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ORIGINAL INVESTIGATION

Short-term antidepressant treatment modulates amygdala response to happy faces

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Abstract
Rationale We have previously demonstrated that antidepressant medication facilitates the processing of positive affective stimuli in healthy volunteers. These early effects of antidepressants may be an important component in the therapeutic effects of antidepressant treatment in patients with depression and anxiety.
Objectives Here we used functional magnetic resonance imaging in a double-blind, randomised, placebo-controlled between-groups design to investigate the effects of short-term (7–10 days) treatment with the selective serotonin reuptake inhibitor, citalopram, on the amygdala response to positive and negative facial expressions in healthy volunteers.
Results Citalopram was associated with increased amygdala activation to happy faces relative to placebo control, without changes in levels of mood or anxiety.
Conclusions These early, direct effects of antidepressant administration on emotional processing are consistent with a cognitive neuropsychological model of antidepressant action.

Keywords fMRI · Citalopram · Depression · Anxiety · Emotion · Unipolar

Introduction

Selective serotonin reuptake inhibitors (SSRIs) are among the most commonly prescribed antidepressants for the treatment of acute depression and anxiety (Artigas et al. 2002). While the cellular actions of these drugs are becoming increasingly well characterised, the mechanisms by which these changes become translated into clinical benefit remain unclear. We have previously suggested that antidepressants affect the processing of emotional information in such a way to maximise positive vs. negative affective stimuli (Harmer 2008). For example, in healthy volunteers, short-term administration (7 days) of the SSRI citalopram has been shown to increase the processing of positive vs. negative emotional information across a broad range of tasks assessing memory, facial expression recognition and attention (Harmer et al. 2004). Importantly, these effects are seen in the absence of measurable differences in mood or anxiety, thereby suggesting a direct effect of drug on emotional processing. Such changes in the relative processing of positive and negative stimuli could be an important therapeutic factor in antidepressant treatment for depression and anxiety. Moreover, according to this view, pharmacotherapy for depression and anxiety is conceptually similar to cognitive theories and treatments for these disorders.

More recently, we have combined functional magnetic resonance imaging (fMRI) with pharmacological probes (pharmaco-fMRI) to provide a better understanding of the interface between neural systems and the effects of antidepressants on emotional processing (Harmer et al.

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2006; Norbury et al. 2007, 2008). Consistent with our earlier behavioural findings (Harmer et al. 2004), short-term SSRI treatment was associated with reduced blood oxygenation level-dependent (BOLD) response in the amygdala to negative facial expressions presented outside of conscious awareness (Harmer et al. 2006)—a brain region implicated in emotional processing and the pathophysiology of depression and anxiety (Canli et al. 2002; Costafreda et al. 2007; Drevets 2003). In addition, a study in depressed patients reported increased neural responses to happy facial expressions following SSRI treatment (Fu et al. 2007) and we also found increased neural responses to happy faces in healthy volunteers after 7 days' treatment with the noradrenaline reuptake inhibitor, reboxetine (Norbury et al. 2007). In the current study, we wished to extend our earlier findings (Harmer et al. 2006; Norbury et al. 2007) and investigate amygdala response to positive and negative facial expressions presented in the context of a task which involved explicit perception and matching of facial expressions. We also wished to examine in more detail whether we could detect effects on the processing of positive stimuli using this approach, given behavioural evidence that repeated citalopram not only reduces fear recognition but also increases bias to happy facial expressions in healthy volunteers (Harmer et al. 2004).

We hypothesised that short-term administration of the SSRI citalopram would be associated with *reduced* BOLD response to fear (consistent with our earlier study) and *increased* response to happy faces in bilateral amygdalae.

Materials and methods

Participants

Thirty-two healthy volunteers were initially recruited into the study. However, due to scheduling problems (three participants) and the presence of a structural abnormality, 28 subjects completed the study. All included subjects were right handed with a mean age of 23 (range 19–32) and a mean predicted full-scale intelligence quotient of 120 [as indexed by the National Adult Reading Test (Nelson 1991)]. All subjects provided written informed consent prior to entry into the study, which was approved by the Berkshire Research Ethics Committee, and received an honorarium for their participation. From assessment with the Structured Clinical Interview for DSM-IV (Spitzer et al. 1995), subjects were determined to be free of current or past axis-1 disorder (including anxiety disorders, depression, eating disorder, psychosis and substance abuse). All subjects were in good physical health and free of current medication. The premenstrual week was avoided for the study period in females. Subjects were briefed on scanner safety and had no contraindications for fMRI examination.

