NeuroReport 10, 2449–2455 (1999)

Left-hemisphere processing of emotional connotation during word generation

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AREAS of the brain's left hemisphere involved in retrieving words with emotional connotations were studied with fMRI. Participants silently generated words from different semantic categories which evoked either words with emotional connotations or emotionally neutral words. Participants repeated emotionally neutral words as a control task. Compared with generation of emotionally neutral words, generation of words with emotional connotations engaged cortices near the left frontal and temporal poles which are connected to the limbic system. Thus, emotional connotations of words are processed in or near cortices with access to emotional experience. *NeuroReport* 10:2449–2455 © 1999 Lippincott Williams & Wilkins.

Key words: Emotion; fMRI; Frontal pole; Language; Limbic system; Semantics; Temporal pole; Word generation

Introduction

Emotions, pleasant and unpleasant, have adaptive significance [1]. They impel us to approach things essential for our survival (e.g. food, sex, affiliation) and to avoid things that threaten our survival (e.g. predators, other dangers). As a symbolic tool, we use language to communicate emotional significance, often by implication. For example, 'The grizzly bear lives in that cave' connotes a place to be avoided, though danger is not directly expressed. Are there specialized brain systems for distinguishing the emotional connotation of verbal stimuli?

Functional neuroimaging and lesion studies have supported the concept that knowledge of an object's sensory attributes is processed in cortical regions proximal to those mediating perception of such attributes, and that knowledge of these attributes is critical for naming or describing the objects [2,3]. Similar claims have been made regarding cortex processing an action's movement parameters, i.e. that cortex that processes movement parameters for learned actions will be involved in naming those actions [4]. Indeed, some investigators have maintained that category-specific deficits for naming or recognizing objects result from impaired processing of attributes that distinguish category members (e.g. visual features for living things *vs* the function of non-living things) [5,6]. Applying this reasoning to emotional attributes, knowledge of emotional connotations should be processed in cortex with access to emotional experience. The limbic system involves structures heavily connected to the hypothalamus such as the the amygdala, the hippocampus, and certain basal forebrain structures (nucleus accumbens, extended amygdala). Because many limbic system structures play a role in mediating emotional experience, cortex heavily connected to the limbic system has access to rich information about emotional experience.

Although a few functional neuroimaging studies have explored processing of words with emotional connotations [7,8], none has directly compared processing a variety of words with different emotional connotations to processing a variety of emotionally neutral words. In one PET study, Beauregard and colleagues [7] compared processing of words with emotional connotations to processing names of animals; unfortunately, since processing animal names tends to evoke its own unique pattern of regional brain activity [2,3], this comparison confounds the attribute of emotional connotation with the semantic category of animals. In an fMRI study comparing judgments regarding words with emotional connotations *vs* emotionally neutral words, Maddock and Buonocore [8] used only threat-related words as emotional stimuli.

We recently derived categories from the Affective Norms for Emotional Words [9] (ANEW) which would elicit words with emotional connotations (positive and negative) or emotionally neutral words. Subjects generated as many words as possible to each category during imaging of left-hemisphere activity with fMRI. The purpose of the study was to determine those regions of the left hemisphere needed to generate words with emotional connotations. Our image acquisition technique limited the number of brain slices we could study, and we chose to cover left-hemisphere activity for several reasons. First, while subtle differences between hemispheres may exist for processing of words with positive *vs* negative emotional connotation, tachistoscopic evidence from neurologically normal subjects indicates that left-hemisphere dominance for processing words, including those with emotional connotations, is substantially more robust than such differences between hemispheres [10]. Second, evidence from patients with right-hemisphere damage confirms left-hemisphere competence for processing the emotional content of verbal communications, as long as the verbal content does not describe emotional facial expressions or emotional prosody [11]. Third, recent functional neuroimaging evidence indicates a significant role for the left hemisphere in processing emotional connotations, even when the stimuli are pictures rather than words [12]. Thus, the left hemisphere plays the dominant, or at least a prominent, role in processing emotional connotations of words. We chose to use word generation as a task because generating words produces differential activation of brain processing mechanisms related to the categories, similar to naming of pictures [13] and because our laboratory recently has been engaged in the study of differential effects of word generation [14].

