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Changes in medial prefrontal cortex neural responses parallel successful antidepressant combination of venlafaxine and light therapy

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ABSTRACT

Few pilot prospective studies performed BOLD fMRI before and after treatment in order to define the neural correlates of antidepressant response. To determine how antidepressant treatment influences the pattern of neural response to a task targeting the depressive biases in information processing (moral valence decision), eight depressed inpatients were treated with combined venlafaxine and light therapy for four weeks. Brain BOLD functional magnetic resonance imaging on a 3.0 Tesla scanner was performed before and after treatment. Treatment and moral value of the stimuli showed the most significant interaction in right medial frontal gyrus (BA 10), where also clinical status was found to be inversely correlated with response to negative stimuli after treatment. A significant interaction of treatment and valence of the stimuli was also detected in other areas that have been widely associated with the depressive illness.

Key words

Light Therapy • Venlafaxine • Bipolar disorder • fMRI

Introduction

Blood oxygen level dependent functional magnetic resonance imaging (BOLD fMRI) allows to study brain local haemodynamic responses to cognitive stimuli. Recent studies have established that BOLD fMRI measures represent temporally stable and reliable indices of brain function.

In the case of Major Depressive Disorder, BOLD fMRI proved useful in exploiting the neural bases of the cognitive (Elliott et al., 2002) and the emotional (Fu et al., 2004; 2007) disturbances that characterize the illness, thus modelling the neural correlates of specific dimensions of the syndrome to gain new insights into the neuropathology underlying the disease.

Dysfunctional cognitions are a regular core symptom of major depression, and include self-deprecatory and self-accusatory thoughts. The sense of worthlessness or guilt associated with a Major Depressive Episode includes unrealistic negative moral evaluations of one's worth and guilty preoccupation and ruminations over minor past failings. According to the fourth edition of the Diagnostic and Statistic Manual of mental disorders (DSM IV), this is criterion A7 needed for the diagnosis of major depression.

The psychopathological feature is that the typical severe self-reproach and the sense of guilt completely revert with remission from the illness episode. This prompted researchers to investigate the

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neuropsychological correlates and the neural basis of information processing in depression.

A consistent literature confirmed a bias toward processing of mood-congruent information, with depressed patients showing a facilitation of performance when responding to stimuli with a negative emotional tone (sad or happy words, Murphy et al., 1999), and a general negative cognitive style with a bias toward the processing of negative information, whereby positive information tends to be neglected. Tasks involving the evaluation of adjectives descriptive of positive and negative individual characteristics (e.g., "brave", "vile", etc.) showed that in contrast to controls, depressed patients react faster to negative than to positive elements, recall and recognize more negative than positive elements, and perceive more often negative information as being self-descriptive.

These negative biases in information processing are the neuropsychological correlate of the negative self-scheme and of the self-reproach of depressed patients and they can be successfully modified with antidepressant treatment. Several clinical studies showed that marked depressive dysfunctional cognitions predict a longer duration of depressive episodes (Williams et al., 1990), depressive chronicity (Bothwell and Scott, 1997) and the development of hopelessness (Cannon et al., 1999), which has been shown to be associated with suicidal behaviour (Beck et al., 1993).

In previous research work we translated the words used in the study by Baving et al. (1997), who assembled four parallel word lists, each consisting of 100 adjectives descriptive of personality characteristics, 50 positive and 50 negative.

We validated our translation, and the possibility to use it in clinical settings, in several hundreds of normal and depressed subjects (Benedetti et al., 2005).

In agreement with the literature, we showed that these depressive cognitive biases are specific of mood disorders, and can be modified by treatment (Florita et al., 2005; Benedetti et al., 2005b).

Few prospective studies performed BOLD fMRI before and after treatment in order to define the neural correlates of antidepressant response, and with heterogeneous time lags. No study explored changes that parallel the 4-weeks treatment lag commonly accepted in drug research to detect antidepressant effects. PET studies have first identified brain regions involved in normal sadness, depression and recovery. Increases in subgenual cingulate and anterior insula and decreases in right dorsolateral prefrontal and inferior parietal cortices were associated with sadness. Recovery from depression was accompanied by the reverse pattern (Mayberg et al., 1999).

