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ORIGINAL ARTICLE

Neural correlates of 'pessimistic' attitude in depression

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Background. Preparing for potentially threatening events in the future is essential for survival. Anticipating the future to be unpleasant is also a cognitive key feature of depression. We hypothesized that 'pessimism'-related emotion processing would characterize brain activity in major depression.

Method. During functional magnetic resonance imaging, depressed patients and a healthy control group were cued to expect and then perceive pictures of known emotional valences – pleasant, unpleasant and neutral – and stimuli of unknown valence that could have been either pleasant or unpleasant. Brain activation associated with the 'unknown' expectation was compared with the 'known' expectation conditions.

Results. While anticipating pictures of unknown valence, activation patterns in depressed patients within the medial and dorsolateral prefrontal areas, inferior frontal gyrus, insula and medial thalamus were similar to activations associated with expecting unpleasant pictures, but not with expecting positive pictures. The activity within a majority of these areas correlated with the depression scores. Differences between healthy and depressed persons were found particularly for medial and dorsolateral prefrontal and insular activations.

Conclusions. Brain activation in depression during expecting events of unknown emotional valence was comparable with activation while expecting certainly negative, but not positive events. This neurobiological finding is consistent with cognitive models supposing that depressed patients develop a 'pessimistic' attitude towards events with an unknown emotional meaning. Thereby, particularly the role of brain areas associated with the processing of cognitive and executive control and of the internal state is emphasized in contributing to major depression.

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Key words: Depression, emotion processing, functional neuroimaging, insula, pessimism, prefrontal cortex.

Introduction

Anticipation is a basic human cognitive function involving the preparation for future events (Gilbert & Wilson, 2007). As we do not know what the future holds, we prepare for expected events in order to deal with the associated pleasant or unpleasant outcome. To be able to cope, it makes sense to consider the worst-case scenario. This appears to be valid also from an evolutionary perspective, as our antecedents had a better chance to survive when they were prepared to cope, for instance, with predators or a hard winter. Thus, pessimism, meaning to expect the disadvantageous outcome when facing events of unknown emotional impact, seems to have positive facets (Nesse, 2000), such as diminishing of risk behaviour (Gibson & Sanbonmatsu, 2004) and avoidance of disappointment by setting low expectations (Norem & Cantor, 1986; Shepperd & McNulty, 2002). However, the overly pronounced expectation that the future will be unpleasant also represents a key cognitive feature in major depression (Pyszczynski *et al*. 1987; Lavender & Watkins, 2004). This is expressed in the concept of the cognitive triad which comprises a negative attitude towards oneself, the environment and the future (Beck, 1967). Recent reports have shown an altered emotion processing in depression compared with the healthy state concerning the perception and also the anticipation of emotional events (e.g. for reviews, see Drevets, 2001; Davidson *et al*. 2002; Phillips *et al*. 2003; Leppanen, 2006; for recent reports, see Keedwell *et al*. 2005; Abler *et al*. 2006; Johnstone *et al*. 2007; Langenecker *et al*. 2007; Lee *et al*. 2007; Dannlowski *et al*. 2008; Fales *et al*. 2008; Grimm *et al*. 2008; Knutson *et al*. 2008; Mitterschiffthaler *et al*. 2008). However, the

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direct comparison of anticipating events of known positive and negative valence with an unknown valence as a model of 'pessimistic' expectation has not yet been performed in depressed patients. In a previous report in healthy subjects, we demonstrated that in the case of expecting an event of unknown emotional valence, emotion processing brain areas are activated in a way that is comparable with the expectation of an event known to be unpleasant but not with that of an event known to be positive (Herwig *et al*. 2007*b*). Further, distinct activations in that study correlated with individual depressiveness: the more depressed, the higher the activity. This finding of a 'pessimistic' bias towards expected unknown emotional events may be interpreted as a neural correlate of our propensity to prepare for a negative outcome. Given this context, we hypothesized that patients with major depression would show a 'pessimistic' bias in their brain activation as measured with functional magnetic resonance imaging (fMRI), meaning a higher activation in key brain regions during the expectation of events with negative and unknown valence than when expecting neutral or positive events. Those activations also were assumed to be more prominent in depressed patients compared with healthy subjects. Apart from the regions found in the healthy subjects to be related to 'pessimism', regions of key interest were also those known to be affected in depression and involved in planning and emotion processing, particularly the amygdala, dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (MPFC) and anterior cingulate cortex (ACC) (e.g. Baxter *et al*. 1989; Fuster, 2000; Phillips *et al*. 2003; Paulus *et al*. 2005; Vogt, 2005; Abler *et al*. 2006; Siegle *et al*. 2007; Knutson *et al*. 2008).

Methods

Subjects

A total of 16 in-patients (14-included in analysis) with a current diagnosis of a major depressive episode were recruited at the Psychiatric University Hospital of Zurich, Switzerland (for demographic and psychometric data, see Table 1). A diagnosis of mildly to moderately severe depressive episode was made by trained psychiatrists according to ICD-10 and DSM-IV criteria. Psychiatric Axis I and other comorbidities such as neurological disorders and MRI contraindications were excluded in a semi-structured interview prior to scanning. After receiving complete description of the study, all participants gave written informed consent. The study was approved by the local ethics committee. The patients were on stable antidepressant medication. They had been off benzodiazepines and neuroleptics for at least four half-lives, and they were not taking any mood-stabilizing medication. The patient group was analysed on its own and it was additionally compared with a group of 14 healthy subjects from a previous report (Table 1; Herwig *et al*. 2007*b*).

Table 1. *Demographic and psychometric data of included subjects*

	Depressed	Healthy	p[a]
n	14	14	
Gender, *n*			
Female	8	8	
Male	6	6	
Mean age, years (S.D.)	40.4 (10.7)	27.6 (3.6)	<0.01
Episodes of depression, *n*			
1–3	9	–	
>3	5	–	
Mean scale scores (S.D.)			
BDI	24.8 (9.9)	–	
HAMD	24.4 (7.2)	–	
MADRS	26.9 (8.1)	–	
SDS	–	35.4 (6.6)	
Mean picture ratings (S.D.)			
Negative	2.58 (0.61)	2.96 (1.35)	0.10
Positive	7.40 (0.85)	7.20 (1.25)	0.533
Neutral	5.22 (0.54)	5.10 (0.67)	0.51

S.D., Standard deviation; BDI, Beck Depression Inventory; HAMD, Hamilton Depression Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; SDS, Self-rating Depression Scale (score <50: not depressed).

