Limbic and prefrontal responses to facial emotion expressions in depersonalization

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Depersonalization disorder, characterized by emotional detachment, has been associated with increased prefrontal cortical and decreased autonomic activity to emotional stimuli. Event-related fMRI with simultaneous measurements of skin conductance levels occurred in nine depersonalization disorder patients and 12 normal controls to neutral, mild and intense happy and sad facial expressions. Patients, but not controls, showed *decreases* in subcortical limbic activity to increasingly intense happy and sad facial expressions, respectively. For both happy and sad expressions, negative correlations between skin conductance measures in bilateral dorsal prefrontal cortices occurred only in depersonalization disorder patients. Abnormal decreases in limbic activity to increasingly intense emotional expressions, and increases in dorsal prefrontal cortical activity to emotionally arousing stimuli may underlie the emotional detachment of depersonalization disorder. *NeuroReport* 18:473–477 © 2007 Lippincott Williams & Wilkins.

Keywords: cerebral cortex, depersonalization disorder, facial expression, functional magnetic resonance imaging, human emotion, limbic system, skin conductance

Introduction

Detachment from emotional experience, together with detachment from the sense of reality and one's own body experience, is a characteristic sign of depersonalization disorder (DPD) [1,2]. Individuals with DPD frequently report detachment from negative and positive emotion displayed by others in social contexts [3,4]. Abnormally increased inhibition of the amygdala by prefrontal cortex resulting in decreased autonomic response to emotive stimuli and reduced emotional experience has been postulated as a putative mechanism for the emotional detachment of DPD [5]. Previous findings in DPD patients have indicated increased ventral prefrontal cortical activity to complex aversive visual stimuli compared with healthy and obsessive-compulsive individuals [4]. Reduced autonomic activity to aversive pictures in DPD individuals compared with healthy and anxiety-disordered individuals has also been demonstrated [6]. We wished to examine the neural mechanism underlying the inability to experience positive and negative emotion in DPD by measuring neural and autonomic responses to socially salient negative and positive emotional stimuli: sad and happy facial expressions, respectively. Previous findings allowed us to hypothesize that DPD would be associated with relative increases in prefrontal cortical activity to emotionally intense happy and sad expressions. We also wished to explore the extent to which emotional expression intensity and objective measures of arousal, measures of autonomic response, further modulated neural responses to emotional stimuli in DPD.

Materials and methods

Participants

All procedures were approved by the Bethlem Royal and Maudsley Ethics Committee (Research) and the Ethics Committee at the Dresden University Medical Center and conducted with informed consent of the participants in accordance with the Helsinki Declaration. Depersonalization patients (nine, four female, age 36.1 ± 2.3 years; M±SEM) were recruited from a specialized clinic, and diagnosis confirmed by a psychiatrist not involved in the study (MXP) according to *Diagnostic and Statistical Manual of Mental Disorder-IV* criteria. Healthy volunteers (12, 5 female, age 27.3 ± 1.9 years) served as a control group (NC). No specific differences in sociodemographic factors (education levels: depersonalization group 2.22 ± 0.14, control group 2.58 ± 2.02, 2=junior college level; SES: depersonalization group 2.22 ± 0.14, control group 1.91 ± 0.34, 2=lower middle class) and sex ratio were found between the two groups. The two groups were well matched on global intellectual functioning as expressed by relatively high education levels.

All depersonalization patients exceeded the Cambridge Depersonalization Scale 70-points clinical cut-off level for DPD (175.8 ± 12.3) [6]. DPD patients were either medicated with lowest effective doses (N=3; paroxetine, fluoxetine, olanzapine) or unmedicated (N=6). A secondary comorbidity of anxiety or depression was present in a subset (N=6) of the clinical group, but any psychotic symptoms had been excluded. All participants were strongly right-handed.

Experimental procedures

Happy and sad facial expressions of emotion in 0–50–100% gradations of intensity were presented in two implicit event-related fMRI tasks, where participants were required to indicate the sex of the face [7]. Each 6-min experiment comprises 10 facial identities that were visually presented for 2 s with random interstimulus intervals averaging 4.9 s. The interstimulus intervals consisted of a fixation cross to maintain participants' focus of attention. A uniform computer-morphed version [8] of the standardized Ekman [9] series of affective faces was employed with all nonfacial components removed.

