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Effects of antidepressant treatment on neural correlates of emotional and neutral declarative verbal memory in depression

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Abstract

Background—Multiple studies have documented deficits in verbal declarative memory function in depression that improve with resolution of symptoms; imaging studies show deficits in anterior cingulate function in depression, a brain area that mediates memory. No studies to date have examined neural correlates of emotionally valenced declarative memory using affectively negative (sad) verbal material that is clinically relevant to understanding depression. Also no studies have examined the effects of treatment on neural correlates of verbal declarative memory. The purpose of this study was to examine the effects of treatment with antidepressants on verbal declarative memory in patients with depression.

Methods—Subjects with ($N=18$) and without ($N=9$) mid-life major depression underwent positron emission tomography (PET) imaging during verbal declarative memory tasks with both neutral paragraph encoding compared to a control condition, and emotional (sad) word pair retrieval compared to a control condition. Imaging was repeated in 13 subjects with depression after treatment with antidepressants.

Results—Patients with untreated depression had a failure of anterior cingulate activation relative to controls during retrieval of emotional word pairs. Antidepressant treatment resulted in increased anterior cingulate function compared to the untreated baseline for both neutral and emotional declarative memory.

Limitations—Limitations include a small sample size and variety of antidepressants used.

Conclusions—These results are consistent with alterations in anterior cingulate function that are reversible with treatment in patients with depression. These findings may have implications for understanding the mechanism of action of antidepressants in the treatment of depression.

Keywords

PET; Memory; Depression; Cingulate; Frontal cortex

1. Introduction

Major depression is an important public health problem that affects about 16% of the population at some time in their lives (Kessler et al., 2003) and is associated with considerable loss of economic productivity (Stewart et al., 2003). One of the most disabling aspects of depression is deficits in cognitive function. Patients with depression have impairments in both verbal declarative memory function, as shown by deficits in paragraph recall and word list learning, as well as a preference for remembrance of words with negative or depressive content (Burt et al., 1995; Cohen et al., 1982; Danion et al., 1991; Roy-Byrne et al., 1986; Sternberg and Jarvik, 1976; Weingartner et al., 1981). The preference for recall of sad emotionally valenced declarative memory suggests an alteration in cognitive processing of emotionally valenced material. Although cognitive deficits in depression were long felt to represent “pseudo-dementia” or a failure of effort, imaging studies now suggest that changes in the brain that may be responsible for these findings (Alexopoulos et al., 1993; Rothschild et al., 1989).

Brain imaging studies in depression have shown alterations in brain regions involved in memory, including the prefrontal cortex and hippocampus (Bremner, 2002; George et al., 1994; Soares and Mann, 1997). Areas of prefrontal cortex implicated in depression include dorsolateral prefrontal cortex (involved in working memory) and medial prefrontal cortex, which consists of several related areas, including orbitofrontal cortex, anterior cingulate (area 25 — subcallosal gyrus, area 24—subgenual gyrus, and area 32—the “Stroop” area), and anterior prefrontal cortex (area 9). These areas were shown in animal and human studies to be involved in the stress response and modulation of emotion (Damasio et al., 1994; Devinsky et al., 1995). Studies have also shown smaller volume of the hippocampus and orbitofrontal cortex in depression (Bremner, 2002).

Multiple PET and SPECT studies found decreased metabolism and/or blood flow in subregions of prefrontal cortex including left (Baxter et al., 1989; Bench et al., 1992; Mann et al., 1996; Martinot et al., 1990) and bilateral (Biver et al., 1994; Mayberg, 1994; Mayberg et al., 1994) dorsolateral prefrontal cortex, medial prefrontal cortex/anterior cingulate (including Brodmann’s areas 25 and 24 (Biver et al., 1994; de Asis et al., 2001; Drevets et al., 1997; George et al., 1997, 1994; Mayberg et al., 1997, 1993, 1990; Ring et al., 1994) and orbitofrontal cortex (Mayberg et al., 1993, 1990; Ring et al., 1994) in patients with untreated depression at baseline. Other studies found alterations in amygdala function (Drevets et al., 2002; Sheline et al., 2001). Positive treatment response to psychotherapy and selective serotonin reuptake inhibitors (SSRIs) is associated with changes in frontal, cingulate, hippocampal, and temporal lobe function (Brody et al., 2001; Mayberg et al., 2000; Saxena et al., 2003; Smith et al., 2002). We also found decreased dorsolateral prefrontal and orbitofrontal cortical function with experimentally induced depressive relapse provoked by serotonin (Bremner et al., 1997) or norepinephrine depletion (Bremner et al., 2003a). Other studies showed blunted anterior cingulate function with the Stroop task (George et al., 1997) or memory tasks (de Asis et al., 2001), and alterations in prefrontal cortical function during processing of emotionally valenced material (George et al., 1994).