[a] Difference by *t* test.

Experimental design

During fMRI scanning, the patients performed a cueing task (programmed with Presentation™, Neurobehavioral Systems, USA) consisting of 56 trials with expectation and presentation of emotional pictures (Fig. 1). The trials comprised of two main conditions: 'known' or 'unknown'. The 'known' condition consisted of three subconditions (negative, positive, neutral). For each trial of the 'known' subconditions a small cue was presented that depicted either a smiling '⌣' ('positive' or 'pleasant', ps), a non-smiling '⌢' ('negative' or 'unpleasant', ng) or a neutral symbol '−' (nt) that indicated the emotional valence of the pictures presented after an anticipation period. In the 'unknown condition', '|' (uk), either pleasant or unpleasant pictures appeared randomly. The cues were of 1/40 of screen height and the pictures filled the screen. The cues were presented for 1000 ms followed by an anticipation period of a further 6920 ms [cue and

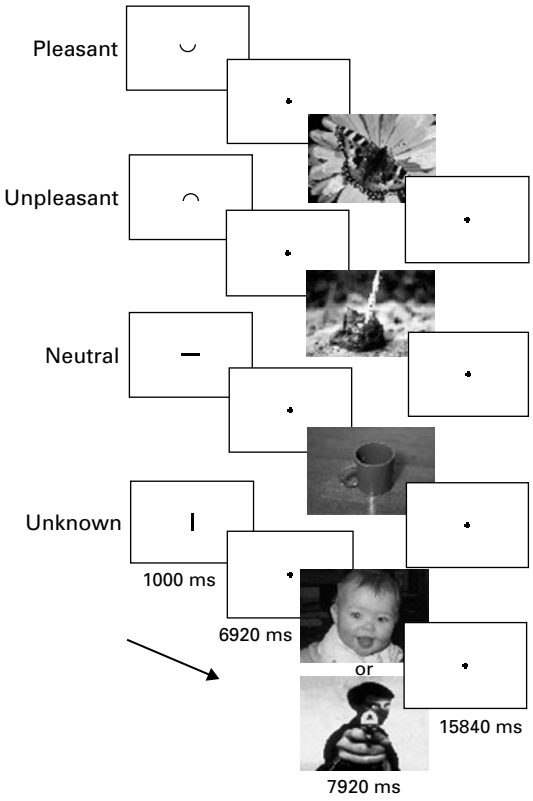

Fig. 1. Experimental task. Cues, presented for 1000 ms, indicated the valence of the picture which appeared after a delay of a further 6920 ms: '⌣', prior to a 'pleasant' picture; '⌢', prior to an 'unpleasant' picture; '−', prior to a 'neutral' picture; and '|', prior to a picture of 'unknown' valence, either pleasant or unpleasant. The cues have been enlarged here for presentation purposes.

anticipation: four times of MR volume repetitions; repetition time (TR) 1980 ms], during which a blank screen with a small fixation point was shown. Subsequently, emotional pictures (International Affective Picture System; Lang, 1995) were presented for 7920 ms (4 TRs). During the following baseline period of 15 840 ms (8 TR) the blood oxygen level-dependent signal could wear off before the next trial. Altogether, 56 pre-cued pictures were shown, 14 for each 'known' trial as positive, negative and neutral, and 14 for 'unknown' (seven ps, seven ng). The different trials appeared in a randomized order. All participants were instructed to expect the emotional stimuli after the cue and to be aware of the emotional valence indicated, and to subsequently look at the following picture. The stimuli were matched for complexity, content of faces, scenery, food and nature, and concerning intensity of positive and negative valence with the same difference in valence ratings from neutral. Arousal was matched as far as possible for pleasant and unpleasant stimuli (Herwig *et al*. 2007*a*). All participants rated the presented pictures after the scanning according to the subjective valence on a visual analogue scale (1 most negative, 9 most positive).

fMRI acquisition and data analysis

Imaging was performed with a 1.5 T Siemens Sonata whole-body scanner (Erlangen, Germany) equipped with a head coil. T1* weighted anatomical volumes ($1 \times 1 \times 1$ mm) were acquired for co-registration with the fMRI. T2* weighted functional magnetic resonance images were obtained using echoplanar imaging in an axial orientation (image size 64×64 pixels, 22 slices covering the whole brain, field of view of 220 mm, flip angle 90°, slice thickness 4 mm with 1 mm gap, voxel size $3.4 \times 3.4 \times 5$ mm, repetition time/echo time (TR/TE) 1980/40 ms, 908 volumes). The subjects watched the stimuli in a mirror attached to the head coil and directed to a screen onto which the stimuli were projected by a video beamer.

fMRI data were analysed using BrainVoyager™ QX 1.8.6 (Brain Innovation, The Netherlands). Preprocessing included motion correction, slice scan time correction, high-frequency temporal filtering and removal of linear trends. Functional images were superimposed on the two-dimensional anatomical images and incorporated into three-dimensional (3D) datasets. The individual 3D datasets were transformed into Talairach space (Talairach & Tournoux, 1988) resulting in a voxel size of $3 \times 3 \times 3$ mm and then spatially smoothed with an 8 mm Gaussian kernel for subsequent group analysis. Eight predictors representing the expectation (exp) and presentation (pres) of each valence (ng, uk, ps, nt) were used to build the design matrix. Expectation period and picture presentation periods were modelled as epochs using the standard two-γ haemodynamic response function provided by BrainVoyager (Glover, 1999).

The fMRI data analysis based on the general linear model (GLM) comprised of the following steps: Fixed-effects analyses were calculated separately for each subject for the six contrasts comparing the emotion expectation conditions 'negative *versus* neutral', 'positive *versus* neutral', 'unknown *versus* neutral', 'unknown *versus* negative', 'unknown *versus* positive' and 'negative *versus* positive', resulting in summary images. The summary images were subjected to second-level analyses, separately for both the groups of the depressed patients and of the healthy subjects. Addressing our main question to evaluate which of the 'known' emotion expectation conditions (ng, ps, nt) revealed activations similar to those in the 'unknown' expectation condition (uk), we applied conjunction analyses based on the single contrasts. These were done with fixed-effects conjunction analyses with separate subject predictors in order to address the

minimum-*t* problem (Nichols *et al*. 2005). We defined 'unknown' expectation-related activity in a certain brain region as being similar to one of the 'known' expectation-related activations, when in this region both activations were significantly different from the activations associated with both remaining 'known' emotion expectation conditions, but were not different in the corresponding single contrast. For example, addressing similarity of the 'unknown' and the 'negative' condition, the 'unknown' condition had to differ significantly from 'positive'- (contrast exp uk > ps) and also 'neutral' (exp uk > nt)-related activity, and 'negative' also had to differ from 'positive' (exp ng > ps) and 'neutral' (exp ng > nt) expectation-related activity. These contrasts therefore also comprised the direct comparisons between the 'known' expectation conditions as 'negative *versus* positive'. The revealed brain regions further should not differ in the direct comparison, for instance when using the contrast exp ng > uk.

