

Mood-congruent amygdala responses to subliminally presented facial expressions in major depression: associations with anhedonia

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Background: Anhedonia has long been recognized as a key feature of major depressive disorders, but little is known about the association between hedonic symptoms and neurobiological processes in depressed patients. We investigated whether amygdala mood-congruent responses to emotional stimuli in depressed patients are correlated with anhedonic symptoms at automatic levels of processing. **Methods:** We measured amygdala responsiveness to subliminally presented sad and happy facial expressions in depressed patients and matched healthy controls using functional magnetic resonance imaging. Amygdala responsiveness was compared between patients and healthy controls within a 2 (group) × 2 (emotion) design. In addition, we correlated patients' amygdala responsiveness to sad and happy facial stimuli with self-report questionnaire measures of anhedonia. **Results:** We included 35 patients and 35 controls in our study. As in previous studies, we observed a strong emotion × group interaction in the bilateral amygdala: depressed patients showed greater amygdala responses to sad than happy faces, whereas healthy controls responded more strongly to happy than sad faces. The lack of automatic right amygdala responsiveness to happy faces in depressed patients was associated with higher physical anhedonia scores. **Limitations:** Almost all depressed patients were taking antidepressant medications. **Conclusion:** We replicated our previous finding of depressed patients showing automatic amygdala mood-congruent biases in terms of enhanced reactivity to negative emotional stimuli and reduced activity to positive emotional stimuli. The altered amygdala processing of positive stimuli in patients was associated with anhedonia scores. The results indicate that reduced amygdala responsiveness to positive stimuli may contribute to anhedonic symptoms due to reduced/inappropriate salience attribution to positive information at very early processing levels.

Introduction

Anhedonia is one of the earliest psychopathological symptoms in clinical descriptions of depression and melancholia, and has long been recognized as a core feature of depressive disorders. The term was first used in 1896 by Ribot¹ to describe the inability to experience pleasure and the with-

drawal from all pleasant daily activities. Later, Chapman and colleagues² divided anhedonia into a social and a physical aspect. Whereas physical anhedonia represents the absence of pleasure from physical or sensory experiences (e.g., pleasures of eating, touching), social anhedonia refers to the inability to enjoy interpersonal or social pleasures (e.g., being, talking and interacting with people). In this context, anhedonia is

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related to the symptoms associated with decreased positive affect in individuals with depressive disorders.^{3,4}

Correspondingly, several behavioural studies indicate that depressed patients show diminished responses to pleasant stimuli,⁵ show less efficient detection of positive facial expressions in a face-in-the-crowd task,⁶ interpret happy facial expressions as more negative (for a review see Bourke and colleagues⁷), rate positive slides as less pleasant and less arousing⁸ and show lesser self-reported reactivity to amusing film clips.⁹ Even on automatic stages of processing, more negative priming effects based on subliminally presented happy faces have been observed in patients with depression than healthy controls.¹⁰

Today, anhedonia is 1 of the 2 key criteria for diagnosing major depression according to DSM-IV-TR, and it particularly characterizes the melancholic subtype of major depression.¹¹ Even the ICD-10 diagnostic system includes the loss of interest in pleasant stimuli as one of the somatic symptoms of major depression.¹²

Despite the importance of anhedonia in depression, relatively few studies have examined the corresponding neural substrates in depressed patient samples. While a growing number of neuroimaging studies investigated discrete reward-related processing in patients with MDD (for example see studies by Drevets and colleagues,¹³ Robinson and colleagues¹⁴ and Gotlib and colleagues¹⁵ and reviews by Price and Drevets¹⁶ and by Der-Avakian and Markou¹⁷), studies focusing on associations between self-report measures of anhedonia and neural responses are rare. Three neuroimaging studies have reported associations between anhedonia in depressed patients and neuronal responses to positive stimuli in, for example, the ventral striatal regions, anterior cingulate cortex, ventromedial prefrontal cortex and medial orbitofrontal cortex;^{18–20} however, to date only 1 study¹⁸ has reported associations with amygdala responsiveness. This study reported a negative association between anhedonia severity and amygdala reactivity to overtly presented happy facial expressions in 12 patients with MDD.

The amygdala could be of particular interest in studying the neural underpinnings of anhedonia in patients with MDD because of its outstanding role in rapidly processing salient stimuli, both negative and positive.^{21–23} Furthermore, increased neuronal amygdala responses to negative emotional stimuli in acute depression have been repeatedly demonstrated, but processing of positive stimuli has received less attention, and findings are rare (for a review see Santos and colleagues²⁴). To our knowledge, 2 independent studies have only recently described differential mood-congruent amygdala responses to subliminally presented negative and positive emotional stimuli in depressed patients.^{25,26} They demonstrated amygdala hyperresponsiveness to negative stimuli and hyporesponsiveness to positive emotional stimuli in depressed patients and the opposite pattern in healthy controls. Notably, these results were found at an early, automatic processing level. To date, it is not known whether anhedonic symptoms are associated with decreased amygdala excitability to positive stimuli at these early stages of emotion processing or whether they occur at later, controlled stages. Therefore, we used functional magnetic res-

onance imaging (fMRI) to examine neuronal responses to subliminally presented positive and negative faces in depressed patients and healthy controls. We employed the identical affective priming paradigm that we used successfully in our previous study²⁵ demonstrating mood-congruent amygdala responsiveness in depression in a larger and independent sample of acutely depressed patients and healthy controls. To assess subjective anhedonic symptoms, we used a revised version of the Chapman physical and social anhedonia self-report scales.^{2,27}

Based on previous research findings,^{25,26} we predicted mood-congruent amygdala biases to subliminally presented happy and sad facial expressions in depressed patients. Second, we hypothesized negative and positive associations between anhedonia scores and amygdala responsiveness to positive and negative stimuli, respectively, in depressed patients.

