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# Acute Antidepressant Drug Administration and Autobiographical Memory Recall: A Functional Magnetic Resonance Imaging Study

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Antidepressants affect memory and neural responses to emotionally valenced stimuli in healthy volunteers. However, it is unclear whether this extends to autobiographical memory for personally experienced events. The current study investigated the effects of acute administration of the antidepressant reboxetine on emotional autobiographical retrieval in healthy volunteers (14 men, 10 women). Functional magnetic resonance imaging was used in a double-blind between-groups investigation with reboxetine (4 mg) and placebo. Consistent with previous reports using lab-based stimuli, neural activation in the processing of positive versus negative memories was reduced following reboxetine compared with placebo in the left frontal lobe (extending into the insula) and the right superior temporal gyrus. This was paired with increased memory speed in volunteers given reboxetine versus placebo. The effect of reboxetine on emotional memory extends to recall of personally experienced events. Such effects may be relevant to the cognitive improvements found with recovery from depression and with the mechanism of action of contemporary antidepressant drugs.

*Keywords:* depression, neuroimaging, neuropsychopharmacology, reboxetine, selective norepinephrine reuptake inhibitor

Both selective serotonin reuptake inhibitors (SSRIs) and selective noradrenaline reuptake inhibitors (SNRIs) are effective antidepressants (Tremblay & Blier, 2006; Papakostas, Nelson, Kasper, & Möller, 2008). We have previously found that acute administration of the SSRI citalopram and the SNRI reboxetine enhance the processing of positive emotional information in the absence of any change in subjective mood (see Harmer, Goodwin, & Cowen, 2009, for a review). For example, a single 4-mg dose of reboxetine

increased the recognition of facial expressions of happiness and improved the recall of positive personal descriptors in healthy volunteers (Harmer, Hill, Taylor, Cowen, & Goodwin, 2003). These behavioral changes are associated with changes in neural substrates of emotional processing. More specifically, a single 4-mg dose of reboxetine was found to reduce neuronal activation in a frontoparietal network during correct recognition of positive target words. This effect was combined with increased speed to recognize positive versus negative words for reboxetine-treated healthy subjects compared to healthy control subjects, indicating facilitated memory for positive self-referent material (Miskowiak et al., 2007). Such findings suggest that antidepressant drugs directly modulate the processing of emotional and social information to enhance positive processing and could therefore remediate the negative biases believed to play a key role in depression (Beck, 1976; Teasdale, 1988). Studies from other labs have also shown that a single dose of SSRIs or SNRIs can modulate the functional network involved in emotional information processing (Brühl, Kaffenbergen, & Herwig, 2010). However, studies to date have examined the effects of antidepressants on the recall and processing of standardized material developed by the experimenter, and it remains unclear whether antidepressants modulate the processing and retrieval of personally experienced events, relevant to the maintenance of depressive illness.

The present study therefore aimed to explore the neural effects of acute reboxetine administration further, by focusing on the recollection of autobiographical memory (a.m.). A meta-analysis has identified a role for medial and ventrolateral prefrontal, medial and lateral temporal, and retrosplenial/posterior cingulate cortices and the cerebellum in autobiographical remembering (Svoboda, McKinnon, & Levine, 2006). This same circuitry appears to be

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involved in remembering *emotional* autobiographical information, although a number of critical differences also exist. First, emotional autobiographical recall is more likely to lead to deactivations in these neural areas consistent with an emotion-related suppression of cognitive processes compared to nonemotional recall. Second, emotional retrieval is more likely to additionally involve areas of the right hemisphere, in addition to the left-lateralized circuitry involved in nonemotional retrieval. Finally, a number of areas involved in emotion tend to be further recruited, including the amygdala, insular, and orbitofrontal cortex (Fink et al., 1996; Markowitsch, Vandekerchove, Lanfermann, & Russ, 2003; Piefke, Weiss, Zilles, Markowitsch, & Fink, 2003).

The current study therefore used an a.m. paradigm to assess the early effects of antidepressant drug administration on the neural underpinnings of personally experienced emotional events. The Autobiographical Memory Test (AMT; Williams & Broadbent, 1986) is a cue-word paradigm and therefore is ideally suited for functional neuroimaging studies. It consists of emotion-laden and neutral cue words, and participants are asked to retrieve specific autobiographical memories in response to each cue word. The AMT was given to healthy volunteers randomized to receive a single 4-mg oral dose of the antidepressant reboxetine or placebo in a double-blind between-groups design. We hypothesized that reboxetine would reduce neural responses within the a.m. circuitry during the retrieval of positive compared to negative and neutral memories consistent with reduced retrieval effort (Miskowiak et al., 2007; Norbury, Mackay, Cowen, Goodwin, & Harmer, 2008).

