

Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices

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Summary

To analyse the functions of different parts of the prefrontal cortex in emotion, patients with different prefrontal surgical excisions were compared on four measures of emotion: voice and face emotional expression identification, social behaviour, and the subjective experience of emotion. Some patients with bilateral lesions of the orbitofrontal cortex (OFC) had deficits in voice and face expression identification, and the group had impairments in social behaviour and significant changes in their subjective emotional state. Some patients with unilateral damage restricted to the OFC also had deficits in voice expression identification, and the group did not have significant changes in social behaviour or in their subjective emotional state. Patients with unilateral lesions of the antero-ventral part of the anterior cingulate cortex (ACC) and/or medial Brodmann area (BA) 9 were, in some cases, impaired on voice and face expression identification, had some change in social behaviour, and had significant changes in their subjective emotional state. Patients with unilateral lesions of the OFC and of the ACC and/or medial BA 9 were, in some cases, impaired on voice and face expression identification, had some changes in social behaviour, and had significant changes

in their subjective emotional state. Patients with dorsolateral prefrontal cortex lesions or with medial lesions outside ACC and medial BA 9 areas (dorsolateral/other medial group) were unimpaired on any of these measures of emotion. In all cases in which voice expression identification was impaired, there were no deficits in control tests of the discrimination of unfamiliar voices and the recognition of environmental sounds. Thus bilateral or unilateral lesions circumscribed surgically within the OFC can impair emotional voice and/or face expression identification, but significant changes in social behaviour and in subjective emotional state are related to bilateral lesions. Importantly, unilateral lesions of the ACC (including some of medial BA 9) can produce voice and/or face expression identification deficits, and marked changes in subjective emotional state. These findings with surgically circumscribed lesions show that within the prefrontal cortex, both the OFC and the ACC/medial BA 9 region are involved in a number of aspects of emotion in humans including emotion identification, social behaviour and subjective emotional state, and that the dorsolateral prefrontal areas are not involved in emotion in these ways.

Keywords: emotion; face expression; personality; social behaviour; voice expression

Abbreviations: ACC = anterior cingulate cortex; DLat/OM = dorsolateral/other medial; OFC = orbitofrontal cortex

Introduction

There is converging evidence from neuroimaging and clinical studies that, although the dorsolateral prefrontal cortex is important on a wide variety of cognitive tasks, especially those with an executive component (Passingham, 1975; Owen *et al.*, 1998; Duncan and Owen, 2000; A.D. Rowe *et al.*,

2001; J.B. Rowe *et al.*, 2001), the orbital and medial regions of the frontal lobe play an important role in processing emotional or emotion-related stimuli, in emotion or reward-related learning, in mediating the subjective experience of emotion and reward, and in normal social behaviour (Bechara

et al., 1994, 1998, 1999; Rolls *et al.*, 1994; Hornak *et al.*, 1996; Lane *et al.*, 1997a, b, 1998; Phillips *et al.*, 1998; Blair *et al.*, 1999; Blood *et al.*, 1999; Morris *et al.*, 1999; Rolls, 1999a, 2000, 2002; O'Doherty *et al.*, 2001; Hadland *et al.*, 2003), as described below.

Patients with large bilateral 'ventromedial' prefrontal cortex lesions show emotional and social impairments (Bechara *et al.*, 1994, 1998, 1999). Rolls *et al.* (1994) and Hornak *et al.* (1996) analysed the changes in emotion-related learning, the subjective experience of emotion, social behaviour, and the interpretation of facial and vocal expression in patients with ventromedial prefrontal cortex lesions. In these studies, the changes were attributed largely to the orbitofrontal cortex (OFC) damage, since neurophysiological and lesion work in monkeys indicates that this region is important in representing rewards and punishers and in learning stimulus-reinforcement associations, and thus in emotion and social behaviour (Jones and Mishkin, 1972; Kling and Steklis, 1976; Thorpe *et al.*, 1983; Gaffan *et al.*, 1993; Critchley and Rolls, 1996; Rolls *et al.*, 1996, 2003; Baxter *et al.*, 2000; Rolls, 2000, 2002; O'Doherty *et al.*, 2001; E. T. Rolls, H. D. Critchley, A. S. Browning, K. Inoue, unpublished results).

However, the 'ventromedial' prefrontal lesions in the human studies cited above, in some cases at least, cover a large territory of the prefrontal cortex including the OFC on the ventral surface, and the rostral anterior cingulate and more anterior medial prefrontal cortical regions. Recent evidence from neuroimaging and from electrophysiological and lesion studies in non-human primates suggests that the orbitofrontal and medial prefrontal cortical areas may have distinct functions (see below). The aim of the present study was to investigate the effects of circumscribed lesions in the orbital and medial prefrontal cortex, to investigate to what extent lesions of these different areas contribute to the social and emotional changes that follow ventromedial prefrontal lesions in humans, and to determine whether these regions can be dissociated in terms of their contribution to different aspects of emotional processing. In pursuing this aim we were able to obtain evidence from patients with surgically circumscribed lesions of different parts of the prefrontal cortex, as described below.

The medial and orbital regions are richly interconnected, especially via the ventromedial part of the frontal lobe (area 14), suggesting that a lesion in either might be expected to disrupt some of the same functions (Cavada *et al.*, 2000; Koski and Paus, 2000; Ongur and Price, 2000). Nevertheless, these regions can be distinguished from each other by both their intrinsic connections and their connections with other parts of the brain (Ongur and Price, 2000). To this extent they would be expected to contribute differently to emotional processing. Thus the orbital regions receive sensory inputs from several modalities, including visual, auditory, somatosensory, taste and olfactory, and are concerned with the analysis

of the reward value or affective significance of stimuli such as facial or vocal expressions of emotion (Barbas and Pandya, 1989; Rolls *et al.*, 1996, 2003; Barbas *et al.*, 1999; Rolls, 2000, 2002; Romanski and Goldman-Rakic, 2002; E. T. Rolls, H. D. Critchley, A. S. Browning, K. Inoue, unpublished results). Less is known functionally about the most anterior parts of the anterior cingulate cortex (ACC), but the pre-callosal cingulate cortex is implicated by neuroimaging studies in emotion (see below), and the subgenual cingulate cortex has strong autonomic output connections (Vogt and Pandya, 1987; Vogt *et al.*, 1987; Paus, 2001).

The importance of orbital prefrontal regions for the perception of facial or vocal emotion is suggested both by neuroanatomical and neurophysiological studies with non-human primates. Direct projections to orbitofrontal/inferior convexity cortex from regions in the temporal lobe where faces and face expressions are represented have been demonstrated (Rolls, 1999a). For vocal stimuli too, there are neuroanatomical connections between temporal auditory cortex and the frontal lobe. It has been suggested that more rostral auditory cortex in the temporal lobe, which projects to the orbitofrontal cortex, is primarily engaged in processing phonetic (vocal) information (Romanski *et al.*, 1999; Cavada *et al.*, 2000), and a recent electrophysiological study (Romanski and Goldman-Rakic, 2002) found neurons responsive to monkey and human vocalization concentrated in an area of orbital cortex. Barbas *et al.* (1999) have also described, in monkeys, both visual and auditory projections from the anterior temporal pole cortex to the ACC, a region long implicated in vocalization (Jurgens, 2002). Recent work by Hadland *et al.* (2003) also found diminished social vocalization in monkeys with anterior cingulate lesions, and also emotional and social changes.

Consistent with the neuroanatomical and electrophysiological findings, neuroimaging studies concerned with vocal expression identification have reported orbital and medial activation. This includes a study by Morris *et al.* (1999) using non-verbal sounds expressing fear, sadness and happiness which, when compared with a neutral condition, activated Brodmann area (BA) 11 (orbital cortex) bilaterally and medial BA 9 on the left. Fear-related increases in activity were also found on the right only in BA 11. In another study, Phillips *et al.* (1998) found that fearful sounds activated medial BA 32 and BA 24 (anterior cingulate at/below the level of the genu of the corpus callosum), again on the right side only. More extensive studies of facial expression identification have been conducted, and these report activation in a number of sites within the both orbital and medial regions, including medial BA 9 and BA 32/24 (anterior cingulate) (Dolan *et al.*, 1996; Blair *et al.*, 1999; Nakamura *et al.*, 1999).

There is also evidence suggesting a role for certain medial regions in the subjective experience of emotion. In

neuroimaging studies with normal human subjects, bilateral activations in medial BA 9 were found as subjects viewed emotion-laden stimuli, and in both medial BA 9 as well as in ventral ACC during self-generated emotional experience (i.e. in the absence of a stimulus) as subjects recalled emotions of sadness or happiness (Lane *et al.*, 1997a, b, 1998). On the basis of a review of imaging studies that consistently emphasize the importance of anterior and ventral regions of ACC for emotion, Bush *et al.* (2000) argue that the ACC can be divided into a ventral 'affective division' (which includes the subcallosal region and the part anterior to the corpus callosum, and is referred to in this paper as ACC), and a dorsal 'cognitive' division, a view strengthened by the demonstration of reciprocally inhibitory interactions between these two regions.

The importance of the ACC to mood and emotion, perhaps especially in the maintenance of positive mood, is also underlined by studies that show changes in this region in psychiatric patients suffering from depression. Thus Drevets *et al.* (1997) found reduced blood flow in depression in the subgenual cingulate (BA 25) with increases during the manic phase in bipolar depressives. In a number of neuropathological studies, this region has been found to have considerably reduced volume, especially on the left, in patients with familial mood disorder, along with reduced density and number of glia (Ongur *et al.*, 1998; Torrey *et al.*, 2000). Others have found that improved mood after treatment for depression was associated with increased activity in the anterior cingulate (Buchsbaum *et al.*, 1997; Mayberg, 1997).

In the present study, patients with unilateral and bilateral surgical excisions in different regions of the frontal lobe were compared on the perception of emotional stimuli, (1) non-verbal vocal emotional sounds and (2) facial expressions; (3) the subjective experience of emotion since the surgery; and (4) social behaviour. Social behaviour was assessed using a social behaviour questionnaire concerning the social adjustment of the patients by a relative or close friend, and this was performed in order to compare changes in the perception of emotional stimuli or in the subjective experience of emotion with post-operative alterations in social functioning. In addition to the main classification of their lesions (as orbital, medial or dorsolateral), the brain maps of individual patients were studied in order to determine whether their excisions encroached upon those medial areas where, as suggested by the literature, a lesion might be expected to affect them most on the measures used. Since medial BA 9 and the ACC (which includes BA 32/24 as well as the more ventral subgenual region) appear to be important for the analysis of affective stimuli or for the quality of emotional experience, or for both, medial lesions were categorized according to whether they encroached upon these regions.

Patients and methods

Subjects

Patients groups

Thirty-five patients were included in the study. They were under the care of the Department of Neurosurgery, King's College Hospital, London. Where possible, the site of the lesion was ascertained by acquiring a MRI or CT scan in addition to neurosurgeons' reports and brain maps. Exclusion criteria included damage outside the prefrontal cortex, alcohol or drug dependence, and a full-scale intelligence quotient (IQ) below a cut-off of 75. Eighteen of the patients were male and 17 were female, and their ages ranged from 19 to 72 years (mean = 44 years, SD = 15 years). The time between surgery and taking part in the study ranged from 1 to 22 years. Thirteen had suffered from focal epilepsy, 14 from meningioma, and one patient had suffered from one of the following: anterior communicating artery aneurysm and subarachnoid haemorrhage; focal head injury; cavernoma; gliodendroblastoma; malignant ependymoma; and astrocytoma. The study was approved by King's College LERC. All patients gave written informed consent.

Normal control group

For the vocal tests, 48 participants formed a normal control group, matched with the patient group for sex, age, level of education and occupational category. For the environmental sounds test there were 18 such normal subjects, similarly matched with the patient group. For the facial expression test, 25 normal subjects took part, matched for sex, age, level of education, occupational category and IQ, as measured on the National Adult Reading Test (Nelson, 1982).

Categorization of lesions

Table 1 and Fig. 1 show the lesion sites for each patient. A method of categorization was used in which the patients were classified according to the prefrontal sectors of functional significance into which the lesions encroached (A.D.Rowe *et al.*, 2001). These were defined anatomically as orbital (BA 10, 11, 12 and 25), medial (BA 8, 9 and 10) and dorsolateral (BA 9 and 46). Patients are shown as having a lesion in a given region if their lesion extended to include at least some part of that region. As shown in Table 1 and Fig. 1, those with bilateral lesions had orbital or they had a combination of orbital and medial lesions.