Experimental design

The study was a double-blind, randomised, placebo-controlled between-groups design. Subjects were randomly allocated to receive either citalopram (n=16, 20 mg/day) or placebo (n=12) for a total of 7–10 days (the variable time of treatment was necessary to allow for scanner availability). Medication was given in identical capsules to maintain blinding. Baseline and endpoint mood and anxiety levels were assessed by questionnaires [Beck Depression Inventory (Beck et al. 1961) and Spielberger State Anxiety (Spielberger et al. 1970)].

fMRI data acquisition

All imaging data were collected using a Varian 3-T scanner located at the Centre for Functional MRI of the Brain (fMRIB), University of Oxford. Functional imaging consisted of 29 T_2*-weighted echo-planar image (EPI) axial oblique slices that began at the cerebral vertex and encompassed the entire cerebrum and the majority of the cerebellum. Acquisition parameters: repetition time (TR)/echo time (TE)=2,000 ms/28 ms; field of view/matrix size=240×240/64×64; slice thickness=4 mm. These parameters were selected to optimise signal across the entire volume of acquisition. The first three EPI volumes in each session were discarded to avoid T_1 equilibration effects.

To facilitate later coregistration of the fMRI data into standard space, we also acquired a Turbo FLASH sequence (TR=12 ms, TE=5.65 ms) voxel size=1 mm^3. These structural scans were collected at a separate session using a 1.5 T Siemens Sonata scanner located at the Oxford Centre for Clinical Magnetic Resonance Research (OCMR).

fMRI task design

During fMRI scanning, subjects completed a perceptual task involving the matching of fearful and happy facial expressions. In this task, nine 30-s blocks of a sensorimotor control task [condition A] were interleaved with eight 30-s blocks of the emotional task (four blocks of fear [condition B] and four blocks of happy [condition C]). To reduce potential carry-over effects, cycles of alternation between conditions were counterbalanced across subjects. Thus, during the course of the 8.5-min experiment, half of the subjects completed the following order: ABACABACA BACABACA, the remaining subjects ACABACABACA BACABA. During the emotional matching task, subjects viewed a trio of faces, all derived from a standard set of pictures of facial affect (Matsumoto and Eckman 1988).

Faces were presented in a triangular configuration and subjects selected the one of two bottom faces (probes) that expressed the same emotion as the target (top) face. Each emotional block consisted of six trials, presented sequentially for 5 s. During the sensorimotor control task, subjects viewed a trio of geometric shapes (rectangles) in a triangular configuration and selected the one of two bottom shapes that matched the orientation (either vertical or horizontal) of the target (top shape). Each sensorimotor control block consisted of six trials, presented sequentially for 5 s. Stimuli were presented on a personal computer using E-Prime (version 1.0; Psychology Software Tools Inc., Pittsburgh, PA, USA) and projected onto an opaque screen at the foot of the scanner bore, which subjects viewed using angled mirrors. Subject responses were made via an MRI-compatible keypad. Both emotion matching accuracy and reaction times were recorded by E-Prime.

fMRI data analyses

Functional MRI data were preprocessed and analysed using FSL, version 4.1 (Smith et al. 2004). Preprocessing included within-subject image realignment (Jenkinson et al. 2002), non-brain removal (Smith 2002) spatial normalisation to a standard template (Montreal Neurological Institute [MNI] 152 stereotactic template) using an affine procedure (Jenkinson and Smith 2001) and spatial smoothing using a Gaussian kernel (5 mm full-width half-maximum). The time series was high pass-filtered (to a maximum of 0.008 Hz).

Analyses of data from individual subjects were computed using the general linear model with local autocorrelation correction (Woolrich et al. 2001). Two explanatory variables were modelled: 'fear faces' and 'happy faces'. These explanatory variables were modelled by convolving each emotion block 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 addition, temporal derivatives were included in the model as covariates of no interest to increase statistical sensitivity.

Individual subject data were combined at the group level using a full mixed-effects analysis (Woolrich et al. 2004). This mixed-effects approach enables generalisation of the results beyond the sample of subjects tested. Characterising between-group differences on task-specific brain activity may be confounded by the possibility that changes in activation are actually produced by a shifting baseline, rather than by a change in the brain response to the task itself. With this in mind, all comparisons we report directly contrast fear with happy facial expressions (i.e. group× emotion interactions) rather than to an under-specified, low level baseline or resting condition. At the whole brain level, significant activations were identified using cluster-based thresholding of statistical images with a height threshold of $Z=2.3$ and a (corrected) spatial extent threshold of $P<0.05$.

