Psychopharmacology (2009) 205:667–677
DOI 10.1007/s00213-009-1573-9

ORIGINAL INVESTIGATION

Neural representation of reward in recovered depressed patients

Ciara McCabe · Philip J. Cowen · Catherine J. Harmer

Received: 2 February 2009 / Accepted: 13 May 2009 / Published online: 16 June 2009

Abstract
Introduction Anhedonia, a loss of interest and pleasure in normally rewarding stimuli, is a key diagnostic criterion for major depression. It has been suggested that deficits in the processing of reward-relevant stimuli could represent an endophenotype for depression. We hypothesized that people at risk of depression by virtue of a personal history of the illness would show impaired neural responses to a primary rewarding stimulus.
Materials and methods Using functional magnetic resonance imaging, we measured the neural response to the sight and flavor of chocolate, and their combination, in 13 unmedicated recovered patients with a history of major depression and 14 healthy controls matched for age and gender. We also examined a control aversive condition consisting of the sight of moldy strawberries and a corresponding unpleasant taste. Participants simultaneously recorded subjective ratings of "pleasantness," "intensity," and "wanting."
Results and discussion Despite no differences between the groups in stimulus ratings, patients showed decreased neural responses to the pleasant stimulus in the ventral striatum and increases in the caudate nucleus to the aversive stimulus. Furthermore, patients had a diminished neural supralinearity response (the potentiation produced by simultaneous presentation of the sight and flavor of the stimuli) in the prefrontal cortex for both aversive and pleasant conditions. Patients recovered from depression appear to have deficits in the neural basis of reward and may also have impairments in the cross-modal integration of sensory stimuli.
Conclusion These findings support the view that abnormal neural responses to reward may be an endophenotype for depression and a potential target for intervention and prevention strategies.

Keywords fMRI · Depression · Reward · Chocolate · Endophenotype

Introduction

Anhedonia, or loss of interest and pleasure in activities customarily enjoyed, is a key diagnostic criterion for depressive disorder in both major psychiatric diagnostic systems: the Diagnostic Statistical Manual (DSM-IV) and the International Statistical Classification of Diseases (ICD). Anhedonia is an important symptom because, although pervasive negative affect is a feature of most emotional disorders, anhedonia is quite specific for depression (Dryman and Eaton 1991). In addition, the presence of anhedonia in depressed patients could have important implications for pathophysiology because it is suggestive of changes in the neurobiological mechanisms that underpin motivation and reward (Nestler and Carlezon 2006).

Anhedonia is usually regarded as a symptom of acute depression which resolves with clinical recovery. However, anhedonia also has some trait characteristics and has been suggested as a potential endophenotypic marker of major depression (Hasler et al. 2004). For example, an epidemiological study showed that the presence of anhedonic features was a strong predictor of the onset of major depression over the following year (Dryman and Eaton 1991). In a group of patients with chronic depression followed up for a year,

C. McCabe (✉) · P. J. Cowen · C. J. Harmer
University Department of Psychiatry,
Warneford Hospital, University of Oxford,
Oxford, UK
e-mail: ciara.mccabe@psych.ox.ac.uk

Schrader (1997) found that anhedonic symptoms remained fairly constant despite a substantial remission in severity of overall depression. In addition, in the same patients, anhedonia scores correlated with the presence of depression in first-degree relatives, suggesting a genetic link between anhedonia and the risk of depression.

Brain imaging studies such as functional magnetic resonance imaging (fMRI) have made substantial progress in identifying the neural systems underlying reward processes in humans. Thus, monetary reward (O'Doherty et al. 2001a), pleasurable responses to music (Blood and Zatorre 2001), and the viewing of pleasant pictures (Lane et al. 1997) have all been associated with increased neural activity within the ventral striatum and ventromedial prefrontal cortex (VMPFC). This is consistent with studies in animals indicating that dopaminergic activity in the ventral striatum is important in mediating positive reinforcing effects of rewards such as food and sex and may play a key role in the incentive motivation and anticipation of these appetitive stimuli. By contrast, the VMPFC appears to integrate sensory experiences from different modalities and contribute to the subjective experiences of reinforcing stimuli (Robbins and Everitt 1996; Cardinal et al. 2002).

Some studies have investigated the neural representation of reward in acutely depressed patients. While the reward stimuli employed have generally been indirect, for example, happy facial expressions or positively valenced words, studies have found abnormalities in the neural circuitry supporting reward mechanisms. For example, reduced ventral striatal responses have been reported to positively valenced words in depression (Epstein et al. 2006), while Knutson et al. (2008) found an altered pattern of responses in the anterior cingulate cortex to monetary reward. A similar network was identified in a study examining behavioral and neural response to feedback information during a gambling task where depressed patients showed decreased responses in the ventral striatum and anterior cingulate to feedback information of "winning" or "losing" money and did not adjust their response times accordingly unlike the control group (Steele et al. 2007). However, it is unknown whether neural differences in responses to reward are seen during remission from depression and may form a trait vulnerability marker for this disorder.