Data acquisition

T_2^* fMRI and T_2 high-resolution data sets were acquired on a Neurovascular GE Signa 1.5 T MRI system with 40 m/mT high-speed gradients: T_2^* – 16 7-mm-thick slices, in-plane resolution 3.44 mm, T_E 40 ms, T_R – 2000 ms, FA $\alpha 70^\circ$, 64^2 matrix, FOV=25 cm; T_2 – 43 3-mm thick slices, in-plane resolution 1.72 mm, T_E 73 ms, T_R – 16 000 ms, FA $\alpha 90^\circ$, 128^2 matrix, FOV=25 cm. Electrodermal responses were measured inside the scanner during task performance. Online electrodermal measures, including both skin conductance average amplitude and latency of response to each stimulus, were analyzed for each stimulus event in 1.3–3.3 s windows at a sensitivity level of 0.01 μSiemens as described previously [10]. Measures showing one-tailed significant (all Ps < 0.05) correlation with blood-oxygen-level-dependent (BOLD) signal change in limbic supra-threshold clusters of activation were determined for each emotion category and intensity in beforehand offline analyses.

fMR data analysis

The statistical inference software package XBAM version 3.4 (Brain Image Analysis Unit, IOP London; www.brainmap.it), which implements mathematical control for signal-to-noise ratio, was used to analyze fMRI data. An event-related analysis was performed to identify differences in BOLD response to target stimuli versus baseline in each condition, regressing the corrected time series data on a linear model produced by convolving each contrast vector to be studied with two Poisson functions parameterizing hemodynamic delays of 4 and 8 s. Nonparametric randomization procedures (50 permutations for trend comparison and for fMRI correlation maps) preceded general linear model statistics, which allow the ascertainment of exact probabilities, rather than corrected ones, in combination with rates for error clusters.

fMR image processing and inference

The statistics of fMR image processing have been described elsewhere in greater detail [10–12]. Briefly, the distributions of the same statistics under the null hypothesis of no experimental effect were calculated by wavelet-based resampling [13,14] of the time-series at each voxel and refitting the models to the resampled data [15]. This resulted in 10 parametric maps (for each individual at each plane) of the sum-of-square quotient (SSQ) estimated under the null hypothesis that SSQ is not determined by periodic stimulation. SSQ reflects a ratio measure of the model fit for BOLD signal against residual noise, similar to the F test in analysis of variance type statistics. Voxels with spatiotemporally combined probability of false-positive activation of $P < 0.005$ were regarded as activated in a resulting generic brain activation map. All parametric maps of SSQ were then registered in the standard space of Talairach and Tournoux [16] to produce median activation maps as described previously [17].

Determination of group differences

To determine cerebral regions, which significantly discriminated between two linear trends, one for happiness and one for sadness for each of the two groups, two 3×2 (emotion level $\times$ group) mixed-model analyses of covariance were computed [18]. The resulting regions were thus constrained by clusters that carried interaction effects of fMRI signal change by expression intensity. The trend comparison maps were used to calculate correlation images between neural and skin conductance response measures to 50% and 100% happy and sad expressions for each group. By using this strategy it was ensured that only those regions whose activation exhibited significant discrimination between DPD and normal control groups, as indexed by the presence of interaction effects in the fMRI signal, were introduced to fMRI correlation maps. All reported results are corrected for optimal rates of expected false-positives of ≤ 0.5 error clusters over the whole brain volume and cluster Ps < 0.005.

Results

Self-report results relevant to clinical cut-off levels

Participants completed the self-report questionnaires Dissociative Experience Scale and Cambridge Depersonalization Scale. Significant between-group differences were revealed by Student's t-tests for all taxons except handedness. All clinical scores were higher for DPD than for normal control (NC) participants (all Ps < 0.01). In depersonalization patients, the scale version of the Cambridge Depersonalization Scale (reporting percentage frequencies of depersonalization states) was significantly positively correlated with our tested electrodermal measures at all four emotion intensity levels (all Ps < 0.05). No systematic association patterns between the Cambridge Depersonalization Scale and any of the brain regions of interest were observed.

Results for regions discriminative for the two groups

The analyses of covariance yielded significant interactions between expression intensity (neutral, mild, intense emotion) by group (depersonalization patients, healthy normal controls) for happiness in a main cluster in right hypothalamus/semilunar gyrus (Brodmann area (BA) 34; x=4, y=−4, z=−13; Talairach [16] coordinates, augmented with Duvernoy [19] region labels). For sadness, a significant interaction was found in right amygdala/uncinate gyrus (BA 34; 10 −11 −13). These interactions were further explored by extracting BOLD signal changes at each emotion and each intensity level in the two participant groups. Repeated measures analyses of variance (happiness