Materials and Methods

Subjects: Seventeen (10 male, seven female) strongly right-handed (Edinburgh Handedness Inventory [15]) subjects participated in the study (age 18–32 years, mean 23.2 years; education 13–20 years, mean 16.4 years). Potential risks were explained, and all subjects gave written informed consent according to procedures established by the Health Center Institutional Review Board of the University of Florida.

Experimental tasks and manipulation check: Periods of silently generating either words with emotional connotations or emotionally neutral words alternated with periods of silent repetition of emotionally neutral words. A category was given at the beginning of an 18.4 s word generation period, and subjects generated as many exemplars as possible. During alternating 18.4 s periods, subjects repeated emotionally neutral words. The top portion of Fig. 1 illustrates the structure of experimental runs. The cue 'generate' or 'repeat' was given at the beginning of each 18.4 s period. All words, cues, and categories were presented in the auditory modality with volume individually adjusted for optimal hearing (Kenwood KR-A4070 amplifier, Realistic 31-2005 Ten band stereo frequency equalizer, JBL 16 Ω speaker, and insulated air conduction transducer with foam insert earphones). During experimental runs, only one type of generation task (words with emotional connotations *vs* emotionally neutral words) was used. Each run consisted of 6.4 cycles of alternation between word generation and word repetition, beginning and ending with repetition. Using ANEW [9], categories were selected that subsumed either words with emotional connotations or emotionally neutral words. ANEW was also used to select emotionally neutral words for repetition. For generating words with emotional connotations, participants alternated between categories that elicited words with positive emotional connotations (e.g. things at an amusement park, desserts) and categories that elicited words with negative emotional connotations (e.g. diseases, things having to do with death). Examples of emotionally neutral categories are birds or types of rooms. We did not attempt to directly evoke emotions by manipulating the context or intonation of words or categories. Thus, emotional connotation was derived purely from the meaning of the categories being processed and the words being retrieved. Experimental runs alternating the generation tasks or repetition with periods of

