

Blunted response to feedback information in depressive illness

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Depressive illness is associated with sustained widespread cognitive deficits, in addition to repeated experience of distressing emotions. An accepted theory, which broadly accounts for features of the syndrome, and its delayed response to antidepressant medication, is lacking. One possibility, which has received considerable attention, is that depressive illness is associated with a specific underlying deficit: a blunted or impaired ability to respond to feedback information. Unlike healthy controls, if patients with a depressive illness commit an error, they can be at increased risk of committing a subsequent error, possibly due to a failure to adjust performance in order to reduce the risk of error. In some speeded tasks, performance adjustment in humans is reliably associated with trial-to-trial change in reaction times (RTs), such as ‘post-error slowing’. Previous studies of abnormal response to feedback have not investigated RT change in any detail. We used a combination of quantitative modelling of RTs and fMRI in 15 patients and 14 matched controls to test the hypothesis that depressive illness was associated with a blunted behavioural and neural response to feedback information during a gambling task. The results supported the hypothesis. Controls responded to negative (‘lose’) feedback by an increase in RT and activation of the anterior cingulate, the extent of which correlated with RT change. Patients did not significantly increase their RTs, nor activate the anterior cingulate. Controls responded to positive (‘win’) feedback by a reduction in RT and activation of the ventral striatum, the extent of which correlated with RT change. Patients neither reduced their RT nor activated the ventral striatum. RT adjustment correlated with self-reported anhedonia for both patients and controls. This behavioural deficit, together with its associated pattern of abnormal neural activity, implies that the anterior midline cortical substrate for error correction, which includes projections from the monoamine systems, is dysfunctional in depressive illness. Many studies have reported abnormalities of the medial frontal cortex in depressive illness; however, the mechanism by which antidepressant medication acts via the monoamine systems remains elusive. Our results suggest a direct link between the core subjective symptom of anhedonia, replicated neuropsychological deficits, electrophysiological and imaging abnormalities, and hypothesized dysfunction of the error correction system.

Keywords: functional imaging; major depressive disorder; phasic monoamine activity; ventral striatum; medial frontal cortex

Abbreviations: ACC = anterior cingulate cortex; BA = Brodmann’s area; BDI = Beck depression rating scale; bl = behavioural ‘lose’ measure; bw = behavioural ‘win’ measure; fMRI = functional MRI; Hamilton = Hamilton depression rating scale; NART = National Adult Reading Scale; RT = reaction time; SH = Snaith–Hamilton hedonia scale; SP = Spielberger state anxiety scale

Received February 2, 2007. Revised April 30, 2007. Accepted May 31, 2007. Advance Access publication July 24, 2007

Introduction

Depressive illness is associated with sustained widespread cognitive impairments (Elliott *et al.*, 1998; Austin *et al.*, 2001; Steffens *et al.*, 2001; Ebmeier *et al.*, 2006). There has been considerable interest in investigating the hypothesis that these are due to a single underlying deficit;

in particular, a specific impairment in responding to feedback information (Beats *et al.*, 1996; Elliott *et al.*, 1996, 1997; Purcell *et al.*, 1997; Elliott *et al.*, 1998; Shah *et al.*, 1999; Steffens *et al.*, 2001). If patients with a depressive illness commit an error, they can be at increased

risk of committing a subsequent error (Beats *et al.*, 1996; Elliott *et al.*, 1996, 1997, 1998; Steffens *et al.*, 2001); however, see also (Purcell *et al.*, 1997; Shah *et al.*, 1999). Although such increased risk was initially interpreted as a ‘catastrophic response to failure’ (Beats *et al.*, 1996), an alternative interpretation is a failure to adjust performance after feedback of error (Elliott *et al.*, 1997).

Abnormal responses to feedback information are consistent with influential theories of depressive illness. From a behavioural perspective, Lewinsohn hypothesized that reinforcement reducing contingencies occur in depressive illness, such that fewer events are potentially reinforcing, fewer are experienced as reinforcing, and social reinforcement is reduced due to impaired social interactions (Lewinsohn *et al.*, 1979; Elliott *et al.*, 1998). Beck’s cognitive theory posits that depressive illness is associated with enduring negative attitudes and assumptions, such dysfunctional schemata biasing the processing of feedback information and impairing performance (Beck, 1979; Elliott *et al.*, 1998).

In some speeded tasks, human performance adjustment is reliably associated with trial-to-trial change in reaction times (RTs), such as ‘post-error slowing’ (Rabbitt and Rogers, 1977; Laming, 1979; Ridderinkhof *et al.*, 2004; Holroyd *et al.*, 2005), which is an increase in RT immediately following feedback that an error has been committed. Previous studies of abnormal response to feedback have not investigated RT change in detail, and focused instead on response selection. Transient post-error slowing in healthy humans is associated with a reduced probability of committing a subsequent error (Laming, 1979; Holroyd *et al.*, 2005). If slowing were absent in depressive illness, it would suggest an increased risk of committing an error, consistent with most (Beats *et al.*, 1996; Elliott *et al.*, 1996, 1997, 1998; Steffens *et al.*, 2001) but not all (Purcell *et al.*, 1997; Shah *et al.*, 1999) reports. A blunted slowing response, after feedback of failure on tasks, has been reported in one study (Elliott *et al.*, 1997). Therefore, we tested the hypothesis that patients would exhibit a blunted RT and neural response to feedback of winning and losing, using quantitative modelling of RTs, a gambling task and fMRI. Control of behavioural response to feedback information involves transient RT and monoamine change (Ridderinkhof *et al.*, 2004). If patients do exhibit a blunted response, this would imply abnormal monoamine activity, and provide a potential link between influential monoamine (Goodwin, 1998) and cognitive-behavioural theories of depressive illness.

