

# Abnormal neural response to feedback on planning and guessing tasks in patients with unipolar depression

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## ABSTRACT

**Background.** It has been suggested that patients with unipolar depression show abnormal responses to negative feedback in the performance of cognitive tasks. Positron emission tomography (PET) has previously identified blood flow abnormalities in depressed patients during cognitive performance. We have also used PET to identify regions where there is differential neural response to performance feedback in normal volunteers. In this study we aimed to test the hypothesis that blood flow in these regions, the medial caudate and ventromedial prefrontal cortex, would be abnormal in depressed patients.

**Methods.** Six patients with unipolar depression and six matched controls were scanned using PET while performing cognitive tasks in the presence and absence of feedback.

**Results.** Compared with controls, depressed patients failed to show significant activation in the medial caudate and ventromedial orbitofrontal cortex. Blood flow was lower and a differential response, observed in normals, under different task and feedback conditions was not seen in the patients.

**Discussion.** The findings suggest that the behavioural response to feedback in depressed patients is associated with an abnormal neural response within the medial caudate and ventromedial orbitofrontal cortex, regions implicated in reward mechanisms. We argue that the observed abnormalities may depend on a combination of psychological factors, with both cognitive and emotive components.

## INTRODUCTION

Influential cognitive and behavioural accounts of depression have proposed a key role for reinforcement in its onset and maintenance. For example, Lewinsohn (1974; Lewinsohn *et al.* 1979) proposed a behavioural model of depression based on reinforcement which hypothesized that various reinforcement-reducing contingencies may apply in depressed patients. Thus, they find fewer events potentially reinforcing, experience fewer of those events which they do find reinforcing and receive reduced social

reinforcement due to impaired social skills. In the depressed state opportunities for social, and other forms of, reinforcement are typically reduced, which further exacerbates the effects of an already abnormally low rate of reinforcement. The concept of feedback response can also be linked to cognitive accounts of the disorder. An influential cognitive theory, developed by Beck (1967) and subsequently modified by Teasdale (1988), argues that individuals vulnerable to depression are characterized by enduring dysfunctional schemata made up of negative attitudes and assumptions. A bias towards the processing of negative reinforcement may detract from their ability to perform normally in response to cognitive challenges.

Reinforcement, in the form of performance

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feedback, is a key component in many laboratory tests of cognitive function. Performance feedback has both evaluative and emotive components; it can be used to guide and monitor performance but also has the emotional consequences of being correct and incorrect. Depression has reliably been shown to be associated with impairments on tests of cognitive function (e.g. Weingartner *et al.* 1981; Austin *et al.* 1992; Brown *et al.* 1994; Elliott *et al.* 1996) and recent evidence indicates a deficit in the response to performance feedback. For example, Hughes *et al.* (1985) showed that depressed patients were less responsive to reinforcement than controls. Using a progressive schedule for financial reward, they found that depressed subjects worked less for reward and so earned less. Similarly, Henriques *et al.* (1994) compared response biases under a neutral and a rewarding pay-off condition and showed that dysphoric subjects showed less difference between these conditions than a non-dysphoric group. There is also evidence to suggest that depressed subjects evaluate their performance in a more negative way than controls. Specifically, Wener & Rehm (1975) found that depressed patients reported a lower self-assessed success rate than controls.

Two recent studies suggest that depressed patients are particularly sensitive to negative feedback during neuropsychological task performance. Beats *et al.* (1996) proposed a 'catastrophic response to executive failure' to explain the rapid deterioration in planning performance of elderly depressed patients after making an error. This catastrophic response to failure was tested more explicitly by Elliott *et al.* (1996) who suggested that patients with unipolar depression showed a greater sensitivity to negative feedback than controls, assessed in terms of its detrimental effect on subsequent performance. Abnormal response to negative feedback has also been shown to be specific to depression and related to clinical severity (Elliott *et al.* 1997). This study reformulated the 'catastrophic response to failure' argument somewhat, suggesting that the discrepancy between depressed patients and controls may also be due to control subjects responding to negative feedback by augmenting performance on subsequent trials. Clearly though, these studies report an abnormality in the behavioural responses of depressed patients to feedback.

These behavioural effects can be seen as an important link between depressed mood and cognitive performance in depression. The present study sought to identify a specific neural substrate for this effect. A recent functional imaging study in normal volunteers (Elliott *et al.* 1997) considered the modulation of cognitive task-related activations by feedback. Regions sensitive to the presence, compared with absence, of feedback were the medial caudate nucleus and the ventromedial orbitofrontal cortex. Significantly greater activation in these structures was seen during a guessing task compared to a planning task. The striatal and cortical loci observed in this study are entirely congruent with animal and human data, which indicate that processing of performance feedback is associated with the ventral striatum (incorporating the medial caudate) and orbitofrontal cortex (e.g. Thorpe *et al.* 1983; Schultz *et al.* 1992; Bechara *et al.* 1994; Rolls *et al.* 1994).