Also non pharmacological interventions like cognitive behavioural therapy (CBT) have proven efficacious in the treatment of depression. A study by Siegle et al. (2006) reported that pre-treatment neural activity in subgenual cingulate cortex and in amygdala predicts clinical response to CBT.

Only few fMRI studies investigate changes in neural response after treatment. Changes in the neural activity to emotional stimuli have been described after 8-week therapy with sertraline, unipolar depressed patients show a left amygdala hyperarousal, this increased amygdala activation normalizes with antidepressant treatment (Sheline et al., 2001). Robertson and colleagues (2007) found an attenuation in amygdala response associated with a positive clinical response and an improved activation in the frontal and pre-frontal areas in depressed patients treated with Bupropion XL (Murphy and Sahakian, 2001). Similar results were reported with fluoxetine (Fu et al., 2004; 2007; Goldapple et al., 2004). Another study investigated the response to positive social stimuli before and after 22-weeks with venlafaxine (Schaefer et al., 2006). Patients in a current episode exhibit hyporeactivity in a variety of networks, including several frontal regions compared with remitted depressed patients and control subjects (Shah and Marsden, 2004).

A study by Davidson and colleagues (2003) explored the neural responses to cognitive paradigms, after 2- and 8-week therapy with venlafaxine and found a reduction in neural activity in some limbic areas after exposure to negative stimuli.

A recent study by our group demonstrated a similar pattern of variation after combined sleep deprivation, light and lithium therapy (Benedetti et al., 2007).

Functional magnetic resonance imaging demonstrated that depressed patients, in respect to control subjects, showed elevated neural responses specific to sad targets in rostral anterior cingulate extending to anterior medial prefrontal cortex (Elliott et al., 2002).

We showed that successful antidepressant treatment was paralleled by specific changes in event-related neural responses to a moral valence decision task in

dorsolateral and medial prefrontal cortex (PFC) in bipolar depressed patients (Benedetti et al., 2007). Responders showed a pattern of change of neural response to positive and negative stimuli opposite to that of non responders, the effect being influenced by genetic factors that modulate antidepressant response. Neural activity of responders after treatment was similar to that of healthy subjects, while neural responses of non responders remained markedly abnormal. The study of the normalization of the neural correlates of depressive cognitive distortions could then be considered a good model for the study of the neural underpinnings of the effects of antidepressant treatment.

Venlafaxine is a serotonin and noradrenaline reuptake inhibitor which has been shown to provide higher rates of remission when compared with serotonin reuptake inhibitors and tricyclic antidepressants (Thase et al., 2001; Lam and Kennedy, 2004). Light therapy has been shown to potentiate and accelerate response to combined antidepressant drugs (Benedetti et al., 2003; Martiny, 2004), thus leading to hastened improvement and fewer residual symptoms (Terman and Terman, 2005).

Phenotypically, no difference is detectable between cognitive distortions affecting unipolar and bipolar depressed patients during a major depressive episode. Though clinically similar, these patients do not share other characteristics such as course of illness, number of episodes, response to treatments and social outcome.

Our previous work on a sample of bipolar patients helped define the neural basis of antidepressant response to sleep manipulation. The present work aims at detecting the possible different neural basis of antidepressant response to different somatic treatment in unipolar and bipolar depression.

In the present pilot study we studied the effect of combined venlafaxine and light therapy on event-related neural responses to a go/no-go task with morally tuned words in a homogeneous sample of patients affected by unipolar depression.

Methods

Sample and treatment

We studied 8 right-handed inpatients (one male, seven females) with a diagnosis of major depressive episode without psychotic features in course of major depressive disorder.

Diagnoses were made by trained psychiatrists using Structured Clinical Interview for DSM Disorders (SCID-I). Clinical and demographic characteristics were (mean ± sd): age 46.25 ± 12.41; age at onset 37.25 ± 13.66; number of previous depressive episodes 2.12 ± 1.35; duration of current episode 21.25 ± 15.19 weeks.