A distinction should be made between responses to rewarding and aversive feedback. A blunted response to rewarding feedback is consistent with anhedonia (Elliott *et al.*, 1998), the core clinical feature of depressive illness. However, aversive feedback in depressive illness is associated with both blunted (Parker, 1996; Power, 2003) and enhanced (Beck, 1979) avoidance responses. Neurophysiological measures have similarly been reported

as blunted (Ruchow *et al.*, 2004, 2005) and enhanced (Chiu and Deldin, 2007). In severe depressive illness, psychomotor retardation and depressive stupor reflect blunted forms of response (Parker, 1996). In contrast, mild to moderate depressive illness and more aversive stimuli, may be associated with active attempts at avoidance (e.g. complaints of symptoms, active avoidance of social interaction, suicidal preoccupation and attempts) (Beck, 1979). This could reflect two types of general behavioural response to perceived aversive stimuli: escape if possible, or give up trying if escape is not possible (i.e. ‘learned helplessness’, Matthews and Reid, 1998). As reported decades ago, many patients vary from day to day in their expression of predominately one or another pattern (Kendell, 1968). This hypothesis, of an interaction between illness severity and aversive stimulus intensity, might help explain other unexpected findings (e.g. Must *et al.*, 2006). Consequently, whilst we predicted that behavioural and neural responses to winning feedback would be blunted in depressive illness, an abnormally blunted or enhanced response to ‘lose’ feedback information was considered equally likely.

Our earlier report (Steele *et al.*, 2004) tested a hypothesis of abnormal neural response to the initial ‘tracking’ of undifferentiated (ignoring valence) feedback information, without considering behavioural response. This work represents the second part of the planned analysis, examining separately the behavioural and neural responses to positive (‘win’) and negative (‘lose’) feedback information, which may occur at a later stage of information processing, and control of response.

Materials and Methods

Subjects

Permission for the study was obtained from the local ethics committee and written informed consent obtained from all subjects. Data was obtained from 15 patients with a moderate-to-severe unipolar depressive illness and 14 controls, matched on the basis of age, percentage of females and NART (Nelson and Wilson, 1991). All subjects completed three self-ratings: depression (BDI) (Beck *et al.*, 1961), anxiety (SP) (Spielberger, 1983) and hedonia (SH—a low score indicating anhedonia) (Snaith *et al.*, 1995). Patients satisfied DSM IV criteria for major depressive disorder, and a Hamilton rating (Hamilton, 1960) was obtained as a measure of illness severity. All except one patient were receiving antidepressants. Medications were: sertraline ($n = 1$, 50 mg/day), fluoxetine ($n = 1$, 60 mg/day), phenelzine ($n = 2$, 45–75 mg/day), venlafaxine ($n = 2$, 150–375 mg/day), mirtazepine ($n = 2$, 15–45 mg/day), moclobemide ($n = 3$, 60 mg/day), citalopram ($n = 2$, 20 mg/day), imipramine ($n = 1$, 150 mg/day), amitriptyline ($n = 1$, 50 mg/day), pindolol ($n = 1$, 15 mg/day), quetiapine ($n = 1$, 300 mg/day), sodium valproate ($n = 1$, 200 mg/day), diazepam ($n = 1$, 5 mg/day), zopiclone ($n = 1$, 7.5 mg/day), L-tryptophan ($n = 1$, 300 mg/day), lithium carbonate ($n = 4$, 700–1000 mg/day). Medications were unchanged for 3 weeks prior to scanning. Other clinical details are summarized in Table 1.

Table 1 Clinical details of subjects

	Patients	Controls	
Age (years)	45.9 (10.7)	43.0 (13.3)	n.s.
Females/total	11/15	7/14	n.s.
NART	12.4 (3.8)	8.5 (5.4)	n.s.
BDI	36.9 (13.3)	1.1 (1.9)	<0.001
SP	59.0 (12.1)	29.3 (9.1)	<0.001
SH	33.8 (8.3)	51.9 (4.6)	<0.001
Hamilton	27.5 (6.1)	–	–

Note: Values are mean (standard deviation). Abbreviations: n.s. difference not significant; BDI, Beck depression inventory (Beck *et al.*, 1961); NART, national adult reading test (Nelson and Wilson, 1991); SP, Spielberger anxiety inventory (Spielberger, 1983); SH, Snaith–Hamilton hedonia scale (Snaith *et al.*, 1995); Hamilton depression rating scale (Hamilton, 1960).

Exclusion criteria were any other psychiatric diagnosis (which includes personality disorder), a history of substance misuse, structural brain abnormality, use of non-antidepressant medication which might alter brain metabolism, or neurological disorder. Patients were also excluded if they had an agitated depressive illness and patients and controls excluded if they had claustrophobia, as such subjects were thought to be very unlikely to tolerate scanning. Preference was given to recruiting patients with a relatively resistant illness, indicated by many months or years of illness despite treatment, as they were likely to be still unwell at the time of scanning.