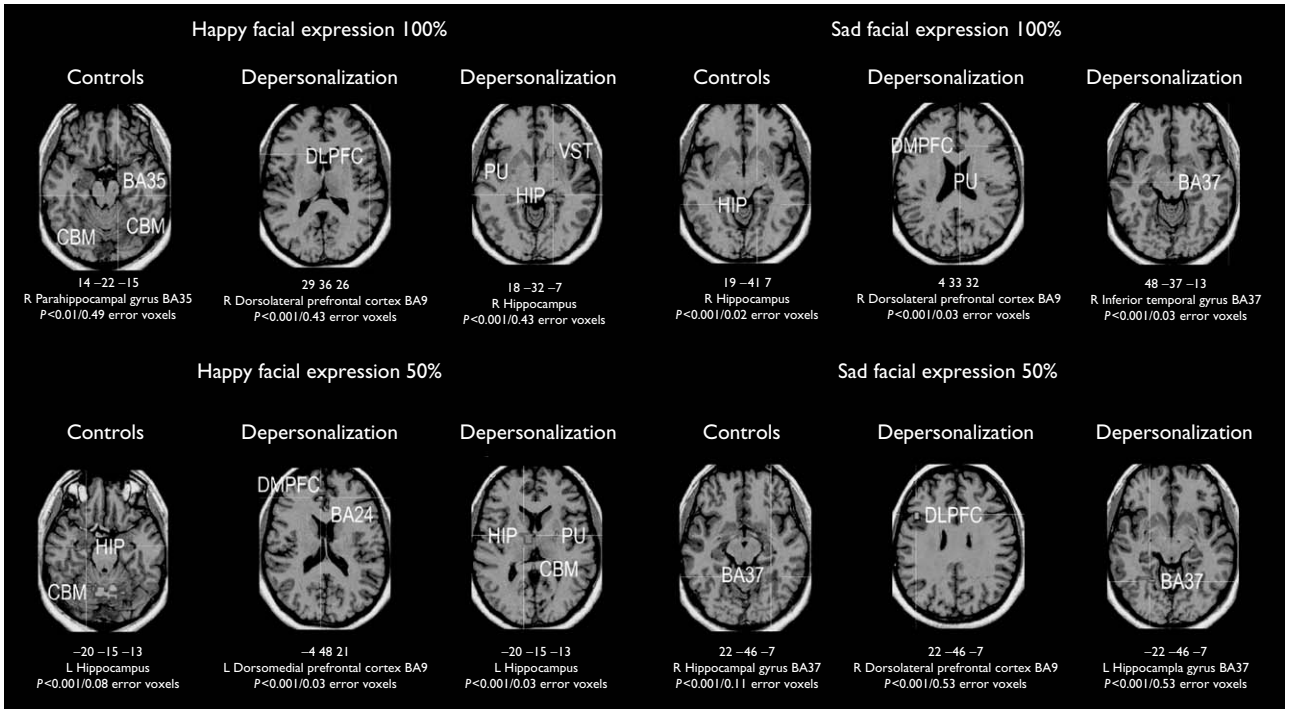

Fig. 1 Correlation fMRI images with emotion and intensity specific skin conductance measures for depersonalization disordered (DPD) patients and normal controls. Neural regions showing correlations between magnitude of neural response in regions that discriminated DPD patients and normal controls for each emotion and skin conductance measures (axial slices, neurological convention, minimum cluster size five contiguous active voxels). The left panels show the regions for happy emotion (normal controls left column, DPD patients middle and right columns), and sad emotion expression (normal controls left column, DPD patients middle and right columns). Note that in each of the categories, limbic regions are partially identical between normal controls and DPD, but that control participants do not coactivate prefrontal region Brodmann area (BA) 9. Statistical inference levels, cluster coordinates and levels of error clusters expected are reported for each emotion intensity.

