Published in final edited form as:

Neuroimage. 2008 September 1; 42(3): 1118–1126. doi:10.1016/j.neuroimage.2008.05.049.

Neural basis of abnormal response to negative feedback in unmedicated mood disorders[☆]

Joana V. Taylor Tavares^{a,b,c,e}, Luke Clark^{d,e,*}, Maura L. Furey^b, Guy B. Williams^c, Barbara J. Sahakian^{a,e}, and Wayne C. Drevets^b

^a Department of Psychiatry, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

^b Section on Neuroimaging in Mood and Anxiety Disorders, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland, USA

^c Wolfson Brain Imaging Centre, University of Cambridge, Cambridge, UK

^d Department of Experimental Psychology, University of Cambridge, Cambridge, UK

^e Behavioural and Clinical Neuroscience Institute, University of Cambridge, UK

Abstract

Depressed individuals show hypersensitivity to negative feedback during cognitive testing, which can precipitate subsequent errors and thereby impair a broad range of cognitive abilities. We studied the neural mechanisms underlying this feedback hypersensitivity using functional magnetic resonance imaging (fMRI) with a reversal learning task that required subjects to ignore misleading negative feedback on some trials. Thirteen depressed subjects with major depressive disorder (MDD), 12 depressed subjects with bipolar disorder (BD) and 15 healthy controls participated. The MDD group, but not the BD group, demonstrated enhanced sensitivity to negative feedback compared to controls, as indicated by the rates of rule reversal following misleading negative feedback. In the control and BD groups, hemodynamic activity was significantly higher in the dorsomedial and ventrolateral prefrontal cortices during reversal shifting, and significantly lower in the right amygdala in response to negative feedback. The extent to which the amygdala showed less activity during negative feedback correlated inversely with the behavioral tendency to reverse after misleading feedback. This effect was not present in the MDD group, who also failed to recruit the prefrontal cortex during behavioral reversal. Hypersensitivity to negative feedback is present in unmedicated depressed patients with MDD. Disrupted top-down control by the prefrontal cortex of the amygdala may underlie this abnormal response to negative feedback in unipolar depression.

Introduction

The World Health Organization ranks major depressive disorder (MDD) as the leading cause of years-of-life lived with disability (World Health Organisation, 2001). Depressed patients commonly attribute their occupational and scholastic impairment to a diminished ability to concentrate or make decisions, a symptom codified as one of the nine diagnostic criteria for a major depressive episode (American Psychiatric Association, 1994). Characterization of this symptom has proven elusive, however, as unmedicated depressed patients studied in early to

[☆]Previous Presentation. This work was presented at the 12th annual meeting of the Organization for Human Brain Mapping, Florence, Italy (June 2006) and at the 45th annual meeting of the American College of Neuropsychopharmacology (ACNP), Florida, USA (December 2006).

*Corresponding author. Department of Experimental Psychology, University of Cambridge, Cambridge CB2 3EB, UK. Fax: +44 1223 333564. E-mail address: lc260@cam.ac.uk (L. Clark).

mid-life show relatively subtle impairments on conventional neuropsychological tests (Grant et al., 2001). One prominent hypothesis holds that depressed patients manifest an abnormal response to negative feedback. On memory or planning tasks, depressed patients respond catastrophically to error feedback, in that they are disproportionately likely to commit an error on a trial that follows negative feedback (Elliott et al., 1996; Steffens et al., 2001). This psychological mechanism may affect cognitive function across a range of task domains. Abnormal response to negative feedback was reported previously on a probabilistic reversal learning (PRL) task where subjects were requested to ignore misleading negative feedback to correct responses on 20% of trials. MDD patients reversed in response to the misleading task feedback, while showing intact rule acquisition and normal levels of response perseveration when the rule actually reversed (Murphy et al., 2003).

These cognitive effects were specific to depression compared to other neuropsychiatric conditions (Elliott et al., 1996), yet it remained unclear how this effect related to the spectrum of depressive disorders (Shah et al., 1999). Psychiatric diagnostic criteria distinguish patients who experience only depressive episodes (i.e. “unipolar depression” or major depressive disorder, MDD) from patients who experience manic as well as depressive episodes (i.e. bipolar disorder, BD). There are few studies comparing patients in the depressed phase of these disorders directly. Dysfunctional attitudes and negative automatic thoughts are central to the problems experienced by patients with MDD, in whom cognitive behavioral treatments have demonstrated efficacy (Hollon et al., 2002). Bipolar depression, in contrast, may show increased prevalence of psychomotor symptoms (Mitchell et al., 2001), and pharmacotherapy and social rhythm therapy are recommended as first-line treatments (Frank et al., 2005).

