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Depersonalization Disorder: A Functional Neuroanatomical Perspective

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Clinical reports of depersonalization suggest that attenuated emotional experience is a central feature of the condition. Patients typically complain of emotional numbness and some patients ascribe their feelings of unreality to a lack of affective "colouring" in things perceived. Recent neuroimaging and psychophysiological studies support these assumptions as they show both attenuated autonomic responses in depersonalization, and decreased activity within neural regions important for the generation of affective responses to emotive stimuli. Furthermore, findings from neuroimaging studies indicate increased prefrontal cortical activity in depersonalised patients, particularly within regions associated with contextualization and appraisal of emotionally-salient information rather than mood induction *per se*. Taken together, these finding suggest that symptoms of depersonalization, and in particular emotional numbing, may be related to a reversal of normal patterns of autonomic and neural response to emotive stimuli.

Keywords: Amygdala; Depersonalization disorder; Derealization; Dissociation; Insula; Emotional numbing

INTRODUCTION

Depersonalization can be understood in terms of a disorder of emotion processing. In this review, we provide a functional neuroanatomical perspective that we believe helps to increase understanding of the neurobiological basis of this relatively under-researched psychiatric disorder.

DEPERSONALIZATION

Depersonalization is an alteration in the perception or experience of the self. The sufferer feels uncomfortably detached from their own senses and surrounding events, as if they were an outside observer (DSM-IV, 1994). Other components of this experience are a sense of emotional numbing, somatosensory distortions, or a feeling that the body does not belong to the person; heightened self-observation and more rarely distortions in the experiencing of time (see Sierra and Berrios, 2001 for a glossary of depersonalization features). The following description gives a flavour of the experience: "*I feel as though I'm not alive, as though my body is an empty, lifeless shell. I seem to be standing apart from the rest of the world, as though I am not really here… I seem to be walking in a world I recognise but don't feel.*"

Descriptions of depersonalization are found in the medical literature from the early 19th century. However, it was only at the end of the 19th century that the term "depersonalization" was coined by Dugas. The term aptly captured his view that at the core of depersonalization there was a failure to "personalize" mental activity (i.e. it no longer felt as belonging to the self), and advanced the view that a form of emotional pathology might be responsible for the condition (Sierra and Berrios, 1997). Struck by the relatively stereotypied nature of the phenomenon, and its presence in a wide range of neuropsychiatric conditions, Mayer-Gross (1935) believed depersonalization to be the expression of a pre-formed functional response of the brain that could be triggered by a wide variety of diseases. A recent systematic, in-depth psychopathological comparison of 200 historical cases of depersonalization reported in the last 100 years with a group of 45 prospective cases of depersonalization disorder, suggests that the phenomenology of depersonalization has remained stable for at least

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the last 100 years. This study also revealed that the most prevalent and stable components of the syndrome are emotional numbing, changes in body experiencing, and visual complaints of unreality and detachment (Sierra and Berrios, 2001).

The symptoms of depersonalization have been found in 2.4% of the general population (Ross *et al.*, 1991) and 80% of psychiatric inpatients, which 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 a whole range of neurological conditions such as epilepsy and migraine (Lambert *et al.*, 2002). Neurological lesions causing depersonalization tend to be localized in the temporal lobes (Lambert *et al.*, 2002), and lesions to cortico-limbic pathways can give rise to symptoms indistinguishable from depersonalization/derealization (Sierra *et al.*, 2002b). In healthy individuals, depersonalization can occur during fatigue, meditation, extreme stress or after use of psychotomimetic drugs (Simeon *et al.*, 1997; Mathew *et al.*, 1999).

In this review, we aim to explore the neural mechanisms underlying one of the core features of depersonalization, emotional numbing, by describing current understanding of the neural basis of normal emotion processing, and evidence from recent studies reporting specific neurobiological abnormalities in response to emotive stimuli in depersonalized patients.

EMOTIONAL NUMBING IN DEPERSONALIZATION

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). Converging evidence suggests that depersonalization patients have attenuated autonomic sympathetic responses. Indeed, early observations showed that patients with depersonalization showed a high resistance, non-fluctuating skin conductance response (Lader, 1975). Similarly, Kelly and Walter (1968) found evidence of reduced autonomic output in depersonalization by using forearm blood flow as an index of sympathetic function. Recently, Sierra *et al.* (2002b) have reported attenuated skin conductance responses (SCRs) to unpleasant visual stimuli (see below). Based on a thorough review of the depersonalization literature, and relevant neuropsychiatric research, Sierra and Berrios (1998) proposed a theoretical model of depersonalization, which suggested that some of the symptoms of depersonalization may be accounted by an inhibitory process acting on emotional processing (Sierra and Berrios, 1998). Few studies have attempted to examine the functional neuroanatomical correlates of the phenomenon of emotional blunting in depersonalized subjects, however.

THE FUNCTIONAL NEUROANATOMY OF NORMAL HUMAN EMOTION PROCESSING

The advent of functional neuroimaging techniques, including Single Photon Emission Tomography (SPET), Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI), in which measures of regional cerebral metabolism or blood flow are acquired as indices of neuronal activity, has allowed the examination of the neural basis of normal and abnormal emotional states in humans. Findings from animal studies, human lesion and stimulation studies, in addition to those employing functional imaging techniques, which have helped to increase understanding of the neural basis of normal human emotion processing have been discussed in more detail elsewhere (Phillips *et al.*, 2003a,b). Findings from studies employing functional neuroimaging techniques indicate a distributed neural system, comprising ventral striatum, amygdala, insula, and ventral and dorsal prefrontal cortical regions in normal human emotion processing. Findings from studies examining neural responses during the identification of emotional stimuli, the generation of affective states, and the regulation of emotional responses, are summarised here in order to provide a framework in which to understand the neural basis of the emotional flattening reported in depersonalised subjects.

Identification of Emotionally-salient Material

Amygdala and fear. Increased blood flow and activation within the amygdala have been demonstrated in response to unfamiliar faces (Dubois *et al.*, 1999), during the detection of eye gaze (Kawashima *et al.*, 1999), to presentations of fearful (e.g. Breiter *et al.*, 1996; Morris *et al.*, 1996; 1998a; Phillips *et al.*, 1997; 2001a,b; Wright *et al.*, 2001), sad (Schneider *et al.*, 1997; Blair *et al.*, 1999), and happy facial expressions (Breiter *et al.*, 1996), emotive scenes (Lane *et al.*, 1997b; Lang *et al.*, 1998; Taylor *et al.*, 2000), and film excerpts (Reiman *et al.*, 1997). The amygdala has also been implicated in the response to visual presentations of threatening words (Isenberg *et al.*, 1999), fearful vocalisations (Phillips *et al.*, 1998), unpleasant olfactory (Zald and Pardo, 1997) and gustatory (Zald *et al.*, 1998; O'Doherty *et al.*, 2001b) stimuli, in the memory for emotional information (Cahill *et al.*, 1996; Hamann *et al.*, 1999; Canli *et al.*, 2000; Dolan *et al.*, 2000), in the enhanced perception of emotionally-salient information (Anderson and Phelps, 2001), and in the response to presentations of fearful and angry facial expressions of which the observer had no conscious awareness (Morris *et al.*, 1998b; Whalen *et al.*, 1998). Other studies have indicated a habituation of the amygdalar response to visual displays of emotionally salient information (Phillips *et al.*, 2001b; Wright *et al.*, 2001), and sex differences in the development of these amygdalar responses (Killgore *et al.*, 2001; Thomas *et al.*, 2001).