We recently found a failure of hippocampal and anterior cingulate activation during a paragraph encoding declarative memory task (Bremner et al., 2004). Imaging findings in depression to date are therefore consistent with dysfunction of prefrontal (specifically anterior cingulate) function in depression. A gap in the literature has been the use of cognitive tasks as probes of brain regions implicated in depression. Studies have also not examined the effects of treatment on neural correlates of cognition in patients with depression. The purpose of this study was to measure neural correlates of an emotionally valenced (sad) verbal declarative memory task in patients with mid-life depression and

controls, and to assess the effect of treatment with antidepressants on neural correlates of declarative memory in patients with depression. We hypothesized decreased anterior cingulate function with emotional verbal declarative memory tasks in subjects with depression compared to subjects without depression, and increased anterior cingulate function in subjects with depression following treatment with antidepressants.

2. Methods

2.1. Subjects

Twenty seven men and women participated in the study, including 9 subjects without a history of major depression and 18 with mid-life depression. Data from this sample has been previously reported on neural correlates of neutral paragraph encoding in the pre-treatment state (Bremner et al., 2004); the current sample comprised a group that overlapped with a larger sample of patients with depression evaluated with measures of neuropsychological testing, cortisol, and MRI based hippocampal volume before and after treatment (Vythilingam et al., 2004). The project was approved by the Yale University Human Investigation Committee. All subjects were recruited through newspaper advertisement. Diagnosis of major depression was established with the Structured Clinical Interview for DSMIV (SCID) (First et al., 1995). All subjects gave written informed consent for participation, were free of major medical illness on the basis of history and physical examination, lab testing, and electrocardiogram, were not actively abusing substances or alcohol (past six months) and were free of all medications for at least four weeks prior to the study. Subjects were not taken off of medication for the purposes of participating in the study. Subjects with a serious medical or neurological illness, organic mental disorders or co-morbid psychotic disorders or PTSD, a history of childhood trauma as measured with the Early Trauma Inventory (ETI) (Bremner et al., 2000), current or past history of alcohol or substance abuse or dependence, retained metal, a history of head trauma, loss of consciousness, cerebral infectious disease, or dyslexia were excluded.

Demographic variables were similar between the healthy subjects and patients with depression. There were no differences in age or years of education (Table 1). Seven out of nine (78%) of the healthy subjects were female and 12/18 (67%) of the patients with depression were female. Patients with depression had 17 mean years of depression. Fourteen out of 18 (78%) had a history of recurrent depression.

2.2. Study measures

Level of depressive symptomatology before and after treatment was assessed with the Yale Depression Inventory (YDI), a reliable and valid measure of depressive symptoms (Mazure et al., 1990). Anxiety was measured with the Hamilton Anxiety Scale, a reliable and valid measure of anxiety (Hamilton, 1959). Intelligence Quotient (IQ) was assessed with the Wechsler Adult Intelligence Scale Revised (WAIS-R) (Wechsler, 1981) using four subtests as previously described (Vythilingam et al., 2004), and baseline memory (outside of the scanner) was assessed using the Wechsler Memory Scale Revised (WMS-R) (Wechsler, 1987). Data on IQ and memory was previously reported in most of the patients in a paper of which the current sample was an overlapping subset (Vythilingam et al., 2004). Patients with depression had higher levels of depression and anxiety, and poorer memory performance on the WMS (Table 1). There were no statistically significant differences in IQ (Table 1).

Current and lifetime psychiatric diagnoses were evaluated with the Structured Clinical Interview for DSMIV (First et al., 1995). All of the depressed patients had current and lifetime unipolar major depression. Three of the patients (17%) had depression with

melancholia; none had atypical depression. Two out of 18 depression patients (11%) fulfilled criteria for a lifetime history of dysthymia and 1/18 (6%) a current history of dysthymia based on the SCID interview. Five out of 18 (28%) had new onset major depression, the rest (72%) had recurrent major depression. None of the subjects had a current or past history of any other co-morbid psychiatric disorder or alcohol or substance abuse or dependence.