Subdivision of medial lesions

In Table 1, the medial lesions are categorized according to whether they included regions of particular interest for the present study, namely medial BA 9 and ACC (affective ACC). Figure 2 (left) shows the divisions of the medial regions as described by Bush *et al.* (2000), and Fig. 2 (right)

shows the position of these medial regions on a standard brain map of the type available for patients in the present study and used in Fig. 1. We emphasize that in this paper ACC refers to the part of the ACC that is anterior to and below the corpus

callosum [and in Fig. 2 is labelled ‘ACC Aff. Division’ after Bush *et al.* (2000)]. Medial lesions lying outside these regions are referred to as ‘other medial’ lesions. Figure 1 shows the brain maps of the patients categorized in the same way as in

Table 1 Performance on four measures in relation to the presence of lesions in orbital, medial and dorsolateral prefrontal cortex

Patient	Side of lesion	Orbital	Medial† BA 9	ACC	Psychological tests			
					Vocal emot. (SD)	Facial expr. (SD)	Subj. emot. total	Social behav. (12) mean
DLat/OM								
R.C.	R			DL	0.1	1.4	0	4.33
F.Z.	R			DL	1.7*	0.2	2.5	3.25
B.S.	R			DL	0.7	-1.2		
R.D.	L			DL	0.7	0.3	0	3.83
F.G.	L			OM		0.4	0.5	4.50
Q.O.	L			DL	0.1	0.7	0	4.33
O.R.	R			OM	DL		0	4.83
U.C.	R			OM	DL	0.7	1	3.33
G.E.	R			OM	DL	-0.9	0.5	4.67
G.D.	R			OM	DL	0.4	-0.6	4.42
A.G.	L			OM	DL	-0.2	-1.4	5.00
Bilateral OFC								
V.O.		(++)				2.4**	1.8*	3.17
J.A.		++		OM	0.1	0.1	3.5	4.50
V.U.		++		OM	1.4	0.1	3	2.50
R.R.		++				2.7**	3.5	
R.F.		++	++	OM	-0.6	1.8*	3	3.58
V.Z.		++	++	OM	4.4**	2.5**		1.58
Orbital								
T.R.	R	+				2.7**	1.1	3.5
L.J.	R	+				-0.2	0.2	2
R.Q.	R	+				2.7**	0.4	3.67
C.L.	R	+				3.4**	1.6	2
R.I.	R	+		OM			0	2.83
S.I.	L	+		OM	0.4	0.4	1.5	4.67
BA 9/ACC								
L.Q.	R		+	(+)	OM	3.0**		4.5
B.R.	R		+	+	OM	3.4**	2.5**	3.75
E.E.	R		+	+	OM	3.4**	2.2*	5.5
O.F.	L		+	+	OM	-0.2	1.2	3.50
BA 9/ACC + orbital								
V.F.	L	+		+	OM	DL	-0.2	3.5
B.Q.	R	+	+	+	OM		2.7**	3
Q.G.	R	+	+	+	OM	DL	2.1*	3.00
L.K.	R	+	+	+	OM	DL	1.7*	4.08
A.R.	L	+	+	+	OM	DL	4.4**	4.67
D.B.	L	+	+	+	OM	DL	2.7**	4.08
R.K.	L	+	+	+	OM	DL	2.1*	2.5
L.S.	L	+	+	+	OM	DL	-1.2	2.5
							0.5	4.25

R/L = right/left; ‘+’ = unilateral lesion in this region; ‘++’ = bilateral lesion in this region; (+) and (++) = the patient’s lesion only just encroached on this subregion; DL = dorsolateral; OM = other medial; DLat/OM = dorsolateral/other medial lesions; bilateral OFC = bilateral orbitofrontal cortex lesions; BA 9/ACC = medial BA 9 and/or ACC lesions; BA 9/ACC + orbital = medial BA 9/ACC plus orbital lesions. †Medial regions are divided into BA 9, ACC (affective division of anterior cingulate cortex), and OM [other medial (medial regions outside BA 9 and ACC)]. Vocal and facial emotional expression identification tests: the number of SDs by which each patient’s total error score exceeded the mean for the normal group. Positive values of SD reflect a greater number of errors. *At or below 5th centile; **at or below 1st centile. Subjective emotional change questionnaire: the total scores are shown, with higher scores reflecting a greater degree of reported change. The total scores ignore the direction of change on individual emotions. Social behaviour: Mean ratings on the 12 questions which best differentiated the bilateral OFC from the DLat/OM group.

Table 1. On this method of categorization the patients fell into five groups, four with unilateral and one with bilateral lesions, as follows.

(A) *Dorsolateral/other medial (DLat/OM)* ($n = 11$). These patients either had dorsolateral prefrontal lesions or medial prefrontal lesions outside BA 9/ACC ('other medial' lesions), or both. None had any orbital lesion.

(B) *Orbital* ($n = 6$). These patients had unilateral orbital lesions without BA 9/ACC lesions. Some additionally had 'other medial' lesions.

(C) *BA 9/ACC* ($n = 4$). These patients had lesions in medial BA 9 and the ACC, and they were without orbital lesions. All had additional 'other medial' lesions, and one also had a dorsolateral prefrontal lesion.

(D) *BA 9/ACC + orbital* ($n = 8$). These patients had medial lesions in BA 9/ACC combined with orbital lesions. All had additional 'other medial' lesions and most also had dorsolateral prefrontal lesions.

(E) *Bilateral orbital lesions* ($n = 6$). Most patients with bilateral lesions had OFC lesions on both sides, and two of these had additional bilateral ACC lesions.

Some patients were unavailable to take part in some of the tests, with the result that numbers of patients are not necessarily the same across different tests. (This situation arose because all the patients were out-patients, and this meant that there were considerable difficulties, due to patients' other commitments, in obtaining 100% participation across tasks.)

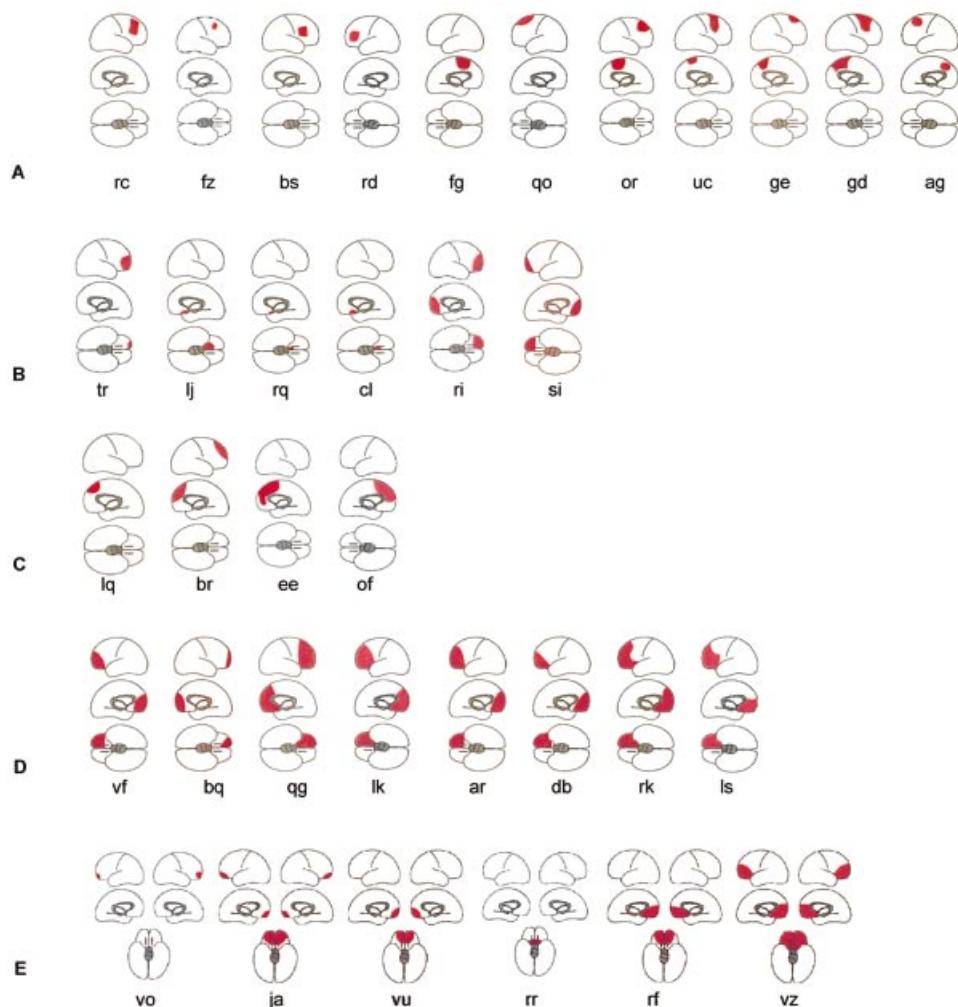


Fig. 1 Brain maps showing lesion sites. (A) Unilateral dorsolateral or dorsolateral and 'other medial' lesions (see C below). (B) Unilateral orbital lesions (some had additional lateral lesions outside the dorsolateral region). (C) Medial BA 9 and 'affective division' of anterior cingulate cortex (ACC) lesions (see Fig. 2). (D) Medial BA 9/ACC and orbital lesions. Most also had 'other medial' and dorsolateral lesions. (E) Bilateral orbital lesions. Some also had bilateral ACC lesions.

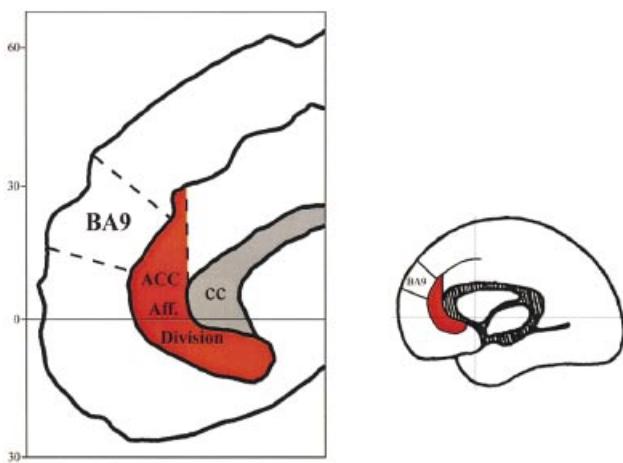


Fig. 2 (Left) The 'affective division' (ventral region) of the ACC (after and modified from Bush *et al.*, 2000). (Right) The corresponding region is indicated on the medial surface of the standard brain map used in Fig. 1, as well as the position of medial BA 9. Aff = affective; ACC = anterior cingulate cortex; CC = corpus callosum.

Statistical analyses

In many cases non-parametric (Kruskal–Wallis) ANOVA (analyses of variance) were used, in order to (conservatively) make no assumptions about the distribution of the data, and to take into account the fact that some groups had few subjects. When *post hoc* (Mann–Whitney) tests were performed to test for differences between groups, these tests were planned, and were many fewer than the possible number of such paired comparisons [$n!/(n - 2)! \cdot 2!$, where n is the number of groups]. However, as a double check, we ensured that all such *post hoc* comparisons survived the Bonferroni correction (in which the P value obtained is divided by the number of tests performed) at $P < 0.05$.

Tests

(1) Vocal emotion

The stimuli used in this test were the same as those used in Hornak *et al.* (1996). Briefly, these were non-verbal emotional sounds corresponding approximately to the seven categories of expression used in studies of facial expression recognition (Ekman and Friesen, 1975). The categories used were: sad, angry, frightened, disgusted, puzzled, contented and neutral.

The sounds, the duration of which ranged from ~1 to 3 s, were produced by three normal volunteers with voices of differing pitch: a man, a woman and a child aged 10 years. In this way, the opportunity for subjects to use pitch as a guide to the emotion categories was reduced. Instead, since the volunteers avoided using consonants, the emotions were discriminable from each other largely in terms of subtle changes in the temporal characteristics of changing pitch within each sound. For the neutral category, the subjects

hummed briefly on one note. A sound corresponding to each emotion was made twice by each of the three volunteers, producing a total of 42 sounds. During the test the emotions appeared in random order, with the constraint that no emotion appeared more than twice in succession, and the three voices were alternated.

The subject and the experimenter each listened to the emotional sounds through separate headphones. In this way the experimenter was able to monitor the progress of the test. After each sound the tape was stopped and the subject was asked to select from a list the adjective that best described the emotion conveyed by the sound. The adjectives (sad, angry, frightened, disgusted, contented, puzzled and neutral) were printed in a vertical array, and appeared in a different random order on each trial. There was no time limit and no feedback was given.

Voice discrimination. The stimuli used in this test had also been used previously by Hornak *et al.* (1996). Briefly, the names of six months of the year were read aloud by female voices. On half of the trials these were read by the same voice throughout, and on the other half two different voices read three months each. There were 20 'same-voice' trials and 20 'different-voice' trials, making a total of 40 trials. 'Same' and 'different' trials occurred in random order, with the constraint that trials of the same type did not occur more than three times in succession.