Accordingly, the following conjunctions were analysed:

(1) The 'pessimism-contrast': expecting unknown events to be negative should be reflected by activity during exp uk resembling the activity during exp ng, but differ from ps and nt: exp uk > ps and uk > nt and ng > ps and ng > nt.
(2) The 'optimism-contrast': assuming the upcoming unknown event to be positive, the brain activity during the exp uk should be similar to the activity during exp ps: exp uk > ng and uk > nt and ps > ng and ps > nt.
(3) The 'indifference-contrast': if subjects anticipate 'unknown', thus either positive or negative events, like neutral events, brain activity might be similar to the 'neutral' expectation: exp uk > ng and uk > ps and nt > ng and nt > ps.

The statistical threshold for these conjunctions was set at a level of $p < 0.001$ (uncorrected considering the conjunction approach with the application of four single contrasts together) with a cluster size of 135 voxels of $1 \times 1 \times 1$ mm corresponding to 5 voxels of $3 \times 3 \times 3$ mm. The results obtained from the healthy subjects have been reported previously (Herwig *et al*. 2007*b*). For the depressed patients, further explorative results with lower cluster size are reported when they complied with the results from the healthy subject group. An analysis of the presentation period and main-effect analyses of emotion and expectation were performed on an exploratory basis not reported here.

Questionnaires and correlation statistics

The patients completed a handedness questionnaire (Annett, 1967) and a depression self-rating [Beck's Depression Inventory (BDI); Beck *et al*. 1961]. Further, depressiveness was assessed by the 21-item Hamilton Depression Scale (HAMD; Hamilton, 1960) and the Montgomery–Åsberg Depression Rating Scales (MADRS; Montgomery & Åsberg, 1979). Immediately after scanning, the patients rated the emotional valence of the pictures (presented again as printouts) on a visual analogue scale. Using Pearson's correlation, we correlated the rating score results of the depression scales with the individual β-weights (mean from all voxels of the respective activated cluster) of the emotion expectation conditions in those regions resulting from the conjunction analyses. Thus, within the regions of interest (ROIs) derived from the conjunction analyses, we correlated the different individual β-weights of the emotion conditions in each ROI with the individual psychometric data. In order to control for an influence of age, we also correlated the β-weights with the age in both groups, healthy and depressed participants, and performed an exploratory partial correlation analysis with age as the control variable.

Comparison between depressed patients and healthy subjects

Activations in depressed patients and healthy subjects were compared. Within the activated clusters in the depressed patients and in the healthy subjects random-effects analyses of the 'emotion *versus* neutral' contrasts were performed by using separate subject predictors and implementing the factor of being depressed or healthy in the GLM. Additionally, we explored group differences of the single contrasts in the bilateral insula based on ROIs derived from the contrast ps > nt in the depressed patients in order to assess whether failing to find hypothesized activations in the 'pessimism'-contrast might be due to an activation during the positive expectation.

Results

Participants and behavioural data

From the 16 depressed patients, one had to be excluded because of movement artefacts (> 3 mm in at least one direction) and one patient reported after scanning that she had not been able to identify the cues correctly. Thus, 14 depressed patients were entered into the analysis. All were right-handed. They were also compared with 14 healthy subjects (Herwig *et al*. 2007*b*), who were younger than the patients. The picture ratings were not different (Table 1). Medication in the depressed patients included mirtazapin (15–45 mg, $n = 5$), venlafaxin (75–150 mg, $n = 2$),

citalopram/escitalopram (60/20 mg, $n=2$), citalopram/escitalopram (20–40 mg) plus mirtazapin (30–60 mg) ($n=3$), trazodone (100 mg, $n=1$) and no medication ($n=1$).

Conjointly activated areas during 'unknown' and 'known' emotion expectation

We performed conjunction analyses to discover which of the 'known' emotion expectation conditions revealed activations similar to those in the 'unknown' condition. Regarding the comparison 'negative' and 'unknown' in the depressed patients we found activity within the MPFC [Brodmann area (BA) 8], left DLPFC (BA 9/46), bilateral inferior frontal gyrus (IFG, BA 45) and insula (BA 13), in a region adjacent to the anterior thalamus and head of the caudate nucleus best fitting the area comprising the bed nucleus of the stria terminalis (BNST; being aware that this structure is small for the applied fMRI resolution), in the anterior and medial thalamus, and in the nucleus ruber (NR; Table 2, Fig. 2). These areas were not different in the direct contrast exp ng > uk in either direction. The equivalent analyses of the relation of 'unknown' and 'positive' expectation ('optimism-contrast') and of 'unknown' and 'neutral' expectation ('indifference-contrast') did not deliver any results even at a level of $p<0.01$ uncorrected. Other regions such as the amygdala were active in the single emotion expectation contrasts not reported here. Results from the healthy subjects have been reported earlier (Herwig *et al*. 2007*b*). In brief, activated areas in that group in the 'pessimism'-contrast were within the right IFG, insular regions, medial thalamus, BNST region, NR and temporo-occipital cortex.

Correlation of brain activation with depression ratings

The assumption was made that subjects with a higher level of depressiveness may exert stronger activity in areas associated with 'unknown' and 'negative' expectation. We tested this by correlating psychometric data obtained from the BDI, HAMD and MADRS with the mean β-weights obtained from the significantly activated clusters of the conjunction analyses (one BDI missing). This analysis revealed significant positive correlations in the MPFC, left DLPFC, IFG/insula regions and NR during 'unknown' and 'negative' expectation (Fig. 2, Table 2). We did not find any correlation of the activations with age, neither in the depressed, nor in the healthy group, and the exploratory correlation analysis controlled for age provided essentially equivalent results as without this control variable.