ROI data analyses

Regions of interest (ROI) for left and right amygdala were generated using a robust model-based segmentation/registration tool (Patenaude et al. 2008) implemented within FSL (see Fig. 1 for an example segmentation). Mean parameter estimates for each explanatory variable, for each subject, across the entire ROI (left and right amygdala separately) were extracted and converted to percent signal change. Percent signal change estimates were subsequently entered into a repeated measures analysis of variance (ANOVA) model with group (placebo, citalopram) as the between-subjects factor and valence (fear, happy) and hemisphere (left, right) as within-subjects factors. Significant interactions were followed up using simple main effects analyses.

To ensure that drug effects were localised to the amygdala and not confounded by activation in adjacent structures, we also extracted mean parameter estimates for each explanatory variable in left and right hippocampi and entered these into the ANOVA model described earlier.

Behavioural data analysis

Behavioural data were analysed using a repeated measures analysis of variance (ANOVA) model with group as the between-subjects factor and valence as the within-subjects factor implemented in SPSS v.15.0 (SPSS Inc., Chicago, IL, USA).

Results

Behavioural results

Citalopram did not affect subjective mood or anxiety (Table 1). Due to technical difficulties, response accuracy and latency was not obtained for one subject in the citalopram-treated group. Subsequent analysis, therefore, included 12 placebo- and 15 citalopram-treated volunteers. Subjects were highly accurate in their behavioural performance (≥80% correct matching identifications) which was not affected by citalopram ($F(1,23)<1$). Similarly, response latency was not affected by group ($F(1,23)<1$). There was a main effect of valence such that all subjects responded more slowly to fearful facial expressions vs. happy faces and shapes ($F(2,46=65.01$, $P<0.001$)).

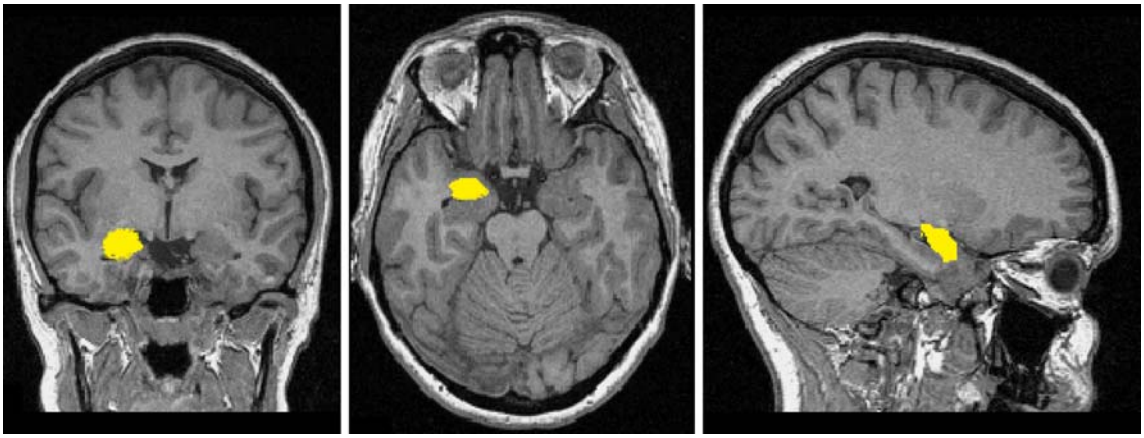

Fig. 1 Amygdala segmentation. Shown are coronal, transverse and sagittal images from a representative subject. Overlaid (*yellow*) is the right amygdala generated by the automated segmentation algorithm. Images are in radiological format

Amygdala ROI

Placebo group (task effect)

As observed in a number of previous neuroimaging studies using a similar task (Arce et al. 2008; Hariri et al. 2005), participants receiving placebo showed a significant bilateral amygdala response to fearful facial expressions (independent measures—left amygdala $t(11)=3.2$, $P=0.008$; right $t(11)=3.24$, $P=0.008$).

Drug effects

ANOVA revealed a significant main effect of valence ($F(1,26)=13.66$, $P<0.001$), but no main effect of group or hemisphere (both $F<1$). The group×valence×hemisphere interaction was also non-significant. There was however, a significant group×valence interaction ($F(1,26)=9.84$, $P<0.004$). Post hoc analysis (see Fig. 2 for details) revealed that in bilateral amygdala (data pooled across left and right amygdala) BOLD response (as percent signal change) to happy facial expressions was significantly greater under citalopram (independent samples t test; $t(26)$ −2.080, $P=0.048$). By contrast, bilateral amygdala response to fearful faces was not affected by citalopram ($P=0.308$, ns) but was also more variable.