## Method

### Participants<sup>1</sup>

Twenty-four healthy volunteers participated in the study (14 men, 10 women; age range: 23–38 years). All participants were free of medication, apart from contraceptive pills. Exclusion criteria included a current or previous history of psychiatric disorder (assessed with the *Structured Clinical Interview for DSM: Clinical Version* [SCID-CV]; Frances, First, & Pincus, 1995), substance abuse, and serious physical and neurological problems. Subjects who reported any current use of illicit drugs were excluded. Exclusion criteria specific to the functional magnetic resonance imaging (fMRI) scanning also included spectacles, heart pacemaker, mechanical heart valve or any mechanical implants, potential pregnancy, and claustrophobia. Participants gave written informed consent and were reimbursed for their time and traveling expenses. The study was undertaken with ethics approval granted by the Oxfordshire Psychiatric Research Ethics Committee.

### Procedure

The study took place using a between-groups, double-blind, randomized design with two groups: (a) reboxetine (administered with a single oral dose [4 mg] of reboxetine on one day) and (b) matched placebo capsule. These groups were matched with respect to age (reboxetine group:  $M = 28.1$  years,  $SD = 3.0$ , placebo group:  $M = 26.5$  years,  $SD = 4.5$ ), sex (7 men and 5 women in each group), and IQ, as measured with the National Adult Reading Test (NART; Nelson, 1982) (test score:  $M = 118.2$ ,  $SD = 9.2$  for the reboxetine group,  $M = 113.7$ ,  $SD = 8.2$  for the placebo group).

Participants attended the hospital having fasted for 3 hours prior to and during study participation to ensure similar rates and levels of reboxetine absorption. They were briefed on scanner safety and gave written consent before the study commenced. The NART, the Beck Depression Inventory (BDI; Beck & Steer, 1993) and the State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1970) were administered at baseline, that is, before the administration of the drug (time  $-15$  min). Mood and subjective state were monitored at baseline,  $+90$  min (before entering the scanner), and  $+300$  min (at the end of the study). Saliva samples were also taken at the same times in order to measure cortisol levels, which are indicative of central norepinephrine levels, and thus reboxetine absorption. Previous work has shown that levels of salivary cortisol peak approximately 2 hr after the administration of reboxetine and remain elevated for at least 2 hr (Hill, Taylor, Harmer, & Cowen, 2003). Psychological testing therefore began 2 hr after the administration of the drug. Participants were given three tasks in the fMRI scanner. This study reports the effects of reboxetine on neural responses during autobiographical remembering. The additional task results have been reported elsewhere (Miskowiak et al., 2007).

### fMRI Task Design

A version of the validated behavioral AMT (Williams & Broadbent, 1986) was used to test for the neural modulation of a.m. Therefore, the a.m. fMRI task is a novel task. A block design was used, with each of the 12 blocks (20 s) consisting of the presentation of a single word (positive, neutral, or negative). The cues were presented visually on screen in a fixed order, with positive, negative, and neutral words alternating (i.e., *nice*, *alone*, *agility*, *tender*, *insult*, *carry*, *kindness*, *dismal*, *client*, *sweet*, *nasty*, and *ginger*), each word presented only once. Participants were asked to recall a specific memory, that is, a memory for an event that lasted less than a day and that occurred at a particular time and place, in response to each cue word. They were asked to press a button as soon as they had retrieved a specific memory and to hold that memory in mind until the word disappeared from the screen. Response time, as an indicator for memory speed, was recorded. After each of the words, a nonword (e.g., *Hwvbxqda*, *Aopexma*, *Iuopwvaq*) appeared on the screen and participants were asked to press a button as soon as they had silently counted the number of letters in the nonsense word. This was a way of displacing the memory so that participants would discontinue thinking about the same event. Neural activation during these blocks was entered as baseline activation into the fMRI analyses reported below. In total, the experimental run lasted approximately 10 min. Prior to the experiment, a training session took place outside the scanner and participants practiced with three neutral words (i.e., *newspaper*, *rain*, and *milk*) and were encouraged to keep searching for a memory until they reported a specific one. All participants were debriefed after exiting the scanner and were asked to report their

<sup>1</sup> This is the same cohort as that used in the Miskowiak et al. (2007) study. Data on National Adult Reading Test scores, salivary cortisol levels, mood and subjective state, as well as the data for the control stimulation task have been also published there. All other data (including graphs, tables, and figures) are previously unpublished.

memories in order to ensure that they had performed the task as required.