2.3. Treatment

Thirteen subjects with depression who were treatment responsive successfully completed the post-treatment scan after an open label course of treatment with antidepressants on a variable dose. Twelve patients were started on fluoxetine and one on venlafaxine (because of a history of prior treatment failure with fluoxetine). Fluoxetine was initiated at 20 mg/day and the dose increased to 40 mg after 4 weeks in the absence of clinical improvement. Venlafaxine was started at 75 mg/day and increased to 150 mg/day or 300 mg/day based on clinical response. One patient was switched from fluoxetine to venlafaxine and later sertraline (150 mg/day) because of lack of treatment response, and one was switched from fluoxetine to venlafaxine because of side effects. Four subjects dropped out due to noncompliance or treatment non-response. The mean duration of treatment was 6 ± 3 months. Mean dose of fluoxetine was 30 ± 10 mg/day (20–40 mg/day) and of venlafaxine 225 ± 75 mg/day (75–300 mg/day). All responders underwent a second PET scan after successful treatment with antidepressants. Fourteen subjects completed treatment with a good response and completed their followup PET scan. One of these PET scans could not be used for technical reasons. Treatment completers with useable scans included 11 women and 2 men. Treatment response was defined as a post-treatment absence of DSMIV based major depression, and judgment of improved or very much improved on the Clinical Global Improvement (CGI) scale. All treatment responding completer subjects had a greater than 15 point decrease in the Yale Depression Inventory. Mean post-treatment YDI score in the study completers was 3 (3 SD).

2.4. Memory task

Six lists of word pairs and two paragraphs were prepared for administration in conjunction with positron emission tomography (PET) imaging. Each list contained 10 word pairs. The first two lists contained ten neutral word pairs used for a control condition (shallow encoding), list 3 contained 10 neutral word pairs used as active condition (deep encoding) which were different than lists 1 and 2, list 4 contained the same word pairs as list 3 but in different order, list 5 contained 10 emotional (sad) word pairs that were also deeply encoded, and list 6 contained the same word pairs as list 5 but in different order. Word pair lists for neutral and emotional (sad) deep encoding are presented in Table 2. The words consisted of nouns, adjectives and verbs in common English usage. The “emotional” words were selected to be words in common usage that have a sad or depressive content. In this paper the word “emotional” is used to indicate sad or depression-related emotions, i.e. the word lists were not designed to represent other emotions such as love or happiness or fear. All words were frequently used in the English language (Zettersten, 1978). There were an equivalent number of syllables in the neutral and emotional word lists. Emotional words had higher “sad” ratings on an analogue scale (0 to 4, with 4 being “extremely sad”) compared to the neutral words in field testing in healthy human subjects using methods previously described (Bremner et al., 2001). Sad words were rated 0.63–2.65 in sadness, with neutral words 0–0.92. Although some of the words in the neutral category had some emotional content, there was minimal overlap in the ratings of emotional valence between the groups. The technique for developing and assessing emotionally valenced words is described in greater detail elsewhere (Bremner et al., 2003b).

2.5. PET imaging

Word pair lists were presented followed by recall during PET imaging. Word pair lists were read over one minute out loud in a normal tone of voice by a research associate at the rate of one word pair every 6 s. For the shallow encoded neutral word pairs, subjects were read the first two neutral word pair lists and were asked to count the number of times they heard a word which contained the letter “D”. This was followed by a PET scan acquisition during the attempted retrieval of the first list of shallow encoded neutral word pairs. Subjects were asked to provide the missing word of the pair with the instructions “for instance if I said Gold–West, and now I said Gold, you would say (‘West’)”. The PET scan was repeated during retrieval of the second shallowly encoded neutral word list. For the neutral deeply encoded word pair condition, subjects were instructed to try to remember word pairs, and were read a new list of ten neutral word pairs (e.g. metal–iron) followed 5 min later by PET imaging during retrieval. This was repeated for a second list of deeply encoded neutral word pairs. For the emotional deeply encoded condition, subjects were instructed to remember, and then were read ten word pairs with emotional content (e.g., evil–death), followed 5 min later by PET imaging of the brain during retrieval. They were then read a second list of emotional words, followed 5 min later by PET imaging of the brain during attempted retrieval. Subjects then underwent PET imaging while listening to a neutral paragraph. Prior to the scan, subjects were asked to try and remember the content of the paragraph and form an image of the scene in their mind. This was repeated for a second paragraph. Accuracy of recall was recorded for all word lists and conditions.

PET imaging was performed on a Posicam PET camera (Positron Corp) (in plane resolution after filtering, 6 mm FWHM, axial resolution 13 mm). The subject was placed in the scanner with their head held in a holder to minimize motion and positioned with the canthomeatal line parallel to an external laser light. An intravenous line was inserted for administration of [^{15}O] H_2O . Following positioning within the camera gantry, a transmission scan of the head was obtained using an external $^{67}\text{Ga}/^{68}\text{Ge}$ rod source, in order to correct emission data for attenuation due to overlying bone and soft tissue. Ten seconds before administration of [^{15}O] H_2O subjects received instructions regarding the task. This was followed by the beginning of the reading of the word pairs which was 60 s in duration. At the same time of the beginning of the reading of the word pairs subjects received a bolus injection of 30 mCi of [^{15}O] H_2O followed 10 s later by a PET scan acquisition which was 60 s in length. The onset of the PET scan acquisition was timed to correspond to the point of maximum rate of increase in uptake of tracer into the brain.