Table 1 Subjective state ratings before and after 7 days' treatment of randomly assigned double-blind intervention with citalopram or placebo

Measure	Placebo ($n=12$)		Citalopram ($n=16$)	
	Before treatment	After treatment	Before treatment	After treatment
BDI	1.8 (2.2)	1.44 (2.1)	1.5 (1.7)	1.5 (2.1)
SAI	27.6 (8.2)	26.0 (6.5)	31.5 (10.9)	33.1 (11.0)
NART	120 (6.8)	N/A	119.9 (4.7)	N/A

Data show mean (SD)

Abbreviations: *BDI* Beck Depression Inventory, *SAI* State Anxiety, *NART* National Adult Reading Test. Values show mean predicted full-scale IQ, (SD). *N/A* not applicable

Whole brain analysis

Placebo group (task effect)

To explore brain areas outside our a priori amygdala regions, we also carried out a whole brain mixed-effects group analysis corrected for multiple comparisons at the cluster level. As expected, placebo-treated participants had significantly greater activation to fear vs. happy facial expressions in bilateral thalamus and fusiform gyrus,

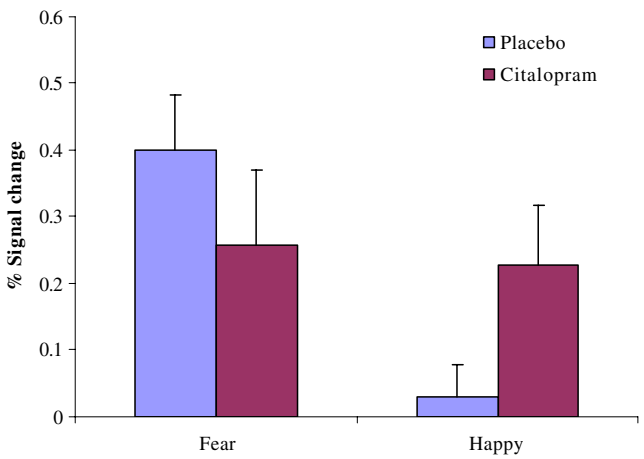

Fig. 2 Plots depicting BOLD activation (expressed as % signal change) in bilateral amygdala (data pooled across left and right amygdalae) for the citalopram- and placebo-treated volunteers. *Bars* show mean, *error bars* standard error

orbitofrontal cortex, right angular gyrus, right inferior frontal gyrus and left supramarginal gyrus (parietal lobule). Comparison of happy with fearful faces revealed significant activation in right frontal medial cortex, left cingulate/precuneus border and right middle temporal gyrus (see Table 2 for details).

Drug effects

We did not observe any significant group×valence interactions using a fully corrected whole brain approach.

Hippocampus ROI

To assess if the between-group differences in amygdala response to happy were restricted to the amygdala, we also estimated percent signal change to fear and happy faces in left and right hippocampi. For the hippocampal regions of interest, there were no significant main effects of group ($F<1$), valence ($F(1,26)=2.57$, $P<0.121$), group ($F<1$) or hemisphere ($F<1$). Nor did we observe a significant group×valence interaction ($F(1,26)=2.10$, $P<0.159$), or group×valence×hemisphere interaction ($F<1$).

Signal-to-noise ratio and amygdala coverage

There were no significant between-group differences in left or right amygdala (independent samples t test; $t(26)$ −1.247, $P=0.224$; $t(26)$ −0.911, $P=0.371$) signal-to-noise ratios (Fig. 3). Both groups also showed adequate T_2* signal in bilateral amygdala suggesting the scanning parameters used in this study allowed for adequate signal detection in this region (Supplementary Fig. 1)