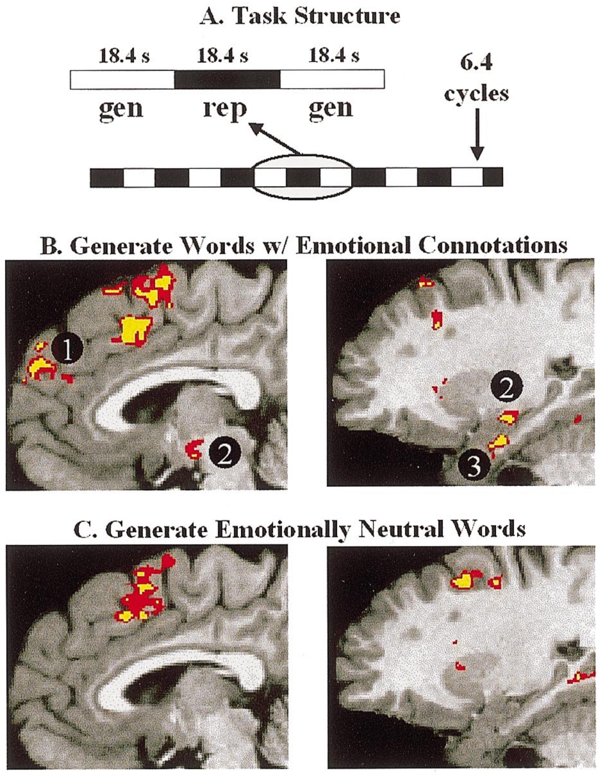

FIG. 1. (Top) 18.4 s periods of word generation (gen) alternated with 18.4 s periods of repeating emotionally neutral words (rep). Participants generated words with emotional connotations and emotionally neutral words in separate experimental runs, alternating word repetition and word generation for 6.4 cycles. Sagittal sections (center and bottom) through the left hemisphere at 3 mm (left) and 23 mm (right) from midline show significant activity increases in red ($p < 0.001$) and yellow ($p < 0.0001$). The anatomical underlay was taken from the structural images of an individual participant. For generation of words with emotional connotations versus repetition (center), activity increases were seen in regions associated with the limbic system near the frontal pole, in a region encompassing portions of the hypothalamus, amygdala, and hippocampus, and in a separate region encompassing portions of the inferior amygdala and anterior, inferior hippocampus. Activity increases in these limbic regions were not seen for generation of emotionally neutral words versus repetition (bottom). Volumes of significant activity increase are also described in Table 1, where limbic regions were referenced with the same numbers.

rest were also done, but this method of data acquisition yielded less sensitive comparisons and will not be further discussed. The order of presentation of tasks during scanning was counterbalanced.

A pilot study with different subjects equated rate of word generation for categories with emotional connotations to rate of word generation for emotionally neutral categories, and the rate of repetition of emotionally neutral words was matched to the rate of word generation. To monitor the rate of word generation for the fMRI experiment, three lists of six categories with emotional connotations and three lists of six emotionally neutral categories were constructed. For each type of generation (words with emotional connotations *vs* emotionally neutral words), a subject was randomly assigned one of the three lists to use in experimental runs alternating with repetition during scanning. To monitor rate of word production for the experimental lists in the experimental sample, a different list of each type was randomly assigned for oral generation immediately after termination of the scanning session. Rate of word production during repetition was also monitored with a list of emotionally neutral words different to that used during scanning. The mean rates of oral word production for six cycles equivalent to a functional imaging run were closely matched: generation of words with emotional connotations, 42.6 words (s.d. 8.9); generation of emotionally neutral words, 43.3 words (s.d. 7.9); repetition of emotionally neutral words, 42.0 (s.d. 0).

Image acquisition: All images were acquired on a 1.5 T GE Signa scanner using a dome-shaped quadrature radio frequency head coil. The head was aligned such that the interhemispheric fissure was within 1° of vertical. The most medial sagittal slice for functional images was placed such that the medial edge of the slice corresponded with the medial boundary of the left hemisphere. Nine slices (6.4–6.9 mm thick, no gap) covered the entire left hemisphere. For functional scans, a series of 64 images was acquired for each of the nine sagittal slices using a gradient echo spiral scan technique [16] with TE = 40 ms, TR = 870 ms, FA = 45°, FOV = 18 cm, matrix size = 128×128, four spirals. Subsequent to functional imaging, structural images were acquired for 124 1.3 mm thick sagittal slices, using a 3D spoiled GRASS volume acquisition (TE = 7 ms, TR = 27 ms, FA = 60°, NEX = 1, FOV = 24 cm, matrix size = 256×192). Prior to functional images, time-of-flight MR angiograms were acquired for the same slices as functional images (TE = 6.6 ms, TR = 40 ms, FA = 60°, FOV = 18 cm, matrix = 256×192).

