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Depersonalization disorder: thinking without feeling

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Abstract

Patients with depersonalization disorder (DP) experience a detachment from their own senses and surrounding events, as if they were outside observers. A particularly common symptom is emotional detachment from the surroundings. Using functional magnetic resonance imaging (fMRI), we compared neural responses to emotionally salient stimuli in DP patients, and in psychiatric and healthy control subjects. Six patients with DP, 10 with obsessive–compulsive disorder (OCD), and six volunteers were scanned whilst viewing standardized pictures of aversive and neutral scenes, matched for visual complexity. Pictures were then rated for emotional content. Both control groups rated aversive pictures as much more emotive, and demonstrated in response to these scenes significantly greater activation in regions important for disgust perception, the insula and occipito-temporal cortex, than DP patients (covarying for age, years of education and total extent of brain activation). In DP patients, aversive scenes activated the right ventral prefrontal cortex. The insula was activated only by neutral scenes in this group. Our findings indicate that a core phenomenon of depersonalization — absent subjective experience of emotion — is associated with reduced neural responses in emotion-sensitive regions, and increased responses in regions associated with emotion regulation.

Keywords: Depersonalized; Emotion; Functional magnetic resonance imaging

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1. Introduction

Depersonalization is an alteration in the perception or experience of the self. Sufferers feel uncomfortably detached from their own senses and surrounding events, as if they were outside observers (American Psychiatric Association, 1994). Such symptoms have been found in 2.4% of the general population (Ross, 1991) and 80% of psychiatric inpatients, and were severe and persistent in 12% (Brauer et al., 1970). Depersonalization can occur as a primary disorder, or accompanying depression, anxiety states, and schizophrenia (Simeon et al., 1997). It also occurs in neurological conditions such as the aura to temporal lobe epilepsy (Kenna and Sedman, 1965), and in healthy individuals during fatigue, meditation, extreme stress or after use of psychotomimetic drugs (Simeon and Hollander, 1993; Mathew et al., 1999). Classical descriptions emphasize reduced, 'numbed', or even absent, emotional reactions: e.g. 'all my emotions are blunted' (Shorvon, 1946), and 'the emotional part of my brain is dead' (Mayer-Gross, 1935). There are further reports that the skin conductance response, a measure of autonomic function and arousal, is abnormally flattened in depersonalized patients in response to emotional stimuli (Lader, 1975; Sierra et al., 2001).

Historically, a neuropsychological basis for depersonalization has been considered (Sierra and Berrios, 1998), stimulated by clinical studies on patients with neurological disorders, and psychophysiological research (Lader, 1975). More recently, functional neuroimaging has highlighted the role of the amygdala in the perception of fear (Morris et al., 1996), and the insula in the perception of disgust (Phillips et al., 1997) and negative emotions (Reiman et al., 1997; Mayberg et al., 1999), the latter study emphasizing the reciprocal roles of the lateral and orbito-medial prefrontal cortex and insula, amongst other regions, in changes in depressed mood. For example, increases in regional cerebral blood flow (rCBF) in the insula and subgenual cingulate gyrus were associated with decreases in rCBF in the right prefrontal cortex [Brodmann area (BA) 47] during induction of sadness in healthy volunteers. Inhibition of limbic centers by the prefrontal cortex (and vice versa) has been inferred from the pattern of rCBF correlations in several human functional neuroimaging studies (Davidson and Sutton, 1995; Drevets and Raichle, 1998). Such studies have paved the way for a neurobiological understanding of a range of mood and anxiety disorders, and have been incorporated into a model (Sierra and Berrios, 1998) for the reduced emotionality in depersonalization.

To date, there have been two functional neuroimaging studies in depersonalization. One was a resting state single photon emission computed tomography (SPECT) case study showing left fronto-temporal activation (Hollander et al., 1992). The authors interpreted this as evidence for a common neurobiological basis for depersonalization and OCD, in which increased frontal activation has been associated with the urge to ritualize (Breiter et al., 1996). The second study employed positron emission tomography (PET) to measure metabolism during performance of a verbal learning task, and demonstrated reduced activity in superior and middle temporal gyri in depersonalized patients compared with healthy volunteers (Simeon et al., 2000). The authors suggested that these findings indicated underlying functional abnormalities in brain regions important for an intact body schema in depersonalization disorder. No study has employed functional magnetic resonance imaging (fMRI), or examined neural responses to emotionally salient stimuli in patients with depersonalization disorder.

In the current study we employed fMRI to demonstrate the neural response to standardized emotionally salient stimuli (aversive scenes), used previously in neuroimaging studies (Lane et al., 1997; Lang et al., 1998) in six depersonalized patients, in contrast to that in healthy volunteers and patients with OCD. We recruited the latter as a separate group of psychiatric patients in whom, as for patients with depersonalization, the experience of anxiety and depression occurs frequently but, unlike in patients with depersonalization, the detachment from their own emotional experiences and emotional blunting is uncommon. We sought to distinguish between the neurobiological basis of depersonalization and OCD,

predicting that, compared with *both* healthy volunteers *and* patients with OCD, depersonalized patients would: (a) rate aversive scenes depicting particularly disgusting material as less emotional; (b) fail to demonstrate the expected increased activation in general visual (occipito-temporal cortex) (Lane et al., 1997; Lang et al., 1998) and emotion-specific regions important for the perception of disgust, particularly the insula (Lane et al., 1997; Phillips et al., 1997; Reiman et al., 1997; Mayberg et al., 1999), in response to such scenes; (c) demonstrate increased activation in regions implicated in the inhibition of the emotional response (lateral prefrontal cortex) (Davidson and Sutton, 1995; Drevets and Raichle, 1998; Mayberg et al., 1999).