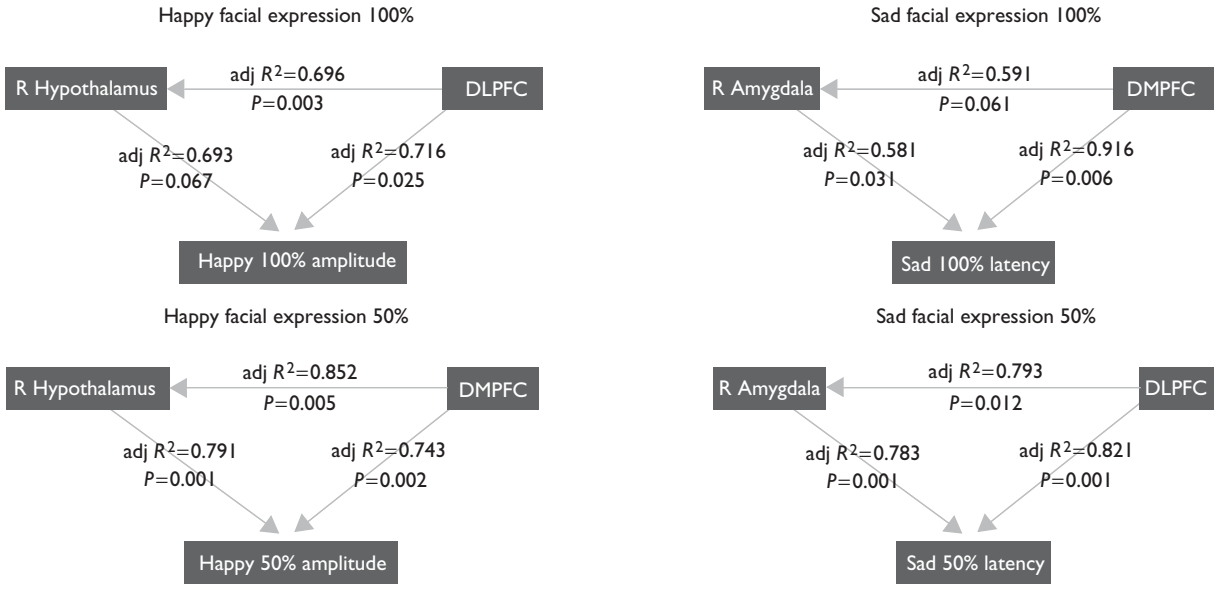

Fig. 2 Models of effective connectivity for 50% and 100% sad and happy emotions. Connectivity models based on multiple hierarchical regression analysis (MRA), specified for each emotion intensity level. Normalized mean percentage BOLD signal change and electrodermal measures were used in MRAs.

model F=4.522, P=0.048; sadness model F=7.808, P=0.005) revealed that for both happy and sad emotions, depersonalization patients responded with BOLD signal *decreases* in these regions to facial expression intensity increases, whereas normal controls showed the opposite pattern. Pairwise post-hoc tests (Ps<0.05) confirmed the largest

group differences existing at the intense levels of emotion expression. Mean percentage BOLD signal changes in the hypothalamus (happy 50%, control 0.126 ± 0.13; depersonalization -0.132 ± 0.39; happy 100%, control 0.212 ± 0.13; depersonalization -0.891 ± 1.01) and the amygdala (sad 50%, control 0.102 ± 0.11; depersonalization -0.020 ± 0.05; sad 100%, control 0.129 ± 0.03; depersonalization -0.063 ± 0.08) were lower for depersonalization patients.

Electrodermal responses

For normal controls, the descriptive values of electrodermal responses were happy 50% amplitude 0.412 ± 0.11 μS, happy 100% amplitude 0.320 ± 0.46 μS, sad 50% latency 1.707 ± 0.27 s, sad 100% latency 1.998 ± 0.16 s. The electrodermal descriptive values for depersonalization patients were happy 50% amplitude 0.522 ± 0.11 μS, happy 100% amplitude 0.652 ± 0.31 μS, sad 50% latency 2.068 ± 0.24 s, sad 100% latency 1.814 ± 0.13 s.

fMRI correlation images

Emotion-intensity-specific skin conductance measures (amplitude for happiness, latency for sadness) were used to calculate fMRI correlation maps (Fig. 1). Regional patterns of correlations between neural and autonomic activity emerged for each emotion and group ($P < 0.05$): for happy expressions with skin conductance amplitude, and for sad expressions with skin conductance latency. Regions activated by happy expressions in the correlation image with skin conductance amplitude are shown in Table 1. Activation patterns in limbic regions (hippocampus, hippocampal gyri, and inferior temporal regions) were comparable for the control and clinical groups. For both emotions, additional correlations between skin conductance amplitude (for happy) and latency (for sad) in bilateral BA 9 occurred exclusively in the DPD group (Table 1). Activations represent both positive (for limbic) and negative (for PFC) correlation. Extracted mean percentages BOLD signal change in BA 9 (DLPFC and DMPFC) were happy 50%, 0.92 ± 0.51; happy 100%, 0.15 ± 0.11; sad 50%, 0.07 ± 0.17; sad 100%, 0.06 ± 0.02.