The primary aim of the present study was to compare the neural basis of feedback processing in depressed subjects with MDD versus healthy controls (HCs). In addition, a depressed BD group was tested to examine specificity of these effects within the depressive spectrum. We studied only unmedicated cases, as feedback processing is known to be modulated by antidepressant drugs (Chamberlain et al., 2006) and the hemodynamic parameters that compose the fMRI signal may be altered by psychotropic drug effects. We employed an fMRI version of the PRL paradigm, which has been used in previous behavioral studies to quantify feedback sensitivity (Chamberlain et al., 2006; Murphy et al., 2003). The inclusion of misleading negative feedback in this task allowed us to distinguish the neural activity related to behavioral reversal from neural activity related to the processing of negative feedback. HCs were shown previously to recruit the ventrolateral prefrontal cortex (vlPFC; which includes part of the lateral orbitofrontal cortex; OFC), the dorsomedial prefrontal cortex (dmPFC) and the ventral striatum during switch trials where negative feedback precipitated behavioral reversal (Cools et al., 2002; Evers et al., 2005). Based on research showing hypofrontality in depression during tasks of cognitive control (Blumberg et al., 2003; Goethals et al., 2005; Kronhaus et al., 2006; Okada et al., 2003), we predicted reduced signal change in vlPFC and dmPFC in the unmedicated mood disorder groups during reversal switches. In addition, previous work has shown greater amygdala responses to negative words (e.g. “failure”) in MDD subjects compared to healthy subjects (Siegle et al., 2002; Siegle et al., 2007), and the functional relationship between the amygdala and the prefrontal cortex has been linked to genetic vulnerability to affective disorders (Pezawas et al., 2005). Consequently, we hypothesised that the amygdala would be recruited during receipt of negative feedback and would be a further locus of between-group differences between depressed patients and controls.

Methods

Participants

We recruited right-handed subjects aged 18 to 55 years who were currently experiencing a MDE and met DSM-IV criteria (American Psychiatric Association, 1994) for either MDD

($n=17$) or BD ($n=16$), or had never met criteria for a major psychiatric disorder (HCs, $n=18$). Psychiatric status was established by the Structured Clinical Interview for DSM-IV and confirmed by an unstructured interview with a psychiatrist. Subjects were excluded if they met DSM-IV criteria for alcohol and/or substance abuse within 1 year prior to screening, had ever met criteria for dependence on alcohol or any substance other than nicotine, were exposed to psychotropic medications within 3 weeks of scanning (8 weeks for fluoxetine), showed structural brain abnormalities on MRI, had a history of medical or neurological disease or clinically significant head injury, had a full scale IQ below 85, or were currently pregnant. All depressed subjects had age-at illness-onset ≤ 40 years. The MDD and BD subjects were recruited through the outpatient clinics of the NIH Clinical Centre, and the controls were recruited via community advertising. Subjects gave written informed consent after receiving a full explanation of the study as approved by the NIMH IRB.

Procedure

Participants were scanned while performing up to 8 successive runs of the PRL task (Cools et al., 2002), with each run lasting approximately 9 min (245 acquisitions). Prior to scanning, subjects completed one run as practice. The test was programmed using E-prime (www.pstnet.com) with responses registered by a two-button keypad. Each run consisted of ten discrimination stages yielding a total of nine reversals. Rule reversals occurred every 10–15 correct responses. Misleading negative feedback (henceforth ‘probabilistic errors’) was presented in a pseudo-randomised sequence on approximately 20% of trials, with 0–4 probabilistic errors per reversal. The task instructions stated that “on some goes, the computer will tell you that you were wrong even if you chose the correct pattern. Your task is to stick to the pattern that is usually correct. So in other words, always choose that pattern that is correct more often than the other pattern” (see Cools et al., 2002 for further details).

Three pairs of stimuli were used for the test, so each subject saw each pair of stimuli during 3 runs (including the practice run). On each trial, the stimulus pair was presented for 2000 ms. Feedback (a green smiley face or red sad face, presented centrally for 500 ms) was presented immediately after the response. Following feedback presentation, stimuli and feedback were replaced by a crosshair for a variable inter-trial interval, so that each trial lasted for 3253 ms, enabling precise desynchronization from the repetition time (TR) of 2200 ms. If no response was made in the 2000 ms window, a message appeared on the screen reading ‘Too Late’.

Image acquisition

Each participant was scanned in a 3 T MRI scanner (Signa; GE Medical Systems, Waukesha, Wisconsin). T2*-weighted echo planar images (EPIs) depicting the BOLD contrast were acquired with a 2.2 s repetition time (echo time 23 ms; field of view 24 cm). Whole-brain acquisitions (245 per run) consisted of 36 sagittally-oriented slices (4 mm thickness; matrix size 64×64). The first four EPI volumes in each session were discarded to avoid T1 equilibrium effects. A high-resolution T1-weighted magnetization-prepared rapid acquisition gradient-echo sequence (MP-RAGE) structural image was acquired for use in spatial normalisation.

Imaging analysis

Data analyses were performed using SPM2 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK). Image pre-processing consisted of slice acquisition time correction, reorientation, within-subject realignment, coregistration between EPI and MP-RAGE images, spatial normalisation to the standard Montreal Neurological Institute (MNI) T1 template and spatial smoothing using a Gaussian kernel (8 mm full-width at half-maximum). Global scaling was applied. The hemodynamic response function was modelled to the onset of the subject's response, which co-occurred with feedback presentation.

Data were excluded from the analysis if there was excessive movement, this was considered to be movement greater than one-half of a voxel within a run.

A canonical hemodynamic response, with time derivatives, was used as a covariate in a general linear model and a parameter estimate was generated for each voxel, for each event type. Six event types were modelled. First, correct responses followed by positive feedback were modelled as a baseline event (event 1). The probabilistic errors where subjects received misleading negative feedback following a rule-adherent ('correct') response were divided into two event types: those errors that prompted reversal on the subsequent trial ('probabilistic switch errors'; event 2) and those errors that did not prompt reversal on the subsequent trial ('probabilistic non-switch errors'; event 3). The reversal errors that occurred after genuine rule reversals were also subdivided into two event types: those 'reversal non-switch' errors where the subject did not reverse their response on the subsequent trial (event 4) and 'final reversal errors' that immediately preceded a reversal in behavioral responding (event 5). In addition, error trials subsequent to incorrect response reversal due to misleading negative feedback were modelled (event 6).