Comparison between depressed patients and healthy subjects

We compared the activity in the revealed clusters from the conjunction analysis in the depressed patients with the activations in healthy subjects (Fig. 3, Table 2). Compared with the healthy subjects, depressed patients showed increased activations during both the negative and unknown conditions in the left DLPFC and anterior MPFC, and for the unknown conditions also in the bilateral IFG/insular regions and left BNST. Concerning regions activated in healthy subjects but not in the patients, the right BNST ($p=0.04$) and left insula ($p=0.04$) were more strongly activated in the respective contrasts in the healthy subjects. The exploratory analysis of group differences in the single contrasts within the ROIs based on the ps > nt contrast found a stronger insular activation in the depressed patients (see Supplementary Fig. 1, available online).

Discussion

Assuming a 'pessimistic' attitude in depression when expecting upcoming events, our hypothesis was that patients with major depression would show brain activation while expecting events of unknown emotional valence as if these events are known to be unpleasant. Further, we assumed that distinct emotion-processing brain areas known to be affected in depression would be activated differently compared with healthy subjects. Our main findings were: (i) while anticipating pictures of unknown emotional valence, the brain activity resembled that observed when expecting pictures known to be negative but not when expecting positive or neutral pictures; (ii) the activity within a prominent part of the corresponding brain regions, particularly within the DLPFC, MPFC and insula/IFG correlated with the grade of depression; and (iii) the activation in these regions differed significantly from that in healthy subjects. This supports the assumption of considering a negative outcome for future scenarios to form a key cognitive feature of depression with distinct neural representations.

Brain regions involved in 'pessimistic' expectation

Activations within the DLPFC and MPFC were associated with 'pessimistic' expectation in depressed patients, which was not the case in the healthy subjects. Further, the activity in these areas correlated with the depression scores: the more depressed, the higher the activation. Notably, the activation of the DLPFC differed between the groups in all, and in the anterior MPFC in most of the contrasts. This provides evidence that the 'pessimistic' expectation in

Table 2. *Conjunction analyses of emotion expectation contrasts, correlations of β-weights with rating scores, and comparison of depressed and healthy groups*

	Depressed patients: uk and ng > ps and nt[a]				Correlations (*p*)							Groups: depressed *v.* healthy, Fig. 3, *p*			
Anatomic regions	BA	Voxel size, mm³	Talairach coordinates (x, y, z)	t_{max}	uk with BDI	uk with HAMD	uk with MADRS	ng with BDI	ng with HAMD	ng with MADRS	Fig.	ng > nt	ng > ps	uk > nt	uk > ps
DLPFC L	46	1021	−39, 31, 29	4.0	0.68 (0.01)	0.73 (0.003)	0.60 (0.02)	0.68 (0.01)	0.65 (0.01)	0.55 (0.04)	2*a*	0.03	0.003	0.002	0.0001
DLPFC/PMC L	6/9	2161	−46, 5, 36	4.6	0.72 (0.006)	0.71 (0.005)	0.63 (0.02)	0.73 (0.005)	0.72 (0.004)	0.59 (0.03)		0.11	0.06	0.08	0.02
IFG L	45/46	932	−47, 20, 2	4.3	0.50 (0.08)	0.55 (0.04)	0.50 (0.07)	0.56 (<0.05)	0.68 (0.008)	0.60 (0.02)	2*b*	0.005	0.04	0.03	0.25
IFG/insula R	45/13	709	41, 24, −2	4.3	0.65 (0.02)	0.40 (0.16)	0.54 (<0.05)	0.66 (0.01)	0.40 (0.15)	0.54 (0.04)		0.42	0.13	0.80	0.37
Insula L	13	383	−31, 17, −9	4.2	0.35 (0.24)	0.15 (0.60)	0.22 (0.46)	0.16 (0.60)	0.07 (0.81)	0.03 (0.91)		0.22	0.19	0.007	0.03
MPFC ant R/L	8	414	0, 32, 41	3.9	0.57 (0.04)	0.48 (0.08)	0.50 (0.07)	0.42 (0.15)	0.46 (<0.10)	0.43 (0.12)		0.35	0.41	0.04	0.21
MPFC post R/L	8	512	1, 7, 54	4.3	0.53 (0.06)	0.60 (0.02)	0.56 (0.04)	0.66 (0.01)	0.65 (0.01)	0.58 (0.03)		0.64	0.06	0.32	0.04
BNST region L		392	−11, 0, 12	4.5	0.37 (0.21)	0.28 (0.33)	0.14 (0.63)	0.68 (0.01)	0.53 (0.05)	0.49 (0.08)		0.71	0.11	0.82	0.01
IFG R[b]	45	37	40, 18, 10	3.7	0.62 (0.02)	0.67 (0.01)	0.54 (0.04)	0.64 (0.19)	0.59 (0.03)	0.57 (0.03)	2*c*	0.71	0.47	0.24	0.07
Medial thalamus[b]		112	1, −14, 5	3.8	0.31 (0.31)	0.51 (0.06)	0.37 (0.19)	0.50 (0.08)	0.26 (0.37)	0.20 (0.49)	2*d*	0.11	0.67	0.18	0.23
Nucleus ruber R[b]		29	8, −21, −10	3.9	0.69 (0.009)	0.57 (0.04)	0.53 (0.06)	0.56 (<0.05)	0.58 (0.03)	0.46 (<0.10)	2*e*	0.21	0.96	0.71	0.46

uk, Unknown expectation; ng, negative expectation; ps, positive expectation; nt, neutral expectation; BA, Brodmann area; BDI, Beck depression inventory; HAMD, Hamilton depression scale; MADRS, Montgomery–Åsberg depression rating scale; DLPFC, dorsolateral prefrontal cortex; L, left; PMC, premotor cortex; IFG, inferior frontal gyrus; R, right; MPFC, medial prefrontal cortex; ant, anterior; post, posterior; BNST, bed nucleus striae terminals.

On the right, results from the random-effects group comparison of activations within the regions of interest from the 'pessimism'-contrast.

[a] Activated regions according to the conjunction analysis of expectation 'unknown' and 'negative' stimuli, both *versus* expecting 'positive' and *versus* 'neutral' stimuli. Indicated are: the amount of voxels (mm³); Talairach coordinates (x, y, z) of the centre of mass of the activation; and maximal *t*-values of the voxels within the regions.

[b] Results from explorative analysis.

