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Are You Upset? Distinct Roles for Orbitofrontal and Lateral Prefrontal Cortex in Detecting and Distinguishing Facial Expressions of Emotion

Ami Tsuchida and Lesley K. Fellows

Department of Neurology & Neurosurgery, Montreal Neurological Institute, McGill University, Montreal, Quebec H3A 2B4, Canada

Address correspondence to Ami Tsuchida, Department of Neurology & Neurosurgery, Montreal Neurological Institute, McGill University, 3801 University Street, Montreal, Quebec H3A 2B4, Canada. Email: ami.tsuchida@mail.mcgill.ca.

Navigating our complex social world requires effective processing of subtle emotional signals, such as those conveyed by facial expressions. Failure to do so may underlie some of the disabling social–emotional deficits common in a range of neuropsychiatric and neurological conditions. Prefrontal cortex (PFC) has long been implicated in these processes, but the particular contributions of subregions within PFC remain unclear. We used a sensitive facial emotion rating task in patients with focal lesions to different regions within PFC to identify distinct contributions of 2 prefrontal regions to recognizing emotions from facial expressions. A combination of region-of-interest and voxel-based lesion–symptom mapping established that damage to ventromedial PFC impaired the detection of subtle facial expressions of emotion. Such patients had difficulty distinguishing emotional from neutral expressions. In contrast, patients with left ventrolateral PFC were able to detect the presence of emotional signals but had difficulty discriminating between specific emotions. These effects were regionally specific: Dorsomedial prefrontal damage had no effect on either aspect of emotion recognition. These findings suggest that separable processes relying critically on distinct regions within PFC responsible, on the one hand, for detecting emotional signals from facial expressions and, on the other, for correctly classifying such signals.

Keywords: emotion recognition, prefrontal cortex, lesion–symptom mapping

Introduction

The ability to recognize subtle emotions from facial expressions is crucial for successful social interaction (Haxby et al. 2000). Lesions to the prefrontal cortex (PFC) in general, and orbitofrontal (OFC) and ventromedial PFC (vmPFC) in particular, have long been associated with disturbed emotional and social behavior (Davidson et al. 2000; Stuss and Levine 2002). There is some evidence that these behavioral problems stem, at least in part, from deficits in processing basic social and emotional signals presented by others (Rolls et al. 1994). An understanding of emotion recognition processes thus has the potential to inform more precise diagnosis and treatment of social difficulties related to PFC dysfunction. Such insights may also provide a brain-based framework for understanding social–emotional deficits in neuropsychiatric conditions, such as autism.

Functional neuroimaging (Wager et al. 2003; Fusar-Poli, Placentino, Carletti, Allen, et al. 2009) and lesion studies (Adolphs et al. 2000; Philippi et al. 2009) have implicated a number of cortical and subcortical structures in the recognition of emotion from facial expressions. While the roles of posterior brain regions and the amygdala have been studied in considerable detail (Adolphs 2002), the contributions of specific regions within PFC to emotion recognition remain a matter of debate. While human lesion studies have focused primarily on vmPFC and OFC, functional neuroimaging studies suggest that other PFC regions are involved: A recent meta-analysis reported consistent activations in bilateral ventrolateral and dorsomedial PFC (dmPFC) across functional neuroimaging studies of various emotional face recognition tasks in healthy subjects (Fusar-Poli, Placentino, Carletti, Allen, et al. 2009).

Given the potential complexity of the processes triggered by emotional stimuli, loss-of-function studies are important in defining the necessary contributions of particular brain regions at the component process level. The functional neuroimaging literature raises the possibility that the vmPFC/OFC focus of PFC lesion studies to date has been overly narrow. Furthermore, even those studies, in aggregate, are inconclusive, with some finding that damage to this region results in impaired identification of facial emotional expressions (Hornak et al. 1996; Heberlein et al. 2008), and others failing to detect effects specific to vmPFC (Hornak et al. 2003; Shamay-Tsoory et al. 2003).

This literature is complicated by the use of different tasks and stimuli. In particular, the forced-choice labeling tasks used in most of the above studies do not differentiate between deficits in detecting emotional signals in general or in discriminating between specific emotions. Also, such tasks typically do not control for differences in confusability between the 6 cardinal emotions typically studied (e.g., forced choice between fear and happiness is easier than between fear and surprise) (Adolphs 2002). Facial emotion rating tasks are one solution to these problems, providing information about the ability to detect the presence of emotional information, and to distinguish one emotion from another (Adolphs et al. 1994, 1996, 2000; Heberlein et al. 2008).

In the present study, we administered a sensitive facial emotion rating task to a large sample of patients with focal damage affecting various regions within the PFC. The first aim was to replicate in a new sample the finding that vmPFC/OFC plays a critical role in emotion recognition from faces (Heberlein et al. 2008). The second aim was to formally test whether dmPFC and lateral PFC play necessary roles in emotion recognition and to directly compare the effects of lesions to these regions with those to vmPFC/OFC. Third, we aimed to clarify the component processes subserved by these 3 regions, if any. Finally, the new sample reported here was combined with the sample reported in Heberlein et al. (2008) to allow the fine detail of regionally specific PFC contributions to facial emotion recognition to be probed using voxel-based lesion–symptom mapping (VLSM).

The results confirmed the specific involvement of vmPFC/OFC in processing emotion signals from facial expressions. Lesions to this area, but not to other PFC regions, led to an overall decrease in sensitivity to emotional expressions. We identified a different deficit in patients with lateral PFC damage, especially in the left hemisphere: Such damage specifically disrupted the ability to discriminate between specific emotions.

