Short-term antidepressant treatment and facial processing

Functional magnetic resonance imaging study

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Summary We used functional magnetic resonance imaging to investigate the effects of short-term treatment with reboxetine, a selective noradrenaline reuptake inhibitor, on emotional facial processing in healthy volunteers. Reboxetine was associated with a reduced amygdala response to fearful faces and increased activation to happy *v.* neutral facial expressions in the right fusiform gyrus, relative to placebo treatment and in the absence of changes in mood. Our results show that reboxetine modulates the neural substrates of emotional processing, highlighting a mechanism by which drug treatment could normalise negative bias in depression and anxiety.

Declaration of interest None.

Cognitive theories of depression emphasise the role of negative biases in information processing as key to the aetiology and maintenance of depression. In contrast, neurobiological theories assert that depression is caused by an imbalance in key neurotransmitters, which can be addressed using pharmacotherapy. However, the mechanisms by which elevating the levels of these neurotransmitters improves the psychological symptoms of anhedonia and poor social functioning remain unknown.

Modelling the effects of antidepressants in healthy volunteers without depression allows behavioural/neural differences in emotional processing to be explored without confounding by changes in symptom state. In addition, well-designed randomised controlled studies with placebo comparison can be more readily undertaken. Thus, we used functional magnetic resonance imaging (fMRI) to investigate emotional facial processing in healthy volunteers randomised to receive either placebo or reboxetine to test the specific prediction that reboxetine would reduce amygdala response to negative (fear) facial expressions. (For the role of the amygdala in processing negative facial expressions see the Discussion below.)

METHOD

Twenty-four healthy volunteers (see Table DS2.1 in data supplement 2 to the online version of this paper) were screened to exclude current or past psychiatric disorder, substance misuse and contraindications for fMRI. The study was approved by the local ethics committee and written informed consent was obtained. We used a double-blind, randomised, placebo-controlled between-group design with random allocation to either reboxetine (4 mg twice daily) or placebo for 7 days. Subjective state was recorded daily throughout the study (for a complete list of measures used see Table DS2.2 in online data supplement 2.

On day 7 fMRI scans were acquired at 1.5 T (for details of acquisition and preprocessing see online data supplement 1). Facial stimuli (Ekman & Friesen, 1976) were presented in a block design. For the covert task, four blocks each of fearful, happy and neutral faces were presented for 17 ms and immediately masked with a neutral face presented for 183 ms. For the overt task, four blocks each of fearful, happy and neutral faces were presented in isolation (no mask) for 200 ms. Blocks were presented in random order for 20 s, with 10 faces/face–mask pairs presented per block and each emotional block interspersed with 20 s of fixation cross. For each facial presentation volunteers were asked to judge the gender of the face (gender discrimination). Significant clusters were determined at a Z threshold of 2.7 ($P=0.05$), corrected for the following four linear contrasts: covert fear/happy *v.* covert neutral; overt fear/happy *v.* overt neutral. Subjective mood and anxiety were analysed using repeated-measures analysis of variance with $\alpha \leqslant 0.05$ considered significant.

RESULTS

Reboxetine did not affect subjective mood, although ratings of energy levels were increased (see Table DS2.2 in online data supplement 2). There were no significant between-group differences in terms of gender discrimination or response time to correctly categorised faces in the scanner ($P>0.05$ for all comparisons). Thus, differences in neural response can be explored in the absence of significant between-group differences in mood or overt differences in behavioural performance measured during scanning.

To examine amygdala response to fear we extracted the percentage signal change for left and right amygdala (Maldjian *et al*, 2003) from individuals' unsmoothed fMRI time series. Using unsmoothed images took full advantage of the high-resolution data and limited blurring of activity from adjacent structures. Right amygdala response to covert fear was significantly attenuated under reboxetine (independent measures, $t_{22}=2.3$, $P=0.03$; Fig. DS3.1, online data supplement 3). There were no significant between-group differences to overt presentations of fear or to covert fear in left amygdala.

