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Emotional memory in depersonalization disorder: A functional MRI study

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Abstract

This study examines emotional memory effects in primary depersonalization disorder (DPD). A core complaint of DPD sufferers is the dulling of emotional responses, and previous work has shown that, in response to aversive stimuli, DPD patients do not show activation of brain regions involved in normal emotional processing. We hypothesized that DPD sufferers would not show the normal emotional enhancement of memory, and that they would not show activation of brain regions concerned with emotional processing during encoding and recognition of emotional verbal material. Using fMRI, 10 DPD patients were compared with an age-matched healthy control group while performing a test of emotional verbal memory, comprising one encoding and two recognition memory tasks. DPD patients showed significantly enhanced recognition for overtly emotive words, but did not show enhancement of memory for neutral words encoded in an emotive context. In addition, patients did not show activation of emotional processing areas during encoding, and exhibited no substantial difference in their neural responses to emotional and neutral material in the encoding and emotional word recognition tasks. This study provides further evidence that patients with DPD do not process emotionally salient material in the same way as healthy controls, in accordance with their subjective descriptions of reduced or absent emotional responses.

Keywords: Depersonalization; Emotional memory; Contextual processing

1. Introduction

Depersonalization (DPD) is defined in the DSM-IV (American Psychiatric Association 1994) as an 'alteration in the perception or experience of the self so that one feels detached from and as if one is an outside observer of ones mental processes or body'. The subjective DPD experience is one of disturbing unreality in the experience of one's physical and emotional state, and often occurs with derealisation (DR), the experience of a similarly strange and unreal quality to one's surroundings. DPD is a relatively common phenomenon, with a prevalence rate variously estimated at 2.4% to 20% in the general population (Simeon et al., 1997). It frequently occurs as a transient phenomenon in

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healthy individuals under certain conditions e.g. when sleep-deprived, or while under the influence (or recovering from the effects) of alcohol or drugs. It may also occur in a range of psychiatric contexts such as panic disorder (Segui et al., 2000) and major depression (Sedman, 1966), and in neuropsychiatric conditions such as temporal lobe epilepsy (Lambert et al., 2002). In a minority of patients, it occurs as a persistent and disabling phenomenon in the absence of other psychopathology, and is then considered to be a primary disorder.

One of the key complaints of many patients with DPD is that they feel their emotional responses are numbed or even non-existent. Davidson (1966) coined the term "de-affectualization" to describe this phenomenon. De-affectualization is not usually accompanied by an objectively blunted affect such as that seen in chronic schizophrenia (Ackner, 1954; Torch, 1978; Sierra and Berrios, 1998). Striking first-person accounts of de-affectualization abound in the literature (Mayer-Gross, 1935; Shorvon et al., 1946; Sedman, 1970), and similar descriptions are common amongst patients attending a specialist DPD clinic (Phillips et al., 2001a; Baker et al., 2003). A recent analysis of responses of DPD patients to a detailed phenomenological questionnaire identified de-affectualization as a key part of the depersonalization syndrome (Sierra et al., 2005). Furthermore, our group have shown that psychophysiological measures of autonomic arousal are reduced in response to aversive stimuli in DPD patients (Sierra et al., 2002). Functional neuroimaging provides an opportunity to examine the effects of emotion on cognition in the brain in DPD.

In a previous fMRI study of patients with primary DPD (Phillips et al., 2001b), we examined the neural correlates of viewing aversive and neutral scenes. A markedly different pattern of brain activation was seen in DPD subjects compared to healthy controls and a patient control group, providing some evidence for abnormal emotional processing in patients with DPD. In particular, DPD patients showed reduced neural responses in emotion-sensitive brain regions (such as posterior occipital–temporal cortex and insula), and increased responses in regions associated with emotion regulation (inferior and lateral frontal cortex), when viewing aversive stimuli. In addition there was evidence that the neural responses to emotive and neutral stimuli were not as distinct in patients with DPD as they were in normals. The current study aimed to build on these findings by examining emotional memory in patients with DPD. Since emotional processing appears to be abnormal in DPD, we hypothesized that performance (and the neural correlates of that performance) of an emotional memory task would also be abnormal in this patient group.