Materials and Methods

Subjects

Twenty-nine subjects with focal damage to the frontal lobes were recruited through the research databases at McGill University and the University of Pennsylvania. All patients with a fixed lesion primarily affecting PFC were eligible for the study; none had participated in the prior study by Heberlein et al. (2008). They were tested at least 6 months after the injury (mean, 46 months; range, 9 months to 16 years). These patients were compared with 47 age- and education-matched healthy control subjects, recruited through local advertisement in Montreal. Healthy controls had no history of neurological or psychiatric disease and were not taking any psychoactive drugs. They were excluded if they scored <28/30 on the mini-mental status exam (Folstein et al. 1975) or <26/30 on the Montreal Cognitive Assessment (Nasreddine et al. 2005). Participants provided written informed consent in accordance with the Declaration of Helsinki and were paid a nominal fee for their time. The study protocol was approved by the Institutional Review Boards of both participating centres.

Patients with PFC damage were first divided into 3 subgroups based on lesion location: 10 subjects with damage involving OFC (areas 11, 13, and 14) and/or vmPFC (area 25 and subcallosal portions of areas 24 and 32) were classified as having ventromedial frontal (VMF) damage. Subjects with damage outside VMF were divided into those with damage centered on dmPFC (DM group, $N = 10$) or lateral PFC (LF group, $N = 9$), in order to explicitly test the contributions of these prefrontal regions. Damage to dmPFC included dorsal anterior cingulate cortex (dACC; dorsal portions of areas 24 and 32) and/or adjacent superior frontal gyrus (areas 8, 9, and anterior portion of 6), while lateral PFC lesions affected areas 44, 45, 46, and 46/9, with some lesions extending to anterior insular cortex. Figure 1 shows the lesion extent and overlap in these 3 groups. Lesions were due to rupture of anterior communicating artery aneurysm, resection of low-grade tumor, or ischemic or hemorrhagic stroke. Table 1 summarizes the demographic information for all participants as well as lesion volume and etiology for frontal patients. Results of a brief screening neuropsychological evaluation are shown in Table 2.

Task

A computerized version of the facial emotion rating task described in Heberlein et al. (2008) was developed using E-Prime software (www.pstnet.com). This task uses the same set of 25 face stimuli as in the Heberlein et al. (2008) study, showing subtle expressions of the 6 basic emotions (fear, anger, disgust, happiness, sadness, and surprise) as well as neutral expressions. These were morphs of a single individual's face (PE) from the Ekman and Friesen (1976) stimulus set and were selected from a series of 19 linear morphs between a neutral face and an emotional face showing each of the 6 prototypic emotions. The morphs for each emotion were chosen to avoid floor and ceiling effects, based on data from healthy subjects (Jansari et al. 2000). This resulted in different numbers of exemplars for some emotions but had the advantage of equating difficulty across emotions: The set included 2 afraid (morph degrees 5 and 6), 5 angry (morph degrees from 5 to 9), 3 disgusted (morph degrees from 7 to 9), 5 happy (morph degrees from 2 to 6), 5 sad (morph degrees from 5 to 9), 2 surprised (morph degrees 5 and 6), and 3 neutral faces.

Subjects were presented with one stimulus at a time and asked to rate the intensity of emotion expressed on the face using a 10-point Likert scale (1—not at all to 10—extremely happy, angry, etc.) with no time limit. All 25 stimuli were presented in a fixed random order. Subjects rated a single emotion for the entire set and then repeated this process for each of the 6 emotions. The order of rated emotion was randomized across subjects.

Data Analysis

The rating task allows us to examine 2 different aspects of emotion recognition; the ability to detect the emotion expressed on faces and the ability to then discriminate the specific emotion being expressed. The first was measured using difference scores (between emotional and neutral face ratings) (Adolphs and Tranel 2004; Heberlein et al. 2008) and the latter by calculating a specificity index that considers the rating of the target emotion compared with the rating of nontarget emotions (see below).

The difference score was calculated as the difference between ratings for the target emotion given to each face expressing that emotion and the average ratings of the 3 neutral faces (i.e., the happy rating of the happy morph faces compared with happy ratings given to neutral faces captures the ability to detect happiness and so on for each emotion). In order to control for individual differences in the range of

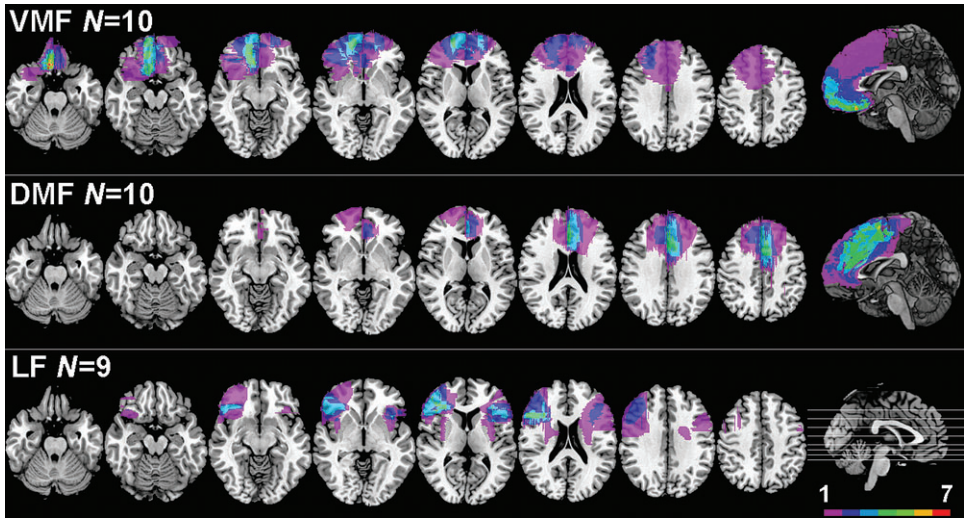

Figure 1. Representative axial slices and midsagittal views of the MNI brain, showing the degree of lesion overlap for subjects with damage affecting OFC and/or vmPFC (VMF group, $N = 10$, top row), dmPFC (DM group, $N = 10$, second row), or lateral PFC (LF group, $N = 9$, bottom row). Colors indicate the degree of overlap across subjects, as shown in the legend.