The voice discrimination trials (also presented via headphones) were alternated with trials from the vocal emotion test. After each trial, the experimenter paused the tape and the subject indicated whether he thought the same voice had read the six months or whether there had been two different voices. There was no time limit and no feedback was given.

Relative difficulty of the two vocal tests. The mean percent correct achieved by the normal control group on the two tests was compared with the percentage correct that would be expected by chance. Since subjects made same/different judgements in the voice discrimination test, chance performance is 50%. In the vocal emotion test by contrast, with seven response categories, chance performance is 14%. The mean percent correct in the normal control group on the two tests was almost identical (74.5% on vocal emotion, and 74.9% on voice discrimination), indicating that the normal group performed closer to chance on the voice discrimination than on the vocal emotion test. By this criterion, the vocal emotion test was the easier of the two tests for the normal control group.

Environmental sounds. For this test a recording was made of 38 familiar everyday sounds produced by indoor and outdoor objects (e.g. a chair scraping across the floor, someone biting into an apple, the sound of an aeroplane, drops of water falling into the sink). The mean number of errors made by 18 normal subjects was 12.6 (SD 4.0).

The sounds were played on a tape-recorder in free field (i.e. headphones were not used). After each sound the tape was stopped and the subject was asked to name the identity of the sound. There was no time limit and no feedback was given.

(2) Facial expression

This task required the subject to identify the emotion expressed on the faces of four different people. The expressions fell into the following seven categories: happiness, surprise, fear, sadness, disgust and anger, and morphed intermediaries between adjacent pairs (Sprengelmeyer, 1996). The morphed expressions were created using software developed by Benson and Perrett (1991). The images were cropped to leave only the face and they were displayed against a black background. The extent to which each emotion from an adjacent pair contributed to the interpolated images was varied along the continuum from 10 to 90% [based on the original Ekman and Friesen (1975) norms]. Thus, the morphed interpolations between, for example, the adjacent pairs happiness and surprise consisted of images that contained 90% happiness and 10% surprise, 70% happiness and 30% surprise, 50% happiness and 50% surprise, 30% happiness and 70% surprise, 10% happiness and 90% surprise. The same procedure was repeated for each of the emotion pairs, creating a total of 30 morphed images for each of the four different individuals who contributed expressions, and therefore a total of 120 stimuli in all for the test.

The 120 face expressions were presented in a pseudo-random sequence on a computer screen. On each trial the subject was presented with one of the face expressions and asked to choose, from a list arranged vertically beneath it, the adjective that best described it. The list of adjectives was: happy, sad, angry, frightened, disgusted and surprised. Although there were no neutral expressions, 'neutral' was included in the list, and the subjects were asked to choose this if they felt that the face displayed no emotion. The order in which the adjectives were arranged on the screen was varied randomly on each trial. There was no time limit and no feedback was given.

Comparison of the task difficulty for the vocal emotion and the face expression tests

Since there were seven response categories, chance performance, as in the vocal emotion test was 14%. The mean percentage correct in the normal control group on the face expression was 75.2, compared to 74% for the vocal emotion test, suggesting that the two tests are of an equivalent level of difficulty.

(3) Subjective emotional change questionnaire

Each patient was asked whether he/she had noticed, since his surgery/head-injury/illness, any change in either the intensity or the frequency of his own experience of the main emotions that featured in the two expression identification tests. He was asked, in turn, about his experience in his daily life, of sadness, anger, fear, happiness and disgust. The questionnaire was administered orally to the patient while he was alone with the tester, so there was no opportunity for the patient to confer

with a spouse, friend or relative about how he should answer the questions.

Any change that was reported, whether an increase or a decrease in frequency or intensity was scored as follows: a small change, 0.5; a change, 1.0; a big change, 1.5. Each patient was then given a total score across all emotions, regardless of whether the change represented an increase or decrease in the emotions which had changed.

(4) Social behaviour questionnaire

This was a 30-item questionnaire that was completed by an informant concerning the social behaviour of the patient. Informants were people who knew the patient well both before and after his surgery, generally a spouse or close friend. Since it was completed confidentially there was no opportunity for the patient and informant to confer over the answers the informant gave to this questionnaire. The questionnaire was completed by 25 informants for a group of normal control subjects. Factor analysis on the responses given by these informants for this control group revealed that a total of 19 of the 30 questions contributed to the following five factors: (1) emotional empathy; (2) emotion recognition; (3) public behaviour; (4) interpersonal relationships; and (5) antisocial behaviour. These 19 questions are shown in Appendix A, as well as the remaining questions that did not contribute to any of the five factors.

For each question the patient could receive a rating from 1 to 5, with the higher ratings indicating better social adjustment. [The aim of the social behaviour questionnaire was to compare the perspective of spouses of patients who have had surgical excisions in different regions of the prefrontal cortex, in order to discover how spouses see the patients' behaviour after surgery. Since the DLAT/OM group achieved high scores (with means of between 4 and the maximum of 5 on most questions) on the social behaviour questionnaire, this group was used as the comparison group for the other lesion groups. It was felt that the normal group of subjects should not be used as the comparison group because the criteria by which the spouses of normal subjects who had not had brain surgery would judge their spouses might well be different from the judgements made of spouses who had had brain surgery.]

Analysis

For the vocal emotion test and the other two auditory comparison tests, as well as for the face expression test, patient scores were compared with the scores of the normal control group for that test. For the emotional change questionnaire there was no normal control group, since the questionnaire concerned changes since the patients had undergone surgery. For this measure, therefore, the scores of other patient groups are compared instead with the scores of the DLAT/OM group, in whom little or no change on these measures would be expected. The results from patients on the

social behaviour questionnaire were analysed in the same way as for the emotional change questionnaire.

We tested for group differences in scores on each of the above tests. Since there were only four patients with medial BA 9/ACC (but without orbital) lesions, these are not

included in the group comparisons. Their results are presented instead with the individual results for each test, either in terms of their total scores or in terms of the number of SDs by which their scores differed from the mean for the comparison group for that test.

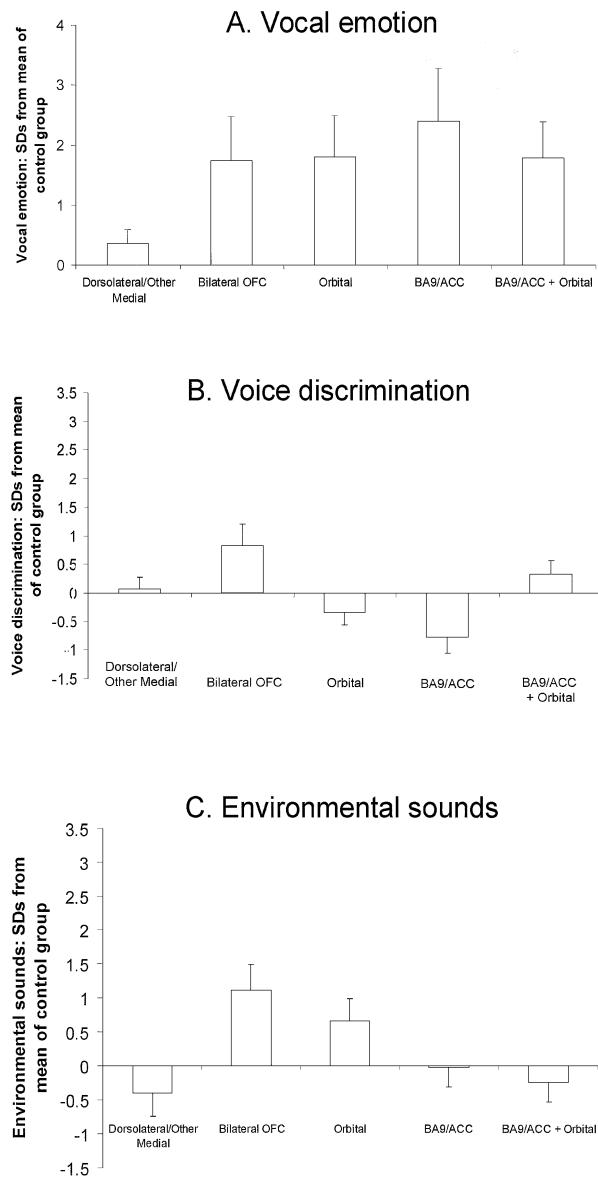


Fig. 3 (A) Vocal emotion: effects of unilateral prefrontal excisions. Patients with either orbital lesions or with lesions in medial BA 9/ACC ('affective' anterior cingulate cortex) or with lesions in both of these regions were impaired at identifying non-verbal vocal emotional sounds. Patients with medial lesions outside BA 9/ACC, or with dorsolateral lesions or with both (dorsolateral/other medial group) performed normally. (B) Voice discrimination. Performance of the same patient groups (as in A) on a test in which they were required to discriminate between pairs of unfamiliar voices. No group was impaired. (C) Environmental sounds. Performance of the same patient groups (as in A and B) on a test in which they were required to identify everyday sounds. No patient group was impaired.

Results

Vocal emotion expression identification

All vocal emotions combined

For each patient and each control subject the total number of errors made across all of the emotion categories was calculated. The performance of the following groups of patients was then compared with the performance of the 48 subjects in the normal control group: DLat/OM ($n = 9$); unilateral OFC (orbital, $n = 5$); BA 9/ACC + orbital ($n = 8$); and bilateral OFC ($n = 6$). [Since there were only four patients with BA 9/ACC (but no orbital) lesions, this group was not included in the group comparisons.]

Statistical comparison showed a highly significant difference overall between the groups [Kruskal–Wallis one-way ANOVA, $\chi^2 (4) = 16.18$, $P = 0.003$]. Paired comparisons between the normal control group and the patient groups revealed that the BA 9/ACC + orbital group made significantly more errors than the normal control group (Mann–Whitney U -test = 78, $P = 0.007$, two-tailed), as did the bilateral OFC group (Mann–Whitney U -test = 59.5, $P = 0.019$, two-tailed). Additionally, on this test the orbital group also made significantly more errors than the normal control group (Mann–Whitney U -test = 42, $P = 0.017$, two-tailed). The DLat/OM group, however, did not differ significantly from the normal control group (Mann–Whitney U -test = 151.5, $P = 0.15$, two-tailed). [Age was shown not to be a confounding difference between the groups, in that there were no significant age differences between ages of the groups with the bilateral OFC group excluded; and there was no correlation with age in the scores between age and performance on the vocal expression identification test across subjects in all the unilateral lesion groups. Although the mean age of the bilateral OFC group was somewhat higher (57 years) and most of the other lesion groups (mean = 40, $SD = 13$), given that unilateral orbital lesions do produce a significant impairment (in a group whose age did not differ from that of the unimpaired DLat/OM group), it is likely that the impairment found in those with bilateral orbital lesions can be attributed to the presence of orbital lesions rather than to age.]

Table 1 shows the number of SDs by which each patient's error score differed from the mean of the normal control group (including the four who had lesions in BA 9/ACC regions but no orbital lesions and who were not included in the group analyses). It should be noted that three of these patients had scores at least 3 SDs outside the mean for the normal control group. For the patients with bilateral OFC lesions, comparison of Table 1 and Fig. 1 shows that,

although as a group the bilateral patients were impaired, some individuals performed normally, perhaps depending on the exact site of the lesion. Interestingly, even small unilateral orbital lesions could in some patients (e.g. RQ and CL, in whom the lesions were far posterior) produce severe impairments.

Figure 3A shows the mean number of SDs by which the different lesion groups differed from the mean for the normal control group. This shows the values for the three groups included in the statistical analysis as well as the group of four patients with BA 9/Aff ACC lesions but no orbital lesions. From this it is clear that either unilateral orbital (orbital), or unilateral BA 9/ACC lesions, or a combination of both, produce severe impairments, whereas DLat/OM prefrontal lesions do not.

Lesion size and performance on the vocal emotion test. When the total area of each patient's lesion is taken into account (i.e. across the whole of the prefrontal cortex), no correlation was found between overall lesion size and performance on the vocal emotion test (Spearman rank correlation, rho = -0.006, P = 0.97). (The total area was estimated approximately by measuring the area of the projected outline of each prefrontal cortex lesion on each of the orthogonal views as illustrated in Fig. 1, and adding together the areas.)

Side of lesion. There was no significant difference between the scores (SDs) of those with left and with right-sided lesions (Mann-Whitney U-test = 50.5, P = 0.1, two-tailed).

Each vocal emotion separately

Table 2 shows the mean number of errors (out of six trials) on each of the emotion categories for each of the patient groups and for the normal control group. We tested statistically for group differences from the normal control group in the total number of errors for each emotion for each group, with the results shown in Table 2. (The performance of individual patients on each emotion is shown in Appendix B.)