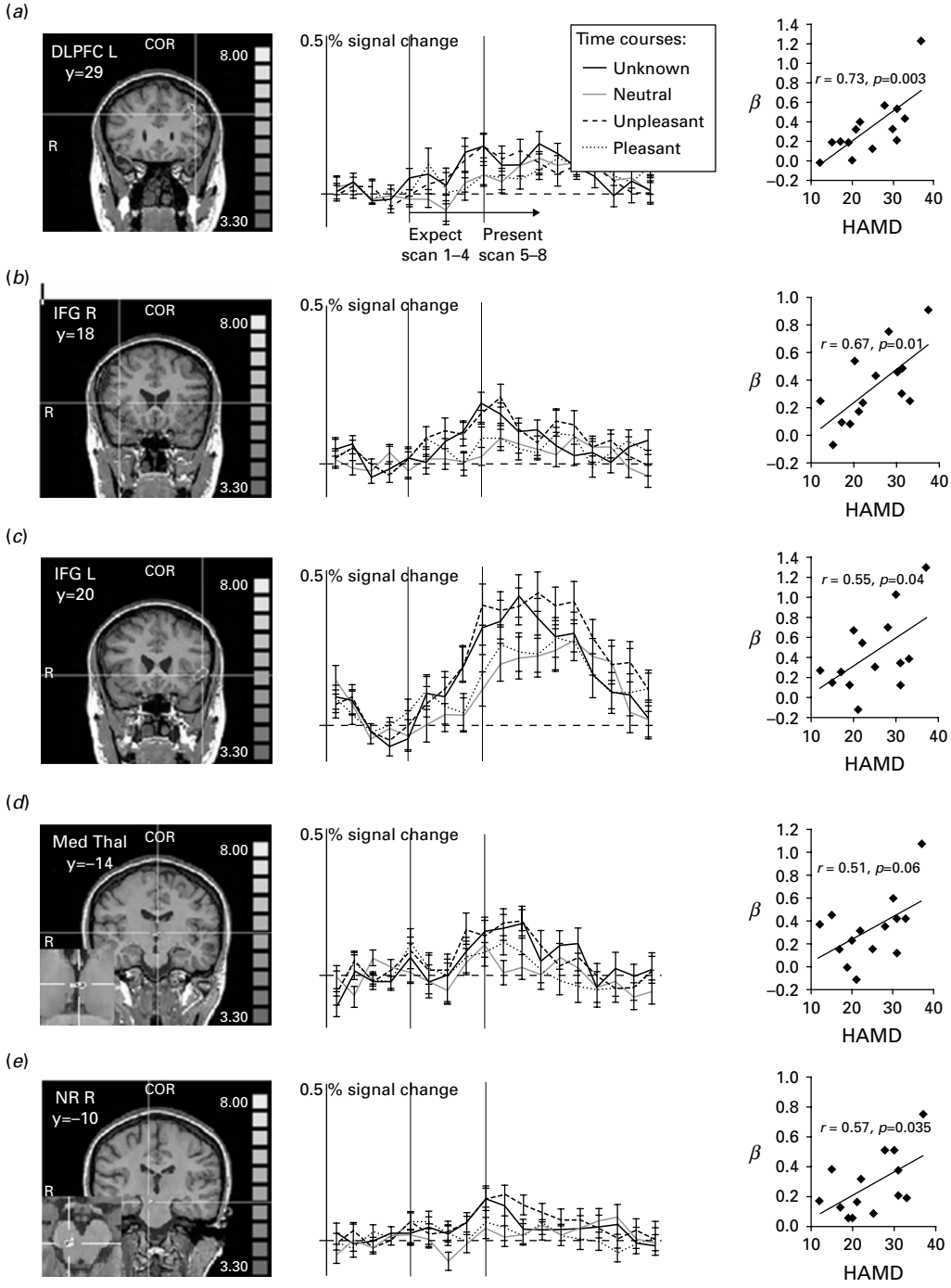

Fig. 2. Comparison of 'known' and 'unknown' expectation. Conjunction analysis of the conditions 'unknown' and 'unpleasant' expectation *versus* 'pleasant' and *versus* 'neutral' (exp uk > ps and uk > nt and ng > nt and ng > ps). The activated voxels were co-registered using structural magnetic resonance imaging and colour coded (consider cross-hair, see coloured version of this figure in Supplementary online material) according to their significance (*t*-value). Presented are coronal (COR) slices of (*a*) the left dorsolateral prefrontal cortex (DLPFC L), (*b*) the right inferior frontal gyrus (IFG R), (*c*) the left IFG (IFG L), (*d*) the medial thalamus (Med Thal) and (*e*) the right nucleus ruber (NR R) and cut-outs of the axial slices of the thalamus and NR R in the lower left of the respective pictures. Further, on the right, the time courses of the activities within the marked regions of interest are shown in percentage BOLD signal change, indicating the conjoint activity of the 'unpleasant' expectation with the 'unknown' expectation. The vertical grey bars represent the beginning of the expectation (Expect) and presentation (Present) periods, comprising each four volumes. When interpreting the time courses, the delayed haemodynamic response function has to be considered. Further, the correlations of the β-weights of the activity during the 'unknown' expectation condition with the Hamilton depression scores (HAMD) are presented.

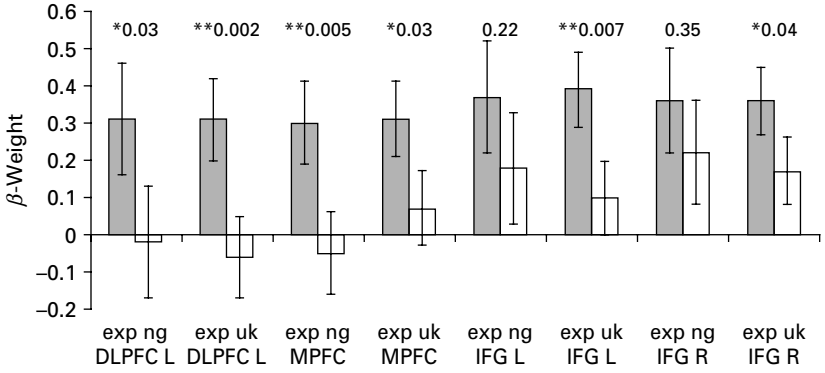

Fig. 3. Comparison of activity in regions of interest (β-weights) in depressed patients (■) compared with healthy subjects (□). Values are means, with standard errors represented by vertical bars. For the different regions and conditions, p values are given for the difference between the depressed and healthy subjects (* $p < 0.05$, ** $p < 0.01$). DLPFC L, left dorsolateral prefrontal cortex; exp uk, expectation unknown; exp ng, expectation negative; MPFC, medial prefrontal cortex; IFG L, left inferior frontal gyrus; IFG R, right inferior frontal gyrus.