### Mood and Subjective State

Mood and subjective state were monitored at  $-15$ ,  $+90$ , and  $+300$  min, by means of the visual analog scale (VAS; Bond & Lader, 1974), the STAI (Spielberger et al., 1970), and the Befindlichkeits Scale (BFS; von Zerssen, Strian, & Schwarz, 1974). The VAS measures happiness, sadness, disgust, anger, fright, anxiety, and alertness, using VASs. The BFS provides a measure of normal variation in mood and energy by asking participants to check one word of a word pair that best describes their current state (e.g., carefree vs. brooding). Monitoring mood and subjective state were used to control effects related to possible major shifts of mood during the experiment. The BDI and the STAI allowed controlling for significant differences in mood between groups.

### Salivary Cortisol

Saliva samples were obtained at  $-15$ ,  $+90$ , and  $+300$  min, in order to confirm the absorption of reboxetine at the time of testing. Salivary cortisol was measured using an in-house double antibody radioimmunoassay (intra- and interassay coefficients of variation were 3% and 10%, respectively; lower limit of detection was 0.5 mmol/L).

### Control Stimulation Paradigm

Neural activation was assessed with a control visual stimulation paradigm, in order to test whether any drug-related effects on neuronal responses during the AMT were not due to global effects of reboxetine on baseline blood flow or neuronal coupling. A flashing checkerboard (frequency = 8 Hz) was presented in blocks of 21 s alternating with 21 s of a fixation cross for a total of 8 cycles, during which time participants were instructed to lie with their eyes open.

### fMRI Data Collection

Imaging was performed at the University of Oxford Centre for Clinical Magnetic Resonance Research Unit, at the John Radcliffe Hospital in Oxford, by using a whole body 1.5-T scanner (Siemens Sonata Medical Systems) with a standard quadrature birdcage head coil. The structural scans were acquired with a 3-dimensional T1-weighted FLASH sequence for each subject (repetition time [TR] = 12 ms, echo time [TE] = 5.6 ms, flip angle =  $19^\circ$ , 1-mm isotropic voxels, matrix =  $256 \times 160 \times 208$ ; elliptical sampling, orientation = coronal, acquisition time = 5 m 14 s) to facilitate later co-registration of the fMRI data into standard space. Functional images were acquired in the form of 32 T2\*-weighted echoplanar imaging slices (TR = 3 s, TE = 50 ms, matrix =  $64 \times 64$ ), 3 mm<sup>3</sup> isotropic voxels. A total of 180 volumes were acquired during the AMT. The first two volumes in each task session were discarded to allow for T1 equilibrium to be reached.

### fMRI Data Analysis

A general linear model of hemodynamic responses was used. Analysis was carried out using FMRI Expert Analysis Tool, Ver-

sion 5.98, part of FSL (FMRIB's Software Library, available at <http://www.fmrrib.ox.ac.uk/fsl>). Data from one volunteer (reboxetine group) was excluded because of structural brain abnormality. The following prestatistics processing was applied: motion correction using Motion Correction FMRIB's Linear Image Registration Tool (Jenkinson, Bannister, Brady, & Smith, 2002), non-brain removal using Brain Extraction Tool (Shastri, 2002), spatial smoothing using a Gaussian kernel of full-width half-maximum of 5 mm; and mean-based intensity normalization of all volumes by the same factor; high-pass temporal filtering (Gaussian-weighted least-squares straight-line fitting (LSF), with  $\sigma = 50.0$  s). Time-series statistical analysis was carried out using FMRIB's improved linear model, with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). We thresholded  $z$  (Gaussianized T/F) statistic images using clusters determined by  $z > 2.0$  and a (corrected) cluster significance threshold of  $p = .05$  (Worsley, 2003). Registration to high resolution and/or standard images was carried out using the FMRIB's Linear Imaging Registration Tool (Jenkinson & Smith, 2001; Jenkinson, Bannister, Brady, & Smith, 2002). The three block types (neutral, negative, and positive) were modeled and compared to each other as well as to the baseline blocks (nonword blocks).

In the second-level analysis, whole brain individual data were combined at the group level (reboxetine vs. placebo) using a mixed-effects group cluster analysis corrected for multiple comparisons based on Gaussian random field theory, with  $z$  (Gaussianized T/F) statistic images thresholded using  $z > 2.0$  and a (corrected) cluster significance threshold of  $p = .05$  (Worsley, 2003). Corresponding Brodmann areas were identified by transforming Montreal Neurological Institute coordinates into Talairach space (Talairach & Tournoux, 1988). The data were analyzed to elucidate the main effect of task across all volunteers, the main effect of drug group irrespective of emotion condition, and the interaction between group and emotion condition.

For regions where a significant effect was observed, the percent blood-oxygen-level-dependent (BOLD) signal change was extracted and examined with analysis of variance (ANOVA). 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 versus placebo within a region of the occipital (calcarine) cortex consistently activated by photic stimuli (Maldjian, Laurienti, Kraft, & Burdette, 2003).