According to the logic of the study design, differences in brain blood flow between the control (shallow encoded) word pairs and the neutral word pairs, and the control (shallow encoded) and the emotional (sad) word pairs, would be secondary to the specific effects of retrieval of word pairs, while keeping other factors equal, including attention, auditory perception, and comprehension of verbal material. Differences in blood flow between retrieval of emotional and neutral word pairs would be specific to the neural correlates of retrieval of emotionally valenced (sad) words, while other factors are controlled including attention, auditory perception, and comprehension of verbal material, as well as success of memory retrieval (Fig. 1).

2.6. Image processing and analyses

Images were reconstructed and analyzed on a SunSparc Workstation using statistical parametric mapping (spm96) (www.fil.ion.ucl.ac.uk/spm) and Matlab software (Mathworks, Natick MA). Images for each patient set were realigned to the first scan of the study session. The data underwent transformation into a common anatomical space and was smoothed with a 3-dimensional Gaussian filter to 16 mm full-width half maximum. This yielded an image

set with 2×2×2 mm voxels. Regional blood flow with global blood flow as a covariate was compared between the two scans in the control (shallow encoding) condition and the scans in the active condition (deep neutral encoding, deep emotional encoding or paragraph encoding) in patients with depression and controls using the general linear model. The interaction between group (depression versus controls) and condition (control versus active memory conditions) was also examined using the general linear model and the multi-study with multiple subjects and replications (two scans per condition) model. First, contrasts were performed comparing blood flow during the active and control tasks within patient groups. Then contrasts were performed of increased blood flow in healthy subjects to decreased blood flow in patients, referred to as “Greater increases in healthy subjects compared to patients”. Statistical analyses yielded image data sets in which the values assigned to individual voxels correspond to *t* statistic (Friston, 1994; Friston et al., 1991). Statistical images were displayed with values of *z* score units. An uncorrected threshold *z* score of 2.58 ($p < 0.005$) was used to examine areas of activation. A *p* value of < 0.005 has been shown to represent the best trade-off between Type I and Type II errors (Reiman et al., 1997). A minimum cluster of 40 adjacent activated voxels (320 mm³) was required for a region to be considered significant. Locations of areas of activation were identified as the distance from the anterior commissure in mm, with *x*-, *y*- and *z*-coordinates, using a standard stereotaxic atlas (Talairach and Tournoux, 1988).

Eighteen patients with untreated major depression started the study and received baseline PET scans. Results for neural correlates of neutral paragraph encoding and emotional word pair retrieval were reported previously in these 18 subjects (Bremner et al., 2004). Thirteen patients received post-treatment PET scans.

Measures of memory retrieval were compared between depressed and comparison subject groups using repeated measures analysis of variance (ANOVA) with memory recall over time as the repeated measure.

3. Results

3.1. Performance on memory task performed in the PET scanner

There were no significant differences between patients with depression and controls in word pair retrieval for either the first (56% (17% SD) versus 61% (21% SD)) or the second (87% (17% SD) versus 89% (15% SD)) neutral word pairs or the first (23% (21% SD) versus 18% (17% SD)) or second (47% (22% SD) versus 46% (29% SD)) emotional (sad) word pairs.

There were no significant differences between baseline and post-treatment in memory retrieval for either the first (56% (19% SD) versus 66% (21% SD)) or the second (85% (19% SD) versus 87% (16% SD)) neutral word pairs, the first (21% (19% SD) versus 28% (13% SD)) or second (44% (21% SD) versus 55% (21% SD)) emotional (sad) word pairs, or the first (25 (6 SD) versus 27 (7 SD)) or second (28 (8 SD) versus 27 (7 SD)) paragraph.

3.2. Brain activation with memory tasks in anterior cingulate: baseline pre-treatment

Retrieval of neutral deeply encoded word pairs compared to shallowly encoded word pairs in the healthy subjects resulted in an increase in blood flow in bilateral anterior cingulate (BA 24, 32) (Table 3). Conversely, patients with depression had a decrease in anterior cingulate function (BA 32) during the deeply encoded neutral memory word pair retrieval compared to the shallowly encoded word pair retrieval. Direct comparison showed no differences between healthy subjects and depressed patients during neutral deeply encoded word pair retrieval versus shallowly encoded word pair retrieval for anterior cingulate (or any other region).

Retrieval of emotional (sad) word pairs compared to neutral deeply encoded word pair retrieval in the healthy subjects resulted in an increase in blood flow in bilateral anterior cingulate (BA 24, 32) (Table 4). Retrieval of emotional deeply encoded word pairs versus neutral deeply encoded word pairs in the patients with depression resulted in a decrease in blood flow in anterior cingulate (BA 24, 32) (Table 5). When healthy subjects were compared to depressed patients, there were greater increases in blood flow during emotional (sad) deeply encoded word retrieval compared to neutral deeply encoded word pair retrieval in anterior cingulate (24, 32) (Table 6; Fig. 2).