Table 1
Demographic information for healthy control (CTL) and frontal patient (FP) groups and for anatomically defined frontal subgroups (orbitofrontal [VMF], dorsomedial frontal [DM], lateral frontal [LF]), mean (SD)

Group	Age (years)	Education (years)	Sex (F/M)	BDI	ANART IQ	Lesion volume (cc)	Etiology (aneurysm/tumor/stroke)
CTL (*N* = 47)	**56.5 (12.3)**	**14.9 (3.0)**	**18/29**	**5.1 (5.0)**	**123.2 (7.4)**	—	—
FP (*N* = 29)	**55.2 (12.4)**	**14.2 (3.9)**	**12/17**	**13.7* (10.5)**	**116.1* (9.4)**	**38.1 (43.8)**	**3/13/13**
VMF (*N* = 10)	58.8 (9.7)	13.4 (4.7)	3/7	16.3 (11.4)	111.3 (8.9)	46.4 (68.9)	3/5/2
DM (*N* = 10)	53.7 (14.6)	14.8 (3.9)	3/6	11.4 (10.0)	120.3 (6.5)	36.1 (26.8)	0/6/4
LF (*N* = 9)	53.4 (13.3)	13.7 (3.3)	6/4	13.8 (10.3)	114.8 (11.5)	30.9 (20.3)	0/2/7

Note: Not all patients were able to complete the ANART. F, female; M, male; SD, standard deviation; BDI, Beckman Depression Inventroy; ANART, American National Adult Reading Test.
* indicates significant differences based on a 2-tailed *t*-test for comparisons between CTL and FP or an ANOVA for comparison across the 3 frontal subgroups ($P < 0.05$).

Table 2
Summary of performance on selected neuropsychological screening tests for CTL and FP groups, mean (SD).

Group	Sentence comprehension accuracy	Fluency-F	Fluency-Animal	Backward digit span	Backward Corsi span
CTL (*N* = 47)	**0.97 (0.07)**	**14.6 (4.9)**	**21.6 (5.2)**	**5.0 (1.9)**	**4.7 (1.1)**
FP (*N* = 29)	**0.97 (0.06)**	**9.8* (5.7)**	**16.7* (5.6)**	**4.4 (1.3)**	**4.3 (0.9)**
VMF (*N* = 10)	0.97 (0.06)	11.7 (4.3)	18.3 (6.2)	4.0 (1.2)	4.1 (0.9)
DM (*N* = 10)	0.98 (0.06)	9.9 (6.5)	17.8 (5.1)	4.9 (1.4)	4.5 (1.0)
LF (*N* = 9)	0.95 (0.07)	7.3 (5.8)	13.4 (4.7)	4.1 (1.1)	4.5 (1.0)

Note: SD, standard deviation.
* indicates significant differences (*t*-test or ANOVA, $P < 0.05$).

the scale used for the rating as well as in the positioning of neutral stimuli within that range, we calculated the maximum difference score for each individual by subtracting the average rating given to the neutral stimuli from the maximum rating provided by the same subject. Difference scores were then divided by the maximum difference score for that subject to obtain a proportional difference (pD) score. This pD score was averaged for each category of emotional stimuli, collapsing across morph degree, to provide a measure of the ability to detect subtle expressions of each of the 6 emotions. The effect of group membership on this ability was assessed by submitting the pD score for each emotion to a mixed analysis of variance (ANOVA), with group membership as a between-subject and emotion category as a within-subject factor. We believe the pD score is the most suitable choice for capturing the perceived relative emotional expression intensity, given the essentially arbitrary nature of emotional rating in an absolute sense. Nonetheless, we confirmed the main findings with the raw difference scores as well and found the same pattern of effects.

Second, in order to examine the ability not simply to detect emotion but to discriminate specific emotional expressions from each other, we calculated a specificity index for each emotion (Adolphs and Tranel 2004). This was calculated as the difference between pD score for the target emotion (e.g., "happy" ratings for the happy morph faces) and the mean pD score for all the other emotions (e.g., ratings for all the other emotion labels for the happy morph faces). The specificity index was calculated for each face expressing a subtle emotion and was then collapsed across morph degree to obtain a mean specificity index for each of the 6 emotions. This index directly captured the ability to discriminate the specific emotion expressed in each face from other emotions. It was then submitted to a mixed ANOVA to test the effect of group membership.

For descriptive purposes, we further probed the specificity of emotion ratings by examining the emotion rating spectrum, expressed as the average pD scores for the faces expressing a given emotion, across all the emotions on which it was rated (e.g., ratings of how "happy," "sad," "surprised," "angry," "fearful," and "disgusted" the face looked, for the objectively "happy" face morphs). Patterns of ratings were compared statistically across groups with mixed ANOVA.

If any significant group effects were detected with ANOVA, post hoc comparisons were made with the Tukey–Kramer method. When significant interactions were detected, simple main effects tests were performed, followed by Tukey–Kramer pairwise comparisons.

Lesion Analysis

Individual lesions were traced from the most recent clinical CT or MRI scans onto the standard Montreal Neurological Institute (MNI) brain using MRIcro software (www.mricro.com) by a neurologist (L.K.F.) experienced in imaging analysis and blind to task performance. This and MRIcroN software (www.mricro.com/mricron) were also used to estimate lesion volumes and to create lesion overlap images.