### Statistical Analysis of Behavioral and Hormonal Data

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

Retrieval-time data were also analyzed using repeated-measures ANOVA with group and valence as factors. One participant was excluded from the retrieval-time data analysis (placebo group), because the button was repeatedly pressed immediately after the word had been presented. The volunteer later indicated that she pressed the button as soon as she had read the word, rather than when the memory had been recalled. The volunteer with the brain structure anomaly (reboxetine group) was also excluded from the retrieval-time data analysis.

## Results

### Mood Assessment

Volunteers in the two groups were similar in terms of initial BDI and STAI scores ( $ps > .13$ ). No significant mood changes took place throughout the study for either group ( $ps < .24$ ), replicating previous findings that acute administration of antidepressants does not affect mood in healthy volunteers (Harmer et al., 2003). However, alertness was increased 300 min following reboxetine administration,  $F(1, 22) = 5.59, p = .03$ .

### Cortisol Responses

Baseline salivary cortisol levels were similar (reboxetine group  $M = 15.71$  mmol/L,  $SD = 6.22$ , vs. placebo group  $M = 15.08$  mmol/L,  $SD = 6.05$ ). The reboxetine group had significantly increased cortisol levels compared to the placebo group at +90 min (reboxetine group  $M = 17.48$  mmol/L,  $SD = 6.67$ ; placebo group  $M = 11.57$  mmol/L,  $SD = 4.72$ ) and +300 min (reboxetine group  $M = 14.85$  mmol/L,  $SD = 5.29$ ; placebo group  $M = 9.29$  mmol/L,  $SD = 3.76$ ),  $F(1, 22) = 6.62, p = .02$ , in line with the expected neuroendocrine effects of the drug.

### Behavioral Data

**Retrieval times.** Reboxetine-treated individuals showed increased memory retrieval speed compared to those given placebo,  $F(1, 20) = 4.29, p = .05$  (reboxetine group  $M = 5.40$  s,

$SD = 2.95$ ; placebo group  $M = 7.25$  s,  $SD = 2.92$ ). There was also a main effect of valence,  $F(2, 40) = 3.15, p = .05$  (neutral words  $M = 5.67$  s,  $SD = 2.35$ ; positive words  $M = 6.72$ ,  $SD = 2.63$ ; negative words  $M = 6.59$ ,  $SD = 2.29$ ), but no interaction between group and valence ( $p = .83$ ). Pairwise comparisons using the least significant difference adjustment showed that the effect of valence was due to the mean recall time for neutral words being significantly faster than the mean recall time for positive words ( $p = .04$ ). Across all participants, memories were retrieved within 10 s in 90% of trials. For the remaining 10% of trials, memories were retrieved within a reasonable time of 13.5 s ( $SD = 2.5$ ) and therefore these trials were not excluded from analyses. Moreover, the trials needing more than 10 s for memory retrieval were spread equally between conditions and valences.

### Task- and Group-Related BOLD Change of a.m. Recall

**Main effect of task.** Across all participants, a.m. recall was related to significant activation in the left inferior frontal gyrus (Brodmann area 47), the left posterior cingulate gyrus (Brodmann area 23), the right hippocampus, and the left lateral occipital cortex (Brodmann area 39) (see Table 1 and Figure 1). Moreover, activation was found in the anterior cingulate gyrus (Brodmann area 25), the left posterior cingulate/parietal cortex (Brodmann area 29), and the thalamus for the contrast between positive versus negative words. No significant clusters were found for the comparison between negative versus positive words.

Table 1

*Peak Cluster Activation in Brain Regions of Significantly Increased BOLD Response During Autobiographical Memory Recall Across All Subjects (Main Effect of Task) and Effects of Reboxetine (Interaction)*

Contrast and region	Brodmann area	x	y	z	z statistics	Voxels
<i>Main effect of task</i>						
Words vs. baseline						
Left inferior frontal gyrus	47	-54	26	-6	5.48	6,697
Left posterior cingulate gyrus	—	-12	-54	8	5.22	2,127
Right hippocampus	—	34	-44	2	5.19	1,265
Left lateral occipital cortex, superior division	39	-46	-68	28	4.10	776
Positive vs. negative words						
Medial anterior cingulate gyrus	25	2	32	2	4.32	1,636
Left posterior cingulate/parietal cortex	29	-12	-44	14	3.43	581
Left thalamus	—	-22	-16	18	3.65	525
Right thalamus	—	20	-26	14	3.44	466
<i>Main effect of reboxetine</i>						
Words vs. baseline (increase reboxetine)						
Frontal medial cortex	11	-2	38	-16	3.51	589
Words vs. baseline (decrease reboxetine)						
Right posterior cingulate gyrus	30	6	-50	20	4.51	11,057
Right occipital cortex	18	20	-90	-6	3.16	1,790
<i>Task × reboxetine interaction</i>						
Positive vs. negative words (decrease reboxetine)						
Left frontal lobe extending into insula	48	-32	-10	28	3.45	474
Left insula	48	-32	-6	30	3.44	
Left middle frontal gyrus	48	-26	6	30	3.28	
Left caudate nucleus	—	-20	0	14	3.23	
Right superior temporal gyrus	48	42	-30	4	3.80	463

*Note.* Montreal Neurological Institute coordinates ( $x, y, z$ ) refer to peak activation within each cluster identified thresholded at  $z = 2.0$  and  $p < .05$ , corrected. BOLD = blood-oxygen-level-dependent.