2. Methods

2.1. Subjects

Six right-handed patients with depersonalization disorder (American Psychiatric Association, 1994) (5 males) were recruited from the inpatient and outpatient departments of the Maudsley Hospital. Depersonalization was defined as a score >2 on the Present State Examination (PSE) (Wing et al., 1974) criteria for depersonalization–derealization (maximum score = 4), and a score on the depersonalization taxon of the Dissociative Experiences Scale (DES) (Bernstein-Carlson and Putnam, 1986) of 13 or more (Simeon et al., 1998). All patients experienced depersonalization as their primary and most distressing syndrome and, because of the chronic nature of their illness, were experiencing depersonalization at the time of scanning. Six right-handed healthy volunteers (4 males) were recruited from hospital staff, and were screened by psychiatric examination to ensure that they neither had a history nor current experience of psychiatric illness, and were not taking any psychotropic (or other) medication. Ten outpatients with obsessive–compulsive disorder (OCD), but without a history or current experience of depersonalization (8 males), were included as psychiatric control subjects.

Table 1
Subject details: demographics and psychopathology ratings

Variable	Normal controls ($n = 6$)	OCD patients ($n = 10$)	Depersonalized patients (DP) ($n = 6$)
Age (years)	33.8 (24–48)	30.9 (24–42)	28.3 (22–34)
Male:female	4:2	8:2	5:1
Years of education	19.2 (15–20)*	14.5 (10–18)	15.2 (10–20)
Duration of illness	–	15.7 (9–35)	11 (9–17)
Present State Examination (0–4)	–	0	3 (2–4)
Dissociative Experiences Scale[a]	–	19.4 (2.5–68.1)	31 (6.4–80.4)
DES–taxon[b]	–	8.8 (0–38.8)	33.3 (13.0–74.3)**
Spielberger Anxiety Scale:			
State	–	42.0 (30–61)	47.2 (36–59)
Trait	–	52.9 (42–75)	53.0 (41–64)
Beck Depression Inventory (S.D.)[c]	–	14.12 (15.14)	23.5 (12.96)
YBOCS (0–40)[d]	–	27.1 (18–37)	–

Figures are means; numbers in parentheses refer to the range.
[a] Dissociative Experiences Scale (DES): (cutoff for dissociative disorder ≥ 30).
[b] Depersonalization taxon of DES score (depersonalization disorder ≥ 13).
[c] Beck Depression Inventory (BDI): mild depression ≥ 10.
[d] YBOCS: Yale–Brown Obsessive–Compulsive Scale score (moderate OCD score ≥ 16).
*ANOVA ($P = 0.05$).
**Independent t-test: $P < 0.05$.

Ratings on the Spielberger State and Trait Anxiety Scales (Spielberger, 1983), and the Beck Depression Inventory (BDI; Beck et al., 1961) were obtained for both patient groups (see Table 1). Four of the depersonalized patients were taking medication: three patients were taking antidepressants (citalopram, fluoxetine and meclobemide). Two were being treated experimentally by their psychiatrists with clozapine (despite not having true schizophrenia symptoms). Eight OCD patients were taking antidepressant medication (fluoxetine, sertraline or clomipramine). Exclusion criteria included a history of head injury, significant alcohol or drug abuse and, by definition, a primary neurological or psychiatric disorder.

The groups did not differ significantly in age ($F_{2,19} = 1.0$; $P = 0.39$), although the normal control subjects were non-significantly older than the two patient groups. The normal volunteers were more educated than the patients ($F_{2,19} = 3.4$; $P = 0.05$). The range of years of education in each subject group indicated a relatively high level of education and a similar psychosocial profile of subjects within each group, however. The two patient groups did not differ on years of education ($t = 0.09$; d.f. = 14; $P = 0.93$), duration of illness ($t = 1.65$; d.f. = 14; $P = 0.12$), or Spielberger State ($t = 0.53$; d.f. = 14; $P = 0.60$) or Trait ($t = 0.14$; d.f. = 14; $P = 0.89$) anxiety scales. The depersonalized patients were slightly more depressed than the OCD patients (higher scores on the BDI), although this difference was not significant ($t = 1.5$; d.f. = 14; $P = 0.15$). The two patient groups did not differ in their DES scores overall ($t = 0.86$; d.f. = 11; $P = 0.41$), but differed significantly in scores on the DES taxon for depersonalization ($t = 3.14$; d.f. = 14; $P = 0.007$). This score reflected the severity of depersonalization experienced by the depersonalized and OCD patients during scanning. After complete description of the study to the subjects, written informed consent was obtained.

2.2. Stimuli

Thirty-five color pictures of aversive scenes (e.g. cockroaches, wounds) and 39 neutral scenes (pastoral scenes, household objects) were chosen from a standard set (Lang et al., 1997). Each picture was rated by a separate group of normal volunteers for visual complexity on a four-point scale (1 = low complexity; 4 = very high complexity). Twenty aversive and 20 neutral matched pictures were selected (mean complexity: 2.45 vs. 2.50, respectively; no significant difference).

2.3. Procedure

Pictures were presented on a screen 3.5 m away from subjects lying in the scanner, in alternating 30-s blocks in a 5-min fMRI experiment. Each block contained 10 pictures (either all aversive and, in particular, disgusting or all neutral scenes), each presented for 2 s, with a 1-s interstimulus interval (ISI). These stimuli have been employed in a previous study examining neural responses to different types of disgusting scenes in normal and psychiatric populations (Phillips et al., 2000). Thus, five blocks of each type of picture were presented over 5 min. Subjects decided whether the picture depicted an outdoor or indoor scene and pressed one of two buttons accordingly with the right thumb. These are implicit tasks with regard to emotional processing: subjects attend to the stimuli throughout without being made aware of the nature of the study so that cerebral regions underlying the perception of emotions but not labeling are activated. The order of individual stimuli within each block, and the starting order of the blocks within each experiment (aversive or neutral scene first) were counterbalanced across subjects.