A number of studies have examined abnormalities of emotional memory in clinical groups e.g. patients with amygdala damage (Phelps et al., 1998), patients with Alzheimer's disease (Mori et al., 1999; Kensinger et al., 2002) but this is the first such study in patients with depersonalization. There is strong evidence that emotion normally enhances episodic memory (Burke et al., 1992; Hamann, 2001). The neural and cognitive mechanisms of this effect have been the subject of much study, and functional neuroimaging has been an important tool in this work. One landmark study (Cahill et al., 1996) examined the neural substrates of the encoding of emotionally salient information and, by correlating this data with the results of memory tests conducted after the scanning session, implicated the activity of the right amygdala at encoding as being crucial in modulating the strength of the subsequent memory trace. Other studies have examined neural correlates of encoding (Hamann et al., 1999; Canli et al., 2000) and recall (Fink et al., 1996) of emotional material, though emphases and methods vary widely. A number of more recent studies have addressed the issue of contextual emotional memory i.e. memory for emotionally neutral stimuli encoded in an emotional context (Maratos et al., 2001; Erk et al., 2003; Smith et al., 2004). This work is discussed in detail in our previous paper presenting the normal control data from this study (Medford et al., 2005), and this discussion is not repeated here. Overall, however, the data suggest a key role for amygdala–hippocampal interactions underlying memory for emotional contextual information. A more recent study (Smith et al., 2006) enlarged on these findings by examining connectivity between amygdala and hippocampus during testing of recognition memory for contextual information encoded in either emotional or neutral contexts. It was found that this connectivity showed a bidirectional increase during explicit retrieval of emotionally salient information, and (as in Medford et al., 2005) that the left amygdala was particularly implicated in retrieval of emotional contextual material compared to neutral contextual material. Fenker et al. (2005) have argued that the concerted action of amygdala and hippocampus co-ordinates a cortical recapitulation of emotionally relevant stored contextual information, thus permitting successful memory retrieval.

A key methodological issue, not addressed in many of these studies, is the differentiation of memory for emotional content from that for surrounding context (Burke et al., 1992). We have previously attempted to

address this problem by the use of stimuli specifically designed to allow separation of the effects of memory for content and memory for context. The design and application of these stimuli have been described in detail elsewhere (Kensinger et al., 2002; Medford et al., 2005; Brierley et al., in press). In essence, we have devised linguistic stimuli for which emotional enhancement of episodic memory can be probed without any re-exposure to any intrinsically emotional items during recognition or recall.

In this study we aimed to examine both these aspects of emotional memory, content and context, in patients with primary depersonalization disorder. There have been only two previous functional neuroimaging studies of patients with depersonalization disorder. A PET study by Simeon et al. (2000) emphasised the idea of abnormal integration of sensory information in DPD, while our previous fMRI study (Phillips et al., 2001b) showed that DPD patients did not show the normal pattern of neural activation in response to emotionally aversive stimuli, consistent with self-reports of a loss of emotional reactivity. Based on these findings we predicted that, in general, there would be little difference in the neural responses to emotional and neutral material in the patient group, and that this would hold true for both encoding and recognition memory components of the experiment. We also predicted that the enhancement of memory for emotionally salient stimuli seen in a control group (Medford et al., 2005) would be absent in the patient group.

2. Methods

Forty-two sentences were created, each containing one emotionally aversive "target" word, rated on measures of arousal and valence (Bradley and Lang, 1999). Affectively neutral words, matched to the aversive words on relevant psycholinguistic variables (Coltheart, 1981), were then used to create 42 neutral sentences identical to the emotional sentences except for the neutral–emotional word swap (see Table 1 for examples). These sentences were sorted into two sets, each containing 21 aversive and 21 neutral sentences. In the scanner, subjects viewed one set each and performed two recognition memory tasks specific to that set.

