Cerebral and autonomic responses to emotional facial expressions in depersonalisation disorder

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Background
Depersonalisation disorder is characterised by emotion suppression, but the cerebral mechanisms of this symptom are not yet fully understood.

Aims
To compare brain activation and autonomic responses of individuals with the disorder and healthy controls.

Method
Happy and sad emotion expressions in increasing intensities (neutral to intense) were presented in an implicit event-related functional magnetic resonance imaging (fMRI) design with simultaneous measurement of autonomic responses.

Results
Participants with depersonalisation disorder showed fMRI signal decreases, whereas the control group showed signal increases in response to emotion intensity increases in both happy and sad expressions. The analysis of evoked haemodynamic responses from regions exhibiting functional connectivity between central and autonomic nervous systems indicated that in depersonalisation disorder initial modulations of haemodynamic response occurred significantly earlier (2 s post-stimulus) than in the control group (4–6 s post-stimulus).

Conclusions
The results suggest that fMRI signal decreases are possible correlates of emotion suppression in depersonalisation disorder.

Declaration of interest
None. Funding detailed in Acknowledgements.

Detachment from vivid emotion experience is one of the signs of depersonalisation, together with detachment from the sense of reality and of one's own body experience. Emotional detachment is an enduring state during which individuals with depersonalisation disorder cannot access any affective movement, be it positive or negative. The exact causes of depersonalisation disorder are unknown, and the neural mechanisms underlying the symptoms of distancing from or freezing of emotional experiences remain poorly understood.[1] Depersonalisation disorder typically involves a sense of detachment from emotions, from body and from reality.[2,3] Two neural systems models – the suppression model of Sierra & Berrios and the imbalance model of Phillips – have been proposed to explain emotion inexperience in depersonalisation disorder.[4,5] Phillips *et al* postulated that emotional detachment in depersonalisation disorder might arise from abnormal increases and decreases in activity of an inhibitory, emotion-suppression neural system centred on the prefrontal cortex, and in an emotion identification/early appraisal neural system centred upon subcortical regions respectively.[5] Findings in support of this model come from a study examining neural activity to aversive *v.* neutral stimuli from the International Affective Picture System (IAPS). Here, participants with depersonalisation disorder showed increased activity in ventrolateral cortex, middle temporal and secondary visual cortices relative to both healthy controls and a group with obsessive–compulsive disorder.[5] The model of Sierra & Berrios postulates that depersonalisation states are characterised by emotional numbing, previously supported by findings of a reduction in autonomic responses (as measured by changes in skin conductance responses to emotional IAPS and startling auditory stimuli) in participants with depersonalisation disorder relative to individuals with anxiety disorder and those who are healthy.[6] However, group differences had been observed between emotion types, indicating a lesser degree of attenuation in positive emotion expressions.[7] In the Sierra & Berrios model, suppression of emotional impulses was linked, by inference from neuro-psychological findings, to left-sided prefrontal activation.[4] Recent findings of group differences in emotional memory between people with depersonalisation disorder led us to further expect the co-activation of superior frontal regions in this disorder.[8] The two models allowed us to predict reduced response in subcortical regions, increased (ventrolateral or dorsolateral) prefrontal cortical response and decreased autonomic activity (as measured by changes in skin conductance) in patients with depersonalisation disorder relative to normal controls for all emotional stimuli. We used happy and sad emotional expressions as experimental stimuli, as these emotions have been shown to optimally represent valence polarities in the hedonic continuum.[9]

Method

Participants

All experimental procedures were endorsed by the Bethlem Royal and Maudsley research ethics committee and the ethics committee at Dresden University Medical Centre. All participants gave written informed consent to the scientific use of their data and were reimbursed for their participation. The study was conducted in compliance with the Helsinki declaration.[10] The study included a sample of 9 individuals (5 men and 4 women, mean age 36.11 years (s.e.m.=2.34; educational level 2.22 (s.e.m.=0.14), where 2 represents undergraduate level), with a primary diagnosis of depersonalisation disorder from the Maudsley Hospital out-patient department. At the time of this investigation the patients were being treated in a specialised clinic for this condition. All patients were re-examined and confirmed with diagnosis of depersonalisation according to DSM–IV criteria by a psychiatrist not involved in the study. Patients with a confirmed diagnosis were separately invited to participate in the study by the

experimenter, who was masked to all medical records (E.L.). The clinical cut-off level of a score above 70 on the Cambridge Depersonalization Scale (CDS) for depersonalisation disorder was exceeded for all patients (175.77, s.e.m.=12.31).[11] Three people with depersonalisation disorder received minimum effective doses of one of three different substances: including selective serotonin reuptake inhibitors (SSRIs) and neuroleptics (paroxetine, fluoxetine, olanzapine). A normal control group of 12 participants (7 men and 5 women, mean age 27.25 years (s.e.m.=1.95); educational level 2.58 (s.e.m.=2.02)) was also included. These participants were chosen to match the sample characteristics of the depersonalisation disorder group, specifically with respect to global intellectual functioning and socio-demographic features. A trend towards significance in age differences seemed tolerable, because none of the study variables showed any association with participants' age.