The aim of the present study was to assess the neural substrate of reward in unmedicated and clinically recovered depressed patients using a paradigm involving the sight and taste of chocolate as a direct reward and an aversive taste and picture condition as a control. This design allows us to examine whether a history of depression affects responses to all tastes and affective pictures or whether there is a specific blunting of response to positive stimuli. The use of similar paradigms, in conjunction with functional neuroimaging, has permitted a clear delineation of the neural systems supporting the representation of reward in humans (Rolls and McCabe 2007). We predicted that recovered depressed patients would have impaired neural responses to the chocolate reward within the anterior cingulate, the VMPFC, and the ventral striatum in which we and other authors have found activations in previous studies to unconditioned reward stimuli (Rolls and McCabe 2007; O'Doherty et al. 2001b; McCabe and Rolls 2007; Rolls et al. 2003). By contrast, we expected the neural response to the aversive taste and sight condition to be enhanced in the recovered depressed patients in neural circuitry mediating disgust and aversive processing including the amygdala, caudate, and anterior insula (Fitzgerald et al. 2004; Zald et al. 2002).

Materials and methods

Participants

Fourteen healthy control volunteers (five men, nine women) and 13 recovered depressed patients (three men, 11 women) were recruited for this study. Ethical approval was provided by the Central Oxford Research Ethics Committee and written informed consent was obtained from all participants before screening and after the complete description of the study was given. Exclusion criteria for all subjects consisted of current or past history of alcohol or drug dependency, pregnancy, and any contra-indications to MRI, e.g., pacemaker, mechanical heart valve, hip replacement, metal implants. Furthermore, the control group were determined to be free of current or past axis 1 disorder (including anxiety disorders, depression, eating disorder, psychosis, and substance abuse) on the structured clinical interview for DSM-IV (Spitzer et al. 2004). To be included in the recovered depressed group, the participants were required to meet the criteria for at least one episode of major depression as a primary diagnosis and also to be free of current or past comorbid axis 1 disorder (including anxiety disorders, eating disorders, psychosis, and substance abuse) on the structured clinical interview for DSM-IV (Spitzer et al. 2004). Recovery was determined in the same week as the study through clinical interview and with the Hamilton Depression Scale (HAM-D; Hamilton 1960) using a cut-off score of 8. None of the participants took current medication apart from the contraceptive pill and the recovered depressed group had been free of antidepressant medication for a mean of 4.9 years (range= 1.7–7 years). Four people in the recovered depressed group had received citalopram for 6 months and one person had citalopram for 1 year. One person in the recovered depressed group received 6 months treatment with fluoxetine and the other seven recovered depressed participants were treatment naïve.

All subjects were rated on the following questionnaires: Beck Depression Inventory (BDI; Beck et al. 1961), the Fawcett–Clarke Pleasure Scale (FCPS; Fawcett et al. 1983), and the Snaith–Hamilton Pleasure Scale (SHAPS; Snaith et al. 1995) approximately 1 week before scanning. The participants also completed a "chocolate questionnaire" to measure liking, craving, and frequency of eating chocolate (Rolls and McCabe 2007) and the body mass index (BMI) for each individual was also calculated.

Overall design

We compared brain responses to reward-related and aversive stimuli in a group of unmedicated recovered depressed volunteers and healthy controls. Each of the following conditions were applied nine times in a randomized order (see Table 1): chocolate in the mouth, chocolate picture, chocolate in the mouth with chocolate picture, strawberry in the mouth, strawberry picture, and strawberry in the mouth with strawberry picture. Examining the responses to each stimulus alone and in combination allowed a supralinearity analysis to be performed to identify those neural circuits which showed a potentiated response with cross-modal presentation of stimuli (e.g., those areas showing greater activation to the combination of the sight and flavor of chocolate than to the sum of the activations produced by the sight alone and by the flavor alone of chocolate). Subjective effects of each stimulus were measured by psychophysical ratings of pleasantness, intensity, and wanting for the stimuli made on every trial by the subjects during the fMRI acquisition. The participants were instructed not to eat chocolate for 24 h before the scan and to eat only a small lunch on the day of scanning. Scanning took place at 2.30–4 P.M. Mood state was recorded on the study day with the BDI.

Table 1 Stimuli

A list of the stimulus conditions	
Condition 1	Chocolate in the mouth + gray visual stimulus
Condition 2	Picture of chocolate
Condition 3	Chocolate in the mouth + a picture of chocolate
Condition 4	Strawberry in the mouth + gray visual stimulus
Condition 5	Picture of moldy strawberries
Condition 6	Strawberry in the mouth + a picture of moldy strawberries
Rinse condition	Tasteless rinse control solution + gray visual stimulus
Supralinearity choc	Condition 3 – Condition 1 – Condition 2
Supralinearity straw	Condition 6 – Condition 4 – Condition 5

The term "chocolate in the mouth" refers to the intraoral delivery through a Teflon tube of 0.5 mL of a fine liquid chocolate, which was identical for all such trials and which could not be seen by the subject. The term "strawberry in the mouth" refers to the intraoral delivery of 0.5 mL of an unpleasant strawberry flavored drink through a tube that was also could not be seen by the subject. The term "picture of chocolate" refers to a picture of a bar of brown, i.e., milk, chocolate shown on the display screen and the term "picture of moldy strawberries" refers to a picture of moldy strawberries

Stimuli

Stimuli were delivered to the subject's mouth through three Teflon tubes (one for the tasteless rinse control described below, one for chocolate taste, and one for strawberry taste) that were held between the lips. Each Teflon tube of approximately 3 m in length was connected to a separate reservoir via a syringe and a one-way syringe activated check valve (Model 14044-5, World Precision Instruments), which allowed 0.5 mL of any stimulus to be delivered manually at the time indicated by the computer. The chocolate was formulated to be liquid at room temperature, with a list of the six stimulus conditions described above in Table 1. A control tasteless solution (distilled H_2O) was used as a rinse between trials (Table 1), and when subtracted from the effects of the other stimuli, allowed somatosensory and any mouth movement effects to be subtracted from the effects produced by the other oral stimuli. This allows the taste, texture, and olfactory areas to be shown independently of any somatosensory effects produced by introducing a fluid into the mouth (O'Doherty et al. 2001b). The aversive stimulus was a strawberry drink (Rosemount Pharmaceuticals) which was reported to be unpleasant by pilot screenings with volunteer tasters. Both the liquid chocolate and the strawberry had approximately the same sweetness and texture which enabled them to pass freely through the Teflon delivery tubes.

