Selective serotonin reuptake inhibitors (SSRIs) are conventionally thought to have a delay of several weeks in the onset of their clinical antidepressant effects. Recent meta-analyses suggest, however, that antidepressants may have a much earlier therapeutic onset than originally thought. This notion of early-onset antidepressant effects is supported by a series of studies in our laboratory demonstrating measurable psychological effects following acute and short-term administration of antidepressant agents to healthy volunteers. One of the most striking features following acute and short-term administration of antidepressant laboratory demonstrating measurable psychological effects is supported by a series of studies in our background of the clinical implications of this finding is problematic. A recent report of decreased amygdala activity of the amygdala and converging evidence demonstrates that one mechanism by which SSRIs may exert their action is by constraining such overactivity. A recent report of decreased amygdala responses to aversive facial expressions following acute intravenous citalopram administration to healthy male volunteers intriguingly suggests that modulating amygdala reactivity may be an immediate effect of SSRI administration. However, interpretation of the clinical implications of this finding is problematic since intravenous SSRI administration is not typically used in the treatment of patients. The present study therefore investigated whether a single oral dose of the SSRI citalopram would have similar effects on the amygdala response to emotional faces in healthy volunteers. Given the likely role of the amygdala in the eventual therapeutic action of SSRIs, a decrease in amygdala reactivity to threat following a single dose of citalopram administered in the form and dose in which it would typically be given to patients would lend support to the notion of an early onset of therapeutically relevant antidepressant effects.

**Method**

**Participants**

Twenty-six right-handed healthy volunteers (13 women and 13 men) aged 19–30 years took part in this study. Volunteers were recruited using adverts in university departments and screened through a medical examination and a psychiatric interview using the Structured Clinical Interview for DSM–IV Axis I disorders. Exclusion criteria were: history of psychiatric disorder (including anxiety disorders, depression, eating disorders, psychosis and substance misuse); any significant medical condition (including migraine, diabetes, epilepsy and hypertension); pregnancy; current medication (excluding the contraceptive pill); or first-degree family history of bipolar disorder. Functional magnetic resonance imaging (fMRI) scanning also required the following exclusion criteria: cardiac pacemaker; mechanical heart valve; or any other mechanical implants. All participants had normal or corrected to normal vision. All participants gave their written consent to participate in the study, which was approved by the local ethics committee.

**Stimuli and task**

An fMRI block design with backwardly masked and unmasked presentations of fearful, happy and neutral facial expressions.
was used to assess the effect of citalopram on the neural response to implicit and explicit threatening stimuli. The facial stimuli were taken from Ekman & Friesen's *Pictures of Facial Affect* series. In the masked condition, fearful, happy and neutral faces were presented for 17 ms and immediately followed by a neutral face presented for 183 ms. In the unmasked condition, fearful, happy and neutral faces were presented in isolation for 200 ms. On each trial, participants were simply asked to stare at a fixation point on an end of the task, there was a 20 s baseline fixation block, where happy and unmasked neutral) and there were ten faces/face-mask presented for 128 matrix), 1.5 mm isotropic voxels. To facilitate later co-registration of the fMRI data into standard space, we also acquired a Turbo FLASH sequence (TR = 12 ms, TE = 5.65 ms), 1 mm3 voxel size. The first two echo-planar image volumes in each session were discarded to avoid T1 equilibrium effects.

### Imaging data analysis

Imaging data were preprocessed and analysed using FEAT (FMRI Expert Analysis Tool) version 5.43, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The following pre-statistics processing was applied: motion correction using FMIRB's linear image registration tool (MCFLIRT); non-brain removal using the Brain Extraction Tool; spatial smoothing using a Gaussian kernel of full width half maximum 5 mm; mean-based intensity normalisation of all volumes by the same factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 s). Registration to high resolution images and to a standard template (Montreal Neurological Institute (MNI) 152 stereotactic template) was carried out using FLIRT, which is a digitised conversion of the original Talairach atlas, which is a canonical haemodynamic response function. Temporal derivatives were included as covariates of no interest to increase statistical sensitivity. All analyses were performed at the group level using mixed-effects analyses. Six experimental conditions were modelled: masked/ unmasked fear, masked/unmasked happy and masked/unmasked neutral. Each condition was modelled separately by convolving trials with a canonical haemodynamic response function.

### Imaging data acquisition

All imaging data were collected using a Siemens Sonata scanner operating at 1.5 T, located at the Oxford Centre for Clinical Magnetic Resonance Research. For the faces task, functional imaging consisted of 35 $T_2^*$-weighted echo-planar image slices (repetition time (TR) = 3000 ms, echo time (TE) = 54 ms, $128 \times 128$ matrix), $1.5 \times 1.5 \times 4.5$ mm voxels. For the visual
For the visual checkerboard task, a region of occipital cortex activated by the task (compared with baseline) was identified. The percentage BOLD signal change was extracted for this region and compared between the citalopram and placebo groups using a one-way analysis of variance (ANOVA) with drug group as the between-participants factor (two levels: citalopram, placebo). Any effect of citalopram in this region would suggest a global drug effect on baseline cerebral haemodynamics or neural coupling.

Two participants’ data (both in the placebo group) were excluded from the fMRI analysis. In one participant there was a fault in the high resolution structural image and in the other, a cerebellar cyst was identified on the structural scan. Thus, the fMRI analysis included 24 participants (13 citalopram, 11 placebo).

Subjective ratings and behavioural data were analysed using a repeated measures ANOVA model. Significant interactions were further corroborated using independent sample t-tests.

**Results**

**Subjective ratings**

A single oral dose of citalopram in healthy volunteers did not significantly affect ratings of mood, anxiety or energy on the subjective rating scales used (all comparisons with placebo $P > 0.15$).