Inclusion criteria were a baseline Hamilton Depression Rating Scale (HDRS) score of 18 or higher; absence of other diagnoses on Axis I; absence of mental retardation on Axis II (WAIS-R was administered to all patients, according to DSM IV only patients with an IQ > 70 were included in the study); absence of pregnancy, history of epilepsy, major medical and neurological disorders; absence of a history of drug or alcohol dependency or abuse within the last six months.

Physical examinations, laboratory tests and electrocardiograms were performed at admission. After complete description of the study to the subjects a written informed consent was obtained. The study have been reviewed by ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

All patients were administered venlafaxine 225 mg/day and light therapy (exposure for 30 minutes to a 400 lux green light) in the morning (Benedetti et al., 2003). Timing of morning LT administration was chosen based on the observed correlation between the magnitude of phase advances to morning LT and improvement in depression ratings, with maximum effects with phase advances of 1.5-2.5 hours (about 7.5-9 hours after the dim-light melatonin onset the evening before). Since scores on the Morningness-Eveningness Questionnaire (MEQ) are strongly correlated with sleep midpoint and melatonin secretion, a predictive algorithm based on MEQ scores was developed to define the individual optimal timing of LT administration (Terman et al., 2001). In the present study, we optimized timing of morning LT for each subject based on the results of this assessment tool. Up-titration was as follows: day 1-3 75 mg/day; day 4-14 150 mg/day; starting from day 15 225 mg/day. The Hamilton Depression Rating Scale (HDRS) was administered in the morning of day 0, 7, 14, 21, and 28.

Image acquisition

Functional images were acquired in the early afternoon of day 0 and 28 using a previously described method (Benedetti et al., 2007).

Gradient echo echo-planar images (EPI) were acquired on a 3.0- Tesla scanner (Gyroscan Intera, Philips, Netherlands) using a 6 channels SENSE head coil. For each functional run, 200 T2*-weighted axial slices, parallel to the AC-PC plane, were acquired using an EPI pulse sequence (TR = 2200 ms; TE = 35 ms; flip angle = 90°; field of view = 230 mm; number of slices = 18; slice thickness = 4 mm; matrix size = 80x80 reconstructed up to 128x128 pixels). Two dummy scans before fMRI acquisition allowed to obtain longitudinal magnetization equilibrium. Total time acquisition was 7 minutes and 29 seconds per trial. On the same occasion and using the same magnet 22 Turbo Spin Echo (TSE) T2 axial slices (TR = 2250 ms; TE = 85 ms; flip angle = 90°; turbo factor 15; 5-mm- thick, axial slices with a 512x512 matrix and a 230x230 mm^2 field of view) were acquired parallel to the AC-PC plane to rule out brain lesions.

Cognitive activation paradigm

The experimental setup was composed of two positive target sessions and two negative target sessions, randomly presented. For each of the four image acquisition sessions, 30 positive and 30 negative for a total of 60 morally tuned adjectives (e.g., brave/vile) were displayed. Each word was presented visually for 1 second. The cognitive activation paradigm was based on a classic go/no-go task. Patients were asked either to push a button for positive targets and ignore negative distractors, or the opposite.

White colored words were randomly shown on a black screen and presented to the participant through a mirror positioned above the head coil. Emotionally tuned stimuli were interspersed by one, two or three TRs, following a 4:2:1 schedule, during which subjects were presented a cross-hair fixation. A 0.1 sec temporal jittering was inserted in order to randomly present every word within the TRs.

Data processing

Images were computed, overlaid on anatomic images, and analyzed using Statistical Parametric Mapping (SPM2. The Welcome Department Of Imaging Neuroscience, London, England). Masking of white matter activations, and conversion from Montreal Neurologic Institute coordinates to the Talairach space were performed with Wake Forest PickAtlas (Maldjian et al., 2003).