Experimental procedure

At the beginning of each trial, one of the six stimuli chosen by random permutation was presented. If the trial involved an oral stimulus, this was delivered in a 0.5-mL aliquot to the subject's mouth. At the same time, at the start of the trial, a visual stimulus was presented, which was either the picture of chocolate, of moldy strawberries, or a gray control image of approximately the same intensity. The image was turned off after 7 s at which time a small green cross appeared on a visual display to indicate to the subject to swallow what was in the mouth. After a delay of 2 s, the subject was asked to rate each of the stimuli for pleasantness on that trial (with +2 being very pleasant and −2 very unpleasant), for intensity on that trial (0 to +4), and for current wanting for chocolate (+2 for wanting chocolate very much, 0 for neutral, and −2 for very much not wanting chocolate). The ratings were made with a visual analog rating scale in which the subject moved

the bar to the appropriate point on the scale using a button box. Each rating period was 5 s long. After the last rating, the gray visual stimulus indicated the delivery of the tasteless control solution that was also used as a rinse between stimuli, and this was administered in exactly the same way as a test stimulus and the subject was cued to swallow after 7 s by the green cross. The tasteless control was always accompanied by the gray visual stimulus. On trials on which only the picture of chocolate was shown, there was no rinse but the gray visual stimulus was shown in order to allow an appropriate contrast as described below. There was then a 2-s delay period similar to other trials that allowed for swallowing followed by a 1-s gap until the start of the next trial. A trial was repeated for each of the six stimulus conditions shown in Table 1, and the whole cycle was repeated nine times. The instruction given to the subject was (on oral delivery trials) to move the tongue once as soon as a stimulus or tasteless solution was delivered (at the time when the gray visual stimulus was turned on) in order to distribute the solution round the mouth to activate the receptors for taste and smell and then to keep still for the remainder of the 7-s period until the green cross was shown, when the subject could swallow. This procedure has been shown to allow taste effects to be demonstrated clearly with fMRI, using the procedure of subtracting any activation produced by the tasteless control from those produced by a taste or other stimulus (O'Doherty et al. 2001b).

fMRI scan

The experimental protocol consisted of an event-related interleaved design using in random permuted sequence the six stimuli described above and shown in Table 1. Images were acquired with a 3.0-T VARIAN/SIEMENS whole-body scanner at the Centre for Functional Magnetic Resonance Imaging at Oxford (FMRIB) where T2*-weighted EPI slices were acquired every 2 s (TR=2). Imaging parameters were selected to minimize susceptibility and distortion artifact in the orbitofrontal cortex (Wilson et al. 2002). Coronal slices (25) with in-plane resolution of 3×3 mm and between-plane spacing of 4 mm were obtained. The matrix size was 64×64 and the field of view was 192×192 mm. Acquisition was carried out during the task performance, yielding 972 volumes in total. A whole-brain T2*-weighted EPI volume of the above dimensions and an anatomical T1 volume with coronal plane slice thickness of 3 mm and in-plane resolution of 1.0×1.0 mm were also acquired.

fMRI analysis

The imaging data were analyzed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). Preprocessing of the data used SPM5 realignment, reslicing with sinc interpolation, normalization to the Montreal Neurological Institute (MNI) coordinate system and spatial smoothing with a 6-mm full width at half maximum isotropic Gaussian kernel and global scaling (Collins et al. 1994). The time series at each voxel were low-pass filtered with a hemodynamic response kernel. Time series nonsphericity at each voxel was estimated and corrected for (Friston et al. 2002), and a high-pass filter with a cut-off period of 128 s was applied. In the single event design, a general linear model was then applied to the time course of activation where stimulus onsets were modeled as single impulse response functions and then convolved with the canonical hemodynamic response function (Friston et al. 1994). Linear contrasts were defined to test specific effects. Time derivatives were included in the basic functions set. Following smoothness estimation (Kiebel et al. 1999), linear contrasts of parameter estimates were defined to test the specific effects of each condition with each individual dataset. Voxel values for each contrast resulted in a statistical parametric map of the corresponding t statistic, which was then transformed into the unit normal distribution (SPM Z). The statistical parametric maps from each individual dataset were then entered into second-level, random effects analyses accounting for both scan-to-scan and subject-to-subject variability. More precisely, the sets of individual statistical maps corresponding to a specific effect of interest were entered as covariates in multiple regression models as implemented in SPM5, and the corresponding group effects were assessed by applying linear contrasts (again following smoothness estimation) to the (second-level) parameter estimates generating a t statistics map for each group effect of interest. SPM converts the t statistics to Z scores (Table 4). Reported p values for each cluster based on this group analysis are fully corrected for the number of comparisons (resels) in the entire brain volume ("whole-brain" multiple comparisons) (Worsley et al. 1996) for which $p<0.05$ FWE. We report small volume corrections for brain regions in which we had an a priori hypothesis (described in the "Introduction" section) as follows: ventral striatum [−4 16 −12] and pregenual cingulate cortex [4 30 8] (Rolls and McCabe 2007; McCabe et al. 2008), medial prefrontal cortex [0 54 −12] and lateral orbitofrontal cortex [−16 28 −18] (Rolls et al. 2003), caudate nucleus [−8 18 10] (Fitzgerald et al. 2004), and amygdala [−18 −10 −14] (Zald et al. 2002). Peaks within 10 mm of these and which had a p value of at least <0.001 uncorrected in the whole-brain analysis and with a cluster threshold of 30 contiguous voxels (k=30) had applied small volume (FDR) corrections for multiple comparisons (Worsley et al. 1996) with a radius corresponding to the full width at half maximum of the spatial smoothing filter used. The percent change in the blood oxygen level-dependent (BOLD) signal was extracted