3.3. Brain activation with memory tasks in anterior cingulate: effects of antidepressant treatment

Antidepressant treatment in the patients with depression resulted in increased anterior cingulate function compared to the untreated baseline for both neutral paragraph encoding (Table 7) and emotional declarative memory (Table 8; Fig. 3).

3.4. Brain activations with memory tasks in comparison regions

In addition to anterior cingulate, retrieval of neutral deeply encoded word pairs compared to shallowly encoded word pairs in the healthy subjects resulted in an increase in blood flow in visual association cortex (BA 19) (Table 3). Neutral deeply encoded word retrieval versus neutral shallowly encoded word retrieval resulted in a decrease in blood flow in the healthy subjects in cerebellum. There were no changes in blood flow with neutral deeply encoded word pair retrieval versus shallowly encoded word pair retrieval in the patients with depression outside of the anterior cingulate (BA 32) blood flow.

Retrieval of emotional (sad) word pairs in the healthy subjects resulted in an increase in blood flow in left putamen, fornix, lingual gyrus, cuneus and primary and secondary visual cortex (BA 17, 18, 19) (Table 4). Emotional (sad) deeply encoded word pair retrieval compared to neutral deeply encoded word pair retrieval resulted in a decrease in blood flow in the healthy subjects in right inferior and middle frontal gyrus (BA 9, 45, 46), left hippocampus and adjacent cortex, cerebellum, right posterior cingulate (BA 31, 24, 30, 23), and left precuneus (BA 7). Retrieval of emotional deeply encoded word pairs versus neutral deeply encoded word pairs in the patients with depression resulted in an increase in blood flow in right middle frontal gyrus (BA 9) (Table 5). Emotional (sad) deeply encoded word retrieval compared to neutral deeply encoded word pair retrieval resulted in a decrease in blood flow in the depressed patients in posterior cingulate (BA 29), right caudate, cerebellum, right superior and middle temporal gyrus (BA 38, 22), uncus (BA 28, 36), left inferior parietal lobule (BA 40), left inferior frontal gyrus (BA 44), left hippocampus, and left fusiform gyrus (BA 38). When healthy subjects were compared to depressed patients, in addition to anterior cingulate, there were greater increases in blood flow during emotional (sad) deeply encoded word retrieval compared to neutral deeply encoded word pair retrieval in lingual gyrus, cuneus and visual association cortex (BA 17, 18), right precentral gyrus (BA 6), and bilateral middle frontal gyrus (BA 46, 9) (Table 6; Fig. 2). Comparison of healthy subjects with depressed patients showed greater decreases in blood flow with emotional (sad) deeply encoded word retrieval compared to neutral deeply encoded word pair retrieval in right fusiform gyrus (BA 20, 37, 36), right precentral gyrus (BA 6), right inferior parietal lobule (BA 40), right precuneus (BA 18), and right middle frontal gyrus (BA 9).

Antidepressant treatment, in addition to causing increased anterior cingulate function, caused increased visual association cortex and lingual gyrus function during neutral paragraph encoding, and increased left inferior/middle frontal gyrus function during emotional (sad) word retrieval. There was an area of left hippocampus that increased with

treatment which was smaller than the threshold for inclusion based on the size of the activation. Treatment resulted in decreased function in dorsolateral prefrontal cortex (superior/middle frontal gyrus), inferior temporal gyrus, and precuneus during both memory tasks. Additionally treatment was associated with decreased function in posterior cingulate and superior temporal gyrus during emotional word retrieval.

4. Discussion

Patients with untreated mid-life depression demonstrated a failure of anterior cingulate activation during retrieval of emotionally valenced (sad) word pairs relative to controls. Differences in neural correlates of retrieval of emotional (sad) word pairs between depressed patients and controls could not be explained by differences in success of retrieval. Treatment with anti-depressants resulted in an increase in anterior cingulate activation during both paragraph encoding and encoding of emotional word pairs. These findings are consistent with a deficit in anterior cingulate function in patients with depression that improves with treatment.

These findings suggest that decreased anterior cingulate function is associated with the negative emotional features of the task used in this study. A number of studies implicate the anterior cingulate in emotion. Because of the link between stress and depression, animal models for depression have involved exposure to stressors. The medial prefrontal dopaminergic system is one of the most sensitive areas in the brain to even mild stressors (Roth et al., 1988). This area also has important inhibitory inputs to the amygdala that mediate extinction to fear responding, which is used as an animal model of emotion. Animals with lesions of the anterior cingulate/medial prefrontal cortex are unable to extinguish fear responses after trials of fear conditioning (Morgan and LeDoux, 1995; Morgan et al., 1993). Dysfunction of the anterior cingulate/medial prefrontal cortex in patients with depression may result in an inability to modulate emotion in a normal way. We hypothesize that anterior cingulate activation is a “normal” brain response to emotional stimuli, and that a relative failure of activation is indicative of dysfunction.