Thus each subject performed three tasks during the scanning session. Firstly, encoding, in which subjects were asked to silently read 42 sentences plus eight "fillers", a total of 50 sentences, each sentence being projected onto a screen for 6 s. After reading each sentence, subjects pressed a button (this was simply to confirm they had read it). Subjects viewed alternating blocks of aversive and neutral sentences (five sentences per block, each block lasting 30 s). The within-task order of these blocks was randomized across subjects, although they were always presented such that emotional blocks alternated with neutral. The eight "filler" stimuli were incorporated to simplify the timing of the blocks, and were equally distributed across emotional and neutral blocks to give a total of 50 sentences for each subject. Two forced-choice recognition tasks followed. For each item, two words were presented, of which one had been seen before in the sentences at encoding, the other being a distracter. Subjects were asked to press one of two buttons to indicate which word had been seen previously. In one recognition task, the correct responses were "target" words, and in the other they were "embedded" words. The incorrect distracters were words matched to the correct responses for relevant psycholinguistic variables (Coltheart, 1981). Each task was presented as an AB boxcar design with alternating blocks of aversive and neutral stimuli. For the recognition memory tasks this meant that the correct responses in one block of stimuli were words that had originally appeared in aversive sentences, while correct responses in the next block were words from neutral sentences. The viewing of previously seen words was thus controlled across both phases. In the target word recognition task, correct responses – and the distracters with which they were paired – were aversive words. In the embedded word recognition task, all responses were neutral words — but those in the "aversive" blocks had originally been seen in aversive sentences. This distinction allows the study of memory for both emotional content and surrounding context. The order of the two recognition memory tasks was counterbalanced across subjects.

A series of studies conducted outside the scanner (Brierley et al., in press) has shown that in healthy control subjects there is a consistent "emotional enhancement effect", with subjects correctly identifying

Table 1
Examples of aversive–neutral sentence pairs

Aversive sentence	Neutral sentence
There was a **bomb** inside the *parcel*	There was a **bowl** inside the *parcel*
He stood on the *balcony* and watched the **riot**	He stood on the *balcony* and watched the **tide**
The **pain** came as he answered the *door*	The **post** came as he answered the *door*

Target words shown in bold, embedded words in italics. Note that subjects see the same embedded word whichever version of the sentence they are shown.

significantly more words from aversive sentences in both target and embedded conditions and overall.

Twelve healthy right-handed male controls (age 22–34, mean 27.8, S.D. 3.6) and ten right-handed patients (nine male, one female, age 23–50, mean 31.2, S.D. 9.3) with primary depersonalization disorder who met DSM-IV criteria, took part in the study. Patients were recruited from the Depersonalization Research Unit Clinic of the Maudsley Hospital, London (Phillips et al., 2001a; Baker et al., 2003). Four of the ten DPD patients were on no medication at the time of the scan. Of the other six, two were taking fluoxetine (40 mg/day), three were taking lamotrigine (250 mg/day) (Sierra et al., 2003), and one was taking a combination of lamotrigine (50 mg/day) and paroxetine (40 mg/day). All subjects completed the National Adult Reading Test (NART), Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI), scoring below clinical cut-offs in every case on the latter two scales. The control and patient groups did not differ significantly in age ($t=-1.11$, $df=11.2$, $P=0.3$).

2.1. Acquisition and analysis of fMRI data

Gradient echo echoplanar images were acquired on a GE Signa 1.5T Neurovascular system (General Electric, Milwaukee WI, USA) at the Maudsley Hospital, London. 100 T2∗-weighted images depicting blood oxygenation level dependent (BOLD) contrast (Ogawa et al., 1990) were acquired over 5 min (for each of the three tasks, one encoding and two recognition) 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 data set provided complete coverage of temporal lobes and almost complete coverage of frontal, occipital and parietal lobes (Simmons et al., 1999).