for the different conditions for illustration from the peak voxel within the regions of significant group difference identified from the contrast analyses using SPM5 plots of contrast estimates and signal effect sizes. For illustration purposes only, WFU Pick Atlas (Maldjian et al. 2003) was used to display activations (http://www.fmri.wfubmc.edu/cms/software). Coordinates of the activations are listed in the stereotactic space of the MNI's ICBM152 brain (Table 4).

Results

Demographic details and mood ratings

The two groups were matched for age, gender, BMI, and chocolate liking (Table 2). There were no differences between the control group and the recovered depressed group in the measures of anhedonia (SHAPS, FCPS) and the HAM-D. However, the recovered depressed group scored significantly higher on the BDI (Table 2).

Ratings of stimuli

Ratings of pleasantness, intensity, and wanting for the stimuli were obtained during the scanning on each trial for every condition for the healthy controls and the recovered depressed subjects. All subjects rated the strawberry picture and taste as unpleasant and the chocolate stimuli as pleasant. Using a repeated-measures analysis of variance for the pleasantness, intensity, and wanting ratings, there were no significant differences between the two groups and their ratings of pleasantness over the six stimuli [$F(1, 25)=0.01$, $p=0.9$], intensity over the six stimuli [$F(1, 25)=0.68$, $p=0.41$], or wanting over the six stimuli [$F(1, 25)=0.126$, $p=0.79$] (see Table 3).

Table 2 Group demographic and psychosocial measures

Measure	Recovered depressed ($n=13$), mean (SD)	Controls ($n=14$), mean (SD)
Age (years)	27.8 (6.6)	28.5 (6.3)
Gender (male)	3/13	5/14
BDI	5.5 (6.3)	0.8 (1.3)*
HAM-D	2.3 (2.9)	0.5 (1.1)
FCPS	118 (33.7)	118 (33.5)
SHAPS	23 (6)	19.25 (6)
BMI	22.1 (2.5)	22.2 (5.14)
Choc craving	6.1 (2.4)	6.8 (2.1)
Choc liking	7.9(1.7)	8.0 (1.7)
Choc freq eat	5.0 (3.2)	5.0 (3.1)

BDI Beck Depression Inventory, *HAM-D* Hamilton Depression Score, *FCPS* Fawcett–Clarke Pleasure Scale, *SHAPS* Snaith–Hamilton Pleasure Scale, *BMI* body mass index

*$p=0.01$ (all other $p>0.1$), independent samples t tests

fMRI responses

Table 4 provides a summary of the results for each contrast, first across all subjects to indicate the main effect of task and then with the interaction with group (recovered depressed vs. control). The fMRI results remained significant when the BDI scores were added as a covariate.

Main effect of task

As expected, the taste stimuli of chocolate and strawberry activated an overlapping region of the anterior insula, i.e., the primary taste cortex, in both the controls and the recovered depressed subjects. The rewarding stimuli chocolate taste and chocolate picture activated reward-relevant circuitry including the ventral striatum, the cingulate cortex, and the VMPFC extending into the medial orbitofrontal cortex. By contrast, the unpleasant stimuli of strawberry taste and sight of the moldy strawberries activated areas involved in aversive processing including the amygdala and a more lateral posterior part of the insula cortex (distinct from that activated by the tastes alone).

Effects of group

As expected, there was no significant difference in response to the taste stimuli between the two groups in the primary taste cortex, confirming that the sensory experience of these stimuli was associated with a similar neural response across groups (Fig. 1a, b).

Chocolate reward: sight and taste

The recovered depressed group showed reduced responses to the sight and taste of chocolate in areas known to play a key role in reward, including the ventral striatum and cingulate cortex (Fig. 2a). There were no areas where the recovered depressed patients showed increased responses relative to the controls for the chocolate reward condition (Table 4).

