

## Neuroanatomical correlates of impaired recognition of emotion in dementia

Howard J. Rosen<sup>a,b,\*</sup>, Michael R. Wilson<sup>a,b</sup>, Guido F. Schauer<sup>f</sup>, Stephen Allison<sup>a,b</sup>,  
Maria-Luisa Gorno-Tempini<sup>a,b</sup>, Catherine Pace-Savitsky<sup>a,b</sup>, Joel H. Kramer<sup>a,b</sup>,  
Robert W. Levenson<sup>c</sup>, Michael Weiner<sup>a,d,e</sup>, Bruce L. Miller<sup>a,b</sup>

<sup>a</sup> University of California at San Francisco Department of Neurology, Memory and Aging Center, 350 Parnassus Avenue, Suite 706, Box 1207, San Francisco, CA 94143-1207, USA

<sup>b</sup> UCSF Memory and Aging Center, CA, USA

<sup>c</sup> University of California at Berkeley Department of Psychology, CA, USA

<sup>d</sup> San Francisco Veterans Affairs Hospital Magnetic Resonance Imaging Unit, CA, USA

<sup>e</sup> University of California at San Francisco Department of Radiology, CA, USA

<sup>f</sup> University of California at Los Angeles Department of Psychology, Los Angeles, CA, USA

Received 4 August 2004; received in revised form 24 May 2005; accepted 9 June 2005

Available online 9 September 2005

### Abstract

Neurodegenerative diseases frequently affect brain regions important for emotional processing, offering a valuable opportunity to study the effects of brain injury on emotion. The current study examined the neuroanatomical correlates of impaired recognition of emotions in patients with neurodegenerative disease. Performance on recognition of facial expressions, as measured by the Florida Affect Battery, was correlated with regional changes in gray matter tissue content in 50 patients with neurodegenerative disease using voxel-based morphometry. Recognition accuracy in the group was poor for negative emotions (fear, anger and sadness) and good for happiness, consistent with previous studies. For negative emotions, a region in the right lateral inferior temporal gyrus (Brodmann's area (BA) 20) extending into the right middle temporal gyrus (BA 21) was correlated with accuracy. This effect appeared to be strongest for sadness, which was also independently correlated with atrophy in the superior temporal gyrus. These data suggest that regions in the right lateral and inferolateral temporal lobe are important for visual processing of negative emotions from faces and that functioning of this right temporal network is most critical for recognition of sad faces.

© 2005 Published by Elsevier Ltd.

**Keywords:** Faces; Temporal; Frontal

### 1. Introduction

The past few years have seen a substantial increase in the number of studies examining the neural basis of emotions. As research in this area expands in the future, it is likely to be enhanced by increased inclusion of patients with neurological disease.

Much of the recent work examining the neural correlates of human emotion has been done with functional neu-

roimaging studies (Dolan, 2002; Phan, Wager, Taylor, & Liberzon, 2002). While such studies are critical for examining task-related activity in the entire system of regions involved in emotional processing, studies examining the effects of brain injury on emotion are necessary to identify which regions are most critical for particular aspects of emotion.

Many recent studies examining the effects of brain injury on emotional processing have been conducted in patients with focal brain lesions. For instance, several investigators have examined the relationship between emotional processing and lesions in the right and the left hemispheres

\* Corresponding author. Tel.: +1 415 476 6880; fax: +1 415 476 4800.  
E-mail address: howie@itsa.ucsf.edu (H.J. Rosen).

and demonstrated that certain aspects of emotional processing are dependent on the right hemisphere (Borod et al., 1998; Bowers, Bauer, Coslett, & Heilman, 1985; Zoccolotti, Scabini, & Violani, 1982). Other studies have focused on specific structures such as the anterior temporal cortex (Anderson, Spencer, Fulbright, & Phelps, 2000), in particular the amygdala (Adolphs et al., 1999), and frontal regions such as the orbitofrontal cortex (Hornak, Rolls, & Wade, 1996) and the anterior cingulate region and adjacent medial prefrontal cortex (Hornak et al., 2003). These studies have indicated that all these regions play a role in emotion recognition. However, a recent study indicated that amygdala damage does not produce inability to recognize emotions per se, but rather it causes inability to analyze faces to extract emotion-specific information. This impairment can be circumvented, which highlights the importance of other brain regions in the recognition process (Adolphs et al., 2005). A few studies have examined emotional processing in large groups of patients with lesion locations throughout the brain to identify locations that are important for emotional processing, and again implicated the right hemisphere (Adolphs, Damasio, Tranel, & Damasio, 1996; Rapcsak et al., 2000). Focal lesion studies usually depend on recruiting patients with lesions from stroke, tumor, trauma or other types of injury, but these types of injuries (in particular strokes) do not commonly affect regions such as the amygdala, temporal pole, anterior cingulate and orbitofrontal cortex, which appear to be critical for emotional processing.

Patients with neurodegenerative disease offer another valuable opportunity to advance our understanding of emotional processing. These disorders commonly affect regions important for emotional processing, including those noted above (Rosen, Gorno-Tempini et al., 2002), and frequently result in abnormalities of social and emotional function (Hamann, Monarch, & Goldstein, 2002; Keane, Calder, Hodges, & Young, 2002; Lavenu, Pasquier, Lebert, Petit, & Van der Linden, 1999; Mychack, Kramer, Boone, & Miller, 2001; Rosen et al., 2004; Sprengelmeyer et al., 1996). Emerging techniques for quantification of cerebral atrophy, such as voxel-based morphometry (VBM), allow correlation of behavioral changes with tissue loss in patients with dementia (Ashburner & Friston, 2000; Boxer et al., 2003; Gorno-Tempini et al., 2004; Kassubek, Juengling, Ecker, & Landwehrmeyer, 2005; Mummery et al., 2000; Williams, Nestor, & Hodges, 2005). Recent studies have quantitatively examined the neuroanatomical correlates of emotional deficits in patients with dementia (Keane et al., 2002; Rosen, Perry et al., 2002), but the potential of these techniques to inform our understanding of emotional processing has hardly been tapped.

