (Crosson *et al.*, 2003) and in language switching in bilinguals (Abutalebi *et al.*, 2008; Wang *et al.*, 2013b). Moreover, besides common symptoms of motor inhibition and apathy, lesions to the basal ganglia may lead to aphasic disorders predominantly affecting automatic speech (such as days of the week or prayers [Ullman, 2004]). These basal ganglia functions might be consistent with an important role in promoting automatic association patterns, as observed here in the close condition for HP. Our results thus point to some impairment in cortico-subcortical circuits in people with mood disorders that may contribute to their difficulties in generating spontaneous verbal associations and possibly new thoughts (Piguet *et al.*, 2010).

In HP, the remote association condition showed specific activations in the right inferior/middle frontal gyrus and right cuneus/precuneus. The former region in right inferior frontal gyrus has consistently been implicated in inhibition processes (Konishi *et al.*, 1999; Depue, 2012). Cuneus/precuneus activations have also been revealed by previous neuroimaging study of Hayling task (Collette *et al.*, 2001; Allen *et al.*, 2008) or verbal suppression (de Zubicaray *et al.*, 2000). These effects therefore support the idea that the remote condition involved an active inhibition of spontaneously generated associations. Moreover, an increase in the cuneus accords with a previous study in bipolar patients (Haldane *et al.*, 2008) that reported that impaired inhibition in Hayling task was linked to reduced cuneus volume. Hence, the lower ability of patients to produce remote associations is associated with lower activation of brain networks involved in response inhibition and visual imagery, two processes crucial to perform the task. These findings suggest deficits in executive cognitive control in mood disorder patients, underpinned by abnormal recruitment of these networks.

In sum, an underactivation of semantic and language production networks in patients appears to underpin their reduced production of words in the close condition (which were also more unusual), whereas underactivation of right prefrontal cortex and medial occipito-parietal areas might account for their difficulty in the remote condition, suggesting that mood disorders involve deficits in both the generation and inhibition of association with distinct neural substrates.

Emotional word processing

Patients recruited additional limbic and paralimbic regions in emotional conditions, including peri-hippocampal and midline cortical structures. A recent study (Laeger *et al.*, 2012) investigating brain response to emotional words in HPs showed greater amygdala activation for both negative and positive words than neutral words, and also a significant correlation for negative words with levels of (subclinical) depression and anxiety. However, this study also revealed greater activation of hippocampus for emotional words (Laeger *et al.*, 2012). This is consistent with previous literature on free word retrieval process (McIntosh *et al.*, 2008; Whitney *et al.*, 2009) and contextual associations (Bar *et al.*, 2007), suggesting modulations by the affective significance of stimuli. In addition, the PHG and mPFC are not only implicated in associative-memory-related processes, but also parts of the default-mode network that has been linked to self-referential

processing (D'Argembeau *et al.*, 2005). Increased activations of self-related regions have consistently been replicated in depression (Grimm *et al.*, 2009; Lemogne *et al.*, 2012) and may reflect greater self-focus and negative affective biases in these patients, possibly contributing to rumination and task interference (Marchetti *et al.*, 2012). We speculate that hyperactivation within these regions might interfere with normal thought pattern and spontaneous associative processes, by preventing the retrieval of typical semantic associations in the close condition, and also by disrupting the ability to generate broader associations in the remote condition. This proposal accords with the theoretical hypothesis of Bar (2009) that mPFC hyperactivation in depression might interfere with (or rather bias) the activation in medial temporal structures linked to associative processing.

Limitations

Because our patient population was heterogeneous and included patients with different mood disturbances, we could not determine distinct patterns of changes as a function of different diagnoses or states. However, this choice was motivated by the fact that thought disorders and underlying anomalies in cognitive processes might represent a dimensional impairment in mood disorders across distinct diagnostic categories (Piguet *et al.*, 2010). Moreover, our subsidiary comparison between sub-groups (MDD *vs* BD, depressed *vs* euthymics participants) did not elicit any distinctive activations in brain regions that were identified by our main contrasts between conditions. The findings reported here are therefore independent of clinical subgroup or current mood state. A second potential limitation is the difficulty of the 'remote' condition that may have limited the opportunity for 'original' responses in patients, since it has been suggested that spontaneous associations are facilitated by low cortical arousal states allowing defocused attention (see Martindale and Hasenfus, 1978). Nevertheless, this condition allowed us to test for the differential ability of patients to resist interference by more automatic associative processing, relative to controls and to the close condition. Third, patients generally had more difficulties producing two words in 5 s when compared with HP, leading to a loss of trials with recorded responses and a potential reduction in the statistical power of our analyses. However, this is unlikely to be a confound, since some comparisons (e.g. with emotional word cues) actually revealed stronger effects in patients. Finally, it would certainly be fruitful to carry out a finer analysis of the verbal answers produced by patients; for example, looking at the semantic distance and relationship between words within individuals and within groups.

Conclusion

In mood disorder patients, pattern of free verbal associations might be influenced by a tendency to retrieve more self-related material, particularly in response to emotional cues, making their production less typical in automatic conditions and more typical when answers are controlled. These effects are paralleled with both hypoactivation of brain areas involved in semantic retrieval and inhibitory executive control, and hyperactivation of regions involved in memory and self-related processing. This combination of impaired generation and impaired control of spontaneous associations might contribute to thought disorders in patients (Piguet *et al.*, 2010; Desseilles *et al.*, 2012).

SUPPLEMENTARY DATA

Supplementary data are available at *SCAN* online.

Conflict of Interest

None declared.

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