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# Short Term Antidepressant Administration Reduces Negative Self-referential Processing in the Medial Prefrontal Cortex in Subjects at Risk for Depression

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## ABSTRACT

Depression has been associated with changes in responses within the medial prefrontal (mPFC) cortex during emotional information processing. Antidepressant drug treatment has been shown to modify neural responses in healthy volunteers early in treatment within similar circuitry. It is unclear, however, whether the same early effect occurs in depressed patients, prior to changes in mood. The current study therefore investigated the effects of 7 days administration of the SSRI citalopram versus placebo in volunteers (n=29) at high risk for the development of depression using the personality phenotype of high neuroticism in a double-blind, between-groups design. On the last day of treatment resting haemoperfusion and functional MRI data were acquired during a self-referential words categorization task. A significant activation in a cluster of mPFC areas, including dorsal anterior cingulate and right orbitofrontal cortex was revealed, driven by decreased responses to negative self-descriptors following citalopram compared to placebo, in the absence of any mood differences. These findings show a normalization of neural abnormalities in an at risk population early in treatment, supporting the theory that antidepressants may indeed act by modifying specific neural dysfunctions correlated to negative cognitive biases.

*Key words: depression, SSRI, emotion, neuroticism, prefrontal cortex, self-referential*

## Introduction

There is increasing evidence to suggest that major depression is characterised by alterations in orbitomedial and ventromedial prefrontal cortex (omPFC; vmPFC) both at a structural and functional level, with decreased grey matter volume and increased metabolism in anterior cingulate (ACC) and ventromedial frontopolar cortex, which may correlate with symptom severity (1). These areas participate in a limbic-cortical-striato-pallido-thalamic circuit implicated in the processing of emotional stimuli (2, 3) and may be specifically involved in assessing salience and value, and regulating response to emotional information (4, 5).

At a behavioural level, depression has also been correlated with mood-congruent aberrant processing of emotional information such as increased attention and memory for negative verbal stimuli (6, 7). Such biases have also been associated with increased neural activation in omPFC areas such as the rostral ACC (8, 9). Thus, emotion processing biases and their neural correlates may reinforce negative thought distortions that maintain affective symptoms according to cognitive theories of depression (10).

Interestingly, different therapies such as antidepressants (11-15), vagus nerve(16) or deep brain stimulation (17), and CBT (8, 18, 19) have been reported to normalise resting metabolism and activation to emotional stimuli in medial PFC areas. These convergent observations suggest that omPFC and vmPFC malfunction could be a central feature of major depression but do not clarify whether its correction occurs as a direct effect of treatment or as a secondary effect consequent to symptoms remission and mood change.

Recent studies suggest that antidepressant drugs may start modifying neuropsychological biases in emotional information processing early on in treatment; such changes could allow depressed subjects to experience environmental stimuli more positively over time and thus correct their negative cognitive biases and lead to symptom remission that is manifest within the usual 2-3

weeks of delay from beginning of treatment (20, 21). Data from healthy volunteers support this model, showing early effects of antidepressants directly on the neural correlates of emotional information processing, namely decreasing fronto-limbic response to negative emotional stimuli and increasing the signal to positive ones (22-24). For example, repeated dose reboxetine administration has been shown to potentiate prefrontal cortical response to positive self-descriptors and diminish the neural memory workload in mPFC and other areas necessary for correct recognition of the same stimuli (25). However, it remains unclear whether antidepressants produce the same early changes in the neural substrates of emotion processing in clinical populations as these seen in healthy volunteers.

Interpretation of results from clinical samples is often problematic due to the confounding presence of concentration deficits and other general cognitive symptoms. Moreover, it is difficult to separate medication effects on mood state from those on emotional information processing during acute depression. Hence, the current study investigated the neural substrates of antidepressant action on subjects that present biases in emotional processing related to increased risk for depression and similar to those shown during low mood states, but without clinical symptoms of affect dysregulation. In particular, subjects with high neuroticism present a well-established vulnerability to affective and anxiety disorders (26, 27). They also show negative biases in facial expression processing and in categorisation and memory for self-descriptors (28) that appear to be underpinned by alterations in a network of brain areas including the medial PFC (29-31) and could be particularly relevant to their vulnerability to depression. We therefore hypothesised that seven days antidepressant administration would reduce the dysfunctional response to negatively valenced self-descriptors present in high neuroticism in brain areas related to evaluation and control of emotional stimuli (e.g. vmPFC).