The goal of the present study was to use VBM to identify regional changes in brain tissue content that correlate with impaired recognition of emotions in patients with neurodegenerative disease.

## 2. Methods

### 2.1. Participants

Neuroimaging and behavioral data were analyzed from 50 individuals who had undergone cognitive testing at the UCSF Memory and Aging Center (MAC), MRI scanning at the San Francisco Veteran's Administration Hospital Magnetic Resonance Unit and whose assessment included testing of emotion recognition using the Florida Affect Battery (FAB, see below). Evaluation at the MAC includes a neurological history and examination, and nursing and neuropsychological evaluation. Memory, executive function, visuospatial ability, language and mood are assessed using a previously described standard protocol (Kramer et al., 2003). Individuals included in this analysis were either normal control subjects ( $n=5$ ) or patients with cognitive impairment from suspected neurodegenerative disease. The diagnoses included Alzheimer's disease (AD,  $n=15$ ), mild cognitive impairment (MCI,  $n=1$ ), frontotemporal lobar degeneration (FTLD,  $n=25$ , which includes the syndromes of frontotemporal dementia, semantic dementia and progressive non-fluent aphasia) and progressive supranuclear palsy (PSP,  $n=4$ ). Diagnoses were based on the clinical impression of the attending neurologist (BLM or HJR) using published research criteria (Boeve, Lang, & Litvan, 2003; Litvan et al., 1996; McKhann et al., 1984; Neary et al., 1998; Petersen et al., 2001). Patients were excluded who had impairment in visual perceptual abilities for faces as indicated by performance greater than one standard deviation below published norms for this age group on subtest 1 of the FAB.

### 2.2. Recognition of facial expressions of emotion

Recognition of emotion was assessed using the Florida Affect Battery (Bowers, Blonder, & Heilman, 1992), which consists of photographs of faces (all females) depicting one of five expressions: happiness, sadness, anger, fear or neutral (no emotion). The first five subtests involve recognition of facial expressions of emotion. The formats of FAB subtests 1–5 are as follows:

1. *Facial identity discrimination*: Two photographs of faces of individuals, both with a neutral expression, are displayed on each trial. Subjects are required to indicate whether the two faces are of the same person or different people.
2. *Facial emotion discrimination*: Two facial photographs, each with a different identity and varying facial expressions, are displayed on each trial. Subjects are required to indicate whether the two faces are depicting the same or different emotions.
3. *Facial emotion naming*: A single photograph depicting a facial expression is presented on each trial. Subjects are required to name the emotion depicted. Four trials of each emotion are presented.

4. *Facial emotion selection*: Five photographs of faces of the same individual, each with a different facial expression, are displayed on each trial. Subjects are required to select the face depicting the emotion requested by the examiner. Four trials of each emotion are presented.
5. *Facial emotion matching*: Two cards are presented simultaneously for this trial: one with a single photograph of an individual depicting a particular emotion and the other with five photographs of faces of different individuals, each with a different facial expression. Subjects are required to choose the face on the second card depicting the emotion shown on the first card. Four trials of each emotion are presented.

For this analysis, performance accuracy was expressed as the percent of responses that were correct for each emotion across the third, fourth and fifth subtests of the battery (the subtests in which a single emotion was tested on each trial). Accuracy scores (percent correct) were averaged across these three subtests, yielding a mean accuracy score for each emotion and creating four variables (one for each emotion) that were entered into the analysis. Data from subtest 2 were not analyzed, because each trial involves more than one target emotion.

### 2.3. Correlation of emotion recognition abilities with other measures of behavior

In order to account for potential confounds in the interpretation of the results, correlations (Pearson's  $r$ , two tailed) between emotion recognition ability and other factors were examined. Variables examined included general intellectual function/dementia severity (MMSE score), naming ability (a 15-item version of the Boston Naming Test (Kaplan, Goodglass, & Wintraub, 1983)), visuospatial processing ability (score on copy of a modified Rey–Osterrieth (Rey–O) figure (Boxer et al., 2003) as well as performance on subtest 1 of the FAB) and depression (Geriatric Depression Scale (Yesavage et al., 1983)). These analyses were carried out using the SPSS software package (Version 10.0.5 for Windows, SPSS Inc., Chicago, IL).

### 2.4. Acquisition of MRI and neuroimaging analysis

#### 2.4.1. MRI scanning

Structural MR imaging was accomplished using a 1.5-T Magnetom VISION system (Siemens Inc., Iselin, NJ), a standard quadrature head coil and previously described sequences (Rosen, Gorno-Tempini et al., 2002) to obtain: (1) scout views of the brain for positioning subsequent MRI slices, (2) proton density and T2-weighted MRIs and (3) T1-weighted (MP-RAGE) images of the entire brain.

#### 2.4.2. Voxel-based morphometry

Voxel-based morphometry is a technique for voxel-wise analysis of local changes in brain tissue content, which has

been used to study several brain disorders, including dementia (Abell et al., 1999; Ashburner & Friston, 2000; Boxer et al., 2003; Burton et al., 2002; Critchley et al., 2003; Good et al., 2001; Gorno-Tempini et al., 2004; Krams et al., 1999; Mummery et al., 2000; Rosen, Gorno-Tempini et al., 2002; Williams et al., 2005). The procedures used for image pre-processing, which includes spatial normalization, segmentation, modulation and smoothing, have been described recently (Gorno-Tempini et al., 2004). One additional procedure in this analysis was the use of study-specific templates and prior probability tissue maps, comprised of all the images to be analyzed, for spatial normalization and segmentation. This procedure minimizes bias introduced by variations in morphology between individual images to be analyzed and the spatial normalization template. Study-specific images were created by normalizing all subject images using the MNI brain provided with SPM, segmenting the images into gray, white and CSF compartments, and averaging the normalized images to create new averaged whole brain, gray, white and CSF images. The original images were then re-normalized and segmented using the new images as templates and prior probability maps for the final segmentation. All image pre-processing steps and statistical analysis were implemented in the SPM2 software package ([www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)).