Strawberry: sight and taste

Contrary to the reduced BOLD responses seen to the chocolate reward, the unpleasant strawberry picture increased activation in the recovered depressed group compared to the control group in the bilateral caudate, as illustrated in Fig. 3a, b. To ensure the results validity and that the activations were not in the ventricles, the peak activations were overlaid on an average individual subject

Table 3 Subjective ratings

Condition	Recovered depressed	Controls	Recovered depressed	Controls	Recovered depressed	Controls
	Pleasantness, mean (SD)		Intensity, mean (SD)		Wanting, mean (SD)	
Chocolate in the mouth + gray visual stimulus	1.09 (0.15)	1.16 (0.28)	1.47 (0.42)	1.83 (0.5)	1.05 (0.21)	1.24 (0.3)
Picture of chocolate	1.14 (0.28)	1.02 (0.36)	1.38 (0.7)	1.36 (0.58)	1.05 (0.35)	1.11 (0.4)
Chocolate in the mouth + a picture of chocolate	1.29 (0.23)	1.4 (0.26)	1.76 (0.29)	2.18 (0.62)	1.27 (0.27)	1.38 (0.29)
Strawberry in the mouth + gray visual stimulus	−0.85 (0.93)	−0.75 (0.95)	1.91 (0.56)	1.97 (0.76)	−0.91 (0.98)	−0.97 (0.87)
Picture of moldy strawberries	−1.02 (0.42)	−1.15 (0.47)	1.34 (0.69)	1.41 (0.84)	−1.35 (0.35)	−1.33 (0.46)
Strawberry in the mouth + a picture of moldy strawberries	−1.14 (0.7)	−1.22 (0.51)	2 (0.68)	2.04 (0.75)	−1.2 (0.77)	−1.31 (0.34)

T1 template. Furthermore, we investigated the individual subjects' activations to this condition across groups to ensure valid registrations and activations within the cortex. No other comparisons were statistically significant between groups.

Supralinearity: the sight and flavor of chocolate compared to the sum of the activations to the sight alone and the flavor alone

In our previous studies in healthy control subjects, we showed that combinations of pictures and tastes induced greater activations in reward areas of the brain than when the pictures or the tastes were presented alone (Rolls and McCabe 2007; McCabe and Rolls 2007). Therefore, in this experiment, we compared activations to a combination of the sight and flavor of chocolate with the sum of the activations to the sight alone and the flavor alone to assess any differences in cross-modal integration of reward between patients and controls. We found greater supralinearity in the VMPFC extending into the medial orbitofrontal cortex in the controls compared to the recovered depressed group, as illustrated in Fig. 4a, b. These findings show that the increased activation due to the combination of the flavor of chocolate in the mouth with the sight of chocolate is less in recovered depressed patients than in controls.

Supralinearity: the sight and flavor of strawberry compared to the sum of the activations to the sight alone and the flavor alone

To investigate whether the groups differed in the cross-modal integration of aversive stimuli, a supralinearity analysis was performed comparing activations to a combination of the sight and flavor of strawberry with the sum of the activations to the sight alone and the flavor alone. We found greater supralinearity in the control subjects in the bilateral lateral orbitofrontal cortex relative to the recovered depressed group (Fig. 4c, d). This appeared to be driven by both decreased responses to the stimuli combined and increased responses to the picture stimulus presented alone.

Discussion

The main finding of our study is that unmedicated recovered depressed patients demonstrate abnormalities in the neural representation of reward to the sight and taste of chocolate. Judged by the visual analog scale ratings, these impaired neural responses were not apparently attributable to subjective changes in how the reward was anticipated or experienced. Moreover, in keeping with their recovered status, the patients did not suffer from symptomatic anhedonia as captured by standardized ratings scales such as the FCPS and the SHAPS. Importantly, the neural representations of the taste of chocolate and strawberry, judged by activations in the insula taste cortex, were not significantly different in recovered patients and controls; this suggests that the sensory qualities of the taste stimuli did not differ between the two groups. Our findings are, therefore, consistent with the proposal that deficiencies in the neural basis of reward mechanisms may be a trait abnormality in people at risk of depression.

The ventral striatum plays a key role in reward processes and is believed to be involved in the anticipation of reward and more specifically in learning to predict rewards, thereby biasing behaviors in a reward-seeking direction (Robbins and Everitt 1996; Hare et al. 2008). Furthermore, studies in acutely depressed patients using secondary rewards such as positive words or monetary reward have shown impaired neural responses in ventral striatum responses (Epstein et al. 2006) and reduced BOLD responses in this brain area correlate specifically with symptomatic anhedonia in medicated patients (Keedwell et al. 2005). Using behavioral and neural response to feedback

Table 4 Regions showing main effect of task and interaction with group (controls vs. recovered depressed)

