Single dose antidepressant administration modulates the neural processing of self-referent personality trait words

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Drugs which inhibit the re-uptake of monoamines in the brain are effective in the treatment of depression; however, the neuropsychological mechanisms which lead to the resolution of depressive symptomatology are unclear. Behavioral studies in healthy volunteers suggest that acute administration of the selective norepinephrine reuptake inhibitor reboxetine modulates emotional processing. The current study therefore explored the neural basis of this effect. A single dose of reboxetine (4 mg) or placebo was administered to 24 healthy volunteers in a double-blind between-group design. Neural responses during categorisation and recognition of self-referent personality trait words were assessed using event-related functional Magnetic Resonance Imaging (fMRI). Reboxetine had no effect on neuronal response during self-referent categorisation of positive or negative personality trait words. However, in a subsequent memory test, reboxetine reduced neuronal activation in a fronto-parietal network during correct recognition of positive target words vs. matched distractors. This was combined with increased speed to recognize positive vs. negative words compared to control subjects and suggests facilitated memory for positive self-referent material. These results support the hypothesis that antidepressants have early effects on the neural processing of emotional material which may be important in their therapeutic actions.
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Introduction

There is still something of a conceptual gap between the psychological and neurobiological approaches to the understanding and treatment of depression. While cognitive psychological theories suggest that negative biases in the cognitive processing and memory of self-referent information are key features in the development and maintenance of depression (Beck et al., 1979), current neurobiological views of depression hypothesize abnormalities in cellular pathology involving, for example, such basic processes as synaptogenesis and neurogenesis in key brain regions involved in emotional regulation (for review, see Duman and Montéggia, 2006). Such views have important implications for the treatment of depression utilizing either psychological approaches which aim to reverse negative biases in information processing or pharmacological strategies targeting underlying cellular or neurotransmitter dysfunction. Although in practice these treatments are often combined, we have little understanding of their interaction or overlapping effects.

Recent behavioral evidence in healthy volunteer studies suggests that antidepressant drugs also modify the cognitive processing of emotional information. In particular, administration of both noradrenergic and serotonergic antidepressants increase the relative processing of positive vs. negative emotional information in healthy volunteers in a variety of paradigms such as facial expression recognition, emotional memory and attention (Harmer et al., 2003, 2004). These effects of antidepressant drugs can be seen from the beginning of treatment. For example, a single dose of the selective noradrenalin reuptake inhibitor (SNRI) reboxetine significantly facilitated speed to categorize positive vs. negative self-referent personality trait words and enhanced memory for these positive words in healthy volunteers (Harmer et al., 2003). Such effects were also found after short-term (7-day) administration of reboxetine in a separate study (Harmer et al., 2004) and in both studies, effects occurred in the absence of changes in subjective mood.

Neuroimaging studies have demonstrated that encoding of emotional self-referent trait words engages the medial prefrontal cortex (mPFC), while subsequent successful memory reactivates the mPFC, as well as lateral prefrontal, premotor, parietal and occipital regions (Fossati et al., 2004). Enhanced occipito-parietal response to emotional compared to neutral information is believed to reflect increased attentional processing of biologically significant or personally relevant events (Vuilleumier, 2005). A study assessing

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the neural basis for the changes in emotional processing after 7 days of reboxetine administration found a distinct pattern of effects in these regions (Norbury et al., submitted for publication). Reboxetine increased neuronal response during self-referent categorisation of positive words and reduced response in during subsequent recognition of positive versus negative words in fronto-parietal regions. This is consistent with increased attention to positive self-referent words paired with reduced cognitive demand during retrieval of these words. Such changes in the relative processing of positive vs. negative self-referent material may be an important mechanism for the therapeutic actions of antidepressant drugs.

The time-course of antidepressant drug action on the neural processing of self-referent emotional information is unknown. The current study therefore investigated the effects of a single dose of reboxetine vs. placebo on the neuronal responses during the self-referent categorisation and incidental memory of personality trait words in healthy volunteers using event-related fMRI. In light of the facilitated processing of positive vs. negative material after single (Harmer et al., 2003) and repeated administration (Harmer et al., 2004; Norbury et al., submitted for publication), we aimed to test the following specific predictions: Firstly, that reboxetine would increase the attentional processing and BOLD response in fronto-parietal regions during the categorisation of positive vs. negative words, introducing a positive bias. Secondly, that reboxetine would reduce BOLD response for positive vs. negative words within these regions during subsequent retrieval memory. This would be consistent with a relative ease of memory for positive self-referent words (e.g. Fletcher et al., 1996; Gould et al., 2003; Harmer et al., 2003).