Sad. Statistical comparison showed a highly significant difference between the groups for Sadness [Kruskal-Wallis one-way ANOVA, χ^2 (4) = 16.7, P = 0.002]. Paired

comparisons between the normal control group and the patient groups showed that neither the DLat/OM group (Mann-Whitney U-test = 191, P = 0.312) nor the orbital group (Mann-Whitney U-test = 86, P = 0.21) differed significantly from the normal control group. In contrast, the BA 9/ACC group (Mann-Whitney U-test = 22, P = 0.005, two-tailed) and the BA 9/Aff ACC + orbital group (Mann-Whitney U-test = 75, P = 0.002, two-tailed) did make significantly more errors than the normal control group, and this was also true for the bilateral group (Mann-Whitney U-test = 49, P = 0.004, two-tailed).

Angry. Statistical comparison showed a significant difference between the groups for anger [Kruskal-Wallis one-way ANOVA, χ^2 (4) = 10.3, P = 0.036]. Paired comparisons showed that neither the DLat/OM group (Mann-Whitney U-test = 148, P = 0.067), nor the orbital group (Mann-Whitney U-test = 102, P = 0.417) nor the BA 9/ACC + orbital group (Mann-Whitney U-test = 151, P = 0.184) differed significantly from the normal control group. In contrast, the BA 9/ACC group (Mann-Whitney U-test = 33, P = 0.019, two-tailed) and the bilateral OFC group (Mann-Whitney U-test = 61, P = 0.12, two-tailed) both made significantly more errors than the normal control group.

Frightened. Statistical comparison revealed no significant group differences on fear [Kruskal-Wallis one-way ANOVA, χ^2 (4) = 5.38, P = 0.25].

Disgusted. Statistical comparison revealed a significant difference between the groups on disgust [Kruskal-Wallis one-way ANOVA, χ^2 (4) = 10.85, P = 0.028]. Paired comparisons revealed that neither the DLat/OM group (Mann-Whitney U-test = 220, P = 0.64), nor the BA 9/Aff ACC group (Mann-Whitney U-test = 76.5, P = 0.371) nor the bilateral OFC group (Mann-Whitney U-test = 126, P = 0.425) differed significantly from the normal control group. In contrast, both the orbital group (Mann-Whitney U-test = 51, P = 0.021, two-tailed) and the BA 9/Aff ACC + orbital group (Mann-Whitney U-test = 126, P = 0.025, two-tailed) both made significantly more errors than the normal control group.

Contented. Statistical comparison revealed no significant group differences on the contented vocal expression [Kruskal-Wallis one-way ANOVA, χ^2 (4) = 6.35, P = 0.174].

Table 2 Vocal emotion identification: group mean number of errors on each emotion (out of six trials)

	Sad††	Angry†	Frightened	Disgusted†	Contented	Puzzled†	Neutral
Control mean (SD)	1.3 (1.1)	3.5 (1.5)	0.7 (0.9)	0.3 (0.5)	2.0 (1.2)	1.3 (1.0)	1.2 (1.5)
DLat/OM	1.7	4.4	0.4	0.6	2.1	2.0	0.7
Orbital	2.4	4.0	1.4	1.2*	1.4	3.0**	2.4
BA 9/Aff ACC	3.3**	5.3*	1.5	0.8	2	2.5	2.8
BA 9/ACC + orbital	2.9**	4.1	1.1	1.3*	2.6	1.8	2.5
Bilateral	3.3**	5.2*	0.5	0.5	3.0	2.2	1.3

Group comparisons using Kruskal-Wallis non-parametric one-way ANOVA revealed significant differences on this emotion: †significant at $P < 0.05$; ††significant at $P < 0.01$. (The data for the group of patients with BA 9/ACC lesions are in italics because they were not included in the ANOVAs because $n = 4$.) Paired comparisons between patient and control groups, using Mann-Whitney non-parametric tests: *significant difference at $P < 0.05$; **significant difference at $P < 0.01$.

Puzzled. Statistical comparison revealed a significant difference between the groups on puzzled [Kruskal–Wallis one-way ANOVA, χ^2 (4) = 10.53, P = 0.032]. Paired comparisons revealed that neither the DLat/OM group (Mann–Whitney U -test = 159, P = 0.83), nor the BA 9/ACC group (Mann–Whitney U -test = 81, P = 0.46), nor the BA 9/Aff ACC + orbital group (Mann–Whitney U -test = 202, P = 0.0816, two-tailed) nor the bilateral OFC group (Mann–Whitney U -test = 141, P = 0.668) differed significantly from the normal control group. In contrast, the orbital group (Mann–Whitney U -test = 27.5, P = 0.002, two-tailed) did make significantly more errors than the normal control group.

Neutral. Statistical comparison revealed no significant group differences on neutral vocal expression [Kruskal–Wallis one-way ANOVA, χ^2 (4) = 6.8, P = 0.147].

Summary. Impairments on sadness and/or anger were found only in the two unilateral groups, whose lesions included BA 9/ACC, and in the bilateral OFC group. The unilateral orbital group was impaired only on disgust and puzzled. Additionally, disgusted was impaired in the BA 9/ACC group. There were no group differences on frightened, contented or neutral.

Voice discrimination and environmental sounds

Voice discrimination. For each patient and each control subject the total number of errors was calculated and the performance of the patient groups was then compared with the performance of the normal control group. Since trials from the vocal emotion and from the voice discrimination tests were interleaved, the number of subjects in each group is the same in these two tests, and the same groups were included in the analysis. Statistical comparison failed to reveal any significant group difference for the voice discrimination test [Kruskal–Wallis one-way ANOVA, χ^2 (4) = 4.247, P = 0.374].

Environmental sounds. Only the group with BA 9/ACC + orbital lesions (n = 7) was large enough for statistical comparison with the normal control group. There was no significant difference between these two groups (Mann–Whitney U -test = 56.5, P = 0.69, two-tailed).

The three auditory tests compared. As was done for the vocal emotion test, the number of SDs by which each patient's error score differed from the control means was also calculated for both the voice discrimination and for the environmental sounds tests, making it possible to compare performance on all three auditory tests. Figure 3B and C shows results for the same groups of unilateral patients as shown in Fig. 3A. On the both voice discrimination and environmental sounds, the means for all of the patient groups were well within 1 SD of the mean for the normal group. Consistent with this, there was no correlation between scores on the vocal emotion test and scores on either the voice discrimination test (Spearman rank correlation, rho = -0.22,

P = 0.27) or on the environmental sounds test (Spearman rank correlation, rho = 0.43, P = 0.07).

Facial emotion expression identification

All facial expressions combined

For each patient and each normal control subject the total number of errors made on the face expression test was calculated. The same patient groups were compared with the normal control group for this test as was done for the vocal emotion test. The numbers in each group were as follows: DLat/OM prefrontal (n = 10); orbital (n = 5); BA 9/Aff ACC + orbital (n = 8); and bilateral OFC (n = 5). We tested for a group difference in the total number of errors made on the facial expression test by the normal control group and by the patient groups. Statistical comparison failed to reveal a significant difference between the groups [Kruskal–Wallis one-way ANOVA, χ^2 (4) = 6.64, P = 0.156].

Although there were no group differences on this test, a number of individual patients did perform significantly less well than the normal control group. Table 1 shows the number of SDs by which each patient's error score differed from the mean of the normal control group. This shows that none of the patients with a unilateral lesion in the DLat/OM, or the unilateral orbital, group scored at or below the 5th centile. Significant impairments were, however, shown by four individuals with unilateral lesions that included BA 9/ACC (patients B.R. and E.E. with BA 9/ACC lesions, patients L.K. and D.B. with BA 9/ACC + orbital lesions). Three patients with bilateral OFC lesions were also impaired (two of whom, R.F. and V.Z., had additional bilateral ACC lesions), but their impairment was no greater than that found in patients with unilateral lesions that included BA 9/ACC. Two patients with bilateral orbital lesions but without BA 9/ACC involvement (patients J.A. and V.U.) were unimpaired.

Each facial expression separately

In the absence of significant group differences in total scores, we performed an exploratory analysis to establish whether performance on separate emotions was associated with lesion site. The performance on each expression by those seven individuals who showed an impairment on all facial expressions combined is shown in Appendix C. No clear pattern emerges of a relatively greater impairment on any expression, although it is notable that no impairment on sad was shown by any of these patients. Appendix C also shows that, amongst the remaining 24 patients whose performance across all facial expressions was unimpaired, a few impairments on separate expressions by individual patients were found, but there no clear pattern of impairment on any expression according to lesion site.

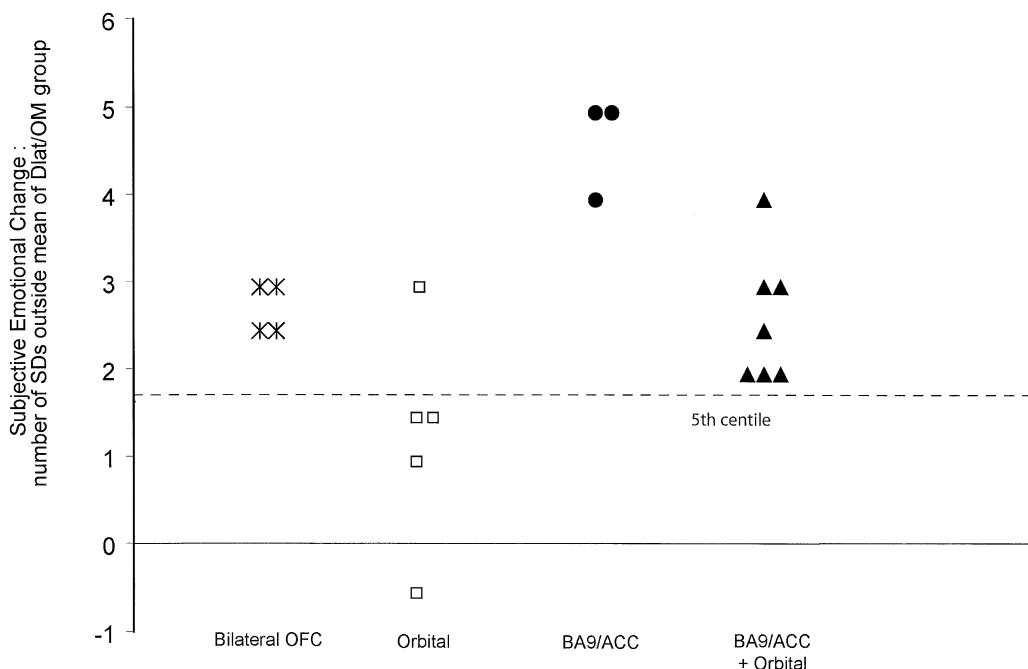


Fig. 4 Subjective emotional change. The total scores of patients with unilateral and with bilateral lesions are shown in terms of the number of SDs by which these differed from the mean of the dorsolateral/other medial group (i.e. those with dorsolateral lesions or with medial lesions outside medial BA 9/ACC or with both).

Comparison of performance on the vocal emotion and the facial expression tests

All emotion categories combined

Table 1 allows comparison of the performance of patients who performed both the vocal emotion and the facial expression tests. It can be seen that, amongst patients with unilateral lesions in the orbital region and/or in BA 9/ACC who did both tests, the majority of those who were impaired on the vocal emotion test performed normally on the facial expression test. It can also be seen that all of the four with unilateral lesions who were impaired on facial expression were also impaired on the vocal emotion test, and all had lesions that included BA 9/ACC. Two of the three with bilateral OFC lesions who were impaired on face expression were also impaired on vocal emotion.

Each emotion category separately (Appendices B and C)

On the vocal emotion test sad was the emotion on which the most significant group differences were found, with the groups whose lesions included BA 9/ACC lesions unilaterally, and the bilateral OFC group, making very significantly more errors than the normal control group (Table 2 and Appendix B). In contrast, no individual patient was impaired on sad in the facial expression test (Appendix C). The difference between performance on sad in the two

modalities cannot be explained in terms of different levels of difficulty, since the mean percent correct for the normal control group was 78% for vocal sad ($SD = 18.3$) 77% and for facial sad ($SD = 18.6$).

A comparison between Appendices B and C reveals other differences between the performance of individual patients on the same emotion in the two tests. Facial anger, for example, was impaired in all four of those with unilateral lesions (in all cases with BA 9/ACC involvement) who showed an overall impairment on the facial emotion expression test. Three of these (patients E.E., L.K. and D.B.), however, were unimpaired on vocal anger. As was true for sad, these differences cannot be explained in terms of different levels of difficulty for the two tests because the mean percent correct was 89% for facial anger, whereas it was only 42% for vocal anger.