Treatment of depressed patients with antidepressants resulted in an increase in anterior cingulate function for both the neutral paragraph encoding task as well as the emotional word pair retrieval. It is not clear from the current study whether the change in anterior cingulate function underlies the improvement in cognition seen with antidepressant treatment, or whether the change in anterior cingulate function merely reflects changes in the neural circuitry of brain regions that are involved in evaluation of the affective component of the encoded information.

Other brain areas outside of the anterior cingulate were examined for the purposes of hypothesis generation for future studies. Areas other than anterior cingulate that activated with memory tasks to a greater degree in controls than in patients with depression included cuneus, visual association cortex, and middle frontal gyrus. Patients with depression relied on fusiform gyrus and parietal cortex (inferior parietal lobule) to a greater degree than in controls. There were no differences between depressed patients and controls in neural correlates of retrieval of neutral word pairs. Treatment with antidepressants resulted in (in addition to anterior cingulate) increased function in ventral caudate during verbal declarative memory tasks in patients with depression. Antidepressant treatment also resulted in decreased function in dorsolateral prefrontal cortex, inferior temporal gyrus, and precuneus during memory tasks in depression. The anterior cingulate has connections with many of these brain areas which are also involved in memory and emotion.

Although we previously reported deficits in hippocampal function during paragraph encoding in depression, we did not find an increase in hippocampal function with antidepressant treatment in this study. There was a small area of increased function, although this was too small for the minimal criteria of activation. These patients are free of childhood abuse and had relatively less severe non-psychotic depressions. These and other factors could explain a lack of change in the hippocampus with treatment.

In the current study there was a pattern of poorer memory for emotional (sad) word pairs than neutral word pairs in both patients and controls. This is consistent with a prior study of recall of emotional words pairs which involved more stressful words (Bremner et al., 2003b). Prior studies have also shown that recall of emotional (sad) words is poorer than neutral words, although patients with depression show a preferential recall of depressive words (Burt et al., 1995; Roy-Byrne et al., 1986). This is likely due to the greater semantic associations of neutral words compared to emotional (stressful, depressive) words. The current sample size was not large enough to replicate prior studies showing preferential recall of depressive words in patients with depression.

There are several limitations of the current study that are worthy of mention. The fixed order of word presentation and fixed order of tasks may have led to order effects. An alternative method would be to rotate words through the different presentations in successive subjects. Order effects should not affect the primary outcome of this study, which is the comparison of pre and post-treatment. Unlike prior studies that showed deficits in memory performance between patients with depression and healthy subjects, the current study did not show such a difference. The subjects in the current study largely overlap with a larger sample that did show deficits in verbal declarative memory function that improved with treatment (Vythilingam et al., 2004), suggesting that a larger sample size may have been able to show such an association. In addition, baseline neuropsychological testing of memory outside of the scanner did show poorer memory performance in patients with depression. Healthy subjects were not scanned during the memory tasks at a second time point. We therefore cannot rule out the possibility that a practice effect from pre to post-treatment affected the results. Although we hypothesize that medication caused changes in brain function in patients with depression, since patients were on medication at the time of the second scan we cannot rule out the fact that the medication itself was responsible for the findings of this study. Some of the patients received venlafaxine, and one sertraline, during the course of the study. In addition to blocking serotonin reuptake, like fluoxetine, venlafaxine also blocks norepinephrine reuptake. Therefore we cannot conclude that the findings of the current study are specific to fluoxetine or serotonin reuptake blockade. We cannot rule out that factors such as the stress of attempting to recall the words during the control condition affected the results. There was a pattern of poorer retrieval of emotional versus neutral word pairs. Therefore we cannot evaluate whether anterior cingulate activation with emotional words is exclusively related to emotional valence or whether retrieval contributes to the findings. The words used for the emotional word pair task were related to depression. We did not evaluate other emotions, like happiness, fear, etc. Therefore we cannot conclude that the study involved an evaluation of emotion generally, outside of the specific emotions invoked by the depressive words. The sample size was small and limited the ability to look at sub groups, relationship to treatment response, or correlations between brain activity and memory function. The study was not designed to examine treatment responders versus non-responders; non-responders did not receive a followup scan after treatment. This study did not exclude subjects with smoking histories. A history of nicotine dependence could have an effect on the outcomes. Arterial lines were not employed, therefore we were unable to quantitate brain blood flow. We cannot rule out the possibility that global changes in blood flow at baseline or with treatment affected the results. Also, data was analyzed with an older version of statistical parametric mapping (spm), while newer versions of spm provide a

broader range of analysis options. Changes in volume of hippocampus and orbitofrontal cortex have been found in depression. Partial volume effects could have affected blood flow measurements in this study. Future studies with higher resolution PET devices can address these methodological issues.