In order to better interpret the results, a variance image was created to illustrate variability in gray matter tissue content across the study group at every voxel in the brain. Regions of low variance would be less likely to correlate with behavioral measures, even if they accounted for significant behavioral effects. The variance image was created by running a one-sample  $t$ -test in SPM2 using the 50 subject images. The ResMS image created by SPM2 represents pixel intensity at each voxel according to the formula  $(n - 1) \times \text{Var}$ , where Var is the variance in the group and  $n$  is the number of subjects.

For statistical analysis, the images and the mean percent correct scores for each emotion in each participant were entered into a "covariates only" design matrix, and the relationship between changes in gray matter content and recognition of facial expressions of emotion was analyzed using the general linear model. The significance of each effect of interest was determined using the theory of Gaussian fields. Total intracranial volume was used as a covariate, and age and MMSE score for each subject were entered into the design matrix as nuisance variables. Analyses included the main effect across emotions (for four emotions, neglecting nuisance variables, this would be a [1 1 1 1]  $t$ -contrast) as well as the effect for each emotion independent of the others ([1 0 0 0], [0 1 0 0], [0 0 1 0] and [0 0 0 1]  $t$ -contrasts). We set a statistical threshold of  $p < 0.05$  after multiple comparisons correction. However, in order to convey a more complete picture of the data, specifically regions that may have a meaningful correlation with behavior but not surpassing our statistical threshold, we also displayed the data at a  $p < 0.5$ . For the regions that were significant for the

main effect across emotions,  $z$ -scores at these locations were also examined in statistical images representing the relationship between tissue content and each individual emotion. Region identification was accomplished by overlaying the  $t$ -maps on the study-specific template and using the AAL and Brodmann's atlases that accompany the MRIcro software package (Rorden & Brett, 2000; Tzourio-Mazoyer et al., 2002). Because of previous findings relating amygdala atrophy in dementia to impaired emotion recognition (Rosen, Perry et al., 2002), we also examined the statistical images after the application of a region of interest for small volume correction that included the amygdala bilaterally using the AAL brain atlas (Tzourio-Mazoyer et al., 2002) and WFU-pickatlas (Maldjian, Laurienti, Kraft, & Burdette, 2003).

### 3. Results

#### 3.1. Recognition of individual emotions

Table 1 shows the demographics and statistics for performance across the group on selected behavioral measures (top) and on each of the individual emotions (bottom). On average, performance was lower with a larger variance for all the negative emotions than for happiness, on which performance was at ceiling in over half the subjects. Because of this near ceiling performance, happiness was left out of the neuroimaging analysis.

Table 1  
Behavioral and emotional features of the study group

	Mean	S.D.	Range
Demographics and cognition			
Age (years)	69.8	9.39	52–84
MMSE	24.42	4.99	9–30
BNT (maximum 15)	9.78	4.74	1–15
Rey figure copy (maximum 17)	14.8	2.47	7–17
GDS (maximum 30)	8.33	6.46	0–22
Emotion recognition performance <sup>a</sup>			
Happiness	92.79	11.30	50–100
Sadness	71.04	21.35	8–100
Anger	72.60	21.07	17–100
Fear	74.13	22.00	17–100

<sup>a</sup> Percent correct.

#### 3.2. Recognition of emotion and other behavioral measures

MMSE score was correlated with recognition of happy ( $r=0.37$ ,  $p<0.01$ ) and fearful ( $r=0.35$ ,  $p<0.05$ ) facial expressions. There were no correlations between naming ability, the ability to copy the modified Rey–O figure, performance on subtest 1 of the FAB, or GDS score and recognition of any emotions. Because of these findings, MMSE was entered into the VBM design matrix as a nuisance variable (see Section 2).

#### 3.3. Variability in tissue content across the study group

Fig. 1 illustrates the variance in gray matter tissue content across the group at each voxel. The variance is highest in the temporal lobes, in particular the amygdala, in part reflecting the inclusion of patients with semantic dementia (SD), who have severe tissue loss in this region, well beyond that seen in other dementia subtypes (Liu et al., 2004).

#### 3.4. Anatomical correlates of emotion recognition abilities

##### 3.4.1. Main effect across fear, anger and sadness emotions

VBM analysis revealed several regions where gray matter tissue content was correlated with recognition of negative emotions (Table 2; Fig. 2A, in red). The largest and most significant cluster of voxels was in the lateral portion of the right inferior temporal gyrus involving Brodmann's area (BA) 20. This region of correlation extended anteriorly into the right middle temporal gyrus (BA 21). A small cluster of voxels more anteriorly in the inferior temporal gyrus and a small cluster of voxels in the right lateral orbitofrontal cortex also survived the statistical threshold. At a lower statistical threshold (Fig. 2B), the regions described above grew larger, but no regions of correlation were revealed in the medial portion of the right temporal lobe or in the left temporal lobe. No significant voxels were found in the amygdala even after small volume correction. When the peak temporal voxels related to negative emotion recognition were probed in the models examining each emotion separately, the highest  $z$ -scores for

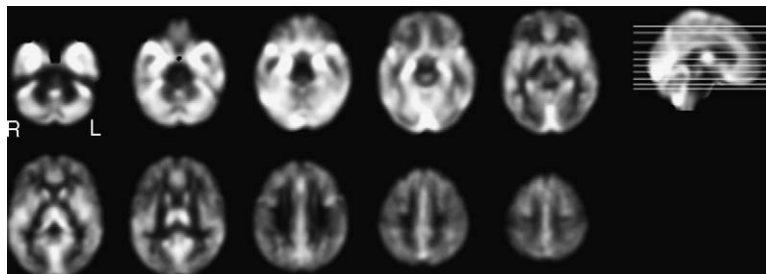


Fig. 1. Map of variability in tissue content at each brain voxel across the study group.