2.4. Rating of scenes

Previous studies have demonstrated that neural responses to emotional stimuli are dependent upon the nature of the task performed during viewing of the stimuli, and that performance of explicit emotion-labeling tasks is associated with reduced limbic and increased prefrontal activation (e.g. Critchley et al., 2000; Hariri et al., 2000). We did not wish subjects to become aware that the aim of the study was to examine neural responses during the experience of emotion, and

thus did not request subjects to label their emotional experiences by rating the intensity with which they experienced emotion at any time during participation in the experiments inside the scanner. Instead, all subjects were re-presented with the scenes outside the scanner after scanning. Subjects rated each scene according to the intensity with which they then experienced disgust, fear and anxiety when viewing the scene. Subjects were requested to rate on a nine-point intensity scale (0–nil; 8–extreme) adjectives describing disgust (e.g. 'nauseous'), fear (e.g. 'afraid'), and general anxiety (e.g. 'worried'). Total scores for all aversive and all neutral scenes on each dimension (disgust, fear and anxiety) were calculated for each subject (maximum = 480), and an aversive–neutral difference was derived.

2.5. Image acquisition and analysis

Gradient echo echoplanar imaging (EPI) data were acquired on a GE Signa 1.5-T system (General Electric, Milwaukee, WI, USA) retrofitted with Advanced NMR hardware (ANMR, Woburn, MA, USA) at the Maudsley Hospital, London. A quadrature birdcage headcoil was used for RF transmission and reception. A total of 100 T_2^*-weighted images depicting BOLD contrast (Kwong et al., 1992) were acquired over 5 min (for each task) at each of 14 near-axial non-contiguous 5-mm-thick planes parallel to the intercommissural (AC–PC) line: TE, 40 ms; TR, 3 s; in-plane resolution, 5 mm; interslice gap, 0.5 mm. This EPI dataset provided complete coverage of the temporal lobes (including hippocampus and amygdala) and almost complete coverage of frontal, occipital and parietal lobes. In the same scanning session an inversion recovery EPI dataset was acquired at 43 near-axial 3-mm-thick planes parallel to the AC–PC line: TE, 80 ms; TI, 180 ms; TR, 16 s; in-plane resolution, 1.5 mm; interslice gap, 0.3 mm; number of signal averages = 8. This higher resolution EPI dataset provided whole brain coverage and was later used to register the fMRI datasets acquired from each individual in standard stereotactic space.

Following motion correction (Bullmore et al., 1999a), periodic change in T_2^*-weighted signal intensity at the (fundamental) experimentally determined frequency of alternation between A and B conditions ($= 1/60$ Hz) was estimated by an iterated least squares fit of a sinusoidal regression model to the fMRI time series observed at each voxel, modeling residual autocorrelation as a first-order autoregressive process (Bullmore et al., 1996). This model included sine and cosine waves at the fundamental AB frequency of the experimental input function, parameterized by coefficients $\{\gamma, \delta\}$. The power of periodic response to the input function was estimated by $(\gamma^2 + \delta^2)$; and fundamental power divided by its standard error yielded a standardized test statistic, the fundamental power quotient (FPQ), at each voxel. Parametric maps representing FPQ observed at each intracerebral voxel were constructed. In order to sample the distribution of FPQ under the null hypothesis that observed values of FPQ were not determined by experimental design (with few assumptions), the 99 images observed in each anatomical plane were randomly permuted and FPQ was estimated exactly as above in each permuted time series. This process was repeated 10 times, resulting in 10 permuted parametric maps of FPQ at each plane for each subject.

Observed and randomized FPQ maps were transformed into the standard space of Talairach and Tournoux (1988) and smoothed by a two-dimensional Gaussian filter with full width half maximum = 11 mm. This filter size was chosen to accommodate regional differences in brain anatomy between subjects (Clark et al., 1996), and has been employed in previous studies examining neural responses to emotional stimuli (e.g. Phillips et al., 1997, 1999). The median observed FPQ at each intracerebral voxel in standard space was tested against a critical value of the permutation distribution for median FPQ ascertained from the permuted FPQ maps (Brammer et al., 1997).

2.6. Between-group comparisons

To estimate between-group differences in mean power of functional activation, we fitted an analy-

sis of covariance model at each intracerebral voxel of the standardized power maps after their co-registration in standard (Talairach) space. For the comparison between comparison subjects and patients with depersonalization disorder, this model included only age as a covariate; for the comparison between comparison subjects and patients with OCD, the model included only total FPQ as a covariate.

We used a non-parametric mode of inference on spatially informed test statistics to identify brain regions that showed a significant difference in mean power of response between diagnostic groups; for full details of this method and its validation, see Bullmore et al. (1999b). Briefly, fitting an ANCOVA model at each intracerebral voxel generated a map of the estimated coefficient of the factor coding group membership; this coefficient, divided by its standard error, was our standardized voxel test statistic b. Equivalent analysis after repeated randomization of the vector coding group generated a distribution under the null hypothesis of no between-group difference. The critical value at $\text{Prob}(b) = 0.05$ ($\text{CV}_{0.05}$) was calculated and the voxel test statistic map was thresholded such that if $|b| > \text{CV}_{0.05}$, the value was set to $b - \text{CV}_{0.05}$; otherwise it was set to zero. This procedure generated a set of suprathreshold voxel clusters in three dimensions, each of which can be described in terms of its mass or the sum of suprathreshold voxel statistics it comprises. The mass of each cluster was tested against a null distribution ascertained by similar thresholding of the voxel test statistic after randomization. The rationale for this non-parametric mode of inference is that test statistics for image analysis which incorporate spatial information, such as three-dimensional cluster mass, are generally more powerful than other possible test statistics, such as b, which are informed only by data at a single voxel.