Methods

Participants

We recruited right-handed inpatients with an acute major depressive episode, as diagnosed with the SCID-I interview,²⁸ and matched, healthy controls for participation in the study. Both subsamples were completely independent of those from our previous study.²⁵ Patients were recruited from the inpatient service of the University of Muenster's Department of Psychiatry. Exclusion criteria were any neurologic abnormalities; substance-related disorders; psychotic symptoms; a history of mania or hypomania; treatment with mood stabilizers, neuroleptics or benzodiazepine; and previous electroconvulsive therapy. For controls, a further exclusion criterion was any current or former psychiatric disorder, as verified with the SCID interview.²⁸ Both groups had to fulfill the general MRI-related requirements, and head movement must not have exceeded 2 mm or 2° in any direction.

We coded patients' use of antidepressants according to the 4-point scale of Sackheim.²⁹ Most of the patients were recruited in the first weeks after admission to hospital and therefore received drug trials with a duration of less than 4 weeks. Only patients with primary major depression were included, as determined by the admission diagnosis, earlier onset of illness and by the clinical therapists. The investigation was conducted with the approval of the Ethics Committee of the University of Münster. Participants provided written informed consent and were financially compensated.

Psychopathological measures

We assessed subjective anhedonia experiences using a validated 43-item revised German version of the self-report Chapman Physical and Social Anhedonia Scales,²⁷ showing adequate psychometric properties.²⁷ The physical anhedonia subscale (PAS) assesses the loss of pleasure from physical or sensory experiences, whereas the social anhedonia subscale (SAS) refers to the inability to enjoy interpersonal or social pleasures. Furthermore, individuals with MDD and controls completed the Hamilton Rating Scale for Depression (HAM-D³⁰), the Beck

Depression Inventory (BDI³¹) and a measure of trait anxiety (State-Trait Anxiety Inventory; STAI, trait version³²). Subsequently, for the depressed sample, we calculated intercorrelations (Spearman correlation coefficients) between all assessed measures and clinical variables.

Task and procedures

Subliminal affective priming paradigm

The subliminal affective priming paradigm was identical to the task used in previously published studies in patients and healthy controls.^{25,33–35} The paradigm is designed to trace rapid, automatic stages of emotion processing. All participants were presented with greyscaled normalized sad, happy, neutral and erased facial expressions of 5 women and 5 men from a standardized picture set.³⁶ Erased faces (no face prime) are composed of a surface without contours that replaces central facial features. After a fixation cross of 800 ms, the facial emotion stimuli were presented for 33 ms, followed by a 467 ms neutral face of the same individual and a black screen (7.7 ms). To avoid identity of prime and mask in the neutral face condition, vertically mirrored faces were used as neutral primes. The duration of each trial was 9 seconds. The paradigm consisted of 80 trials — 20 trials for each condition. The overall presentation time was 12 minutes. The participants' task was to evaluate whether the neutral face (mask) expressed negative or positive feelings and respond by pressing 1 of 4 buttons (–1.5, –0.5, +0.5 and +1.5). Participants were not informed about the presence of a prime stimulus. Participants held 1 of 2 positive responses with the left hand and the other with the right hand. We recorded judgments and reaction times.

Prime detection task

After the fMRI experiment, we asked all participants whether they had noticed any features of the subliminally presented faces in the affective priming task. In addition, participants completed a forced-choice prime detection task outside the scanner that was intended to assess potential objective awareness. The prime detection task involved the same facial stimuli and presentation conditions applied in the fMRI experiment and consisted of 40 trials (33 ms prime presentation followed by a neutral face mask for 467 ms). Participants were asked to indicate via button press which of the 4 prime conditions was presented before the neutral mask. As in our previous study,²⁵ we calculated A' (a nonparametric measure of sensitivity, including hit rates and false alarm rates) separately for each priming condition. Chance level is indicated by $A' = 0.5$. For a detailed description of how we calculated A' , see Grier.³⁷

Image acquisition

We acquired MRI data using a 3 T scanner (Gyrosan Intera 3 T; Philips Medical Systems). For spin excitation and resonance signal acquisition, we used a circularly polarized transmit/receive birdcage head coil with a high-frequency reflecting screen at the cranial end. We acquired T_2^* functional data using a single shot echoplanar sequence (EPI) with parameters selected to minimize distortion in the region of cen-

tral interest while retaining adequate signal to noise ratio and T_2^* sensitivity: 34 slices, matrix 64×64 , resolution $3.6 \times 3.6 \times 3.6$ mm; repetition time [TR] 2.1 ms, echo time [TE] 30 ms, flip angle 90° . The slices were tilted 25° from the anterior and posterior commissure line to minimize dropout artifacts in the orbitofrontal and mediotemporal regions. In addition, we acquired T_1 -weighted high-resolution anatomic images for each participant to control for any anatomic abnormalities.