VLSM Analysis

In contrast to conventional region-of-interest analysis, VLSM allows lesion–behavior associations to be tested without assigning patients to arbitrary groups. In this method, a behavioral measure is entered as the dependent variable, with lesion status of each voxel (lesioned or not lesioned) comprising the independent variable. Then, for each voxel, statistical comparisons are made between the performance of subjects with lesions affecting that voxel and subjects with lesions sparing that voxel. The output is a statistical map indicating voxels associated with poor performance when lesioned (Bates et al. 2003). We pooled the present data with the data reported in Heberlein et al. (2008) (combined sample $N = 44$) to increase the power of this analysis and used *t*-tests, implemented with VoxBo (Kimberg et al. 2007) (www.voxbo.org), to make voxelwise comparisons for those voxels lesioned in at least 3 patients, using a cluster extent threshold of $k = 100$ voxels. Statistical maps thresholded at an uncorrected P value < 0.05 were generated to show the relative effects of voxels within PFC. This method can only test structure–function hypotheses in regions with sufficient lesion overlap. We tested voxels damaged in at least 3 subjects (Supplementary Fig. 1). Although variable lesion size is a potential confound in VLSM analysis (Kimberg et al. 2007), there was no correlation between the lesion size and the behavioral measures used in this study (difference score: $r = -0.004$, $P = 0.98$; specificity index residuals: $r = 0.076$, $P = 0.62$). There was also no effect of lesion chronicity on these measures (difference score: $r = 0.115$, $P = 0.48$; specificity index residuals: $r = 0.120$, $P = 0.46$).

Results

Detecting Emotion from Facial Expressions

Patients with frontal lobe damage ($N = 29$) were divided into 3 subgroups according to lesion location, as described above. In order to test for differences in the ability to detect subtle emotional expressions, the pD scores of these patient groups as well as those of healthy control subjects were submitted to a mixed ANOVA, with subject group (VMF, DM, LF, and CTL) as a between-subject factor and emotion (anger, fear, happiness, disgust, surprise, and sadness) as a within-subject factor. There were significant effects of group ($F_{3,72} = 4.87$, $P = 0.004$) and emotion ($F_{5,360} = 2.94$, $P = 0.01$) but no significant interaction ($F_{15,360} = 0.73$, $P = 0.75$) (Fig. 2). Post hoc Tukey–Kramer tests revealed that VMF, but not DM or LF groups, had significantly lower pD scores compared with the CTL group across all emotions ($P < 0.05$). The same test on the effect of emotion

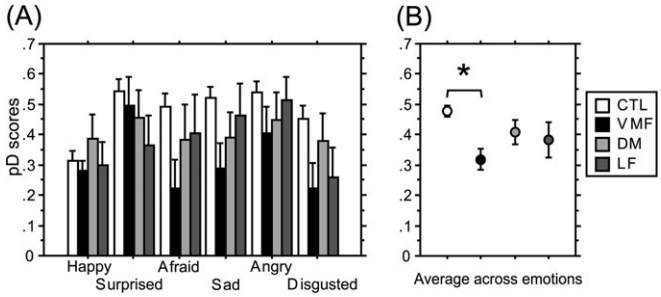

Figure 2. The ability to detect emotion from facial expressions, measured as pD scores, for each group, for different emotions (*A*) and averaged across emotions (*B*). Error bars indicate standard error of the mean. * denotes significant difference for pairwise comparisons for groups (Tukey–Kramer test, $P < 0.05$).

category revealed that overall, subjects gave significantly lower ratings for happy faces than for surprised, sad, and angry faces (all $P < 0.05$), indicating that happy faces were perceived as less intense relative to these emotions and thus more difficult to distinguish from neutral faces. This effect of emotion category appeared to be similar across groups. Failing to detect a significant interaction between group and emotion category may be due to lack of power, so we explored this question directly by comparing the VMF group directly with the CTL group. This yielded similar results, with a significant effect of group ($F_{1,55} = 13.66$, $P = 0.0005$) and emotion ($F_{5,275} = 3.26$, $P = 0.007$) but no interaction ($F_{5,275} = 1.19$, $P = 0.32$).

VLSM of Facial Emotion Detection

The region-of-interest analysis indicates that VMF damage, but not damage elsewhere in PFC, impairs emotion recognition from faces across emotions. However, these groups are based on arbitrary boundaries and may miss other structure–function relationships. VLSM does not require a priori assumptions about the critical areas, and so was undertaken to supplement the region-of-interest approach. This method is most useful with larger sample sizes. We therefore combined the present data set with that from Heberlein et al. (2008), which used the identical task, for this analysis (Supplementary Fig. 1).

We used the average pD score collapsed across all emotions as the dependent measure in the VLSM analysis to identify prefrontal regions which, when lesioned, are associated with poor ability to distinguish facial expressions of emotion from neutral faces. Figure 3 shows the resulting statistical map, converted to z score and thresholded at $P < 0.05$, uncorrected, and the coordinates of statistically significant voxel clusters are summarized in Table 3. No voxels survived correction for multiple comparisons at the rigorous thresholds required for this massively univariate method, whether using Bonferroni correction based on distinct lesion patterns or permutation thresholding. Nonetheless, the statistical map provides complementary evidence when interpreted in light of the primary region-of-interest analysis, which provides protection against false positives. The largest cluster and the highest z score identified in the VLSM analysis was in the left subcallosal cingulate region, continuing into the underlying white matter. This fell within our predefined VMF boundaries, arguing that the region-of-interest approach we adopted was appropriate for capturing key PFC effects. The VLSM result indicates that the poor performance of the VMF group was mainly driven by damage to vmPFC.

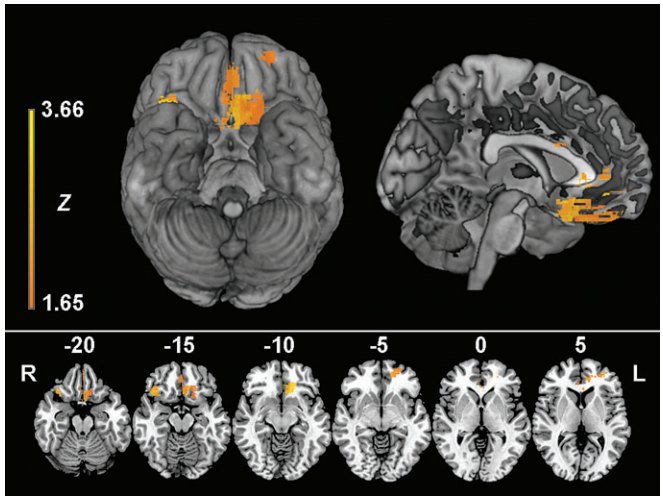

Figure 3. VLSM statistical map computed for pD score shown on 3D views of the MNI brain in the top panel, with representative axial slices below. The color scale indicates *t*-test results converted into *z* scores, thresholded at $P < 0.05$, uncorrected.