Previous PET studies have demonstrated abnormal prefrontal blood flow in depressed patients (e.g. Cohen *et al.* 1989; Bench *et al.* 1992; Drevets *et al.* 1992) that may relate to clinical features of the disorder. It should be noted however, that the reported prefrontal abnormalities in these studies did not include the ventromedial orbitofrontal cortex, which may have been outside the field of view of early imaging techniques. More recent studies have reported orbitofrontal abnormalities in depressed patients (Mayberg *et al.* 1994, 1997; Drevets *et al.* 1997) and therefore it is reasonable to hypothesize abnormalities in this region. Findings of reduced activity in the caudate nucleus of depressed patients in the resting state have also been reported (Buchsbaum *et al.* 1986; Cohen *et al.* 1989; Drevets *et al.* 1992). Further, a recent cognitive activation study of patients performing a planning task has indicated functional abnormalities in prefrontal structures as well as the caudate nucleus (Elliott *et al.* 1997).

The present study used the paradigm developed in our recent study of normal volunteers (Elliott *et al.* 1997) to determine whether the reported abnormal behavioural response to performance feedback in depressed patients could be related to abnormal neural function. Specifically, we hypothesized that in depression, the presence of performance feedback would be associated with an abnormal neural response in

the ventral striatum and orbitofrontal cortex, structures we conjecture to be important substrates of reinforcement mediated behaviour.

## METHOD

### Subjects

Six right-handed male patients with a diagnosis of recurrent major depressive disorder (DSM-IV, APA, 1994) were recruited for this study. Patients with history of neurological disorder, head injury or substance abuse were excluded as were patients who had received ECT in the preceding 12 months. The mean age of the patients was 41 (range 24–54). The severity of their depression was assessed using the 17-item Hamilton Depression Scale (HAM-D, Hamilton, 1960); mean score 26.0 (range 19–33); and the Montgomery–Åsberg Depression Rating Scale (MADRS, Montgomery & Åsberg, 1979); mean score 34.7 (range 28–38). All of the patients were on antidepressant medication; one on 100 mg atenolol+210 mg lofepramine, one on 30 mg paroxetine, one on 30 mg paroxetine+lithium, one on 300 mg venlafaxine+15 mg zopiclone, one on 200 mg imipramine and one on 200 mg sertraline.

These patients were compared with the six right-handed male control volunteers (mean age 35) scanned in our previous study (Elliott *et al.* 1997). The groups were matched for age and educational attainment. As this study used false feedback, all subjects were thoroughly debriefed after their participation. The study was approved by the Addenbrooke's Hospital Local Research Ethics Committees and the Advisory Committee on the Administration of Radioactive Substances (ARSAC) UK. All subjects gave informed consent.

### Cognitive activation paradigm

The design of this experiment was a two by two by three factorial design with subject group (two levels; patients and controls) as one factor, experimental task (two levels; planning and guessing) as another, and feedback condition (three levels; positive, negative and no feedback) as the third.

#### *Planning task*

This task was based on the Tower of London task (Shallice, 1982), using the one-touch ap-

proach developed by Owen *et al.* (1995). The present version was the variant of this paradigm, used in an earlier study of normal volunteers (Elliott *et al.* 1997). Subjects were presented two arrays of coloured balls and asked to work out the minimum number of moves needed to make one array match the other, according to rules which were explained before scanning. Ten seconds were allowed, after which the arrays disappeared and subjects had to press one of six labelled buttons that corresponded to their solution. Problems were all of three to six moves and subjects typically require in the region of 15–25 s to solve problems of this difficulty (Owen *et al.* 1995; Elliott *et al.* 1996) when no time constraint is imposed. The time limit therefore prevented subjects being certain of their answers, thus rendering them more likely to believe false feedback. Ten unique problems were presented during each scan, the sequence starting 60 s prior to scanning to ensure the establishment of the appropriate cognitive set. Subjects were explicitly told to optimize performance before the start of each scan.

#### *Guessing task*

Subjects were presented with two identical arrays of coloured balls and asked to watch until they disappeared (after a mean of 10 s). This was a signal for them to press one of the six response buttons. They were told that on each trial, three of the buttons would be randomly assigned as correct. Subjects were told before each sequence that this assignment was purely chance so that each response constituted a 50:50 guess. Again 10 problems were performed during each scanning period, starting 60 s before scanning.

#### *Feedback conditions*

Both the above tasks were performed under three different conditions. Feedback was given after every trial and constituted a large green tick and the words 'YOU ARE RIGHT' or a large red cross and the words 'YOU ARE WRONG', presented on the screen for 1 s immediately after each response. In the positive feedback condition, subjects were told they were correct on every trial, regardless of their actual performance. In the negative condition, subjects were told they were wrong on 80% of trials, regardless of whether their responses were actually correct. In the neutral condition, no

feedback was given. Between trials subjects saw a display comprising a large triangle and the words 'PLEASE WAIT'. Each of the six conditions in this factorial design was performed twice in a fully counterbalanced order within and between subjects.