Self-report questionnaire data

All participants completed self-report forms before being introduced to the experimental protocol inside the scanner. Right-handedness was verified with the Edinburgh Handedness Inventory.[12] Further to the CDS clinical cut-off measure for depersonalisation,[11] clinical dimensions potentially relevant for depersonalisation disorder were assessed on the day of scanning, using the Dissociative Experience Scale,[13] the Screening for Somatoform Disorders,[14] the Toronto Alexithymia Scale (20-item version),[15,16] the Frankfurt Body Concept Scales,[17] the Beck Depression Inventory,[18] and the State–Trait Anxiety Inventory.[19] Discriminative cut-off levels for depersonalisation disorder have not been established for these instruments; however, they served as additional measures of symptom severity.

Implicit facial expression neuroimaging tasks

The participants completed two 6 min experiments employing event-related functional magnetic resonance imaging (fMRI). In each experiment, participants were presented with ten different facial identities, each expressing twice 50% and 100% intensities of one emotion (either happiness or sadness) in addition to a neutral expression (0%) (60 facial stimuli, 12 non-facial stimuli). Each facial stimulus was presented for 2 s. During the inter-stimulus interval, the duration of which varied from 3 s to 8 s according to a Poisson distribution at an average interval of λ=4.9 s, participants viewed a fixation cross, as described elsewhere.[20,21] Further details of the fMRI paradigm are presented in a data supplement to the online version of this paper.

Psychophysiological recording

Derivations of electrodermal activity related to the task were made online during neuroimaging data acquisition. The method of simultaneous fMRI and psychophysiology data acquisition and analysis used here has been described in detail elsewhere.[22] Applying criteria of 0.01 μS, electrodermal activity was analysed in an event-related manner for each of the three different emotion expression intensities in each participant using the software program SC-ANALYZE (Neuroimaging Research Group, Institute of Psychiatry, London, UK). Latency windows of 1.2–3.3 s post-stimulus onset were evaluated to ensure that electrodermal activity was not contaminated by non-specific skin conductance response (SCR) discharges (increasing skin conductance level, (SCL)), such as those to the following stimulus. The following electrodermal activity variables were submitted to statistical analysis: SCR rates, SCL latency, SCL amplitude height, mean SCL, minimum SCL and maximum SCL in each time window. Following standard

procedures, two variables were computed, ΔSCL and relative SCL (rSCL), expressing individual spans between minima and maxima within each condition, and the relative means normalised to these.[22]

Image acquisition and analysis

Gradient echo echoplanar imaging (EPI) data were acquired on a neurovascular GE Signa 1.5 T system (General Electric, Milwaukee, Wisconsin, USA), equipped with 40 m/mT high-speed gradients, at the Maudsley Hospital, London. A quadrature birdcage head-coil was used for radiofrequency transmission and reception. For each of the two tasks, 180 T_2*-weighted images were recorded over 6 min at each of 16 near-axial non-contiguous 7 mm thick planes parallel to the anterior–posterior commissural (AC–PC) line: echo time (TE) 40 ms, repetition time (TR) 2000 ms, in-plane resolution 3.44 mm, interslice gap 0.7 mm, flip angle (FA) α=70°, matrix 64 × 64, field of view (FOV) 25 cm providing whole brain coverage. During the same session a high-resolution anatomical data-set was acquired with an EPI pulse sequence. The structural images were acquired at 43 near-axial planes 3 mm thick parallel to the AC–PC line: TE 73 ms, inversion time (TI) 180 ms, TR 16 000 ms, in-plane resolution 1.72 mm, interslice gap 0.3 mm, matrix size 128 × 128, FOV 25 cm, FA α=90°. The high-resolution EPI data-set was later used to register the fMRI data-sets acquired from each individual in standard stereotaxic space. The program package XBAM for UNIX (www.brainmap.it) with mathematical control for signal-to-noise ratio was used to perform the analysis of fMRI data. A detailed description of the fMRI analysis method is presented as a data supplement to the online version of this paper.