Image analysis

Functional imaging data were motion-corrected (using a set of 6 rigid body transformations determined for each image), spatially normalized to standard Montreal Neurological Institute (MNI) space and smoothed (Gaussian kernel, 8 mm full-width at half-maximum) using Statistical Parametric Mapping (SPM8; Wellcome Trust Centre for Neuroimaging; www.fil.ion.ucl.ac.uk/spm).

We used an event-related analysis design. For each participant, trials were averaged separately for each prime condition (sad, happy, neutral, no face), reducing the data to 4 average trials per participant. A vector of prime onset times of the emotional and neutral primes and the no face condition was convolved with a canonical hemodynamic response function, generating individual fixed-effects contrast maps for the 4 conditions and the contrasts of interest (sad > neutral, happy > neutral). The 6 movement parameters of the realignment procedure were included as covariates of no interest into the first-level model. For the second-level analysis, we entered the 2 first-level contrasts (sad > neutral, happy > neutral) into an analysis of variance using the flexible factorial model, with emotion as a within-subjects factor and group as a between-subjects factor. In addition, "subjects" was included as a third factor in the model to account for the individual constants. Furthermore, we entered detection task performance (A' for sad, happy and neutral faces) and sex as nuisance regressors. We used the model to calculate the main effects of group (patients v. controls) and emotion (happy v. sad) as well as the group \times emotion interaction.

According to our hypotheses on mood-congruent amygdala responses, we performed a region of interest (ROI) analysis of the bilateral amygdala. The amygdala was defined according to the AAL atlas,³⁸ and we created the amygdala mask using the WFU pickatlas (<http://fmri.wfubmc.edu/software/PickAtlas>). We maintained a statistical threshold of $p < 0.05$, family wise error (FWE)-corrected, for the bilateral amygdala. To explore the nature of the group \times emotion interaction, we used t tests to investigate the effect of emotion within each group separately (paired t tests) and to compare the activation due to masked sad and happy faces between groups. To control for multiple post hoc tests, we used the sequential Holm–Bonferroni multiple test procedure³⁹ to correct for the 4 post hoc comparisons.

To test our a priori hypothesis on the modulatory role of anhedonia on amygdala responsiveness in patients with MDD, we entered patients' anhedonia scores (total score and subscales) as regressors to sad > neutral and happy > neutral facial expressions separately ($p < 0.05$, FWE-corrected). Finally, we

extracted the mean contrast values of the peak voxel from the significant result of the regression analysis for each patient and further analyzed them with PASW Statistics software version 18. We conducted a multiple regression model predicting amygdala responsiveness with anhedonia scores, age, total years of education, depression severity (BDI and HAM-D), trait anxiety (STAI, trait version) and medication score.²⁹ In addition, we conducted a nonparametric correlation of anhedonia scores and amygdala responsiveness.

Given previous neuroimaging results of hedonia/reward in depressed patients and nonclinical samples,^{18,40–43} we conducted a supplementary ROI analysis for the ventral striatum and anterior cingulate cortex (ACC) at $p < 0.05$, FWE-corrected. The ventral striatum was defined according to the suggestions of Forbes and colleagues.⁴⁴ We created the ACC mask using the WFU pickatlas. We calculated the emotion \times group interaction separately for the ventral striatum and ACC, as described previously. Furthermore, we set up regression models for anhedonia scores (sum and subscale scores) and ventral striatal/ACC responsiveness to sad > neutral, happy > neutral and sad > happy faces in the patient sample.

Results

Participants

A data set of 35 right-handed inpatients with an acute major depressive episode, most of whom fulfilled the criteria for

melancholic depression subtype according to DSM-IV criteria¹¹ as diagnosed with the SCID-I interview,²⁸ and 35 matched, healthy controls were included in our final analysis. All but 2 of the patients were receiving antidepressant treatment (Appendix 1, Table S1, available at cma.ca/jpn). Of the 35 patients, 23 had no additional Axis 1 diagnosis, 8 had 1 comorbid disorder and 4 had 2 comorbid disorders. Secondary diagnoses were panic disorders ($n = 1$), social phobia ($n = 3$), dysthymia ($n = 2$), pain disorders ($n = 2$), posttraumatic stress disorder ($n = 2$), specific phobia ($n = 2$) and generalized anxiety disorder ($n = 1$). Table 1 summarizes the sociodemographic and clinical characteristics of the final study sample.