Materials and methods

Subjects

Ethical approval of the study's methods was obtained from the Oxford Psychiatry Research Ethics Practice (OPREC). Healthy volunteers between the ages of 23 and 38 years were screened using the Structured Clinical Interview for DSM-Clinical Version (SCID-IV) (Frances et al., 1995) to exclude current or previous history of psychiatric disorder and/or substance or alcohol abuse, and/or serious neurological or physical problems. Subjects who reported any current use of illicit drugs were excluded. Participants were also screened to be free of medication other than contraceptives. Functional magnetic resonance scanning also required the following exclusion criteria: spectacles, heart pacemaker, mechanical heart valve or any mechanical implants, potential pregnancy, and claustrophobia. After complete description of the study to the subjects, written informed consent was obtained.

Experimental design

Twenty four healthy volunteers were randomly allocated to receive either reboxetine (4 mg) or placebo in a double-blind between-groups design. The reboxetine and placebo groups were matched for: gender (7 males and 5 females in each group), age (mean=28.1 years, S.D.=3.0, and mean=26.6 years, S.D.=4.5, respectively) and IQ measured with the National Adult Reading Test (Nelson, 1982) (test score: mean=118, S.D.=9, and mean=114, S.D.=8, respectively). Subjects fasted for 3 h prior to and during study participation to ensure similar rates and levels of reboxetine

absorption. As previous work indicates that levels of salivary cortisol (indicative of central norepinephrine levels) peak approximately 2 h after the administration of reboxetine and remain elevated for at least 2 h (Hill et al., 2003), fMRI and psychological testing were initiated 2 h after drug/placebo administration.

Verbal stimuli

For the emotional categorisation task, a list of 60 personality trait words was constructed from the Anderson's list of personality trait words (Anderson, 1968). Within this list, there were an equal number of unambiguously positive and negative words (e.g. perceptive, talented, generous, selfish, hostile, and pompous). Positive and negative words were matched on length, written frequency (Francis and Kucera, 1982), and meaningfulness (Anderson, 1968). Each word occurred only once leading to a total of 60 presentations.

For the incidental memory task, a list of 120 personality trait words was created from the Anderson's list (1968), of which 60 had been encoded previously in the categorisation task (old words) and 60 were distractors (new words). There were an equal number of unambiguously positive and negative distractor words, which were matched to the old words on length, written frequency, and meaningfulness.

Task design

fMRI scans were acquired while subjects first performed the emotional categorisation task, immediately followed by the incidental recognition task. Stimuli were presented on a personal computer using e-prime software (version 1.0; Psychology Software Tools Inc., Pittsburgh, PA) and projected onto a opaque screen at the foot end of the scanner bed.

In the emotional categorisation task, each trial consisted of a fixation cross displayed for 500 ms immediately replaced by a personality trait word displayed for 500 ms. The words were presented in random order, the inter-trial interval (ITI) varied between 4000 and 9000 ms, and the total task time was 7.5 min. During this time subjects were instructed to, as quickly and accurately as possible, categorize the words as likeable or dislikeable in a self-referential fashion. Hence, each personality trait word prompted a 'likeable' or 'dislikeable' response and participants indicated their decision by pressing either a left or right key on a response pad with their right middle and index fingers. Response keys (left vs. right) were counterbalanced across the two experimental groups.

Emotional categorisation was immediately followed by an unexpected incidental recognition task. In this task, subjects were asked to indicate, as quickly and accurately as possible, whether or not they remembered having seen the particular words in the preceding task, again by pressing either a right or left key on the response pad according to the version administered. Trial presentation was identical to that during the emotional categorisation task, and total task time was 12 min. During both tasks, accuracy and reaction time were recorded with e-prime software.

Visual stimulation paradigm

To explore whether any drug-related effects on neuronal responses during categorisation and retrieval of personality trait words were due to global effects of reboxetine on baseline blood flow or neuronal coupling, neural activation was assessed with a

control visual stimulation paradigm. A flashing checkerboard (frequency = 8 Hz) was presented in blocks of 21 s alternating with 21 s of a stationary fixation cross for a total of 8 cycles, during which time subjects were instructed to lie with their eyes open.