Table 2

Regions where gray matter tissue content was correlated with emotion recognition ability

Anatomical region <sup>a</sup>	BA <sup>b</sup>	X, Y, Z <sup>c</sup>	z-Score <sup>d</sup>	Cluster size <sup>e</sup>	z-Sad <sup>f</sup>	z-Anger <sup>f</sup>	z-Fear <sup>f</sup>
Negative emotions, $p < 0.05$ , corrected							
R ITG	20	64, -31, -19	5.03	1142	5.04	3.05	2.82
R ITG	20	60, -6, -42	4.71	49	5.31	3.03	2.35
R IFG, lateral OFC	47	33, 35, -4	4.69	6	3.88	3.79	3.25
Sadness (vs. other emotions), $p < 0.05$ , corrected							
R STG	48/22	51, -7, -2	4.93	156	5.43	2.86	<1

<sup>a</sup> Based on the AAL brain, R: right/L: left, ITG: inferior temporal gyrus, STG: superior temporal gyrus, IFG: inferior frontal gyrus, OFC: orbitofrontal cortex.<sup>b</sup> BA: Brodman's area.<sup>c</sup> Coordinate for peak voxel in the cluster.<sup>d</sup> z-Score for the effect of interest (e.g. negative emotions or happiness).<sup>e</sup> In voxels.<sup>f</sup> z-Scores for this location in the statistical image for the effect of each individual emotion.

the correlations between tissue content and emotion recognition was for sadness.

### 3.4.2. Emotion-specific effects

For fear and anger, no significant regional effects were seen independent of the other emotions. For sadness, a region in the right superior temporal gyrus (Table 2; Fig. 2A, in green) showed a significant correlation with performance independent of the effects for other emotions.

### 3.5. Variability across emotion tasks

The three emotions tasks (naming, selection and matching of emotional faces) were significantly correlated with each other, with Pearson correlation coefficients ranging from 0.61 to 0.66. In the main analysis, these tasks were averaged together to perform the emotion–anatomy correlation. However, we also examined the relationship between impaired recognition for negative emotions and tissue loss for each

task separately in order to verify that all tasks showed similar effects. For all three tasks, the largest cluster of voxels with correlated tissue loss included the right inferolateral temporal cortex, although the effect was not significant for any of the tasks alone. z-Scores for the first inferolateral temporal peak in Table 2 (64, -31 and -19) were 3.44, 4.39 and 3.44 for naming, selection and matching, respectively.

## 4. Discussion

The goal of the current study was to identify brain regions where tissue loss is correlated with impaired recognition of emotions in a group of patients with neurodegenerative disease. The main finding was that decreased tissue content in the lateral portion of the right inferior and middle temporal gyri was associated with impaired comprehension of negative emotions, in particular sadness. This association was independent of mood, overall cognitive function, naming ability

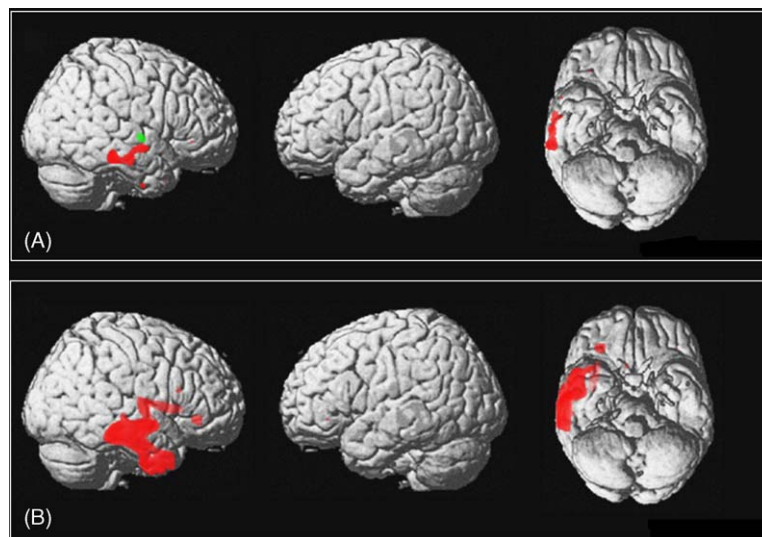


Fig. 2. (A) Regions where tissue content was correlated with recognition of negative emotions (in red) and sadness, independent of other emotions (green). All voxels  $p < 0.05$  corrected. (B) Correlations with negative emotions,  $p < 0.5$  corrected.

and visual processing abilities. Recognition of happy faces was relatively unimpaired, consistent with previous studies indicating that many brain injuries have a very limited effect on recognition of happiness (Adolphs et al., 1996, 1999; Adolphs & Tranel, 2004; Bowers et al., 1985; Rapcsak et al., 2000). These data suggest that specific regions within the inferolateral temporal lobe are utilized for identification of facial expressions conveying negative emotions, in particular sadness.