Detection task

At the end of the fMRI procedure, all participants reported that they had not recognized any briefly presented emotional prime faces before the neutral face mask, even after being informed about their presence (subjective awareness). However, about one-third of the participants in each group perceived a short “flickering” or “lightning.” The results of the additional detection task confirm the participants’ unawareness of the emotional primes. According to t tests (all $p > 0.08$), the average prime detection sensitivity of healthy controls and patients did not differ significantly owing to chance for happy (controls: $A' = 0.55$; patients: $A' = 0.55$), sad (controls: $A' = 0.52$; patients: $A' = 0.47$) or neutral prime faces (controls: $A' = 0.53$; patients: $A' = 0.47$; objective awareness). The groups did not differ in terms of their sensitivity indices

Table 1: Sociodemographic, clinical, questionnaire and behavioural data of study participants and mean reaction times and evaluative responses

Variable	Group; mean (SD) [range]						p value according to χ^2 or t tests (2-tailed)
	Patients, $n = 35$			Controls, $n = 35$			
Age, yr	40.1	(12.0)	[19–58]	40.3	(12.0)	[19–58]	0.93
Sex, male:female		14:21			14:21		> 0.99
Education, yr	13.9	(2.0)	[10–18]	14.3	(1.8)	[10–18]	0.27
Antidepressant potency	1.7	(1.1)	[0–4]	—	—	—	—
No. of episodes	4.6	(5.2)	[1–24]	—	—	—	—
Lifetime hospitalization, wk	10.8	(14.8)	[0–65]	—	—	—	—
Duration of illness, mo	35.3	(38.5)	[2.5–180]	—	—	—	—
Hamilton Rating Scale for Depression ³⁰ score	23.7	(5.6)	[18–44]	1.3	(1.4)	[0–4]	< 0.001
Beck Depression Inventory ³¹ score	27.5	(8.7)	[12–47]	1.3	(1.6)	[0–5]	< 0.001
State-Trait Anxiety Inventory, trait version, ³² score	62.2	(7.9)	[47–77]	31.9	(5.9)	[21–43]	< 0.001
Anhedonia sum score*	16.1	(7.6)	[3–36]	7.5	(5.1)	[0–19]	< 0.001
Social anhedonia scale	11.1	(5.6)	[1–21]	4.4	(3.4)	[0–11]	< 0.001
Physical anhedonia scale	5.0	(2.9)	[1–15]	3.0	(2.1)	[0–8]	0.002
Mean evaluation							
Sad prime condition	−0.24	(0.33)		0.00	(0.30)		0.003
Happy prime condition	−0.27	(0.38)		0.02	(0.33)		0.002
Neutral prime condition	−0.22	(0.37)		−0.01	(0.29)		0.011
No face prime condition	−0.23	(0.35)		0.03	(0.33)		0.003
Reaction time, ms							
Sad prime condition	1585.0	(426.4)		1470.1	(419.5)		0.48
Happy prime condition	1501.8	(408.3)		1387.5	(319.3)		0.10
Neutral prime condition	1456.0	(396.8)		1370.7	(342.9)		0.62
No face prime condition	1492.5	(390.6)		1386.4	(350.0)		0.33

SD = standard deviation.

*Measured using a validated 43-item revised German version of the self-report Chapman Physical and Social Anhedonia Scales.²⁷

for emotional or neutral faces (all $p > 0.16$). Behavioural data of 2 patients were missing owing to technical problems.

Behavioural results

Table 1 lists mean reaction times and evaluative responses of the experimental conditions. Again, behavioural results of 2 patients were missing owing to technical problems. Patients and controls did not differ in their reaction times, irrespective of prime condition. However, as in our previous study, patients significantly assessed the neutral face masks as more negative under all prime conditions than controls. Importantly, reaction times and evaluative responses were not significantly associated with amygdala responsiveness to sad or happy faces.

fMRI results

Amygdala ROI analysis

No main effect of group or emotion on activity in the right or left amygdala could be detected. However, the hypothesized emotion \times group interaction was significant in a cluster within the left and right amygdala (left: $x, y, z = -26, -4, -14$; $t_{68} = 3.9$; Cohen $d = 0.95$; $p < 0.001$, uncorrected; $p = 0.013$, FWE-corrected; cluster size $k = 7$; right: $x, y, z = 22, -2, -12$; $t_{68} = 3.73$; Cohen $d = 0.9$; $p < 0.001$, uncorrected; $p = 0.022$, FWE-corrected; cluster size $k = 3$; see Fig. 1). The cluster with the strongest emotion \times group interaction was located in the laterobasal nuclei of the amygdala, as labelled by the SPM Anatomy Toolbox, version 1.8.⁴⁵ Also if detection performance (A') and sex were not included as covariates, the emotion \times group interaction remained almost identical. Furthermore, including evaluative ratings of the participants did not alter the pattern of results.

Post hoc analysis indicated the expected pattern: depressed patients showed significantly greater bilateral amygdala activity in reaction to sad than to happy faces and greater right amygdala activity than healthy controls when presented with

sad faces. The comparison between patients and controls for left amygdala responses to sad faces failed to meet the $p < 0.05$, corrected, threshold for multiple comparisons. In contrast, healthy controls showed the opposite pattern: bilateral amygdala activity was significantly greater in reaction to happy than to sad faces, and bilateral amygdala activity in response to happy faces was significantly greater in controls than patients (Table 2). There were no effects of medication intake, number of episodes or duration of illness on bilateral amygdala responsiveness to happy $>$ neutral or sad $>$ neutral faces at the location of the group \times emotion interaction in the left and right amygdala (all $p > 0.13$).