### PET scanning technique

An ECAT HR + scanning system (CTI Siemens, Knoxville, TN) was used to measure regional cerebral blood flow (rCBF). For each scan, 555 Mbq of  $H_2^{15}O$  was flushed with normal saline through a cannula in the left antecubital vein over 20 s at a rate of 10 ml/min by an automatic pump. After a delay of approximately 35 s, a rise in counts could be detected at the head. This peaked 30–40 s later, the exact interval depending on individual subjects. Data were acquired during a single 90 s frame, beginning 5 s before the head curve began to rise. Twelve scans were performed in all at 8 min intervals. A transmission scan with an exposed  $^{68}Ge/^{68}Ga$  external ring source was performed before each session to correct for attenuation. Filtered back projection was used to reconstruct the images, giving a resolution of 6.0 mm at full width half maximum and displayed in a  $128 \times 128$  pixel format with 63 planes rendering the voxels approximately cubic.

### Data analysis

Statistical Parametric Mapping (SPM96, Wellcome Department of Cognitive Neurology, London, UK) was used to analyse the data implemented in MATLAB (Mathworks, Inc., Sherborn, MA, USA) and run on a SPARC workstation (Sun Microsystems Inc., Surrey, UK). Scans were realigned using the first as a reference and were then transformed into the standard space of Talairach & Tournoux (1988) using MNI templates (Montreal Neurological Institute). Images were smoothed with a 16 mm full width half maximum Gaussian filter.

Conditions for each subject were specified in the appropriate design matrix, which included global activity as a confounding covariate, so this can be considered an ANCOVA. Effects at each and every voxel were estimated according to the general linear model and regionally specific effects were compared using linear contrasts. The resulting set of voxel values for each contrast constituted a statistical parametric map of the  $t$

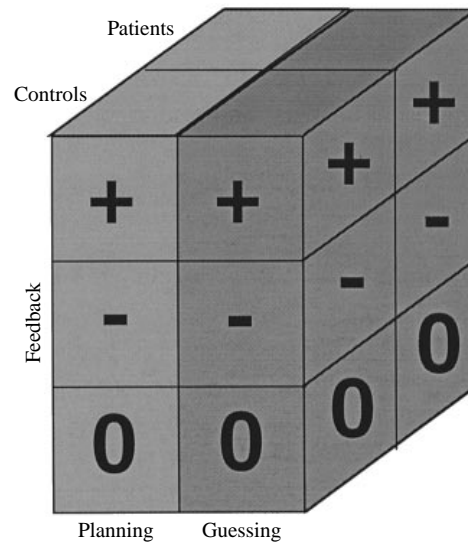


FIG. 1. Graphical depiction of the  $2 \times 2 \times 3$  factorial study design.

statistic ( $SPM\{t\}$ ) which was then transformed to the unit normal distribution,  $SPM\{Z\}$  (Friston *et al.* 1995).

The design of this experiment was a  $2 \times 2 \times 3$  factorial with subject group as one factor, task as another and feedback type as the third (see Fig. 1). In the analysis of these data, the critical questions were which regions of those activated in normal subjects in association with performance feedback showed abnormal activation in depressed patients. Our earlier study had identified the medial caudate and ventromedial prefrontal cortex as the key foci and we hypothesized that abnormalities in these regions would be seen in depression. Since specific neuroanatomical hypotheses are being considered, we report uncorrected  $P$  values with respect to predicted regions of difference. In PET studies where there is no anatomical hypothesis, it is necessary to correct  $P$  values for multiple comparisons since comparisons are being made at every voxel and there is therefore a high chance of Type 1 errors. In this study, we were hypothesizing focal abnormalities in two distinct regions; the medial caudate and the ventromedial orbitofrontal cortex.

Given that this is an anatomically constrained hypothesis, the issue of correction for multiple comparisons is not of the sort usually encountered in SPM analyses of this type. Hitherto, one would normally have accepted a threshold

Table 1. Co-ordinates of maximal significant change in rCBF associated with the key feedback-related comparisons in the normal subjects only (see Elliott et al. 1997)

rCBF increases	Region of activation					Z value (3.09 for $P < 0.001$ )
	Left/Right	Brodmann's area	Talairach co-ordinates			
			x	y	z	
Feedback present-absent						
Medial caudate nucleus	R		8	16	16	3.67
	L		-10	16	4	3.56
Superior temporal gyrus	L	22	-32	-34	4	3.72
	R	38	42	8	-8	3.25
Guessing-planning feedback present-absent						
Ventromedial orbitofrontal cortex	R	25	4	30	-20	3.61
	L	25	-4	22	-12	3.18
Anterior frontal cortex	R	10	14	58	-4	3.35
Inferior frontal gyrus	L	47	-28	22	0	4.05
Present-absent guessing only						
Ventromedial orbitofrontal cortex	R	11	10	30	-20	3.64
Medial caudate nucleus	R		8	20	8	4.08
Inferior frontal gyrus	L	47	-22	22	0	3.96
Superior temporal gyrus	R	38	40	8	-12	3.53

Table 2. Co-ordinates where rCBF changes were seen in control subjects relative to depressed patients associated with comparisons of different feedback conditions

Relative activations presence-absence	Region of activation					Z value (3.09 for $P < 0.001$ )
	Left/Right	Brodmann's area	Talairach co-ordinates			
			x	y	z	
Medial caudate nucleus	R		4	20	16	3.18
	L		-4	16	4	2.87
Posterior caudate	L		-20	-14	28	3.28

of  $P < 0.001$  (uncorrected) as being an adequate correction for an effect that was specified regionally but where the precise voxel was unknown. Recent advances in Gaussian Field Theory have now enabled us to provide exact critical values for small specified volumes (Worsley *et al.* 1996). Applying these results to the data reported in the current paper, they survive a correction for the small volume analysed.