Gambling task

As described in more detail elsewhere (Critchley *et al.*, 2000; Steele *et al.*, 2004), during fMRI, pairs of playing cards were presented to subjects who had to guess within 2.5 s which was the ‘correct’ card, indicating this with a button press. Visual feedback indicating ‘win’ or ‘lose’ (a ‘tick’ or ‘cross’) was then provided for 1 s and the next trial begun. Subjects were led to believe their responses determined the feedback and agreed to try to win as often as possible. Unknown to subjects, the feedback sequence was fixed and unrelated to the presented cards. This ensured all subjects received identical feedback irrespective of ability. The paradigm therefore consisted of a two-choice pseudo-instrumental task and card choices made by subjects were not meaningful. With regard to ‘cognitive control’ concepts (Ridderinkhof *et al.*, 2004), since there was no contingency to learn, only ‘feedback’ and not ‘response’ events occurred. For each subject, two behavioural values were derived (*bw* and *bl*), which reflected change in RT in response to ‘win’ (‘correct’) and ‘lose’ (‘error’) feedback, respectively.

Subjects were told that if they failed to respond, ‘the computer will make a random choice for you’. They were encouraged to always try to respond. This obscured the fact that the sequence of feedback was predetermined, but meant that subjects received ‘win’ feedback on about 50% of omitted responses. Consequently, for analysis, trials with a non-response were planned to be omitted. Blocks of 12 trials were delivered 24 times, resulting in 288 trials over 22 min.

Behavioural model

The change in observed RT as a consequence of feedback information was modelled as:

$$RT(n) - RT(n - 1) = bw * win(n - 1) + bl * lose(n - 1)$$

where *n* is the trial number, *win* was the sequence of feedback of winning coded as ‘0’ or ‘1’ (win); *lose* was similarly coded ‘0’ or ‘1’ (lose). The *bw* and *bl* terms were constants obtained by a linear regression of the observed change in RT on the stream of winning and losing feedback information.

Behavioural analysis

Behavioural measures were tested for significant deviations from normality using the one-sample Kolmogorov–Smirnov test and scatter plots inspected for outliers. Null hypotheses were tested using *t*-tests. Mean values, standard deviations, 95% confidence intervals, significance values and effect sizes were reported.

Image acquisition

Gradient echoplanar T2*-weighted BOLD contrast images were obtained using a GE Medical Systems Signa 1.5 T MRI scanner. A total of 30 axially orientated 5 mm thick contiguous interleaved slices were obtained for each volume, 500 volumes being obtained with a TR of 2.5 s, TE 40 ms, flip 90°, FOV 24 and matrix 64 × 64. The first four volumes were discarded to allow for transient effects. Image acquisition was asynchronous with respect to stimulus and feedback presentation events.

Image analysis

Using SPM2 (Friston, 2004), images were slice time corrected, realigned, spatially normalised and smoothed with a 8 mm Gaussian kernel. For analysis, images were scaled and high pass filtered (Frackowiak *et al.*, 2003). Both fMRI analyses used random effects event-related designs. One and two group *t*-tests were used at the 2nd level to test null hypotheses with small volume corrections for multiple testing defined by *a priori* identified regions of interest, as below.

Feedback analysis method—1st level

Event times were the feedback times for ‘win’ and ‘lose’ information obtained from each subject’s logfile. Two conditions were defined at the 1st level; the ‘win’ feedback times and the ‘lose’ feedback times. At the 1st level, the design matrix therefore consisted of ‘win’ feedback onset times modelled as δ -functions convolved with a haemodynamic response function, and ‘lose’ feedback onset times similarly modelled as δ -functions convolved with a haemodynamic response function. In addition, a constant term was included to model the baseline of unchanged BOLD activity, as a covariate of no interest (Frackowiak *et al.*, 2003). For ‘win’ feedback analysis, the contrast [win – lose] images for each subject were taken to a 2nd level analysis. Similarly, for ‘lose’ feedback analysis, the contrast [lose – win] images for each subject were taken to a 2nd level analysis.

RT analysis method—1st level

The events consisted of the onset times for the card presentations modulated by the observed RT on each trial obtained from each

subject's logfile. The 1st level design matrix therefore consisted of the card presentation times modelled as δ -functions multiplied by the RT for the trial, the result convolved with a haemodynamic response function, as the covariate of interest. The covariates of no interest consisted of card presentation times modelled as δ -functions convolved with a haemodynamic response function, and a constant term modelling the baseline of unchanged BOLD activity. SPM2 'beta' images (Frackowiak *et al.*, 2003), defined as the regression of observed BOLD on RT for each voxel, were taken to 2nd level analyses.

2nd level analyses

This was the same for both feedback and RT analyses. Two types of test were done. *One group t-tests* were used to test the null hypothesis of no activation for the 1st level contrast of interest; e.g. no ventral striatal activation in response to 'win' feedback for controls, no ventral striatal correlate with transient RT reduction in patients. *Two group independent t-tests* were used to test the null hypothesis of no difference between patient and control groups. The advantage of using one group *t-tests* in addition to two group *t-tests* was that it clarified the origin of any difference identified from a two group test; e.g. if locally increased brain activity in controls relative to patients was found using a two group *t-test*, one group *t-tests* indicated whether this was due to an increase in controls, a decrease in patients, or some combination of both.

Presentation of images and small volume corrections for multiple testing: All images were initially thresholded at $P < 0.005$ uncorrected. All tests were two-tailed.