## Materials and Methods

Thirty-four healthy volunteers (17 females) were initially recruited from the general population into the study with a mean age of 25.8 ( $SD \pm 7.1$ ). Written informed consent was provided prior to entry into the study, as approved by the local Ethics Committee. All subjects presented a score above 16/24 on the Neuroticism scale of the Eysenck Personality Questionnaire (32) (mean =  $17.82 \pm 2.1$ ) and were screened with a Structured Clinical Interview for DSM-IV I (33) for current or past Axis I disorders. All subjects were right-handed, in good physical health and free of any medication, excluding the contraceptive pill, and had no contraindications for fMRI scanning. Subjects also completed the State and Trait Anxiety Inventory (34), Beck Depression Inventory (35), Dysfunctional Attitudes Scale (36) and Life Events Rating Scale (37).

A double-blind, placebo-controlled, randomised design was used, with subjects randomly allocated to either 7 days of citalopram 20 mg/day ( $n=19$ ) or placebo ( $n=15$ ). During treatment daily mood, anxiety and side effects ratings were collected with the Befindlichkeit Scale (38) (BFS), Visual Analogue Scales (VAS) measuring happiness, sadness, hostility, alertness, anxiety and calmness and a side effects questionnaire.

On the last day of treatment subjects participated in a single 12 minute experiment employing rapid event-related fMRI while performing a word categorisation task, using positive and negative self-descriptors. For this task, a list of 90 personality adjectives was constructed, of which half were unambiguously positive and half negative (39). Positive and negative words were matched on length, frequency (40) and meaningfulness. Ten presentations each of 'left' and 'right' words were included as a baseline control words condition. The words 'left' and 'right' were selected in order to control for the sensorimotor aspects of the task without requiring subjective assessment of the positive or negative aspects of the word. Thus, 110 words were presented in total, with the order randomised across subjects. Stimuli were presented on a personal computer using E-Prime (version 1.0; Psychology Software Tools Inc., Pittsburgh, PA)

and projected onto an opaque screen behind the scanner bore, which subjects viewed using angled mirrors. During the categorisation task subjects were instructed to characterise the words as 'like' or 'dislike' in a self-referential fashion as quickly and accurately as possible. Specifically, subjects were asked to imagine whether they would like or dislike it if they overheard someone referring to them as possessing each of these personality traits. This instruction was previously used in behavioural studies (28, 41) and other behavioural and neuroimaging studies (25, 42) with healthy unselected and high neurotic volunteers. Subjects indicated their decision as 'like' or 'dislike' by pressing a button with the right and left index or middle finger, respectively. For the control words 'right' and 'left', subjects responded with their right and left index or middle finger respectively. Subject responses were recorded using an MRI-compatible keypad. Like and dislike responses and reaction times were recorded by E-Prime. Each trial consisted of a fixation cross (500ms) immediately followed by a personality or control word (1000ms). The duration of the intertrial interval (ITI) varied between 4000 and 8000ms according to a Poisson distribution, with a mean ITI of 5000 ms.

Subjects also underwent a 12 minute resting state acquisition while cerebral blood flow (CBF) levels were measured using an single shot three-dimensional (3D) gradient and spin echo Arterial spin labelling technique (GRASE-ASL). During this time they were instructed to watch a black screen and remain awake.