We performed a slice timing adjustment on all the acquired volumes in order to correct images for time acquisition between first and last slice, and realigned the scans to correct for head movement. Data were then normalized to a standard EPI template volume, based on the Montreal Neurological Institute reference brain (Cocosco et al., 1997) in the space of Talairach and Tournoux (Talairach and Tournoux, 1997) and smoothed using a 10-mm full-width at half-maximum isotropic Gaussian kernel. The evoked hemodynamic responses were modelled as a delta function convolved with a hemodynamic response function and its temporal derivative within the context of the general linear model. All events were time locked to the onset of emotionally tuned words.

fMRI data analysis

At the individual level, we first compared (t test; threshold $p < 0.001$) both "no-go" and "go" trials to fixation, thereby isolating regions that were engaged by the task during both trial types; and then contrasted "no-go" and "go" images thus creating "double-subtraction" images (("no-go" > fixation) > ("go" > fixation)) at the single subject level (t test, threshold $p < 0.001$) that were used at the random-effects level. The resulting four double-subtraction images for each subject (positive/negative, before/after treatment) were then entered into a second-level random-effect two-way ANOVA with moral valence of the stimuli and time (before/after treatment) as factors. Second level analyses were thresholded at $p < 0.05$, and limited to gray matter areas: the resulting threshold in a priori ROIs was then $p < 5^{-5}$. Thus, increasing alpha level protect us against false positives.

The primary analysis of interest was the two-way interaction, which allowed us to identify the areas were treatment and moral valence of the stimuli interacted in influencing the BOLD response to the task.

We then performed a correlation between neural activity for negative stimuli after treatment and HDRS scores at week 4. The activation-based dependent measures were the voxel values from each subject at the regional maxima identified in the

group-by-time analyses: analysis was restricted to a sphere of 3mm radius centred in the voxel were the ANOVA revealed maximal effects of treatment x valence interaction.

Results

Treatment was paralleled by significant decrease of HDRS scores, which were (mean ± sd): 25.88 ± 4.39 at baseline; 17.62 ± 7.96 at week 1; 12.75 ± 7.48 at week 2; 13.25 ± 7.48 at week 3; and 10.62 ± 5.37 at week 4 (Friedman ANOVA: $\chi^2 = 21.43$, d.f. 4, $p < 0.00026$). Half of the patients achieved the strict remission criterium of HDRS score lower than 8 at week 4 and could be rated as full responders to treatment.

Treatment caused marked changes to the pattern of response to the moral valence decision task. Significant valence x treatment interactions were detected in multiple brain areas, including medial and dorsolateral PFC, anterior cingulate, hippocampus and parahippocampal cortex (see Table I and Fig. 1).

ANOVA showed maximal effects in right medial frontal gyrus, Brodmann area 10, where patterns of change of BOLD signal before/after treatment differed according to the moral valence of the stimuli: activation for negative stimuli decreased after treatment, while activation for positive stimuli increased (Fig. 2). In the same voxels final HDRS scores were inversely correlated with response to negative stimuli after treatment (Fig. 3).

Discussion

Combined treatment with venlafaxine and light therapy resulted in a variation of neural activity in a diffuse network including frontal and prefrontal

Table I. - Gray matter areas where a significant effect of the interaction of moral valence of the stimuli (negative-positive) and treatment (before /after) was detected. Data are shown for the maximal activations in each Broadmann's area (BA): lateralization, MNI coordinates (x, y, z) of voxels with higher Z values (signal peaks); and level of significance. Glass-brain images of these data are shown in Fig. 1.

Region	Side	BA	Signal peak	F	Z	p
Medial prefrontal cortex						
Medial Frontal Gyrus	Right	10	14 52 -4	47.74	5.11	0.000
	Left	10	-6 60 4	20.75	3.74	0.000
Dorsolateral prefrontal cortex						
Inferior Frontal Gyrus	Right	9	60 20 28	17.37	3.46	0.000
	Left	47	-28 26 -18	17.09	3.44	0.000
	Right	45	52 28 8	14.93	3.24	0.001
Superior Frontal Gyrus	Right	10	22 56 -8	15.09	3.25	0.001
Orbitofrontal cortex						
Superior Frontal Gyrus	Right	11	18 60 -10	22.50	3.86	0.000
Frontal cortex						
Middle Frontal Gyrus	Left	6	-36 -2 44	21.24	3.77	0.000
Cingulate cortex						
Anterior cingulate	Left	24	-6 38 4	20.50	3.72	0.000
	Left	32	-16 44 -2	15.66	3.31	0.000
	Right	32	14 42 6	14.66	3.21	0.001
Dorsal cingulate	Left	24	-12 12 34	14.01	3.14	0.001
Hippocampus	Left	-	-32 -28 -12	23.36	3.92	0.000
Temporal cortex						
Parahippocampal Gyrus	Left	36	-26 -30 -16	18.79	3.58	0.000
	Right	28	20 -28 -12	15.82	3.32	0.000
Thalamus	Right	-	22 -26 -2	14.99	3.24	0.001