Regression analysis

The regression analysis yielded a strong negative association between the physical anhedonia subscale score (PAS) and right amygdala responsiveness to happy $>$ neutral faces within the patient sample (right: MNI coordinates $x, y, z = 30, 0, -14$; coordinates of the peak voxel $r = -0.56$; $t_{33} = -3.89$; $p < 0.001$, uncorrected; $p = 0.022$, FWE-corrected; Cohen $d = 1.35$; cluster size $k = 1$; Fig. 2). Nevertheless, the correlation did not survive FWE correction for the entire brain. No further correlations between anhedonia scores (PAS or SAS) and left or right amygdala responsiveness to sad $>$ happy, sad $>$ neutral or happy $>$ neutral faces survived the conservative FWE correction threshold.

The subsequent multiple regression analysis showed that the negative association between physical anhedonia and right amygdala responsiveness to happy faces (contrast values happy $>$ neutral: MNI coordinates $x, y, z = 30, 0, -14$) was not confounded by age, education level, depression severity (BDI and HAM-D), trait anxiety level, SAS subscale score or medication score. A multicollinearity check for these variables revealed variance inflation factors smaller than 2.7, falling below the cut-off value of 10 proposed by Kutner and colleagues.⁴⁶ The effect of physical anhedonia remained unchanged ($\beta = -0.77$, $t_{34} = -3.36$, $p = 0.002$), whereas none of the other

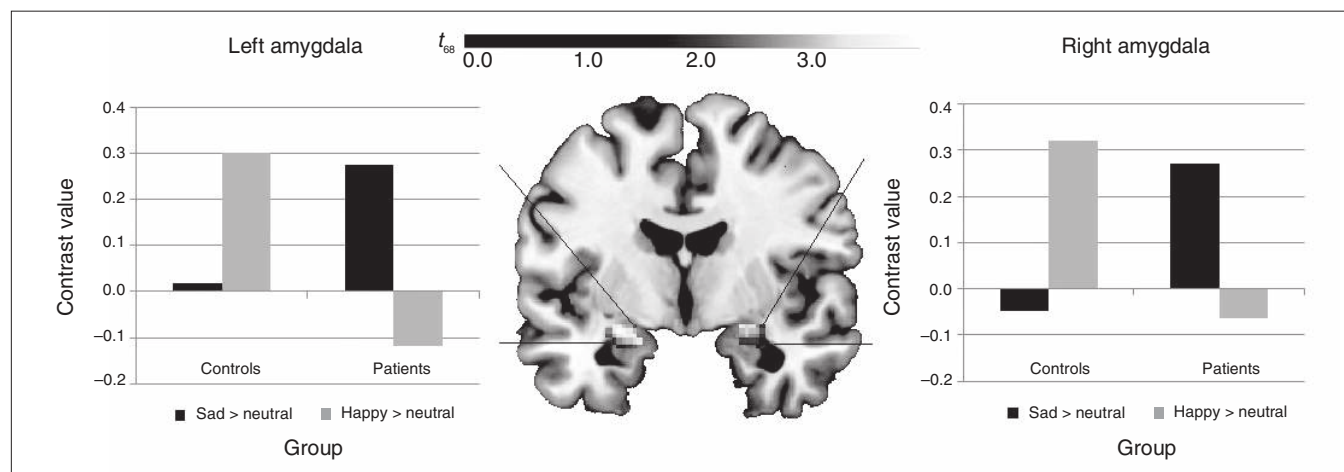


Fig. 1: Coronal view (MNI coordinate $y = 0$) depicting significant group \times emotion interaction in the right and left amygdala, thresholded at $p < 0.05$, uncorrected. Bar graphs depict the mean contrast value for happy–neutral and sad–neutral extracted from the right amygdala (MNI coordinates $x, y, z = 22, -2, -12$) and left amygdala (MNI coordinates $x, y, z = -26, -4, -14$), dependent on emotion and study group. MNI = Montreal Neurological Institute.

predictors had any significant effect (all $p > 0.14$). As shown in the correlation matrix in Table 3, the anhedonia sum and subscales moderately to highly correlated with each other, whereas correlations with depression severity and trait anxiety were small to moderate. Also, a nonparametric correlation (Spearman rho) of physical anhedonia scores and right amygdala responsiveness to happy faces was significant ($r_s = -0.51, p = 0.002$).

Supplementary ROI analysis

The subsequent ROI analysis revealed no significant emotion \times group interaction effect at the FWE correction threshold for the ventral striatum or the ACC. Furthermore, the correlation model between patients' anhedonia scores and sad > happy, sad > neutral or happy > neutral faces for the ventral striatum and ACC separately yielded no significant effects at the FWE correction threshold.

Discussion

To our knowledge, this is the first study providing evidence for an association between automatic mood-congruent amygdala processing and anhedonia in depressed patients that is present already at early, unconscious processing levels. Depressed patients showed amygdala hyper-responsiveness to subliminally presented sad facial expressions and hyporesponsiveness to subliminally presented happy facial expressions, the opposite pattern to that found in healthy controls.