Ventral striatum region of interest: If loci were present in the *a priori* defined ventral striatal region, a small volume correction for multiple testing was applied to test null hypotheses using the false discovery rate method (FDR) (Genovese *et al.*, 2002) as implemented for SPM2 (Friston, 2004). The location of the ventral striatum was determined from a high-resolution T1-weighted MRI image in MNI space ('Colin', Montreal Neurological Institute). Using this method, the ventral striatum was assumed to be centred at $(+/-18, 14, -9)$. The small volume correction used a 10-mm radius sphere. Five hypotheses were tested: that this region became more active in response to 'win' feedback (controls and patient groups tested separately), that the extent of activation correlated with transient RT reduction (controls and patient groups tested separately), and that patients had less activation in this region compared with controls in response to 'win' feedback. Overall, this tested whether the extent of increased activation associated with transient RT reduction occurred at the same location as those regions activated in response to 'win' feedback.

Medial frontal cortex region of interest: Images were initially thresholded at $P < 0.005$ uncorrected and a correction for multiple testing using the FDR method was made using a mask of the region of interest (Brodmann's area, BA 6, 8, 24, 32), (Ridderinkhof *et al.*, 2004) created using the 'PickAtlas' SPM tool (Maldjian *et al.*, 2003). Only midline regions significant after correction for multiple testing were of interest. Five hypotheses were tested: that the loci within this region became more active in response to 'lose' feedback (controls and patient groups tested separately), that the extent of activation correlated with transient RT increase (controls and patient groups tested separately), that patients had less activation in this region compared with controls in response to 'lose' feedback. Localized regions of activation after 'lose' feedback, significant after

correction for multiple testing, were used to centre 10 mm regions of interest for subsequent analyses. Overall, this tested whether the extent of increased activation with transient RT increase occurred at the same location as that activated in response to 'lose' feedback.

Results

Behavioural data

For controls the average *bw* was -31.28 (47.98); 95% confidence interval (CI) of -59.98 to -3.57 . The standard deviation is given in parenthesis. The average *bl* was 29.22 (47.85); 95% CI of 1.59 to 56.85 . Consequently, control subjects slowed after information they had committed an error (Laming, 1979) and responded faster after information they had chosen correctly. For patients, the average *bw* was 7.80 (47.79); 95% CI of -18.66 to 34.26 . The average *bl* was -9.51 (54.10); 95% CI of -39.48 to 20.44 . Therefore, the change in RT for patients was not significantly different from zero, for both 'win' and 'lose' feedback. The control and patient group *bl* values differed significantly ($P < 0.05$) as did the *bw* values ($P < 0.04$). These differences correspond to effect sizes of 0.61 and 0.65 and are in the moderate-to-large range, indicating a marked blunting of RT response to both 'win' and 'lose' feedback information in depressive illness.

Self-reported anhedonia as measured by the Snaith–Hamilton score (Snaith *et al.*, 1995) correlated negatively with *bl* (patients, $P = 0.032$; controls, $P = 0.013$) and positively with *bw* (patients, $P = 0.057$; controls $P = 0.008$). Since *bw* and *bl* correlated with the extent of anhedonia for both the medicated patient group and *unmedicated* control group, this suggests RT adjustment in response to feedback was independent of medication status. No other clinical variables correlated significantly. These findings are illustrated in Fig. 1. Therefore, we confirmed our hypothesis and replicated and extended previous observations.

It should be noted that patients and controls did not differ with respect to the average RT over all the trials, and the percentage of non-response trials ($P > 0.5$). Many subjects had no non-response trials, and for all other subjects, the non-response trials comprised no more than a few percent of total trials. Furthermore, discussion with subjects indicated that none had suspected that the feedback sequence was predetermined, and all were trying their best to maximise their 'wins'. Consequently, there was no clear evidence that patients were trying less hard than controls.

Image data and 'win' feedback

The random effects fMRI analysis of the effects of 'win' feedback indicated that control subjects responded by significant activation ($P = 0.02$, corrected) of the bilateral ventral striatum (Fig. 2A). As above, behavioural analysis indicated that the next response made by controls tended to