Table 3
Coordinates of the regions associated with low pD scores in the VLSM analysis, in MNI space

Region	Hemisphere	*x*	*y*	*z*	*Z* Max	*n* voxels
Gyrus rectus	Left	−8	30	−16	3.66	4531
Inferior frontal gyrus, orbital part	Right	38	24	−16	3.10	810
Middle frontal gyrus, white matter	Left	−22	44	5	2.85	748
Anterior cingulate and paracingulate gyri	Bilateral	1	32	2	2.85	244
Superior frontal gyrus, orbital part, white matter	Left	−17	34	−3	2.52	124
Corpus callosum	Left	−5	13	24	2.29	127

Note: Cortical region labels are taken from the automated anatomical labeling template (Tzourio-Mazoyer et al. 2002). The MNI coordinates indicate the center of mass for each significant cluster. The maximum *t*-statistics, converted into *z* scores are also shown. *z* scores greater than 2.3 are significant at $P < 0.01$ and greater than 1.6 at $P < 0.05$, uncorrected.

Discrimination of Specific Emotions

The rating task also allows us to capture a different aspect of emotion recognition: that is, the ability to discriminate emotions from each other. By comparing the pD scores for the correct emotion label with those for the other, incorrect emotion labels, it is possible to derive a specificity index (Adolphs and Tranel 2004). This measure is not independent of the pD score for the target emotion, since a low rating for the target emotion is likely to result in a low pD score (difference from neutral face rating) as well as in low specificity (difference from ratings given to nontarget emotion faces). Indeed, the 2 measures were tightly correlated in our sample ($r = 0.88$, $P < 0.0001$). In order to compare the ability to discriminate specific emotions independent of the ability to simply detect emotional expressions, the mean pD scores were regressed out from the mean specificity indices for each of the 6 emotion (for a similar approaches in another context, see Amorapanth et al. 2010; Wencil et al. 2010). The resulting residuals were submitted to a mixed ANOVA, with subject group as between-subject and emotion category as within-subject factors. This revealed a significant effect of group ($F_{3,72} = 4.28$, $P = 0.008$) and emotion ($F_{5,360} = 14.88$, $P < 0.0001$) but no interaction between group membership and emotion category ($F_{15,360} = 0.60$, $P = 0.87$) (Fig. 4). Post hoc Tukey–Kramer pairwise comparisons revealed that only the LF group, and not VMF or DM groups, had disproportionately low specificity indices,

relative to their pD scores, compared with healthy control subjects ($P < 0.05$). Tukey tests on the effect of emotion category revealed that specificity indices were significantly higher for happy faces than for all other emotions (all $P < 0.05$) and also significantly lower for fearful faces than for all other emotions (all $P < 0.05$). This contrasts with the pD score finding, suggesting that despite the subtlety of the expressions, happy faces were relatively easy to distinguish from other emotions, while subjects in general had particular difficulty distinguishing fear from other emotions.

VLSM Analysis of Facial Emotion Discrimination

The residual scores of the specificity indices were averaged across the 6 emotion categories in order to conduct a VLSM analysis aimed at identifying prefrontal voxels necessary for fine discrimination of emotions, after accounting for the basic ability to detect emotion. Again, none of the voxels reached stringent thresholds corrected for multiple comparisons. At the $P < 0.05$ threshold, uncorrected, the analysis yielded highly localized results, identifying a single cluster of voxels centered in left inferior frontal gyrus and extending to left insular cortex (max z value = 3.50, MNI coordinates for the center of mass [x = −38, y = 12, z = 5]) and no other prefrontal regions (Fig. 5). This complements the region-of-interest analysis, demonstrating that the groupwise deficit in the ability to distinguish specific emotions is driven by damage to left, not right, lateral PFC (and adjacent insular cortex).

Emotion Rating Profile

Although the specificity index allows us to quantify the ability to discriminate between specific emotions, it does not capture how the patients' rating profiles differ from those of healthy subjects. For example, patients may be poor at discriminating facial expressions that even healthy subjects tend to confuse, such as "anger" and "disgust." Alternatively, they might have very different interpretations of a given emotional expression, resulting in rating profiles distinct from those of healthy control subjects. As a follow-up to the VLSM result, we characterized how rating profiles of patients differ from healthy subjects by plotting pD ratings for each emotion category, by group (Fig. 6). A series of mixed ANOVAs was conducted, comparing the rating profiles given to the faces expressing a given emotion by each patient group against healthy control subjects. In the light of the lateralized VLSM results, the LF group was divided into right (RLF) and left (LLF) lateral groups to assess potential differences in rating patterns between these patient groups. This analysis was conducted on the same pooled data set used for VLSM (VMF group, $N = 17$; DM group, $N = 12$; RLF group, $N = 8$; and LLF group, $N = 7$).

This revealed that both VMF and LLF groups had rating profiles that differed significantly from healthy subjects for most of the emotions, as indicated by the significant interaction between group and emotion labels (all Ps < 0.05), with the exception of "happy" face ratings in both groups. The rating profile of the RLF group differed significantly from control subjects only for "surprised" and "fearful" faces. Importantly, the direct comparison of the DM group to healthy subjects did not reveal any significant differences in rating patterns (all interaction Ps > 0.09). As can be seen in Figure 6, while the rating profiles of VMF patients differed from those of the CTL group mainly at the rating given to the target emotion (e.g., lower "sad" ratings given to the faces expressing sadness), the profiles of LLF patients were characterized by higher ratings of nontarget, "nearby" emotions (e.g., higher "surprised," "fearful," and "sad" ratings given to faces expressing anger). Therefore, despite their relatively intact ability to recognize target emotions compared with neutral facial expressions, LF patients appear to have difficulty discriminating between specific negative emotions. The RL group also showed a similar, but much weaker, tendency for some emotions.