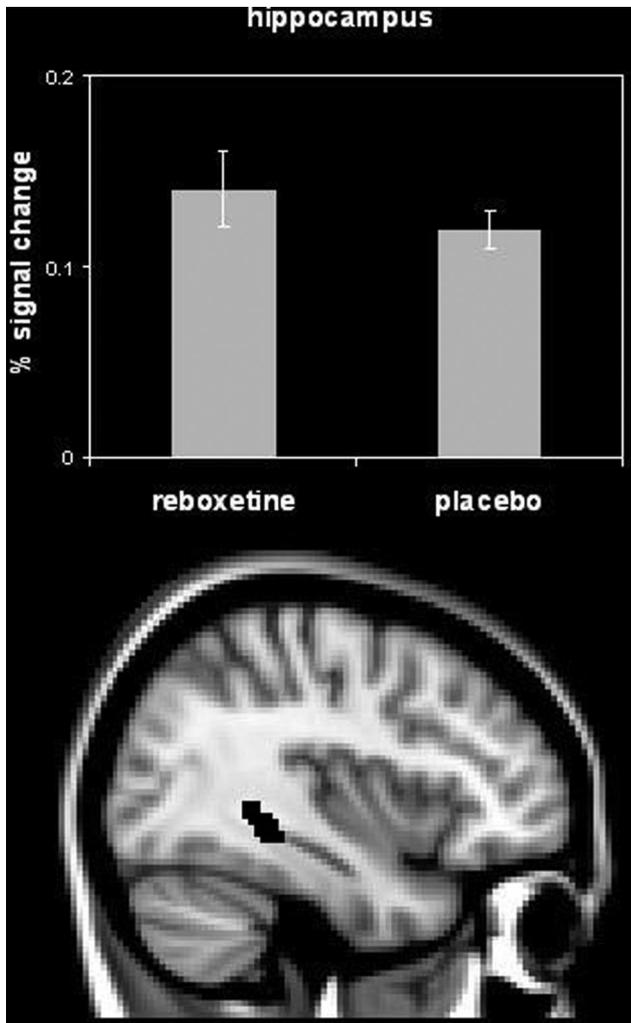


Figure 1. Neural response during the recollection of autobiographical memories modeled against baseline (nonword blocks) under reboxetine and placebo. The marked area is localized in the hippocampus.

**Main effect of group.** The whole brain analysis revealed that, compared to the placebo group, participants in the reboxetine group showed increased activation in the left frontal medial cortex (Brodmann area 11) and decreased activation in the right occipital cortex (Brodmann area 18) and in the right posterior cingulate gyrus (Brodmann area 30) during a.m. recall (see Table 1 and Figure 2). Two-way ANOVAs for the extracted mean percent signal change in each of these three areas, including group (reboxetine, placebo) and sex as factors, revealed no main effect of sex,  $F_s(1, 19) < .13$ ,  $p_s > .582$ , and no interaction of sex with the effects of the drug,  $F_s(1, 19) < .62$ ,  $p_s > .442$ .

**Group  $\times$  Task interactions.** The whole brain analysis revealed that reboxetine was related to a significant decrease in activation during a.m. recall cued by positively versus negatively valenced words in the left frontal lobe (this area consists of several functional subareas, with three local maxima: the left insula, the left middle frontal gyrus, and the left caudate nucleus extending into the putamen) and the right superior temporal gyrus compared

to placebo (see Table 1 and Figure 3). Extraction and analysis of mean percent signal change in the frontal lobe revealed a significant Group  $\times$  Valence (positive vs. negative) interaction,  $F(1, 21) = 78.08$ ,  $p < .001$ , driven by a specific decrease in neuronal activation during memories cued by positively valenced words,  $t(21) = 3.91$ ,  $p = .001$ , and an increase in neuronal activation during memories cued by negatively valenced words,  $t(21) = 3.49$ ,  $p = .002$ , under reboxetine versus placebo. In the superior temporal gyrus, extraction and analysis of mean percent signal change similarly revealed a significant Group  $\times$  Valence (positive vs. negative) interaction,  $F(1, 21) = 34.08$ ,  $p < .001$ , driven by a specific decrease in neuronal activation during memories cued by positively valenced words,  $t(21) = 2.64$ ,  $p = .015$ , and an increase in neuronal activation during memories cued by negatively valenced words,  $t(21) = 2.32$ ,  $p = .030$ , under reboxetine versus