Imaging data were acquired on a 3T TIM Trio scanner located at the Oxford Centre for Clinical and Magnetic Resonance Research (OCMR). fMRI data were acquired with a voxel resolution of  $3 \times 3 \times 3 \text{ mm}^3$ , TR=3s, TE=30ms, Flip angle=87°. Field maps were also acquired using a dual echo 2D gradient echo sequence with echos at 5.19 and 7.65 ms, and repetition time of 444ms ( $64 \times 64 \times 40$  grid; voxel resolution of 3mm isotropic). T1-weighted structural images were acquired for subject alignment using an MPRAGE sequence with the following parameters: Voxel resolution  $1 \times 1 \times 1 \text{ mm}^3$  on a  $176 \times 192 \times 192$  grid, Echo time(TE)= 4.53 ms, Inversion time(TI)= 900 ms, Repetition time (TR)= 2200 ms. For ASL acquisition parameters see (43).

Due to rapid movement artefacts and/or registration problems of the perfusion MRI images, 5 subjects were excluded from the final analysis ( $n = 16$ , citalopram treated). Data were analysed using FSL version 4.1 (44). Pre-processing included slice acquisition time correction, within-subject image realignment (45), non-brain removal (46), spatial normalisation (to Montreal Neurological Institute [MNI] 152 stereotactic template), spatial smoothing, and high-pass temporal filtering to a maximum of 0.008 Hz. Susceptibility-related distortions were corrected as far as possible using FSL field-map correction routines. Given that the sample investigated was expected to present with high levels of baseline anxiety which could result in worse compliance to the scanner environment and increased motion during the experiment session, we included an additional pre-processing procedure to reduce motion related artefacts. Briefly, individual subject's data were subjected to an Independent Component Analysis (ICA) implemented within FSL. The resulting spatial maps were visually inspected and obvious motion /physiological artefacts were removed(47).

In the first-level analysis, individual activation maps were computed using the general linear model with local autocorrelation correction (48). Three explanatory variables were modelled: 'negative', 'positive' and 'control' words. All variables were modelled by convolving the onset of each word with a haemodynamic response function, using a variant of a gamma function (i.e. a normalisation of the probability density function of the gamma function) with a standard deviation of 3 s and a mean lag of 6 s. In the second-level analysis, individual data were combined at the group level (citalopram vs. placebo) using a mixed-effects group cluster analysis across the whole brain corrected for multiple comparisons (49). This mixed effects approach accounts for intra-subject variability and allows general population inferences to be drawn. Significant activations were identified using a cluster-based threshold of statistical images [height threshold of  $Z = 2.3$  and a (corrected) spatial extent threshold of  $p < 0.05$ ] (50). To check for potential confounding effects of sub-threshold differences in blood perfusion levels, demeaned CBF values obtained during resting state GRASE-ASL were entered in the analysis as a



voxel-wise covariate of no interest. Activation during the categorisation of self-referent emotional words was analysed in three separate contrasts: negative vs. control, positive vs. control and positive vs. negative words. Only trials where the 'like' or 'dislike' response corresponded to the word valence (i.e. 'like' for positive words and 'dislike' for negative words) were included in the analysis. Significant interactions were characterized by extracting percent blood oxygenation level-dependent (BOLD) signal change within the areas of significant difference, and then subjected to a repeated measures ANOVA (between subjects variable = group; within subjects variable = word valence) followed by appropriate *post-hoc t*-tests (SPSS v.14.0). Corresponding Brodmann Areas (BA) were identified by transforming MNI coordinates into Talairach space (51).

Perfusion MRI data were analysed based on the method described in (52). A nonparametric permutation-based (5000 iterations) independent-samples *t*-test was used to test for whole brain voxel-wise between-group differences in CBF perfusion levels (53).

Behavioural data ('correct words matching' and mean reaction time) were analysed using repeated measures ANOVA, with group as the between-subject variable and valence as the within-subjects variable (positive, negative and control words). Herein, 'correct matching' refers to the trials where participants categorised positive words as 'like' or negative words as 'dislike' and pressed the right button for the control word 'right' and left button for the control word 'left'. Independent samples *t*-tests were performed to clarify significant interactions, as well as to examine group differences in mood and personality ratings.