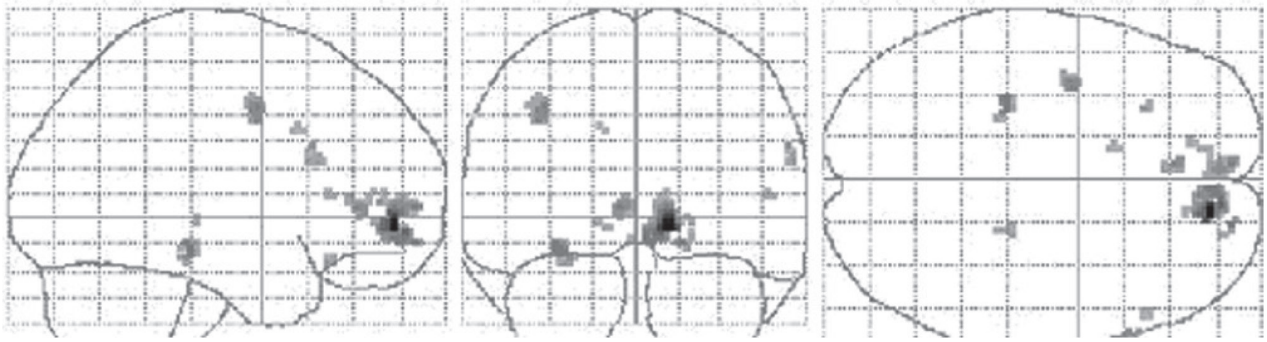

Fig. 1. - Glass-brain images of gray matter areas where a significant interaction of valence x treatment was detected.