Based on the six event types, the following contrasts were computed for each session: Contrast 1: probabilistic switch errors minus correct response baseline (event 2 minus event 1). Contrast 2: probabilistic non-switch errors minus correct response baseline (event 3 minus event 1). Contrast 3: probabilistic switch errors minus probabilistic non-switch errors (event 2 minus event 3). Contrast 4: all negative feedback events minus correct response baseline (event types 2, 3, 4, 5, 6 minus event 1). Contrast 5: errors where the subject subsequently reversed responding (events 2 and 4) minus errors where the subject did not subsequently reverse responding (events 3 and 5). Individual contrast images were taken to a second level analysis.

For the between-group contrasts, the *a priori* hypotheses were tested using a region-of-interest (ROI) analysis in 5 regions. The MarsBar tool (Brett et al., 2002) was used to average signal within ROIs derived from the activation peaks identified by Cools et al. (2002) and as applied in Evers et al. (2005). The ROIs were spheres of 10 mm radius centred around the following MNI coordinates: dmPFC ($x, y, z=8, 32, 52$), left vlPFC ($-32, 24, -4$) and right vlPFC ($38, 24, -2$). These ROI thus encompassed the grey matter of the superior frontal gyrus (dmPFC) and lateral orbital cortex (i.e., Brodmann Area 47; vlPFC), respectively (Ongur et al., 2003; Talairach and Tournoux, 1988). In addition, ROIs for left and right amygdala were employed from the Automated Anatomical Labelling map (Tzourio-Mazoyer et al., 2002). The initial spherical dmPFC ROI was situated near the brain edge, and was cropped by multiplying the spherical ROI used by Evers et al. (2005) by the binary brain masks used for each subject. Between-group differences in ROI signal change were only reported if the overall group $\times$ condition ANOVA was significant for that region. Stereotaxic coordinates were converted from MNI spatial array to that of Talairach and Tournoux (1988) using an algorithm by M. Brett (www.mrc-cbu.cam.ac.uk/imaging).

To identify other regions where task-related neurophysiological activity differed across groups, an exploratory whole-brain SPM analysis was performed *post hoc*. A one-way ANOVA was computed voxel-by-voxel and *t*-values were calculated for each voxel, treating inter-subject variability as a random effect. The significance threshold for regional differences in BOLD contrast between groups was set at $p \leq 0.05$ after applying corrections for multiple comparisons using the cluster test (Poline et al., 1997).

Behavioral data analysis

On the PRL task, the rate of errors per rule reversal was calculated (total reversal errors/total rule reversals), and the rate of behavioral switches following misleading negative feedback ('probabilistic switch rate') was calculated by dividing the number of probabilistic switches

by the total number of trials where misleading negative feedback was presented. Further dependent measures were the mean reaction time (RT) on correct responses, the mean number of correct responses per run, and the mean number of spontaneous errors that could not be attributed to misleading feedback or rule reversal. Between-group differences were assessed using univariate analysis of variance (ANOVA) thresholded at $p \leq 0.05$ (two-tailed), with Tukey tests for between-group comparisons. Correlational analyses were used to investigate the relationship between test performance and task-related fMRI activity based on extracted signal within the ROIs, using Pearson's (r) correlation coefficients.

Results

Of the subjects recruited, 3 HCs, 4 MDD and 5 BD subjects were excluded from the analysis due to excessive movement (i.e., greater than one-half of a voxel within a run). The clinical, behavioral and imaging results presented henceforth and in the tables and figures pertain only to those subjects whose image data were included in the analyses. The three subject groups did not differ significantly in age, gender, education status or IQ ($p > 0.01$). Both depressed groups displayed elevated scores on the Montgomery–Asberg Depression Rating Scale ($F = 72.1$, $p < 0.001$) relative to the HCs. The BD and MDD groups showed comparable ratings of depression severity (see Table 1), and both groups evidenced relatively low mania ratings (Young Mania Rating Scale mean MDD = 4.3, mean BD = 5.8, $t = -0.80$, $p = 0.43$). The BD group was more anxious than the MDD group on the Hamilton Anxiety Rating Scale ($p = 0.011$).

The behavioral data on the PRL indicated no between-group differences in errors per rule reversal, number of correct responses, reaction time on correct responses, or spontaneous errors ($p > 0.1$). The probabilistic switch rate differed significantly across groups ($F = 4.54$, $p = 0.02$), due to a higher probabilistic switch rate in the MDD group compared to the HC ($p = 0.017$) and a trend towards a higher rate in the MDD group compared to the BD group ($p = 0.087$). The BD and HC groups did not differ significantly ($p = 0.84$) (see Fig. 1A).