For other regions, we have descriptively reported  $P$  values at  $P < 0.001$  uncorrected, corresponding to  $Z = 3.09$ , although strong conclusions cannot be drawn about these regions in the absence of correction for multiple comparisons.

The stereotactic coordinates of Talairach & Tournoux (1988) are used to report the observed activation foci. However, the descriptions of the anatomical localization of these foci were de-

termined using the averaged structural MRIs of the group and the atlas of Duvernoy (1991). We have found that this method provides a more accurate localization than the Talairach & Tournoux atlas (1988).

## RESULTS

### Within-group comparisons: normal volunteers

These findings have been reported in detail in our earlier paper (Elliott *et al.* 1997). The main points are summarized here because the regions of significant rCBF changes in normals are used to constrain our anatomical hypothesis about depressed patients. The critical comparisons in this study are those associated with different feedback conditions. The two feedback present conditions (positive and negative averaged) compared with the no feedback condition were associated with significant activations in the

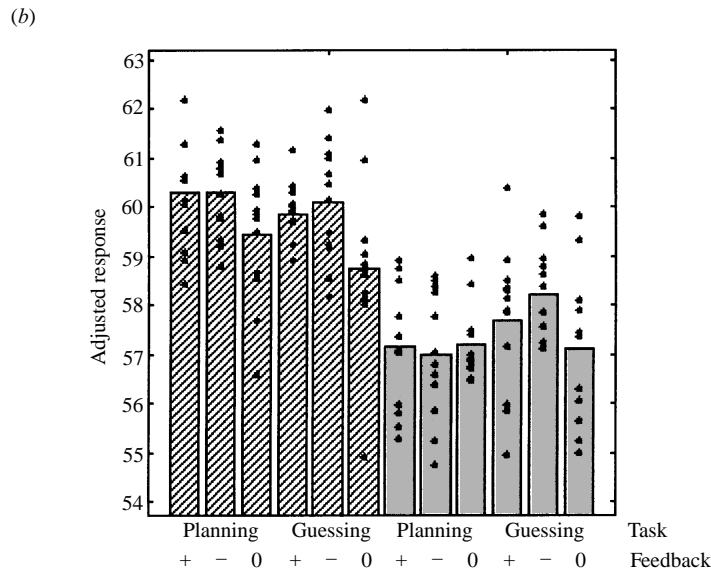
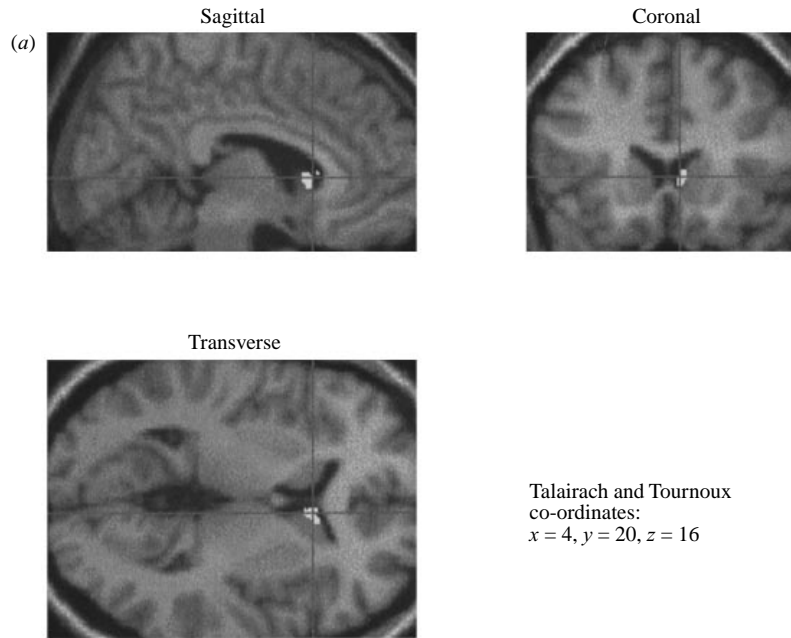


FIG. 2. Activations associated with the presence compared to the absence of feedback. (a) Shows the statistical parametric map of the *t* statistic (after transformation to a SPM(*Z*)) thresholded at  $P < 0.01$  rendered onto a standard MRI template and focused on the medial caudate nucleus activation. (b) Shows absolute values of blood flow for the two subject groups (▨, controls; ▤, patients) under the six experimental conditions in the medial caudate nucleus.

bilateral medial caudate nuclei and the right superior temporal gyrus (see Table 1). No significant deactivations were seen. Comparison between positive and negative feedback showed

no significant rCBF differences and, therefore, the feedback conditions were combined in the interaction terms.