Mood scales

Mood and subjective state were assessed at three intervals; at baseline before drug administration (time −15 min), before the scan (+90 min), and at the end of the study (+300 min). This was achieved by administering the visual analogue scales (VAS) of happiness, sadness, disgust, anger, fright, anxiety, and alertness, the State and Trait Anxiety Questionnaires (STAI), and the Befindlinchkeits Scale (BFS). The BFS provides a measure of normal variation in mood and energy by asking the participants to check one word of a word pair which best describes their current state (e.g. carefree vs. brooding). Monitoring mood and subjective state allowed for the control of any effects related to major shifts of mood during the experiment. The Beck Depression Inventory (BDI) and the Trait Anxiety Questionnaire were used to control for any significant differences in mood between groups.

Salivary cortisol

To confirm the absorption of reboxetine at the time of testing, saliva samples were obtained three times during the experiment (−15 min, +90 min, and +300 min). Saliva cortisol was measured using an in-house double antibody radioimmunoassay (intra- and inter-assay coefficients of variation were 3% and 10%, respectively; lower limit of detection was 0.5 mmol/l).

fMRI data acquisition

Imaging data were collected using a Siemens Sonata scanner operating at 1.5 T located at the Oxford Centre for Clinical Magnetic Resonance Research (OCMR). Functional imaging consisted of 35 T2∗-weighted echo-planar image slices [repetition time (TR) = 3000 ms, echo time (TE) = 50 ms, matrix = 64 × 64], 3 mm^3 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] voxel size = 1 mm^3. A total of 154 volumes were acquired during the emotional categorisation task, 244 volumes throughout the subsequent recognition task, and 56 volumes in the control visual stimulation paradigm. The first two volumes in each session were discarded to avoid T1 equilibration effects.

fMRI data analysis

fMRI data were pre-processed and analyzed using FEAT (FMRIB Expert Analysis Tool) version 3.0, part of FSL (FMRIB Software Library) (www.fmrib.ox.ac.uk/fsl). Data from two volunteers (one from each drug group) was excluded because of claustrophobia during scanning and failure to record behavioral data, respectively; fMRI analysis was consequently run on 22 volunteers. Pre-processing included within-subject image realignment, non-brain removal, spatial normalisation to a standard template (Montreal Neurological Institute [MNI] 152 stereotactic template) using an affine procedure and spatial smoothing using a Gaussian kernel (5 mm full-width-half-maximum). The time series in each session was high pass-filtered (Gaussian-weighted LSF

straight line fitting, with sigma = 40 s). FSL was used to compute individual subject analyses in which the time series were pre-whitened to remove temporal autocorrelation (Jezzard et al., 2001).

An event-related design was employed to explore the rapid BOLD responses triggered by categorisation and recognition of personality trait words. Events were specified as occurring at the presentation of word stimuli and were modeled separately by convolving the onset of each word using a canonical haemodynamic response function with a standard deviation of 3 s and a mean lag of 6 s (Jezzard et al., 2001). For the emotional categorisation task, events were designated according to affect (positive and negative words). For the recognition task, events were identified according to whether or not the word had been presented in the previous categorisation task (old vs. new), whether the word was positive or negative, and whether the word was correctly identified as old (hit) or new (correct rejection). Four event types were therefore modeled: positive/hit, positive/correct rejection, negative/hit and negative/correct rejection. To identify any drug effects in areas involved in retrieval processes for positive and negative words rather than valence *per se*, we contrasted positive/hits with positive/correct rejections and negative/hits with negative/correct rejections (i.e. drug by task interactions).

Individual subject data were combined at the group level using random effects analyses (Woolrich et al., 2004). Z (Gaussian T) statistic images were thresholded using clusters determined by Z = 2.0 and a corrected cluster significance of p = .05. Correction of p-values was based on spatial extent according to random field theory. Foci of activation were localized using Talairach co-ordinates (Stereotactic Atlas of the Human Brain) (Talairach and Tournoux, 1988). For regions where a significant drug group by task interaction was observed, percent BOLD signal change was extracted and examined with analysis of variance. Significant interactions were explored further with simple main effect analyses to identify the profile of drug effect. For the control stimulation paradigm, we compared mean percent BOLD signal change in subjects given reboxetine vs. placebo within a region of the occipital (calcarine) cortex consistently activated by photic stimuli (Maldjian et al., 2003).