Image analysis: Functional images were analyzed and overlaid onto anatomic images with the Analysis of Functional Neuroimaging (AFNI) program [17]. To reduce effects of motion, images were spatially registered in-plane to a base image using an iterative procedure minimizing the variance in voxel intensity ratios of the two images [17]. Mean signal intensity for individual image sequences was normalized to the group mean, and voxels where the standard deviation of the signal change exceeded 5% of the mean signal were set to zero to attenuate large vessel effects and residual motion artifacts. Images were visually inspected for gross artifact and viewed in a cine loop to detect residual motion. If any time series of a subject was judged to contain a significant number of images with gross artifacts or residual motion, the subject's data were eliminated from analyses. Data from one of 18 subjects who participated were eliminated because of motion and artifact, leaving the 17 subjects who were described above. Linear drift in the time series was removed using Gram-Schmidt orthogonalization. A composite functional image was generated using magnitude of least squares fit between the acquired time series from each voxel and an ideal, sinusoidal reference waveform, time-locked to the alternating cycles of word generation and word repetition [18]. Because each spiral of the various slices was collected at a slightly different time, nine phase-shifted sinusoidal reference waveforms were used to compensate for the temporal difference. The waveform generating the highest correlation was used for each voxel. The magnitude of least squares fit is an additive index that contains information about the goodness of least squares fit of the acquired time series with the selected reference wave form and the amplitude of the acquired time series. Whole-brain anatomic images and functional images were linearly interpolated to 1 mm^3 voxels, co-registered and converted to stereotaxic coordinate space [19]. Functional image volumes were smoothed (3 mm FWHM Gaussian filter) to compensate for intersubject variability in structural and functional anatomy. Student's t-tests were conducted on a voxel-by-voxel basis as follows: (1) alternations between generation of words with emotional connotations and emotionally neutral word repetition were compared to a null hypothesis of no change, (2) alternations between generation of emotionally neutral words and emotionally neutral word repetition were compared to a null hypothesis of no change, and (3) differences between generation of words with emotional connotations and emotionally neutral word repetition were compared to differences between emotionally neutral word generation and emotionally neutral word repetition on a repeated measures basis. For each t-test procedure, minimum volumes of significant activity ($p < 0.001$) were required to exceed the largest volume generated from conducting the procedure with nine random reference waveforms or the volume of six acquisition voxels (82 μl), whichever was larger. Retrospectively, individual-subject activity maps were overlaid onto each subject's MR angiogram. When an area of significant activity was in a large vessel for more than one-third of the subjects, it was eliminated from consideration. Individual functional images also were examined retrospectively to ensure that activity was substantially within the parenchyma and not merely at the edge of the brain.

Results

As described above, alternations between word generation and word repetition were analyzed separately for categories with emotional connotations and emotionally neutral categories. After evaluating individual subject functional activity overlaid onto MR angiograms, areas above the superior edge of the thalamus and around retrosplenial cortex were removed from consideration in both generation tasks compared to repetition because they were in large vessels for more than a third of the subjects. When comparing each generation task to repetition of emotionally neutral words (Fig. 1; Table 1), a number of common areas of activity arose. These areas included Broca's area, which is involved in language production [20]; perilimbic medial frontal cortex and pre-supplementary motor area, which are involved in initiation of language production [14,20]; portions of the caudate nucleus, thought to play a role in initiation of activity [21]; areas in the middle frontal gyrus that may be involved in semantic processing [22] and areas of striate and peristriate visual cortex. In some brain regions, activity reached statistical significance criteria for comparing generation with emotional connotations to repetition but not for comparing emotionally neutral generation to repetition. These regions were dominated by limbic system components and cortex heavily connected to limbic structures. These regions included cortex near the frontal pole, inferior medial temporal cortex, the amygdala, the hippocampus, and the hypothalamus.

In a separate analysis, differences between generation of words with emotional connotations and repetition were compared to differences between generation of emotionally neutral words and repetition. Two brain regions showed activity above statistical thresholds (Fig. 2). The first of these was near the superior aspect of the frontal pole (peak atlas coordinates −13, 62, 27; maximum $t = 6.09$; vol = 167 μl). This was the same region showing activity differences in the emotional generation versus repetition analysis (see above). This region of the frontal lobe receives input from limbic cortex including the anterior cingulate gyrus and the posterior parahippocampal cortex. Because of these connections, this cortex is thought to integrate internal need states (i.e. emotional and drive states) with external sensory input in order to plan action sequences [23]. The second region of activity increase for generation of words with emotional connotations *vs* emotionally neutral words was located at the temporal pole (peak atlas coordinates −48, 17, −15; maximum $t = 6.70$; vol = 166 μl). This region of cortex was too small to meet the empirically determined criterion for activity increase when generation of words with emotional connotations was compared to repetition (above), suggesting that the area of overlapping activity between subjects was relatively small. Temporal polar cortex connects not

Table 1. Regions of activity change for both word generation tasks *vs* repetition