Brain area	*x*	*y*	*z*	*Z* score	*p* value
	MNI coordinates				
Chocolate in the mouth (all subjects)					
Anterior insula	34	18	0	5.3	<0.001
	−34	14	4	4.94	<0.003
Ventral striatum	10	10	0	4.31	<0.001
	−10	6	−2	4.34	<0.001
Chocolate in the mouth (controls vs. rec dep)					
Ventral striatum	−6	−2	−6	3.13	0.03**
Pregenual cing	−6	34	2	3.3	0.02*
Subgenual cing	10	38	−20	3.08	0.03*
Sight of chocolate (all subjects)					
Striatum	−10	2	2	5.6	<0.001
	16	2	2	5.49	<0.001
Cingulate cortex	−6	2	46	6.5	<0.001
Pregenual cing	−4	30	2	5.52	<0.001
Orbito/insula trans area	44	14	−2	6.5	<0.001
	−34	24	0	5.82	<0.001
Thalamus	−10	−18	−8	6.35	<0.001
	12	−22	−10	6.2	<0.001
Chocolate in the mouth with the sight of chocolate (controls vs. rec dep)					
Ventral striatum	−8	8	−12	3.42	<0.03
Caudate	−6	−6	8	3.64	<0.03
Anterior cing	−8	38	14	3.41	<0.02
Pregenual cing	−10	36	4	3.34	<0.02
Posterior cing	0	0	50	4.08	<0.001
S temporal gyrus	−54	−4	−8	3.73	<0.03
Supralinearity: chocolate taste and sight of chocolate minus chocolate taste alone and chocolate picture alone (controls vs. rec dep)					
VMPFC/mOFC	8	56	−12	3.06	0.03*
Strawberry in the mouth (all subjects)					
Anterior insula	34	22	2	5.62	<0.001
	−32	16	8	5.38	<0.001
Sight of moldy strawberries (all subjects)					
Insula	42	14	−2	6.04	<0.001
Putamen	26	−8	4	6	<0.001
Thalamus	10	−20	−6	6	<0.001
Amygdala	22	−4	−20	5.29	<0.001
	−20	−2	−18	5.04	<0.01
Supralinearity: strawberry taste and sight of moldy strawberries minus the strawberry taste alone and the strawberry picture alone (controls vs. rec dep)					
lOFC	20	22	−14	3.22	0.01*
Region of increased activation in the recovered depressed group compared to the control group					
Sight of moldy strawberries (rec dep vs. controls)					
Caudate	12	10	22	3.5	0.004*
	−8	8	16	3.2	0.01*

rec dep recovered depressed, *cing* cingulate cortex, *s* superior, *mOFC* medial orbitofrontal cortex, *lOFC* lateral orbitofrontal cortex

*$p<0.05$, whole-brain corrected (FWE), FDR small volume correction; **$p=0.06$, after adding the BDI as a covariate of no interest

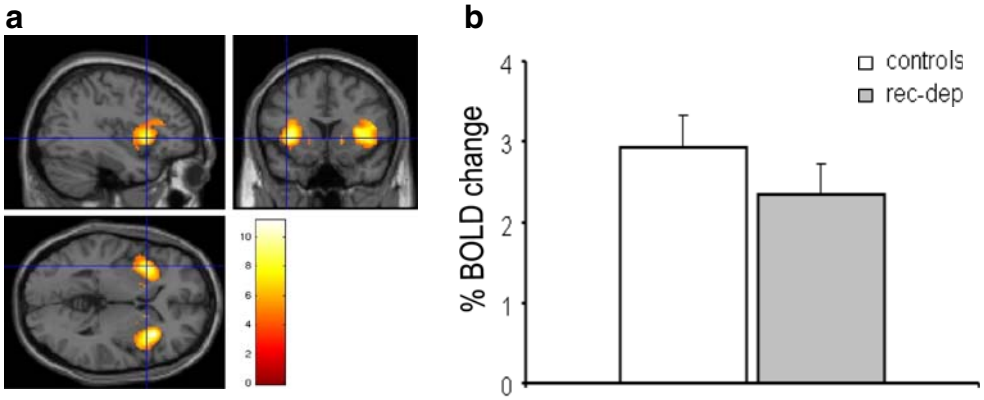

Fig. 1 The effects of taste in the mouth, across all subjects for taste stimuli. **a** Axial, coronal, and sagittal images depicting activation in the primary taste cortex in the anterior insula. **b** The % BOLD signal change in the anterior insula for the recovered depressed and control groups, no significant group difference

information during a gambling task, a recent study has shown that patients compared to controls have decreased activations in the ventral striatum to the positive reinforcement of "wins" and that they failed to adjust their response times to the positive feedback and that this correlated with measures of anhedonia (Steele et al. 2007). Our findings indicate that abnormalities in ventral striatal response to primary reward experience can also be seen in unmedicated patients who have recovered from depression and show no differences in subjective experience of the reward stimulus. Such results suggest that impaired ventral striatal activity may, at least in part, be independent of symptomatic state and could form part of the vulnerability to experience future depressive episodes. For example, McClure et al. (2004) proposed that impaired activity in the ventral striatum to reward could be associated with a lessened ability to learn stimulus–reward associations resulting in a failure to bias goal-directed behavior appropriately. Accordingly, trait deficits of this sort could result in difficulties in making complex social decisions leading to the consequent selection of potentially adverse environments. Individuals thus affected might be expected to run a greater risk of experiencing clinical mood disorders. Such a pattern is consistent with the hypothesis that deficits in the neural basis of reward anticipation or the reward experience itself may be an endophenotype for depression. Since the current sample were predominantly female, however, it will be important to confirm whether similar effects are seen in male recovered depressed patients or whether there are any sex differences in these responses.