Results

Behavioural performance during the gender decision task

Judgement accuracies in the gender decision task for facial expressions were evaluated as the percentage of correct answers in each of the six categories (neutral, mild and intense, for both happiness and sadness expressions). Complete descriptive data for the two study groups are presented in a data supplement to the online version of this paper. Correct overall answers were 49.54% for the depersonalisation disorder group and 51.31% for the control group. These rates around chance reflect relative task difficulty and are in line with other studies using similar fast implicit facial paradigms.[21,23,24] No systematic difference between the depersonalisation disorder group and the control group emerged for reaction times or response accuracies.

Psychometric evaluation

The descriptive values for the questionnaire data are listed in a data supplement to the online version of this paper. No significant difference in handedness or on any of the nine taxons of the Frankfurt Body Concept Scales was found between the two groups. Significant between-group differences were observed for the Dissociative Experience Scale, the Screening for Somatoform Disorders, the CDS, the Toronto Alexithymia Scale (except its taxon for external-concrete cognitive style), the Beck Depression Inventory and the Spielberger State–Trait Anxiety Inventory. In all of these dimensions, scores were higher for participants with depersonalisation disorder than for the control group. The significant group differences, however, do not address clinical cut-off levels for specific disorders, except for the CDS (see Method).

Skin conductance levels

All SCL variables exhibited between-condition stability and between-emotion discrimination at each level (data not shown). Descriptive data are presented in the data supplement to the online version of this paper for ΔSCL and rSCL. Electrodermal activity data were not confounded by recording times and dates, but gender and education exhibited significant interaction effects in preliminary analyses. Consequently, the contribution of these confounding variables was removed by treating them as covariates in analyses of covariance (ANCOVAs). Significant between-group differences were apparent for five of the six stimulus types, and a near-significant difference for 50% sadness. Delta SCL was the electrodermal activity variable showing between-group differences to neutral (happy context), neutral (sad context), 50% sadness and 50% happiness stimuli (data presented in a data supplement to the online version of this paper), whereas rSCL was the variable showing a significant between-group difference to 100% happiness and 100% sadness stimuli ($P < 0.05$). Comparison of the error diagrams (presented in a data supplement to the online version of this paper) (Fig. 1) revealed that the depersonalisation disorder group had much larger variabilities in electrodermal activity to facial stimuli than the control group. Both ΔSCL and rSCL means were higher in the depersonalisation disorder group, with the sole exception of rSCL in the 100% sadness condition. These findings suggest that it is the magnitude of the span between individual minima and maxima that discriminates best between depersonalisation disorder and control groups at 0% and 50% intensity levels; at the 100% level, the mean corrected measure was most effective in discriminating between groups.

Polynomial trend analyses of neural response

Linear trend maps reflecting greater neural response with linear increase in emotion intensity of expressions from neutral through mild to intense emotion are shown in Fig. 1. Talairach coordinates for regions showing significant linear increases in response to expressions of increasing emotion intensity are listed in a data supplement to the online version of this paper. The trend map for happy expressions in the control group (Fig. 1(a)) showed activation in the left orbital gyrus (Brodmann area (BA) 11), left middle frontal gyrus (BA 9), left angular gyrus (BA 39), left posterior cingulate gyrus (BA 31) and right fusiform gyrus (BA 19). In depersonalisation disorder the trend map for happy expressions (Fig. 1(b)) showed activation in the right superior frontal gyrus (BA 8), left temporal pole (BA 38), posterior insula and bilateral fusiform gyrus (BA 19). The trend map for sad expressions in the control group (Fig.1(c)) showed activation in the bilateral middle frontal gyrus (BA 8), posterior inferior temporal cortex (BA 20/39), left supramarginal gyrus (BA 40) and bilateral middle occipital gyri (BA 19). The corresponding map in the depersonalisation disorder group (Fig.1(d)) showed activation in the right superior frontal gyrus (BA 9/45), posterior insula, left supramarginal gyrus (BA 40), bilateral middle occipital gyri (BA 19) and left fusiform gyrus (BA 37).