2.2. Statistical analysis

Following motion correction (Bullmore et al., 1999) periodic change in T_2∗-weighted signal intensity at the (fundamental) experimentally determined frequency of alternation between A and B conditions (30 s each) was estimated by an iterated least squares fit of a sinusoidal regression model to the fMRI time series observed at each voxel (there were thus 10 blocks per 5 min experiment). A standardised test statistic, the standardised power (SP), was obtained for each voxel (Bullmore et al., 1996). Parametric maps representing SP observed at each intracerebral voxel were constructed. In order to sample the distribution of SP under the null hypothesis that observed values of SP were not determined by experimental design (with few assumptions), the 99 images observed in each anatomical plane were randomly permuted and SP was estimated exactly as above in each permuted time series. This process was repeated 10 times at each voxel, resulting in 10 permuted parametric maps of SP at each plane for each subject. The observed and randomized SP maps were transformed into standard space (Talairach and Tournoux, 1988) and smoothed by a 2D Gaussian filter with full width at half maximum=11 mm. This procedure is described in detail elsewhere (Brammer et al., 1997; Bullmore et al., 1999). The median observed SP at each intracerebral voxel in standard space was tested against a critical value of the null distribution of median SPs constructed from the permuted SP maps (Brammer et al., 1997). For a test at any desired P-value, the critical value is extracted from the randomization distribution such that $1/P$ of the randomizations exceed that value. In the observed data, voxels with SPs exceeding this critical value had a probability under the null hypothesis less than or equal to the chosen P-value. The particular P-value was determined by setting the expected number of false positive voxels (EPI), so that P=EPI/total search volume. For this study the EPI was set at 50 voxels so that the threshold P-value was 50/14,000 (approximate search volume) or 0.0036. Table 3 presents specific P-values for individual activations.

To estimate the differences in mean SP between the two recognition memory experimental conditions (target and embedded), we fitted repeated measures analysis of variance (ANOVA) models at each voxel of the observed SP maps in standard space. Differences in mean SP between the two conditions were tested for significance only at those voxels which were generically activated by one or both of the conditions considered independently, thereby substantially reducing the search volume or number of tests conducted. The ANOVA method was also used to compare data between patients and controls.

3. Results

Behavioural and neuroimaging data for the normal control group have been reported elsewhere (Medford et al., 2005), but are summarised here for clarity. Behavioural data are summarised in Table 2 and neuroimaging data in Table 3.

Across the two recognition memory tasks, control subjects correctly identified significantly more words

Table 2
Summary of recognition memory scores and comparisons within and between groups

(A) Within group comparisons (paired *t*-tests, significance two-tailed)

Comparison	Group	Means (E, N)	S.D. (E, N)	*t*	*P*
All E vs. N	Controls	33.6, 31.0	4.18, 4.35	2.58	0.027
	Patients	33.1, 31.0	2.47, 3.71	1.8	0.11
Target E vs. N	Controls	17.8, 16.5	2.59, 2.28	1.67	0.12
	Patients	17.9, 15.5	1.91, 1.78	3.58	0.006
Embedded E vs. N	Controls	15.8, 14.4	2.40, 2.54	1.93	0.083
	Patients	15.2, 15.5	1.75, 2.88	−0.26	0.798

(B) Between group comparisons (controls vs. patients, independent samples *t*-tests, significance two-tailed)

		Mean	*df*	*t*	*P*
All E	Controls	33.6	16.46	0.36	0.722
	Patients	33.1			
All N	Controls	31.0	18.94	0.52	0.959
	Patients	31.0			
Target E	Controls	17.8	19.77	−0.69	0.945
	Patients	17.9			
Target N	Controls	16.5	19.94	1.16	0.261
	Patients	15.5			
Embedded E	Controls	15.8	18.20	0.68	0.506
	Patients	15.2			
Embedded N	Controls	14.4	18.10	−0.96	0.352
	Patients	15.5			

Recognition memory scores. E=emotional words, N=neutral words.

from aversive sentences than from neutral sentences, but subtest comparisons (aversive target vs. neutral words and neutral words embedded in aversive sentences vs. neutral words in neutral sentences) did not reach significance.