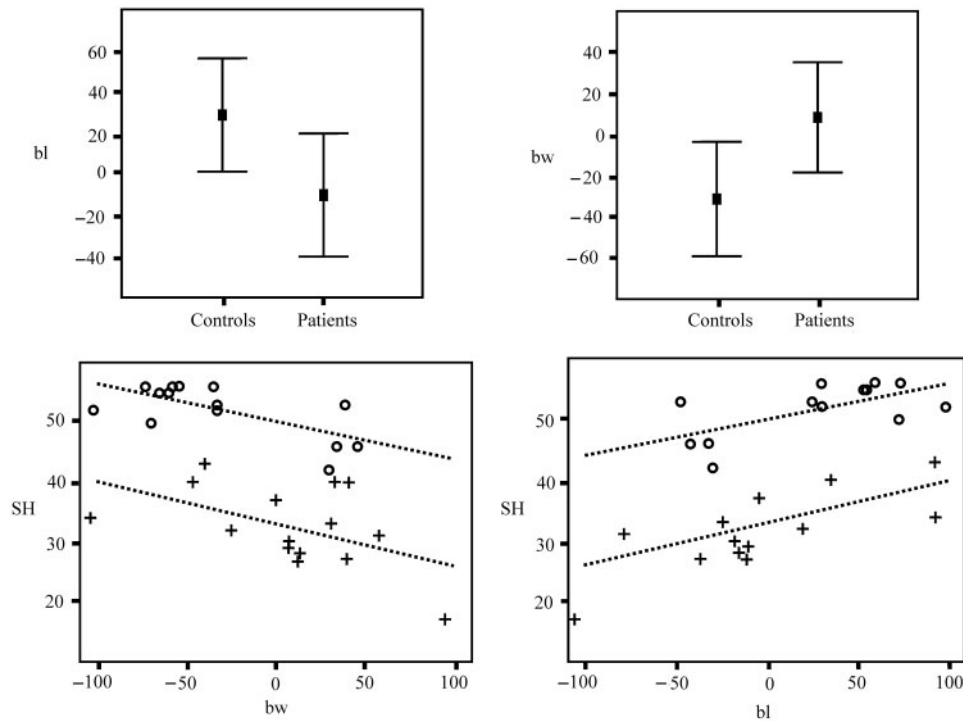


Fig. 1 Behavioural regression coefficients for patients and controls. **(A)** Average *bl* and *bw* values differed significantly ($P < 0.05$ and $P < 0.04$, respectively) for patients with a depressive illness and matched healthy controls. Controls slowed after feedback of an error and speeded up after feedback they were correct; patients did not. 95% confidence intervals are shown. **(B)** For both patient and control groups, *bw* and *bl* correlated significantly ($P < 0.05$) with anhedonia. The best fit linear regression lines are also indicated. Abbreviations: SH, Snaith–Hamilton hedonia scale (low score indicates anhedonia); o controls; + patients.

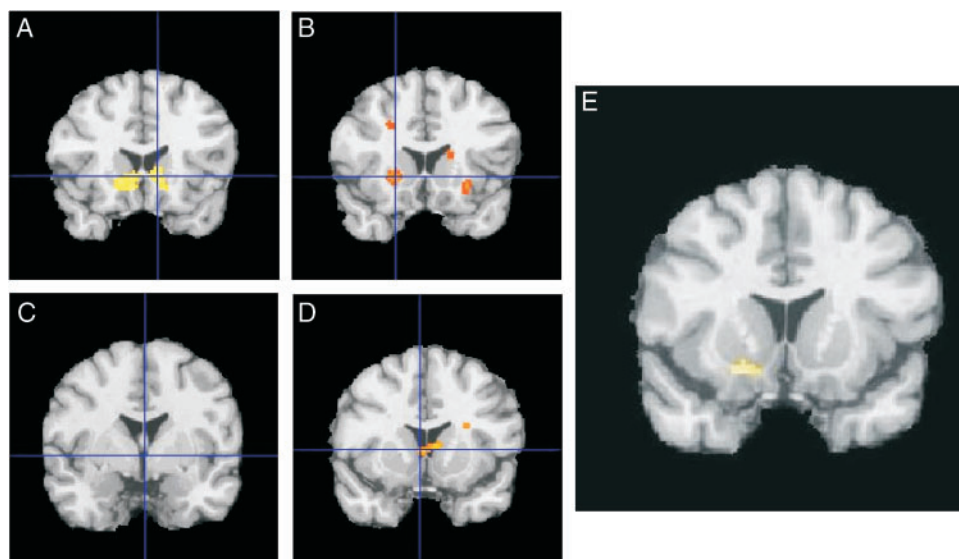


Fig. 2 Response to ‘win’ feedback in controls and patients. **(A)** Significant activation of the bilateral ventral striatum in response to ‘win’ feedback in control subjects; $(8, 20, 2)$, $z = 3.15$, $P = 0.02$ corrected and $(-16, 16, -8)$, $z = 3.25$, $P = 0.01$ corrected. **(B)** Positive correlation of ventral striatal activity with RT reduction in controls; $(-22, 18, -2)$, $z = 3.17$, $P = 0.036$ corrected. **(C)** Failure to activate the ventral striatum in response to ‘win’ feedback in depressive illness; $P > 0.005$ uncorrected. **(D)** Lack of correlation of ventral striatal activity with RT reduction in patients; $P > 0.005$ uncorrected. **(E)** Reduced ventral striatal activity in patients compared to controls in response to ‘win’ feedback, $P = 0.04$ corrected.