Region-of-interest analyses of fMRI data

The one-way ANOVA results for the predefined ROIs showed significant between group differences for the ROIs located in the dmPFC and the right and left vIPFC. In the dmPFC ROI (Fig. 2C), signal change differed significantly across groups for the contrasts of probabilistic switch errors minus correct responses [$F(2,37) = 3.90$, $p = 0.029$], probabilistic non-switch errors minus correct responses [$F(2,37) = 3.30$, $p = 0.048$], and all negative feedback against correct responses [$F(2,37) = 3.50$, $p = 0.041$]. In the right vIPFC ROI (Fig. 2B), signal change differed significantly across groups in the contrasts of probabilistic switch errors minus correct responses [$F(2,37) = 4.17$, $p = 0.023$], probabilistic switch minus probabilistic non-switch errors (event 2–event 3) [$F(2,37) = 4.00$, $p = 0.016$] and in the overall comparison of all switch-related activity minus all non-switch related errors (event 2+4 minus event 3+5) [$F(2,37) = 3.72$, $p = 0.034$]. In the left vIPFC ROI (Fig. 2A), there were significant between-group differences for the contrast of probabilistic switch minus probabilistic non-switch errors [$F(2,37) = 3.75$, $p = 0.033$]. Follow-up between-group comparisons for these contrasts are summarised in Table 2.

Overall, the controls recruited the bilateral vIPFC and dmPFC ROIs on trials in which misleading negative feedback triggered reversal, compared to trials in which misleading negative feedback did not precipitate reversal (Fig. 2). A comparable pattern of activity was evident in the BD group. In contrast, the MDD group failed to recruit the vIPFC and medial PFC ROIs on trials where negative feedback triggered reversal. The fMRI data confirmed that this network was also recruited during appropriate reversal switches in the HCs (see Supplementary material), replicating the results of previous studies (Cools et al., 2002; Evers et al., 2005; Kringelbach and Rolls, 2003; Remijne et al., 2005).

In the right amygdala ROI, the hemodynamic activity *decreased* significantly during receipt of negative feedback (relative to correct responses) in the HC and BD groups, but this reduction was not significant in the MDD group (Fig. 3D). Using a planned contrast coefficient to directly compare the MDD and HC groups (Cardinal and Aitken, 2006), less of a reduction in amygdala activity was identified in the MDD group during receipt of negative feedback, compared to HCs ($t=1.69$, $p=0.05$). Furthermore, in the HC group, the extent of this decrease in amygdala activity was negatively correlated with the probabilistic switch rate ($r=0.63$, $p=0.01$) (see Fig. 3A). This negative correlation was also apparent at a trend in the BD subjects ($r=0.50$, $p=0.096$) (Fig. 3B). The correlation between the response in the right amygdala ROI and the probabilistic switch rate was not significant in the MDD subjects ($r=-0.16$, $p=0.59$) (Fig. 3C), and the correlation coefficients differed significantly between the MDD and HC groups (Fisher's r to z : $z=2.13$ $p=0.03$).

Post-hoc correlations between response to negative feedback for the other ROIs (vlPFC and dmPFC) and probabilistic switch rate were performed. These were considered exploratory and were not corrected for multiple comparisons. In the BD group, left vlPFC responses to negative feedback correlated inversely with probabilistic switch rate ($r=-0.635$, $p=0.027$). Thus, increased neurophysiological response to negative feedback in this region was associated with a lower probabilistic switch rate. No other correlations were significant.

Whole-brain between-group comparisons

Tables 3–4 display the between-group whole-brain comparisons for the Contrasts 1–5 (defined above). No results for the MDD–HC, HC–BD and BD–HC remained significant after applying corrections for multiple testing. The contrast of probabilistic switch errors minus correct responses (contrast 1), revealed areas of increased activity in the dmPFC and right vlPFC in the BD compared to the MDD groups, consistent with the ROI group differences outlined above. In addition, this contrast showed an area of increased activity in the posterior cingulate cortex in the MDD compared to the BD group (see Supplementary Figs. S1 and S2).

Discussion

Adaptive behavior in daily living requires that individuals are able to learn in situations where feedback is unclear and potentially inconsistent. The present data confirm earlier findings that depressive illness compromises individuals' ability to use and respond to feedback. Specifically, individuals with MDD were more likely to reverse responding following misleading negative feedback. This effect appeared relatively specific to MDD, as similarly-depressed individuals with BD showed behavioral performance which did not differ significantly from that of controls, and also showed quantitatively-similar patterns of neural activity to the control group. An important strength of the present study is that all patients were unmedicated at the time of testing.

The neuroimaging findings indicate complementary mechanisms in prefrontal cortical and limbic circuitry for utilizing trial-by-trial feedback to optimize task performance. Flexible adaptation of behavior on the reversal task was accompanied by increased hemodynamic activity in the vlPFC and dmPFC. In addition, healthy subjects displayed deactivation, presumably signifying a reduction in neural transmission (Drevets et al., 1995; Drevets and Raichle, 1998), in an amygdala ROI, in response to negative feedback compared to correct responses. This reduced amygdala activity was directly predictive of their ability to suppress reversal in response to misleading feedback. Recent work has suggested that the lateral and medial PFC may implement top-down control over amygdala activity in situations where subjects are required to inhibit or re-appraise emotional responses to negatively-valenced stimuli (Ochsner et al., 2002; Pezawas et al., 2005; Phelps and LeDoux, 2005). The amygdala forms part of a limbic circuit comprising the ventral PFC, ventral anterior cingulate and ventral

striatum that has wide-ranging involvement in processing motivational salience and emotional learning and memory (Phelps and LeDoux, 2005; Phillips et al., 2003).