Our results demonstrate that a lack of amygdala responsiveness to happy faces in currently depressed patients is associated with subjectively reported anhedonia, particularly with physical anhedonia scores. Importantly, this association was unaffected by current overall depression or anxiety scores but seemed to be specific for anhedonia. Furthermore,

Table 2: Post hoc exploratory analysis of the group \times emotion interaction ($p < 0.05$, corrected): differences between depressed patients and controls in amygdala responses to subliminally presented sad and happy facial expressions compared with neutral faces

Result	Side	MNI coordinate			Cluster size	<i>t</i> score	Effect size	<i>p</i> value (uncorrected)
		<i>x</i>	<i>y</i>	<i>z</i>				
Between-group								
Patients > controls: sad > neutral faces	Right	32	-8	-12	27	2.77	0.67	0.004
	Left	—	—	—	—	—	—	—
Control > patients: happy > neutral faces	Right	-18	-6	-18	56	3.10	0.75	0.001
	Left	22	-2	-18	29	2.11	0.51	0.019
Within-group								
Patients: sad > happy faces	Right	32	-2	-24	41	3.16	1.08	0.002
	Left	-18	-2	-16	86	3.09	1.06	0.002
Controls: happy > sad faces	Right	22	-4	-12	75	4.26	1.46	< 0.001
	Left	-24	-4	-12	84	4.39	1.5	< 0.001

MNI = Montreal Neurological Institute.

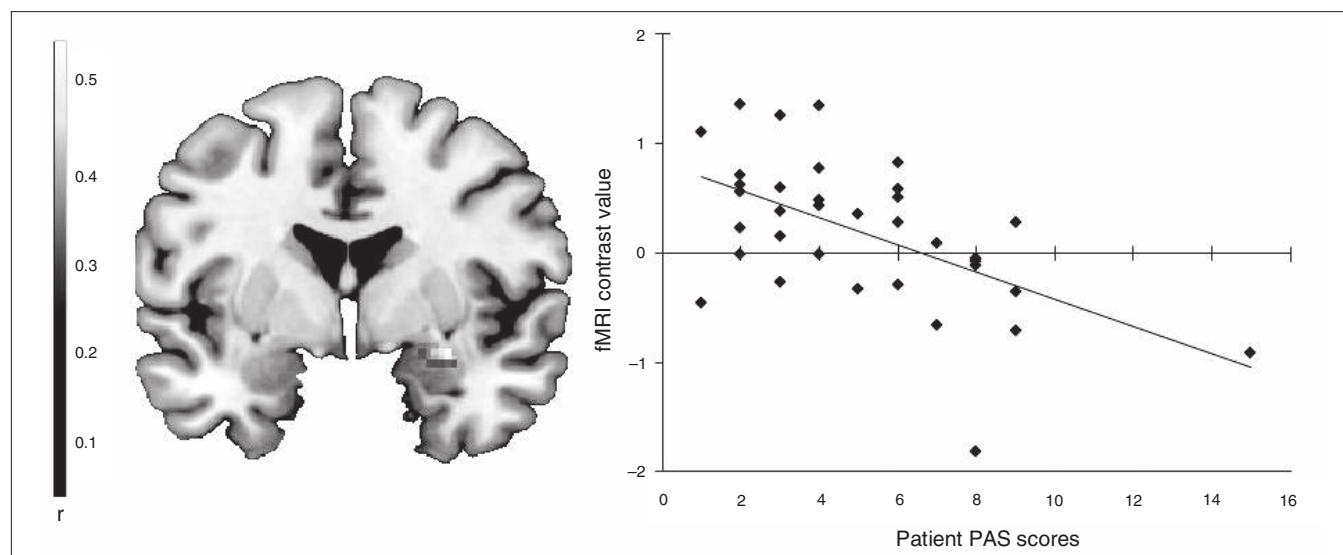


Fig. 2: Physical anhedonia (PAS score) in patients with major depressive disorder is negatively associated with right amygdala responsiveness to happy > neutral facial expressions. (Left) Coronal view (MNI coordinate $y = -2$) depicting amygdala responsiveness modulated by PAS scores in the patient sample, thresholded at $p < 0.05$, uncorrected. (Right) Scatter plot depicting the negative correlation between the peak voxel response (MNI coordinates $x, y, z = 30, 0, -14$) and PAS scores in patients ($r = -0.56$). MNI = Montreal Neurological Institute; PAS = physical anhedonia scale.

the finding of automatic mood-congruent amygdala responses in depressed patients represents a close replication of our previous report²² using the same paradigm in a large and independent sample. These reports support the validity of our hypothesis that patients with acute major depression are characterized by mood-congruent processing of emotional stimuli in the amygdala.

The detection task results and the participants' reports of not having seen any of the prime faces confirmed that the neurobiological processing of the presented stimuli occurred automatically, below the level of conscious awareness.

The analysis of behavioural data revealed that neither controls nor patients showed affective priming effects compared with the neutral baseline. This concurs with the findings of our previous study that reported the absence of priming effects using the same paradigm.²⁵ We suggested that neurobiological responses might provide a more sensitive assessment of subtle emotion processing than behavioural measures. However, within the current investigation, behavioural responses indicated that depressed patients' evaluations show an overall negative shift by experiencing the neutral mask more negatively than controls in all (sad, happy and neutral) prime conditions. This finding is consistent with previous behavioural findings that depression is characterized by negative evaluation shifts in late, as well as automatic processing stages.^{7,47-49}

While previous studies also reported associations of other structures with anhedonia (e.g., the ventral striatum or the anterior cingulate gyrus^{18,40-43}), we did not find any significant interaction effect nor associations with anhedonia using these structures instead of the amygdala as ROIs. However, this might be related to the early, unconscious processing stage investigated by our backward-mask paradigm in contrast to conscious stages of reward processing in these previous studies.