depression may be associated with the functional domains of the DLPFC and MPFC as a final evaluation of situations, response planning, and cognitive and executive control (Fuster, 2000; Gross & John, 2003). The DLPFC has been associated with hypometabolism in depression (Soares & Mann, 1997), or with hypofunctionality in cognitive tasks (Siegle *et al*. 2007), possibly leading also to compensatory activation (Harvey *et al*. 2005). One may assume that DLPFC resources in depression might be absorbed due to a bias towards depressive cognition by focusing on corresponding situations and stimuli (Grimm *et al*. 2008), for instance, due to a negative attitude towards future events according to the cognitive triad (Beck, 1967). This may be represented within neural network concepts by information processing modules in the DLPFC acting as attractors (Yuste *et al*. 2005) for depressive cognition. We also found the MPFC to be active during unknown and negative expectation, with the 'unknown'-related activity being more prominent in depressed than in healthy subjects. Whereas the DLPFC is involved in evaluating and preparing action in the external world (Fuster, 2000), the MPFC was reported to be involved in the cognitive control of internal emotional processes (Gross & John, 2003; Herwig *et al*. 2007*a*). It might be recruited in depression in order to exert cognitive control onto subcortical emotion-associated areas, possibly with an ineffective compensatory over-activation. Basically, a complex disturbance of the information processing within and between functional systems for integrating emotional–cognitive information is assumed (Pessoa, 2008). In this context, one may consider primary modulating regions on emotion processing such as the DLPFC or the amygdala working as 'connector hubs' for information processing (Sporns *et al*. 2007).

In our previous study with healthy subjects, we found the IFG, insular regions and the medial thalamus to be associated with 'pessimistic' expectation (Herwig *et al*. 2007*b*). This was essentially also the case in the depressed patients, with the exception that certain insular regions revealed different activation patterns. The IFG, in the region of the ventrolateral prefrontal cortex, was assumed to represent multimodal sensory cues with high emotional salience (Yamasaki *et al*. 2002) and to be involved in emotional–cognitive integration (Mayberg, 2003). It may provide a link between the evaluation of the internal state associated with an emotional situation and its cognitive processing, for instance, by propagating 'internal' information to upstream prefrontal areas. Medial thalamic regions receive input from viscero-sensitive and pain-mediating brainstem areas and are considered to form a relay within the visceroceptive pathway towards, for example, insular regions (Craig, 2002; Vogt, 2005). The insula was found to be involved in the processing of multimodal sensory and emotional stimuli, supporting views of a general role of the insula in emotion processing (Damasio *et al*. 2000; Calder *et al*. 2001; Craig, 2002; Critchley *et al*. 2004; Paulus & Stein, 2006; Simmons *et al*. 2008). It was proposed that the physical sensation of emotional responses depends on sensations from the viscera represented in the insula (Critchley *et al*. 2004). In this context, the insula may be involved in the mediation of bodily viscero-sensitive signals for decision making and behavioural planning according to emotional valences. We found activations in the depressed patients during both the 'unknown' and the 'negative' expectation as hypothesized, but also increased activation during the 'positive' expectation compared with the healthy subjects. This may be interpreted as an insular

'unpleasantness'-signal not only during 'negative' or 'unknown' expectation but also during 'positive' expectation, and may be associated with anhedonia (Keedwell *et al*. 2005). Being depressed is often associated with unpleasant somatic feelings and a negative self-perception. This may result from a dysregulation of interoceptive areas such as the insula due to a misinterpretation of external cues based on unpleasant previous experiences, inducing subjective unpleasantness (Davidson *et al*. 2003). These considerations lead to further concepts of the insula to be involved in self-representation and 'self-awareness' (Churchland, 2002; Craig, 2002) and to disturbed 'self' functions in depression (Northoff & Bermpohl, 2004).

At the brainstem level, we found, in both the depressed and the healthy group, a region covering the NR to be associated with 'negative' and 'unknown' expectation. The NR has been assumed to be involved in psychomotor modulation and in behavioural attendance (Horn *et al*. 2002). During expectation, it may prime or facilitate the readiness for a later motor reaction.

Two main brain regions hypothesized as being associated with functional disturbance in depression were not found to be activated in the 'pessimism'-contrast: the amygdala (e.g. Abler *et al*. 2006; Lee *et al*. 2007) and the ACC (Bermpohl *et al*. 2006; Nitschke *et al*. 2006). For the amygdala, this might be explained by the fact that it also showed activation during the positive expectation condition (Herwig *et al*. 2007*b*) and thus not fulfilling the criteria for the 'pessimism'-contrast but being more generally associated with valence-independent emotional arousal (Anderson *et al*. 2003; McClure *et al*. 2004). However, though being difficult to distinguish anatomically, a region covering and best fitting the bed nucleus of the stria terminalis was activated in the 'pessimism'-contrast. This region was considered to form a functional unit with the 'extended' amygdala (Heimer & Van Hoesen, 2006) and may be a link to further emotion-processing circuits. The ACC may be activated more in the context of conflict monitoring between functional state and perceived new information with potential affective or motivational consequences (Carter *et al*. 2000; Vogt, 2005) and not in the specific context of 'pessimistic' expectation.

Principally, one may assume that a circuit for biasing the organism towards potentially disadvantageous or even dangerous events makes evolutionary sense. Whenever we may also have an optimistic bias for certain personal long-term attitudes towards the future (Sharot *et al*. 2007), the chances of survival for our early ancestors who for instance anticipated a predator when hearing a rustling sound in the vicinity, and prepared for it appropriately, were conceivably higher than for those who did not. Hence, one may speculate that a certain degree of depressiveness may be of evolutionary advantage (Nesse, 2000; Panksepp, 2006), in that uncertain future events are more likely to be evaluated as unpleasant and that the person is better prepared for when negative events actually do occur.

Limitations

In reflecting on possible limitations, we addressed the issue of the differing age of both groups. Whenever the main analysis of this report was based on the depressed group, we also performed a group comparison with the healthy subjects. One may argue that the higher activation in the depressed patients might be accounted for by their higher age. This, however, would be in contrast with findings of attenuated emotion processing-related brain activity with increasing age (Erk *et al*. 2008). Furthermore, age-dependence is unlikely in view of the fact that the activations correlated with depressiveness, but not with age, which would have been the case if age had an influence on the activation. The same holds true for the medication in the depressed patients. The fact of being medicated does not explain the correlations with psychopathology, such that depressiveness, not age or medication, can be accounted for by our results. Nevertheless, our findings should be interpreted as applying to medicated patients because any influence of medication on activations cannot be excluded entirely.