Trend comparison analyses of neural response

The trend comparison maps reflecting interaction effects, i.e. regions where polynomial trends in neural response to expressions of increasing intensity of happy or sad emotion differed significantly between groups, are shown in Fig. 2. Note that these can also include non-linear (i.e. quadratic) effects. The graphs in this figure illustrate these interaction effects by showing the percentage blood oxygen level dependent (BOLD) signal change extracted from each identified region in the trend comparison map for each separate expression intensity. Analyses of between-group differences for happiness trends (Fig. 2(a)) identified the right hypothalamus (anterior portion at paraventricular nucleus, superior to the hypophyseal peduncle) and for sadness (Fig. 2(b)) the right amygdala (centromedial nucleus close to the processus uncinatus) as main clusters. Repeated-measures analyses of variance (ANOVAs) conducted on extracted signal intensities to examine between-group differences in polynomial trends for each emotion trend map (happiness $F_{1,20} = 4.522$, $P = 0.048$; sadness $F_{1,20} = 7.808$, $P = 0.005$) confirmed the findings from the above whole-brain trend comparison maps. Between-group differences to emotional stimuli, based on logarithmised fMRI signal effect sizes from the above regions extracted at 6 s post-stimulus, were greatest at 100% intensity levels: happiness, $t_{18,20} = -2.134$ (95% CI 0.019 to -2.551), $P = 0.047$; sadness, $t_{18,20} = -2.103$ (95% CI 0.009 to -2.224), $P = 0.050$. The profile plots for these and the secondary clusters (not shown) showed that the depersonalisation disorder group exhibited decreases in fMRI signal to expressions of increasing intensity of emotion. The opposite pattern was evident for the control group.

BOLD time course examination for neutral, mild and intense expressions

To examine further neural responses in the main clusters in the trend comparison maps discriminating between control and depersonalisation disorder, time courses for each of the three expression intensity levels (neutral–mild–intense) were extracted from regions in which between-group effects were shown in the trend comparison maps. The averaged time series of percentage change in BOLD signal are plotted in Fig. 3. Time points represent units of 2 s post-stimulus (TR units; repetition time 2 s). To fulfil the criterion for a 'peak' in haemodynamic response, a positive or negative deflection in BOLD response had to exceed the preceding data-point by the standard deviation indicated by its error bar. The depersonalisation disorder group showed early positive or negative peak haemodynamic responses at TR=1, as indicated by error bars (representing 1 standard deviation). The control group showed initial peak haemodynamic responses at TR=2 or later. The average haemodynamic response is expected 4–6 s post-stimulus in non-visual heteromodal areas.[25,26]