Insula, ventral striatum and disgust. Other regions, including the insula, together with ventral striatum and thalamus, have been implicated in the identification of facial expressions of disgust (Phillips *et al.*, 1997; Sprengelmeyer *et al.*, 1998), and in taste perception (Small *et al.*, 1999).

Generation of Affective States

Ventral striatum and reward. Paradigms designed to examine neural correlates of affective states *per se* have included studies of mood induction, fear conditioning, and decision-making to maximize reward. These have highlighted the role of the ventral striatum, including ventral putamen and caudate nucleus, in craving (Breiter *et al.*, 1997), in the anticipation and time-locked processing of reward (Knutson *et al.*, 2001; Pagnoni *et al.*, 2002), and in romantic love (Bartels and Zeki, 2000), whilst a positive correlation has been reported between the euphoric response to dextroamphetamine and the magnitude of dopamine release in anteroventral striatal areas (Drevets *et al.*, 2001).

Amygdala and mood states. Other studies have demonstrated amygdala activation in response to induction of positive and negative emotional states (Reiman *et al.*, 1997; Schneider *et al.*, 1997), and during fear conditioning (Buchel *et al.*, 1998; 1999; LaBar *et al.*, 1998).

Anterior insula and negative emotional states. Increased activity within the anterior insula has been demonstrated during pain perception (Casey *et al.*, 1996), induced sadness and anticipatory anxiety in healthy subjects, lactate- or cholecystokinin-induced panic attacks in patients with panic disorder, exposure to phobic stimuli in patients with animal phobias, in major depressive episodes in patients with major depressive disorder, and during exposure to trauma-related stimuli in post-traumatic stress disorder patients (Charney and Drevets, 2002). Studies have also highlighted the role of the insula during recall of internally generated emotion (Reiman *et al.*, 1997), and during the experience of guilt (Shin *et al.*, 2000). Studies have also implicated the insula in delayed fear conditioning (Buchel *et al.*, 1999), and during the anticipation of an aversive stimulus (Phelps *et al.*, 2001), suggestive of a role for this structure in conveying the representation of aversive, sensory information to the amygdala.

Subgenual anterior cingulate gyrus and mood induction. Increased blood flow and activation have also been demonstrated within the subgenual anterior cingulate gyrus during mood induction compared with rest (George *et al.*, 1995; Schneider *et al.*, 1997; Mayberg *et al.*, 1999; Teasdale *et al.*, 1999; Shin *et al.*, 2000), and in response to rewards (Elliott *et al.*, 2000b).

Orbitofrontal cortex and reward and punishment. Activation within the orbitofrontal cortex has been demonstrated during the perception of pleasant and unpleasant odours, flavours and tactile stimuli (Zald and Pardo, 1997; Zald *et al.*, 1998; Francis *et al.*, 1999; O'Doherty *et al.*, 2001b), including the perception of odours of foods not eaten to satiety compared with those of foods eaten to satiety (O'Doherty *et al.*, 2000), during the performance of gambling tasks (O'Doherty *et al.*, 2001a), during guessing and decision-making on the basis of reward value (Elliott *et al.*, 2000a,b), and when engaging emotion processing during the consideration of moral dilemmas (Greene *et al.*, 2001). Increased regional cerebral blood flow within orbitofrontal cortex has been demonstrated during imagery of an event precipitating anger (Dougherty *et al.*, 1999; Kimbrell *et al.*, 1999), and during imagined *restraint* of physical aggression compared with imagined aggressive behaviour (Pietrini *et al.*, 2000), although decreased cerebral blood flow to this region has been demonstrated during imagined physical aggression compared with neutral behaviour (Pietrini *et al.*, 2000). Animal studies have demonstrated a role for the orbital cortex in inhibiting sympathetic autonomic and defensive behaviours elicited by amygdala stimulation (Timms, 1977), whilst left ventromedial prefrontal cortical lesions have been demonstrated to inhibit autonomic, behavioural and endocrine responses to fear conditioned stimuli and restraint stress (Sullivan and Gratton, 1999). Taken together, these findings suggest that the orbitofrontal cortex may be important for the mediation of autonomic responses during the generation of affective states in response to emotionally salient material.

Ventrolateral prefrontal cortex and contextual appraisal of emotional material. Studies have demonstrated increased blood flow and activation within the ventrolateral prefrontal cortex, including lateral and rostral regions of Brodmann Area 47 and part of Brodmann area 45, during a variety of tasks, including the induction of sad mood (Pardo *et al.*, 1993) and guilt (Shin *et al.*, 2000), during the recall of personal memories (Andreasen *et al.*, 1995; Fink *et al.*, 1996; Markowitsch, 1997) and emotional material (Reiman *et al.*, 1997), and in response to facial expressions displaying different negative emotions (Sprengelmeyer *et al.*, 1998), particularly when specific tasks are performed in response to facial expressions (Lange *et al.*, 2003). Increased activity has been reported in this region additionally in depressed patients to negative stimuli (Elliott *et al.*, 2002), and during mood induction (Liotti *et al.*, 2002). Other studies, however, have demonstrated decreased activity within this region in these patients during cognitive task performance, a negative correlation between activity in this region and depression severity (Kimbrell *et al.*, 2002), and negative correlations between ventrolateral prefrontal cortical blood flow and psychomotor retardation (Videbech *et al.*, 2002). It has previously been suggested that this region may be associated with symptoms such as negative cognitions and ruminations, which occur only in mildly depressed patients (Liotti *et al.*, 2002). These findings implicate the ventrolateral prefrontal cortex in the contextual appraisal

of emotionally-salient information and memories, although the role of this region in the generation of affective states *per se* remains unclear.

Controlled Regulation of Affective States

Controlled rather than automatic regulation of arousal accompanying affective states has been associated with dorsal prefrontal cortical regions, including dorsal and rostral anterior cingulate gyrus, dorsomedial and dorsolateral prefrontal cortices, regions associated with attention and executive task performance (e.g. Goldman-Rakic, 1987; Drevets and Raichle, 1998).