The current results add to the growing literature examining social and emotional functions in patients with dementia. Early studies documented impaired emotion recognition in AD (Brosigole, Kurucz, Plahovinsak, Sprotte, & Haveliwala, 1983) and suggested that such impairments could be explained by other neuropsychological impairments (Albert, Cohen, & Koff, 1991). However, subsequent studies have examined patients with other dementia subtypes, in particular frontotemporal dementia (FTD), where social and emotional impairments are a central feature of the disorder and emotion recognition impairments are more profound than in AD (Lavenex et al., 1999). Such studies demonstrated that impaired emotion recognition abilities were not accounted for by other domains of cognitive impairment, as was true in the current study (Keane et al., 2002; Rosen, Perry et al., 2002). Based on visual inspection of images and region-of-interest based measurements of selected cerebral volumes, prior studies suggested that impaired recognition of emotions is related to disease in the ventromedial frontal cortex and amygdala (Keane et al., 2002; Rosen, Perry et al., 2002). The current analysis included a larger group than previous studies and included patients with more varied pathology. More importantly, it assessed the relationship between emotion recognition and focal pathology across the whole brain, revealing the importance of a temporal lobe region that was not assessed in previous studies.

The fact that emotion recognition in this analysis was not associated with amygdala pathology is consistent with our recent finding that emotion recognition is equally impaired in SD and FTD (Rosen et al., 2004), despite the fact that the latter group has much less amygdala damage (Liu et al., 2004). That analysis suggested the possibility that other regions could account for emotion recognition impairments in these patients. A recent case study indicated that emotion recognition impairment from amygdala damage is due to impaired visual exploration of faces, rather than inability to recognize the emotion per se, highlighting the importance of non-amygdala regions in the recognition process (Adolphs et al., 2005). Also, some studies have suggested that amygdala damage may cause impaired emotional recognition only when it occurs relatively early in development (Anderson et al., 2000; Hamann et al., 1996), which is unlikely to be the case in patients with neurodegenerative disease.

Although many lesion-behavior analyses have suggested the importance of the right hemisphere in the processing of emotions (Adolphs et al., 1996; Anderson et al., 2000; Borod et al., 1998; Bowers et al., 1985; Rosen, Perry et al.,

2002), the role of the inferior temporal gyrus has rarely been addressed in previous studies. Earlier studies using the FAB showed that patients with right hemisphere lesions are worse than patients with left hemisphere lesions at facial expression recognition, but the effect of lesion location within the right hemisphere was not assessed (Bowers et al., 1985). A subsequent analysis, using a different set of pictures of facial affect, suggested that emotion recognition abilities are most impaired with injury to the right parietal region, with the effect being strongest for fear (Adolphs et al., 1996). That analysis included relatively few patients with lesions in the inferior temporal region described here. Similarly, studies of patients with temporal lobectomy have demonstrated the importance of the right anterior temporal region (including the amygdala) for processing of some negative emotions, but temporal lobectomy usually involves regions anterior to the temporal region identified in the current analysis (Anderson et al., 2000). Accordingly, beyond the specific findings, the current results suggest that studying patients with dementia, particularly through the use of more advanced approaches for measuring brain volumes, provides a potentially unique window into the functions of some brain regions infrequently affected by pathology from other causes.

The temporal region identified here is also rarely identified in activation studies of emotional processing, almost all of which have been performed using fMRI. One reason for this may be that the anterior, inferior and lateral portions of the temporal lobe are regions where a large degree of magnetic susceptibility artifact results in loss of BOLD signal (Gorno-Tempini et al., 2002; Ojemann et al., 1997), making fMRI relatively blind to neuronal activity in this region. On the other hand, PET studies are not affected by the susceptibility artifacts characteristic of MRI. A recent PET study identified a region in the inferolateral temporal lobe/BA 20 that showed activation during viewing of sad faces (Blair, Morris, Frith, Perrett, & Dolan, 1999). Given that both structural MRI and PET activation studies have suggested an important role for the inferolateral temporal lobes in processing emotional faces, it is important that fMRI studies interested in neural processing of emotional stimuli (particularly visual ones—see below) attempt to develop methods to recover activation in these regions.

Of the three negative emotions evaluated in this study, sadness was most reliably correlated with temporal lobe atrophy. Recent studies have indicated that fear recognition is impaired with a lesion in any location in the brain, and even with normal aging (which also affects anger and sadness to a lesser degree) (Calder et al., 2003; Rapcsak et al., 2000). Thus, impaired recognition of fear and anger in our group may have been attributable to normal aging to some degree (mean age in this group was 69.8 years), as well as to atrophy in several different brain regions, while sadness was best accounted for by tissue loss in a relatively circumscribed portion of the temporal lobe. A particular role for this region in the processing of sadness is supported by the aforementioned PET study, which demonstrated stronger activation in infe-

rior temporal region/BA 20 with viewing of sad, as compared with angry facial expressions (Blair et al., 1999).

It seems most likely that this region is part of the network of cortical regions important for face processing. The region identified in the current analysis is anterior and lateral to the fusiform region responsible for general face processing, which also shows enhanced activation during processing of emotions (Winston, Henson, Fine-Goulden, & Dolan, 2004). However, we would assert that the observed correlations are unlikely to be related directly to general face processing abilities, because patients with impaired face processing for identity were excluded from this analysis, and the included patients' emotion recognition abilities were not correlated with measures of facial identity discrimination or visual constructive ability. We hypothesize that some temporal regions have specialized functions for processing facial expressions, and that these functions may be more critical for identifying negative emotions, in particular sadness. In fact, neurons sensitive to facial expression as opposed to facial identity have been identified in monkeys, though these neurons were in the superior temporal sulcus rather than inferolateral temporal cortex (Hasselmo, Rolls, & Baylis, 1989). The fact that tissue loss in inferolateral temporal cortex did not affect recognition of happiness may relate to the relative ease with which happy faces can be detected (Hager & Ekman, 1979). Conceivably, a picture set using subtler positive expressions may have demonstrated associations between recognition of positive emotions and this region or other brain regions.