## Results

### *Affect ratings and behavioural results*

Groups did not differ in terms of state and trait anxiety, depressive symptoms, dysfunctional attitudes and life events, or in reported psychiatric family history. Citalopram did not affect subjective ratings of state or mood as measured by VAS and BFS (all  $P$ 's  $>.050$ ) (Table 1). Subjects receiving citalopram reported significantly more side effects of nausea, particularly on the first three days of treatment (time x group Anova: main group effect  $F_{(1,30)}=11.38$ ,  $p=.002$ ).

There were no significant differences between the groups in task performance ('correct matching': valence x group Anova  $F_{(2,64)}=.269$ ,  $p=.675$ ; RT: valence x group Anova  $F_{(2,64)}=.295$ ,  $p=.745$ ) during the words categorisation task (Table 2).

### *Perfusion results*

In the analysis of cerebral blood perfusion GRASE-ASL data acquired during resting state, no differences were found in CBF levels across the whole brain between subjects treated with citalopram or placebo. Also, no significant correlations were found between cerebral perfusion and haemodynamic response to the different task conditions.

### *BOLD fMRI results*

#### *Main effect of task (across groups)*

Relative to control words, response to negative words was characterised by significant activations in the bilateral occipital cortex (BA17,18,19), bilateral temporo-parietal cortex (BA20, BA22, BA39, BA40), right motor cortex (BA4), precuneus (BA7), right prefrontal cortex (BA6), medial prefrontal cortex (BA8), frontal pole (BA10), orbitofrontal cortex (BA11) and bilateral putamen and caudate. Positive words contrasted with control words also activated the

following areas across the whole sample: bilateral occipital cortex (BA17,18,19), bilateral temporo-parietal cortex (BA20,22,39,40), left motor cortex (BA4), right prefrontal cortex (BA6,9), precuneus (BA7), medial prefrontal cortex (BA9), frontal pole (BA10), orbitofrontal cortex (BA11) and bilateral putamen and caudate. In addition, for negative vs. positive and positive vs. negative words a significant response cluster was present across the whole sample in the bilateral primary somatosensory and motor cortex (BA2,3,4), and bilateral cerebellum (Table 1 in supplementary material).

### *BOLD fMRI between-group differences*

At the whole brain level, corrected for multiple comparisons, we observed a significant group x word valence interaction (negative vs. control words) in the ventromedial prefrontal cortex (cluster size (voxels) = 565,  $Z=3.41$ ,  $p=.005$ , corrected; MNI  $x=0$ ,  $y=40$ ,  $z=16$ ) (Figure 1a). Visual inspection of this cluster showed that it spanned rostral ACC (BA32), right orbitofrontal cortex (BA11) and frontal pole (BA10), also including the right caudate (Table 3). *Post hoc* analysis on BOLD signal change extracted from the mean activation voxel (BA32, MNI: 0, 40, 16) showed that the interaction was driven by a difference in response to negative words (word type x group interaction:  $F_{(1,27)}=5.488$ ,  $p=.027$ ; negative words:  $t_{(27)}=1.644$ ,  $p=.112$ ; control words:  $t_{(27)}=-.883$ ,  $p=.385$ ). In particular, citalopram decreased the response to negative self-referred words showing a deactivation pattern in the ventromedial prefrontal cortex (Figure 1b).

No significant interaction effect was found neither in the contrast between positive and control words, nor in the contrast between negative vs. positive words. Exploratory analysis at a  $Z=2.8$  uncorrected threshold for the negative vs. positive contrast are reported in Table 2 in supplementary material.

## Discussion

The results from our study suggest that short term SSRI administration can modulate PFC responses to negative self-referential stimuli in individuals at high risk of depression. Such effects replicate those seen in healthy non-selected volunteers (25, 42) and translate them in to a clinically relevant sample. Such an action would be expected to normalise dysfunctional patterns of activation found in subjects with high neuroticism, and may be involved in the evolution of later clinical effects over time in clinically depressed subjects.

The cluster modulated by antidepressant administration falls within a relatively extended area in the vmPFC (Figure 1a). Lesions to the vmPFC produce recognised changes in a range of emotional and social behaviours and in decision-making (54). Although it is not possible to extrapolate from our data whether any of the subregions encompassed within the cluster (anterior cingulate (ACC), orbitofrontal and frontopolar cortex) plays a more specific role, two main functions of the vmPFC could be related to the differential activation observed.