Besides greater sensitivity to between-group differences in brain function that are located over a spatial neighborhood of voxels, another advantage of cluster-level inference compared with voxel-level testing is that it substantially mitigates the multiple comparisons problem. The search volume or number of clusters to be tested is typically 1–2 orders of magnitude less than the

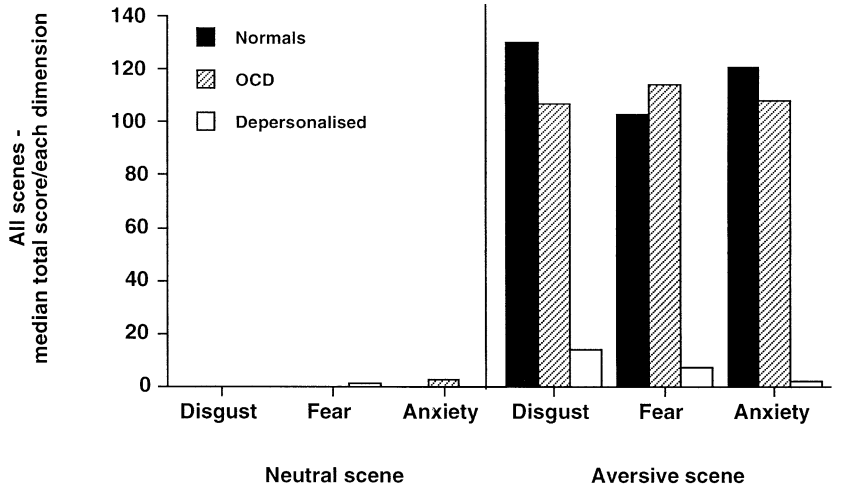

Fig. 1. The median total scores for the neutral and aversive scenes are shown on the disgust, fear and anxiety dimensions for each subject group. The ranges of scores for the normal control subjects for the neutral scenes on each dimension were: 0–2 (disgust), 0–2 (fear), and 0–6 (anxiety), and for the aversive scenes, 52–251 (disgust), 31–286 (fear), and 31–310 (anxiety). The ranges of scores for the OCD patients for the neutral scenes were: 0–5 (disgust), 0–43 (fear), and 0–28 (anxiety), and for the aversive scenes, 7–410 (disgust), 7–421 (fear), and 20–416 (anxiety). The ranges of scores for the depersonalized patients for the neutral scenes were 0–21 (disgust), 0–126 (fear), and 0–100 (anxiety), and for the aversive scenes, 0–223 (disgust), 0–261 (fear), and 0–250 (anxiety).

number of voxels, meaning that satisfactory type 1 error control can be obtained without an unacceptably severe risk of type 2 error. For example, here we have consistently applied a cluster-wise probability threshold $P < 0.005$. At this size of test, and over a search volume V of 200 clusters

Table 2
Normal control subjects, patients with OCD, and patients with depersonalization: generically activated brain regions to aversive vs. neutral scenes

Region (approx. Brodmann area)	Side	x[a]	y[a]	z[a]	No. of voxels	Significance[b]	Conditions of signal increase[c]
(a) Normal controls							
Lingual gyrus (18)	R	23	−75	−7	33	0.00004	
Middle occipital	R	40	−72	9	4	0.001	
gyrus (18/19)	L	−38	−78	4	22	0.00002	
Inferior occipital gyrus (18)	L	−26	81	−2	18	0.0001	
Inferior temporal gyrus (19)	R	43	−69	−2	14	0.000008	
Fusiform gyrus (18)	R	26	−75	−13	7	0.0001	
Superior temporal	L	−46	11	−7	6	0.0001	
gyrus (38/22)		−46	6	−2	4	0.002	
Cerebellum	L	−32	−67	−13	5	0.0008	
Middle temporal gyrus (37)	R	46	−64	9	5	0.002	
Insula	R	38	−17	15	3	0.001	
(b) Patients with OCD							
Middle occipital	R	40	−56	−7	64	0.000006	
gyrus (19)		43	−67	−2	62	0.000006	
		14	−44	−2	39	0.000006	
		6	−81	4	17	0.0002	
	L	−40	−72	−2	61	0.000006	
		−23	−64	−7	40	0.000006	
		−12	−56	4	14	0.000006	
Middle temporal	R	46	−61	4	63	0.000006	
gyrus (21/37/39)		46	−53	9	26	0.0001	
	L	−26	−69	26	38	0.000006	
		−49	−53	9	24	0.000002	
Primary visual cortex (17)	R	3	−81	9	40	0.000006	
Posterior cingulate	R	12	−44	26	32	0.000006	
gyrus (23/29/31)	L	−17	−61	15	24	0.0002	
Parahippocampal gyrus	R	20	−47	4	32	0.000006	
Superior temporal	R	61	−25	4	29	0.000006	
gyrus (22/39)		40	−56	20	20	0.000006	
Middle prefrontal cortex (44)	R	43	8	26	14	0.0005	
Precuneus (7)	R	14	−36	48	11	0.00004	
	L	−26	−50	48	9	0.00007	
Fusiform gyrus (18)	L	−23	−81	−13	10	0.000006	
Thalamus	R	3	−31	4	10	0.00002	
Insula	L	−43	0	9	5	0.0005	

Table 2 (*Continued*)

Region (approx. Brodmann area)	Side	x[a]	y[a]	z[a]	No. of voxels	Significance[b]	Conditions of signal increase[c]
(c) Patients with depersonalization							
Ventral prefrontal cortex (47)	R	35	25	−7	6	0.0002	A
Middle temporal gyrus (37)	R	46	−61	9	5	0.0003	A
Lingual gyrus	L	−12	−67	−2	4	0.001	A
(18/19)	R	20	−47	−2	4	0.002	A
Ventral prefrontal cortex (47)	L	−40	33	−2	20	0.000008	N
Superior temporal gyrus(38)	R	26	8	−13	9	0.0001	N
Middle temporal gyrus (21)	L	−49	−33	−2	7	0.0004	N
Putamen	R	26	8	4	6	0.0001	N
Insula	L	−40	3	−2	3	0.002	N

[a] The cluster with the largest number of voxels within each region is reported. Talairach co-ordinates refer to the voxel with the maximum FPQ (fundamental power quotient) in each cluster.