While the temporal regions described here appear to be important for visual processing of emotions, they are unlikely to be critical for emotional processing in general because many emotional stimuli provide other features (movement and sound) that can be used to identify specific emotions. A recent case study of a patient with diffuse anterior and inferior temporal injury that was more prominent on the right provides support for this hypothesis. This patient showed intact recognition of nearly all emotions from dynamic facial displays and stories describing actions. However, he showed severe impairments in recognition of negative emotion with intact recognition of positive emotions from static pictures, consistent with the current findings (Adolphs, Tranel, & Damasio, 2003).

Recognition of sadness was also partly dependent on tissue content in a nearby portion of superior temporal gyrus (BA 48/22). This region has not commonly been associated with emotional processing, but more anterior portions of the superior temporal gyrus, in the temporal pole, have been activated during generation of sadness (Lane, Reiman, Ahern, Schwartz, & Davidson, 1997; Levesque et al., 2003). The potential relationship of superior temporal tissue loss to emotion perception will require further study.

In addition to the regions discussed above, a small cluster of voxels more anteriorly in the inferior temporal gyrus, and a small lateral orbitofrontal cluster also correlated with recognition of negative emotions. Although still labeled as BA 20, the temporal region is anatomically quite distant

from the main area of correlation. Many of the same issues regarding the temporal region discussed above apply to this area, including its vulnerability to artifactual signal loss with MRI and its likely involvement in visual processing, although more anterior temporal structures likely process more multimodal information (Mesulam, 1998). Temporal polar structures are very likely to be involved in emotional processing based on their connectivity (Amaral & Price, 1984; Amaral, Price, Pitkanen, & Carmichael, 1992) and functional activity (Lane et al., 1997; Reiman et al., 1997). Similarly, OFC has been implicated in emotional processing, particularly when explicit processing of facial expressions of emotion is required (Gorno-Tempini et al., 2001). We have inferred that, because of its large area, the more posterior temporal region is the most likely to contain neurons that contribute to emotion recognition in this group of patients. We have interpreted the other small clusters as being related to generalized temporal and orbitofrontal atrophy in patients with poor emotion recognition. However, all voxels in Fig. 2A survived the significance threshold, and cluster size appears to be an inappropriate criterion for assessment of statistical significance in VBM (Ashburner & Friston, 2000). Thus, we cannot exclude the fact that these more anterior temporal and/or orbitofrontal regions participate or will ultimately prove more relevant for emotion recognition in patients with neurodegenerative disease. However, given the low-threshold image shown in Fig. 2B, our data provide very strong evidence that right inferolateral temporal structures, rather than medial temporal or left hemisphere structures, provide the best account for emotion recognition impairments in this group of patients with widely varying degrees of anatomical injury across the brain.

In conclusion, the current results highlight the importance of right inferolateral temporal region in the recognition of facial expressions conveying negative emotion, likely reflecting its role in visual processing. More careful study of emotional processing in patients with neurodegenerative disease is likely to provide further insights into the roles of this and other regions in emotional functioning.

## Acknowledgements

This work was supported by National Institute on Aging (NIA) grants 1K08AG020760-01, AG10129, P50-AG05142 and AG16570, the State of California Alzheimer's Disease Research Center of California (ARCC) grant 01-154-20, NIH grant number M01 RR00079 (UCSF General Clinical Research Center) UCSF School of Medicine Quarterly Research Grant.

## References

- Abell, F., Krams, M., Ashburner, J., Passingham, R., Friston, K., Frackowiak, R., et al. (1999). The neuroanatomy of autism: A voxel-based whole brain analysis of structural scans. *Neuroreport*, *10*(8), 1647–1651.