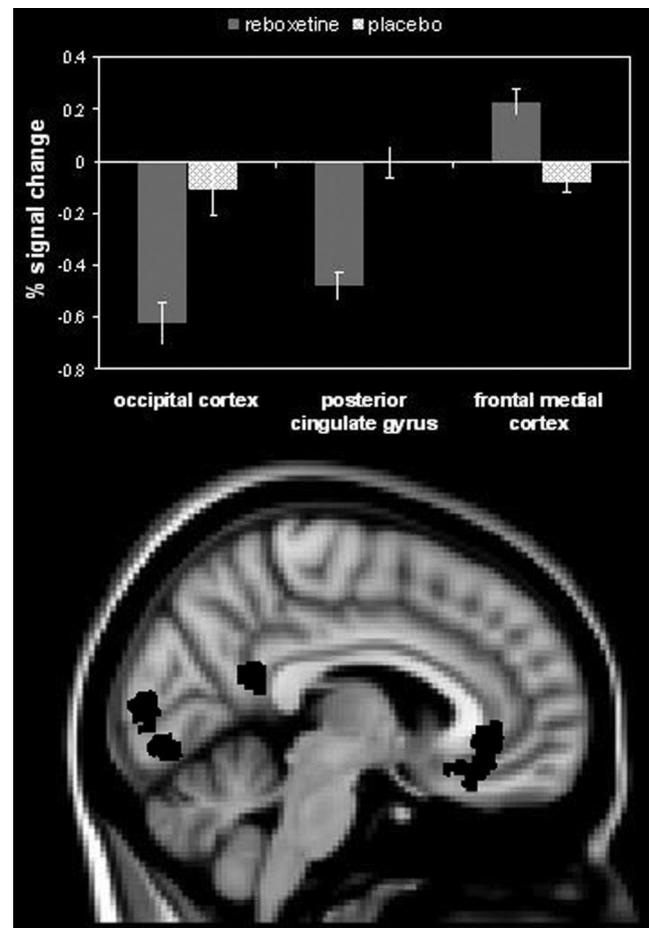
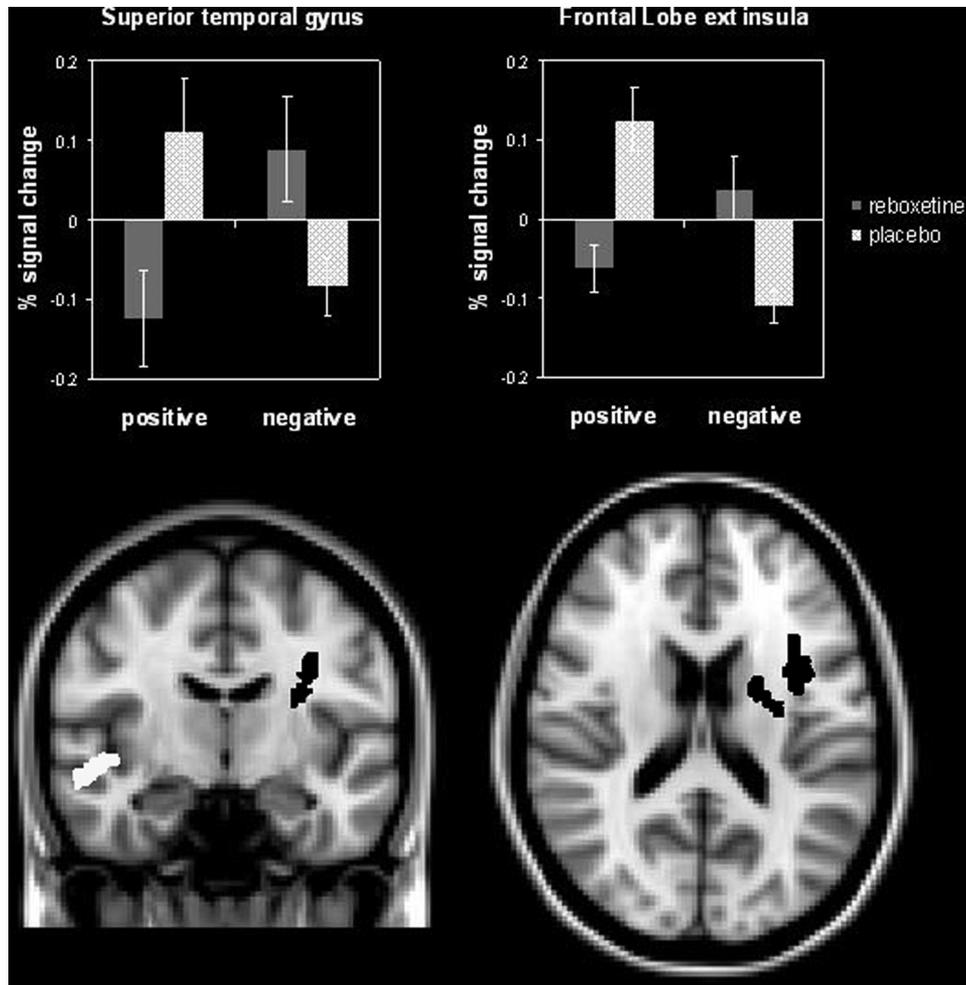