[b] All such voxels were identified by a one-tailed test of the null hypothesis that median FPQ is not determined by experimental design. The probability threshold for activation was $P \leq 0.004$. No regions were more active in the neutral vs. aversive scenes in either the normal control subjects or the OCD patients.

[c] A, aversive; N, neutral.

or less, the expected number of false-positive tests under the null hypothesis PV is less than one for each ANOVA map reported.

3. Results

All subjects were able to identify scenes accurately as either outdoor or indoor (> 95%).

3.1. Ratings of scenes

In view of the relatively small numbers of subjects within each group, we employed non-parametric statistical analyses to compare the ratings for the intensity of emotion experienced when viewing the scenes across the three subject groups. The median values and ranges of the ratings by each subject group for all aversive and all neutral scenes on each of the three dimensions are shown

Fig. 2. Generic brain activation (GBAM) in the normal control subjects ($n = 6$), OCD patients ($n = 10$), and depersonalized patients (DP) ($n = 6$) in response to aversive (red voxels) and neutral scenes (yellow voxels). The left side of the brain is shown on the right side of the image, and vice versa. The probability threshold for activation was $P \leq 0.004$. Five transverse brain slices are shown at 7 and 1.5 mm below (left side), 4 mm (middle), and 9.5 and 15 mm above (right side) the transcallosal plane. The positions of the planes 1.5 mm below and 15 mm above the transcallosal plane are shown in the inset. In the normal control subjects, major regions of activation in response to the aversive scenes are shown in the right insula (I); regions important for visual processing: right lingual, bilateral middle and left inferior occipital gyri (BA 18); and right inferior (BA 19), right middle (BA 37), and left superior (22/38) temporal gyri, and bilateral anterior cingulate gyri (BA 24). In the OCD patients, major regions of activation in response to the aversive scenes are shown in the left insula (I); bilateral visual regions: bilateral middle occipital gyri (BA 19) and left primary visual cortex (BA 17); right superior temporal gyrus (22); and right inferior frontal cortex (BA 44). Neither group demonstrated major activation in response to the neutral scenes. In the depersonalized patients, major regions of activation are shown primarily in response to the neutral scenes in the left insula (I), left inferior frontal gyrus (BA 47), and right putamen (P), and in response to the aversive scenes in the right inferior frontal gyrus (BA 47) and right middle temporal gyrus (BA 37).

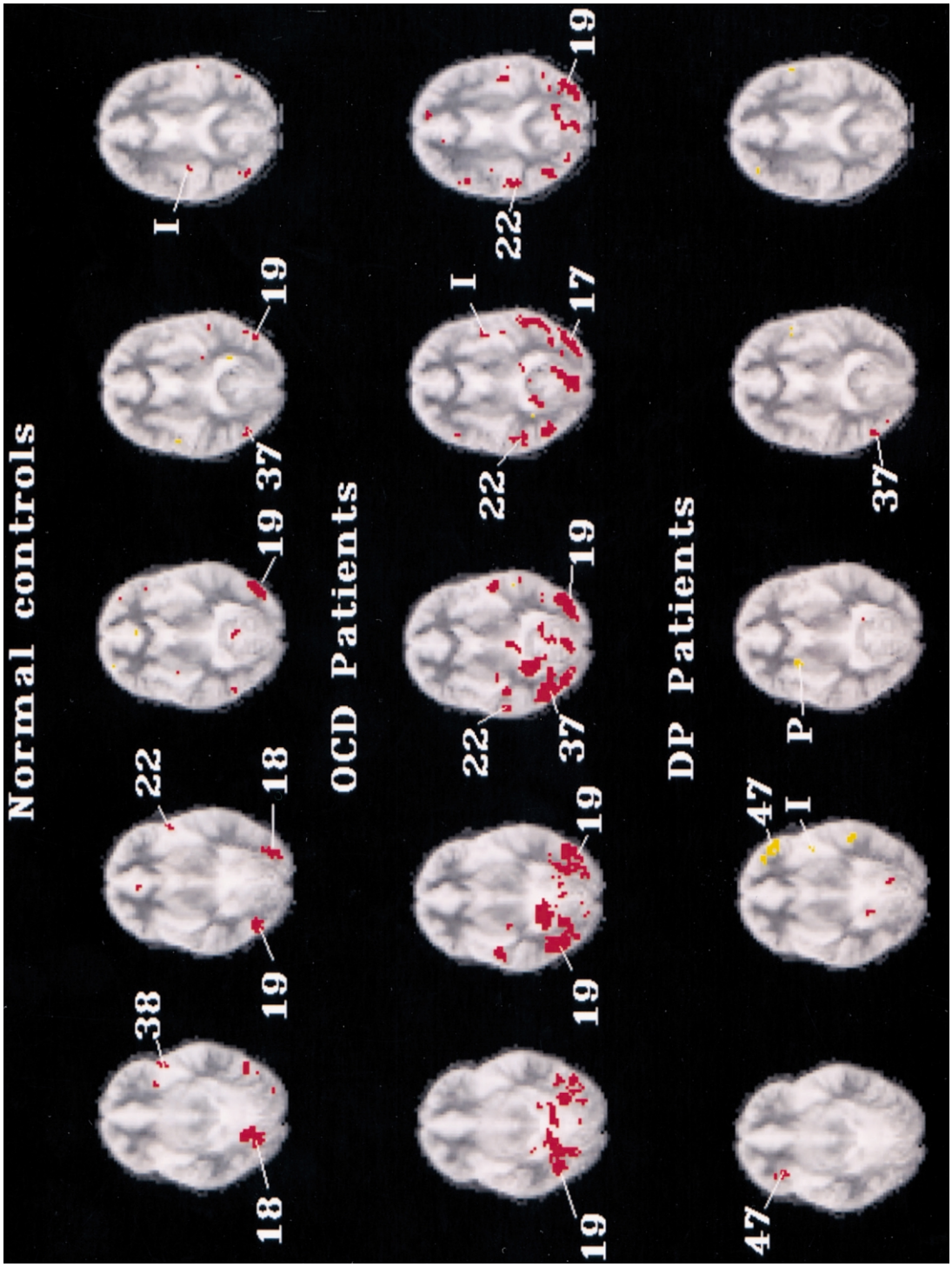
Normal controls
OCD Patients
DP Patients
38
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Fig. 2.