To investigate further the time-course pattern exhibited by the depersonalisation disorder group, we decided to examine haemodynamic responses in other regions. We correlated statistical maps of the subtraction contrast intense–mild expression intensity (thereby removing face-related activations, and preserving mid-to-high range emotion activation) for each of the emotions with the respective SCL measures that had discriminated between depersonalisation disorder and control (rSCL and ΔSCL). From the resulting equal number of regions in which significant positive correlations were shown (14 for each group), we extracted time series of haemodynamic responses. These regions included in both groups subcortical, ventral prefrontal cortical and visual processing neural regions, previously implicated in the response to emotional facial expressions.[20] The average BOLD response time courses for the three expression intensity levels for each emotion were plotted for all regions detected in whole-brain correlation images in each group. To fulfil the criterion for a peak in haemodynamic response, a positive or negative deflection in BOLD response had to exceed the preceding data-point by the standard deviation indicated by its error bar. There were 14 clusters for depersonalisation disorder, 13 of which had a peak at 2 s post-stimulus, and 1 at 4 s post-stimulus or later. In contrast, in the control group, one region of interest had a first peak at 2 s post-stimulus and 13 first peaks at 4 s post-stimulus or later. The difference between groups in number of early (TR=1) and late
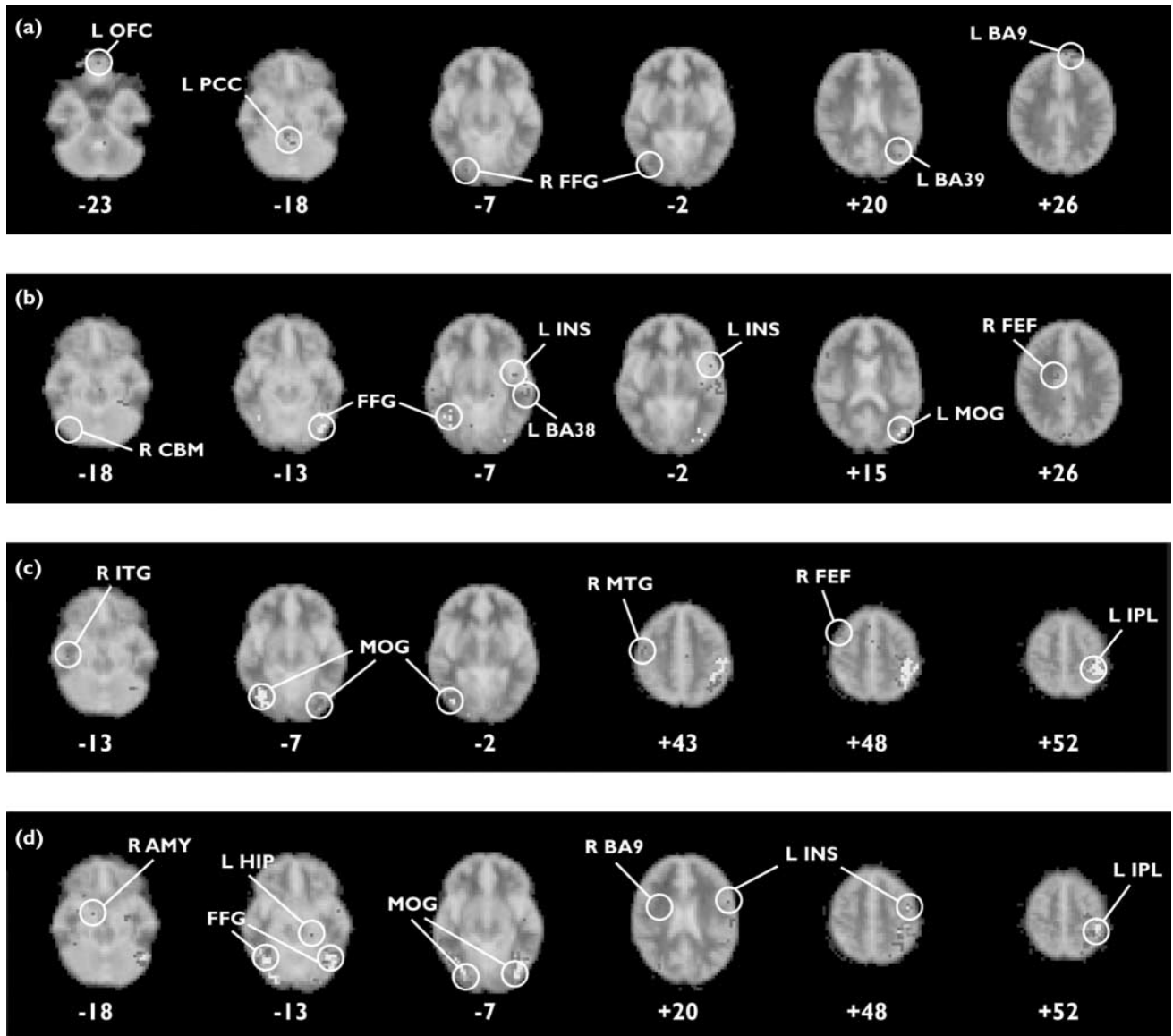
Fig. 1 Emotion-specific trend maps. Happiness and sadness intensity linear trend maps for the control and depersonalisation disorder groups (<0.14–0.16 error clusters over the entire brain). (a) Happiness, control group; (b) happiness, disorder group; (c) sadness, control group; (d) sadness, disorder group. Regions shown exhibit main effects for continual increases from neutral expression to 50% to 100% intensity of expression, relative to fixation cross baseline. Numbers below the slices indicate Talairach *z* coordinates. A colour version of this figure showing regions of activation can be found on the online version of this paper.

AMY, amygdala; BA, Brodmann area; CBM, cerebellum; FEF, frontal eye fields; FFG, fusiform gyrus; HIP, hippocampus; INS, insula; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex.

(TR=2 or later) peaks was significant ($\chi^2_{1,28}$=14.640, Fisher's exact test $P<0.001$). In a majority of the regions of interest in correlation maps for depersonalisation disorder, each of the higher emotion intensity expressions was associated with earlier (positive or negative) peaks in the time series compared with neutral expression. This supported the findings regarding timings of first peak in haemodynamic response for analysis of time series in the trend comparison maps (Fig. 3). Time series data for all evaluated regions of interest are given in a data supplement to the online version of this paper.