In conclusion, patients with depression showed a failure of anterior cingulate activation with neutral paragraph encoding and emotional word pair retrieval tasks compared to healthy subjects, and these deficits reversed with antidepressant treatment.

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Fig. 1.

Study design of PET imaging of neural correlates of neutral and emotional declarative memory. Arrows refer to individual PET image acquisitions. There were a total of 8 image acquisitions. Learning of all word pairs took place before or in between scan acquisitions. The first two scans were acquired during retrieval of neutral shallowly encoded word pairs (NEU SHALL), followed by two during retrieval of deeply encoded neutral word pairs (NEU DEEP), two during retrieval of deeply encoded emotional word pairs (EMOT DEEP), and two during deep encoding of a neutral paragraph (NEU PAR).

Fig. 2. Statistical parametric map overlaid on an MRI template of areas of greater increases in blood flow during retrieval of emotional (e.g. “sad–devil”) compared to neutral word pairs in healthy subjects ($N=9$) compared to patients with depression ($N=18$). Areas of greater increases in blood flow included the anterior cingulate ($p<0.005$).

Fig. 3. Statistical parametric map overlaid on an MRI template of areas of greater increases in blood flow during an emotional memory task following treatment with fluoxetine compared to the baseline untreated state in patients with depression ($N=13$). Areas of greater increases in blood flow (in yellow) included the anterior cingulate ($p<0.005$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Demographic and psychometric information in patients with depression ($N=18$) and healthy subjects ($N=9$)

	Mean (SD) (or %)		F value	df	p
	Healthy subjects	Depression			
Age	35 (12)	40 (13)	1.09	1,25	0.31
Sex	7 female (78%)	12 female (67%)	0.35 ^a	1	0.55
Years of education	16 (3)	16 (2)	0.58	1,24	0.45
IQ	126 (17)	115 (14)	2.82	1,22	0.11
Yale Depression Inventory (YDI) score	1 (2)	33 (9)	100.94	1,25	<0.0001
Hamilton Anxiety Scale score	1 (1)	16 (7)	46.49	1,25	<0.0001
Wechsler Memory Scale Logical–Immediate Recall	32 (6)	25 (7)	5.14	1,23	0.03
Wechsler Memory Scale Logical–Delayed Recall	29 (6)	22 (7)	5.69	1,23	0.03
Wechsler Memory Scale Logical–Percent Retention	89 (7)	81 (23)	1.1	1,23	0.3
Years of depression		17 (13)			

^aValue for the chi square.

Table 2

Neutral and emotional word pairs in declarative memory task

Neutral word pairs	Emotional word pairs
Metal–iron	Lousy–worthless
Baby–cries	Hopeless–pain
Crush–dark	Evil–death
School–grocery	Bad–nowhere
Rose–flower	Devil–faithless
Obey–inch	Sin–sad
Fruit–apple	Grief–regret
Cabbage–pen	Tear–failure
Clip–pen	Rotten–terrible
Tape–bottle	Broken–destroyed

Table 3
Areas of greater increases and decreases in blood flow with retrieval of neutral paired associates compared to control in healthy subjects ($N=9$)

Increased blood flow				Decreased blood flow			
z score [*]	Voxel number ^{**}	Talairach coordinates			z score [*]	Voxel number ^{**}	Brain region
		x	y	z			
3.10	785	10	36	0	3.22	1396	R. anterior cingulate (24)
2.83		8	34	16	2.98		R. anterior cingulate (32)
2.93	450	-30	32	24	2.88		L. anterior cingulate (32)
2.90		-22	28	34			
2.84		-24	46	6			
2.92	195	0	-88	46			Visual cortex (19)

* z score>2.58, $p<0.005$.
** Number of voxels within the activated cluster.
Areas in bold represent the voxel with greatest activation in a contingent group of voxels; non-bold areas are other areas of activation within the same group.

Table 4

Areas of greater increases and decreases in blood flow with retrieval of emotional versus neutral word pairs in healthy subjects ($N=9$)

Increased blood flow				Decreased blood flow			
z score*	Voxel number**	Talairach coordinates			z score*	Voxel number**	Brain region
		x	y	z			
4.77	2687	-34	30	20	3.84	1134	2 R. inferior frontal gyrus (45)
4.12		-26	36	8	3.77	289	-18 L. hippocampus/parahippocampal region
3.44		-28	14	-4	3.76	907	-44 Cerebellum
3.73	656	14	28	2	3.11		-30
3.29	238	22	6	26	3.01		-40
3.23	95	16	-28	22	3.31	521	26 R. posterior cingulate (31, 24, 30, 23)
3.58	320	-16	-72	-4	2.68		8
2.98	85	-14	-100	0	3.00	116	56 L. precuneus (7)
3.34	436	12	-100	-6	2.98	163	2 R. middle frontal gyrus (9, 46)
3.27		26	-92	4			

* z score > 2.58, $p < 0.005$.