Emotional arousal (McClure *et al*. 2004) or experience of uncertainty (Simmons *et al*. 2008) may also contribute to the revealed activation. However, again, the correlations with depressiveness point to an association of the activation with depression and not to these factors. Further, valence-independent arousal would also have occurred through positive expectation and thus would have led to non-fulfilling the criteria of 'pessimism'. Nevertheless, uncertainty and heightened arousal towards unpleasant events might be inherent factors for 'pessimistic' expectation (Simmons *et al*. 2008).

The experimental task was designed to focus on the mental process during expectation. Therefore, the highly abstract and graphically comparable cues were intuitively understandable, so that no prominent working memory component was necessary to establish their meaning. Further, no motor reaction was required, the preparation and exertion of which might have interfered with processes of emotional anticipation. However, the task thus did not comprise an implemented behavioural control. We decided not to use such a control, for instance by motor reaction, in

order to avoid interfering and noisy other brain activation. On the other hand, a behavioural measure implemented in our task demonstrating a 'pessimistic' bias also on the level of behavioural outcome could have further strengthened the assumption of 'pessimistic' expectation in depression. However, here we focused on the neural correlates considering that neural aspects, and also subjective emotional experience, must not necessarily be reflected by observable behaviour. We asked the subjects and patients afterwards whether if they had been able to attend to the task and we attempted to verify this by checking appropriate activation in the visual cortex. If the participants had not attended, one would have expected noisy data and no specific activations.

In conclusion, the similarity of 'unknown' and 'unpleasant' expectation-related brain activity may be attributed to a 'pessimistic' bias towards future events as expressed particularly in depressed patients. This supports cognitive models of a 'pessimistic' attitude in depression at the neurobiological level. Dorsolateral and medial prefrontal regions, known to be involved in executive and cognitive control, and viscerosensitive areas such as the insula appear to play a key role in biasing the organism towards preparation for the worst-case scenario and to contribute to depressiveness.

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Note

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org/psm).

Declaration of Interest

None.

References

Abler B, Erk S, Herwig U, Walter H (2006). Anticipation of aversive stimuli activates extended amygdala in unipolar depression. *Journal of Psychiatric Research* **41**, 511–522.

Anderson AK, Christoff K, Stappen I, Panitz D, Ghahremani DG, Glover G, Gabrieli JD, Sobel N (2003). Dissociated neural representations of intensity and valence in human olfaction. *Nature Neuroscience* **6**, 196–202.

Annett M (1967). The binomial distribution of right, mixed and left handedness. *Quarterly Journal of Experimental Psychology* **19**, 327–333.

Baxter Jr LR, Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE, Gerner RH, Sumida RM (1989). Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Archives of General Psychiatry* **46**, 243–250.

Beck AT (1967). *Depression: Clinical, Experimental and Theoretical Aspects*. Harper & Row: New York.

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961). An inventory for measuring depression. *Archives of General Psychiatry* **4**, 561–571.

Bermpohl F, Pascual-Leone A, Amedi A, Merabet LB, Fregni F, Gaab N, Alsop D, Schlaug G, Northoff G (2006). Dissociable networks for the expectancy and perception of emotional stimuli in the human brain. *NeuroImage* **30**, 588–600.

Calder AJ, Lawrence AD, Young AW (2001). Neuropsychology of fear and loathing. *Nature Reviews Neuroscience* **2**, 352–363.

Carter CS, Macdonald AM, Botvinick M, Ross LL, Stenger VA, Noll D, Cohen JD (2000). Parsing executive processes: strategic vs. evaluative functions of the anterior cingulate cortex. *Proceedings of the National Academy of Sciences of the USA* **97**, 1944–1948.

Churchland PS (2002). Self-representation in nervous systems. *Science* **296**, 308–310.

Craig AD (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nature Reviews Neuroscience* **3**, 655–666.

Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ (2004). Neural systems supporting interoceptive awareness. *Nature Neuroscience* **7**, 189–195.

Damasio AR, Grabowski TJ, Bechara A, Damasio H, Ponto LL, Parvizi J, Hichwa RD (2000). Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nature Neuroscience* **3**, 1049–1056.

Dannlowski U, Ohrmann P, Bauer J, Deckert J, Hohoff C, Kugel H, Arolt V, Heindel W, Kersting A, Baune BT, Suslow T (2008). 5-HTTLPR biases amygdala activity in response to masked facial expressions in major depression. *Neuropsychopharmacology* **33**, 418–424.

Davidson RJ, Irwin W, Anderle MJ, Kalin NH (2003). The neural substrates of affective processing in depressed patients treated with venlafaxine. *American Journal of Psychiatry* **160**, 64–75.

Davidson RJ, Pizzagalli D, Nitschke JB, Putnam K (2002). Depression: perspectives from affective neuroscience. *Annual Reviews of Psychology* **53**, 545–574.

Drevets WC (2001). Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Current Opinions in Neurobiology* **11**, 240–249.

Erk S, Walter H, Abler B (2008). Age-related physiological responses to emotion anticipation and exposure. *Neuroreport* **19**, 447–452.

Fales CL, Barch DM, Rundle MM, Mintun MA, Snyder AZ, Cohen JD, Mathews J, Sheline YI (2008). Altered emotional interference processing in affective and cognitive-control brain circuitry in major depression. *Biological Psychiatry* **63**, 377–384.

Fuster JM (2000). Executive frontal functions. *Experimental Brain Research* **133**, 66–70.

Gibson B, Sanbonmatsu DM (2004). Optimism, pessimism, and gambling: the downside of optimism. *Personality and Social Psychology Bulletin* **30**, 149–160.

Gilbert DT, Wilson TD (2007). Prospection: experiencing the future. *Science* **317**, 1351–1354.

Glover GH (1999). Deconvolution of impulse response in event-related BOLD fMRI. *NeuroImage* **9**, 416–429.

Grimm S, Beck J, Schuepbach D, Hell D, Boesiger P, Bermpohl F, Niehaus L, Boeker H, Northoff G (2008). Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. *Biological Psychiatry* **63**, 369–376.

Gross JJ, John OP (2003). Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. *Journal of Personality and Social Psychology* **85**, 348–362.

Hamilton M (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry* **23**, 56–62.

Harvey PO, Fossati P, Pochon JB, Levy R, Lebastard G, Lehericy S, Allilaire JF, Dubois B (2005). Cognitive control and brain resources in major depression: an fMRI study using the n-back task. *NeuroImage* **26**, 860–869.