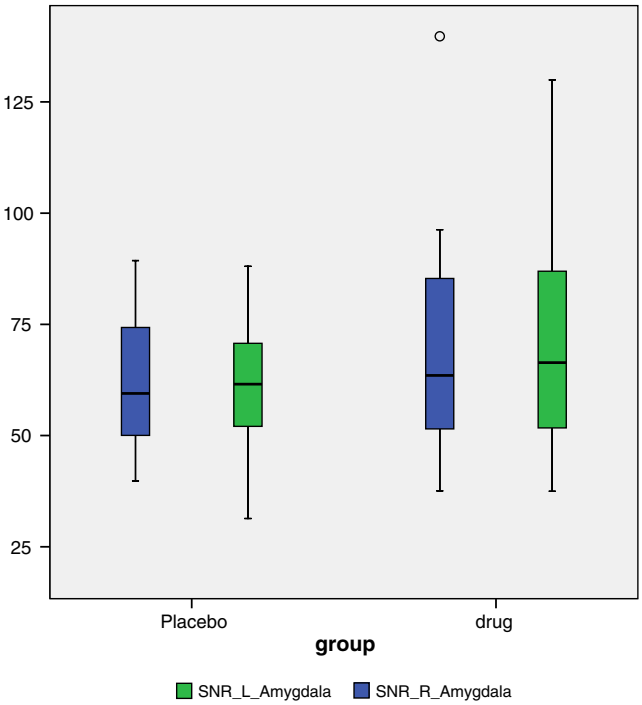

Fig. 3 Signal-to-noise ratios for placebo-treated ($n=12$) and citalopram-treated ($n=16$) volunteers in left and right amygdala ROIs. *Boxes* show interquartile range; *horizontal lines*, median; *limit lines*, range excluding outliers; and *open circle*, outliers. SNR were similar between groups (independent samples t tests, ns)

Discussion

The current study demonstrated that short-term administration of the SSRI citalopram was associated with increased amygdala activation to happy faces without observable changes in mood. This effect was localised to the amygdala and did not extend into the hippocampus. Our results suggest a rapid direct effect of citalopram on emotional processing, highlighting a mechanism by which drug treatment could reverse the negative bias seen in depression and anxiety that is consistent with cognitive theories and treatments for these disorders.

There are a number of limitations associated with this study, and these should be taken into consideration when interpreting the results. For example, based on our earlier

Table 2 Regions showing increased activation in the placebo-treated volunteers to the orthogonal contrasts fear vs. happy and happy vs. fear faces

Brain region	Cluster size (voxels)	Z value	x	y	z
Main effect of fear vs. happy (placebo)					
Right occipital/fusiform gyrus	2,319	3.82	50	−72	−6
Right lateral occipital cortex (angular gyrus)	1,640	4.12	28	−58	46
Right inferior frontal gyrus	1,465	4.07	38	12	24
Orbitofrontal cortex	1,445	3.72	−22	12	−24
Bilateral thalamus	936	3.58	8	−12	0
Left parietal cortex	772	3.4	−32	−50	48
Left occipital/fusiform gyrus	730	3.71	−34	−78	−18
Main effect of happy vs. fear (placebo)					
Ventromedial frontal cortex	1,449	3.69	−4	34	−20
Left cingulate/precuneus border	1,040	3.88	−12	−52	4

Coordinates refer to the position (x, y and z mm) for the peak voxel in each cluster according to the Montreal Neurological Institute (MNI) template

behavioural findings (Harmer et al. 2004) of reduced recognition to fearful faces and an increased bias towards happy faces, we included only fear and happy expressions. We therefore cannot exclude the possibility that citalopram would modulate the neural response to other negative expressions (e.g. sadness or disgust). Indeed, others have reported reduced amygdala response to sad faces following successful antidepressant treatment in depressed patients (Fu et al. 2004). Studies that assay a number of facial expressions are warranted. A second limitation is that we did not assess social function or personality in our subjects and relate these to changes in neural response. Future studies that measure not only mood and anxiety, as reported here, but also the potential relationship between antidepressant treatment, neural dynamics and social function are required. Another consideration is that we did not employ sufficient spatial resolution to distinguish between the dorsal and basolateral subregions of the amygdala. Importantly, neuroimaging studies in humans (Etkin et al. 2004) suggest these regions can be dissociated based on whether threat-related stimuli are processed consciously (dorsal amygdala) or unconsciously (basolateral complex). Others (Whalen et al. 2001) have differentially implicated superior and inferior regions of the amygdala in the processing of negative emotional expressions. Therefore, by averaging across the entire amygdala, it is possible that we may have failed to detect subtle differences in amygdala activation. Future studies with a reduced imaging volume significantly increased spatial resolution (2 mm isotropic voxels) and at a higher field strength, e.g. 7 T, would undoubtedly help to identify the specific roles of different amygdala nuclei—although at the expense of acquiring whole brain data. Finally, our relatively small sample size (12 placebo controls and 16 citalopram-treated volunteers) may have left us exposed to type 2 error in detecting effects of citalopram on amygdala responses to fear. However, we have previously reported both behavioural (Harmer et al. 2004) and neural effects (Harmer et al. 2006) of citalopram with fewer subjects. To fully elucidate the effects of short-term antidepressant treatment on amygdala processing, future studies should directly compare implicit vs. explicit processing of emotional stimuli.