The modulation of task by feedback was

Table 3. Co-ordinates where control subjects show significantly elevated rCBF compared to depressed patients associated with the modulation of guessing compared to planning performance by different feedback conditions

Relative activations presence-absence	Region of activation					
	Left/Right	Brodmann's area	Talairach co-ordinates			Z value (3.09 for $P < 0.001$ )
			x	y	z	
Ventromedial orbitofrontal cortex	L	25	-6	22	-16	2.57
	R	25	4	30	-16	2.36

associated with significant activation in the ventromedial orbitofrontal cortex (BA 11/25), anterior frontal cortex (BA 10) and left inferior frontal gyrus (BA 47). These activations were associated with greater activity in the presence of feedback in the guessing compared to the planning task. The significant interaction was characterized further by considering the simple main effects of feedback in the two tasks separately. There were no significantly increased activations associated with the presence compared to the absence of feedback in the planning task. In the guessing task, significant increases in activation were observed in the medial caudate nucleus extending rostrally to the ventral orbitofrontal cortex and in the left inferior frontal gyrus (BA 47).

#### Between group comparisons

These comparisons address whether there are differences, with respect to hypothesized regions, between subject groups associated with different feedback conditions. The explicit hypothesis being tested was that the depressed patients would show abnormal blood flow in the regions associated with feedback in the normal group as described above. Where abnormalities were observed in these pre-specified regions, significance levels are determined using the analysis recommended by Worsley *et al.* (1996). Elsewhere a level of  $P < 0.001$ , uncorrected, is used, which is usually considered acceptable for exploratory analyses. As in the within-group analysis, contrasts between positive and negative feedback were not informative and are therefore excluded for clarity.

#### Activity changes related to the presence compared to absence of feedback

These comparisons represent main effects of feedback across the two tasks (see Table 2).

#### Changes in activity associated with presence compared with absence of feedback

When the activations associated with the presence of feedback were directly compared with the two subject groups, the controls showed significantly greater activation than depressed patients in the right ( $P < 0.001$ ) and left ( $P < 0.01$ ) medial caudate nuclei (Fig. 2a) and the tail of the caudate on the left. Using the analysis recommended by Worsley *et al.* (1996), the distance between the observed and the hypothesized focus in the right medial caudate was 5.6 mm. The corrected  $P$  value for the  $Z$  score reported in Table 2 (employing a spherical region of 6 mm radius) would be 0.0164. For the left medial caudate focus, this value would be 0.0374. Adjusted rCBF values in the right medial caudate focus showed that there was lower activity overall in the depressed patients and that there were no changes associated with the different feedback conditions (Fig. 2b). There were no significant differences in deactivations associated with presence compared to absence of feedback between the two subject groups.

#### Activity changes related to the modulation of task performance by different types of feedback

These comparisons represent the interaction terms in the analysis (Table 3, Fig. 3).

#### Changes in activity associated with feedback compared with no feedback conditions in planning compared with guessing tasks

There were no significant differences between the two subject groups.

#### Changes in activity associated with feedback compared with no feedback conditions in guessing compared with planning tasks