The response to task feedback contains both emotional and informational components. Psychological theories of depression have highlighted an increased sensitivity to negative emotional information (Gotlib et al., 2004; Murphy et al., 2003), thought to contribute to the instantiation of a negative cycle (Teasdale, 1983). In addition, depressed individuals are unable to use the informational component conveyed in feedback to facilitate task performance (Murphy et al., 2003). Translational models of depression have highlighted how affective responses may be regulated by top-down control processes (Amat et al., 2005; Robbins, 2005), which may confer resilience to affective illness in the healthy population. For example, it is known that a perceived lack of control over one's environment leads to future inaction, which has provided the influential cognitive model of depression termed "learned helplessness" (Seligman, 1972).

Phillips et al. (2003) proposed a dorsal system involved in the regulation of affective states and consequent behavior in an effortful manner and a ventral system that modulates the automatic regulation of emotion. Decreases in dorsal PFC metabolism have been identified in depressed subjects with BD (Ketter et al., 2001) and MDD (Baxter et al., 1989). In contrast, increased activity has been identified in the ventral PFC during the depressed phase of MDD (Drevets et al., 1992) and BD (Ketter et al., 2001). Goel and Dolan (2003) identified differential activation between dorsal/dorsolateral and ventromedial PFC networks during 'hot' and 'cold' reasoning, with increased dorsal/lateral PFC activity and reduced ventromedial PFC activity during 'cold' reasoning and a reciprocal pattern for 'hot' reasoning. This supports the argument that increased activity in dorsal and lateral areas in HC and BD subjects may be associated with attempts to exert cognitive control over an emotional response. It should be noted that activity in the dmPFC and vlPFC was particularly elevated in HC and BD subjects when they incorrectly reversed their responses following misleading negative feedback. Drevets et al. (1998) proposed that increased activity in these areas may compensate for or modulate activation in limbic structures during emotional processing. Activity in dorsal PFC has been associated with suppression of sad responses (Levesque et al., 2003). Increased dmPFC and vlPFC activity in the HC and BD groups may be central to the ability to maintain correct responding in the face of misleading negative feedback and in suppressing responses to the immediate emotional feedback.

Behavioral reversal on the PRL task activated a circuit comprising the vlPFC in the control group, consistent with earlier work using this task (Cools et al., 2002) (see Supplementary material). The vlPFC signal change was previously shown to be significantly greater on reversal switches than on other trials where negative feedback was received, but where subjects did not switch responding (Cools et al., 2002). The vlPFC may play a role in behavioral inhibition, by modulating the transmission of motivational information from limbic areas to the motor system. O'Doherty et al. (2003) identified an adjacent area of caudolateral OFC where activity increased during trials on which punishing feedback resulted in a response reversal on the next trial. In the present data, increased vlPFC activity in response to negative feedback was correlated with subjects' ability to inhibit inappropriate switches, in the BD group. This further supports the role for this region in behavioral inhibition.

Some limitations should be noted. The final group sizes were relatively small ($n=12-15$ per group) after several subjects were excluded due to excessive movement, and these findings merit replication in larger samples. The between-group differences in reversal- and feedback-related brain activity were not statistically significant at the whole-brain level after voxel-wise correction for multiple comparisons, but were evident in *a priori* regions of interest in the PFC (vlPFC, dmPFC) and amygdala. The PFC ROIs were defined as spheres of 10 mm radius around

the peak voxels from an earlier experiment using the same task (Cools et al., 2002), in order to capitalise on the high degree of replicability in the pattern of frontal activation associated with this task. Nonetheless, we accept that spherical ROIs do not capture the complex morphology of these frontal subregions. In order to test our predictions of amygdala dysregulation in mood disorders, we used anatomical ROIs based on the AAL template (Tzourio-Mazoyer et al., 2002), given that the earlier work using the PRL task had not identified any changes in amygdala signal (Cools et al., 2002; Evers et al., 2005). It is likely that the earlier studies may have overlooked the amygdala signal change through the use of one-tailed statistical tests that would only detect regions where negative feedback was associated with signal *increases*.

In conclusion, this novel study in unmedicated, depressed subjects with mood disorders clarifies the mechanism by which the normal processing of feedback is dysfunctional in MDD. The MDD subjects showed attenuated prefrontal cortical responses during reversal shifting and additionally failed to deactivate the amygdala in response to misleading feedback relative to positive feedback. This latter response was predictive of healthy subjects' capacity to ignore misleading feedback and may confer resilience in the face of uncontrollable or stressful situations. Notably, abnormalities in response to misleading negative feedback appeared specific to unipolar depressive illness, as they did not extend to BD subjects who scored similarly on depression severity ratings. These findings hold profound implications for pharmacological and psychological approaches to treatment in unipolar and bipolar depressions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

JVTT was funded by the NIMH Intramural Research Program as part of the NIH–University of Cambridge Health Science Scholars Program. LC and BJS were funded by a Wellcome Trust program grant, GBW by an MRC co-operative group grant (G0001237), and MLF and WCD by the NIMH Intramural Research Program. The work was completed with the University of Cambridge Behavioural and Clinical Neuroscience Institute, supported by a consortium award from the Medical Research Council (U.K.) and the Wellcome Trust. We thank Michele Drevets and Joan Williams for their assistance with patient recruitment and assessment, and Steve Fromm, Paul Fletcher and Mike Aitken for providing advice on image analysis.

Appendix

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.neuroimage.2008.05.049.