- Adolphs, R., Damasio, H., Tranel, D., & Damasio, A. R. (1996). Cortical systems for the recognition of emotion in facial expressions. *Journal of Neuroscience*, *16*(23), 7678–7687.
- Adolphs, R., Gosselin, F., Buchanan, T. W., Tranel, D., Schyns, P., & Damasio, A. R. (2005). A mechanism for impaired fear recognition after amygdala damage. *Nature*, *433*(7021), 68–72.
- Adolphs, R., & Tranel, D. (2004). Impaired judgments of sadness but not happiness following bilateral amygdala damage. *Journal of Cognitive Neuroscience*, *16*(3), 453–462.
- Adolphs, R., Tranel, D., & Damasio, A. R. (2003). Dissociable neural systems for recognizing emotions. *Brain and Cognition*, *52*(1), 61–69.
- Adolphs, R., Tranel, D., Hamann, S., Young, A. W., Calder, A. J., Phelps, E. A., et al. (1999). Recognition of facial emotion in nine individuals with bilateral amygdala damage. *Neuropsychologia*, *37*(10), 1111–1117.
- Albert, M. S., Cohen, C., & Koff, E. (1991). Perception of affect in patients with dementia of the Alzheimer type. *Archives of Neurology*, *48*(8), 791–795.
- Amaral, D. G., & Price, J. L. (1984). Amygdalo-cortical projections in the monkey (*Macaca fascicularis*). *Journal of Comparative Neurology*, *230*(4), 465–496.
- Amaral, D. G., Price, J. L., Pitkanen, A., & Carmichael, S. T. (1992). Anatomical organization of the primate amygdaloid complex. In J. P. Aggleton (Ed.), *The amygdala: Neurobiological aspects of emotion, memory and mental dysfunction* (pp. 1–66). New York: Wiley/Liss.
- Anderson, A. K., Spencer, D. D., Fulbright, R. K., & Phelps, E. A. (2000). Contribution of the anteromedial temporal lobes to the evaluation of facial emotion. *Neuropsychologia*, *14*(4), 526–536.
- Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry—The methods. *NeuroImage*, *11*(6 Pt 1), 805–821.
- Blair, R. J., Morris, J. S., Frith, C. D., Perrett, D. I., & Dolan, R. J. (1999). Dissociable neural responses to facial expressions of sadness and anger. *Brain*, *122*(Pt 5), 883–893.
- Boccardi, M., Pennanen, C., Laakso, M. P., Testa, C., Geroldi, C., Soininen, H., et al. (2002). Amygdaloid atrophy in frontotemporal dementia and Alzheimer's disease. *Neuroscience Letters*, *335*(2), 139–143.
- Boeve, B. F., Lang, A. E., & Litvan, I. (2003). Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia. *Annals of Neurology*, *54*(Suppl. 5), S15–S19.
- Borod, J. C., Cicero, B. A., Obler, L. K., Welkowitz, J., Erhan, H. M., Santschi, C., et al. (1998). Right hemisphere emotional perception: Evidence across multiple channels. *Neuropsychology*, *12*(3), 446–458.
- Bowers, D., Bauer, R. M., Coslett, H. B., & Heilman, K. M. (1985). Processing of faces by patients with unilateral hemisphere lesions: I. Dissociation between judgments of facial affect and facial identity. *Brain and Cognition*, *4*(3), 258–272.
- Bowers, D., Blonder, L., & Heilman, K. M. (1992). *The Florida Affect Battery*. Gainesville, FL: Center for Neuropsychological Studies, University of Florida.
- Boxer, A. L., Kramer, J. H., Du, A.-T., Schuff, N., Weiner, M. W., Miller, B. L., et al. (2003). Focal right inferotemporal atrophy in AD with disproportionate visual constructive impairment. *Neurology*, *61*, 1485–1491.
- Brosigole, L., Kurucz, J., Plahovinsak, T. J., Sprotte, C., & Haveliwala, Y. A. (1983). Facial- and postural-affect recognition in senile elderly persons. *The International Journal of Neuroscience*, *22*, 37–46.
- Burton, E. J., Karas, G., Paling, S. M., Barber, R., Williams, E. D., Ballard, C. G., et al. (2002). Patterns of cerebral atrophy in dementia with Lewy bodies using voxel-based morphometry. *NeuroImage*, *17*(2), 618–630.
- Calder, A. J., Keane, J., Manly, T., Sprengelmeyer, R., Scott, S., Nimmo-Smith, I., et al. (2003). Facial expression recognition across the adult life span. *Neuropsychologia*, *41*(2), 195–202.
- Critchley, H. D., Good, C. D., Ashburner, J., Frackowiak, R. S., Mathias, C. J., & Dolan, R. J. (2003). Changes in cerebral morphology consequent to peripheral autonomic denervation. *NeuroImage*, *18*(4), 908–916.
- Dolan, R. J. (2002). Emotion, cognition, and behavior. *Science*, *298*(5596), 1191–1194.
- Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N., Friston, K. J., & Frackowiak, R. S. (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. *NeuroImage*, *14*(1 Pt 1), 21–36.
- Gorno-Tempini, M. L., Dronkers, N. F., Rankin, K. P., Ogar, J. M., Phengrasamy, L., Rosen, H. J., et al. (2004). Cognition and anatomy in three variants of primary progressive aphasia. *Annals of Neurology*, *55*(3), 335–346.
- Gorno-Tempini, M. L., Hutton, C., Josephs, O., Deichmann, R., Price, C., & Turner, R. (2002). Echo time dependence of BOLD contrast and susceptibility artefacts. *NeuroImage*, *15*(1), 136–142.
- Gorno-Tempini, M. L., Pradelli, S., Serafini, M., Pagnoni, G., Baraldi, P., Porro, C., et al. (2001). Explicit and incidental facial expression processing: An fMRI study. *NeuroImage*, *14*, 465–473.
- Hager, J. C., & Ekman, P. (1979). Long-distance transmission of facial affect signals. *Ethology and Sociobiology*, *1*, 77–92.
- Hamann, S., Monarch, E. S., & Goldstein, F. C. (2002). Impaired fear conditioning in Alzheimer's disease. *Neuropsychologia*, *40*(8), 1187–1195.
- Hamann, S. B., Stefanacci, L., Squire, L. R., Adolphs, R., Tranel, D., Damasio, H., et al. (1996). Recognizing facial emotion. *Nature*, *379*(6565), 497.
- Hasselmo, M. E., Rolls, E. T., & Baylis, G. C. (1989). The role of expression and identity in the face-selective responses of neurons in the temporal visual cortex of the monkey. *Behavioural Brain Research*, *32*(3), 203–218.
- Hornak, J., Bramham, J., Rolls, E. T., Morris, R. G., O'Doherty, J., Bullock, P. R., et al. (2003). Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. *Brain*, *126*(Pt 7), 1691–1712.
- Hornak, J., Rolls, E. T., & Wade, D. (1996). Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. *Neuropsychologia*, *34*(4), 247–261.
- Kaplan, E., Goodglass, H., & Wintraub, S. (1983). *The Boston Naming Test*. Philadelphia: Lea and Febiger.
- Kassubek, J., Juengling, F. D., Ecker, D., & Landwehrmeyer, G. B. (2005). Thalamic atrophy in Huntington's disease co-varies with cognitive performance: A morphometric MRI analysis. *Cerebral Cortex*, *15*(6), 846–853.
- Keane, J., Calder, A. J., Hodges, J. R., & Young, A. W. (2002). Face and emotion processing in frontal variant frontotemporal dementia. *Neuropsychologia*, *40*(6), 655–665.
- Kramer, J. H., Jurik, J., Sha, S. J., Rankin, K. P., Rosen, H. J., Johnson, J. K., et al. (2003). Distinctive neuropsychological patterns in frontotemporal dementia, semantic dementia, and Alzheimer disease. *Cognition and Behavioural Neurology*, *16*(4), 211–218.
- Krams, M., Quinton, R., Ashburner, J., Friston, K. J., Frackowiak, R. S., Bouloux, P. M., et al. (1999). Kallmann's syndrome: Mirror movements associated with bilateral corticospinal tract hypertrophy. *Neurology*, *52*(4), 816–822.
- Lane, R. D., Reiman, E. M., Ahern, G. L., Schwartz, G. E., & Davidson, R. J. (1997). Neuroanatomical correlates of happiness, sadness, and disgust. *American Journal of Psychiatry*, *154*(7), 926–933.
- Lavenex, I., Pasquier, F., Lebert, F., Petit, H., & Van der Linden, M. (1999). Perception of emotion in frontotemporal dementia and Alzheimer disease. *Alzheimer Disease Association of Disorder*, *13*(2), 96–101.
- Levesque, J., Eugene, F., Joannette, Y., Paquette, V., Mensour, B., Beaudoin, G., et al. (2003). Neural circuitry underlying voluntary suppression of sadness. *Biological Psychiatry*, *53*(6), 502–510.
- Litvan, I., Agid, Y., Calne, D., Campbell, G., Dubois, B., Duvoisin, R. C., et al. (1996). Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele–Richardson–Olszewski syndrome): Report of the NINDS-SPSP international workshop. *Neurology*, *47*(1), 1–9.