Differential mood-congruent amygdala responses to subliminally presented negative and positive stimuli in healthy controls and depressed patients have previously been reported in studies by Suslow and colleagues²⁵ and Victor and colleagues.²⁶ In both studies, healthy controls had stronger automatic amygdala responses to happy than to sad faces, and they had stronger responses to happy faces than depressed patients, a pattern that was replicated in the present

study. Interestingly, Suslow and colleagues observed the emotion \times group interaction predominantly in the right amygdala, whereas Victor and colleagues reported significant bilateral amygdala activation. Showing significant clusters with similar effect sizes in the left and right amygdala, our results support the notion that mood-congruent amygdala processing occurs bilaterally. Again in accordance with the results of Suslow and colleagues, the strongest group \times emotion interaction we found was in the basolateral sub-region of the amygdala, further strengthening its special role for rapid, unconscious, altered emotion processing in depressed patients.⁵⁰ It should be stressed here, that such replications (including replication failures) are needed in this field of neuroscience. Furthermore, as the results are in line with those from similar studies from other laboratories,²⁶ we think that such a replication has great additional merit in itself. We are not aware of any similar replication in psychiatric neuroimaging so far.

Stronger amygdala responses to masked happy faces compared with sad faces in a group of healthy women were also reported by Killgore and colleagues.⁵¹ The results are in line with growing neuroimaging results in healthy participants pointing out that the amygdala has a pivotal role in processing all forms of salient information, negative as well as positive.^{22,23,52,53} Furthermore, the result may also indicate a "hedonic processing bias," favouring positive stimuli in early, basal processing stages in individuals without mood disturbances.⁵⁴⁻⁵⁶ In contrast, the data on depressed patients showed stronger automatic amygdala responses to negative than positive facial stimuli, and they showed stronger reactions than healthy controls to negative facial stimuli. To date, numerous neuroimaging studies have provided compelling support that amygdala hyperactivity to negative stimuli is associated with negatively biased emotion processing in patients with MDD and that this hyperactivity is prominent not only during conscious processing, but also during unconscious processing (for an overview, see Stuhmann and colleagues²⁴ and Elliott and colleagues⁴⁸). Unfortunately, results showing decreased limbic responses to positive stimuli in depressed patients compared with healthy controls are rare;^{25,26,57,58} however, they confirm predictions of cognitive theories of depression,

Table 3: Spearman correlation coefficients between anhedonia scores, depression severity, state anxiety and clinical parameters in the patient sample, $n = 35$

Variable	1	2	3	4	5	6	7	8	9
1. SASPAS	1								
2. SAS	0.943*	1							
3. PAS	0.773*	0.519†	1						
4. BDI	0.462†	0.440†	0.350‡	1					
5. HAM-D	0.473†	0.418‡	0.418‡	0.618*	1				
6. STAI, trait version	0.228	0.322	-0.03	0.627*	0.475†	1			
7. No. of episodes	0.165	0.225	-0.006	0.131	0.076	-0.003	1		
8. Duration of illness, mo	0.177	0.162	0.137	0.146	0.093	0.009	0.725*	1	
9. Lifetime hospitalization, wk	0.179	0.174	0.127	0.007	0.001	0.083	0.504‡	0.495‡	1

BDI = Beck Depression Inventory;³¹ HAM-D = Hamilton Rating Scale for Depression;³⁰ PAS = physical anhedonia subscale; SAS = social anhedonia subscale; SASPAS = Chapman Physical and Social Anhedonia Scales;²⁷ STAI = State-Trait Anxiety Inventory.³²

* $p < 0.001$.

† $p < 0.01$.

‡ $p < 0.05$.

suggesting potentiation of negative affective information and attenuation of positive information (for an overview see Beck,⁵⁹ Disner and colleagues⁶⁰ and Mathews and MacLeod⁶¹).

As hypothesized, the present data are, to our knowledge, the first to show that reduced amygdala responsiveness to subliminally presented happy facial stimuli is associated with higher anhedonia scores in depressed patients. There was no evidence for confounding effects of age, education, trait anxiety levels, medication score and overall severity of depression. The latter one is of particular interest comparing the current results with former studies by Suslow and colleagues²⁵ and Victor and colleagues.²⁶ Both of these studies reported an inverse association between reduced amygdala responses to subliminally presented happy faces and depression severity measured with the HAM-D in depressed patients. As described previously⁶² and confirmed by our data, the Chapman self-report scale moderately correlates with objective and subjective measurements of depression severity (i.e., HAM-D and BDI), indicating that subjectively reported anhedonic experiences seem to accompany general measurements of depressive symptoms.⁶² However, considering that measures of depression severity condense a range of psychopathological symptoms of major depressive disorders, the current analysis extends the association to amygdala responsiveness by highlighting the separate, specific role of subjectively experienced anhedonia.