First, this area is widely interconnected with sub-cortical structures that regulate autonomic function and receives projections from temporal lobe areas of multimodal sensory association, processing elaborate stimuli such as facial expressions (55). These reciprocal projections are believed to mediate complex emotional responses, including integration and conflict monitoring of emotional and cognitive information via allocation of attentional resources, thus guiding choices and behaviour (56). In a previous study, using the same words categorisation task, we have shown that high neuroticism is correlated with higher activation to negative words in the ACC, close to the activation site highlighted in the present study (29). Similarly, ACC recruitment was also found to increase parallel to neuroticism scores during presentation of trials of emotional conflict in an emotional Stroop task combining words and facial stimuli (57)

and to relate to higher self-criticism tendencies (58-60). These data suggest that altered ACC function may contribute to the biased attention towards negative stimuli and higher emotional conflict seen in vulnerability to depression, which mirror those seen in patients with major depression and are suggested to reflect the tendency to dwell excessively on negative stimuli typical of dysphoria (8, 9, 61). Therefore our finding of a reduced activation in the vmPFC, including parts of the rostral ACC (BA32), to negative self-descriptors in high neuroticism following treatment is consistent with the idea that antidepressants reduce allocation of attentional resources to negatively valenced stimuli in subjects who usually show higher emotional conflict and a preference for negative attributions (Figure 1b).

Second, the vmPFC is also implicated in the attribution of emotion to oneself and others with medial regions possibly more activated in response to self-judgements and ventral areas representing the affective value of the stimuli (62). For example, frontopolar areas within the vmPFC have been proposed to play a role in regulation and inhibition of emotionally salient stimuli particularly if they are related to the distinction between self and others (63). These circuits are highlighted during resting state when subjects are more or less automatically engaged in baseline monitoring of internal states (64) and have therefore been referred to as a default mode network of the brain which appears to deactivate during the performance on cognitive tasks. Failure to deactivate these areas during various tasks has then been interpreted as a difficulty to disengage from self-reflection and self-monitoring or as a tendency to relate aspects of the task to the self. Recently it has been proposed that a general inability to regulate self-referential activity, underpinned by alterations in the whole default mode network during emotion processing, may contribute to depressive illness (65, 66). In particular neural alterations during specific processing of self-referential material, for example during response to personality traits (67) or judgments of self-relatedness (68), in the dorsomedial and dorsolateral prefrontal cortex seem to correlate with the severity of symptoms such as hopelessness. These signals could correspond to the neural representation of negative self-related rumination, a

cognitive process considered to be one of the crucial mechanisms responsible for the development and maintenance of clinical depression (69).

Our task, which required volunteers to relate different personality characteristics to themselves, revealed a failure to deactivate vmPFC areas in particular during response to negative self-descriptors in the placebo group (Figure 1b). This pattern is consistent with the evidence that high neurotic subjects present with a higher propensity to negative self-attributions and rumination levels (31). Consistent with this, the deactivation signal to negative self-referential words induced by citalopram administration may correspond to decreased self-referent processing and a diminished perceived intensity of the negative valence of words potentially referring to the self. As such, short term antidepressant treatment could lead to less attentional resources being allocated to self-attribution of negative stimuli. Further studies are needed to explore whether such effects may with prolonged treatment help to resolve the difficulties in disengaging from self-focused rumination and negative emotions that predispose to and maintain depression.