Comparison of covert happy with covert neutral facial expressions revealed greater activation under reboxetine in the right fusiform gyrus (Montreal Neurological Institute coordinates $x=44$, $y=-59$, $z=-20$; Fig. DS3.2, data supplement 3). To ensure that the effects of reboxetine on task-specific brain activity are not confounded by drug effect on baseline activation, the individual's percentage signal change to covert happy and neutral faces was computed for the above cluster. Reboxetine significantly increased brain activation to covert happy faces without affecting response to neutral faces (analysis of variance: expression × group interaction, F (1,22)=24.3, $P<0.001$; *post hoc* independent measures: happy $t_{22}=3.4$, $P=0.003$, neutral $t_{22}=-0.50$, $P=0.64$; Fig. DS3, data supplement 3.3). There were no significant between-group differences to covert fear *v.* covert neutral or for either overt comparisons.

DISCUSSION

Consistent with our hypothesis, short-term treatment with reboxetine reduced amygdala activation to subliminal *negative* facial expressions. We also saw increased

activation to subliminal *positive* faces in the right fusiform gyrus. Depression is associated with an increased amygdala response to subliminal presentation of fearful facial expressions which resolves following remission of symptoms after chronic treatment with antidepressants (Sheline *et al*, 2001; Fu *et al*, 2004). However, it is not known whether this normalisation of amygdala response with time is a direct effect of treatment or a marker of current symptom state. We suggest that, in healthy volunteers, reboxetine has rapid and direct effects on the amygdala response to subliminal fear, which are unconfounded by changes in mood.

Notably, we saw decreased amygdala response to covert fear only, consistent with the hypothesis that antidepressants affect early automatic aspects of processing rather than strategic or elaborative stages. In line with this, data from animal studies suggest that noradrenaline inhibits cell firing in the basolateral amygdala (Aroniadou-Anderjaska *et al*, 2006), a division of the amygdala that, in humans, is activated by covert but not overt fearful stimuli (Etkin *et al*, 2004). We have previously reported a similar reduction in the amygdala fear response following 7-day treatment with citalopram (Harmer *et al*, 2006). These findings together with those of the present study suggest that two antidepressant compounds, putatively acting through different neurochemical signalling mechanisms, have similar rapid effects on fear processing in the amygdala. These results are consistent with animal studies suggesting an inhibitory effect of serotonin (Stutzmann & LeDoux, 1999) and noradrenaline (Aroniadou-Anderjaska *et al*, 2006) on neuronal excitability within the amygdala. These neural effects are also consistent with the behavioural reductions in fear recognition seen following short-term reboxetine and citalopram administration (Harmer *et al*, 2003).

In addition, we observed increased activation to subliminal *positive* faces in the right fusiform gyrus. 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). In depression, right fusiform activation in response to happy faces is reduced compared with healthy controls (Surguladze *et al*, 2005), and modulation of activity in this face processing sensory area has been suggested to contribute to changes in salience of such emotional stimuli in attracting attention (Vuilleumier, 2005). As such, the increased response in the fusiform gyrus specifically to happy facial expressions is consistent with our hypothesis and the behavioural increases in positive emotional processing following reboxetine that have been reported previously (Harmer *et al*, 2004), as well as with the well characterised antidepressant effects of this drug in clinical groups.

A number of limitations to our study should be noted. Although studies in healthy volunteers allow the assessment of drug effects unconfounded by changes in clinical state, it remains to be tested whether similar effects occur in patients with depression at this early stage in treatment and whether they are related to therapeutic improvement. The present study was also powered to detect differences in neural responses to emotional stimuli rather than changes in subjective mood. It is therefore possible that subtle changes in mood might accompany these changes in neural responses which we could not detect. Further studies using larger samples are therefore needed to test whether these effects are truly independent.

Our finding of reduced amygdala response to fear was also seen in an independent sample following administration of the selective serotonin reuptake inhibitor citalopram, suggesting that this effect might represent a common downstream action of effective pharmacological treatment for depression. However, there were also some differences in these effects: namely the increased fusiform gyrus response to happy facial expressions following reboxetine and the decreased hippocampal and medial prefrontal cortex response to fear following citalopram. Further studies are required to directly compare the profile of effect produced by selective serotonin and noradrenaline reuptake inhibitors on emotional processing to examine whether there are distinct as well as overlapping effects.

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