The VMPFC is involved in the integration of reward-relevant information from different sensory modalities and in mediating the subjective hedonic experiences of these stimuli (Robbins and Everitt 1996; Cardinal et al. 2002). Consistent with this, the supralinearity analysis revealed a diminished response in recovered depressed patients in the VMPFC extending down into the medial part of the orbitofrontal cortex. This supralinearity response is believed to represent cross-modal sensory potentiation where combined visual and taste stimuli produce a greater combined effect on reward than the individual sensory components added together, consistent with real-world reward experiences (i.e., seeing and tasting food together). This part of the brain has been implicated specifically in the evaluation of positive rewards, so the impaired response in recovered depressed patients may be consistent with a further attenuation of neural reward mechanisms in a key cortical region believed to contribute to hedonic state. Such

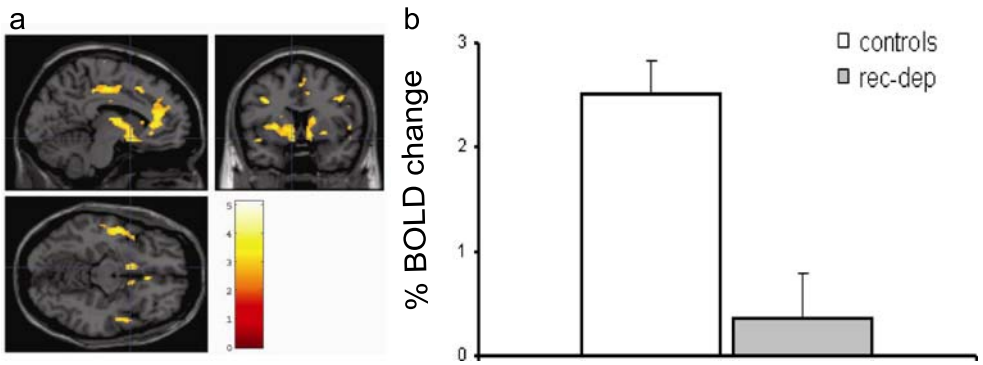

Fig. 2 Chocolate in the mouth with the sight of chocolate condition: controls vs. recovered depressed. **a** Axial, coronal, and sagittal images depicting significantly decreased activations in the recovered depressed group in bilateral ventral striatum, caudate, pregenual, and anterior cingulate cortex. **b** The % BOLD signal change in the ventral striatum for the recovered depressed and control groups ([−8 8 −12], $p<0.03$, fully corrected)

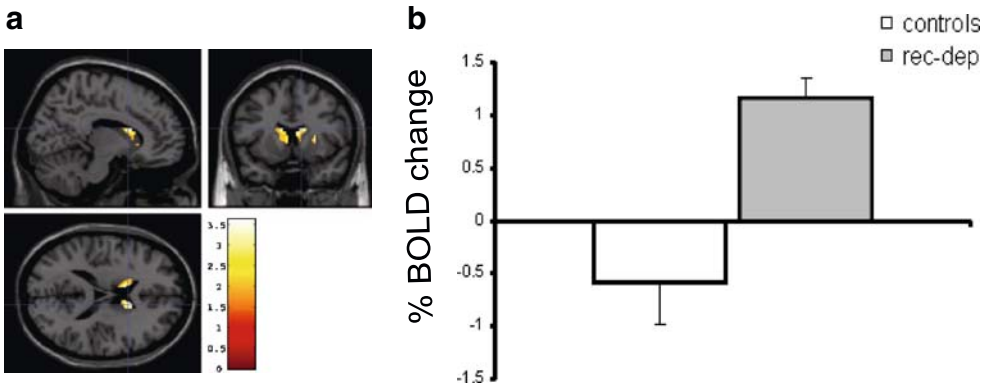

Fig. 3 Sight of moldy strawberries: recovered depressed vs. controls. **a** Axial, coronal, and sagittal images depicting significantly increased activations in the recovered depressed group in the bilateral caudate. **b** The % BOLD signal change in the caudate for the recovered depressed and control groups ([12 10 22], $p<0.004$, small volume correction)

impairments may arise either as direct deficits in the function of the medial prefrontal cortex or through poor communication and integration of individual sensory inputs.

We also assessed the response of patients and controls to an aversive sight and taste condition to determine whether any decrease in neural responses to the reward of chocolate might represent a general blunting of neural responses to motivational stimuli in general, whether positive or negative. Both patients and controls rated the strawberry taste and picture as equally aversive and we found no blunting of neural response in the recovered depressed subjects to either stimulus considered separately. However, once again, the supralinearity analysis revealed a blunting of BOLD response in the recovered depressed patients relative to controls, this time in the lateral orbitofrontal cortex. The extraction of the signal change for this comparison, however, revealed that this may be partly driven by exaggerated neural response in this area when the aversive picture stimulus was presented alone but not in combination with the taste.

The lateral orbitofrontal cortex is believed to be particularly involved in the representation of unpleasant stimuli (Rolls et al. 2003; Elliott et al. 2000; Kringelbach and Rolls 2004) and in the selection of actions that override automatic and motivationally (reward) driven response tendencies (Elliott et al. 2000; Passingham et al. 2000; Rushworth et al. 2007). This suggests that depressed patients may also have impairments in the cortical representations of aversive stimuli. Clinically, for example, it has long been known that some depressed patients experience a rather general loss of emotional response; for