Subjective emotional change questionnaire

Total amount of change reported

For each patient a score was calculated that reflected the total amount of change across all emotions regardless of the direction of change (see Table 1). Since there were only three patients in the BA 9/ACC group, they were excluded from the Kruskal-Wallis ANOVA that was performed on the following groups: DLat/OM ($n = 8$); bilateral OFC ($n = 4$); orbital ($n = 5$); and BA 9/ACC + orbital ($n = 7$). We tested for group differences in the total scores. The Kruskal-Wallis analysis showed a highly significant difference across the four groups

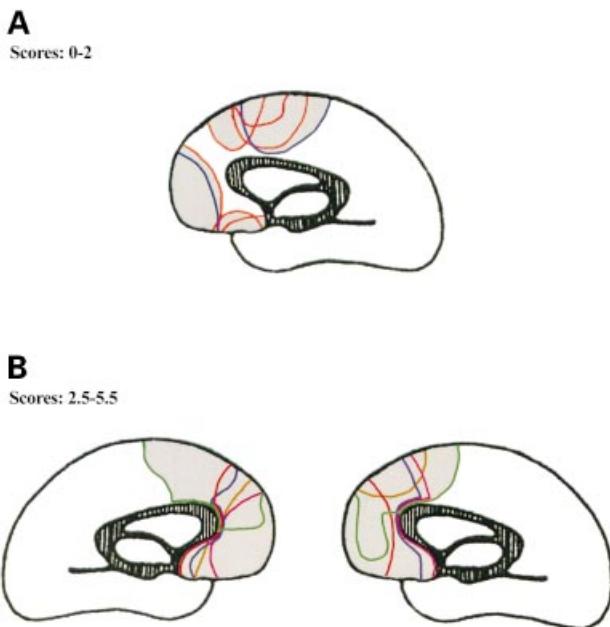


Fig. 5 Subjective emotional change. (A) Scores 0–2: medial lesions of those with scores from 0–2. The unilateral medial lesions of those with total scores of from 0–2 are superimposed. Six had right-sided (shown in red) and two had left-sided lesions (shown in blue), but all are shown together on the medial aspect of a right hemisphere. The region which was spared by these lesions corresponds approximately to medial BA 9 and anterior cingulate cortex (ACC) (i.e. the ventral ‘affective division’ of the ACC; Bush *et al.*, 2000). (B) Scores 2.5–5.5: medial lesions of those with scores from 2.5–5.5. The unilateral medial lesions of those who scored from 2.5–5.5 are superimposed, separately for the five patients with right and for the five patients with left-sided lesions. Medial BA 9 and/or ACC was included in all of those with medial lesions who reported marked changes.

Colour	Left-sided	Right-sided
Green	OF	EE
Red	RK	BQ
Blue	LS	LK
Brown	DB	LQ
Pink	VK	QV

$[\chi^2(3) = 15.09, P = 0.002]$. Paired comparisons using Mann-Whitney *U*-tests between the groups revealed that two groups were significantly different from the DLat/OM group (bilateral group, *U*-test = 0, $P = 0.004$, two-tailed; BA 9/Aff ACC + orbital group *U*-test = 1.5, $P = 0.001$). It was also found that the BA 9/Aff ACC + orbital group reported significantly greater changes than the orbital group (*U*-test = 5.0, $P = 0.048$, two-tailed). The (unilateral) orbital group showed a smaller difference from the DLat/OM group (see Fig. 4), which did not reach statistical significance (*U*-test = 8.5, $P = 0.076$).

Figure 4 shows the results for patients in the different groups in terms of the number of SDs from the mean of the DLat/OM group, a group that reported little or no change. From this and Table 1, it is clear that all patients in the bilateral OFC group had changed subjective emotional states. Also, as shown in Fig. 4 and Table 1, it is apparent that

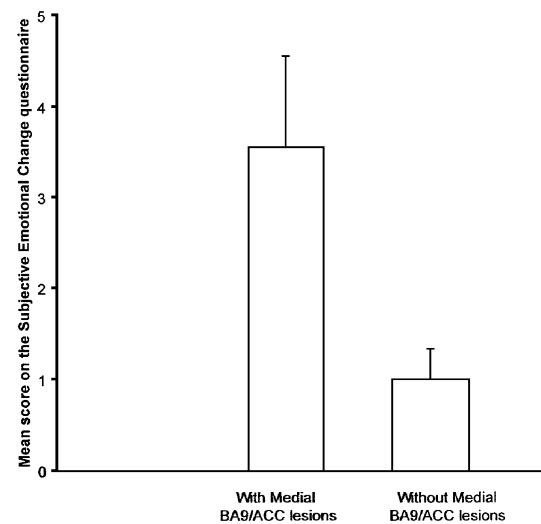


Fig. 6 Subjective emotional change questionnaire. Total amount of change in the experience of emotion reported by patients with unilateral excisions. The figure shows the mean total score for patients whose lesions encroached upon medial BA 9/ anterior cingulate cortex (ACC) (i.e. ventral ‘affective division’ of the ACC; Bush *et al.*, 2000). Also shown is the total mean score for patients without lesions in these medial BA 9/ACC regions ($n = 13$).

unilateral lesions in the BA 9/ACC group and in the BA 9/ACC + orbital group produced marked changes in the subjective experience of emotion, whereas unilateral orbital lesions did not. From this it is clear that the BA 9/ACC region if damaged unilaterally can alter the subjective experience of emotion.

The importance of the medial BA 9/ACC region in the normal experience of emotion is illustrated in Fig. 5A and B, which shows the extent of medial involvement of each patient with a unilateral lesion. The medial lesions of those who reported little or no change are shown together (superimposed) in Fig. 5A. For the purposes of illustration the lesions of the two left-sided and the six right-sided patients are shown together on the medial aspect of a brain map of a right hemisphere. In Fig. 5B, the medial lesions of those reporting marked changes are shown, superimposed separately for the five patients with left and for the five with right-sided lesions. Figure 5A and B shows that those with higher scores had medial lesions that included the medial BA 9/ACC regions, whereas those who scored between 0 and 2 had lesions which lay outside these regions, in some cases skirting them closely. Moreover, it is evident that the part of the ACC involved is the most antero-ventral part, which corresponds to what has been termed the ‘affective’ part of the ACC (see Fig. 2; Bush *et al.*, 2000). The lesions in those with low scores were either more dorsal, more anterior or more ventral than the lesions of those who reported marked changes.

In an additional comparison, all of the patients with unilateral lesions who completed the subjective emotional questionnaire (shown in Table 1) were recategorized according to whether they did or did not have a medial lesion in BA

Table 3 Subjective emotional change questionnaire: individual patient responses on each of the emotions

Patients	Sad	Angry	Frightened	Happy	Disgusted	Total
Unilateral						
DLat/OM						
B.Q.	--					0
F.Z.	--	**	*			2.5
R.D.						0
F.G.		*				0.5
Q.O.						0
O.R.						0
U.C.	**					1
G.E.						0
Orbital						
T.R.	**	***		**		3.5
L.J.	--	--				2
C.L.		**	**			2
R.I.						0
S.I.	--			-		1.5
BA 9/ACC						
L.Q.	***	***	***			4.5
E.E.	***	--	--	***		5.5
O.F.	--	-	**	--	--	5.5
BA 9/ACC + orbital						
V.F.	*	--	--	**		3.5
B.Q.		--		***		3
Q.G.	**	*	--	**		3.5
L.K.	***	**		**	**	4.5
D.B.	--	**	-			2.5
R.K.	*	**	**			2.5
L.S.	**	*		**		2.5
Bilateral OFC						
J.A.	--	***	--			3.5
V.U.		--	--			3
R.R.	**	**	***			3.5
R.F.	**		--	**		3

An increase in the frequency or intensity of the experience of this emotion was reported; '-' = a decrease was reported. '/-' = a small change (score = 0.5); '**/- -' = a change (score = 1.0); '***/- --' = a big change (score = 1.5). The total scores ignore the direction of change. Where neither an increase nor a decrease is shown, the patient stated that he/she had experienced no change in that emotion.

9/ACC. (The three patients with unilateral BA 9/ACC but no orbital lesions, L.Q., O.F. and E.E., were now included in the comparison.) Statistical analysis comparing the incidence of low scores (0–2) and high scores (2.5–5.5) in patients with ($n = 10$) and without ($n = 13$) BA 9/ACC lesions showed that the difference was highly significant (Fisher's exact test, $P = 0.006$, two-tailed), and a comparison of the total scores in these two groups gave a similar result, with the scores of those with medial BA 9/ACC lesions being very significantly larger than the scores of those without (Mann–Whitney U -test = 1.5, $P < 0.0001$, two-tailed). The means of the two groups categorized in this way are shown in Fig. 6. In contrast, and as is apparent from inspection of Table 1, there was no significant difference between the groups if the patients were recategorized instead according to the presence of any of the other types of lesion shown in Table 1, i.e. according to whether they did or did not have either a unilateral orbital lesion, or a dorsolateral prefrontal lesion (DLat/OM group), or a medial lesion outside the key regions ('other medial'). In all of these comparisons the incidence of low and of high scores in patients with and without these lesions did not differ

significantly (for all comparisons, Fisher's exact test, $P > 0.05$). Additionally, statistical comparison of those with and without unilateral orbital lesions demonstrated that there was no significant difference between the scores of patients classified in this way (Mann–Whitney U -test = 45.5, $P = 0.2$). The same was true if patients were classified according to whether they did or did not have a dorsolateral lesion (Mann–Whitney U -test = 54.5, $P = 0.47$), or according to whether they did or did not have an 'other medial' lesion (Mann–Whitney U -test = 38.5, $P = 0.38$).

Subjective emotional change and identification of emotion expressed by others. The orbital group (with unilateral orbital lesions but no BA 9/ACC lesions) reported little or no emotional change, but was significantly impaired on the vocal emotion test, showing that the perception of vocal emotion can be impaired without there being marked subjective changes in reported emotional states. The opposite pattern could also be found. Amongst those whose lesions included the BA 9/ACC region, three of those with left-sided lesions (patients O.F., V.F. and L.S.) performed well on vocal emotion, but reported marked emotional changes, with O.F.

Table 4 Social behaviour: individual questions that revealed differences between the Dorsolateral/other medial group and the other patient groups

	Dorsolateral [mean (SD)] (n = 10)	Bilateral (n = 5)	Orbital (n = 6)	BA 9/ACC (n = 3)	BA 9/ACC + orbital (n = 8)
Q13 Notices when other people are <i>sad</i>	4.50 (0.71)	2.80**	3.83	4.33	4.25
Q18 Notices when other people are <i>angry</i>	4.60 (0.69)	3.60*	4.17	3.33**	4.13
Q9 Notices when other people are <i>disgusted</i>	4.50 (0.85)	3.60*	3.83	3.33*	4.25
Q4 Notices when other people are <i>happy</i>	4.50 (0.53)	4.20	4.83	3.67*	4.63
Q27 When others are <i>sad</i> he/she comforts them	4.30 (0.82)	3.20*	4.00	4.33	4.00
Q30 When others are <i>afraid</i> he reassures them	4.40 (0.69)	3.60*	3.67*	4.67	4.13
Q26 When others are <i>happy</i> he/she is happy for them	4.70 (0.68)	3.40**	4.83	4.00*	4.38
Q17 He/she does (not do) what he wants and doesn't care what others think	3.90 (1.29)	2.00*	3.17	2.67*	3.00
Q21 Is close to his/her family	4.70 (0.48)	3.20**	4.50	2.67**	4.13
Q8 Cooperates with others	4.60 (0.84)	3.60*	4.50	3.67*	4.00
Q3 Is (not) critical of others	2.70 (1.57)	1.80	2.83	2.67	2.00
Q10 Is (not) impatient with others	3.60 (1.43)	2.00*	2.67	3.00	2.25
Q7 Is (not) aggressive	4.60 (1.27)	3.40	4.50	3.33*	3.50
Q19 Does (not) do things without thinking	4.10 (1.10)	2.80*	3.17	2.00**	2.88*
Q14 Is sociable	4.40 (0.97)	4.00	4.67	4.33	4.50
Q12 Has (no) difficulty making or keeping close relationships	4.30 (1.06)	3.20*	4.00	2.67*	3.38
Q23 Keeps in touch with old friends	3.90 (1.10)	4.00	3.67	2.33*	3.63

*Questions on which mean ratings for this group were at least 1 SD below the mean of the dorsolateral/other medial (DLat/OM) group.

**Questions on which the mean ratings for this group were at least 1.65 SDs below the mean of the DLat/OM group. Bold type: the 12 questions that comprised the set used for the ANOVA; italics: these questions did not contribute to the five factors (see Appendix 1). n = number of patients included in the sample from which the mean was calculated.