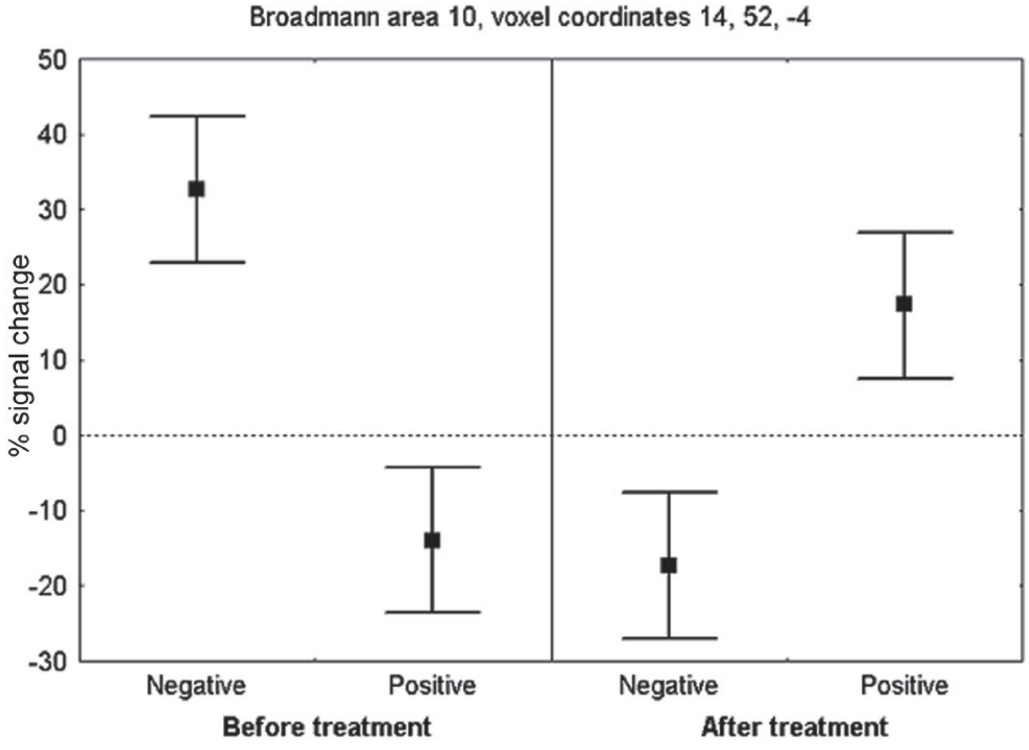

Fig. 2. - Direction and size effects of the significant interactions of treatment and moral valence of the stimuli on the event-related BOLD activations in right medial frontal gyrus, (Brodmann area MNI coordinates 14, 52, -4). Points are estimated regression coefficients for the tasks (percent of whole brain mean T2* BOLD signal) before and after treatment. Whiskers are standard errors.

areas, cingulate and temporal cortex and the hippocampus. Such change was accompanied by clinical amelioration of depressive symptoms over 4 weeks of treatment.

Treatment and moral value of the stimuli showed the most significant interaction in right medial frontal gyrus (BA 10). This area is involved in self-referential processing of all emotional stimuli, regardless of emotional valence, thus providing a neural basis for the personal perspective in the evaluation of emotional stimuli (Fossati et al., 2003). In animal models descending pathways from orbitofrontal and medial PFC, which are also linked with the amygdala, provide the means for the influence of PFC in processes underlying appreciation and expression of emotions (Barbas et al., 2003; Hariri et al.,