Discussion

We aimed to examine the potential neural mechanisms underlying the phenomenon of emotional numbing, or freezing, in depersonalisation disorder by measuring neural responses to both positive and negative emotional expressions. Trend comparison analyses for happy and sad emotions in depersonalisation disorder *v.* a control group supported our first hypothesis, namely that emotional freezing in depersonalisation may be associated with decreases rather than increases in subcortical limbic response to emotional expressions of increasing intensity of emotion. In contrast, increases in limbic responses have been described for other disorders such as major depression.[23] The between-group difference in trends in neural response was observed in the right amygdala to expressions of increased intensity of sadness, and in the right hypothalamus to expressions of increased intensity of happiness. Activation of the hypothalamus has been found in autonomic regulation during happy emotion states in previous fMRI studies,[27,28] and in laughing seizures resulting from neurological disorders.[29] The amygdala is a structure commonly activated by both facial expressions and affective scenes during
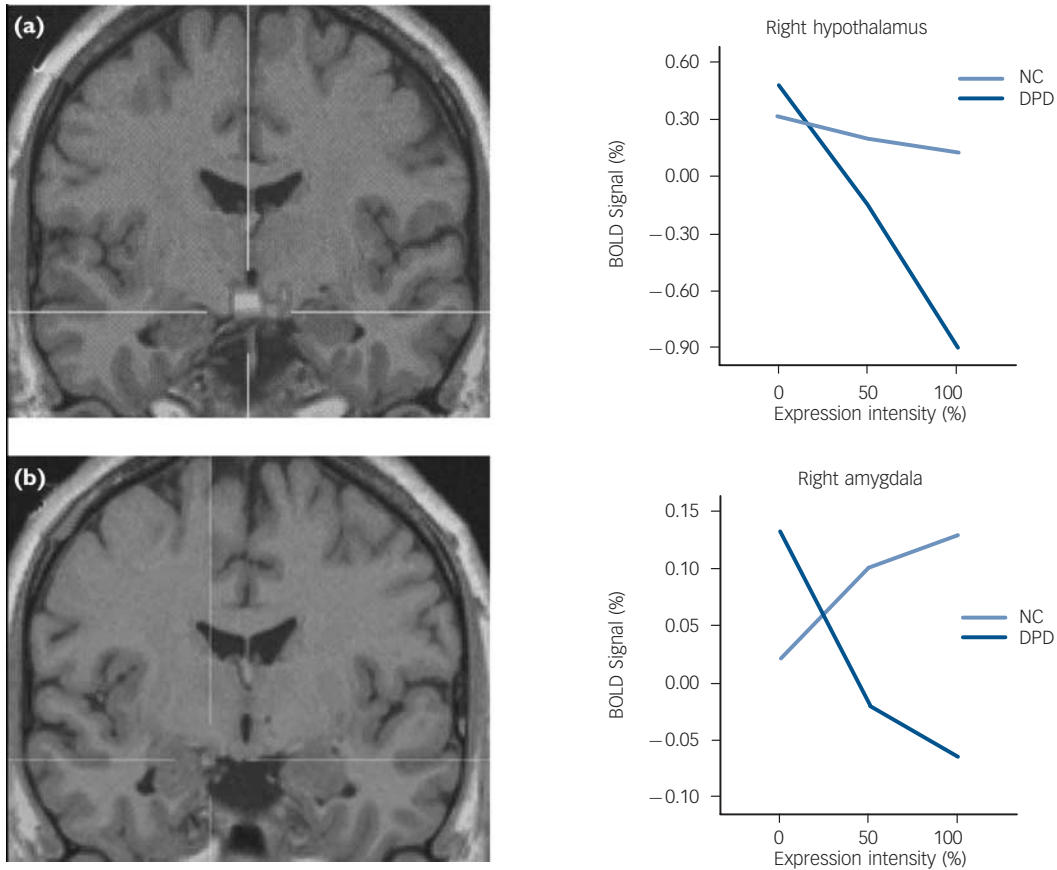
Fig. 2 Between-group trend comparison maps for happiness and sadness, representing blood oxygen level dependent (BOLD) signal by expression intensity interaction effects. Displayed in coronal sections are main clusters for each trend comparison, based on effect sizes of BOLD signal intensities (radiological convention; Talairach coordinates x, y, z). (a) Comparison of happy expression trends between the depersonalisation disorder and control groups. Regions moderated by expression intensities and group at cluster level threshold $P<0.005$ with 0.42 error clusters expected over the entire brain: right hypothalamus (4, −4, −13). (b) Comparison of sad expression trends between the depersonalisation disorder and control groups. Regions moderated by expression intensities and group at cluster level threshold $P<0.0005$ with 0.071 error clusters expected over the entire brain: right amygdala (10, −11, −13).