Statistical analysis of behavioral and mood data

Behavioral data were analyzed using repeated-measures analysis of variance (ANOVA) with group and valence as factors. To obtain a further measure of memory accuracy corrected for the subject's response tendency, signal detection theory was applied. The proportion of correctly recognized words (cr) and of falsely recognized words (fr) constitute the parametric sensitivity measure: $d' = .5((cr − fr) (1 + cr − fr)/4c (1 − fr))$, with a higher d-value reflecting greater accuracy of memory (Grier, 1971).

Subjective state ratings were also analyzed using repeated measures ANOVA with group as the between-subjects factor and time of rating (3 levels: −15 min, +90 min, and +300 min) as the within-subjects factors.

Results

Subjective state and absorption of drug

The two groups were similar in terms of general mood, indicated by no significant differences in BDI and STAI scores

($p > .1$ for all comparisons). Control of the relevant transient mood changes revealed that there were in no significant differences between the two groups overall (all $p > .2$). However, volunteers receiving reboxetine reported feeling subjectively more alert ($F(1,22) = 5.59$, $p = .03$). Baseline salivary cortisol levels were similar; 15.7 vs. 15.1 mmol/l in the reboxetine and placebo groups, respectively. However, reboxetine significantly increased cortisol levels compared to placebo at the latter time points ($F(1,22) = 6.6$, $p = .02$), in line with the expected neuroendocrine effects of this drug.

Performance

Accuracy in both categorisation and memory tasks was high in both groups (average accuracy in categorisation: 92%, incidental memory 74%; Table 1). There was a main effect of valence on categorisation speed with reduced response times to positive vs. negative words ($F(1,20) = 9.26$, $p = .006$). Reboxetine had no significant effect on speed ($p > .1$) or accuracy ($p > .08$) of emotional categorisation (Table 1). Accuracy of recognition corrected for response bias was also not affected by reboxetine (all $p > .7$; Table 1). Reboxetine-treated subjects were, however, significantly faster at recognizing positive compared with negative words than those receiving placebo (valence × group: ($F(1,20) = 4.67$, $p = .04$; Table 1 and Fig. 1).

Task- and group-related BOLD change

Emotional categorisation

Main effect of task

Self-referent categorisation of positive and negative personality trait words activated the left medial and inferior frontal gyri and the right occipito-temporal cortex (for cluster maxima see Table 2). Negative trait words specifically activated right-side precentral and cingulate gyri, while positive words also produced a significant left-lateralized precuneus response (Table 2).
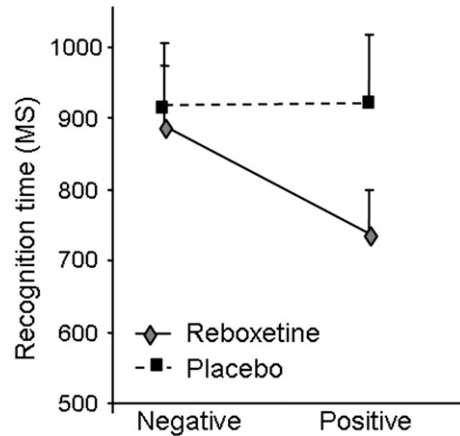

Fig. 1. Speed to recognize positive vs. negative personality trait words under reboxetine ($n = 11$) and placebo ($n = 11$). Lines show the mean response times; error bars show the standard error (σ_M).

Effects of reboxetine

A whole brain analysis revealed no interaction between group and valence and also no effect of reboxetine on neuronal responses when considering positive and negative words separately. Extraction of mean percent signal change from the network of regions activated by self-referent categorisation of positive and negative words, including the hypothesized medical prefrontal cortex, revealed no effects of reboxetine on neural responses to these words (all $p > .6$).

Incidental memory

Main effect of task

Correct recognition of negative target (vs. negative distractor) words produced significant activation within the left-lateralized middle temporal gyrus and inferior and superior parietal cortex (for cluster maxima see Table 2), whereas correct recognition of positive target words vs. matched distractors specifically activated a partly

Table 1

Performance during the emotional categorisation and incidental memory tasks for the reboxetine and placebo groups