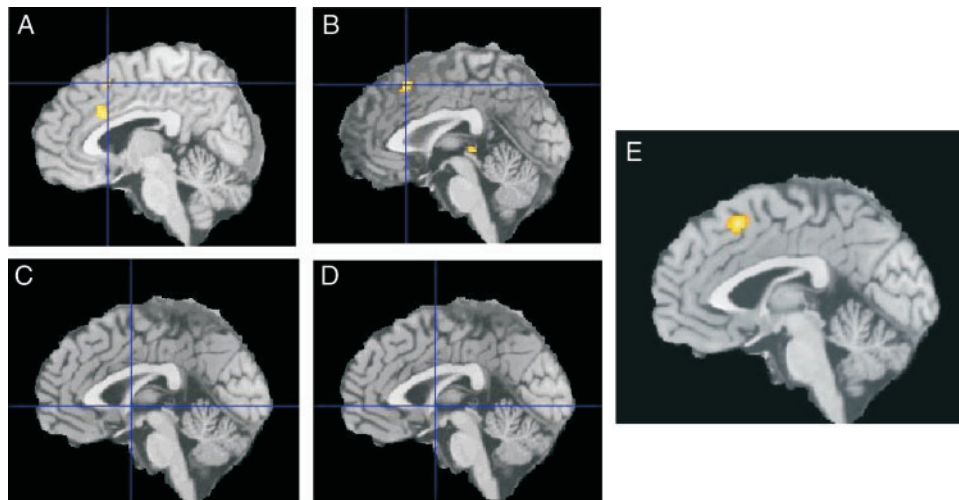


Fig. 3 Response to 'lose' feedback in controls and patients. (A) Significant activation of the medial frontal cortex in controls in response to 'lose' feedback; $(-6, 18, 52)$, $z = 3.30$, $P < 0.05$ corrected and $(-8, 22, 30)$, $z = 3.93$, $P < 0.05$ corrected. (B) Correlation of activation in medial frontal cortex with RT increase in controls; $(-2, 22, 50)$, $z = 2.86$, $P = 0.04$ corrected. (C) Failure to activate medial frontal cortex in depressive illness in response to 'lose' feedback; $P > 0.05$ uncorrected (D) lack of correlation between medial frontal activity and RT increase in depressive illness; $P > 0.05$ uncorrected. (E) Reduced medial frontal activity in patients with a depressive illness compared with controls following 'lose' feedback; $P = 0.03$ corrected.

be faster. The relation between RTs and neural activity was investigated in the separate RT random effects analysis. This found that the extent of ventral striatal activation in controls correlated significantly ($P = 0.036$, corrected) with speed of response (Fig. 2B). In contrast, patients did not respond to 'win' feedback by activation of the ventral striatum (Fig. 2C), behavioural analysis found no tendency for patients to respond faster on the next trial, and RT image analysis found no correlation between speed of response and ventral striatal activation (Fig. 2D). The decrease in ventral striatal activity in patients compared with controls was significant ($P = 0.04$ corrected; Fig. 2E).

Image data and 'lose' feedback

Analysis of the effects of 'lose' feedback indicated that controls responded by significant ($P < 0.05$, corrected) activation of the medial frontal cortex (Fig. 3A). This is in a region very similar to that reported in an fMRI study of healthy subjects designed to detect error signals associated with 'lose' feedback (Holroyd *et al.*, 2004). As above, behavioural analysis indicated that controls tended to be slower in responding to the next trial after feedback that they had committed an error. Image RT analysis found that the extent of slowing correlated significantly ($P = 0.04$, corrected) with activation of one of the regions in the medial frontal cortex (Fig. 3B). In contrast, patients did not activate the medial frontal cortex in response to feedback that they had committed an error (Fig. 3C), behavioural analysis found no tendency for patients to slow down on the next trial, and RT image analysis found no correlation between slowing and medial

frontal cortical activity (Fig. 3D). The decrease in medial frontal activity in patients compared with controls was significant ($P = 0.03$ corrected; Fig. 3E).

Discussion

The medial frontal cortical substrate for behavioural and cognitive control (response to negative feedback and error correction, including post-error slowing) in healthy subjects is of considerable current interest (Ridderinkhof *et al.*, 2004; Holroyd *et al.*, 2005). The 'error related negativity' (ERN) is an electrophysiological signal generated in a broad midline anterior cingulate region which includes BA 6, 8, 24 and 32, in response to feedback of error (Ridderinkhof *et al.*, 2004). A similar signal can be detected using fMRI (Holroyd *et al.*, 2004). Lack of post-error slowing in depressive illness suggests abnormal behavioural control and abnormal ERNs. Consistent with this, two studies have described reduced ERNs in depressive illness (Ruchow *et al.*, 2004, 2005); however, abnormally increased ERNs have also been reported (Chiu and Deldin, 2007).

There is considerable evidence that the ventral striatum encodes a monoamine 'phasic' ('burst' and 'pause' activity, distinct from constant baseline firing) prediction signal for rewarding events (Schultz *et al.*, 1997; Schultz and Dickinson, 2000; Montague *et al.*, 2004), and both the ERN and 'post-error-slowness' may reflect such signals (Holroyd and Coles, 2002; Holroyd *et al.*, 2005). This signal has also been reported in the ventral striatum of healthy human subjects learning to predict rewarding and aversive events (O'Doherty *et al.*, 2003, 2004; Seymour *et al.*, 2004, 2005). Reduced activity in the ventral striatum, associated with an abnormal response to feedback in

depressive illness, has been reported (Elliott *et al.*, 1998). Blunted RT responses may therefore be consistent with reduced ERNs and reduced ventral striatal activity. Consequently, our results confirmed our initial hypotheses, replicated a previous report of blunted ventral striatal activity (Elliott *et al.*, 1998), and extended previous observations. The pattern of blunted neural and behavioural response to feedback implies that the anterior cingulate substrate for error correction (Ridderinkhof *et al.*, 2004; Holroyd *et al.*, 2005), which includes projections from the monoamine systems (Holroyd and Coles, 2002; Ridderinkhof *et al.*, 2004), is dysfunctional in depressive illness.

As mentioned above, in early studies, the tendency for depressed patients to commit an error, following feedback they had committed an error, was interpreted as a ‘catastrophic response to failure’ (Beats *et al.*, 1996). However, later studies reported that these data were also consistent with a quite different interpretation; a reduced or blunted response to feedback in depressive illness (Beats *et al.*, 1996; Elliott *et al.*, 1996, 1997, 1998; Steffens *et al.*, 2001). From this perspective, depressive illness is associated with a specific failure to reduce the risk of future error, given feedback that an error has just been committed. The results of this study are consistent with the latter interpretation (lack of RT increase in response to ‘lose’ feedback), though actual card choices were not meaningful, as the feedback sequence was predetermined.