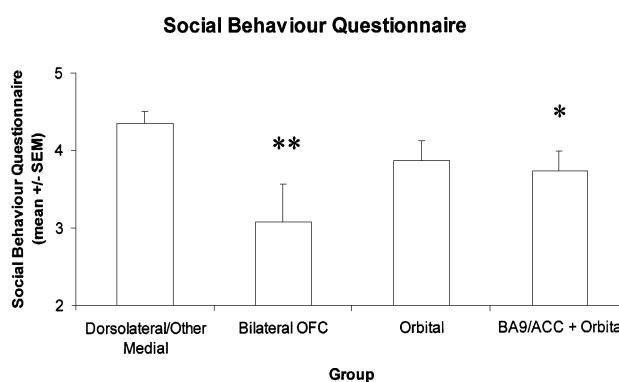


Fig. 7 Social behaviour questionnaire. The mean score (\pm SEM) over 12 questions in the Social behaviour questionnaire given by the informants for the different patient groups. The maximum score was five, and the minimum score was 0. **P = 0.0015 with respect to the dorsolateral/other medial (DLat/OM) group.

* P<0.05 with respect to the DLat/OM group.

having one of the two highest scores. This shows that vocal emotions expressed by others can be perceived normally by some patients whose own experience of these emotions has been greatly altered by their surgery. This dissociation can be illustrated with reference to some individual emotions. For example, although the identification of vocal disgust was significantly impaired in the orbital group (Table 2), none of the four patients who provided scores on both measures (T.R., L.J., C.L. and S.I.) reported any change in the subjective experience of this emotion (Table 1). Conversely, all patients

whose lesions included BA 9/Aff ACC reported changes in the experience of anger, but no patient was significantly impaired on this vocal emotion.

Lesion size. When the total area of each patient's lesion is taken into account (i.e. across the whole of the prefrontal cortex), no correlation was found between lesion size and total score on the subjective emotional change questionnaire (Spearman rank, rho = 0.33, P = 0.12, two-tailed).

Side of lesion. There was no difference between the total scores of patients with left- and right-sided lesions (Mann-Whitney U-test = 60.5, P = 0.87, two-tailed).

Individual patients' reports of change on different emotions

Amongst those with BA 9/ACC lesions who reported very marked emotional changes, some described such profound effects on daily life that they felt that they had in some ways become different people since their surgery. In many cases the patients described how these changes had had an adverse effect on the patients' relationships with family or friends. Table 3 shows the responses of each patient to questions about each of the emotions. Overall, increases in the intensity/frequency of emotions were reported approximately twice as often as decreases in patients with medial BA 9/ACC lesions. Increases in sadness, anger and happiness were the most common increases, whereas decreases in anger and fear were the most common decreases. Five patients reported that both sadness and happiness had increased in intensity/frequency,

suggesting that lesions in medial BA 9/ACC regions can produce an exaggeration of both positive and negative affective responses.

A hypersensitivity to sad events was reported by seven of the 10 patients whose lesions included the medial BA 9/ACC region, and many of these patients described themselves as having become far more 'emotional' than before their surgery, as getting upset far more easily and as being more likely to cry. A number of patients described having exaggerated emotional responses to sad films. Patients generally gave less detail about their increases in happiness, but patient E.E. described a much-increased pleasure in nature and music, and a greater appreciation of his friends. L.K. described herself as experiencing more extreme excitement, which could, however, 'swing quickly into sadness'.

Social behaviour questionnaire

Of the 30 questions in the social behaviour questionnaire, 12 had mean values for the bilateral OFC group and the control group with dorsolateral prefrontal lesions (DLat/OM) that differed by more than 1 SD. We therefore focused the remainder of the analysis on these 12 questions, as there was *prima facie* evidence that they provided measures on the clinical differences found in previous studies (Rolls *et al.*, 1994; Hornak *et al.*, 1996) between patients with orbitofrontal and dorsolateral prefrontal cortex damage. (They are questions 8, 9, 10, 12, 13, 17, 18, 19, 21, 26, 27 and 30, as shown in Appendix A and Table 4.) For this analysis, the DLat/OM group was used as the control or comparison group, because those in this group achieved mean scores between 4 and 5 on most questions, and this group was therefore deemed to be socially well adjusted [one-way ANOVA produced $F(3,25) = 3.79$, $P < 0.025$ (two-tailed)]. (For this comparison, the three subjects in the BA 9/Acc group were excluded as this was too small a number to form a separate group. A parametric analysis was used for this analysis because the score for each subject was already a mean over 12 questions, so that by the central limit theorem the means scores were normally distributed.) *Post hoc* least significant difference analyses showed that there was a significant difference ($P = 0.0015$, one-tailed because this was the expected direction) in the social behaviour measure over these 12 questions between the DLat/OM and bilateral OFC groups. There was also a significant difference between the DLat/OM and BA 9/ACC + orbital group ($P = 0.038$ with a one-tailed test *post hoc* least significant difference test). These group differences are illustrated in Fig. 7.

Individual questions from the social behaviour questionnaire

The mean values for the different groups on each question of the social behaviour questionnaire are shown in Table 4. Questions where the mean scores on a question for a group

were more than 1 (*) or 1.65 (**) SDs from the DLat/OM group are also indicated. It is of considerable interest that the questions on which the bilateral OFC group had lower scores included three from the emotion recognition group of questions [see Appendix A; the bilateral OFC patients were less likely to notice when others were sad (Q13) or happy (Q18) or disgusted (Q9)]; three from the emotional empathy group (Q27, does not comfort those who are sad; Q30, does not reassure those who are afraid; and Q26, does not feel happy for others who are happy); two from the interpersonal relationships group (Q17, does not care what others think; and Q21, is not close to his/her family); one from the public behaviour group (Q8, does not cooperate with others); one from the antisocial behaviour group (Q10, is impatient); and Q19 (the patients were described as impulsive) and Q12 (difficulty in making and keeping close relationships).

The BA 9/ACC group had scores that were more than 1.65 SDs from the mean of the DLat/OM group on Q18 (were less likely to notice when other people were angry); Q21 (were not close to his or her family); and Q19 (does things without thinking). The mean score of these patients was also more than 1 SD from the mean of the DLat/OM group on eight more questions (see Table 4). However, this group consisted of only three patients for whom data were available for the social behaviour questionnaire, and their data must be treated with caution, given that there were no questions on which the BA 9/ACC + orbital lesion group performed more than 1 SD from the DLat/OM group, and that *post hoc* analysis did not show that the BA 9/ACC + orbital lesion group had lower scores than the DLat/OM group.

From Tables 1 and 4 it is also clear that unilateral orbital lesions produced a negligible effect on the social behaviour questionnaire.

Questions revealing normal social adjustment in patients with bilateral orbitofrontal cortex lesions

Previous studies have described very marked changes in social behaviour after large ventral or ventromedial prefrontal cortex lesions produced by closed head injury, aneurysm, etc. (Bechara *et al.*, 1994; Rolls *et al.*, 1994). Rolls *et al.* (1994) found that the most common behavioural abnormalities present in the group with ventral prefrontal cortex lesions were: disinhibited or socially inappropriate behaviour; misinterpretation of other people's moods; impulsiveness; unconcern or underestimation of the seriousness of his/her condition; and lack of initiative. Furthermore, patients who were reported to be 'disinhibited and socially inappropriate' in the earlier study (Rolls *et al.*, 1994) were often aggressive, verbally abusive, sexually uncontrolled, boastful and had a childish sense of humour.

In contrast, in the present study patients with bilateral surgical lesions primarily of the OFC were not as severely affected. Although, as shown in Table 4, the bilateral OFC

patients (with the comparison control group being the DLat/OM group) did have impairments on some questions (see above), on some other questions the difference between the bilateral OFC group and the DLat/OM group was not even as much as 1 SD. For example, the bilateral OFC group were considered to express emotion appropriately in public (Q1), they were not liable to be too outspoken (Q2), nor too ready to let people know if he/she finds them attractive (Q22). They were also considered not to be either argumentative or aggressive (Q5 and Q7), and they were considered to have good manners (Q20), and to notice others' happiness (Q4) or fear (Q25), as well as scoring well on many other questions of the 30 shown in Appendix A. Even on questions relating to impulsivity (Q16), the bilateral OFC group did not differ significantly from the DLat/OM group, whereas on one of these questions (Q19 'Does things without thinking') the BA 9/ACC group did show a significant difference.

Discussion

The present study examined the relationship between lesions in different regions of the prefrontal cortex and results on different measures of emotion-related function: the perception of emotional stimuli, social behaviour and the subjective experience of emotion.

Bilateral OFC lesions

Patients with bilateral lesions of the OFC, in that the lesions were surgical and circumscribed, were impaired in all these aspects of emotion relative to patients with lesions in the dorsolateral prefrontal cortex/'other medial' areas who did not have problems with these measures of emotion. This is an important finding, as it shows that the OFC itself is important for these aspects of emotion. Indeed, patients J.A., V.U. and R.R. in the present series had bilateral OFC lesions and very little medial prefrontal cortex damage, and between them displayed a set of deficits that included voice expression identification, subjective emotional state (in all cases) and social behaviour problems, providing evidence that damage to the OFC is sufficient to produce these changes if the lesions are bilateral. In the sense that the findings are from patients with circumscribed lesions, the conclusion is an important extension to earlier work which had shown that voice and face expression deficits (Hornak *et al.*, 1996), changes in subjective emotional state and changes in emotional behaviour (Rolls *et al.*, 1994) can follow somewhat larger and more varied lesions of the ventromedial prefrontal cortex. However, it was notable that although the patients with circumscribed bilateral OFC lesions do have altered social behaviour, they are not as socially inappropriate and disinhibited as patients with closed head injuries, where the ventromedial prefrontal cortex damage must be more extensive (Rolls *et al.*, 1994; Hornak *et al.*, 1996). It was also found that the patients with bilateral OFC damage were as a group

impaired at visual discrimination reversal (Hornak *et al.*, 2003), a measure that reflects flexible stimulus-reinforcement association learning, itself an important aspect of emotion (Rolls, 1999a).

Vocal expression identification

Patients with unilateral orbital lesions, or with unilateral medial lesions in BA 9 or in the most anterior ventral division of the ACC (which includes BA 32/24, and has been termed the 'affective' ACC; Bush *et al.*, 2000) were severely impaired on the identification of non-verbal vocal emotional sounds, whereas those with dorsolateral lesions or with medial lesions outside these areas (DLat/OM group) were unimpaired. The finding that patients with unilateral orbital lesions were severely impaired on this task is consistent with our previous study, in which patients with ventral prefrontal lesions were impaired on the same test (Hornak *et al.*, 1996). However, the present study extends these earlier findings by showing that even small unilateral lesions to the orbital prefrontal cortex are sufficient to cause as severe an impairment on the test as bilateral orbital lesions, and in fact, there was no correlation between performance on this test and lesion size (total amount of prefrontal cortex excised). Just as importantly, the present study is the first to show that unilateral medial lesions in BA 9/ACC, even without orbital involvement, can produce comparably severe impairments.

The presence of auditory projections specialized for phonetic information from anterior temporal lobe to regions in OFC in monkey (Romanski *et al.*, 1999), as well as to the ACC (Barbas and Pandya, 1989), is consistent with our finding that either unilateral orbital lesions or unilateral BA 9/ACC lesions were each sufficient to cause severe impairment in vocal expression identification in humans. Also consistent with our findings are the results of a recent electrophysiological study, which found neurons in the orbital region of monkey that were responsive to vocalization (Romanski and Goldman-Rakic, 2002), and neuroimaging studies that found activation both in orbital regions as well as in medial BA 9 and adjacent ACC (BA 32/24) as normal subjects listened to non-verbal vocal emotional sounds (Phillips *et al.*, 1998; Morris *et al.*, 1999). Also, a recent PET study, which found posterior orbital activation in normal subjects as they listened to unpleasant auditory stimuli (Frey *et al.*, 2000), is consistent with our results, since most of the emotions in the vocal emotion test were negatively valenced. In fact, two patients with severe impairments on the vocal emotion tests had small far posterior orbital lesions (R.Q. and C.L.) (see Table 1 and Fig. 1).

Although further investigation with larger samples might show a greater effect of lesions in the right hemisphere, there was no difference between the effect of left- and right-sided lesions on performance on the vocal emotion test in the present study, supporting the view that these orbital and medial regions form part of an interconnected system for the

analysis of this type of information, which generally depends on the integration of neural activity across the two hemispheres (Morris *et al.*, 1999). This view is further supported by the fact that bilateral lesions did not increase the impairment produced by unilateral lesions. However, another possibility logically consistent with the results is that a system for vocal expression identification is represented unilaterally, in some individuals on the left and in others on the right.