In the DPD patient group, in the target word task, aversive words were recognised significantly better than neutral words. There was a contrasting result for the embedded word task, where there was no difference for the recognition of neutral words from aversive contexts compared with those from neutral contexts. These data are summarised in Table 2, section A.

There were no differences approaching significance between patients and controls on individual recognition memory subtests (all $P>0.26$). This data is summarised in Table 2, section B.

Neuroimaging data for both groups is summarised in Table 3. The data for the control group have been presented and discussed elsewhere. In brief, encoding activated inferior and medial frontal structures including the anterior cingulate cortex. "Target" emotional word recognition again activated the anterior cingulate plus superior temporal gyrus and most notably right medial temporal lobe structures including amygdala, hippocampus and parahippocampal gyrus. Recognition of "embedded" targets (i.e. neutral words encoded in an aversive context) yielded activation in the left parahippocampal gyrus and left inferior parietal lobule.

Neuroimaging data for the DPD patient group were as follows: In the encoding task, no areas of significant activation were seen to either aversive or neutral sentences, suggesting equivalent processing of the two types of input.

In the target word recognition task, there was a significant activation in an area of right precentral gyrus in the aversive phase, and in right precentral gyrus and left middle temporal gyrus in the neutral phase.

In the embedded word recognition task, activations in the aversive phase were seen in right corpus striatum, right hippocampus, left precentral gyrus and right precuneus. Activations in the neutral phase were seen in cerebellum, bilateral primary visual cortex, left corpus striatum, and right ventrolateral prefrontal cortex.

Comparing patients and controls (Table 4) showed no significant differences between groups for encoding. For target word recognition, there were significantly greater activations in bilateral frontal areas, bilateral precuneus, and cerebellum in the control group. For embedded word recognition, there were significantly greater activations in cerebellum and primary visual cortex in the patient group.

Table 3
Summary of neuroimaging findings in normal control subjects and DPD patients

Phase	Region (approximate Brodmann Area)	Side	*x**	*y**	*z**	No. of voxels	*P*[a]
(A) Control subjects							
Encoding:							
E	Anterior cingulate gyrus (32)	L	−11	33	31	17	0.00009
	Precuneus (7)	L	−7	−52	31	6	0.0004
N	Medial prefrontal cortex (9)	R	4	43	15	42	0.000007
	Lingual gyrus (18)	L	−17	−69	−2	15	0.00004
Target word recognition:							
E	Middle temporal gyrus (39/21)	L	−40	−60	26	78	0.000007
	Posterior cingulate gyrus (31)	L	−7	−43	37	73	0.00008
	Medial prefrontal cortex (11)	L	−4	39	−13	53	0.000007
	Precuneus (7)	L	−4	−46	31	50	0.000007
	Anterior cingulate gyrus (32)	R	15	46	−2	42	0.00003
	Superior temporal gyrus (38)	L	−40	−13	13	28	0.000007
	Anterior insula (47)	L	−40	13	−2	23	0.00002
	Inferior frontal gyrus (47)	L	−47	17	4	18	0.0002
	Parahippocampal gyrus (30)	R	25	−43	−2	18	0.00002
	Amygdaloid complex	R	36	−10	−7	12	0.00002
	Hippocampus	R	40	−10	−13	8	0.0002
N	Superior temporal gyrus (42)	L	−43	−17	9	20	0.000007
	Precentral gyrus (43)	L	−43	−7	20	8	0.0003
	Precentral gyrus (6)	R	47	0	20	7	0.0007
Embedded word recognition:							
E	Parahippocampal gyrus (36)	L	−26	−33	−13	5	0.0007
	Inferior parietal lobule (40)	L	−26	−36	42	5	0.0012
(B) Depersonalisation patients							
E/N	Encoding: no significant activations						
Target word recognition:							
E	Precentral gyrus (6)	R	47	0	15	2	0.0012
N	Precentral gyrus (6)	R	47	0	26	4	0.0002
	Middle temporal gyrus (21)	L	−53	−37	−2	3	0.0003
Embedded word recognition:							
E	Corpus striatum	R	17	7	−2	10	0.00002
	Precentral gyrus (6)	L	−40	−10	37	6	0.00002
	Hippocampus	R	40	−23	−13	2	0.0012
	Precuneus (7)	R	7	−50	31	2	0.0012
N	Lingual gyrus (18)	R	7	−73	−7	36	0.000007
	Cerebellum	R	11	−67	−13	14	0.00003
	Cerebellum	L	−11	−67	−13	10	0.0002
	Lingual gyrus (19)	L	−17	−60	4	4	0.00002
	Corpus striatum	L	−11	7	−2	2	0.0003
	Ventrolateral prefrontal cortex (47)	R	32	20	−18	2	0.0012