Generation of emotionally evocative words	Generation of emotionally neutral words
Generation > repetition	Generation > repetition
Perilimbic cortex (−4, 17, 47; t = 9.63; vol = 2381 µl)	Perilimbic cortex and pre-SMA (−7, 22, 43; t = 8.42; vol = 2077 µl)
Pre-SMA (−2, 7, 60; t = 8.25; vol = 1924 µl)	
Frontal pole (−7, 60, 28; t = 9.01; vol = 1952 µl)[1]	
	Superior frontal sulcus (−21, 11, 50; t = 6.97; vol = 1803 µl)
Middle frontal gyrus (−47, 30, 24; t = 6.27; vol = 1402 µl)	Middle frontal gyrus (−44, 37, 14; t = 6.67; vol = 1157 µl)
Middle frontal gyrus (−41, 46, 1; t = 6.06; vol = 349 µl)	
Broca's area (−51, 22, 3; t = 7.40; vol = 1554 µl)	Broca's area (−51, 20, 3; t = 8.05; vol = 1139 µl)
Inferior medial temporo-occipital cortex (−15, −49, −7; t = 7.54; vol = 380 µl)	
	Posterior inferior temporal cortex (−55, −51, −5; t = 9.49; vol = 519 µl)
Striate and peristriate cortex and cerebellum (−14, −87, 5; t = 9.68; vol = 4031 µl)	Striate and peristriate cortex† (−7, −72, 5; t = 5.99, vol = 929 µl)
Amygdala, hippocampus and hypothalamus (−15, −10, −7; t = 7.76; vol = 1340 µl)[2]	
Amygdala and hippocampus (−21, −7, −22; t = 7.12; vol = 687 µl)[3]	
Head of caudate nucleus (−16, 12, 8; t = 6.87; vol = 401 µl)	Head of caudate nucleus and putamen† (−20, 12, 5; t = 7.93; vol = 2182 µl)
Lateral cerebellum (−48, −58, −24; t = 6.65; vol = 711 µl)	
Repetition > generation	Repetition > generation
Superior temporal gyrus (−53, −9, 4; t = −7.02; vol = 636 µl)	Superior temporal gyrus (−56, −13, 13; t = −12.92; vol = 3306 µl)

In parentheses are the Talairach coordinates for the peak *t* value, the peak *t* value, and the volume of the activity change in µl. When activity volumes occupy more than one structure, multiple gray matter structures are listed. Superscript numbers indicate corresponding areas in Fig. 1. Areas just superior to the thalamus and in retrosplenial cortex were excluded from consideration for both comparisons because they were in major vessels for more than one-third of the subjects. †Connected areas over major vessels were removed from these volumes.

only with other cortices associated with the limbic system such as medial frontal cortex, medial temporal regions, insular cortex, and orbitofrontal cortex, but also directly with the amygdala. The fact that temporal polar cortex also receives input from sensory association cortex has led to speculation that it is important in identification of external stimuli relevant to internal emotional and motivational states [23].

Discussion

When generation of words with emotional connotations was contrasted with repetition of emotionally neutral words, prominent activity was seen in cortical and subcortical structures of the limbic system. Activity increases in these areas were not seen when contrasting generation of emotionally neutral words with repetition. However, frontal and temporal polar cortices were the only brain areas preferentially activated when the retrieval of words with emotional connotations was directly compared to retrieval of emotionally neutral words. The latter finding may reflect the role these cortical regions play in processing information relevant to internal emotional and motivational states.

Findings of Canli and colleagues [24] confirm a role for cortex near the temporal pole in processing emotional stimuli. In viewing pictures with positive *vs* negative emotional valence, these investigators found increased activity in right and left temporal polar cortex. Unfortunately, cortex near the frontal pole was not imaged in this study by Canli *et al.* Lane and colleagues [12] did not find activity near the temporal pole in their PET study where subjects viewed pictures from the same corpus as Canli and colleagues' study. Nevertheless, these investigators did image prefrontal cortex and found activity approaching the left frontal pole when viewing of affectively positive pictures was compared to viewing affectively neutral pictures. These data suggest that cortex at or near the left frontal and temporal poles is not only involved in retrieving words with emotional connotations but also in processing emotional meaning in the visual modality. Thus, these cortices appear to play a more general role in recognition of emotional significance of varying stimuli, i.e. their activity does not appear to be limited to processing connotations of words.