Our study presents some limitations which should be taken into consideration when interpreting the results. First, we did not find any differences when directly comparing positive and negative self-descriptors, but only in the contrast between negative and control words (which does not account for arousal and repetition effects). Hence, the results will need to be replicated by future experiments to confirm a valence specific effect of antidepressant action on negative self-referential processing. A second limitation is that we did not include a direct control group with low neuroticism. Our study, however, was directly built upon data from previous research comparing individuals with high and low neuroticism scores, and the finding of an antidepressant modulatory effect on a region shown to be altered in high neuroticism (such as the ACC) suggest that this effect could be specific to this population at risk. Future studies should include both high and low risk samples in the design to allow for a more exact interpretation of the results and validate this hypothesis. Last, it has to be noted that neuroticism is an unspecific risk factor

for anxiety and mood disorders. Nevertheless, the discussion of our results has been restricted within the framework of the neurobiological correlates of depression, because previous literature suggests that biases in processing of verbal stimuli are more likely to be linked to low mood rather than anxiety symptoms (21). Notwithstanding these limitations, to our knowledge these are the first data that present antidepressant effects on BOLD haemodynamic response after having controlled for potential confounding effects on general haemoperfusion, hence strengthening the validity of the data presented. We believe that this approach could be an important way to increase the reliability of interpretations extrapolated from pharmaco-fMRI data.

In conclusion, the cognitive neuropsychological model of antidepressant drug action (70) suggests that delayed symptom remission is built on early treatment effects, which modulate the neural correlates of emotional processing. Findings backing this hypothesis from healthy volunteers' samples (23, 24, 42, 71) have been recently extended to a clinical population study showing that at a behavioural level a single dose of reboxetine was able to decrease response latency and improve memory for positive words in depressed patients before the initiation of any subjective symptom change (72). Although preliminary, our data then further support this model by translating evidence of early antidepressant effects on neural responses to emotional stimuli from healthy samples to a population at risk presenting subclinical features of depressive cognitive-emotional biases.

Further studies are needed to translate these findings to depressed patients, to explore the time course of this effect in relation to subjective modifications in affect and to establish the degree to which this normalisation can predict later symptom remission and relapse prevention.

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### **Conflict of Interest**

MD and RN report no conflicts of interest. CJH has served as a consultant for P1vital, GlaxoSmithKline, Servier, Astra Zeneca, Johnson & Johnson, Lundbeck and is on the advisory board and holds shares of P1vital.

Supplementary information is available at *Molecular Psychiatry's* website

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## Figure legends

### Figure 1a

Significant cluster of activation depicting greater signal response in the ventromedial prefrontal cortex (vmPFC) in the placebo vs. citalopram treated group during recognition of negative self-descriptors vs. control words. Images thresholded at  $Z > 2.3$ ,  $P < 0.05$ , corrected.

### Figure 1b

The group x emotion interaction in the ventromedial prefrontal cortex displaying deactivation to negative words (green bar) under citalopram. Percent signal change plotted on the y axis is extracted from the mean activation voxel taken from the whole brain analysis significant cluster in the negative vs. control words contrast. Signal from activation to positive words is included for illustration purposes.

Table 1. Personality and affect ratings

Measure <sup>a</sup>	Placebo (n=16)	Citalopram (n=18)	Analysis
EPQ neuroticism	17.2 (1.6)	18.32 (2.3)	$t_{(32)}=-1.564, p=.128$
STAI Trait Anxiety	43.9 (5.7)	49.7 (10)	$t_{(32)}=-1.92, p=.064$
STAI State Anxiety	37.4 (9.7)	42.6 (10.4)	$t_{(32)}=-1.485, p=.147$
BDI	7 (5.7)	10 (5.9)	$t_{(32)}=-1.445, p=.158$
DAS total	138.3 (19)	141.5 (26)	$t_{(32)}= -.384, p=.703$
LES total	1 (1.1)	1.5 (1.5)	$t_{(32)}=-1, p=.323$
Day 7 - BFS	30.8 (25)	34.5 (22)	$t_{(32)}=-.432, p=.669$
Day 7 - VAS happiness	7.7 (1.5)	7.6 (2.3)	$t_{(32)}=.186, p=.853$
Day 7 - VAS sadness	3 (2.2)	1.9 (1.9)	$t_{(32)}=1.508, p=.142$
Day 7 - VAS hostility	2.5 (2)	1.3 (1.6)	$t_{(32)}=1.812, p=.080$
Day 7 - VAS alertness	6.2 (2.9)	6.5 (2.6)	$t_{(32)}=-.261, p=.796$
Day 7 - VAS anxiety	3.5 (2.6)	3.8 (2.8)	$t_{(32)}= -.331, p=.743$
Day 7 - VAS calmness	6.4 (2.6)	5.6 (2.7)	$t_{(32)}=.787, p=.437$