in Fig. 1. Normal subjects and OCD patients rated aversive scenes with significantly higher values on each dimension compared with the neutral scenes: Wilcoxon signed ranks tests for normal subjects: $z = 2.20$, $P = 0.03$ (disgust rating); $z = 2.20$, $P = 0.03$ (anxiety rating); $z = 3.46$, $P = 0.03$ (fear rating); Wilcoxon signed ranks tests for OCD patients; $z = 2.80$, $P = 0.005$ (disgust rating); $z = 2.80$, $P = 0.005$ (anxiety rating); $z = 2.50$, $P = 0.01$ (fear rating). The depersonalized patients did not rate the aversive scenes significantly differently from neutral scenes.

3.2. Generic brain activation maps

Motion: A value representing the mean of six separate head motion measurements at the frequency of the experimental input function (the extent of rotation and translation in the x, y and z planes) was calculated for each subject during the scanning procedure. There was no significant difference in the extent of stimulus-correlated head motion during the experimental procedure amongst the three subject groups ($F_{2,19} = 1.44$; $P = 0.26$).

3.3. Activation in response to aversive and neutral scenes

In both the healthy volunteers and the OCD patients, the aversive scenes activated the insula and occipito-temporal (visual) cortex (Table 2a,b; Fig. 2). The aversive scenes did not activate the insula in the depersonalized patients (Table 2c). In response to these scenes, both the depersonalized and OCD patients but not the healthy volunteers demonstrated activation in right prefrontal cortex. In the OCD patients, the activation was within the middle prefrontal cortex (BA 44), whilst in the depersonalized patients, this activation was within a more ventral region of the frontal cortex (BA 47). Healthy volunteers and the OCD patients demonstrated a greater neural response overall (i.e. more activated voxels) to aversive compared with neutral scenes; the depersonalized patients, however, had an apparently greater neural response (more activated voxels) to the neutral scenes, including activation in the left insula.

3.4. Differences between groups in neural response to aversive and neutral scenes

Globally, there was a significant difference amongst the three groups in the total extent and strength of activation (total FPQ) in response to the aversive and neutral scenes ($F_{2,21} = 17.52$; $P < 0.0001$). This was due to the significantly greater total FPQ of the neural response of the OCD patients compared with either the normal control subjects ($t = -5.09$; d.f. = 10.7; $P < 0.0001$) or patients with depersonalization ($t = -4.48$; d.f. = 14; $P = 0.001$). There was no significant difference in total FPQ between the normal control subjects and patients with depersonalization.

3.4.1. Normal control subjects and patients with depersonalization

Comparison of neural responses in normal control subjects and patients with depersonalization, covarying for the effect of mismatching of age and years of education, revealed three three-dimensional clusters activated to a significantly greater extent in the normal control subjects in response to the aversive scenes ($P = 0.01$; number of false-positive activated three-dimensional clusters = 1). These clusters of activation were demonstrated predominantly in left insula, bilateral cingulate gyrus (BA 24/32) and regions involved in visual processing: left inferior occipital (BA 18), lingual (BA 19) and superior temporal gyri (BA 22/42), and left inferior parietal lobule (BA 40) (Table 3a).

3.4.2. Patients with depersonalization and OCD

Comparison of neural responses to the aversive and neutral scenes in patients with depersonalization and OCD, covarying for the total FPQ, revealed three three-dimensional clusters activated to a significantly different extent between the two groups ($P = 0.01$; number of false-positive activated three-dimensional clusters = 0). In the patients with OCD compared with the depersonalized patients, in response to the aversive scenes there was significantly greater activation in slices in two three-dimensional clusters predominantly within the right superior temporal gyrus (BA

Table 3
Significant differences in activation between normal control subjects vs. depersonalized patients: covarying for age and years of education, and between OCD vs. depersonalized patients: covarying for total FPQ

Region (approx. Brodmann area)	Side	x^a	y^a	z^a	No. of voxels
(a) Normal controls vs. depersonalized patients					
Inferior parietal lobule (40)	L	−53	−27	32	103
Superior temporal gyrus (42)	L	−48	−32	20	92
Insula	L	−35	12	8	86
Lingual gyrus (19)	L	−25	−63	1	81
Posterior cingulate gyrus (23)	L	−1	−31	32	72
Inferior occipital gyrus (18)	L	−31	−76	−4	62
Inferior parietal lobule (40)	L	−51	−38	24	39
Anterior cingulate gyrus (24/32)	R	1	36	16	38
	L	−3	44	−1	27
(b) OCD vs. depersonalized patients					
Superior temporal gyrus (22)	R	31	−24	16	135
	L	−39	−21	16	63
Inferior parietal lobule (40)	L	−38	−29	28	81
Middle temporal gyrus (37)	R	49	−60	12	22
Insula	R	36	−22	4	22
Putamen	R	18	12	8	20

In the table are the results of cluster-level inference, with a search volume less than 200 clusters, the probability threshold for the comparison between groups, $P < 0.005$, and the expected number of false positive activated clusters < 1.

[a] The cluster with the largest number of voxels within each region is reported. Talairach co-ordinates refer to the voxel with the maximum FPQ (fundamental power quotient) in each cluster. All regions were activated significantly more in the healthy volunteers. Regional activation significantly greater in the OCD groups is shown.

22/42), middle temporal gyrus (BA 37/39), and insula, and in the left inferior parietal lobe (BA 40) (Table 3b). In the patients with depersonalization compared with those with OCD, in response to the aversive scenes there was significantly greater activation in a cluster within bilateral posterior visual association cortical regions only.