We have previously reported reduced amygdala response during implicit processing of fearful faces following short-term citalopram treatment (Harmer et al. 2006). Here we observed significantly greater amygdala response to happy faces as compared to placebo-treated volunteers. The amygdala has been suggested to act as a relevance detector independent of valence (Fitzgerald et al. 2006; Sander et al. 2007) and individual differences in amygdala activation to positive stimuli are associated with a metric of sociability (Canli et al. 2002). Taken together, these results suggest that SSRI drug treatment may increase salience or relevance of happy vs. fearful facial expressions. Such effects could underlie increased bias in recognition of happy facial expressions (Harmer et al. 2004) and improvements in social function also seen with antidepressant administration in healthy volunteers and in depressed patients (Tse and Bond 2003).

It is of interest however that while the current study found *increased* BOLD responses to happy facial expressions, our earlier study found *decreased* BOLD responses to fearful facial expressions (Harmer et al. 2006). These complementary results may reflect the differing nature of the cognitive tasks employed. We have hypothesised that, during the processing of non-conscious threat cues, citalopram inhibits the 'automatic' amygdala response to threat (Harmer et al. 2006). However, during explicit, sustained presentation of fearful faces (as in the current paradigm), citalopram has no effect on amygdala response to threat. We cannot exclude the possibility that citalopram initially inhibits amygdala response [as in our previous study (Harmer et al. 2006)] but that over the longer duration stimulus presentation used here with explicit focus on the facial expression the amygdala response evolves to a level comparable with placebo controls. By contrast, during sustained presentation of happy facial expressions, the processing of positive cues may be enhanced. Growing evidence from cognitive psychological studies suggests that fast attentional processing is particularly relevant to anxiety, whereas sustained and more strategic processing may be more relevant to depression (Mogg et al. 2007). As such, the effects seen with the implicit vs. explicit versions of a face processing task may highlight the effects of SSRI drug treatments on processes relevant to anxiety vs. depression, respectively. Future studies employing techniques with high temporal resolution (e.g. magnetoencephalography [MEG]) and/or fMRI in conjunction with eye-tracking methodologies to measure initial orienting vs. sustained eye gaze to negative and positive emotional stimuli are required to further explore SSRI modulation of amygdala function.

Given the importance of the amygdala in emotion processing, this brain structure has received much attention in the context of affective disorders. Functional MRI studies in depressed patients have reported amygdala *hyper*activity at rest (Drevets 2003) and in response to masked fear (Sheline et al. 2001) and implicitly processed sad faces (Fu et al. 2004), which normalises following successful pharmacotherapy (Fu et al. 2004; Sheline et al. 2001). Recent evidence also suggests that successful SSRI treatment normalises *hypo*activity in ventral temporal cortex in response to happy facial expressions (Fu et al. 2007) and prefrontal, temporal and limbic cortices in response to positive social stimuli (Schaefer et al. 2006). However, it is not known whether this normalisation of response with time is a direct effect of treatment or a

marker of improvement in clinical state. We have suggested that the facilitation of positive emotional processing is a general mechanism of action of antidepressant drugs which is important to their therapeutic effects (Harmer et al. 2004). As such, the increased amygdala response reported here, and our earlier observation of increased fusiform response to happy facial expressions under reboxetine (Norbury et al. 2007), are consistent with our hypothesis and the behavioural increases in positive emotional processing following short-term antidepressant administration that have been reported previously (Harmer et al. 2004) as well as with the well-characterised antidepressant effects of this drug in clinical groups.

It is widely held that significant antidepressant treatment effects are not reliably demonstrated until after several weeks of treatment. However, the results from a meta-analysis (Taylor et al. 2006) suggest that antidepressant treatment is associated with significant symptomatic improvement by the end of the first week of use. It is tempting to speculate that the rapid, antidepressant-induced positive bias reported here and in our earlier behavioural and fMRI studies (Harmer et al. 2006; Harmer et al. 2004) form an important component of early antidepressant action which precede and ultimately contribute to subjective improvement in mood. Future studies in clinical populations are required to expand these initial findings and establish if the early positive effects of antidepressants we have observed apply equally to clinical populations.

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