When the subject groups were compared directly,

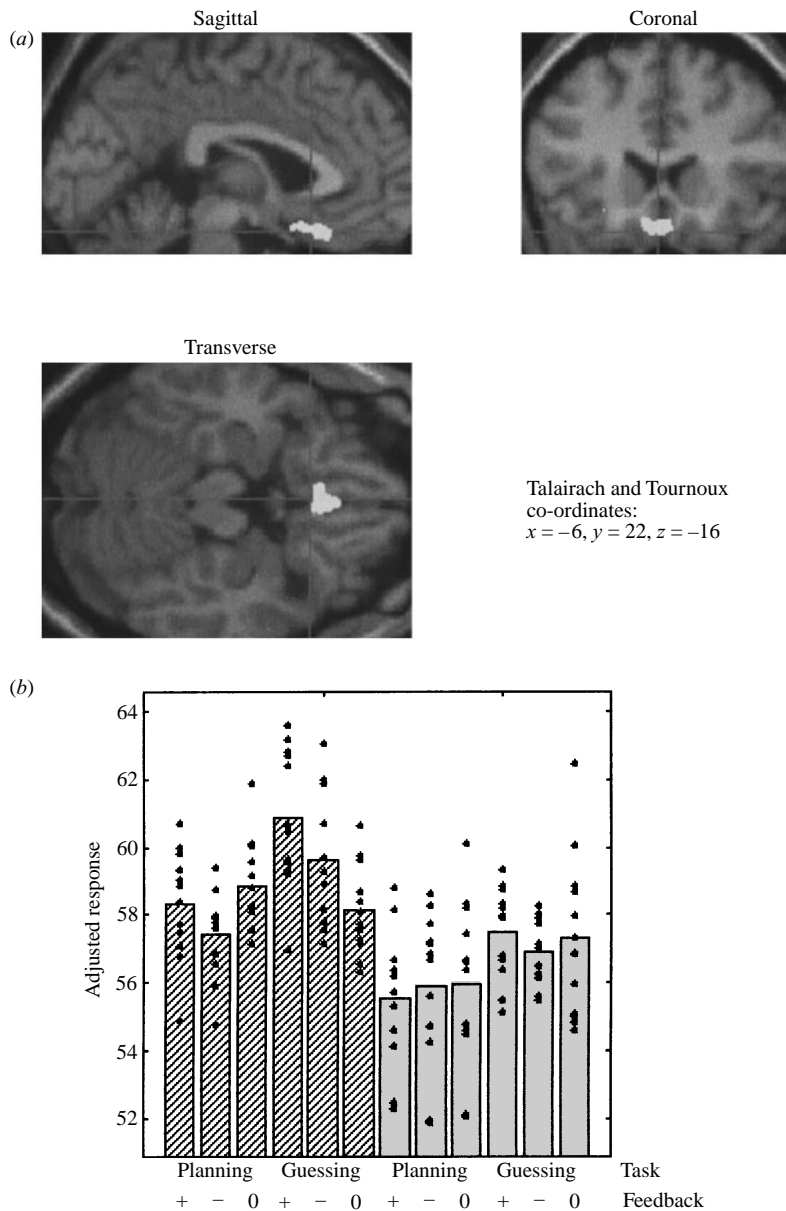


FIG. 3. Activations associated with the modulation of guessing compared to planning by presence compared to the absence of feedback, i.e. those areas more activated by the presence of feedback in the planning task than in the guessing task. (a) Shows the statistical parametric map of the  $t$  statistic (after transformation to a SPM{Z}) thresholded at  $P < 0.01$  rendered onto a standard MRI template and focused on the ventromedial orbitofrontal activation. (b) Shows absolute values of blood flow under the six experimental conditions in the ventromedial orbitofrontal cortex in the two subject groups (▨, controls; ▩, patients).

significantly greater activation ( $P < 0.01$ ) was seen in the controls relative to the depressed patients in ventromedial orbitofrontal cortex (BA 25) (see Fig. 3a). Using the analysis recommended by Worsley *et al.* (1996), the

distance between the observed and the hypothesized focus in the left ventromedial orbitofrontal cortex was 4.5 mm. The corrected  $P$  value for the  $Z$  score reported in Table 3 (employing a spherical region of 4.5 mm radius)



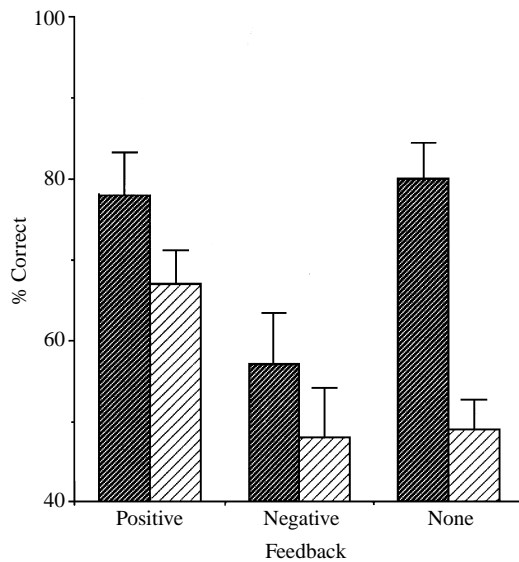


FIG. 4. Cognitive performance of the subjects (■, controls; ▨, patients) on the planning task under the three feedback conditions. Mean percentage of problems solved correctly is shown. Bars show standard errors of the mean. Note that each condition was performed twice (1st and 2nd presentation) in a counterbalanced order.

would be 0.048. For the right ventromedial orbitofrontal focus, this value would be 0.063. Adjusted rCBF values (Fig. 3b) showed that in normal subjects blood flow was similar in the two feedback absent conditions but was higher in the feedback present conditions in the guessing task than in the planning task. Activity was lower overall in the depressed patients and the differential response associated with the different feedback conditions in the two tasks normal subjects was not evident.

#### Performance data

When subjects were debriefed after scanning, all the controls reported that they became aware the feedback was irrelevant to performance approximately halfway through the study session. By contrast, only a single depressed patient reported being aware that the feedback given was false. Fig. 4 shows the performance of both subject groups on the planning task in the different feedback conditions. Depressed patients performed less accurately overall, which is consistent with other neuropsychological studies using the Tower of London task (Beats *et al.* 1996; Elliott *et al.* 1996). Both groups performed less accurately in the negative feed-

back condition than the positive condition. However, while the performance of control subjects on the neutral condition was similar to that on the positive condition, depressed patients receiving no feedback performed at a similar level to the negative feedback condition. On all conditions both subject groups performed substantially above chance levels (17%) indicating that they were planning solutions rather than guessing. It is, therefore, not feasible that the differential task-related activations discussed below are due to depressed patients responding close to chance in the planning task. In fact, the overall percentages correct were not markedly different from those in our study of the Tower of London task performance with no time constraint (Elliott *et al.* 1997).