Discussion

This study used a sensitive rating task to clarify the distinct contributions of 2 prefrontal regions to emotion recognition from faces and also established that DMF does not play a critical role. We first demonstrated that intact VMF, in particular vmPFC, is necessary for detection of subtle emotional facial expressions. In addition, we were able to reveal a deficit in discrimination of specific emotions in patients with LF damage. VLSM indicated that this deficit was lateralized, with lesions to left ventrolateral PFC and adjacent left anterior insula particularly associated with poor discrimination between specific emotions. The different patterns of impairment in

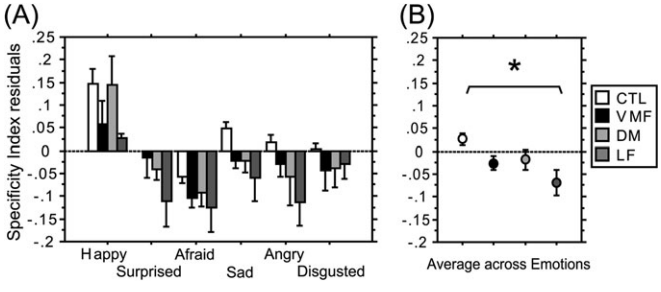

Figure 4. The ability to discriminate emotions from each other, measured as specificity index residuals after pD scores were regressed out, for each group, for different emotions (*A*) and averaged across emotions (*B*). Error bars indicate standard error of the mean. * denotes significant difference for pairwise comparisons for groups (Tukey–Kramer test, $P < 0.05$).

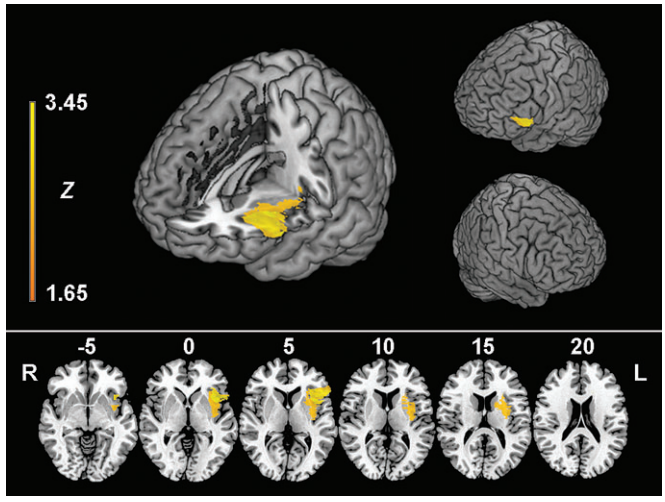

Figure 5. VLSM statistical map computed for specificity index residuals shown on 3D views of the MNI brain in the top panel, with representative axial slices below. The color scale indicates *t*-test results converted into *z* score, thresholded at $P < 0.05$, uncorrected.