Since most patients with medial BA 9 lesions also had Aff ACC lesions (which includes area BA 32/24), a separate evaluation of the effects of lesions in these two regions was not possible in the present study. However, neuroimaging studies have found activation in both BA 9 and BA 32/24 when normal subjects listen to non-verbal vocal expression of emotion, making it more likely that lesions restricted to one or other of these two regions would have comparable effects on the present task. It may also be relevant that BA 32 shares some of the same cytoarchitectonic features as medial areas that include BA 9 (Koski and Paus, 2000). Although smaller, more circumscribed, lesions might have more consistently different effects on the identification of different vocal emotions than were found in the present study, the fact that vocal sadness was the emotion producing the most significant group difference (and that, amongst those with unilateral lesions, only those groups with BA 9/Aff ACC involvement were significantly impaired) is at least consistent with role of anterior and subgenual cingulate cortical areas in the maintenance of positive mood (see below).

The fact that the patients with severe impairments on vocal emotion identification performed normally on the voice discrimination and environmental sounds tests shows that this impairment cannot be explained as being due to a difficulty in processing information conveyed by the voice, nor in identifying or labelling non-vocal sounds. Instead it reflects a selective impairment in the ability to extract affective significance from the voice. This is confirmed by the fact that there was no correlation between performance on vocal emotion and either of the other two auditory tasks. The impairment also cannot be explained in terms of task difficulty since, for example, the normal control group performed closer to chance on the voice discrimination test than they did on the vocal emotion test. Additionally, since most of those impaired on the vocal emotion test performed normally on the face expression test (a task in which patients were also required to match a stimulus to one of a list of seven emotion categories, and whose level of difficulty was equivalent to that of the vocal emotion test), this shows that they are also not impaired at categorizing stimuli in relation to a list.

Overall, the deficits found on the vocal emotion identification test support the hypothesis that a factor which contributes to the emotional and social difficulties produced by damage in these brain regions is a difficulty in correctly identifying emotional signals present in vocal communication (Hornak *et al.*, 1996; Rolls, 1999b).

Facial expression identification

Although some individual patients whose lesions included BA 9/ACC regions unilaterally were impaired on facial expression identification, no significant difference was found between the groups, and it was noted particularly that none of the individual patients with unilateral orbital lesions was impaired. Since orbital and medial activations to facial expressions have been reported in a number of different studies (see Introduction), one might have expected a comparable effect of lesions in these regions to that which was found for the vocal emotion test. The explanation for this difference cannot be that the facial expression test was easier for normal subjects, since the mean percentage correct on the two tests, which in each case had seven response categories, did not differ. Nevertheless, it may be that it is easier for patients to use some form of verbal strategy on the facial test that is harder to use on the vocal test. Indeed, some patients did make comments to this effect, such as saying: 'His mouth is turned down at the edges, so he must be sad'. (In fact no patient was impaired on this emotion.) Possibly, too, the fact that, in non-human primates, visual projections to the prefrontal cortex from the temporal lobe are more widely distributed than auditory projections (Romanski and Goldman-Rakic, 2002) may explain the relatively greater resilience of facial expression compared with vocal emotion processing after the same lesion. The finding that some of those with bilateral orbitofrontal cortex lesions were impaired is consistent with an earlier study (Hornak *et al.*, 1996), and extends the earlier study because in the present study the lesions were circumscribed surgically.

Subjective experience of emotion

Another important result from the present study was that patients with unilateral medial lesions on either side in BA 9 or in ACC also reported very marked changes in the subjective experience of emotion after their surgery, and on this measure they differed significantly from those with unilateral medial lesions outside this region or those with unilateral dorsolateral lesions, who reported little or no change. Patients with unilateral orbital lesions also reported small amounts of change, as would be expected from the presence of rich interconnections between the orbital and medial regions. However they did not, as a group, differ significantly on this measure from this DLat/OM group. Patients with bilateral orbital lesions did report large changes in the subjective experience of emotion, showing that lesions of either the OFC bilaterally or of the medial BA 9/ACC area unilaterally can alter subjective emotional state. There was no correlation between the total size of the prefrontal lesion and amount of emotional change reported, showing that these emotional changes cannot be explained as the consequence of having a large prefrontal lesion. The claim for regional specificity of function was supported in particular by the analysis that overlapped unilateral medial lesions across

patients. Those who reported marked changes had medial lesions extending into the key regions medial BA 9 and/or ACC. Those who reported little or no change had medial lesions either dorsal, anterior or ventral to these key regions, in some cases skirting them closely. Since many of the unilateral lesions encompassed quite a number of cytoarchitectonically defined prefrontal areas, the clear difference between patients whose lesions did and did not encroach upon these key medial regions is impressive. The results on the emotional change questionnaire are consistent with neuroanatomical and lesions studies with non-human primates, with imaging studies of normal subjects, and with both imaging and neuropathological studies of psychiatric patients (Lane *et al.*, 1997a, b, 1998; Bush *et al.*, 2000; Hadland *et al.*, 2003), all of which indicate a role for emotion in those medial regions excised in the patients who reported marked emotional changes. Since most of these patients had lesions both in medial BA 9 and the adjacent ventral anterior cingulate, the effect of lesions in these two regions on this measure cannot be compared in the present study. However, and the same point can be made for voice expression identification, the neuroimaging studies that have shown activation in the ACC and medial BA 9 in normal subjects during the experience of emotion (Lane *et al.*, 1997a, b, 1998) are consistent with the present lesion study, which provides clear evidence for a causal connection between these regions and the normal subjective experience of emotion.

There was no difference between the effects of left and of right-sided lesions on the amount of emotional change reported and, regardless of the side of the lesion, changes in both positive and negative emotions occurred in the same individual, suggesting a greater lability of mood. These findings are consistent with neuroimaging studies with normal subjects in which the same medial regions (BA 9 and ventral ACC) were activated bilaterally, while subjects recalled both positive and negative memories or while they viewed positive or negative pictures or film excerpts (Lane *et al.*, 1997a, b, 1998). The hypersensitivity to sad events or greater 'emotionality' described by most patients after lesions that included the subgenual anterior cingulate is also consistent with studies that have found abnormalities in this region in depression, namely reduced blood flow in neuroimaging studies and volume reduction in neuropathological studies (Buchsbaum, 1997; Drevets *et al.*, 1997; Mayberg, 1997; Ongur *et al.*, 1998; Torrey *et al.*, 2000). Since these studies report greater changes on the left than on the right side, it is possible that differences in subjective emotion after left- and right-sided lesions would also be found with larger samples of patients. It is also possible that more restricted lesions might have more clearly different effects on positive and on negative emotions, with subgenual lesions producing symptoms more consistently comparable with those of depression.

It is true that as a subjective report measure of emotional change, the answers to the questionnaire might have been misleading if the subjects had limited insight into their

subjective states. However, there is some external validation to support the view that lesions in the two groups with medial BA 9/ACC lesions and the bilateral OFC lesions really do produce greater subjective emotional change than do the DLAT/OM lesions, in that patients with medial BA 9/ACC lesions and bilateral OFC lesions achieved lower scores on the social behaviour questionnaire (completed by informants) than patients with DLAT/OM lesions. Moreover, the patients with DLAT/OM lesions had high (normal) scores (between 4 and 5 on most of the questions with the maximum score being 5) on the social behaviour questionnaire (Table 4). Thus, to this extent, the social behaviour questionnaire provides an objective counterpart to the subjective emotion questionnaire, and it does seem very likely that the subjective changes reported by the patients with BA 9/ACC or bilateral orbital lesions do reflect a well-reported change in their subjective emotional experience, and that the lack of change in the subjective emotional experience reported by patients with DLAT/OM lesions reflect little if any change in their perceived emotional state.

Finally, autonomic responses were not measured in the present study. However, since the subgenual 'affective division' of the ACC is, via its inputs to the hypothalamus, involved in the autonomic component of emotion (Barbas and Pandya, 1989; Koski and Paus, 2000; Ongur and Price, 2000), it will be of interest to include such measures in future research.

Another important question concerns the relationship between alterations in the subjective experience of emotion and the ability to identify that emotion when expressed by another. Although patients with BA 9/ACC lesion were impaired on vocal sadness and reported changes in in their own experience of sadness, the same comparisons for other emotions did not reveal a consistent picture. For example, many patients reported changes in the experience of anger, but few of these were impaired on the identification of vocal anger. Additionally, since the unilateral orbital group was impaired at the identification of vocal emotion but reported little or no emotional change, whereas three patients with left-sided BA 9/ACC lesions showed the opposite pattern (reporting marked emotional change while performing well on the identification of both vocal and facial emotion), it is clear that these functions can be dissociated. It remains possible, however, that further studies with smaller lesions may reveal correspondences between the experience and the perception of particular emotions.

Social behaviour

The significant group differences on the social behaviour questionnaire showed that the bilateral OFC group were rated by the informants as having lower scores on social behaviour than the DLAT/OM group, used as a comparison group because their scores were high on the questionnaire, indicating good social adjustment. Unilateral lesions had less marked effects on social behaviour, although there was a

significant reduction in the social behaviour score for the group of patients with BA 9/ACC + orbital lesions. The individual questions on which these groups scored low reflected a prototypical picture of the social behaviour of these patients, in that there were low scores on questions that included: not noticing when others were sad, happy or disgusted; not comforting others who are sad or afraid; not caring what others think; not being close to his/her family; not cooperating with others; being impatient and impulsive; and having difficulty in making and keeping close relationships. The changes produced by these surgically circumscribed lesions were smaller than in a previous investigation of patients with larger lesions of the ventromedial prefrontal cortex resulting from head injury or stroke (Rolls *et al.*, 1994; Hornak *et al.*, 1996). In our earlier studies, patients with larger ventral lesions were reported to be 'disinhibited and socially inappropriate' were often verbally abusive, aggressive, sexually uncontrolled, boastful and had a childish sense of humour. In the present study, patients with bilateral orbital lesions, which in some cases extended to include ACC bilaterally, clearly did not show such an extreme profile. Instead the informants scores for some questions suggested that these patients could express emotion appropriately in public, were not aggressive and had good manners, etc. This shows that surgically produced bilateral orbital lesions do not result such pronounced changes as those that can be produced by head injury or stroke, and the implication is that some of the changes in these latter patients may be contributed to by diffuse axonal injury or concomitant damage outside the orbitofrontal cortex. This point is reinforced by the finding that unilateral BA 9/ACC + orbital lesions produced some effects on social adjustment as indicated by their scores on the social behaviour questionnaire.

Conclusion

In previous studies describing changes in emotion and social functioning after frontal lobe lesions (Bechara *et al.*, 1994, 1998, 1999; Rolls *et al.*, 1994; Hornak *et al.*, 1996), the lesions covered a large territory of prefrontal cortex on the ventral surface, with also in some cases damage to rostral anterior cingulate and more anterior medial prefrontal cortex regions, making it impossible to evaluate separately the contributions of orbital and of medial regions, or to specify which medial regions were crucial for these effects. The present study is the first to describe marked emotional changes after unilateral surgical excisions on either side when these include medial BA 9/ACC. Although these patients did not exhibit the more flagrantly disinhibited and socially inappropriate behaviour common especially after head injury, the effects of the surgery were often described by the patients as having profound effects on their emotional responses in daily life, and the patients with bilateral OFC damage were impaired in their social behaviour as assessed by others (on the social behaviour questionnaire). As such the results of the present study have implications for the clinical assessment of

the problems that such patients are likely to face both within the family and when they return to work. The finding that patients with orbital or with medial BA 9/ACC lesions were additionally severely impaired at identifying non-verbal expression of emotion in others provides further evidence of the difficulties that such patients must encounter in the social interactions of daily life, especially since these impairments were sometimes marked enough to be noted by informants in the social behaviour questionnaire.