DPD, depersonalisation disorder group; NC, normal control group.

sadness.[30,31] Our findings support existing models of depersonalisation disorder postulating decreased rather than increased response in neural regions underlying emotion processing as a mechanism for the emotional blunting.

Findings from the investigation of linear trends also support our second hypothesis predicting increases in prefrontal cortical response to expressions in depersonalisation disorder. Participants with the disorder co-activated in both emotion experiments dorsolateral prefrontal regions (BAs 8, 9, 45), consistent with the notion that emotion expressions invoked inhibitory neural responses in this group. When comparing the frontal co-activations in both groups, it is evident that the depersonalisation disorder group showed posterior dorsal prefrontal activations at lateral and medial sites, whereas the control group exhibited anterior frontal activations at rostral sites. Recent experiments have shown that the anterior prefrontal cortex is responsible for 'release' functions, and contrasting posterior prefrontal regions subserving true 'inhibitory' mechanisms.[32]

To examine further the responses in these neural regions distinguishing depersonalisation disorder from controls, evoked haemodynamic responses to each of the three expression intensity levels (neutral, mild and intense) were extracted from these regions. Our findings indicate that the depersonalisation disorder group showed early positive or negative initial peak haemodynamic responses (at 2 s post-stimulus onset), whereas the control group showed later initial peak haemodynamic responses (at 4 s or later post-stimulus onset). This pattern of early haemodynamic peaking of response in depersonalisation disorder was confirmed in further analyses of regions whose amplitude of neural response showed a positive correlation with skin conductance level measures that had discriminated depersonalisation disorder from controls. Earlier peaks in haemodynamic response to emotionally salient faces in depersonalisation disorder suggest faster cerebral processing of facial emotional signals in this group. Recent research underlined that BOLD peak timing in a variety of brain regions depends on the type of cognitive processes.[33,34] Emotion appraisal processes require fast perceptual processing, and it has been demonstrated that an extraction of affective information exhibits electrophysiological modulation even prior to the face-related N170 response.[35,36] Our findings suggest that a combination of early coupling between neural and autonomic responses to positive and negative emotional stimuli, and overall decreases in amplitude of response in neural regions implicated in emotion processing to emotional stimuli of increased relative to those of decreased emotional intensity, underlie the emotional blunting observed in depersonalisation disorder. This conclusion
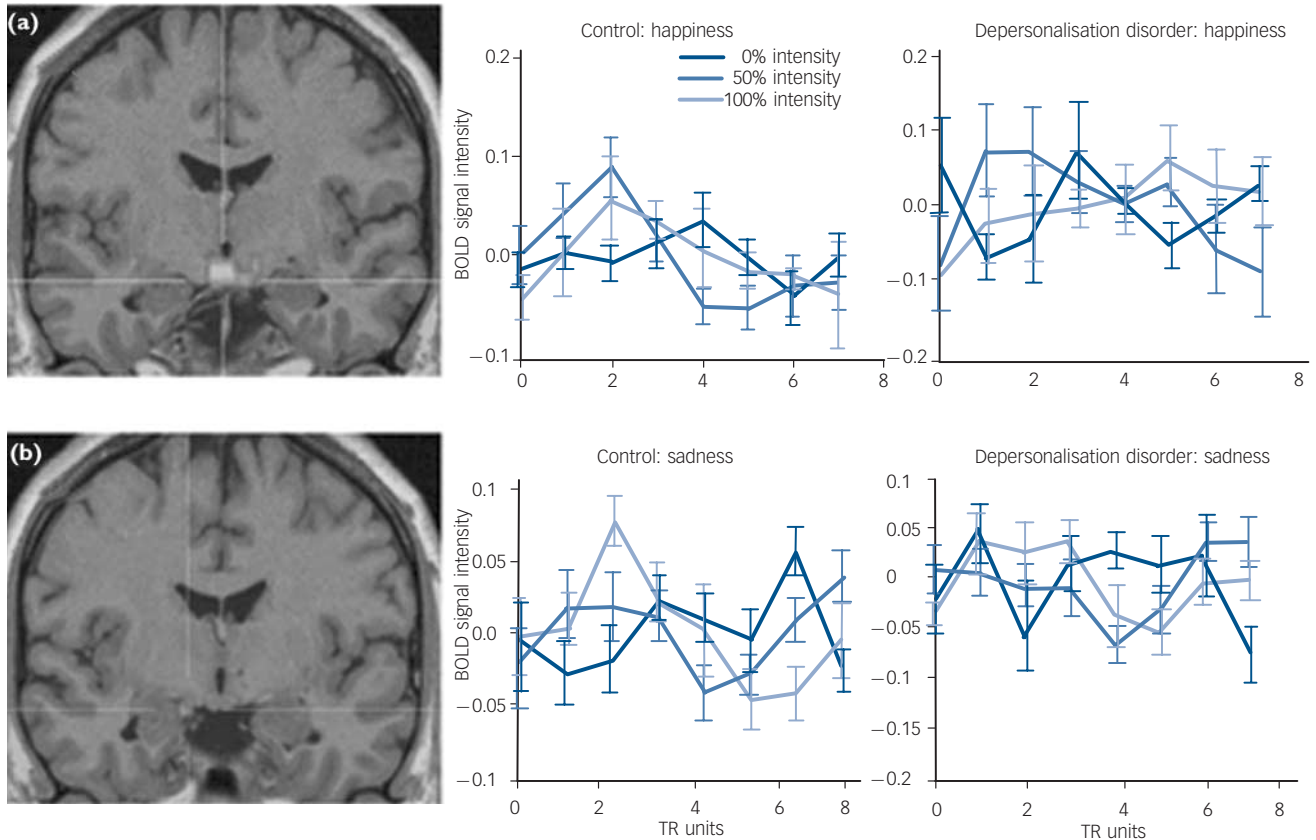
Fig. 3 Extracted blood oxygen level dependent (BOLD) time series from hypothalamus and amygdala: coronal sections of main clusters of trend comparison maps as also shown in Fig. 2 (radiological convention). The time series of extracted haemodynamic responses are displayed based on mean percentage BOLD signal intensities (ordinate). Time courses are represented for 0–16 s in repetition time units (1 TR=2 s; abscissa). Error bars represent standard deviations. Graph lines represent 0%, 50% and 100% expression intensity level effect sizes; (a) right hypothalamus (4, −4, −14); (b) right amygdala (10, −11, −13).