Dorsal anterior cingulate gyrus and inhibition of arousal. Dorsal regions of the anterior cingulate gyrus are activated during the encoding of the perceived unpleasantness of pain (Casey *et al.*, 1994; Rainville *et al.*, 1997), anticipatory arousal and uncertainty (Critchley *et al.*, 2001a), intentional regulation of autonomic arousal and performance of relaxation tasks (Critchley *et al.*, 2001c), and in the regulation and second-order mapping of internal bodily states (Damasio, 1999; Critchley *et al.*, 2001b). Increased blood flow has also been reported in dorsal and rostral regions of the anterior cingulate gyrus during attention to subjective emotional states and experiences (Lane *et al.*, 1997a; 1998; Gusnard *et al.*, 2001), and during self-inhibition of sexual arousal generated by viewing erotic stimuli (Beauregard *et al.*, 2001). Activity within regions along the border between rostral anterior cingulate gyrus and medial prefrontal cortex (the paracingulate gyrus) has been associated with mentalization and the representation of mental states of the self (Frith and Frith, 1999), and is activated during self-reflective thought (Johnson *et al.*, 2002).

Dorsomedial prefrontal cortex and inhibition of negative emotion. Studies have demonstrated an inverse relationship between blood flow in the dorsomedial prefrontal cortex and measures of autonomic function and anxiety during performance of a novel cognitive task (Simpson *et al.*, 2001), decreased blood flow during the induction of sad mood in healthy volunteers (Mayberg *et al.*, 1999), and increased activation during self-referential judgments made when viewing emotionally-salient stimuli (Gusnard *et al.*, 2001), during anticipation of pain (Ploghaus *et al.*, 1999), and during voluntary suppression of sadness (Levesque *et al.*, 2003).

Dorsolateral prefrontal cortex and non-emotional information processing. Other studies have demonstrated increased blood flow and activation within dorsolateral prefrontal cortex (Brodmann Areas 44 and 46) to positive and negative facial expressions during the performance of explicit, emotion labelling tasks compared with more implicit tasks (Nakamura *et al.*, 1999; Hariri *et al.*, 2000). This region may therefore be associated with the cognitive appraisal of non-emotive visuospatial and verbal components of salient stimuli.

Conclusion

Findings from studies employing functional neuroimaging techniques in humans have implicated a distributed neural system in normal human emotion processing. Ventral limbic and prefrontal cortical regions, including the amygdala, insula, ventral striatum and ventral regions of the anterior cingulate gyrus and prefrontal cortex, are important for the identification of the emotional significance of environmental stimuli and the generation of affective states. Ventromedial prefrontal cortex, and, in particular, orbitofrontal cortex, has also been implicated in the mediation of autonomic changes accompanying the generation of affective states produced in response to emotive stimuli. Ventrolateral prefrontal cortex has been associated with the contextual appraisal of emotionally-salient stimuli, which may then lead to the generation of affective states. It remains unclear, however, as to whether ventromedial and ventrolateral prefrontal cortical regions are important for the experience of emotion *per se*. Dorsal regions of the anterior cingulate gyrus and prefrontal cortex, regions where cognitive processes are integrated with and can be biased by emotional input, have been implicated in effortful rather than automatic regulation of affective states.

TOWARDS AN UNDERSTANDING OF THE FUNCTIONAL NEUROANATOMICAL BASIS OF DEPERSONALIZATION

Earlier functional neuroimaging studies have demonstrated in patients with depersonalization disorder left fronto-temporal activation (Hollander *et al.*, 1992), and reduced activity in superior and middle temporal gyri during performance of a verbal learning task (Simeon *et al.*, 2000). Findings from the former study have been interpreted as evidence for a common neurobiological basis for depersonalization and obsessive compulsive disorder (OCD), in which increased frontal activation has been associated with the urge to ritualize (Breiter *et al.*, 1996), whilst those from the latter have been interpreted as underlying functional abnormalities in brain regions important for an intact body schema in the disorder. Drug-induced depersonalization has also been associated with increased prefrontal but reduced subcortical blood flow (Matthew *et al.*, 1999). The latter finding is suggestive in depersonalized states of a pattern of reduced activity in regions important in the response to emotional stimuli, i.e. subcortical regions including amygdala and striatum, and increased activity in regions potentially involved in the regulation of emotional responses, i.e. predominantly prefrontal cortical regions.

In order to determine the functional neuroanatomical basis of the emotional blunting associated with the disorder, we examined neural correlates of emotion processing in patients with depersonalization disorder (Phillips *et al.*, 2001a). We compared neural responses to