A limitation of the study was that patients were medicated, controls were not. This was because it was impractical to investigate this severity of depressive illness in an unmedicated state due to ethical considerations. The blunted RT responding to feedback information is unlikely to reflect a medication effect, as the extent of blunting correlated significantly and very similarly, with self-report anhedonia, in both unmedicated control and patient groups. However, medication may still affect these observations, so we are currently investigating the effects of medication on healthy controls with a similar paradigm. A further limitation of the study is that patients with major comorbidity were excluded from the study. Comorbidity is very common in mood disorder, so the results may not reflect all patients. However, such exclusion criteria are commonly applied and usually considered necessary for interpretation of findings.

Behaviour occurs in the context of a stream of feedback information, with feedback becoming internalised through learning (Ridderinkhof *et al.*, 2004; Holroyd *et al.*, 2005). The monoamine systems such as dopamine and serotonin are crucial for learning about reward and punishment (Schultz *et al.*, 1997; Schultz and Dickinson, 2000; Daw *et al.*, 2002; Montague *et al.*, 2004) and are linked to emotional response (Daw *et al.*, 2002). It has long been known that diverse antidepressants act directly on the monoamine systems; however, the mechanisms by which such actions result in a delayed alleviation of the clinical

features of depressive illness remain obscure. Furthermore, the medial frontal cortex, and in particular the anterior cingulate, is repeatedly reported to be functionally abnormal in neuroimaging studies of depressive illness. Again though, the mechanisms by which such replicated abnormalities are linked to the clinical features of illness remain obscure.

This study suggests a direct link between the core subjective symptom of anhedonia, replicated neuropsychological deficits (Elliott *et al.*, 1996, 1997, 1998; Steffens *et al.*, 2001), electrophysiological (Ruchow *et al.*, 2004, 2005) and imaging (Elliott *et al.*, 1998) abnormalities of the anterior cingulate and ventral striatum, in the context of hypothesized dysfunction of the error correction system. Since ERNs may reflect phasic decrease of dopamine (Holroyd and Coles, 2002; Holroyd *et al.*, 2005), reduced ERNs and anterior cingulate error-related activity in depressive illness may reflect reduced phasic dopamine decrease. Since there is evidence for reciprocal dopaminergic and serotonergic activity (Daw *et al.*, 2002), an alternative interpretation is reduced phasic serotonergic increase. There is evidence that in the basal ganglia, serotonin release promotes dopamine release (Daw *et al.*, 2002), so reduced dopamine activity could account for the observed blunted ventral striatal response to ‘win’ feedback. This interpretation, of abnormal phasic monoamine activity in depressive illness, appears consistent with the monoamine theory of mood disorder (Goodwin, 1998), and warrants further investigation.

In summary, this study places abnormal behavioural and neural responses to positive and negative feedback information in depressive illness, in the context of current neurobiological work on behavioural and cognitive control. The findings are consistent with a hypothesis of blunted RT and phasic neural responses to oppositely valenced stimuli in depressive illness. Nevertheless, the aversive feedback used in this study was mild, and the illnesses were in the moderate to severe range. As discussed previously, more aversive feedback in milder illness may provoke an opposite response. This requires further study.

Acknowledgements

We thank all the volunteers who participated in this study. The work was supported by the Gordon Small Charitable Trust. We thank Peter Dayan and Quentin Huys for behavioural modelling discussions and John Steele for proof-reading the text.

References

- Austin MP, Mitchell P, Goodwin GM. Cognitive deficits in depression: possible implications for functional neuropathology. *Br J Psychiatry* 2001; 178: 200–6.
- Beats BC, Sahakian BJ, Levy R. Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. *Psychol Med* 1996; 26: 591–603.