3.4.3. Normal control subjects and patients with OCD

No regions were activated to a significantly greater extent in either the normal control subjects or patients with OCD covarying for total FPQ and the effect of age (with $P \leq 0.01$).

3.5. Examination of the functional relationship between the insula and the right prefrontal cortex

Our findings demonstrated left insular activation in response to neutral scenes and right ventral prefrontal cortical activation to aversive scenes, suggesting an inverse functional relationship between these two regions in the depersonalized patients. We therefore wished to examine further the nature of the functional relationship between these two regions in the depersonalized patients. We also wished to examine the nature of the functional relationships between insular and right prefrontal cortical responses in normal con-

trol subjects and OCD patients. We used, as a measure of the power of response in all subjects in each of the three groups, the peak FPQ in index voxels defining the following regions of generic activation: in the depersonalized patients, the left insula ($x = -40$, $y = 3$, $z = -2$) and right ventral prefrontal cortex ($x = 35$, $y = 25$, $z = -7$); in the OCD patients, the left insula ($x = -43$, $y = 0$, $z = 9$) and right middle prefrontal cortex ($x = 43$, $y = 8$, $z = 26$); and in the normal control subjects, the right insula ($x = 38$, $y = -17$, $z = 15$). The right prefrontal cortex was not activated significantly to aversive scenes within the normal control subjects. In the examination of the nature of the functional relationship between right prefrontal cortex and insula within the normal control subjects, we therefore used the peak FPQ in index voxels defining regions of the right prefrontal cortex that were activated to aversive scenes in the depersonalized and OCD patients, the right ventral prefrontal cortex and right middle frontal cortex, respectively.

The power of response was averaged over each index voxel and its eight nearest neighbors in two dimensions (total cortical volume = 0.57 cm^3 for each region). In view of the relatively small numbers of subjects within each of the three subject groups, we used non-parametric correlation analyses to determine the nature of the functional relationships between the insula and right prefrontal cortex in each group. Spearman's rank correlation coefficients were therefore determined for the FPQs within insular and right prefrontal cortical regions in each subject group. These analyses revealed a strong positive correlation, which just missed significance at $P = 0.05$, between FPQs within the left insula to neutral scenes and right ventral prefrontal cortex to aversive scenes in the depersonalized patients (Spearman's rank correlation coefficient = 0.8; $P = 0.07$). There were small positive and non-significant correlations between FPQs within the right insula and right ventral prefrontal cortex in the normal control subjects (Spearman's rank correlation coefficient = 0.26; $P > 0.1$), and between the left insula and right middle prefrontal cortex in the OCD patients (Spearman's rank correlation coefficient = 0.38; $P > 0.1$). There was also a small negative and non-significant correlation between the right insula and right middle prefrontal cortex in the normal control subjects (Spearman's rank correlation coefficient = -0.3; $P > 0.1$).

4. Discussion

We employed fMRI to investigate the neural response in depersonalized patients to aversive and neutral scenes. As predicted, depersonalized patients rated the aversive, disgusting scenes as less emotive than control subjects and, in response to these stimuli, showed reduced activation in structures implicated in the perception of disgust. The patients clearly attended to the stimuli since their ratings of location were nearly perfect. Many depersonalized patients said that they saw and understood the content of the pictures but did not experience an emotional response.

Healthy volunteers and OCD patients, but not the depersonalized patients, activated the insula in response to the aversive scenes, and statistical contrasts between the depersonalized patients and the other groups were significant. This brain region has been implicated previously in the neural response to disgust (Phillips et al., 1997), other negative moods (Reiman et al., 1997; Mayberg et al., 1999) and unpleasant visceral sensations such as pain (Ploghaus et al., 1999). Paradoxically, this area was activated in the depersonalized patients, and to a significantly greater extent compared with normal control subjects, when they were shown *neutral* scenes. Regions important for visual object and spatial perception (middle and superior temporal gyri, and the inferior parietal lobe) were also activated to a significantly greater extent in normal control subjects and OCD patients compared with depersonalized patients when they viewed the aversive scenes. These findings are similar to those of a previous study, in which depersonalized patients demonstrated reduced metabolism within middle and superior temporal gyri during performance of a variant of the California Verbal Learning Test (Simeon et al., 2000). Activation of occipito-temporal cortex has been demonstrated in the response to expres-

sions of fear and disgust (Morris et al., 1996; Phillips et al., 1997), and to the same unpleasant scenes we used (Lane et al., 1997; Lang et al., 1998). The increased activation in these regions in both normal control subjects and OCD patients, in particular, middle and superior temporal gyri, may reflect the heightened visual attention and processing induced by aversive stimuli in these subjects but not the depersonalized patients. The normal control subjects also demonstrated significantly greater activation in bilateral anterior cingulate gyri and the left posterior cingulate gyrus in response to the aversive scenes compared with the depersonalized patients. These areas have been previously associated with the experience of negative mood (Mayberg et al., 1999) and emotional appraisal (Maddock, 1999), respectively.

The OCD patients activated more brain regions overall than either the healthy volunteers or the depersonalized patients. This might be thought to be due to increased visual scanning of the stimuli by patients with OCD compared with the other two groups, in view of the increase in checking behavior noted in such patients. A recent study has demonstrated, however, that patients with anxiety disorders, in whom hypervigilance has been postulated (Eysenck, 1992), have similar viewing strategies to those of normal volunteers when regarding different types of pleasant and unpleasant scenes (Freeman et al., 2000). Furthermore, activity in the frontal eye fields was not detected in any of the subjects. It is also difficult to explain the observed finding of an inverse functional relationship between right ventral prefrontal cortex and left insula in the depersonalized patients in terms of abnormal visual scanning.