Task and performance measure	Reboxetine ($n=11$)		Placebo ($n=11$)		Analysis					
	Mean	S.D.	Mean	S.D.	Main effect of valence		Interaction		Main effect of group	
					F	P	F	P	F	P
Emotional categorisation										
Accuracy (proportion correct responses)										
Positive words	0.97	0.04	0.89	0.14	$F(1,20)=0.52$	0.48	$F(1,20)=1.42$	0.25	$F(1,20)=3.35$	0.08
Negative words	0.94	0.05	0.89	0.10						
Response times (ms)										
Positive words	525.8	217.1	689.2	286.4	$F(1,20)=9.26$	0.006	$F(1,20)=0.007$	0.93	$F(1,20)=2.59$	0.12
Negative words	625.4	225.7	794.4	281.0						
Incidental memory										
Accuracy (proportion correct responses)										
Positive hits	0.82	0.11	0.72	0.24	$F(1,20)=4.63$	0.04	$F(1,20)=2.89$	0.11	$F(1,20)=0.58$	0.46
Negative hits	0.72	0.16	0.70	0.21						
Accuracy corrected for response bias										
Positive d' values	0.082	0.05	0.075	0.073	$F(1,20)=0.58$	0.47	$F(1,20)=0.13$	0.73	$F(1,20)=0.01$	0.91
Negative d' values	0.070	0.061	0.071	0.065						
Response times (ms)										
Positive hits	737.3	199.3	921.4	317.4	$F(1,20)=4.25$	0.05	$F(1,20)=4.67$	0.04	$F(1,20)=0.91$	0.35
Negative hits	889.3	276.4	917.8	289.2						

Table 2
Peak cluster activation in brain regions of significantly increased BOLD response during the emotional categorisation and incidental memory tasks across all subjects (main effect of task) and effects of reboxetine (interaction)

Task and region	Z-value	Coordinates		
		x	y	z
Emotional categorisation				
Main effect of negative words				
L inferior frontal gyrus (BA 19)	4.59	−52	−72	−4
R precentral gyrus (BA 6)	4.14	52	−6	52
R cingulate gyrus (BA 24)	3.96	10	8	36
R occipito-temporal junction (BA 37/19)	5.28	50	−60	−10
Main effect of positive words				
L inferior frontal gyrus (BA 44)	5.2	−54	16	28
L precuneus (BA 7)	3.37	−20	−68	44
L inferior occipital gyrus (BA 19)	6.08	−44	−82	−12
R inferior occipital gyrus (BA18)	5.3	46	−84	−6
Incidental memory				
Main effect of correct discrimination				
of negative targets vs. distractors				
L middle temporal gyrus (BA 21)	4.03	−56	−30	−10
L inferior parietal cortex (BA 40)	4.01	−40	−58	50
Main effect of correct discrimination				
of positive targets vs. distractors				
R parieto-occipital sulcus (BA 7/19)	4.56	20	−62	20
Interaction (positive targets-				
positive distractors × group)				
R superior parietal cortex (BA 7)	4.47	20	−66	59
R medial frontal gyrus (BA 6)	4.91	20	−14	60

MNI coordinates (*x*, *y*, *z*) refer to peak activation within each cluster identified thresholded at *Z*=2.0 and *P*<.05, corrected. BA: Brodmann area.

overlapping cluster encompassing the right precuneus, superior parietal cortex and parieto-occipital sulcus (Fig. 2, for cluster maxima see Table 2).

Effects of reboxetine

The whole brain analysis revealed a significant group by task interaction during correct recognition of positive target words vs. matched distractors within a right-lateralized fronto-parietal network, including the medial frontal gyrus, precuneus, and superior and inferior parietal cortex (Fig. 2, for cluster maxima see Table 2). Extraction and analysis of mean percent signal change in these regions revealed a significant main effect of recognizing positive targets vs. distractors (*F*(1,20)=7.75, *p*=.01; Fig. 2). Further, signal change analysis demonstrated that the group by task interaction in this network represented a specific decrease in neuronal activation during retrieval of positive words (*F*(1,20)=36.36, *p*=.01; positive/hits: *t*=−3.9, *df*=20, *p*=.001; Fig. 2) and increased response to novel distractor words (positive/correct rejections: *t*=2.67, *df*=20, *p*=.02; Fig. 2) under reboxetine vs. placebo. Recognition of negative target words vs. matched distractors in these regions was not significantly modulated by reboxetine; if anything, there was a trend in the opposite direction (*F*(1,20)=3.29, *p*=.09), suggesting that the effects in these regions were specific for retrieval of positive words.

Visual stimulation control experiment

Analysis of mean percent BOLD signal change within the occipital ROI during presentation of visual checkerboard stimuli

revealed no differences between groups (*p*>.1), suggesting that the observed effects of reboxetine were not caused by non-specific haemodynamic changes.