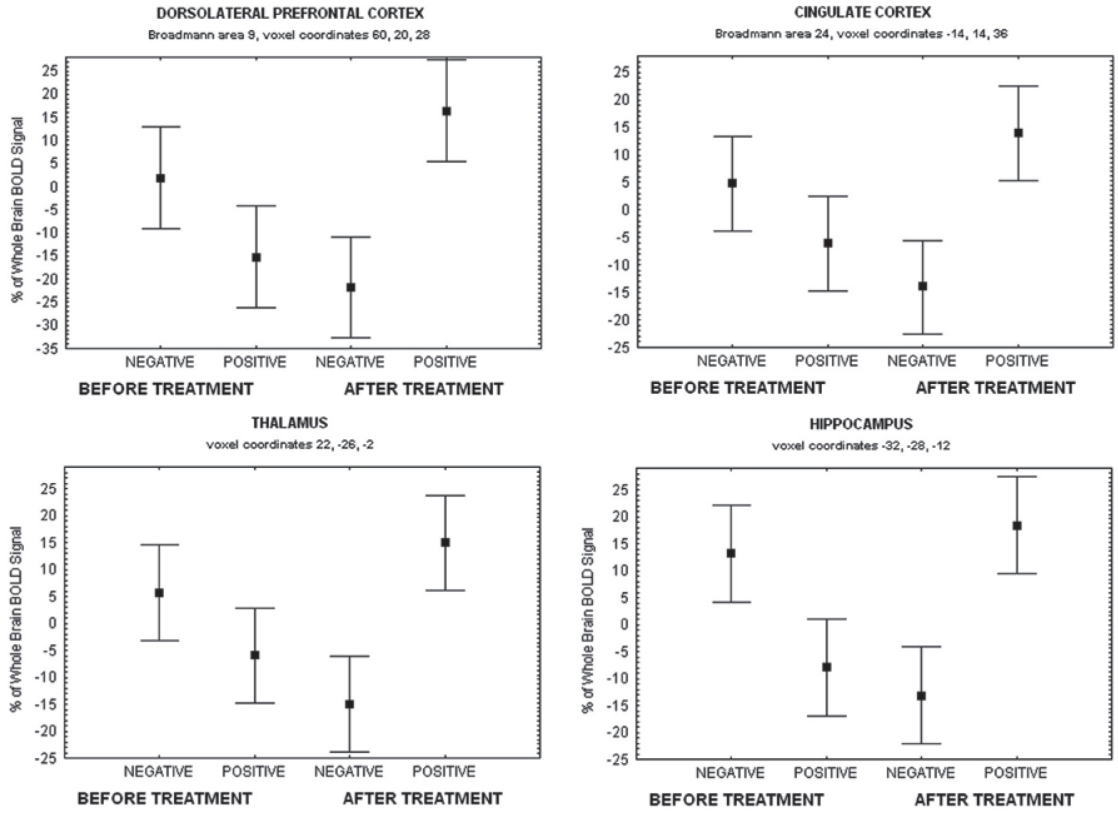

Fig. 3. - Direction and size effects of the significant interactions of treatment and moral valence of the stimuli on the event-related BOLD activations. Points are estimated regression coefficients for the tasks (percent of whole brain mean T2* BOLD signal) before and after treatment. Whiskers are standard errors.

2003). PET studies showed a reduction in medial PFC activity (BA 10) after successful antidepressant sleep deprivation (Wu et al., 1999), pharmacological treatments (Holthoff et al., 2004), and cognitive behavioural therapy (Goldapple et al., 2004). Chen and co-workers reported a correlation between gray matter abnormalities in medial prefrontal cortex and baseline HDRS scores (Chen et al., in press).

The study of self-referential processing of positive and negative words in healthy human subjects showed higher activity in medial PFC for positive than for negative words (Fossati et al., 2003): here we found an opposite pattern of higher activity for negative than for positive words at baseline, which changes after treatment (Fig. 2), when the neural responses to negative stimuli were proportional to the residual symptoms of the depressive syndrome, as measured by HDRS (Fig. 4). A recent PET study found that response to venlafaxine was associated with decreased glucose metabolism bilaterally in the orbitofrontal cortex and left medial prefrontal cortex (BA10) (Kennedy et al., 2007).

Changes in self-evaluation process that paralleled mood improvement might explain the increased activation for positive stimuli detected after treatment. On the other hand this finding is supported by the robust activation for negative stimuli found in more severely depressed patients after treatment.

A significant interaction of treatment and valence of the stimuli was also detected in other areas that have been widely associated with the depressive illness by morphometric and functional studies (Davidson et al., 2002). ACC is implicated in the detection and evaluation of cognitive and emotional conflict and incompatible responses (Carter et al., 1998; Etkin et al., 2006), its metabolism changes with depression and depression recovery (Mayberg et al., 1999; Wu et al., 2001), and its neural responses to affective stimuli correlate with depressive cognitive distortions (Elliott et al., 2002) and change with successful antidepressant treatment (Benedetti et al., 2007).

A wide and consistent literature on positron emission tomography measures of metabolic activity in the perigenual ACC in major depression at baseline