Both patient groups but not normal control subjects demonstrated significant activation in the right prefrontal cortex in response to the aversive scenes. This activation was within a region of the ventral prefrontal cortex (BA 47) in the depersonalized patients and within the middle prefrontal cortex (BA 44) in the OCD patients. Only in the depersonalized patients, however, did activation within the right ventral prefrontal cortex occur in the *absence* of activation within the insula in response to the aversive scenes. Furthermore, a measure of the maximal regional power of response, the peak FPQ, within the left insula during presentation of the *neutral* scenes was strongly positively correlated with the peak FPQ within the right ventral frontal cortex during presentation of the *aversive* scenes in all depersonalized patients but not the OCD patients or normal control subjects. This therefore indicates an inverse correlation between BOLD signal changes within the left insula and right ventral prefrontal cortex during presentation of the aversive scenes, and an inverse functional relationship between these two neural regions during presentation of emotionally salient stimuli in the depersonalized patients.

Frontal regions are richly interconnected in primates with 'limbic' structures (Shi and Cassell, 1998; Cipolloni and Pandya, 1999), and the prefrontal cortex has been implicated in the regulation of fear extinction in rats (Morgan et al., 1993). Earlier studies have demonstrated prefrontal activation in subjects with repressive–defensive coping styles (Tomarken and Davidson, 1994), and an inverse relationship between the insula and right dorsolateral prefrontal cortex activation has been demonstrated during induction of sadness in healthy volunteers (Mayberg et al., 1999). Drug-induced depersonalization seems to produce analogous effects, namely increased inferior frontal and reduced sub-cortical blood flow (Mathew et al., 1999). In more recent studies, activation within the right middle and dorsolateral prefrontal cortices (BA 44 and 45) has been reported during the performance of explicit, emotion-labeling tasks (Nakamura et al., 1999; Hariri et al., 2000), and activation within right BA 47, during the performance of emotional facial expression delayed matching-to-sample tasks (Narumoto et al., 1999). These findings suggest that the right prefrontal cortex, including the right ventral prefrontal cortex, may have a role in the appraisal of emotional stimuli and regulation of emotional experience. The inverse functional relationship between the left insula and right ventral frontal cortex during presentation of the aversive scenes demonstrated by the depersonalized patients, but not by the normal control subjects or the OCD patients, may therefore reflect a

greater regulation or 'inhibition' by the right ventral frontal cortex of the normal insular response to emotional stimuli in the depersonalized patients.

It is possible that the depersonalized patients were able to attend to the emotional content of the stimuli more explicitly and overtly than the normal control subjects and OCD patients, and thereby inhibit their emotional response to the stimuli during the scanning procedure. It is, however, difficult to distinguish between this possibility and the alternative interpretation of the findings described above, in which it is suggested that the reduced insular response to the aversive stimuli is associated with and may result in the emotional blunting of depersonalized patients, instead of occurring as a result of the performance of explicit rather than implicit emotional tasks by these patients. Additionally, the depersonalized patients were able to perform the implicit task as accurately as the other subjects, and thereby demonstrated an ability to attend to the non-emotional components of the stimuli.

Differences in medication between the depersonalized and the OCD patients may have contributed to the above findings. Patients in both groups were taking antidepressant medication, and two depersonalized patients were treated with clozapine for intractable depersonalization symptoms (two were not taking any medication). In a previous study, we reported that medicated schizophrenic patients, although impaired compared with healthy volunteers on recognition of emotive visual stimuli, did not demonstrate such a marked reduction in neural response as shown in the depersonalized patients described here, and did not demonstrate activation in response to *neutral* stimuli (Phillips et al., 1999). It is therefore unlikely that the pattern of behavioral and neural responses demonstrated in the depersonalized patients was the effect primarily of neuroleptic medication and/or other psychiatric symptoms.

Differences in the number of years of education, age and gender amongst the three groups are unlikely explanations for all the differences in activation between the patients with depersonalization and the two control groups. A significant difference in years of education was found only between the normal control subjects and each of the patient groups, and not between the two patient groups. Despite this, there were significant differences in patterns of generic activation between the two patient groups, as described above. Furthermore, the range of years of education within each group indicated a relatively high level of education in all participating subjects. Although there were proportionally more males in the depersonalized and OCD patient groups than the normal control subjects, all three groups comprised mainly male subjects: 67% in the normal control subjects, 80% in the OCD patients, and 83% in the depersonalized patients. Although it is possible that this difference in the proportion of males in the patient groups compared with the normal control subjects accounted for some of the differences in generic activation to aversive scenes across the three groups, the similar proportion of males within the two psychiatric populations renders it unlikely that gender differences were responsible for the significant difference in generic activation to aversive scenes between the two patient groups.

It could be argued that structural brain abnormalities in the depersonalized patients may have contributed to the reduced activation in regions normally activated by emotionally salient stimuli observed in depersonalized patients. Again, this is an unlikely explanation for all the results of the voxel-wise functional analyses, since activation in specific regions in the depersonalized patients ranged from reduced to increased depending on the stimulus condition (neutral or aversive). In addition, there were similar significant differences in activation between patients with OCD, in whom structural brain abnormalities have been demonstrated (Jenike et al., 1996) and those with depersonalization. Furthermore, an experienced neuroradiologist reviewed all structural scans and none were deemed abnormal. Nevertheless, subtle quantitative differences may not be excluded by this method. Detailed neuroanatomical studies of depersonalization disorder are awaited with interest.

Depersonalization disorder is a distressing, previously under-researched psychiatric disorder in

which patients frequently report flattening of emotional experience. This is the first study to examine the neural correlates of cognitive-emotional processing in patients with this disorder. Our findings confirm the presence of impaired behavioral and neural responses to emotionally salient stimuli in patients with depersonalization disorder, and they also suggest a plausible neural mechanism for the abnormality in emotion perception demonstrated in these patients. The study highlights the need for future studies examining neural responses to emotional stimuli in larger groups of depersonalized patients, and the development of treatment strategies employing techniques to optimize the perception and experience of emotion in these patients.

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