References

- Barbas H, Pandya DN. Architecture of intrinsic connections of the prefrontal cortex in the rhesus monkey. *J Comp Neurol* 1989; 286: 353–75.
- Barbas H, Ghashgaeli H, Dombrowski SM, Rempel-Clower NL. Medial prefrontal cortices are unified by common connections with superior temporal cortices and distinguished by input from memory-related areas in the rhesus monkey. *J Comp Neurol* 1999; 410: 343–67.
- Baxter MG, Parker A, Lindner CCC, Izquierdo AD, Murray EA. Control of response selection by reinforcer value requires interaction of amygdala and orbital prefrontal cortex. *J Neurosci* 2000; 20: 4311–9.
- Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 1994; 50: 7–15.
- Bechara A, Damasio H, Tranel D, Anderson SW. Dissociation of working memory from decision making within the human prefrontal cortex. *J Neurosci* 1998; 18: 428–37.
- Bechara A, Damasio H, Damasio AR, Lee GP. Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *J Neurosci* 1999; 19: 5473–81.
- Benson PJ, Perret DI. Synthesising continuous-tone caricatures. *Image Vis Comput* 1991; 9: 123–9.
- Benton AL, Hamsher KS, Varney NR, Spreen O. Facial recognition: stimulus and multiple choice pictures. In: New York: Oxford University Press; 1983.
- Blair RJR, Morris JS, Frith CD, Perrett DI, Dolan RJ. Dissociable neural responses to facial expressions of sadness and anger. *Brain* 1999; 122: 883–93.
- Blood AJ, Zatorre RJ, Bermudez P, Evans AC. Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions. *Nat Neurosci* 1999; 2: 382–7.
- Buchsbaum MS, Wu J, Siegel BV, Hackett E, Trenary M, Abel L, et al. Effect of sertraline on regional metabolic rate in patients with affective disorder. *Biol Psychiatry* 1997; 41: 15–22.
- Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci* 2000; 4: 215–22.
- Cavada C, Company T, Tejedor J, Cruz-Rizzolo RJ, Reinoso-Suarez F. The anatomical connections of the macaque monkey orbitofrontal cortex. *Cereb Cortex* 2000; 10: 220–42.
- Critchley HD, Rolls ET. Hunger and satiety modify the responses of

- olfactory and visual neurons in the primate orbitofrontal cortex. *J Neurophysiol* 1996; 75: 1673–86.
- Dolan RJ, Fletcher P, Morris J, Kapur N, Deakin JFW, Frith CD. Neural activation during covert processing of positive emotional facial expressions. *Neuroimage* 1996; 4: 194–200.
- Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M, et al. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 1997; 386: 824–7.
- Duncan J, Owen AM. Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci* 2000; 23: 457–83.
- Ekman P, Friesen WV. Pictures of facial affect. Palo Alto (CA): Consulting Psychologists Press; 1975.
- Frey P, Kostopoulos P, Petrides M. Orbitofrontal involvement in the processing of unpleasant auditory information. *Eur J Neurosci* 2000; 12: 3709–12.
- Gaffan D, Murray EA, Fabre-Thorpe M. Interaction of the amygdala with the frontal lobe in reward memory. *Eur J Neurosci* 1993; 5: 968–75.
- Hadland KA, Rushworth MFS, Gaffan D, Passingham RE. The effect of cingulate lesions on social behaviour and emotion. *Neuropsychologia* 2003; 41: 919–31.
- Hornak J, Rolls ET, Wade D. Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. *Neuropsychologia* 1996; 34: 247–61.
- Hornak J, O'Doherty J, Bramham J, Rolls ET, Morris RG, Bullock PR, et al. Reward-related reversal learning after surgical excisions in orbitofrontal and dorsolateral prefrontal cortex in humans. *J Cogn Neurosci*. In Press. 2003.
- Jones B, Mishkin M. Limbic lesions and the problem of stimulus-reinforcement associations. *Exp Neurol* 1972; 36: 362–77.
- Jurgens U. Neural pathways underlying vocal control. *Neurosci Biobehav Rev* 2002; 26: 235–58.
- Kling A, Steklis HD. A neural substrate for affiliative behavior in non-human primates. *Brain Behav Evol* 1976; 13: 216–38.
- Koski L, Paus T. Functional connectivity of the anterior cingulate cortex within the human frontal lobe: a brain-mapping meta-analysis. *Exp Brain Res* 2000; 133: 55–65.
- Lane RD, Reiman EM, Ahern GL, Schwartz GE, Davidson RJ. Neuroanatomical correlates of happiness, sadness, and disgust. *Am J Psychiatry* 1997a; 154: 926–33.
- Lane RD, Reiman EM, Bradley MM, Lang PJ, Ahern GL, Davidson RJ, et al. Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia* 1997b; 35: 1437–44.
- Lane RD, Reiman EM, Axelrod B, Yun L-S, Holmes AH, Schwartz GE. Neural correlates of levels of emotional awareness. Evidence of an interaction between emotion and attention in the anterior cingulate cortex. *J Cogn Neurosci* 1998; 10: 525–35.
- Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. *J Neuropsychiatry Clin Neurosci* 1997; 9: 471–81.
- Morris JS, Scott SK, Dolan RJ. Saying it with feeling: neural responses to emotional vocalizations. *Neuropsychologia* 1999; 37: 1155–63.
- Nakamura K, Kawashima R, Ito K, Sugiura M, Kato T, Nakamura A, et al. Activation of the right inferior frontal cortex during assessment of facial emotion. *J Neurophysiol* 1999; 82: 1610–4.
- Nelson HE. National Adult Reading Test (NART): test manual. Windsor (UK): NFER-Nelson; 1982.
- O'Doherty J, Kringelbach ML, Rolls ET, Hornak J, Andrews C. Abstract reward and punishment representations in the human orbitofrontal cortex. *Nat Neurosci* 2001; 4: 95–102.
- Ongur D, Price JL. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cereb Cortex* 2000; 10: 206–19.
- Ongur D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. *Proc Natl Acad Sci USA* 1998; 95: 13290–5.
- Owen AM, Stern CE, Look RB, Tracey I, Rosen BR, Petrides M. Functional organization of spatial and nonspatial working memory processing within human lateral frontal cortex. *Proc Natl Acad Sci USA* 1998; 95: 7721–6.
- Passingham R. Delayed matching after selective prefrontal lesions in monkeys (*Macaca mulatta*). *Brain Res* 1975; 92: 89–102.
- Paus T. Primate anterior cingulate cortex: where motor control, drive and cognition interface. *Nat Rev Neurosci* 2001; 2: 417–24.
- Phillips ML, Young AW, Scott SK, Calder AJ, Andrew C, Giampietro V, et al. Neural responses to facial and vocal expressions of fear and disgust. *Proc R Soc Lond B Biol Sci* 1998; 265: 1809–17.
- Rolls ET. The brain and emotion. Oxford: Oxford University Press; 1999a.
- Rolls ET. The functions of the orbitofrontal cortex. *Neurocase* 1999b; 5: 301–12.
- Rolls ET. The orbitofrontal cortex and reward. *Cereb Cortex* 2000; 10: 284–94.
- Rolls ET. The functions of the orbitofrontal cortex. In Stuss DT, Knight RT, editors. Principles of frontal lobe function. New York (NY): Oxford University Press; 2002. p. 354–75.
- Rolls ET, Hornak J, Wade D, McGrath J. Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. *J Neurol Neurosurg Psychiatry* 1994; 57: 1518–24.
- Rolls ET, Critchley HD, Mason R, Wakeman EA. Orbitofrontal cortex neurons: role in olfactory and visual association learning. *J Neurophysiol* 1996; 75: 1970–81.
- Rolls ET, O'Doherty J, Kringelbach ML, Francis S, Bowtell R, McGlone F. Representations of pleasant and painful touch in the human orbitofrontal and cingulate cortices. *Cereb Cortex* 2003a; 13: 308–17.
- Romanski LM, Goldman-Rakic PS. An auditory domain in primate prefrontal cortex. *Nat Neurosci* 2002; 5: 15–6.
- Romanski LM, Tian B, Fritz J, Mishkin M, Goldman-Rakic PS, Rauschecker JP. Dual streams of auditory afferents target multiple

domains in the primate prefrontal cortex. *Nat Neurosci* 1999; 2: 1131–6.

Rowe AD, Bullock PR, Polkey CE, Morris, RG. 'Theory of mind' impairments and their relationship to executive functioning following frontal lobe excisions. *Brain* 2001; 124: 600–16.

Rowe JB, Owen AM, Johnsrude IS, Passingham RE. Imaging the mental components of a planning task. *Neuropsychologia* 2001; 39: 315–27.

Sprengelmeyer R, Young AW, Calder AJ, Karnat A, Lange H, Homberg V, et al. Loss of disgust. Perception of faces and emotions in Huntington's disease. *Brain* 1996; 119: 1647–65.

Thorpe SJ, Rolls ET, Maddison S. The orbitofrontal cortex:

neuronal activity in the behaving monkey. *Exp Brain Res* 1983; 49: 93–115.

Torrey EF, Webster M, Knable M, Johnston N, Yolken RH. The Stanley Foundation Brain Collection and Neuropathology Consortium. *Schizophr Res* 2000; 44: 151–5.

Vogt BA, Pandya DN. Cingulate cortex of the rhesus monkey: II. Cortical afferents. *J Comp Neurol* 1987; 262: 271–89.

Vogt BA, Pandya DN, Rosene DL. Cingulate cortex of the rhesus monkey: I. Cytoarchitecture and thalamic afferents. *J Comp Neurol* 1987; 262: 256–70.

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Appendix A. Social behaviour questionnaire

Questions which contributed to the five factors when informants were asked about normal control subjects.

Emotion recognition

- Q13 He/she notices when other people are *sad*
- Q18 He/she notices when other people are *angry*
- Q25 He/she notices when other people are *frightened*
- Q9 He/she notices when other people are *disgusted*
- Q4 He/she notices when other people are *happy*

Emotional empathy

- Q27 When others are *sad* he/she comforts them
- Q28 When others are *angry* he/she calms them down
- Q30 When others are *afraid* he/she reassures them
- Q26 When others are *happy*, he/she is happy for them

Interpersonal relationships

- Q2 He/she speaks her mind (R)
- Q17 He/she does what he/she wants and does not care what others think (R)
- Q21 He/she is close to his family

Public behaviour

- Q1 He/she expresses emotion appropriately in public
- Q8 He/she cooperates with others
- Q11 He/she is confident meeting new people (R)

Antisocial behaviour

- Q3 He/she is critical of others (R)
- Q10 He/she is impatient with other people (R)
- Q5 He/she avoids arguments.
- Q7 He/she is not aggressive

Questions which did not contribute to the five factors

Impulsivity

- Q19 He/she does things without thinking (R)
- Q16 He/she takes a long time to make decisions

Sociability/social skills

- Q14 He/she is sociable
- Q24 He/she prefers being alone than with others (R)
- Q20 He/she has good manners †
- Q6 He/she is amusing
- Q15 He/she is apologetic
- Q22 He/she lets someone know when he/she finds them attractive (R)
- Q12 He/she has difficulties making and keeping close relationships (R)
- Q23 He/she keeps in touch with old friends†5

Empathy

- Q31 When others are disgusted, he/she is appalled for them.

R = reversed. On these questions a high score indicates poor social adjustment. Scores for these questions were therefore 'reversed' before contributing to a patient's final score. Note that there is no question 29. †Bilateral mean score was higher than DLat/OM mean score.⁶

Appendix B. Vocal emotion identification: performance on each emotion by individual patients

Patients	Sad	Angry	Frightened	Disgusted	Contented	Puzzled	Neutral
Dorsolat/OM							
R.C.			*	*			
F.Z.				**	**		
B.S.	*					*	
R.D.						**	
Q.O.	**						
U.C.	*			*			
G.E.							
G.D.		*					
A.G.							
Orbital							
T.R.	*		*	**		**	
L.J.	*					*	
R.Q.		*		*			**
C.L.	**		**	*		**	
S.I.				**			
BA 9/ACC							
L.Q.	*			*		**	**
B.R.		*	*	**		**	
E.E.	**		**		**		
O.F.	*						
BA 9/ACC + orbital							
V.F.				*			
B.Q.	*					**	
Q.G.					*		**
L.K.	**		*	*			
A.R.	*		*	**		**	*
D.B.	**		*	**			
R.K.				*	**		*
L.S.							
Bilateral OFC							
V.O.	**	*					
J.A.	**						
V.U.	*			*			
R.R.		*		*		**	
R.F.							
V.Z.	**	*		*	*	**	

*Patients whose score fell at or below the 5th centile for that emotion (1.65 SDs outside the control mean). **Patients whose score fell at or below the 1st centile for that emotion (2.32 SDs outside the control mean).

Appendix C. Face expression identification: number correct (out of 16) on each expression by those patients whose total score fell at or below the 5th centile

Patients	Sad	Angry	Frightened	Disgusted	Happy	Surprised
Control mean (SD)	12.24 (2.98)	14.24 (1.42)	11.28 (3.25)	9.20 (3.12)	15.56 (1.26)	10.84 (2.43)
BA 9/ACC						
B.R.	9	12*	6*	3*	14*	7*
E.E.	9	11**	7	7	15	5**
BA 9/ACC + orbital						
L.K.	9	9**	5*	1**	14*	3**
D.B.	8	12*	8	8	14*	6*
Bilateral OFC						
V.O.	8	13	7	5	16	8
R.F.	13	14	7	0**	16	7*
V.Z.	8	7**	3**	9	16	8

*At or below the 5th centile. **At or below the 1st centile.