E = emotional phase, N = neutral phase. The cluster with the largest number of voxels within each region is reported. Talairach co-ordinates refer to the voxel with the maximum fundamental power quotient (FPQ) in each cluster.

[a] 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 $P < 0.003$.

There is some evidence that SSRI antidepressants may reduce the BOLD response to emotional material (e.g. Fu et al., 2004; Del-Ben et al., 2005), while lamotrigine may have mood-stabilising properties which might influence response to such stimuli. The effects of lamotrigine on BOLD response patterns in humans have not been studied, but it has recently been shown to reduce the BOLD response to somatosensory stimulation in rodents (Kida et al., 2006). To examine the possibility that the reduced response to emotional stimuli in the patient group might be due to some patients being on medication, we performed additional group analyses on the data from the four patients who were unmedicated at the time of study. For each fMRI condition, we undertook voxel-level analyses for this group of four patients, using the data analysis method already described. In each of the three fMRI conditions (encoding, target word recognition, embedded word

Table 4
Summary of areas of significantly different activation between groups

Region (approximate Brodmann Area)	Side	*x**	*y**	*z**	No. of voxels	*P*
(A) Content recognition [a]						
Medial prefrontal cortex (9)	R	0	33	31	17	0.00002
Precuneus (7)	R	4	−52	42	16	0.00002
Orbitofrontal cortex (11)	L	−7	48	−13	14	0.00008
Medial prefrontal cortex (8)	R	0	33	37	11	0.0003
Precuneus (7)	L	−4	−48	31	9	0.0003
Cerebellum	R	11	−56	−13	5	0.00012
(B) Context recognition a						
Cerebellum	R	4	−70	−7	20	0.00007
Primary visual cortex (18)	R	4	−74	−2	4	0.0003

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

[a] For content recognition, all areas listed were activated significantly more in controls than patients, all in the emotional phase. For context recognition, areas listed were activated significantly more in patients than controls, all in the neutral phase. No areas were significantly more activated in either group in the neutral phase of the target word experiment, or the emotional phase of the embedded word experiment.

recognition), there were no significant differences in activation to neutral or emotional stimuli.

Figs. 1 and 2 show key areas of activation in the DPD group for the two recognition memory tasks. In Fig. 1 these are contrasted with corresponding activation maps from the control group.

4. Discussion

The aim of this study was to examine two aspects of emotional memory (content and context) in a patient population who describe disturbance of emotional responses and experiences. For the recognition memory tasks, the pattern of results in the DPD patient group is strikingly different from results obtained in normal controls in experiments conducted inside and outside the scanning environment (Kensinger et al., 2002; Medford et al., 2005; Brierley et al., in press). Overall the prediction that "emotional enhancement" of recognition memory would be absent in the patient group was supported. However when content and context were examined separately, this lack of emotional enhancement was seen only for context: the patients show an "emotional enhancement" effect on the target word recognition task; this effect appears to be at least as strong in the DPD group as the control group. However, the DPD group showed no emotional enhancement effect on the embedded word task, while the effect approaches significance in the controls, and has been consistently demonstrated in normal controls tested outside the scanning environment (Brierley et al., in press).