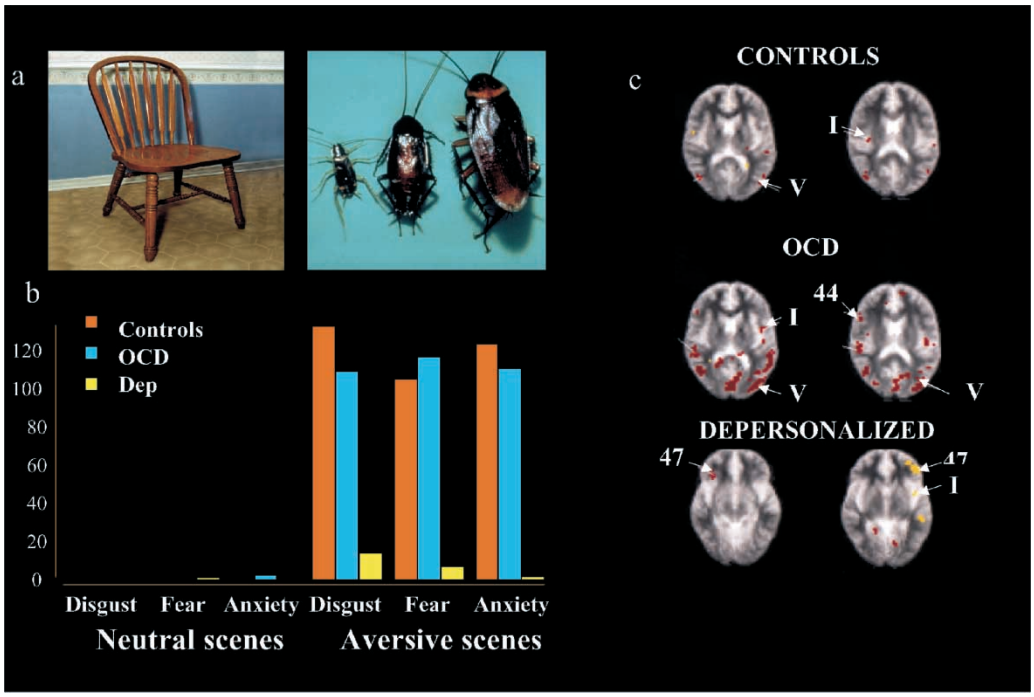

FIGURE 1 (a) Depersonalized patients, those with obsessive compulsive disorder (OCD) and normal controls viewed alternating blocks of neutral and aversive scenes from a standardized series (Lang *et al.*, 1998). One example each of the neutral (left) and aversive (right) scenes are depicted. (b) Median total scores for subjective ratings of neutral and aversive scenes are shown for all three-subject groups on three dimensions: disgust, fear and anxiety. The maximum total score for each subject for rating each dimension for all aversive (or all neutral) scenes was 480. Score ranges for normal controls for neutral scenes on each dimension were: 0–2 (disgust), 0–2 (fear), and 0–6 (anxiety), and for 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). 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); $z = 3.46$; $p = 0.03$ (fear rating); $z = 2.20$ $p = 0.03$ (anxiety rating); Wilcoxon signed ranks tests for OCD patients; $z = 2.80$; $p = 0.005$ (disgust rating); $z = 2.50$; $p = 0.01$ (fear rating); $z = 2.80$; $p = 0.005$ (anxiety rating). Depersonalized patients did not rate the aversive scenes significantly differently from neutral scenes. (c) Two transverse brain slices from brain activation maps acquired with functional Magnetic Resonance Imaging representing group-averaged neuronal activity to aversive (red voxels) and neutral scenes (yellow voxels) are shown for all three groups. The left side of the brain is on the right side of the image, and vice versa. In normal controls ($n = 6$), major regions of neuronal activity in response to aversive scenes are shown in the right insula (I), and visual cortex (V). In OCD patients ($n = 10$), major regions of neuronal activity in response to aversive scenes are shown in the left insula (I); visual cortex (V), and right dorsolateral prefrontal frontal cortex (Brodmann Area 44). Neither group demonstrated significant neuronal activity in response to the neutral scenes. In depersonalized patients ($n = 6$), major regions of neuronal activity are shown primarily in response to the neutral scenes (i.e. in yellow) in the left insula (I) and left ventrolateral prefrontal cortex (Brodmann Area 47), and in response to the aversive scenes in right ventrolateral prefrontal frontal cortex (Brodmann Area 47). Adapted from Phillips *et al.* (2001a).

emotionally-salient stimuli (stimuli depicting aversive, and particularly disgusting, scenes) from a standardised series (Lang *et al.*, 1997; Fig. 1a) in six depersonalized patients with such responses in healthy volunteers and psychiatric control subjects, patients with OCD, in whom, as for depersonalised patients, the experience of anxiety and depression occur frequently, but emotional blunting is uncommon. *We predicted that*, compared with healthy and psychiatric control groups, depersonalized patients would rate aversive scenes as less emotional and fail to demonstrate in response to these scenes activation in neural regions important for the identification of disgust, particularly the anterior insula.

As predicted, depersonalized patients rated the aversive scenes as less emotive than controls (Fig. 1b), and, in response to these stimuli, showed reduced insula activation (Fig. 1c). Depersonalized patients demonstrated increased insula activation compared with healthy volunteers to neutral scenes, however. Both patient groups but not normal controls demonstrated activation in the right prefrontal cortex in response to the aversive scenes, within ventrolateral prefrontal cortex (Brodmann Area 47) in depersonalized patients and within dorsolateral prefrontal cortex (Brodmann Area 44) in OCD patients. Only in depersonalized patients, however, did activation within the right ventrolateral prefrontal cortex occur in the *absence* of activation within the insula in response to the aversive scenes. Activation also occurred in ventrolateral prefrontal cortex to neutral scenes in these patients. Additionally, the maximal activation within the left insula during presentation of *neutral* scenes was strongly positively correlated with the maximal regional power of response within the right ventrolateral prefrontal cortex during presentation of *aversive* scenes only in depersonalized patients, indicating an inverse correlation between changes in neural response within the left insula and right ventrolateral cortex during presentation of emotionally-salient stimuli in depersonalized patients (Fig. 1c).

The role of the ventrolateral prefrontal cortex in emotion processing has been discussed in an earlier section. Studies have associated this region with autobiographical memory retrieval, appraisal of facial expressions and ruminations in mild depression, but not with emotion experience *per se*. This region may be important for the contextual appraisal of emotionally-salient material. The insula is activated during mood induction, but has not been associated with contextual appraisal of emotionally-salient information. The pattern of neural response to aversive stimuli in depersonalized patients suggests that whilst appraisal of the emotional significance of emotive stimuli is intact, an affective state is not induced in response to this material in these patients. It is therefore possible that over-contextualization of emotive material serves to reduce the extent to which an affective state is generated in these patients. Interestingly, in response to neutral stimuli, activation occurred within the insula and ventrolateral prefrontal cortex in depersonalized patients. This pattern of neural response may reflect in depersonalized patients a reduction in appraisal of material, together with a relative increase in the magnitude of the affective response to this material, as its emotional salience decreases. This reversal of the normal pattern of neural response to emotive and neutral stimuli in depersonalized patients may be responsible for the emotional blunting frequently reported in this population.

EXAMINATION OF AUTONOMIC RESPONSES TO EMOTIVE STIMULI IN DEPERSONALIZED PATIENTS

In keeping with the above findings, Sierra *et al.* (2002b) have recently found that, in comparison to normal controls and patients with anxiety disorders, patients with depersonalization disorder have a selectively decreased autonomic response, measured by the number of skin conductance responses (SCRs) to emotional pictures (more marked for unpleasant pictures). In fact, patients with depersonalization disorder not only showed fewer measurable SCRs to the unpleasant pictures, but on those occasions when they showed a response, the amplitude of the SCR was markedly attenuated (see Fig. 2). In addition to this, patients with depersonalization had a longer SCR latency to unpleasant but not to pleasant, or neutral pictures. Although no impairment was found in the subjective assessment of valence, patients with depersonalization rated the unpleasant pictures as less arousing than the normal and clinical controls. In contrast to autonomic responses to emotional stimuli, both patients with depersonalization and anxiety disorders had similarly increased SCRs (Sierra *et al.*, 2002a,b), and shortened response latency to non-specific elicitors of a SCR such as a startling noise (Fig. 3).

These findings suggest the presence of simultaneous inhibitory and facilitatory mechanisms on specific components of autonomic activity. One the one hand, patients with depersonalization had similarly high anxiety ratings and SCRs to non-specific stimuli, hence suggesting a state of heightened arousal. On the other hand, the presence of a reduced basal skin conductance, and selectively attenuated SCRs to unpleasant emotional stimuli in patients with depersonalization, suggests a selective inhibition of normal autonomic responses to unpleasant emotional stimuli in these patients. Future studies are needed to clarify further the neurobiology of such a mechanism and its relationship with the perception of bodily states.