Discussion

In the current study, a single dose of the antidepressant reboxetine to healthy volunteers had no effect on neural response during self-referent categorisation of positive and negative words. However in a subsequent incidental memory task, reboxetine-treated volunteers displayed a specific reduction in right-lateralized fronto-parietal network during the retrieval of positive words, accompanied by increased speed to recognize positive vs. negative words. The present results complement previously reported behavioral effects of acute administration of reboxetine to healthy volunteers (Harmer et al., 2003) and highlight key neural areas, which may be involved in these actions.

Neural systems subserving emotional categorisation

Self-referent categorisation of both positive and negative trait words activated a largely overlapping network of left-lateralised inferior and medial frontal gyri and right-side occipito-temporal regions. This is consistent with medial and inferior frontal involvement in the processing of self-referent (Fossati et al., 2003) and emotional (Kuchinke et al., 2005) information, respectively, and with attentional recruitment of occipito-temporal areas in response to emotional vs. neutral stimuli (e.g. Kuniecki et al., 2003; Moratti et al., 2004). Increased activation in the cingulate to negative words
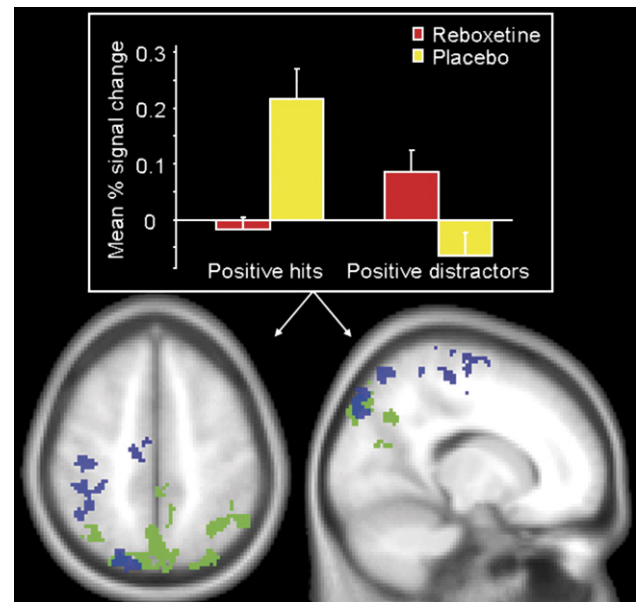

Fig. 2. Neural response during the recognition of positive personality trait words vs. matched positive distractors and effects of reboxetine. Areas marked with green are the regions significantly activated during successful retrieval across all subjects. Reboxetine reduced activation during successful retrieval in a fronto-parietal network (marked with blue) compared to placebo. Images are thresholded at *Z*=2.0, *p*=.05, corrected. Plot of mean percent BOLD signal change during recognition of positive personality trait words and matched distractors modelled against Baseline (fixation periods) in the region of significant drug group×task interaction (blue areas). Bars show the mean; error bars show the standard error (σ_M).

and in the precuneus to positive words is compatible with a role of these regions in the processing of and attention to emotional information (Vogt et al., 1992; Maddock et al., 2003; Aalto et al., 2002; Paradiso et al., 1999).

Emotional categorisation: effects of reboxetine

Contrary to our hypothesis and to previous evidence that acute administration of reboxetine increases speed to categorisation positive vs. negative words (Harmer et al., 2003), we found no effects of reboxetine on the speed of categorisation or neuronal response to self-referent positive or negative words. These results also contrast with the effects of 7 days reboxetine administration which increased activation within frontal and parietal cortex during classification of self-referent likeable trait words (Norbury et al., submitted for publication). Taken together, these observations imply that repeated administration of antidepressants may have greater or more robust effects on emotional categorisation than acute administration.

Neural systems subserving incidental memory

Successful recognition of negative self-referent personality trait words vs. matched distractors activated the left-hemisphere inferior parietal and inferior temporal gyrus. These areas have also been highlighted in previous studies exploring the neural correlates of self-referent processing (Kircher et al., 2000), emotional processing (Bremner et al., 2003; Ruby and Decety, 2004), and successful retrieval memory (van der Veen et al., 2006). Correct recognition of positive target vs. distractor words activated a cluster of parietal regions overlapping with the areas activated during retrieval of negative words as well as the right precuneus. This is consistent with the involvement of the precuneus in emotion processing (Teasdale et al., 1999; Ochsner et al., 2004), spatial attention (Cavanna and Trimble, 2006) and recognition memory (von Zerssen et al., 2001; Cavanna and Trimble, 2006).