- Liu, W., Miller, B. L., Kramer, J. H., Rankin, K., Wyss-Coray, C., Gearhart, R., et al. (2004). Behavioral disorders in the frontal and temporal variants of frontotemporal dementia. *Neurology*, 62(5), 742–748.
- Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *NeuroImage*, 19(3), 1233–1239.
- McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, 34(7), 939–944.
- Mesulam, M. M. (1998). From sensation to cognition. *Brain*, 121(Pt 6), 1013–1052.
- Mummary, C., Patterson, K., Price, C., Ashburner, J., Frackowiak, R., & Hodges, J. (2000). A voxel-based morphometry study of semantic dementia: Relationship between temporal lobe atrophy and semantic memory. *Annals of Neurology*, 47(1), 36–45.
- Mychack, P., Kramer, J. H., Boone, K. B., & Miller, B. L. (2001). The influence of right frontotemporal dysfunction on social behavior in frontotemporal dementia. *Neurology*, 56(11 Suppl. 4), S11–S15.
- Neary, D., Snowden, J. S., Gustafson, L., Passant, U., Stuss, D., Black, S., et al. (1998). Frontotemporal lobar degeneration: A consensus on clinical diagnostic criteria. *Neurology*, 51(6), 1546–1554.
- Ojemann, J. G., Akbudak, E., Snyder, A. Z., McKinstry, R. C., Raichle, M. E., & Conturo, T. E. (1997). Anatomic localization and quantitative analysis of gradient refocused echo-planar fMRI susceptibility artefacts. *NeuroImage*, 6(3), 156–167.
- Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V., et al. (2001). Current concepts in mild cognitive impairment. *Archives of Neurology*, 58(12), 1985–1992.
- Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in PET and fMRI. *NeuroImage*, 16(2), 331–348.
- Rapcsak, S. Z., Galper, S. R., Comer, J. F., Reminger, S. L., Nielsen, L., Kaszniak, A. W., et al. (2000). Fear recognition deficits after focal brain damage: A cautionary note. *Neurology*, 54(3), 575–581.
- Reiman, E. M., Lane, R. D., Ahern, G. L., Schwartz, G. E., Davidson, R. J., Friston, K. J., et al. (1997). Neuroanatomical correlates of externally and internally generated human emotion. *American Journal of Psychiatry*, 154(7), 918–925.
- Rorden, C., & Brett, M. (2000). Stereotaxic display of brain lesions. *Behavioural Neurology*, 12(4), 191–200.
- Rosen, H. J., Gorno-Tempini, M. L., Goldman, W. P., Perry, R. J., Schuff, N., Weiner, M., et al. (2002). Patterns of brain atrophy in frontotemporal dementia and semantic dementia. *Neurology*, 58(2), 198–208.
- Rosen, H. J., Pace-Savitsky, K., Perry, R. J., Kramer, J. H., Miller, B. L., & Levenson, R. W. (2004). Recognition of emotion in the frontal and temporal variants of frontotemporal dementia. *Dementia and Geriatric Cognitive Disorders*, 17(4), 277–281.
- Rosen, H. J., Perry, R. J., Murphy, J., Kramer, J. H., Mychack, P., Schuff, N., et al. (2002). Emotion comprehension in the temporal variant of frontotemporal dementia. *Brain*, 125(Pt 10), 2286–2295.
- Sprengelmeyer, R., Young, A. W., Calder, A. J., Karnat, A., Lange, H. W., Homborg, V., et al. (1996). Loss of disgust: Perception of faces and emotions in Huntington's disease. *Brain*, 119, 1647–1665.
- Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*, 15(1), 273–289.
- Williams, G. B., Nestor, P. J., & Hodges, J. R. (2005). Neural correlates of semantic and behavioural deficits in frontotemporal dementia. *NeuroImage*, 24(4), 1042–1051.
- Winston, J. S., Henson, R. N., Fine-Goulden, M. R., & Dolan, R. J. (2004). fMRI-adaptation reveals dissociable neural representations of identity and expression in face perception. *Journal of Neurophysiology*, 92(3), 1830–1839.
- Yesavage, J. A., Brink, T. L., Rolse, T. L., Lum, O., Huang, V., Adey, M., et al. (1983). Development and validity of a Geriatric Depression Scale: A preliminary report. *Journal of Psychiatric Research*, 17, 37–49.
- Zoccolotti, P., Scabini, D., & Violani, C. (1982). Electrodermal responses in patients with unilateral brain damage. *Journal of Clinical Neuropsychology*, 4(2), 143–150.