CONCLUSION

Clinical reports have emphasised in depersonalized patients emotional numbing, whilst neuroimaging and electrophysiological studies have indicated in these patients in response to emotive stimuli significant reductions in the magnitude of autonomic responses, and

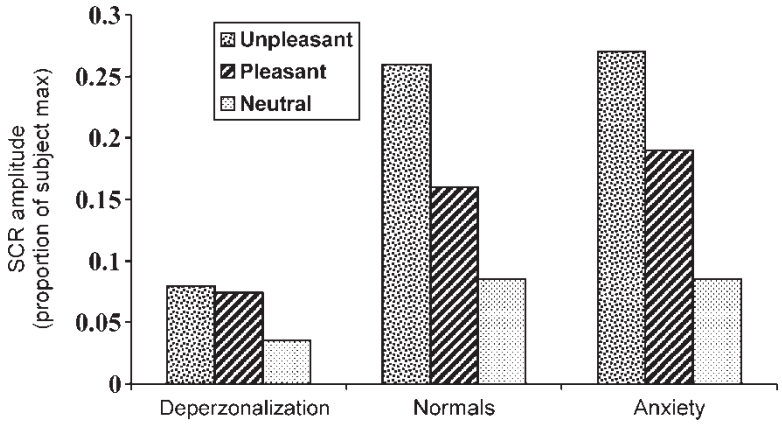

FIGURE 2 Skin conductance response (SCR) magnitude to unpleasant, pleasant and neutral pictures in patients with depersonalization disorder ($n = 15$), normal controls ($n = 15$) and patients with anxiety disorders ($n = 11$). As can be seen the skin conductance response to unpleasant pictures was significantly reduced in patients with depersonalization disorder ($P = 0.01$). Because the range of SCR amplitudes can vary across subjects, SCR magnitudes (ordinate; in μsiemens) were computed as a proportion of each subject's largest response. Adapted from Sierra *et al.* (2002b).

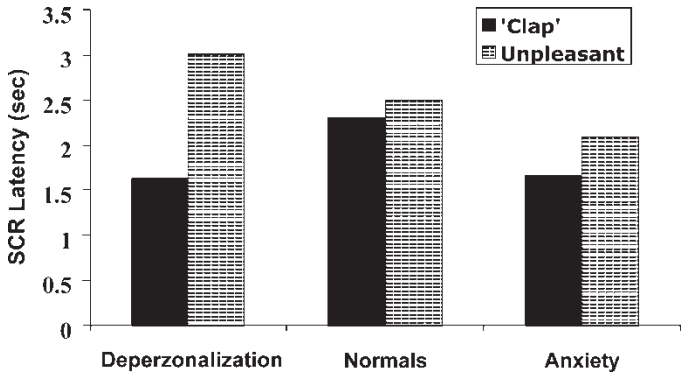

FIGURE 3 The latency of the skin conductance response (SCR) to unpleasant pictures was significantly prolonged in the group with depersonalization disorder (3.01 s compared with 2.5 and 2.1 s in the control and anxiety groups, respectively; $p = 0.02$). In contrast, latency to non-specific stimuli (unannounced clap) was significantly shorter in the depersonalization and anxiety groups (1.6 s) than in controls (2.3 s; $p = 0.03$). The finding that patients with depersonalization disorder respond earlier to a startling noise suggests that they are in a heightened state of alertness, and that the longer latency to the unpleasant pictures is caused by a selective inhibitory mechanism on negative emotional processing. Adapted from Sierra *et al.* (2002b).

decreased activity within neural regions important for the generation of normal affective responses to these stimuli. Furthermore, findings from neuroimaging studies indicate increased prefrontal cortical activity in depersonalised patients, particularly within regions associated with contextualization and appraisal of emotionally-salient information rather than emotional experience *per se*. Taken together, these findings suggest that symptoms of depersonalization, and in particular emotional numbing, may be associated with specific abnormalities in the neural mechanisms underlying normal emotion processing, namely, an inhibition of the normal patterns of autonomic and neural responses to emotive material.

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References

American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. (APA, Washington, DC).

Andreasen, N.C., O'Leary, D.S., Cizadlo, T., Arndt, S., Rezai, K., Watkins, G.L., Ponto, L.L. and Hichwa, R.D. (1995) Remembering the past: two facets of episodic memory explored with positron emission tomography, *Am. J. Psychiatry* **152**, 1576–1585.

Anderson, A.K. and Phelps, E.A. (2001) Lesions of the human amygdala impair enhanced perception of emotionally salient events, *Nature* **411**, 305–309.

Bartels, A. and Zeki, S. (2000) The neural basis of romantic love, *NeuroReport* **11**, 3829–3834.

Beauregard, M., Levesque, J. and Bourouin, P. (2001) Neural correlates of conscious self-regulation of emotion, *J. Neurosci.* **21**, 1–6.

Blair, R.J.R., Morris, J.S., Frith, C.D., Perrett, D.I. and Dolan, R.J. (1999) Dissociable neural responses to facial expressions of sadness and anger, *Brain* **122**, 883–893.

Bockner, S. (1949) The depersonalization syndrome: report of a case, *J. Ment. Sci.* **95**, 968–971.

Brauer, R., Harrow, M. and Tucker, G.J. (1970) Depersonalization phenomena in psychiatric patients, *Br. J. Psychiatry* **117**, 509–515.

Breiter, H.C., Etcoff, N.L., Whalen, P.J., Kennedy, W.A., Rauch, S.L., Buckner, R.L., Strauss, M.M., Hyman, S.E. and Rosen, B.R. (1996) Response and habituation of the human amygdala during visual processing of facial expression, *Neuron* **17**, 875–887.

Breiter, H.C., Gollub, R.L., Weisskoff, R.M., Kennedy, D.N., Makris, N., Berke, J.D., Goodman, J.M., Kantor, H.L., Gastfriend, D.R., Riorden, J.P., Mathew, R.T., Rosen, B.R. and Hyman, S.E. (1997) Acute effects of cocaine on human brain activity and emotion, *Neuron* **19**, 591–611.

Buchel, C., Morris, J., Dolan, R.J. and Friston, K.J. (1998) Brain systems mediating aversive conditioning: an event-related fMRI study, *Neuron* **20**, 947–957.

Buchel, C., Dolan, R.J., Armony, J.L. and Friston, K.J. (1999) Amygdala-hippocampal involvement in human aversive trace conditioning revealed through event-related functional magnetic resonance imaging, *J. Neurosci.* **19**, 10869–10876.

Cahill, L., Haier, R.J., Fallon, J., Alkire, M.T., Tang, C., Keator, D., Wu, J. and McGaugh, J.L. (1996) Amygdala activity at encoding correlated with long-term, free recall of emotional information, *Proc. Natl Acad. Sci. USA* **93**, 8016–8021.

Canli, T., Zhao, Z., Breweer, J., Gabrieli, J.D.E. and Cahill, L. (2000) Event-related activation in the human amygdala associates with later memory for individual emotional experiences, *J. Neurosci.* **20**, 1–5.

Casey, K.L., Minoshima, S., Berger, K.L., Koeppe, R.A., Morrow, T.J. and Frey, K.A. (1994) Positron emission tomographic analysis of cerebral structures activated specifically by repetitive noxious heat stimuli, *J. Neurophysiol.* **71**, 802–807.

Casey, K.L., Minoshima, S., Morrow, T.J. and Koeppe, R.A. (1996) Comparison of human cerebral activation pattern during cutaneous warmth, heat pain, and deep cold pain, *J. Neurophysiol.* **76**, 571–581.