is also justified by the fact that early peaks are measured at 2 s post-stimulus, whereas correlates of emotion suppression as indicated by signal decrease are measured at 6 s post-stimulus.

Previous findings report decreased amplitude of autonomic response to emotional stimuli in depersonalisation disorder.[4] The between-group differences in skin conductance levels in our study, however, do not support our prediction of a general dampening of autonomic response in depersonalisation disorder in response to discrete emotion categories. Our findings indicate that people with depersonalisation disorder have a greater range of skin conductance levels than normal controls, irrespective of emotional valence.[6] They further indicate increased rather than decreased mean change in SCL in depersonalisation disorder relative to controls. Our findings also do not give any indication for an assumption of a greater impairment in negative emotion in depersonalisation disorder.[6] Similar patterns of both attenuated and elevated SCL have previously been described in people with alexithymia,[37] who typically show impaired labelling of emotional experiences and may have functional impairments in neural systems underlying emotion processing similar to those in depersonalisation disorder. The earlier coupling between autonomic and neural responses to facial expressions in depersonalisation disorder relative to controls may also underlie the heightened states of alertness previously reported in individuals with this disorder.[4]

Limitations of the study

Among the limitations of this study is the small size of the sample, owing to the rarity of depersonalisation disorder as a primary or

single diagnosis. Potential medication effects could not be partialled out statistically for three reasons: the small number of participants receiving medication (n=3, all with depersonalisation disorder); the low dosages of the medication; and the different medication sub-classes taken by these participants. It is emphasised, however, that the majority of individuals with depersonalisation disorder were unmedicated, and three received the lowest doses known to be effective. Additional group maps (not shown) for the unmedicated participants with depersonalisation disorder revealed highly similar cerebral activation patterns compared with the complete sample; we are thus able to rule out medication effects as the source of the presented results.

Directions for further research

Decreases in amplitude of response in neural regions implicated in emotion processing to emotional stimuli of increased, relative to those of decreased, emotional intensity, co-engagement of inhibitory prefrontal regions, together with early coupling between neural and autonomic responses to positive and negative emotional stimuli, may underlie the emotional blunting observed in depersonalisation disorder. It is likely that accelerated emotional appraisal of facial cues may lead to the subsequent downregulation of emotional experiences reported in depersonalisation disorder. Future studies measuring neural and autonomic responses to emotional stimuli in larger numbers of individuals with depersonalisation disorder will help elucidate the neural mechanisms underlying the emotional blunting in this disorder,

and will help to increase understanding of the neural mechanisms underlying involuntary inhibition of emotional experiences *per se*.

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