**Imaging data**

**Main effect of task**

The main effect of task in the placebo group revealed significantly greater responses to the unmasked fear stimuli compared with the unmasked neutral stimuli in the right amygdala (peak cluster activation MNI coordinates: $x = 22$, $y = 7$, $z = 218$; Fig. 1) and the medial frontal gyrus (peak cluster activation MNI coordinates: $x = 0$, $y = 36$, $z = 22$). There were no main effects of task in the placebo group for the unmasked happy or unmasked neutral contrast, or for the masked fear, masked neutral and masked happy contrast.

**Effect of citalopram administration**

In order to examine the effect of citalopram on the neural response to fearful and neutral facial expressions, we extracted the percentage BOLD signal change for the two clusters identified in the main effect of task analysis and compared the citalopram and placebo groups. In the right amygdala cluster, there was a significant interaction between drug group and facial expression ($F(2,44) = 11.867$, $P = 0.001$) in the unmasked condition. This interaction was further corroborated by independent sample t-tests of each facial expression, which revealed significantly decreased activation in the citalopram group to fearful facial expressions ($t(22) = 3.467$, $P = 0.002$) but no significant differences between groups to happy or neutral facial expressions in this region (Fig. 1). There was no significant main effect of drug group and no significant interaction with facial expression in the medial frontal gyrus cluster for the unmasked condition and in either region for the masked condition.

**Visual stimulation paradigm**

In the checkerboard task, visual stimulation was associated with a large and highly significant activation cluster in the occipital cortex. There were no significant effects of drug group on
The amygdala response to masked fearful facial expressions and the emotion-potentiated startle response have all been shown to critically involve the amygdala, it has been previously hypothesised that increased activity in this structure might underpin the acute anxiogenic effects of SSRIs. However, the present study and the one previous study reporting reduced amygdala activation following acute citalopram do not support this notion, suggesting that the amygdala may not be the locus of the acute anxiogenic effects of SSRIs. It is important to note, however, that these acute effects of SSRIs only affect a subset of patients clinically and the effects of acute manipulations of serotonin have been shown to be dependent on a number of factors such as gender and genotype. This raises the possibility that the amygdala may be involved in the acute anxiogenic effects of SSRIs but that the sample used in the current study were not susceptible to such an anxiogenic effect. Consistent with this hypothesis, the citalopram group showed the expected increase in the recognition of happy facial expressions on the behavioural facial expression recognition task but, unlike participants in a number of previous studies of acute serotonergic manipulation, they did not show an increase in the recognition of fearful facial expressions. Although this may be due to the reduced sensitivity of this measure as a result of habituation effects resulting from repeated exposure to fearful faces during the fMRI scan, the involvement of the amygdala in the acute anxiogenic effect of SSRIs remains unresolved. Future studies are needed to examine the reactivity of the amygdala to threatening stimuli in those individuals who demonstrate a measurable behavioural increase in fear processing in response to acute SSRI treatment.

**Amygdala response to masked emotional faces**

Repeated administration of citalopram to healthy volunteers has previously been shown to reduce the amygdala response to fearful faces when they are presented in a backwardly masked paradigm. In contrast, in the present study there was no significant effect of acute citalopram on the amygdala response to masked fearful or happy faces. However, caution must be exercised in the interpretation of this lack of drug effect in the masked condition. In the placebo group, the amygdala response was not increased to masked fearful relative to neutral or happy facial expressions, which is inconsistent with some but not all previous findings. The amygdala response to masked fearful facial expressions appears to be a variable effect which is sensitive to individual variation in factors such as state anxiety and also the processing.
load of the task. In the absence of the basic main effect of the task, it is not possible to draw conclusions about the effect of acute citalopram on non-conscious processing of threat.

Pharmacological fMRI

The use of BOLD fMRI to investigate the pharmacological modulation of brain activity by psychoactive drugs is a growing area of research. However, in such studies it must be considered whether pharmacological modulations of the BOLD signal reflect global influences on neurovascular coupling, rather than specific modulations of neural activity. For example, changes in the BOLD signal following drug administration could reflect influences of the drug not only on neural activity, but also on the synaptic and metabolic signalling to the blood vessels that control the cerebral blood flow responses, as well as the reactivity of the cerebral vasculature. One method that is often used to control for such non-specific global modulations of signalling or vasculature reactivity by the drug is the inclusion of a control task to assess the BOLD response in a region that is not expected to be modulated by the drug, such as the visual stimulation paradigm used in this study. Using this paradigm, it was found that citalopram has no significant effect on the BOLD signal change in the occipital region activated by this task, which suggests that global vascular effects of the drug cannot account for the presence of citalopram-mediated modulations of the BOLD response to threat-related stimuli. However, it is important to note that such a control task does not preclude the possibility of non-specific effects that are restricted to the regions that are engaged by the main task of interest. Future studies employing perfusion methodologies for comparison of absolute values of blood flow during baseline conditions are needed to address this issue further.

Summary

The present study demonstrates that SSRIs have immediate and discernable effects on neural circuitry that appear to be important in their eventual therapeutic action. This mirrors previous behavioural findings that demonstrate measurable psychological changes following a single dose of an antidepressant and suggests that altered processing of emotionally valenced stimuli may represent an important mechanism through which antidepressants eventually exert their clinical effects on subjective mood. It is possible that the rapid reduction in amygdala activity by antidepressant drugs is an important mechanism for subsequent clinical antidepressant effects.

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Effect of a single dose of citalopram on amygdala response to emotional faces

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BJP 2009, 194:535-540.
Access the most recent version at DOI: 10.1192/bjp.bp.108.056093

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