Analyses of effective connectivity

To test effective connectivity, all extracted BOLD signal change values (mean percentage) and electrodermal measures were normalized. Multiple hierarchical regression models [20] were fit for each emotion intensity level, by inclusion of Cambridge Depersonalization Scale scores as the regressor of no interest. The regression results replicated the ascertainment of functional connectivity as evident in the fMRI correlation maps. The resulting effective connectivity models linking limbic and prefrontal to electrodermal measures, and correlated to Depersonalization states, are shown in Fig. 2. Adjusted R^2 coefficients reflect the fit of the respective regression slope, and are always positive, for both positive and negative association.

Table 1 Regions appearing in fMRI correlation maps with emotion and intensity-specific electrodermal measures for depersonalization disordered participants and controls

Region	BA	*X*	*Y*	*Z*
100% happiness intensity normal controls				
R parahippocampal gyrus	35	14	−22	−15
L cerebellum		−7	−81	−23
R cerebellum		7	−59	−23
100% happiness intensity depersonalization disorder				
R hippocampus		18	−33	−7
L putamen		−22	0	−2
R ventral striatum		1	1	−7
R dorsolateral prefrontal cortex	9	29	36	26
50% happiness intensity normal controls				
L hippocampus		−20	−15	−13
L cerebellum		−8	−53	−18
50% happiness intensity depersonalization disorder				
L cerebellum		−4	−39	−4
R putamen		25	0	−2
R dorsal anterior cingulated	24	2	33	15
L dorsomedial prefrontal cortex	9	−4	48	21
100% sadness intensity normal controls				
R hippocampus		19	−41	−7
100% sadness intensity depersonalization disorder				
R inferior temporal gyrus	37	48	−37	−13
R dorsal anterior cingulated	24	30	−5	32
R dorsomedial prefrontal cortex	9	4	33	32
50% sadness intensity normal controls				
R hippocampal gyrus	37	22	−46	−7
50% sadness intensity depersonalization disorder				
L hippocampal gyrus	37	−22	−46	−7
L dorsolateral prefrontal cortex	9	−40	19	26

BA, Brodmann area; cluster *P*-levels, Fig. 1; *XYZ*, Talairach coordinates.

Discussion

Limbic signal decreases in depersonalization disorder

Happiness and sadness are discrete emotion categories that best represent positive and negative affective valence [21]. This study used facial expressions to measure neural and autonomic responses to these oppositely valenced emotional stimuli to examine the neural basis of the phenomenon of emotional detachment in DPD. DPD patients showed BOLD signal decreases in hypothalamus and amygdala to happy and sad facial expression intensity increases, respectively, whereas NC showed the opposite trends in these regions.

Prefrontal recruitment for emotion suppression

Furthermore, whereas both groups showed correlations between autonomic and neural responses to mild and intense expressions predominantly within subcortical regions implicated in the normal response to emotional stimuli, only DPD showed negative correlations between autonomic and neural responses in dorsal prefrontal cortex to these stimuli. These findings suggest that DPD may be associated with two phenomena: (i) decreases rather than increases in hypothalamus and amygdala activity to emotional stimuli of increasing intensity; together with (ii) abnormal recruitment of dorsal prefrontal cortex to stimuli evoking increased autonomic activity. Functional coupling between limbic and prefrontal regions in processing of emotional stimuli have been described repeatedly (e.g. [22]). Activity within similar dorsal prefrontal cortical regions have previously been reported in the attempt to reduce the intensity of emotional experience evoked by emotional stimuli through reappraisal [23,24]. A pattern of distribution of inhibitory prefrontal activations to more dorsolateral or more dorsomedial sites under emotion suppression demands, similar to the pattern here observed, has been found previously [25].

Relevance of the effective connectivity models to depersonalization states

The frequency and extent of depersonalization states was positively correlated to our electrodermal measures (see above). This demonstrates that self-report measures of depersonalization are sensitive to changes in sympathetic outflow. The regression models represent demonstrations of effective connectivity [20], while most parsimoniously estimating intrinsic associations. The regression models are bidirectional by nature, and demonstrate that linear causal relations exist between (i) limbic regions and electrodermal activity, (ii) prefrontal regions and electrodermal activity and (iii) prefrontal and limbic regions, at all four emotion intensity levels. Depersonalization, as measured by self-report, is thus moderated by electrodermal response, which in turn is regulated by the interplay of limbic and prefrontal regions.

Conclusion

We conclude that both neural mechanisms identified to be specific for DPD play a role in dysfunctional emotion regulation in this clinical group. It is likely that the decreasing signal intensity to increasing induced emotion intensity is a neural correlate of the inexperience of emotion in DPD. The inhibitory role of prefrontal regions has repeatedly been described in emotion suppression experiments. The abnormal increases in activity in this prefrontal cortical region to emotionally arousing stimuli may thus be a mechanism involved in emotional detachment of DPD.

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