References

- Amat J, Baratta MV, Paul E, Bland ST, Watkins LR, Maier SF. Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. *Nat Neurosci* 2005;8:365–371. [PubMed: 15696163]
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders — Text Revision*. Vol. 4th. American Psychiatric Association; Washington, DC: 1994.
- Baxter LR Jr, Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE, Gerner RH, Sumida RM. Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Arch Gen Psychiatry* 1989;46:243–250. [PubMed: 2784046]

- Blumberg HP, Leung HC, Skudlarski P, Lacadie CM, Fredericks CA, Harris BC, Charney DS, Gore JC, Krystal JH, Peterson BS. A functional magnetic resonance imaging study of bipolar disorder: state- and trait-related dysfunction in ventral prefrontal cortices. *Arch Gen Psychiatry* 2003;60:601–609. [PubMed: 12796223]
- Brett M, Anton JL, Valabregue R, Poline JB. Region of interest analysis using an SPM toolbox. *NeuroImage* 2002;16abstract
- Cardinal, RN.; Aitken, MRF. ANOVA for the Behavioural Sciences Researcher. Lawrence Erlbaum Associates; New Jersey, USA: 2006.
- Chamberlain SR, Muller U, Blackwell AD, Clark L, Robbins TW, Sahakian BJ. Neurochemical modulation of response inhibition and probabilistic learning in humans. *Science* 2006;311:861–863. [PubMed: 16469930]
- Cools R, Clark L, Owen AM, Robbins TW. Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging. *J Neurosci* 2002;22:4563–4567. [PubMed: 12040063]
- Drevets WC, Burton H, Videen TO, Snyder AZ, Simpson JR Jr, Raichle ME. Blood flow changes in human somatosensory cortex during anticipated stimulation. *Nature* 1995;373:249–252. [PubMed: 7816140]
- Drevets WC, Ongur D, Price JL. Neuroimaging abnormalities in the subgenual prefrontal cortex: implications for the pathophysiology of familial mood disorders. *Mol Psychiatry* 1998;3:220–226. [PubMed: 9672897]
- Drevets WC, Raichle ME. Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: implications for interactions between emotion and cognition. *Cogn Emotion* 1998;12:353–385.
- Drevets WC, Videen TO, Price JL, Preskorn SH, Carmichael ST, Raichle ME. A functional anatomical study of unipolar depression. *J Neurosci* 1992;12:3628–3641. [PubMed: 1527602]
- 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;26:975–989. [PubMed: 8878330]
- Evers EA, Cools R, Clark L, van der Veen FM, Jolles J, Sahakian BJ, Robbins TW. Serotonergic modulation of prefrontal cortex during negative feedback in probabilistic reversal learning. *Neuropsychopharmacol* 2005;30:1138–1147.
- Frank E, Kupfer DJ, Thase ME, Mallinger AG, Swartz HA, Fagioli AM, Grochocinski V, Houck P, Scott J, Thompson W, Monk T. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. *Arch Gen Psychiatry* 2005;62:996–1004. [PubMed: 16143731]
- Goel V, Dolan RJ. Reciprocal neural response within lateral and ventral medial prefrontal cortex during hot and cold reasoning. *NeuroImage* 2003;20:2314–2321. [PubMed: 14683732]
- Goethals I, Audenaert K, Jacobs F, Van de Wiele C, Ham H, Pyck H, Vandierendonck A, Van Heeringen C, Dierckx R. Blunted prefrontal perfusion in depressed patients performing the Tower of London task. *Psychiatry Res* 2005;139:31–40. [PubMed: 15927455]
- Gotlib IH, Krasnoperova E, Yue DN, Joormann J. Attentional biases for negative interpersonal stimuli in clinical depression. *J Abnorm Psychol* 2004;113:121–135. [PubMed: 14992665]
- Grant MM, Thase ME, Sweeney JA. Cognitive disturbance in outpatient depressed younger adults: evidence of modest impairment. *Biol Psychiatry* 2001;50:35–43. [PubMed: 11457422]
- Hollon SD, Thase ME, Markowitz JC. Treatment and prevention of depression. *Psychol Sci Publ Interest* 2002;3:39–77.
- Ketter TA, Kimbrell TA, George MS, Dunn RT, Speer AM, Benson BE, Willis MW, Danielson A, Frye MA, Herscovitch P, Post RM. Effects of mood and subtype on cerebral glucose metabolism in treatment-resistant bipolar disorder. *Biol Psychiatry* 2001;49:97–109. [PubMed: 11164756]
- Kringelbach ML, Rolls ET. Neural correlates of rapid reversal learning in a simple model of human social interaction. *NeuroImage* 2003;20:1371–1383. [PubMed: 14568506]
- Kronhaus DM, Lawrence NS, Williams AM, Frangou S, Brammer MJ, Williams SC, Andrew CM, Phillips ML. Stroop performance in bipolar disorder: further evidence for abnormalities in the ventral prefrontal cortex. *Bipolar Disord* 2006;8:28–39. [PubMed: 16411978]