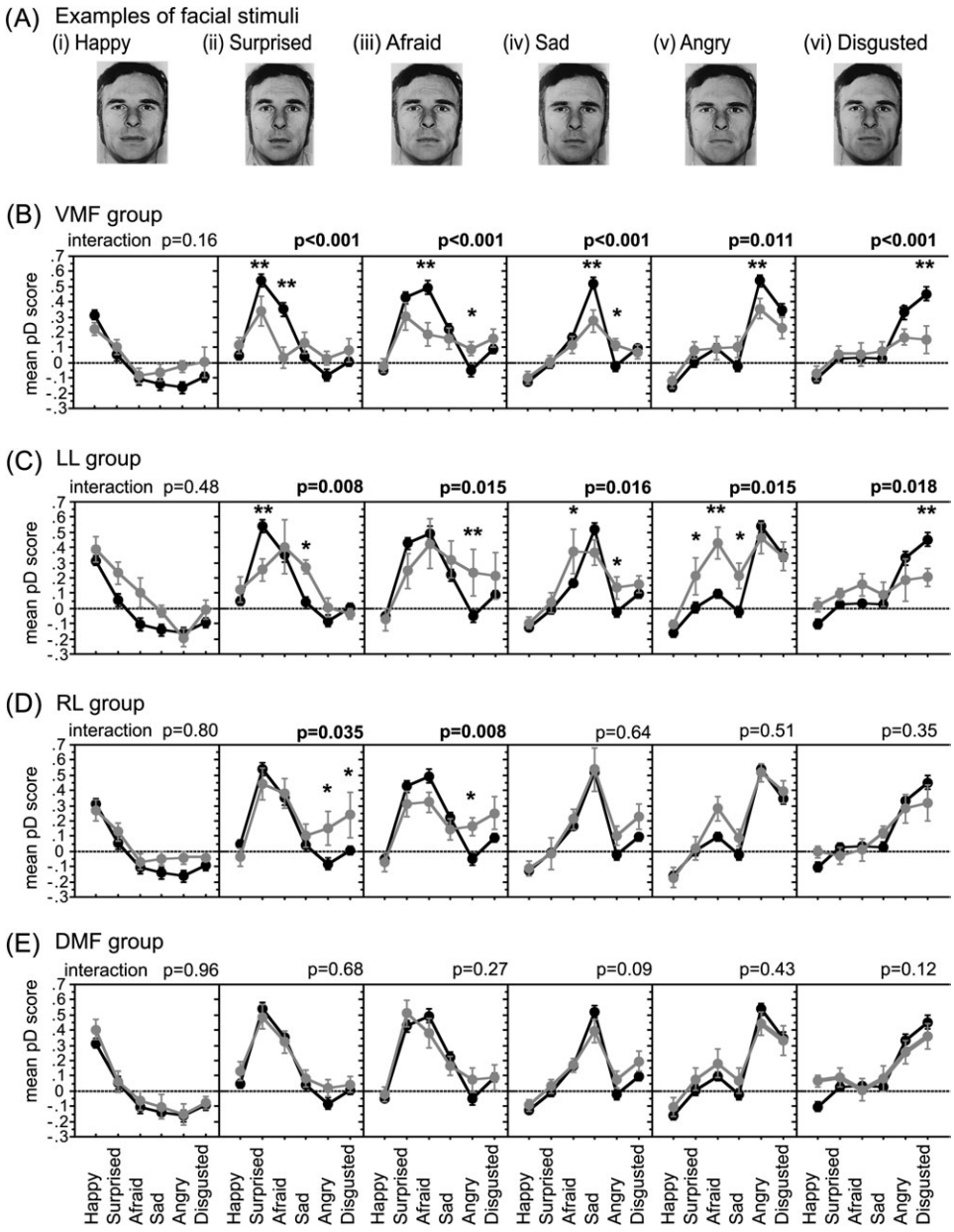

Figure 6. Examples of facial expressions for each emotion (*A*) and rating profiles given to each emotional expression by (*B*) VMF group, (*C*) LLF group, (*D*) RLF group, and (*E*) DM group compared with rating profiles by CTL group. Rating profiles given by each lesion group are shown in gray and CTL group in black. *P* values at the top of each graph indicate the interaction between group and emotion label, which provide a measure of similarity between the rating profile given by each patient group and healthy control subjects. Significant interactions, indicated in bold, suggest substantial differences in the rating patterns between the patient group and the control group. * indicates significant differences in the rating at a particular emotion label between groups (simple main effects test, $P < 0.05$). Emotion labels at the bottom are ordered according to the similarity of representations, based on the study by Dailey et al. (2002).

these 2 patient groups were also evident in an emotion rating profile analysis. While the rating pattern of VMF patients across emotions was characterized by low pD scores for the target emotion, reflecting difficulty in differentiating subtle emotional expressions from neutral expressions, that of LLF patients was characterized by broader tuning curves for each emotional expression, indicating a deficit in matching specific expressions to specific emotion categories.

Previous work by our group and others has identified a key role for VMF within PFC in emotion recognition (Hornak et al. 1996; Hornak et al. 2003; Heberlein et al. 2008). This conclusion is strongly supported by the present findings in the new sample studied here. The VLSM analysis on the combined sample pointed more specifically to vmPFC as the region necessary for detecting subtle emotional expressions. Other studies have failed to detect effects of vmPFC damage, instead emphasizing contributions of more posterior regions (right somatosensory regions and parietal cortex) on performance of this task (Adolphs et al. 1996, 2000; Philippi et al. 2009). This likely reflects relatively poor coverage of this rarely injured region in those cohorts (Adolphs 2002).

In addition to vmPFC effects, we also identified a critical role for the LF lobe. Detailed examination of task performance led us to conclude that VMF and LLF regions are involved in

different component processes. To our knowledge, this is the first study to demonstrate dissociable component processes in this simple emotion recognition task. Previous work has typically used correlation methods to compare the rating patterns of patients to healthy subjects, thus assessing the "normalness" of the rating profile provided by patients (Adolphs et al. 1996, 2000; Heberlein et al. 2008; Philippi et al. 2009). However, that measure does not reveal how the patients' rating patterns deviate from those of control subjects. By closely examining the different aspects of rating performance, we were able to demonstrate that while VMF damage disrupted the ability to detect emotion from faces, LLF damage impaired the ability to discriminate between different (negative) emotional expressions. Once the impairment in emotion detection was taken into account, those with VMF damage did not have disproportionate impairment in discriminating one emotion from the other.

VmPFC, through interactions with the amygdala, has been implicated in top-down regulation of emotional processing, such as the dampening of unwanted emotional reactions to task-irrelevant stimuli (Etkin et al. 2011). Our findings may reflect a broader role for this region in directing attention to motivationally and affectively significant information, perhaps biasing sensory processing via amygdala or other subcortical structures like the pulvinar (Pessoa and Adolphs 2010) or directly influencing visual sensory processing in ventral temporal cortex (Rolls 2004). Such attentional biasing may be particularly critical in decoding subtle emotional information from complex facial stimuli (Adolphs et al. 2005).

Damage to left ventrolateral PFC and adjacent anterior insula was associated with a specific difficulty in discriminating different negative emotions but relatively intact detection of subtle emotions compared with neutral faces. Our data do not allow us to determine which of these 2 regions is critical or whether both play a role. In particular, patients were recruited on the basis of frontal lobe damage. The anterior insula finding in the VLSM analysis is difficult to interpret definitively because damage to that region is correlated with LLF damage in this data set. The anterior insula has been implicated in social emotions and empathic processes (Kurth et al. 2010; Lamm and Singer 2010), and it has been suggested that this region coordinates attentional processes to detect and respond to salient events in the environment (Menon and Uddin 2010). Although such a mechanism might explain the impairments we observed, there is no strong evidence for lateralization of this hypothesized general function (Ibañez et al. 2010). An alternative explanation is that left ventrolateral PFC damage disrupts the mapping of stimuli to conceptual knowledge of emotion, a process which may be more plausibly left lateralized: In other contexts, lesions to left ventrolateral PFC, with or without adjacent insula involvement, have been associated with impaired selection of appropriate semantic and conceptual knowledge from among competing representations (Thompson-Schill et al. 1997; Robinson et al. 2010). The impairment observed in our study cannot be simply attributed to a failure to retrieve lexical knowledge of each emotion, since the subjects were not asked to generate or choose a verbal label in this task. Instead subjects were asked to judge the intensity of each (named) emotion. The rating patterns in those with left ventrolateral PFC damage are in keeping with blurred categorical boundaries of conceptual representations for negative emotional expressions, leading to poorly tuned matching of these concepts to the available perceptual information.