- Beck AT. Cognitive theory of depression. New York: John Wiley and Sons; 1979.
- Beck AT, Ward HC, Mendelson M. An inventory for measuring depression. *Arch Gen Psychiatry* 1961; 4: 561–71.
- Chiu PH, Deldin PJ. Neural evidence for enhanced error detection in major depressive disorder. *Am J Psychiatry* 2007; 164: 608–16.
- Critchley HD, Elliott R, Mathias CJ, Dolan RJ. Neural activity relating to generation and representation of galvanic skin conductance responses: a functional magnetic resonance imaging study. *J Neurosci* 2000; 20: 3033–40.
- Daw ND, Kakade S, Dayan P. Opponent interactions between serotonin and dopamine. *Neural Netw* 2002; 15: 603–16.
- Ebmeier KP, Donaghey C, Steele JD. Recent developments and current controversies in depression. *Lancet* 2006; 367: 153–67.
- Elliott R, Sahakian BJ, Herrod JJ, Robbins TW, Paykel ES. Abnormal response to negative feedback in unipolar depression: evidence for a diagnosis specific impairment. *J Neurol Neurosurg Psychiatry* 1997; 63: 74–82.
- Elliott R, Sahakian BJ, McKay AP, Herrod JJ, Robbins TW, Paykel ES. Neuropsychological impairments in unipolar depression: the influence of perceived failure on subsequent performance. *Psychol Med* 1996; 26: 975–89.
- Elliott R, Sahakian BJ, Michael A, Paykel ES, Dolan RJ. Abnormal neural response to feedback on planning and guessing tasks in patients with unipolar depression. *Psychol Med* 1998; 28: 559–71.
- Frackowiak RS, Ashburner JT, Penny WD, Zeki S, Friston KJ, Frith CD, et al. Human brain function. Second Edition. London: Academic Press; 2003.
- Friston K. Introduction to statistical parametric mapping. In: Frackowiak RSJ, editor. Human brain function. London: Academic Press; 2004.
- Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage* 2002; 15: 870–8.
- Goodwin G. Mood disorder. In: Johnstone EC, Freeman CPL, Zealley AK, editors. Companion to psychiatric studies. Edinburgh: Churchill Livingstone; 1998.
- Hamilton M. Rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23: 56–62.
- Holroyd CB, Coles MG. The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. *Psychol Rev* 2002; 109: 679–709.
- Holroyd CB, Nieuwenhuis S, Yeung N, Nystrom L, Mars RB, Coles MG, et al. Dorsal anterior cingulate cortex shows fMRI response to internal and external error signals. *Nat Neurosci* 2004; 7: 497–8.
- Holroyd CB, Yeung N, Coles MG, Cohen JD. A mechanism for error detection in speeded response time tasks. *J Exp Psychol Gen* 2005; 134: 163–91.
- Kendell RE. The classification of depressive illness. London: Oxford University Press; 1968.
- Laming D. Choice reaction performance following an error. *Acta Psychologica* 1979; 43: 199–224.
- Lewinsohn PM, Youngren MA, Grosscup SJ. Reinforcement and depression. In: Depue A, editor. The psychobiology of depressive disorders: implications for the effects of stress. New York: Academic Press; 1979.
- Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 2003; 19: 1233–9.
- Matthews K, Reid I. Animal models for depression: the anhedonic rat. In: Ebert D, Ebmeier KP, editors. New models for depression. Basel: Karger; 1998.
- Montague PR, Hyman SE, Cohen JD. Computational roles for dopamine in behavioural control. *Nature* 2004; 431: 760–7.
- Must A, Szabo Z, Bodi N, Szasz A, Janka Z, Keri S. Sensitivity to reward and punishment and the prefrontal cortex in major depression. *J Affect Disord* 2006; 90: 209–15.
- Nelson HE, Wilson JR. The revised national adult reading test - test manual. Winsor: NFER-Wilson; 1991.
- O'Doherty J, Dayan P, Schultz J, Deichmann R, Friston K, Dolan RJ. Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science* 2004; 304: 452–4.
- O'Doherty JP, Dayan P, Friston K, Critchley H, Dolan RJ. Temporal difference models and reward-related learning in the human brain. *Neuron* 2003; 38: 329–37.
- Parker G. Melancholia: a disorder of movement and mood. Cambridge: Cambridge University Press; 1996.
- Power M, editor. Mood disorders: a handbook of science and practice. New York: John Wiley and Sons; 2003.
- Purcell R, Maruff P, Kyrios M, Pantelis C. Neuropsychological function in young patients with unipolar major depression. *Psychol Med* 1997; 27: 1277–85.
- Rabbitt PMA, Rogers B. What does man do after he makes an error? An analysis of response programming. *Q J Exp Psychol* 1977; 29: 727–43.
- Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S. The role of the medial frontal cortex in cognitive control. *Science* 2004; 306: 443–7.
- Ruchow M, Herrnberger B, Beschoner P, Gron G, Spitzer M, Kiefer M. Error processing in major depressive disorder: Evidence from event-related potentials. *J Psychiatr Res* 2005; 40: 37–46.
- Ruchow M, Herrnberger B, Wiesend C, Gron G, Spitzer M, Kiefer M. The effect of erroneous responses on response monitoring in patients with major depressive disorder: a study with event-related potentials. *Psychophysiology* 2004; 41: 833–40.
- Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. *Science* 1997; 275: 1593–9.
- Schultz W, Dickinson A. Neuronal coding of prediction errors. *Annu Rev Neurosci* 2000; 23: 473–500.
- Seymour B, O'Doherty JP, Koltzenburg M, Wiech K, Frackowiak R, Friston K, et al. Opponent appetitive-aversive neural processes underlie predictive learning of pain relief. *Nat Neurosci* 2005; 8: 1234–40.
- Seymour B, O'Doherty JP, Dayan P, Koltzenburg M, Jones AK, Dolan RJ, et al. Temporal difference models describe higher-order learning in humans. *Nature* 2004; 429: 664–7.
- Shah PJ, O'Carroll RE, Rogers A, Moffoot AP, Ebmeier KP. Abnormal response to negative feedback in depression. *Psychol Med* 1999; 29: 63–72.
- Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. *Br J Psychiatry* 1995; 167: 99–103.
- Spielberger CD. State-trait anxiety inventory for adults, STAI Form Y-1. Palo-Alto: Mind Garden; 1983.
- Steele JD, Meyer M, Ebmeier KP. Neural predictive error signal correlates with depressive illness severity in a game paradigm. *NeuroImage* 2004; 23: 269–80.
- Steffens DC, Wagner HR, Levy RM, Horn KA, Krishnan KR. Performance feedback deficit in geriatric depression. *Biol Psychiatry* 2001; 50: 358–63.