Charney, D.S. and Drevets, W.C. (2002) The neurobiological basis of anxiety disorders, In: Davis, K., Charney, D.S., Coyle, J. and Nemeroff, C.B., eds, Psychopharmacology The Fifth Generation of Progress (Lippencott).

Critchley, H.D., Mathias, C.J. and Dolan, R.J. (2001a) Neural activity in the human brain relating to uncertainty and arousal during anticipation, *Neuron* **29**, 537–545.

Critchley, H.D., Mathias, C.J. and Dolan, R.J. (2001b) Neuroanatomical basis for first- and second-order representations of bodily states, *Nat. Neurosci.* **4**, 207–212.

Critchley, H.D., Melmed, R.N., Featherstine, E., Mathias, C.J. and Dolan, R.J. (2001c) Brain activity during biofeedback relaxation. A functional neuroimaging investigation, *Brain* **124**, 1002–1012.

Damasio, A.R. (1999) The Feeling of What Happens: Body and Emotion in the Making of Consciousness (Harcourt Brace, New York).

Dolan, R.J. Lane, R., Chua, P. and Fletcher, P. (2000) Dissociable temporal lobe activations during emotional episodic memory retrieval, *Neuroimage* **11**, 203–209.

Dougherty, D., Shin, L.M., Alpert, N.M., Pitman, R.K., Orr, S.P., Lasko, M., *et al.* (1999) Anger in healthy men: a PET study using script-driven imagery, *Biol. Psychiatry* **46**, 466–472.

Drevets, W.C. and Raichle, M. (1998) Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: implications for interactions between emotion and cognition, *Cogn. Emotion* **12**, 353–385.

Drevets, W.C., Gautier, C., Price, J.C., Kupfer, D.J., Kinahan, P.E., Grace, A.A., Price, J.L. and Mathis, C.A. (2001) Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria, *Biol. Psychiatry* **49**, 81–96.

Dubois, S., Rossion, B., Schiltz, C., Bodart, J.M., Michel, C., Bruyer, R. and Crommelinck, M. (1999) Effect of familiarity on the processing of human faces, *Neuroimage* **9**, 278–289.

Elliott, R., Dolan, R.J. and Frith, C.D. (2000a) Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies, *Cereb. Cortex* **10**, 308–317.

Elliott, R., Friston, K.J. and Dolan, R.J. (2000b) Dissociable neural responses in human reward systems, *J. Neurosci.* **20**, 6159–6165.

Elliott, R., Rubinsztein, J.S., Sahakian, B.J. and Dolan, R.J. (2002) The neural basis of mood-congruent processing biases in depression, *Arch. Gen. Psych.* **59**, 597–604.

Fink, G.R., Markowitsch, H.J., Reinkemeier, M., Bruckbauer, T., Kessler, J. and Heiss, W.D. (1996) Cerebral representation of one's own past: neural networks involved in autobiographical memory, *J. Neurosci.* **16**, 4275–4282.

Francis, S., Rolls, E.T., Bowtell, R., McGlone, F., O'Doherty, J., Browning, A., Clare, S. and Smith, E. (1999) The representation of pleasant touch in the brain and its relationship with taste and olfactory areas, *NeuroReport* **10**, 453–459.

Frith, C.D. and Frith, U. (1999) Interacting minds—a biological basis, *Science* **286**, 1692–1695.

George, M.S., Ketter, T.A., Parekh, P.I., Horwitz, B., Herscovitch, P. and Post, R.M. (1995) Brain activity during transient sadness and happiness in healthy women, *Am. J. Psychiatry* **152**, 341–351.

Goldman-Rakic, P.S. (1987) Topography of cognition: parallel distributed networks in primate association cortex, *Annu. Rev. Neurosci.* **11**, 137–156.

Greene, J.D., Sommerville, R.B., Nystrom, L.E., Darley, J.M. and Cohen, J. (2001) An fMRI investigation of emotional engagement in moral judgment, *Science* **293**, 2108–2195.

Gusnard, D.A., Akbudak, E., Sulman, G.L. and Raichle, M. (2001) Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function, *Proc. Natl Acad. Sci. USA* **98**, 4259–4264.

Hamann, S.B., Ely, T.D., Grafton, S.T. and Kilts, C.D. (1999) Amygdala activity related to enhanced memory for pleasant and aversive stimuli, *Nat. Neurosci.* **2**, 289–293.

Hariri, A.R., Bookheiner, S.Y. and Mazziotta, J.C. (2000) Modulating emotional responses: effects of a neocortical network on the limbic system, *NeuroReport* **11**, 43–48.

Hollander, E., Carrasco, J.L., Mullen, L.S., Trungold, S., DeCaria, C.M. and Towey, J. (1992) Left hemispheric activation in depersonalization disorder: a case report, *Biol. Psychiatry* **31**, 1157–1162.

Isenberg, N., Silbersweig, D., Engelien, A., E, S., Malavade, K. and Beattie, B. (1999) Linguistic threat activates the human amygdala, *Proc. Natl Acad. Sci. USA* **96**, 10456–10459.

Johnson, S.C., Baxter, L.C., Wilder, L.S., Pipe, J.G., Heiserman, J.E. and Prigatano, G.P. (2002) Neural correlates of self-reflection, *Brain* **125**, 1808–1814.

Lader, M.H. (1975) The Psychophysiology of Mental Illness (Routledge & Kegan Paul, London).

Liotti, M., Mayberg, H.S., McGinnis, S., Brannan, S.L. and Jerabek, P. (2002) Unmasking disease-specific cerebral blood flow abnormalities: mood challenge in patients with remitted unipolar depression, *Am. J. Psychiatry* **159**, 1830–1840.

Kawashima, R., Sugiura, M., Kato, T., Nakamura, A., Hatano, K. and Ito, K. (1999) The human amygdala plays an important role in gaze monitoring: a PET study, *Brain* **122**, 779–783.

Kelly, D.H.W. and Walter, C.J.S. (1968) The relationship between clinical diagnosis and anxiety, assessed by forearm blood flow and other measurements, *Brit. Jul. Psychiatry* **114**, 611–626.

Killgore, W.D., Oki, M. and Yurgelun-Todd, D.A. (2001) Sex-specific developmental changes in amygdala responses to affective faces, *NeuroReport* **12**, 427–433.

Kimbrell, T.A., Ketter, T.A., George, M.S., Little, J.T., Benson, B.E., Willis, M.W., Herscovitch, P. and Post, R.M. (2002) Regional cerebral glucose utilization in patients with a range of severities of unipolar depression, *Biol. Psychiatry* **51**, 237–252.

Kimbrell, T.A., George, M.S., Parekh, P.I., Ketter, T.A., Podell, D.M., Danielson, A.L., Repella, J.D., Benson, B.E., Willis, M.W., Herscovitch, P. and Post, R.M. (1999b) Regional brain activity during transient self-induced anxiety and anger in healthy adults, *Biol. Psychiatry* **46**, 465.