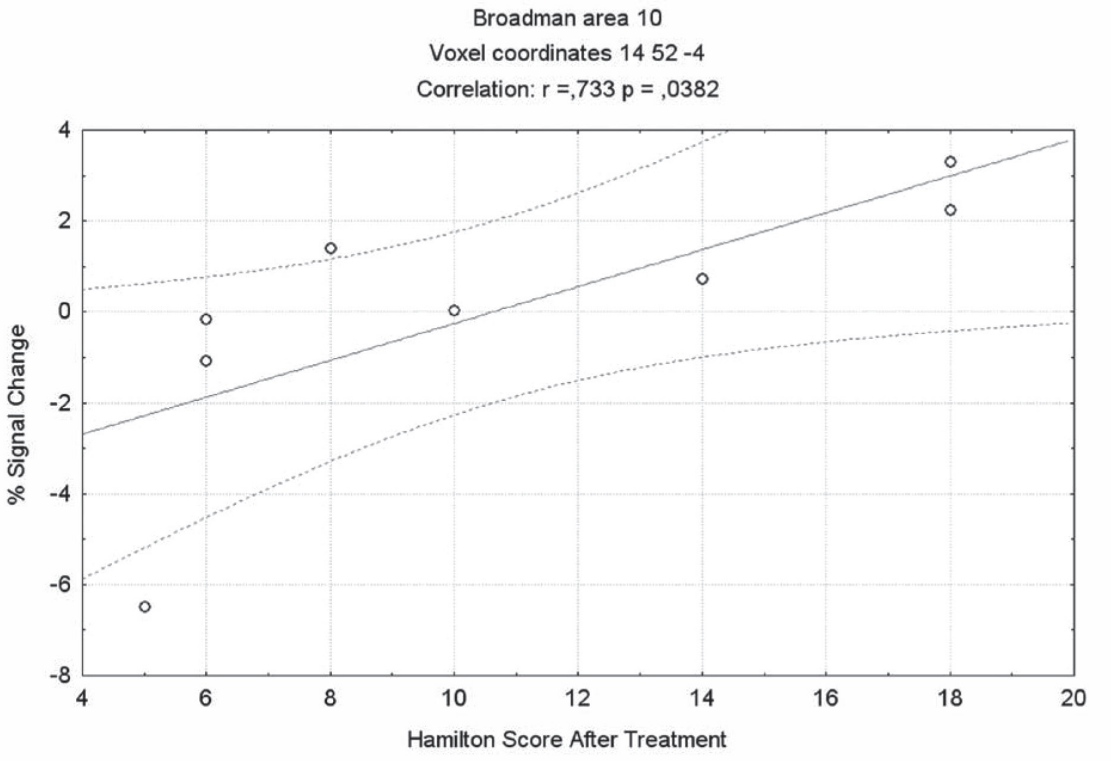

Fig. 4. - Simple correlation analysis between neural activity for negative stimuli after treatment and HDRS scores at week 4. Analysis was restricted to a sphere of 3mm radius centred in the voxel were ANOVA revealed maximal activation (14, 52, -4).

and after recovery, showed higher metabolic rates at baseline, with a decrease during treatment that was proportional to the clinical amelioration (Mayberg, 2003). In a recent study by our group (Benedetti et al., 2007), we showed that the baseline activation in the dorsal ACC is paralleled by a decreased activation for negative stimuli. The present finding confirm the direction of the activation in the cingulate cortex after antidepressant treatment (Fig. 3).

Dysfunction of the dorsolateral and orbitofrontal PFC may also impair the ability to modulate emotional responses in mood disorders (Drevets et al., 2002), and these regions showed gray matter loss in unipolar depression (Lavretsky et al., 2005).

Neural responses in the dorsolateral PFC to negative stimuli have been shown to be linked to voluntary suppression of sadness in healthy subjects (Levesque et al., 2003) and positron emission tomography scans showed that local metabolism was decreased by induction of transient sadness in healthy subjects (Liotti et al., 2000) and activated by response to treatment in patients with depression (Mayberg et al., 1999). We found that response to antidepressant therapy is paralleled by decreased activation of negative stimuli and increased activation of positive stimuli (Fig. 3).

Hippocampus consistently showed reductions in gray matter volume and functional impairment (Sheline et al., 2003; Bertolino et al., 2003).

Videbech et al (2001) showed that patients with major depression had increased activity of the hippocampus and the cerebellum compared to the healthy controls. Here we found an increased activity for positive stimuli and a decreased activity for negative ones after treatment (Fig. 3).

Regarding thalamic activation only a few studies focused the attention on this area, Anand et al (2005) found that depression is associated with increased activation of medial thalamus. We found that thalamic activity decreased for negative stimuli and increased for positive after treatment (Fig. 3).

Despite the low number of subjects studied, which limits interpretation of our findings, we replicated and extended previous findings about the neural correlates of mood congruent biases in depressed information processing (Elliott et al., 2002) and about

the neural correlates of antidepressant response (Benedetti et al., 2007; Davidson et al., 2003), and found that the regions of interest were the same implicated by previous research work in the physiopathology of depression (Davidson et al., 2002). This suggests that BOLD fMRI may provide a useful method to study the neural correlates of antidepressant response even in small samples and with the usual 4 weeks time lag. A major limitation of the study is the uncorrected p-thresholding that does not account for multiple comparisons, despite surviving the threshold of $p < 0.001$ in a priori selected ROIs, our results did not survive FWE or FDR corrections and may have not efficiently protected us against false positives.

On the other hand many research groups use uncorrected thresholds, such as $p < 0.001$, considering clusters of ≥ 5 voxels as significant on basis of control studies finding no false positive activations during visual fixation using these conventions (Zarahn et al., 1997).

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