Figure 2. Neural responses during the recollection of autobiographical memories under reboxetine and placebo. Images were thresholded at  $z = 2.0$ ,  $p = .05$ , corrected. The plot shows the mean percent blood-oxygen-level-dependent signal change during recollection of positive and negative autobiographical memories in the regions related to a significant main effect of reboxetine (marked areas). Error bars show the standard error of the mean. Compared to the placebo group, participants in the reboxetine group showed increased activation in the left frontal medial cortex and decreased activation in the right occipital cortex and in the right posterior cingulate gyrus.



*Figure 3.* Neural responses during the recollection of autobiographical memories in response to positive versus negative cue words under reboxetine and placebo. Areas marked with black were localized in the left frontal lobe (extending into the insula) and areas marked with white were localized in the right superior temporal gyrus. Images are thresholded at  $z = 2.0$ ,  $p = .05$ , corrected. The plot of mean percent blood-oxygen-level-dependent signal change during recollection of autobiographical memories is modeled against baseline (nonword blocks) in the regions of significant Drug  $\times$  Valence interaction (marked areas). Error bars show the standard error of the mean.

placebo. Neither of these interactions was influenced by sex,  $F_s(1, 19) < .29$ ,  $p_s > .600$ .

### Control Stimulation Paradigm

Analysis of mean percent BOLD signal change within the occipital region of interest during presentation of visual checkerboard stimuli revealed no differences between groups ( $p > .14$ ), suggesting that the observed effects of reboxetine were not caused by nonspecific hemodynamic changes.

### Discussion

The present results identified a network similar to that of previous studies involved in the retrieval of autobiographical memories (Svoboda et al., 2006). Furthermore, activity within this network was affected by a single dose of the antidepressant

reboxetine. In particular, reboxetine increased neural activation during the processing of negative memories while decreasing neural activation during positive memory retrieval in the left frontal lobe (extending into the insula, the caudate nucleus, and the putamen) and the right superior temporal gyrus. More general effects during the retrieval of negative and positive memories were seen in the medial prefrontal cortex, cingulate gyrus, and occipital cortex. With regard to the behavioral data, it was found that reboxetine increased the speed of a.m. retrieval. The current findings add to experimental evidence suggesting that reboxetine directly modulates the processing of emotional information and extends this to the retrieval of previously encoded positive and negative a.m. These effects occurred in the absence of differences in mood and anxiety levels and suggest a direct effect of drug treatment on cognitive processes important in depression.

The temporal gyrus (Brodmann area 21) is considered a core region for a.m. retrieval (Svoboda et al., 2006), with most imaging studies of a.m. reporting activation in the area (e.g., Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004; Graham, Lee, Brett, & Patterson, 2003; Markowitsch et al., 2003; Piefke et al., 2003). This activation is considered to reflect the role of the lateral temporal cortex and related regions to the semantic memory component of a.m. recall, that is, providing broad themes for the recollection of specific events and providing semantic representations related to the remembered event. Indeed, neuroimaging studies provide converging evidence for the role of the temporal cortex in semantic memory tasks, such as semantic fluency or generation tasks (Lee et al., 2002) and semantic decision making tasks (Chee, O'Craven, Bergida, Rosen, & Savoy, 1999), as well as in the retrieval of semantic information and memory for public events (Maguire, Vargha-Khadem, & Mishkin, 2001). The placebo-treated participants showed a deactivation of this area during retrieval of affectively negative memories compared to baseline, which is consistent with interruption of ongoing activity typically seen in this area during rest periods (Svoboda et al., 2006), perhaps through suppression of cognitive processes. Such a pattern may indicate, for example, that negative memories require less semantic detailing, with the emotional arousal taking a more prominent role. If so, acute antidepressant administration may enhance default cognitive processing during negative affective memory processing (Harmer, 2008; Harmer, O'Sullivan, et al., 2009) contrary to that seen in depression (Fossati et al., 2003; Sheline et al., 2001).