Influential models concerning the lateralization of emotional perception (Demaree et al. 2005) include the "Right Hemisphere Hypothesis" that posits right hemisphere dominance for all emotion processing (Borod et al. 1998) and the "Valence-Specific Hypothesis" that proposes right hemisphere dominance for processing negatively valenced emotions (Canli et al. 1998; Jansari et al. 2000). Both hypotheses would predict impaired perception and recognition of emotions, particularly, negatively valenced emotions, following right- but not left-sided damage, which is the opposite of what we find. Recent meta-analyses of functional imaging studies of various emotion processing (Wager et al. 2003) or emotional face processing (Fusar-Poli, Placentino, Carletti, Allen, et al. 2009) that directly tested these hypotheses may offer a partial explanation for this apparent contradiction. Both found no support for lateralization of emotional processing in general and at most limited support for the valence-specific lateralization hypotheses, suggesting that any lateralized processing may be more specific, from both structure and function points of view. This is consistent with findings from recent large-scale lesion studies (Adolphs et al. 2000; Philippi et al. 2009), which reported right-lateralized effects of lesions to somatosensory cortex, but left-lateralized effects in lateral frontal regions, on facial emotion recognition.

As in most previous lesion studies (Adolphs et al. 1996, 1999, 2000; Mandal et al. 1999; Adolphs and Tranel 2004; Philippi et al. 2009), we found impairment in negative emotion recognition with relatively spared ability to recognize happy faces (Fig. 6). This does not necessarily mean that happiness was easier to identify. In fact, across groups, including the healthy control group, subjects consistently rated happy faces as less intense than other emotions in our study, suggesting that these particular happy expression morphs were more difficult to differentiate from neutral expressions. Nonetheless, the specificity index indicated that happy expressions were easier to distinguish from other emotions. These results, consistent with the wider literature, are likely explained by the greater perceptual and conceptual distance between happy and other (negative) basic emotional expressions (Adolphs 2002; Posamentier and Abdi 2003) rather than by the existence of valence-specific emotional processing systems.

Our data do not support distinct cortical systems for the recognition of specific emotions, at least within PFC, albeit studied at an admittedly coarse level of anatomical resolution and with relatively few (though well matched) exemplars of each emotion. Other work has argued for emotion-specific neural circuits: the amygdala is activated specifically in response to fearful facial stimuli in functional imaging studies (Morris et al. 1996; Whalen et al. 1998), and lesion studies of patients with amygdala damage identify specific impairment in recognition of fearful expressions (Adolphs et al. 1994, 1995; Calder 1996). Facial expressions of disgust commonly elicit insula activation (Phillips et al. 1997, 1998; Sprengelmeyer et al. 1998), and one case study found impaired recognition of disgust and not other emotions in a patient with a left insula lesion (Calder et al. 2000). However, in the present study, as in our previous study (Heberlein et al. 2008), impairments in emotion detection or discrimination were not consistently emotion specific. In the literature as a whole, impairments specific to a particular emotion appear to be more often

observed in individual patients and more difficult to replicate in groups of patients, including those with amygdala (Adolphs et al. 1999; Rapcsak et al. 2000) and insula (Straube et al. 2010) damage. Our own data suggest that subjects with left lateral PFC lesions, in some cases, including anterior insula, show impairment across different categories of emotions and are not limited to decoding expressions of disgust. It remains possible that there are specific neural substrates dedicated to specific categories of social and emotional stimuli; if so, our findings and the literature to date suggest they are likely to be both anatomically variable from individual to individual and intertwined.

Our findings suggest that the dmPFC activations consistently found in tasks that involve the explicit processing of facial expressions of emotion (Dolan et al. 1996; Morris et al. 1998; Blair et al. 1999; Fusar-Poli, Placentino, Carletti, Landi, et al. 2009) do not represent necessary involvement of this region in emotion recognition per se: Despite good lesion coverage in this area, we did not detect any voxels associated with low pD score or specificity index when lesioned in VLSM analyses, and as a group, patients with medial PFC damage which spared ventral regions had rating profiles very similar to those given by the control group. This agrees with functionally segregated views of dorsal and rostral/ventral sectors of medial PFC and ACC (Bush et al. 2000; Etkin et al. 2011). These activations may reflect the role of the dmPFC in epiphenomenal processes triggered by emotional and social stimuli, such as emotional or autonomic reactions or appraisal of their significance (Etkin et al. 2011).

The ability to detect and interpret subtle facial expressions of emotion is fundamental to successful social interactions. The present study sheds light on the component processes involved in the processing of subtle social stimuli, providing evidence for 2 regionally distinct PFC contributions: VmPFC plays a critical role in detecting subtle emotional signal from the faces, while left lateral PFC contributes to the discrimination of the specific emotion being expressed. This suggests that the possibility of distinct behavioral effects from damage or dysfunction in these 2 regions. VmPFC dysfunction may lead the affected individual to appear indifferent to emotional cues, while left lateral PFC dysfunction might lead to confusion about the specific emotion being signaled. The former might be perceived as apathy, emotional blunting, or social disinhibition (Rosen et al. 2005; Rankin et al. 2006), while the latter might be more likely to lead to inappropriate responses to emotional displays, such as mistargeted empathy or poorly tuned responses (e.g., reacting with fear or anger to a misinterpreted expression of sadness or disgust). These distinctions may provide a useful neurobiologically grounded starting point for understanding behavioral changes in neurological conditions, such as frontotemporal dementia (Keane et al. 2002; Kessels et al. 2007) as well as in many neuropsychiatric conditions.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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Notes

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