The neuroimaging findings also show important differences between patients and controls. The hypothesis that the patient group would show little difference in response to aversive and neutral phases was largely supported. In the encoding task, no such differences were observed. This is in contrast to the findings in normals, where significant activations in anterior

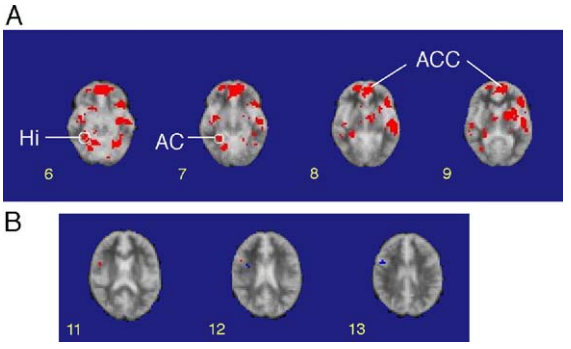

Fig. 1. Activations during content word recognition memory task. Top: Control subjects. Areas of activation in emotional condition (in red) include hippocampus (Hi), amygdaloid complex (AC), anterior cingulate cortex (ACC). Bottom: DPD patients. Small activations in right precentral gyrus in both emotional (red) and neutral (blue) conditions. For full list of activations in both groups see Table 3.

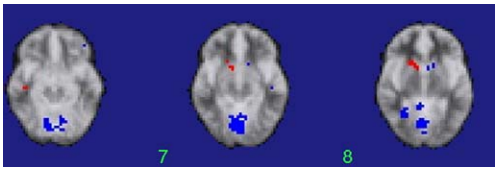

Fig. 2. Activations in DPD patients during context word recognition memory task. Activations in R hippocampus and R putamen during emotional condition. Large, widespread activations (particularly primary visual areas) during neutral condition.

cingulate cortex (ACC) and precuneus were demonstrated, and in fact the SP score for the ACC activation showed a significant negative correlation with performance on the target word task (Medford et al., 2005). It should be noted that the statistical test of an interaction of group by encoding task activation did not exceed the significance threshold. Nevertheless the results of the within-group contrast suggest that in DPD, aversive and neutral sentences elicit similar responses and are processed in a similar way. In the target word recognition task, the only activation in the aversive phase in the DPD group was in right precentral gyrus, with activation in a similar area also observed in the neutral phase. The precentral gyrus is, in the context of this experimental paradigm, a rather non-specific area, implicated in motor and possibly working/spatial memory, but its activation here is unlikely to reflect any specific "emotion effect", particularly as a similar area of activation was seen in the neutral condition. There were no activations in areas thought to be specifically involved in emotional processing — again in contrast to the results in controls, where the right amygdaloid complex and hippocampus were activated, in combination with a large number of left-sided cortical regions, including superior temporal gyrus and anterior insula.

In the embedded word recognition task, the prediction was partially supported, in that greater activation to embedded words from neutral contexts was seen than to words from emotional contexts. However the right ventral striatum was activated in response to embedded words from emotional contexts. This area is known to be activated by tasks involving emotional processing (Calder et al., 2001). However, it is interesting to note that there was also a small activation in the corpus striatum (on the left) in response to embedded words from neutral contexts, so striatal response was not specific to the emotional condition. Overall, results for the embedded word task again reflect an alteration of the normal distinction between emotionally salient and neutral material. In the patient group, the major areas of activation are seen in the neutral phase. In particular there are a number of activations in primary visual cortex (lingual gyrus).