- Levesque J, Eugene F, Joanette Y, Paquette V, Mensour B, Beaudoin G, Leroux JM, Bourgouin P, Beauregard M. Neural circuitry underlying voluntary suppression of sadness. *Biol Psychiatry* 2003;53:502–510. [PubMed: 12644355]
- Mitchell PB, Wilhelm K, Parker G, Austin MP, Rutgers P, Malhi GS. The clinical features of bipolar depression: a comparison with matched major depressive disorder patients. *J Clin Psychiatry* 2001;62:212–216. [PubMed: 11305713]
- Murphy FC, Michael A, Robbins TW, Sahakian BJ. Neuropsychological impairment in patients with major depressive disorder: the effects of feedback on task performance. *Psychol Med* 2003;33:455–467. [PubMed: 12701666]
- O'Doherty J, Critchley H, Deichmann R, Dolan RJ. Dissociating valence of outcome from behavioral control in human orbital and ventral prefrontal cortices. *J Neurosci* 2003;23:7931–7939. [PubMed: 12944524]
- Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD. Rethinking feelings: an fMRI study of the cognitive regulation of emotion. *J Cogn Neurosci* 2002;14:1215–1229. [PubMed: 12495527]
- Okada G, Okamoto Y, Morinobu S, Yamawaki S, Yokota N. Attenuated left prefrontal activation during a verbal fluency task in patients with depression. *Neuropsychobiology* 2003;47:21–26. [PubMed: 12606841]
- Ongur D, Ferry AT, Price JL. Architectonic subdivision of the human orbital and medial prefrontal cortex. *J Comp Neurol* 2003;460:425–449. [PubMed: 12692859]
- Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, Egan MF, Mattay VS, Hariri AR, Weinberger DR. 5-HTTLPR polymorphism impacts human cingulate–amygdala interactions: a genetic susceptibility mechanism for depression. *Nat Neurosci* 2005;8:828–834. [PubMed: 15880108]
- Phelps EA, LeDoux JE. Contributions of the amygdala to emotion processing: from animal models to human behavior. *Neuron* 2005;48:175–187. [PubMed: 16242399]
- Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: the neural basis of normal emotion perception. *Biol Psychiatry* 2003;54:504–514. [PubMed: 12946879]
- Poline, JB.; Holmes, AP.; Worsley, KJ.; Friston, KJ. Making statistical inferences. In: Frackowiak, RSJ.; Friston, KJ.; Frith, CD.; Dolan, RJ.; Mazziotta, JC., editors. *Human Brain Function*. Academic Press; San Diego, CA: 1997.
- Remijne PL, Nielen MM, Uylings HB, Veltman DJ. Neural correlates of a reversal learning task with an affectively neutral baseline: an event-related fMRI study. *NeuroImage* 2005;26:609–618. [PubMed: 15907318]
- Robbins TW. Controlling stress: how the brain protects itself from depression. *Nat Neurosci* 2005;8:261–262. [PubMed: 15746909]
- Seligman ME. Learned helplessness. *Ann Rev Med* 1972;23:407–412. [PubMed: 4566487]
- Shah PJ, O'Carroll RE, Rogers A, Moffoot AP, Ebmeier KP. Abnormal response to negative feedback in depression. *Psychol Med* 1999;29:63–72. [PubMed: 10077294]
- Siegle GJ, Steinhauer SR, Thase ME, Stenger VA, Carter CS. Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biol Psychiatry* 2002;51:693–707. [PubMed: 11983183]
- Siegle GJ, Thompson W, Carter CS, Steinhauer SR, Thase ME. Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. *Biol Psychiatry* 2007;61:198–209. [PubMed: 17027931]
- Steffens DC, Wagner HR, Levy RM, Horn KA, Krishnan KR. Performance feedback deficit in geriatric depression. *Biol Psychiatry* 2001;50:358–363. [PubMed: 11543739]
- Talairach, J.; Tournoux, P. *Co-planar Stereotaxic Atlas of the Human Brain*. Thieme Medical Publishers; New York: 1988.
- Teasdale JD. Negative thinking in depression: cause, effect, or reciprocal relationship? *Adv Behav Res Ther* 1983;5:3–25.
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage* 2002;15:273–289. [PubMed: 11771995]

World Health Organisation. The world health report: mental health: new understanding, new hope. 2001.
www.who.int

Fig.1.

Subjects with Major Depressive Disorder (MDD) were oversensitive to misleading negative feedback. (A) The probabilistic switch rate (the number of reversals after misleading negative feedback/total number of probabilistic errors) was increased in the MDD group compared to healthy controls, and tended to be higher in the MDD subjects than in the subjects with Bipolar Disorder (BD), who displayed a similar degree of depression. (B) There were no differences between the three groups in the reversal switch rate (the number of reversal errors/total number of rule reversals). Error bars depict standard error of the mean.

Fig.2.

A region-of-interest analysis was used to assess differences in the hemodynamic responses, measured as the mean changes in BOLD contrast units, to the task conditions across the three diagnostic groups. The bars represent the following contrasts: Negative Feedback [events (2 +3+4+5+6)-1]; Error Switches (events 2-1); Error Non-switches (events 3-1) and the contrast Error Switches-Error Non-Switches (event 2-3). Error bars depict standard error of the mean. The regions-of-interest were defined as spheres of 10 mm radius centred around the following coordinates: (A) in dorsomedial PFC ($x, y, z=8, 32, 52$), hemodynamic activity was elevated in HC and BD subjects compared to MDD subjects during error switches, and in addition the BD group had elevated activity compared to MDD and HC groups for error non-switches and

to MDD for the contrast for all negative feedback; (B) in right ventrolateral PFC (38, 24, -2), hemodynamic activity was elevated in HC and BD groups compared to the MDD group when error switches were compared to error non-switches, and when error switches were compared to correct responses; (C) in left ventrolateral PFC (MNI coordinates $x, y, z = -32, 24, -4$), hemodynamic activity was elevated in both *HC* and *BD* groups compared to MDD when error switches were compared to error non switches or correct responses.