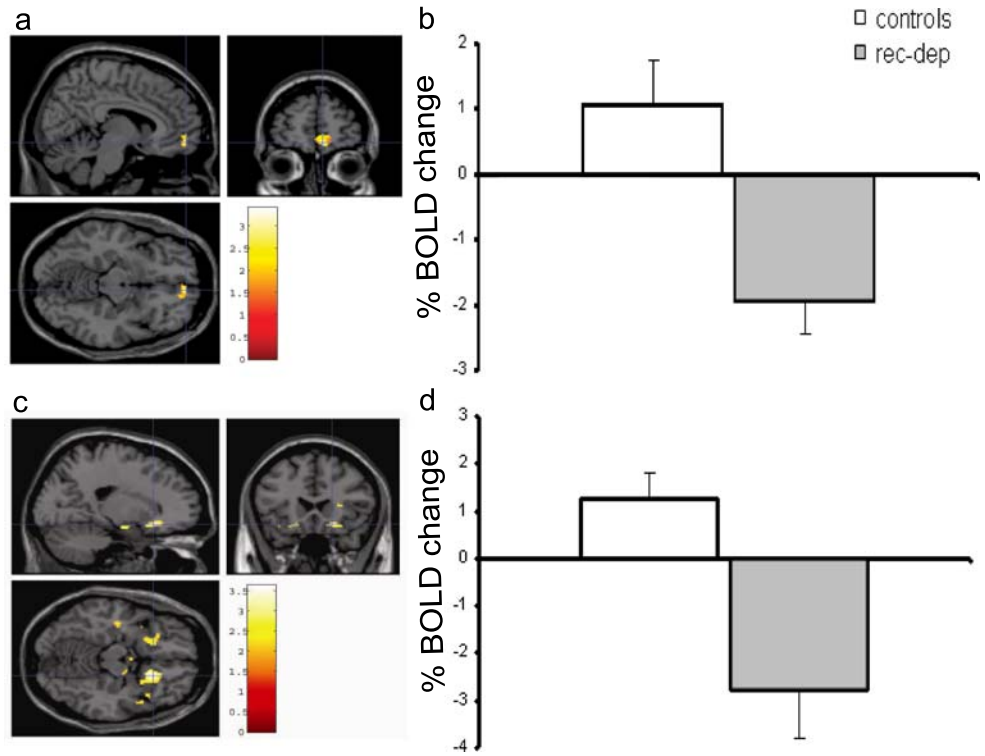

Fig. 4 Supralinearity condition for chocolate and strawberry conditions: controls vs. recovered depressed. **a** Axial, coronal, and sagittal images depicting significantly decreased activations in the recovered depressed group in the VMPFC/medial orbitofrontal cortex. **b** The % BOLD signal change for the chocolate picture plus chocolate taste condition minus the chocolate picture alone minus the chocolate taste alone in the VMPFC/medial orbitofrontal cortex ([8 56 −12], $p=0.03$, small volume correction). **c** Axial, coronal, and sagittal images depicting significantly decreased activations in the recovered depressed group in the lateral orbitofrontal cortices. **d** The % BOLD signal change for the strawberry picture plus strawberry taste condition minus the strawberry picture alone minus the strawberry taste alone in the lateral orbitofrontal cortex ([20 22 −8], $p=0.01$, small volume

example, Jaspers (1963) noted that "…patients complain that they no longer feel gladness or pain…." Thus, this blunting of response within the lateral orbitofrontal cortex to the combination of the strawberry taste and picture may reflect deficits in the integration of cross-modal sensory input similar to that seen in the VMPFC/medial orbitofrontal cortex. However, future research is required to assess to what extent this supralinearity effect occurs because of reduced impact of multimodal stimuli presentations vs. exaggerated responses to aversive pictorial stimuli.

Consistent with this, the recovered depressed patients also showed increased responses in the caudate nucleus to the aversive sight of the moldy strawberries. This is of interest because the emotion of disgust has been shown to activate the caudate (Phillips et al. 1998; Shapira et al. 2003; Fitzgerald et al. 2004) and this suggests that the recovered depressed patients, in this brain region, show increased processing of aversive cues, consistent with negative biases reported across paradigms in depression (Bradley et al. 1997; Murphy et al. 1999; Surguladze et al. 2004). Such a pattern of effect with increased responses in subcortical areas to aversive stimuli but flattened responses within the prefrontal cortex when cross-modal information is combined in recovered depressed patients provides a compelling parallel to reports of increased negative bias yet often subjective experiences of emotional blunting. This seemingly paradoxical state could arise through increased drive and responses to aversive or ambiguous stimuli at a fairly automatic level coupled with a failure to integrate this fully into subjective experience with multimodal stimuli presentations. At a more practical level, the increased BOLD response at the level of the caudate also suggests that the current results cannot be explained by nonspecific decreases in neural responsivity or neural coupling, but rather that the differences in responses might underlie a vulnerability to experience anhedonia and, therefore, depression.

In conclusion, our findings suggest that patients with a history of depression have impaired neural responses to a primary rewarding stimulus, consistent with the proposal that deficient neural reward processes could be part of an endophenotype of depression. However, it is not clear from the present data whether impairments in reward are present prior to onset of clinical illness or may instead represent a "scar" of the illness or its treatment. Studies in people at high risk of depression, before illness onset, will be needed to resolve this issue. It will also be important to determine whether abnormal neural representations of reward correlate with increased risk of depressive relapse and how far the abnormalities may be reversible with specific psychological and pharmacological treatments.

Acknowledgments We would like to acknowledge Mr. Leo McCabe for the photography and Mrs. Lara Waldenmaier for the help with the questionnaire data analysis. This work has been supported by the Medical Research Council grant no. HQRORVO.

Conflicts of interest Dr Harmer has acted as a consultant for the following companies: Lundbeck, P1Vital, Merck, and Sharpe and Dohme and has received grant income from Merck and Sharpe and Dohme. Professor Cowen has been a paid member of advisory boards of Eli Lilly, Servier, Wyeth, and Xytis and has been a paid lecturer for Eli Lilly, Servier, and GlaxoSmithKline.

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