#### DISCUSSION

The main finding of this study was that while normal subjects showed a neural response in the medial caudate nucleus and the ventromedial orbitofrontal cortex as a function of level of performance feedback, this response was significantly attenuated in patients with unipolar depression. Activation within this network under feedback was modulated by task type in the normal subjects, with stronger activation seen during a guessing task than during a planning task. This profile of neural response to feedback, as a function of task type, was not seen in depressed patients.

In normal volunteers, caudate activation was seen in the feedback conditions of both tasks; it relates to the feedback itself, regardless of the cognitive processes that are being reinforced. This suggests that this activation may represent the emotive component of the response to feedback that is likely to be relatively independent of the task. In our earlier study (Elliott *et al.* 1992), we hypothesized that caudate activity might be associated with central representations of reward. This is compatible with the observation of Schultz *et al.* (1992) that neurons in the ventral striatum (which includes the medial caudate) of monkeys are activated before the expected delivery of reward. If the caudate signal is associated with anticipation of feedback rather than response to it, this may explain why there are no differences between activity in the positive and negative feedback conditions in

either subject group. The present study suggests that depressed patients may have reduced activity associated with the expectation of reward. A decreased expectation of reward in depressed patients is consistent with the striking difference in the performance data for the two subject groups. Both groups solved fewer problems in the negative than the positive feedback condition. However, in the no feedback condition, normal controls solved as many problems as in the positive condition while depressed patients solved only as many as in the negative condition. In the absence of feedback therefore, normal subjects behave as if they are expecting success while depressed patients behave as if they are expecting failure. That is, in the absence of information to the contrary, the behaviour of patients suggests they may have significantly lower expectation of reward than controls. This account is consistent with psychological descriptions of depressed patients during reinforcement-related tasks, for example, the finding of Hughes *et al.* (1985) that patients are less motivated than controls to respond for financial reward.

The activation of the ventromedial orbitofrontal cortex in normal controls was modulated by task type, with greater activation in a guessing compared to a planning task. This differential neural response was not seen in depressed patients. In our earlier paper, we proposed several explanations for the pattern of activity in the orbitofrontal cortex. One explanation accounted for the observed differences in terms of the perceived controllability of the tasks. In the planning task subjects believe that they have control over the type of feedback they receive; while in the guessing task they have no control. This difference in controllability may be related to the phenomenon of learned helplessness (Seligman, 1975) which behavioural theories have suggested may be associated with, or even model, depression (e.g. Abramson *et al.* 1978).

An alternative, but not unrelated, suggestion was that activity in the ventromedial orbitofrontal cortex was associated with an implicit requirement to process feedback across trials. In the planning task, each trial, incorporating problem, response and feedback, is a discrete and meaningful entity. In the guessing task however, feedback to a single trial is less meaningful; it is only when feedback is assimilated across a number of trials that subjects can

assess their performance against chance. Furthermore, although subjects were told to guess at random, anecdotal evidence of behaviour in response to chance determined events would predict that they probably monitored performance and chose their responses in the light of previously rewarded responses. Certainly, a consideration of the actual sequences produced by both subject groups in the guessing task, suggests they are not genuinely random, for example, no subject ever made the same response on successive trials. In the guessing task, the feedback is the only information the subjects have about performance and the orbitofrontal component of the response may thus represent this informational aspect of response to feedback.

An involvement of orbitofrontal cortex in acquiring and monitoring stimulus-reinforcement relations has been reported in studies of monkeys (Thorpe *et al.* 1983; Dias *et al.* 1996) and patients with orbitofrontal lesions (Bechara *et al.* 1994, 1996; Rolls *et al.* 1994). Depressed patients failed to show the normal activation of the orbitofrontal cortex and this may be related to an impaired ability to process response–outcome associations or reward contingencies across trials. This suggestion would be compatible with the observation that while all the control subjects realised the feedback was false by the end of the experiment, only one of the depressed patients did so, and even he was unsure. Failure to process response–outcome associations may contribute to learned helplessness in depression. Impaired learning about correlations between behaviour and positive outcomes is a crucial component in determining the extent to which a situation can be controlled.