<sup>a</sup> All questionnaires completed at baseline; Visual Analogue Scales (VAS) and Befindlichkeit Scale (BFS) scores reported refer to measures on day 7 prior to testing fMRI scan. EPQ= Eysenck personality Questionnaire, STAI= Spielberger Stait and Trait Anxiety Inventory, BDI=Beck depression Inventory, DAS=Dysfunctional Attitudes Scale, LES=Life Events Scale.

Table 2. Behavioural performance on self-descriptors categorisation task

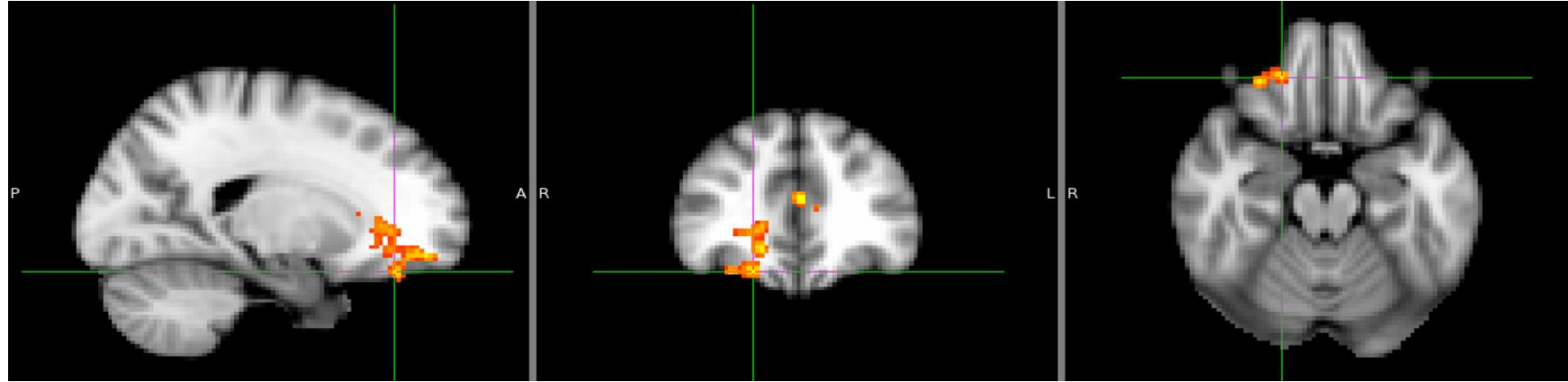
Measure <sup>a</sup>		Placebo (n=16)	Citalopram (n=18)
Negative self-descriptors	Correct matching	84.1 (15)	80.5 (22)
	RT (ms)	1282.6 (282)	1285.9 (223)
Positive self-descriptors	Correct matching	93.9 (7)	91.8 (13)
	RT (ms)	946.6 (227)	967.7 (247)
Control words	Correct matching	94.6 (5.8)	95.2 (11.6)
	RT (ms)	887.2 (196)	862.4 (137)

<sup>a</sup> Values show Mean (SD).

Table 3. Areas of significant activation during categorisation of negative self-descriptors

Brain Region <sup>a</sup>	Broadmann Area	Cluster size (voxels)	Z value	x	y	z
Ventromedial Prefrontal Cortex		565	3.41	0	40	16
Rostral Anterior Cingulate Cortex	32		3.29	30	36	-20
Frontopolar Cortex	10		3.06	20	52	-12
Orbitofrontal cortex	11		3.05	20	38	-20

<sup>a</sup> Regions showing increased activation in the placebo vs. citalopram group in the group x emotion interaction in the contrast of negative self-descriptor words vs. control words; MNI coordinates refer to the mean activation voxel of the cluster and the peak activation voxels of main sub-regions within the same cluster.



### Response to self-descriptors in the mPFC after 7 days citalopram administration in High Neurotic subjects