Fig.3.

Scatter graphs depicting the relationship between the signal change in the right amygdala during receipt of negative feedback (minus the correct response baseline) and the probabilistic switch rate. The probabilistic switch rate was calculated from the total number of response reversals after misleading negative feedback, divided by the total number of trials where misleading negative feedback was presented. (A) The correlation between the amygdala response to negative feedback and the probabilistic switch rate was significant in the healthy control (HC) group ($r=0.63$, $p=0.011$) and (B) was apparent at trend level in the bipolar depressed group (BD) ($r=0.50$, $p=0.096$). (C) There was no significant association between right amygdala response and probabilistic switch rate in the major depressive disorder (MDD) group ($r=-0.16$, $p=0.59$), and the correlation between HC and MDD groups differed significantly (Fisher's r to z : $z=2.13$ $p=0.033$). (D) For the all negative feedback contrast there was less of a reduction in right amygdala activity in the MDD group compared to the HC group ($p=0.05$). Error bars depict standard error of the mean.

Table 1

Demographic and clinical characteristics of the healthy control and depressed subject groups and behavioral results from the probabilistic reversal learning task

	Controls	MDD	BD
N	15	13	12
Female:male	11:4	10:3	9:3
Age	33.9 (2.33)	38.3 (2.30)	33.4 (3.16)
Age at onset	NA	20 (3.0)	17 (1.6)
Time off meds (weeks)	NA	95 (57)	70 (25)
WASI-IQ	118 (2.75)	116 (2.73)	120 (3.67)
HSE total	47.9 (1.74)	48.4 (2.31)	47.4 (3.65)
MADRS	0.27 (0.27) ^{a,b}	23 (1.7)	26 (2.8)
YMRS	0.13 (0.13) ^{a,b}	4.3 (0.80)	5.8 (1.6)
HAM-A	0.20 (0.20) ^{a,b}	13 (1.6) ^a	19 (1.9)
Reversal learning data			
Probabilistic switch rate	0.125 (0.0195)	0.329 (0.081) ^a	0.184 (0.042)
Reversal error rate	1.28 (0.114)	1.34 (0.199)	1.42 (0.134)
Correct responses (per block)	101 (4.57)	95.4 (1.62)	97.5 (2.02)
Correct latency (ms)	690 (51.6)	608 (22.7)	612 (20.6)
Spontaneous errors	4.28 (1.30)	10.3 (3.93)	9.17 (4.79)

Data in parentheses are S.E.M.

WASI-IQ Wechsler Abbreviated Scale of Intelligence to estimate full IQ; HSES Hollingshead and Redlich's scale of socioeconomic status; MADRS Montgomery-Asberg Depression Rating Scale; YMRS Young Mania Rating Scale; HAM-A Hamilton Anxiety Rating Scale.

^aDenotes $p \leq 0.05$ versus the MDD group.

^bDenotes $p < 0.5$ versus the BD group.

Table 2
Significant results for the dorsomedial and ventrolateral prefrontal cortical regions-of-interest

Group comparison	Contrast	Laterality	T value	p value
<i>Dorsomedial prefrontal cortex</i>				
BD>MDD	Error switches		3.09	0.002
	Error non-switches		2.19	0.017
	All negative feedback		2.73	0.005
BD>HC	Error non-switches		1.92	0.031
HC>MDD	Error switches		2.02	0.025
<i>Ventrolateral prefrontal cortex</i>				
BD>MDD	Error switches	Right	2.10	0.021
	Error switches–non-switches	Left	1.87	0.034
		Right	2.32	0.013
	Reversal	Right	2.21	0.017
HC>MD	Error switches	Right	2.83	0.004
	Error switches–non-switches	Left	2.22	0.016
		Right	2.87	0.003
	Reversal	Right	2.42	0.010

Table 3

Regions where hemodynamic activity during the probabilistic reversal learning test was significantly higher in healthy controls than in depressed MDD subjects in the whole brain analysis

General region	Specific location	Error switches			Error non-switches			Error switches-error non-switches			Negative feedback			Reversal			
		t value	Coordinates			t value	Coordinates			t value	Coordinates			t value	Coordinates		
Ventrolateral PFC	R ventrolateral PFC (IFG)	4.8	x	y	z		x	y	z		x	y	z		x	y	z
			44	44	16												
		3.98	40	26	8												
Dorsolateral PFC	L dorsolateral PFC	4.18	-48	5	22	4.66	-48	5	22	4.47	-50	5	20				
		3.48	-48	9	33												
Frontal pole	L premotor C																
		3.96	18	44	20												
Temporal lobe	R frontal polar C																
		3.57	59	-48	8												
	R middle temporal G																
	R superior temporal G	3.48	51	-48	19												

Differences between in the BOLD signal measured during each task condition relative to the baseline condition (“correct” responses) are compared across groups.

Results remain significant at $p \leq 0.05$ after applying corrections for multiple comparisons using the cluster test (Poline et al., 1997); coordinates correspond to the stereotaxic array of Talairach and Tournoux (1988) and denote the distance in mm from the anterior commissure, with positive x =right of midline, positive y =anterior to the anterior commissure, and positive z =dorsal to a plane containing both the anterior and the posterior commissures. Abbreviations: C, cortex; HC, Healthy Control; MDD, Major Depressive Disorder; BD, Bipolar Disorder; G, gyrus; L, left; R, right and PFC, prefrontal cortex.