In this study, depressed patients are under-responsive to feedback compared to controls in terms of neural response. Our recent neuropsychological study (Elliott *et al.* 1997) suggested that compared with controls, depressed patients fail to show an elevated probability of correctly solving a problem directly after a failure. That is, controls respond to failure by improving performance to increase their chance of success on the subsequent problem. Depressed patients do not. This could actually be characterized as an undersensitivity to negative feedback and may depend on a combination of cognitive and emotional factors. Thus, patients may be less

able than controls to use the information conveyed by feedback to monitor and correct subsequent performance. They may also show impaired motivation to respond for positive feedback. It is not entirely clear how this account relates to the behavioural data presented in this study. We have proposed that controls respond to negative feedback by improving performance while patients do not. In fact the controls in this study performed worse under negative feedback than when no feedback was given. However, a crucial point is that these data are for a task where the feedback is not related to performance so that no amount of trying to improve performance has the desired outcome. In fact, in the negative feedback condition, the feedback may misleadingly encourage control subjects to change successful performance strategies, resulting in an increased error rate. Depressed patients perform no worse in the negative than the neutral condition, perhaps implying that this inappropriate monitoring does not occur. In cognitive terms, the situation in this study is different from the usual one where feedback relates to performance. This is an issue that would merit clarification by a neuropsychological study but is not central to the neurobiological argument of the present study.

The account of the neuropsychological finding as a reduced ability of depressed patients to improve performance in the face of negative feedback is more consistent with the neural hypoactivity in response to feedback seen in the present study. It is also consistent with the many animal models of depression that have used decreased responding for reward as a critical analogue of human depression (e.g. Zacharko & Anisman, 1991; Moreau *et al.* 1994). Many cognitive and behavioural accounts of depression also stress a role for reduced reward-related behaviour. Layne (1980) explicitly argued that depression 'consists' of low reward motivation while other accounts have also proposed reduction in experience of positive reinforcement as an important factor (Lewinsohn *et al.* 1979).

A striking finding of this study was that within the structures activated in the presence of performance feedback, there were no differences associated with different types of feedback (positive compared to negative). If the activations in the medial caudate or orbitofrontal cortex were specific to the actual experience of

reward, this would not have been the case. Instead, we have argued that the ventral striatal activation may be associated with the expectation of reward and the orbitofrontal activation with learning about response–outcome relations. Reduced activation in the depressed patients could thus be interpreted as related to reduced expectation of reward and impaired ability to learn about stimulus–reward relations rather than an impaired response to reward *per se*.

Many previous functional imaging studies have suggested that depression is associated with reduced activity in the anterior cingulate and medial prefrontal cortex (George *et al.* 1993; Goodwin *et al.* 1993; Dolan *et al.* 1994). The present study did not show cingulate abnormality but demonstrated a much more ventral medial prefrontal abnormality. In this version of the paradigm, task performance was not associated with cingulate activation in the normal subjects. We argued that this may be due to this structure also being activated in the guessing task, which was more demanding than the original control task. It may be, therefore, that cingulate activity was indeed lower in depressed patients but this was not revealed by the contrasts used in the present study. We suggest that medial prefrontal dysfunction in depression may be relatively extensive with the focus of the identified dysfunction depending on the precise study conditions. Both the present and our earlier study identified reduced activation of the caudate nucleus, an area also implicated in other functional imaging studies of depression (Buchsbaum *et al.* 1992; Drevets *et al.* 1992). Striatal pathophysiology may compromise function in cortico-striatal loops that feed back to the orbital, cingulate and medial prefrontal cortex (Alexander *et al.* 1986). It has been suggested that depression is associated with disrupted function within frontostriatal loops (Robbins *et al.* 1992) and our functional imaging studies suggest that the prefrontal expression of this abnormality may depend on the specific cognitive requirements imposed on patients.

It should be noted that the patients in this study were taking antidepressant medication at the time of scanning and it will obviously be important to replicate these results in unmedicated patients in order to rule out possible confounding effects of treatment. There is some

recent evidence suggesting that abnormalities in medial prefrontal areas may be to an extent independent of medication effects. For example George *et al.* (1997) demonstrated blunted response in the anterior cingulate of unmedicated depressed patients performing the Stroop task. Mann *et al.* (1996) showed that a group of drug-free depressed patients failed to show the normal increase in metabolism in medial prefrontal regions in response to the serotonergic drug fenfluramine. There is also evidence though, that antidepressant treatment may have a direct effect on these areas. Mayberg *et al.* (1997) reported that SSRI treatment decreased ventromedial frontal glucose metabolism and therefore it is possible that some of the overall reduction in ventromedial blood flow in the present study is a drug effect. However, only half the patients were taking selective serotonin reuptake inhibitors and the blood flow pattern we observed was consistent across patients. Also, although a drug effect may explain the lower overall blood flow, it cannot necessarily account for the lack of condition specific effects. These issues can only fully be clarified by further studies in unmedicated patients and it is important to note the caveat imposed by this limitation of the present data.

In conclusion, the results of this study suggest that response to feedback in patients with unipolar depression is associated with attenuation of activation within a network including the medial caudate nucleus and ventrolateral orbitofrontal cortex. Modulation of feedback related activity by task type suggests that different components of this network subserve subtly different functions in the response. We have proposed that these neural abnormalities in depressed patients reflect a decreased expectation of reward and an impaired ability to learn response–outcome contingencies, possibly contributing to learned helplessness. While these results cannot be regarded as conclusive, they suggest that a crucial link between affect and cognitive impairment in depression may depend on a clearly circumscribed neural substrate.

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