It is also worth noting that Lane *et al.* found activity in the hypothalamus (for viewing affectively positive *vs* neutral pictures and for viewing affectively negative *vs* neutral pictures), amygdala (for viewing affectively negative *vs* neutral pictures), and hippocampus (for viewing affectively negative *vs* neutral pictures) [12]. These results also suggest that

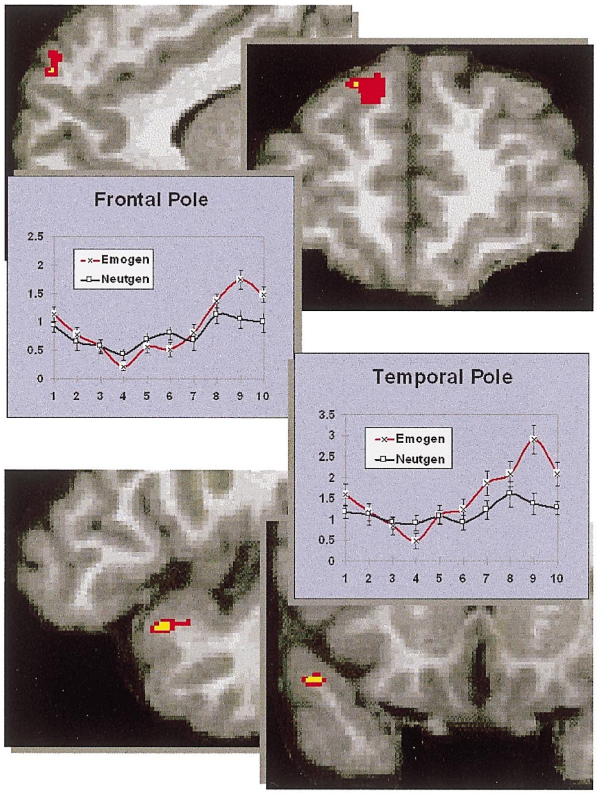

FIG. 2. Significant areas of activity for generating words with emotional connotations *vs* emotionally neutral words were found near the left frontal pole (top: peak atlas coordinates −13, 62, 27; maximum $t = 6.09$; vol = 167 µl) and near the left temporal pole (bottom: peak atlas coordinates −48, 17, −15; maximum $t = 6.70$; vol = 166 µl). Sagittal (left) and coronal (right) sections through the active areas are represented. Activity volumes in red ($p < 0.001$) were larger than the cut-off volume established with random waveforms (82 µl). Activity in yellow represents a more stringent level of probability ($p < 0.0001$). When word production tasks differ only in semantic content, as in the current study, direct comparison of tasks can lead to relatively small volumes of activity difference [4]. Graphs represent percent change in fMRI signal (y-axis) for the average 10-image cycle alternating between generation and repetition (x-axis). A single voxel was selected for each subject in the activated areas for both generation of words with emotional connotations (emogen, red line) and generation of emotionally neutral words (neutgen, black line). Time series within the voxel were then collapsed into an average cycle and converted into percentage change from the lowest point in the cycle. The average cycle for each subject was then averaged across subjects to obtain the mean percentage change and s.e.

activity in the hypothalamus, amygdala, and hippocampus, which we found when we compared generating words with emotional connotations to repeating emotionally neutral words, is not unique to word processing. These subcortical and archicortical structures appear to more active when processing stimuli with emotional meaning than when processing emotionally neutral stimuli.