Knutson, B., Fong, G.W., Adams, C.M., Varner, J.L. and Hommer, D. (2001) Dissociation of reward anticipation and outcome with event-related fMRI, *NeuroReport* **12**, 3683–3687.

LaBar, K.S., Gatenby, C., Gore, J.C. and Phelps, E.A. (1998) Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study, *Neuron* **20**, 937–945.

Lambert, M.V., Sierra, M., Phillips, M.L. and David, A.S. (2002) The spectrum of organic depersonalization: a review plus four new cases, *J. Neuropsychiatry Clin. Neurosci.* **14**, 141–154.

Lane, R.D., Fink, G.R., Chau, P.M. and Dolan, R.J. (1997a) Neural activation during selective attention to subjective emotional responses, *NeuroReport* **8**, 3969–3972.

Lane, R.D., Reiman, E.M., Ahern, G.L., Schwartz, G.E. and Davidson, R.J. (1997b) Neuroanatomical correlates of happiness, sadness, and disgust, *Am. J. Psychiatry* **154**, 926–933.

Lane, R.D., Reiman, E.M., Axelrod, B., Yun, L.S., Holmes, A. and Schwartz, G.E. (1998) Neural correlates of levels of emotional awareness. Evidence of an interaction between emotion and attention in the anterior cingulate cortex, *J. Cogn. Neurosci.* **10**, 525–535.

Lang, P.J., Bradley, M.M. and Cuthbert, B.N. (1997) International Affective Picture System (IAPS) (NIMH Center for the Study of Emotion and Attention).

Lang, P.J., Bradley, M.M., Fitzsimmons, J.R., Cuthbert, B.N., Scott, J.D., Moulder, B. and Nangia, V. (1998) Emotional arousal and activation of the visual cortex: an fMRI analysis, *Psychophysiology* **35**, 199–210.

Lange, K., Williams, L.M., Young, A.W., Bullmore, E.T., Williams, S.C.R., Brammer, M.J., Gray, J.A. and Phillips, M.L. (2003) Task instructions modulate neural responses to fearful facial expressions, *Biol. Psychiatry* **53**, 226–232.

Levesque, J., Eugene, F., Joanette, Y., Paquette, V., Mensour, B., Beaudoin, G., Leroux, J.-M., Bourgouin, P. and Beauregard, M. (2003) Neural circuitry underlying voluntary suppression of sadness, *Biol. Psychiatry* **53**, 502–510.

Markowitsch, I.I.J. (1997) The functional neuroanatomy of episodic memory retrieval, *Trends in Neurosciences* **20**, 557–558.

Mathew, R.J., Wilson, W.H., Chiu, N.Y., Turkington, T.G., Degrado, T.R. and Coleman, R.E. (1999) Regional cerebral blood flow and depersonalization after tetrahydrocannabinol administration, *Acta Psychiatr. Scand.* **100**, 67–75.

Mayberg, H.S., Liotti, M., Brannan, S.K., McGinnis, S., Mahurin, R.K., Jerabek, P.A., Silva, J.A., Tekell, J.L., Martin, C.C., Lancaster, J.L. and Fox, P.T. (1999) Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness, *Am. J. Psychiatry* **156**, 675–682.

Mayer-Gross, W. (1935) On depersonalization, *Br. J. Med. Psychol.* **15**, 103–122.

Morris, J.S., Friston, K.J., Buchel, C., Frith, C.D., Young, A.W., Calder, A.J., *et al.* (1998a) A neuromodulatory role for the human amygdala in processing emotional facial expressions, *Brain* **12**, 47–57.

Morris, J.S., Frith, C.D., Perrett, D.I., Rowland, D., Young, A.W., Calder, A.J. and Dolan, R.J. (1996) A differential neural response in the human amygdala to fearful and happy facial expressions, *Nature* **383**, 812–815.

Morris, J.S., Ohman, A. and Dolan, R.J. (1998b) Conscious and unconscious emotional learning in the human amygdala, *Nature* **393**, 467–470.

Nakamura, K., Kawashima, R., Ito, K., Sugiura, M., Kato, T., Nakamura, A., Hatano, K., Nagumo, S., Kubota, K., Fukuda, H. and Kojima, S. (1999) Activation of the right inferior frontal cortex during assessment of facial emotion, *J. Neurophysiol.* **82**, 1610–1614.

O'Doherty, J., Rolls, E.T., Francis, S., Bowtell, R., McGlone, F., Kobal, G., Renner, B. and Ahne, G. (2000) Sensory-specific satiety-related olfactory activation of the human orbitofrontal cortex, *NeuroReport* **11**, 893–897.

O'Doherty, J., Kringelbach, M.L., Rolls, E.T., Hornak, J. and Andrews, C. (2001a) Abstract reward and punishment representations in the human orbitofrontal cortex, *Nat. Neurosci.* **4**, 95–102.

O'Doherty, J., Rolls, E.T., Francis, S., Bowtell, R. and McGlone, F. (2001b) Representation of pleasant and aversive taste in the human brain, *J. Neurophysiol.* **85**, 1315–1321.

Pagnoni, G., Zink, C.F., Montague, P.R. and Berns, G.S. (2002) Activity in human ventral striatum locked to errors of reward prediction, *Nat. NeuroScience* **5**, 97–98.

Pardo, J.V., Pardo, P.J. and Raichle, M.E. (1993) Neural correlates of self-induced dysphoria, *Am. J. Psychiatry* **150**, 713–719.

Phelps, E.A., Lee, J.T., Fluegel, K.W. and Pardo, J.V. (1998) Aversive gustatory stimulation activates limbic circuits in humans, *Brain* **121**, 1143–1154.

Phillips, M.L., Young, A.W., Senior, C., Brammer, M., Andrew, C., Calder, A.J., Bullmore, E.T., Perrett, D.I., Rowland, D., Williams, S.C.R., Gray, J.A. and David, A.S. (1997) A specific neural substrate for perception of facial expressions of disgust, *Nature* **389**, 495–498.

Phillips, M.L., Young, A.W., Scott, S.K., Calder, A.J., Andrew, C., Giampietro, V., *et al.* (1998) Neural responses to facial and vocal expressions of fear and disgust, *Proc. R. Soc. Lond. B* **265**, 1809–1817.

Phillips, M.L., Medford, N., Senior, C., Bullmore, E.T., Suckling, J., Brammer, M.J., Andrew, C., Sierra, M., Williams, S.C. and David, A.S. (2001a) Depersonalization disorder: thinking without feeling, *Psychiatry Res.* **108**, 145–160.

Phillips, M.L., Medford, N., Young, A.W., Williams, L., Williams, S.C., Bullmore, E.T., Gray, J.A., Brammer, M.J. and Gray, J.A. (2001b) Time courses of left and right amygdalar responses to fearful facial expressions, *Hum. Brain Mapp.* **12**, 193–202.

Phillips, M.L., Drevets, W.C., Rauch, S.L. and Lane, R.D. (2003a) The neurobiology of emotion perception I: towards an understanding of the neural basis of normal emotion perception, *Biol. Psychiatry*, In press.