Reboxetine administration also affected the response of the left frontal lobe (extending into the insula, the caudate nucleus, and the putamen) during the retrieval of positive versus negative a.m. memories. This finding is consistent with previous studies that have shown that autobiographical remembering includes networks in the frontal lobes, especially during the period that the retrieval starts and even in the preretrieval phase, when the cue to begin memory search is being sought (Piefke et al., 2003). Moreover, the caudate nucleus and the putamen are relevant to learning and memory, and they have been recently associated with increased memory sensitivity for negative stimuli in major depression (Hamilton & Gotlib, 2008). Although areas within the prefrontal cortex and the insula have been associated with negative emotion (Goldin, McRae, Ramel, & Gross, 2008; Straube & Miltner, 2011), it is of interest that volunteers receiving reboxetine tended to show increased activity levels in this circuit with recall of negative versus positive autobiographical memories. Such a pattern may occur if the volunteer has to work harder to remember details of the positive compared to the negative memories. Thus, effortful retrieval has been related to significant blood flow increase in frontal regions in an explicit memory task in which effort to recall an event was dissociated from the actual recollection of it (Schacter, Alpert, Savage, Rauch, & Albert, 1996), and to increased positivity at frontal sites in a face recognition task using event-related potentials (Itier & Taylor, 2002). Rugg and Wilding (2000) have further 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. The further finding that reboxetine reversed this pattern of activation also implies that this drug treatment may decrease retrieval effort for personally experienced positive versus negative a.m.

In addition to the specific effects of reboxetine in the recollection of positive versus negative memories, more general effects during the retrieval of negative and positive memories were found in the medial prefrontal cortex, cingulate gyrus, and occipital cortex. Because a nonmemory control condition was not included here, such effects are difficult to interpret, but may represent general effects of the drug on cognitive processing and/or neural reactivity. Moreover, reboxetine increased general alertness, which may have affected the cognitive process of attention. However, it is important to note that such nonspecific effects cannot account for the differences seen explicitly in the contrast between the positive and negative cued memories.

The present study investigated acute effects of the SNRI reboxetine, even though the therapeutic effect of antidepressant treatments requires chronic administration. Nevertheless, it has been argued that causal change takes place immediately, and that it is due to a time lag needed for neuropharmacological actions, such as desensitization of autoreceptors or the requirement for neurogenesis, as well as time needed for social reinforcement that symptom amelioration is detectable after weeks of antidepressant administration (Harmer, 2008). Therefore, a therapeutic delay should not be taken to assume that a clinical benefit is not present after a single dose of an antidepressant (Harmer, O'Sullivan, et al., 2009) or that acute effects are not representative of effects of chronic drug administration. Indeed, these findings have implications for understanding the constituents of psychopharmacological mechanisms of antidepressant actions. This understanding is important for the development of models of emotional processing that may be useful in drug development and screening (Harmer, O'Sullivan, et al., 2009).

## Study Limitations

There were a number of limitations to the current study. First, although assessment of healthy volunteers allows us to explore the effects of drug treatment unconfounded by changes in mood, these findings need to be replicated in acutely depressed patients to help understand their clinical relevance, following the replication of such effects using lab-based stimuli in depressed patients early in treatment (Harmer, O'Sullivan, et al., 2009). In addition, each person has his or her own unique memories of their life experiences and hence they provided different responses, which may have led to differences in neural responses. Moreover, as pointed out by Markowitsch et al. (2003), fresh experiences may have more detail and vividness, whereas old experiences may still be remembered exactly because of their emotional severity, and this was not controlled for in the current study. It will also be important to establish whether an effect of reboxetine can be seen on behavioral measures of autobiographical memory retrieval. This will help us test the interpretation of the directional effects seen here. Another limitation is that menstrual cycle phase, which can influence responses in the arousal circuitry, was not controlled for in normally cycling women (Cosgrove, Mazure, & Stanley, 2007; Goldstein et al., 2005; Weis & Hausmann, 2010). Moreover, the number of oral contraceptive users was not recorded. Future studies might also consider a within-subjects design, whereby placebo participants would receive a single dose of reboxetine and perform the task again on a different day with a new set of words, and,

similarly, the reboxetine group would get the placebo for testing on a different day.

## Conclusion

The current results suggest that reboxetine increases the speed of a.m. retrieval and enhances neural responses in areas involved in cognitive processing during the retrieval of positive versus negative experiences. These effects are consistent with behavioral effects of reboxetine seen in negative bias tasks (Harmer et al., 2003; Harmer, Shelley, Cowen, & Goodwin, 2004) and extend these effects to personally experienced a.m. processes. Antidepressants may make patients with depression feel better because they make it easier to recall positive specific memories and more effortful to recall negative events (the arguments, failures, and disappointments of the past). If such negative events are not being constantly rehearsed, they have a greater chance of being forgotten.

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