Results of previous studies of emotional word processing have not been so revealing. One recent fMRI study found changes near the restrosplenial cortex when subjects made judgments regarding the pleasantness *vs* unpleasantness of threat-related words compared to making this judgment about emotionally neutral words [8]. However, the authors noted this region was proximal to a major vein. In the current study, we found similar activity for generation both of words with emotional connotations and emotionally neutral words compared to repetition. Since the location of this activity in a major vein raises questions regarding the precise origin of the activity, we excluded this site from further interpretation. A second PET study found increased activity primarily in the inferior and medial frontal cortex bilaterally for passively viewing emotional words compared to passively viewing animal names [7]. However, viewing animal names as a comparison task confounds emotional connotation with the effects of category. In the same study, activity from passive viewing of emotional words was also compared to activity that occurred just after receiving a set of instructions for viewing random letter sequences but before the actual task began. Among numerous other areas of significant activity, this comparison yielded an area of left frontal activity that was near the Talairach coordinates of our study's frontal pole activity. In a recent study in our laboratory, subjects monitored words with emotional connotations for semantic characteristics. When compared to a tone monitoring control task, monitoring of emotional words yielded extensive left frontal activity, including the same region near the frontal pole as the current study and left temporal activity just posterior to the region activated in the current study.

Future imaging studies should ascertain if right-hemisphere structures are involved in processing the emotional connotation of words. Even in processing of the same affective picture set, findings regarding right-hemisphere participation have varied. A vast majority of Lane and colleagues' active areas were in the left hemisphere for both positive and negative affective pictures compared with neutral pictures [12]. In posterior regions of the hemispheres (inferior and superior parietal lobules, fusiform gyrus, visual association cortex), on the other hand, Lang *et al.* found greater activity in the right *vs* the left hemisphere for viewing affective (positive and negative) as opposed to neutral pictures [25]. In yet another study, Canli *et al.* eliminated subjects from their sample to equalize subject-reported arousal ratings for positive and negative affective pictures. They demonstrated greater left-hemisphere activity in the frontal and temporal lobes for positive compared to negative affective pictures and greater right-hemisphere activity in the inferior and medial frontal lobe and superior temporal lobe for negative compared to positive affective pictures [24]. Although tachistoscopic evidence suggests left-hemisphere dominance for processing words with both positive and negative emotional connotations, subtle differences between the hemispheres may exist in processing these words [10]. Finally, it must be acknowledged that our task alternated between categories with positive and negative emotional valence during generation of words with emotional connotations. This design did not allow us to determine differences in processing words with positive *vs* negative emotional valence. Further, it is possible that results were influenced by alternating generation of words with positive emotional valence and generation of words with negative emotional valence. Thus, the next step in functional imaging may be to compare left- *vs* right-hemisphere processing of words with positive and negative connotations.

Conclusion

The most salient finding from our study is that compared to generating emotionally neutral words, generating words with emotional connotations engages cortex near the frontal and temporal poles. There is support for this finding in the previous functional imaging literature on emotional picture and word processing. This result is important for three reasons. First, it provides functional neuroimaging evidence that brain organization respects knowledge about semantic attributes, i.e. emotional properties, other than purely sensory or motor attributes. Second, this result provides further support for the suggestion of Martin and colleagues [3] and Damasio and colleagues [2] that processing semantic attributes, even indirectly, engages cortex proximal to that used to process fundamental information related to the attribute. This axiom appears to be an underlying principle of brain organization regarding the processing of semantic attributes. Third, this finding indicates clearly that the location of left-hemisphere cortical mechanisms used to process emotional connotations is in regions regarded by many as limbic association cortex. Thus, the brain uses cortex with access to emotional experience to process the emotional significance of words, creating a link between language symbols and emotional experience.

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ACKNOWLEDGEMENTS: Supported by University of Florida Brain Institute and grant R01-DC03455 from NIDCD. Thanks to NIMH Center for the Study of Emotion and Attention (Grant P50-MH52384, P. J. Lang, Director; Margaret M. Bradley; Bruce N. Cuthbert) for consultation; Douglas C. Noll for spiral scan sequences; Jeffrey R. Fitzsimmons for head coil; Wayne King for sound transducer; and Alex Martin and Stephen M. Rao for comments on manuscript.

Received 18 May 1999; accepted 9 June 1999