Overall, the patient group showed a reduced effect of emotion compared to that seen in controls, in terms of both recognition memory performance and activation of areas known to be involved in emotional processing. In the encoding task, the patient group showed no significant difference in response to emotional and neutral material, supporting the idea that in DPD there is less discrimination between these categories. Clinical reports suggest no difference in perception or experience of neutral and emotion material, in line with patient self-reports of derealization, which commonly stress that everything seems more or less equally unreal or unfamiliar irrespective of emotional content.

Comparison between controls and patients (see Table 4) again suggests that patients do not show the normal response to emotional stimuli. In the content word recognition task, controls showed significantly greater activation in the emotional phase in bilateral prefrontal cortical areas, and in precuneus and cerebellum (although activation in amygdaloid complex, seen in the control group in the emotional phase, was not significantly different between groups). Conversely, there were no significant differences between groups in the neutral phase.

The patient group showed more areas of activation in the neutral phase of the context word recognition task than any other part of the experiment. This is broadly in line with the findings of our previous fMRI study of depersonalization (Phillips et al., 2001b), where we found that patients with DPD showed greater activation in response to neutral scenes compared to aversive scenes. A previous study of autonomic response to aversive and neutral stimuli in DPD suggested that patients with DPD may be in a heightened state of alertness or vigilance, but have selectively dampened responses to aversive stimuli (Sierra et al., 2002), and the selective inhibition of emotional responses may explain why in both this and our previous fMRI study, the greatest activation in DPD patients was in response to neutral stimuli.

In the patient group, there was a significant difference in behavioural performance between the emotional and neutral conditions of the content word recognition task, which is not reflected by any significant difference in neural activation pattern. There are two possible reasons for this: firstly, it may be that different neural circuits are involved, but that differences in activation do not reach the threshold of statistical significance. A second possibility is that the difference in behavioural performance is due to a successful cognitive strategy for recognising the aversive words, which engages the same brain areas used for the neutral words, and does not place a significantly greater demand on these areas. The end result would be that no difference in regional blood flow is seen. Given that the other data from this and our previous study (Phillips et al., 2001b) suggest that, in terms of neural response, DPD patients make little distinction between aversive and neutral material, we favour the latter interpretation. Normal controls, on the other hand,

utilise affect and arousal which aid memory consolidation (Cahill et al., 1996). In the embedded word task, the patient group shows activation in ventral striatum to the emotional component, although the extent of this is very small. Activations were also seen in primary visual cortex. Previous neuroimaging work in control populations has suggested that sensory cortex is activated to a greater degree by emotional material, an effect thought to represent modulation of the sensory response by other brain areas sensitive to emotional salience (e.g. the amygdala) via back projections (Morris et al., 1998). However, in the current study, such activations were seen in both neutral and emotional phases of this particular task — but in DPD patients, predominantly greater visual cortex activations were seen in the neutral phase, similar to the findings of our previous neuroimaging study. Thus these data again imply an absence of the normal distinction between emotionally salient and neutral material in DPD. Such an absence may be due either to reduced response to emotionally salient material, or increased activation (e.g. a threat response) to neutral material — or by some more general abnormality of processing which encompasses both.

One limitation of the current study is that some of the DPD patient group were on medication at the time of scanning, and this may have influenced the results, particularly the lack of emotion-related response seen in this group. However, subgroup analyses of the four unmedicated patients showed no significant differences in activation in response to either emotional or neutral stimuli. While one must be cautious in interpreting results from this small subgroup, this does suggest that the lack of emotion-related activation seen in the patient group as a whole cannot be due solely to medication: if this were the case then one would expect the unmedicated patients to show a rather different pattern, perhaps more akin to that seen in normals.

Overall the results suggest that patients with depersonalization may be utilising different mechanisms for the processing of emotionally aversive material. The lack of subjective emotional responses seen clinically in this group is likely to be related to this difference in the neural processing of emotional material. Future work will include longitudinal studies to examine whether patterns of neural activation in DPD are "normalised" following successful treatment or remission of the condition.

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