Incidental memory: effects of reboxetine

An incidental recognition task was used in the place of the free recall approach employed in the previous behavioral studies (Harmer et al., 2003) because of its compatibility with the fMRI procedure. Although a scanning environment may be sub-optimal for detection of behavioral effects of drugs (e.g. Miskowiak et al., 2007; Norbury et al., submitted for publication), this task revealed increased efficiency (in this case speeded reaction times) to recognize positive words following reboxetine, consistent with the positive bias in free recall previously reported (Harmer et al., 2003).

To explore effects of reboxetine on the neural systems involved in retrieval processes rather than valence *per se*, we contrasted responses for successfully recognized words with matched distractor words. No effects of reboxetine on neuronal activation were observed during retrieval of negative material. However, during the successful recognition of positive words, reboxetine decreased activation in a fronto-parietal network involving the medial frontal gyrus and increased response in these regions to matched positive distractor words. By contrast, there was no effect of reboxetine in these regions during retrieval of negative words suggesting a valence-specific modulation. Extraction of BOLD signal change revealed activation of this fronto-parietal network during retrieval processes across all subjects, which indicates that reboxetine modulated memory-relevant neural processes.

The decreased recruitment of neural resources during retrieval of positive target words under reboxetine is consistent with reduced cognitive load for positive material as predicted and is similar to the effects seen following 7 days administration of reboxetine which also decreased medial frontal and parietal response during retrieval of positive self-referent characteristics (Norbury et al., submitted for publication). Specifically, increased retrieval effort has been associated with blood flow increase within frontal regions in an explicit memory task in which effort to recall an event was dissociated from the actual recollection of it (Schacter et al., 1996). Indeed, Rugg and Wilding (2000) have suggested that the neural correlates of increasing effort is manifest as increased activity of whatever brain regions are engaged by the retrieval task in question. Such a hypothesis is consistent with neuroimaging studies of cognitive function in schizophrenia (Callicott et al., 2003) which report that patients whose working memory performance is similar to that of healthy control subjects use greater prefrontal resources, while patients without such exaggerated prefrontal activity achieve lower memory accuracy. Indeed, our interpretation that the reduced recruitment of neural resources represents facilitated memory for positive words receives support by the speeded recognition of positive vs. negative target words in volunteers given reboxetine vs. placebo.

Pharmacological fMRI

It is important when examining the effects of a drug manipulation on BOLD responses with fMRI to assess whether the observed effects could be the result of more global effects of the drug on blood flow or neural coupling. However in the present study, reboxetine had no effect on neural response within the ROI in primary visual cortex consistently activated by photic stimulation. It is therefore likely that the observed effect of reboxetine on fronto-parietal activation was specific for retrieval of positive personality trait words rather than a result of global haemodynamic changes.

The use of healthy non-depressed subjects

Together with our previous findings (Harmer et al., 2003, 2004, 2006), the current data indicate that monoaminergic antidepressants increase the relative processing of positive vs. negative emotional information in healthy volunteers both in terms of behavioral and neural responses. In light of this and the prevalent negative biases in emotional processing in depressed patients, we have hypothesized that the facilitation of positive vs. negative emotional processing is a general mechanism of antidepressant drugs important in their therapeutic actions (Harmer et al., 2004). Studying the mechanisms of these drugs in healthy non-depressed subjects has the advantage of avoiding certain confounding variables, such as effects of changes in mood and medication. However, it remains necessary to assess whether the same processes occur in depressed patients early on in antidepressant drug treatment.

Conclusions

In summary, we demonstrated that a single dose of reboxetine to healthy volunteers reduced neuronal activation in a fronto-

parietal network during retrieval of positive personality trait words and increased recognition speed for positive vs. negative words. Together these findings provide support for the hypothesis that antidepressants may bias memory and learning in a positive fashion quickly after commencement of antidepressant treatment. Such a mechanism would be compatible with cognitive–behavioral theories of depression, which emphasize the importance of negative biases in the maintenance of depressive illness. Future studies are required to assess the effects of longer term administration of reboxetine in depressed subjects and to assess whether these early effects of antidepressants on emotional processing are predictive of the therapeutic response to these drugs.

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