Heimer L, Van Hoesen GW (2006). The limbic lobe and its output channels: implications for emotional functions and adaptive behaviour. *Neuroscience and Biobehavioral Reviews* **30**, 126–147.

Herwig U, Baumgartner T, Kaffenberger T, Bruhl A, Kottlow M, Schreiter-Gasser U, Abler B, Jancke L, Rufer M (2007*a*). Modulation of anticipatory emotion and perception processing by cognitive control. *NeuroImage* **37**, 652–662.

Herwig U, Kaffenberger T, Baumgartner T, Jancke L (2007*b*). Neural correlates of a 'pessimistic' attitude when anticipating events of unknown emotional valence. *NeuroImage* **34**, 848–858.

Horn KM, Pong M, Batni SR, Levy SM, Gibson AR (2002). Functional specialization within the cat red nucleus. *Journal of Neurophysiology* **87**, 469–477.

Johnstone T, van Reekum CM, Urry HL, Kalin NH, Davidson RJ (2007). Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. *Journal of Neuroscience* **27**, 8877–8884.

Keedwell PA, Andrew C, Williams SC, Brammer MJ, Phillips ML (2005). The neural correlates of anhedonia in major depressive disorder. *Biological Psychiatry* **58**, 843–853.

Knutson B, Bhanji JP, Cooney RE, Atlas LY, Gotlib IH (2008). Neural responses to monetary incentives in major depression. *Biological Psychiatry* **63**, 686–692.

Lang PJ (1995). The emotion probe. Studies of motivation and attention. *American Psychologist* **50**, 372–385.

Langenecker SA, Kennedy SE, Guidotti LM, Briceno EM, Own LS, Hooven T, Young EA, Akil H, Noll DC, Zubieta JK (2007). Frontal and limbic activation during inhibitory control predicts treatment response in major depressive disorder. *Biological Psychiatry* **62**, 1272–1280.

Lavender A, Watkins E (2004). Rumination and future thinking in depression. *British Journal of Clinical Psychology* **43**, 129–142.

Lee BT, Seong Whi C, Hyung Soo K, Lee BC, Choi IG, Lyoo IK, Ham BJ (2007). The neural substrates of affective processing toward positive and negative affective pictures in patients with major depressive disorder. *Progress in Neuropsychopharmacology and Biological Psychiatry* **31**, 1487–1492.

Leppanen JM (2006). Emotional information processing in mood disorders: a review of behavioral and neuroimaging findings. *Current Opinions in Psychiatry* **19**, 34–39.

Mayberg HS (2003). Positron emission tomography imaging in depression: a neural systems perspective. *Neuroimaging Clinics of North America* **13**, 805–815.

McClure SM, York MK, Montague PR (2004). The neural substrates of reward processing in humans: the modern role of fMRI. *Neuroscientist* **10**, 260–268.

Mitterschiffthaler MT, Williams SC, Walsh ND, Cleare AJ, Donaldson C, Scott J, Fu CH (2008). Neural basis of the emotional Stroop interference effect in major depression. *Psychological Medicine* **38**, 247–256.

Montgomery SA, Åsberg M (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry* **134**, 382–389.

Nesse RM (2000). Is depression an adaptation? *Archives of General Psychiatry* **57**, 14–20.

Nichols T, Brett M, Andersson J, Wager T, Poline JB (2005). Valid conjunction inference with the minimum statistic. *NeuroImage* **25**, 653–660.

Nitschke JB, Sarinopoulos I, Mackiewicz KL, Schaefer HS, Davidson RJ (2006). Functional neuroanatomy of aversion and its anticipation. *NeuroImage* **29**, 106–116.

Norem JK, Cantor N (1986). Defensive pessimism: harnessing anxiety as motivation. *Journal of Personality and Social Psychology* **51**, 1208–1217.

Northoff G, Bermpohl F (2004). Cortical midline structures and the self. *Trends in Cognitive Sciences* **8**, 102–107.

Panksepp J (2006). Emotional endophenotypes in evolutionary psychiatry. *Progress in Neuropsychopharmacology and Biological Psychiatry* **30**, 774–784.

Paulus MP, Feinstein JS, Castillo G, Simmons AN, Stein MB (2005). Dose-dependent decrease of activation in bilateral amygdala and insula by lorazepam during emotion processing. *Archives of General Psychiatry* **62**, 282–288.

Paulus MP, Stein MB (2006). An insular view of anxiety. *Biological Psychiatry* **60**, 383–387.

Pessoa L (2008). On the relationship between emotion and cognition. *Nature Reviews Neuroscience* **9**, 148–158.

Phillips ML, Drevets WC, Rauch SL, Lane R (2003). Neurobiology of emotion perception II: Implications

for major psychiatric disorders. *Biological Psychiatry* **54**, 515–528.

Pyszczynski T, Holt K, Greenberg J (1987). Depression, self-focused attention, and expectancies for positive and negative future life events for self and others. *Journal of Personality and Social Psychology* **52**, 994–1001.

Sharot T, Riccardi AM, Raio CM, Phelps EA (2007). Neural mechanisms mediating optimism bias. *Nature* **450**, 102–105.

Shepperd JA, McNulty JK (2002). The affective consequences of expected and unexpected outcomes. *Psychological Science* **13**, 85–88.

Siegle GJ, Thompson W, Carter CS, Steinhauer SR, Thase ME (2007). Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. *Biological Psychiatry* **61**, 198–209.

Simmons A, Matthews SC, Paulus MP, Stein MB (2008). Intolerance of uncertainty correlates with insula activation during affective ambiguity. *Neuroscience Letters* **430**, 92–97.

Soares JC, Mann JJ (1997). The anatomy of mood disorders – review of structural neuroimaging studies. *Biological Psychiatry* **41**, 86–106.

Sporns O, Honey CJ, Kotter R (2007). Identification and classification of hubs in brain networks. *PLoS ONE* **2**, e1049.

Talairach J, Tournoux P (1988). *Co-planar Stereotaxic Atlas of the Human Brain*. Thieme: Stuttgart.

Vogt BA (2005). Pain and emotion interactions in subregions of the cingulate gyrus. *Nature Reviews Neuroscience* **6**, 533–544.

Yamasaki H, LaBar KS, McCarthy G (2002). Dissociable prefrontal brain systems for attention and emotion. *Proceedings of the National Academy of Sciences of the USA* **99**, 11447–11451.

Yuste R, MacLean JN, Smith J, Lansner A (2005). The cortex as a central pattern generator. *Nature Reviews Neuroscience* **6**, 477–483.