** Number of voxels within the activated cluster.

Areas in bold represent the voxel with greatest activation in a contingent group of voxels; non-bold areas are other areas of activation within the same group.

Table 5

Areas of increases and decreases in blood flow with retrieval of emotional versus neutral word pairs in patients with depression ($N=18$)

Increased blood flow				Decreased blood flow			
z score [*]	Voxel number ^{**}	Talairach coordinates			z score [*]	Voxel number ^{**}	Brain region
		x	y	z			
3.42	163.00	44	28	38	3.84	178	R. middle frontal gyrus (9)
							R. anterior cingulate (29)
					3.76	676	R. caudate
					3.05		
					2.63		
					3.75	514	R. anterior cingulate (24, 32)
					3.36	211	R. anterior cingulate (32)
					3.15	357	Cerebellum
					2.92		R. superior temporal gyrus (38)
					2.41		
					2.87	45	Uncus (28, 36)
					2.84	66	L. inf. parietal lobule (40)
					2.75	85	R. middle temporal gyrus (22)
					2.63	42	L. inf. frontal gyrus (44)
					2.56	43	L. hippocampus
							L. fusiform gyrus (38)

* z score > 2.58, $p < 0.005$.

** Number of voxels within the activated cluster.

Areas in bold represent the voxel with greatest activation in a contingent group of voxels; non-bold areas are other areas of activation within the same group.

Table 6

Areas of greater increases and decreases in blood flow with retrieval of emotional versus neutral word pairs in healthy subjects ($N=9$) relative to patients with depression ($N=18$)

Increased blood flow				Decreased blood flow			
z score*	Voxel number**	Talairach coordinates			z score*	Voxel number**	Brain region
		x	y	z			
4.15	1335.00	14	14	10	3.32	144	R. fusiform gyrus (20, 37, 36)
3.64		18	38	-10	2.73		
2.62		24	40	12	2.99	102	R. precentral gyrus (6)
4.11	1797.00	-38	24	18	3.02	99	R. inf. parietal lobule (40)
3.23		-22	26	14	2.77	119	R. precuneus (18)
3.04		-14	46	8	2.77	66	
3.44	319.00	-18	-68	-10	2.72	88	R. middle frontal gyrus (9)
3.17		-14	-100	-2			
2.98	324.00	14	-98	-6			
2.68		24	-94	4			
2.65	87.00	26	-12	-14			
2.59		30	-2	-24			
3.05	38.00	-36	-56	48			
2.99	85.00	28	8	28			

* z score > 2.58, $p < 0.005$.

** Number of activated voxels in a cluster.

Areas in bold represent the voxel with greatest activation in a contingent group of voxels; non-bold areas are other areas of activation within the same group.

Table 7

Areas of increases and decreases in blood flow with verbal memory encoding following treatment of patients with depression ($N=13$)

Increased blood flow				Decreased blood flow			
z score [*]	Voxel number ^{**}	Talairach coordinates			z score [*]	Voxel number ^{**}	Brain region
		x	y	z			
3.69	157	-16	24	24	3.79	396	Precuneus (BA 7)
3.57	322	-6	48	2	3.07	129	Anterior cingulate (BA 32)
3.57	443	18	16	12	3.02	59	Anterior cingulate (BA 32)
2.76		32	26	8	2.86	105	Ventral caudate
2.63		32	32	22			
3.05	125	22	-98	2			Visual association cortex (BA 18)
2.96	224	14	-76	6			Lingual gyrus (BA 18)

* z score > 2.58, $p < 0.005$.

** Number of voxels within the activated cluster.

Areas in bold represent the voxel with greatest activation in a contingent group of voxels; non-bold areas are other areas of activation within the same group.

Table 8
Areas of increases and decreases in blood flow with emotional memory retrieval following treatment of patients with depression (N=13)

Increased blood flow				Decreased blood flow			
z score*	Voxel number**	Talairach coordinates			z score*	Voxel number**	Brain region
		x	y	z			
3.27	103	-48	-52	-2	3.80	190	Inf. temporal gyrus (BA 20)
3.01	83	-38	16	10	3.50	94	Sup. frontal gyrus ((BA 10)
2.81	49	18	14	10	3.46	361	Post. cingulate (BA 31)
2.58	97	-4	48	4	3.09	125	Sup. temp. gyrus (BA 22)
					2.97	110	Precuneus (BA 7)

* z score>2.58, $p<0.005$.
** Number of voxels within the activated cluster.
Areas in bold represent the voxel with greatest activation in a contingent group of voxels; non-bold areas are other areas of activation within the same group.