It is known that the amygdala has the ability to process information rapidly, without conscious awareness,⁶³ presumably through direct projections from the thalamus.⁶⁴ Furthermore, conceptualizations of the amygdala highlight its pivotal role in signalling salience to biologically relevant stimuli of both pleasant and unpleasant valences.^{21,23,65–67} It seems plausible that anhedonic symptoms in patients with MDD may be associated with reduced amygdala responsiveness to positive stimuli owing to inappropriate or reduced salience attribution to positive stimuli even at very early stages of processing.^{60,68} Further, this may reduce the recruitment of attentional resources that can raise positive emotional stimuli to conscious awareness.⁶⁰ One might assume decreased amygdala responsiveness to positive stimuli to even be a distinctive feature of depression in comparison to exaggerated amygdala responsiveness to negative stimuli, which has been repeatedly shown in patients with depressive and anxiety disorders.^{4,69} However, these interpretations are made with caution since the correlative nature of the presented data do not reveal cause and effect.

Interestingly, the negative association between anhedonia scores and right amygdala responsiveness to happy faces was only found on the PAS. The subsequent multiple regression analysis showed that the association was not confounded by SAS scores. These findings correspond to the results in patients with schizophrenia reported by Dowd and Barch⁶⁸ that showed a negative association between bilateral amygdala activation to positive versus negative stimuli (pictures, words, faces) and higher physical, but not social, anhedonia scores. First, anhedonic symptoms assessed by the Chapman PAS may be more strongly linked to amygdala responsiveness by focusing more on experiencing pleasure

from physical and sensory experiences than rewarding social interactions and activities with other people. Second, physical anhedonia could be related more directly with neurobiological abnormalities than social anhedonia, which could be more influenced by long-term relationships and the activities and initiatives of family and friends. This could be especially relevant for unconscious, rapid amygdala processes. So far, it is not clear if physical and social anhedonia, as defined by Chapman and colleagues,² are related to different neuronal underpinnings in patients with MDD.

In addition, one should draw attention to possible laterality effects. In contrast to our finding of significant emotion \times group interaction in the bilateral amygdala, our regression analysis showed differences in laterality: physical anhedonia was negatively correlated with right, but not left, amygdala response to happy faces. A similar result was reported by Keedwell and colleagues,¹⁸ who described a negative correlation between anhedonia scores and right amygdala responses to happy faces. However, the results should be treated with caution, since none of the studies explicitly investigated laterality effects.

In sum, it remains undetermined whether decreased amygdala responses to positive stimuli are specific to depressive disorders and whether they represent a possible vulnerability factor. It will be an aim for future studies to further clarify the neuronal underpinnings of different aspects of anhedonia (i.e., physical and social anhedonia) in depressed patients. To improve validity and to confirm our results, subsequent investigations should assess hedonic symptoms with additional measurements, such as the Fawcett–Clark Pleasure Capacity Scale⁷⁰ and the Snaith–Hamilton Pleasure Scale,⁷¹ as these 2 scales do not completely overlap with the Chapman scales.⁷² The ecological validity could also be improved by measuring outpatients' mood states in daily life, as shown very well by Forbes and colleagues⁴¹ and Ben-Zeev and colleagues.⁷³ This approach could also prevail against retrospective recall biases.⁷³ Furthermore, neuroimaging studies combined with molecular and genetic methods are needed to delineate the neurobiological basis of anhedonic symptoms in patients with depression.^{17,74} The results may contribute to individualized treatment of depressed patients who predominantly experience symptoms related to decreased positive affect.⁷⁵

Limitations

Several limitations of the current study need to be pointed out. First, all but 2 of the patients with MDD were taking antidepressive medication, which potentially constitutes a confounding factor. However, anhedonia scores did not correlate with the dose of antidepressants, and the association between amygdala responsiveness to happy stimuli and physical anhedonia in the depressed group remained stable if medication dose was regressed out. Taking into account previous reports that amygdala responsiveness to sad faces decreases and amygdala responsiveness to happy faces increases with antidepressant treatment,^{26,76} it may be possible that results in unmedicated patients would be even stronger. Second, owing to the correlative analysis approach, our results exclusively

reflect associations between subjectively measured anhedonia and neuronal amygdala responses, and we cannot rule out a possible effect of third variables not assessed in the present study. Furthermore, our results are limited by the definition and subjective questionnaire measurement of Chapman and colleagues.² The use of additional questionnaire measurements would certainly improve the validity of the presented data. Finally, our participants were moderate to severely depressed inpatients, most of whom had diagnoses of the melancholic subtype. Consequently, the generalizability of the findings to outpatients and those with less severe, non-melancholic depression is limited.

Conclusion

To our knowledge, this is the first study to show an association between amygdala mood-congruent biases and subjectively measured anhedonia in depressed patients, even at early, unconscious processing levels. Reduced automatic amygdala responsiveness to happy stimuli in depressed patients may be associated with symptoms of anhedonia in MDD due to inappropriate or reduced salience attribution to positive stimuli. Our results help to refine the understanding of the neural basis of mood-congruent biases in patients with depression and related emotional experiences.

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