Phillips, M.L., Drevets, W.C., Rauch, S.L. and Lane, R.D. (2003b) The neurobiology of emotion perception II: implications for understanding the neural basis of emotion perceptual abnormalities in schizophrenia and affective disorders, *Biol. Psychiatry*, In press.

Pietrini, P., Guazzelli, M., Basso, G., Jaffe, K. and Grafman, J. (2000) Neural correlates of imagined aggressive behaviour assessed by positron emission tomography in healthy subjects, *Am. J. Psychiatry* **157**, 1772–1781.

Ploghaus, A., Tracey, I., Gati, J.S., Clare, S., Menon, R.S., Matthews, P.M. and Rawlins, J.N. (1999) Dissociating pain from its anticipation in the human brain, *Science* **284**, 1979–1981.

Rainville, P., Duncan, G.H., Proce, D.D., Carrier, B. and Bushnell, M.C. (1997) Pain affect encoded in human anterior cingulate but not somatosensory cortex, *Science* **277**, 968–971.

Reiman, E.M., Lane, R.D., Ahern, G.L. and Scwartz, G.E. (1997) Neuroanatomical correlates of externally and internally generated human emotion, *Am. J. Psychiatry* **154**, 918–925.

Ross, C.A., Joshi, C. and Currie, R. (1991) Dissociative experiences in the general population: a factor analysis, *Hosp. Comm. Psychiatry* **3**, 297–301.

Schneider, F., Grodd, W., Weiss, U., Klose, U., Mayer, K.R., Nagele, T. and Gur, R.C. (1997) Functional MRI reveals left amygdala activation during emotion, *Psychiatry Res.: Neuroimaging* **76**, 75–82.

Shin, L.M., Dougherty, D.D., Orr, S.P., Pitman, R.K., Lasko, M., Macklin, M.L., Alpert, N.M., Fischman, A.J. and Rauch, S.L. (2000) Activation of anterior paralimbic structures during guilt-related script-driven imagery, *Biol. Psychiatry* **48**, 43–50.

Shorvon, H.J. (1946) The depersonalization syndrome, *Proc. R. Soc. Med.* **39**, 779–792.

Sierra, M. and Berrios, G.B. (1997) Depersonalization: a conceptual history, *Hist. Psychiatry* **8**, 213–229.

Sierra, M. and Berrios, G.E. (1998) Depersonalization: neurobiological perspectives, *Biol. Psychiatry* **44**, 898–908.

Sierra, M. and Berrios, G.B. (2001) The phenomenological stability of depersonalization: comparing the old with the new, *J. Nerv. Ment. Dis.* **189**, 629–636.

Sierra, M., Lopera, F., Lambert, M.V., Phillips, M.L. and David, A.S. (2002a) Separating depersonalisation and derealisation: the relevance of the 'lesion method', *J. Neurol. Neurosurg. Psychiatry* **72**, 530–532.

Sierra, M., Senior, C., Dalton, J., McDonough, M., Bond, A., Phillips, M.L., O'Dwyer, A.M. and David, A.S. (2002b) Autonomic response in depersonalisation disorder, *Arch. Gen. Psychiatry* **59**, 833–838.

Simeon, D., Gross, S., Guralnik, O., Stein, D.J., Schmeidler, J. and Hollander, E. (1997) Feeling unreal: 30 cases of DSM-III-R depersonalization disorder, *Am. J. Psychiatry* **154**, 1107–1113.

Simeon, D., Guralnik, O., Hazlett, E.A., Spiegel-Cohen, J., Hoolander, E. and Buchsbaum, M.S. (2000) Feeling unreal: a PET study of depersonalization disorder, *Am. J. Psychiatry* **157**, 1782–1788.

Simpson, J.R., Drevets, W.C., Snyder, A.Z., Gusnard, D.A. and Raichle, M.E. (2001) Emotion-induced changes in human medial prefrontal cortex: II. During anticipatory anxiety, *Proc. Natl Acad. Sci. USA* **98**, 688–693.

Small, D.M., Zald, D.H., Jones-Gotman, M., Zatorre, R.J., Pardo, J.V., Frey, S. and Petrides, M. (1999) Human cortical gustatory areas: a review of functional neuroimaging, *NeuroReport* **10**, 7–14.

Sprengelmeyer, R., Rausch, M., Eysel, U.T. and Przuntek, H. (1998) Neural structures associated with recognition of facial expressions of basic emotions, *Proc. Natl Acad. Sci. USA* **265**, 1927–1931.

Sullivan, R.M. and Gratton, A. (1999) Lateralized effects of medial prefrontal cortex lesions on neuroendocrine and autonomic stress responses in rats, *J. Neurosci.* **19**, 2834–2840.

Taylor, S.F., Liberzon, I. and Koeppe, R.A. (2000) The effect of graded aversive stimuli on limbic and visual activation, *Neuropsychologia* **38**, 1415–1425.

Teasdale, J.D., Howard, R.J., Cox, S.G., Ha, Y., Brammer, M.J., Williams, S.C.R. and Checkley, S.A. (1999) Functional MRI study of the cognitive generation of affect, *Am. J. Psychiatry* **156**, 209–215.

Thomas, K.M., Drevets, W.C., Whalen, P.J., Eccard, C.H., Dahl, R.E., Ryan, N.D., Birmaher, B., Eccard, C.H., Axelson, D., Whalen, P.J. and Casey, B.J. (2001) Amygdala response to facial expressions in children and adults, *Biol. Psychiatry* **49**, 309–316.

Timms, R.J. (1977) Cortical inhibition and facilitation of the defence reaction, *J. Physiol. Lond.* **266**, 98P–99P.

Whalen, P.J., Rauch, S.L., Etcoff, N.L., McInerney, S.C., Lee, M.B. and Jenike, M.A. (1998) Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge, *J. Neurosci.* **18**, 411–418.

Wright, C.I., Fischer, H., Whalen, P.J., McInerney, S.C., Shin, L.M. and Rauch, S.L. (2001) Differential prefrontal cortex and amygdala habituation to repeatedly presented emotional stimuli, *NeuroReport* **12**, 379–383.

Videbech, P., Ravnkilde, B., Pedersen, T.H., Hartvig, H., Egander, A., Clemmensen, K., Rasmussen, N.A., Andersen, F., Gjedde, A. and Rosenberg, R. (2002) The Danish PET/depression project: clinical symptoms and cerebral blood flow. A regions-of-interest analysis, *Acta Psychiatr. Scand.* **106**, 35–44.

Zald, D.H., Lee, J.T., Fluegel, K.W. and Pardo, J.V. (2003) Task instructions modulate neural responses to fearful facial expressions, *Biol. Psychiatry* **53**, 226–232.

Zald, D.H. and Pardo, J.V. (1997) Emotion, olfaction, and the human amygdala: amygdala activation during aversive olfactory stimulation, *Proc. Natl Acad. Sci. USA* **94**, 4119–4124.