Processing Words with Emotional Connotation: An fMRI Study of Time Course and Laterality in Rostral Frontal and Retrosplenial Cortices

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Abstract

Responses of rostral frontal and retrosplenial cortices to the emotional significance of words were measured using functional magnetic resonance imaging (fMRI). Twenty-six strongly right-handed participants engaged in a language task that alternated between silent word generation to categories with positive, negative, or neutral emotional connotation and a baseline task of silent repetition of emotionally neutral words. Activation uniquely associated with word generation to categories with positive or negative versus neutral emotional connotation occurred bilaterally in rostral frontal and retrosplenial cortices. Furthermore, the time courses of activity in these areas differed, indicating that they subserve different functions in processing the emotional connotation of words. Namely, the retrosplenial cortex appears to be involved in evaluating the emotional salience of information from external sources, whereas the rostral frontal cortex also plays a role in internal generation of words with emotional connotation. In both areas, activity associated with positive or negative emotional connotation was more extensive in the left hemisphere than the right, regardless of valence, presumably due to the language demands of word generation. The present findings localize specific areas in the brain that are involved in processing emotional meaning of words within the brain’s distributed semantic system. In addition, time course analysis reveals diverging mechanisms in anterior and posterior cortical areas during processing of words with emotional significance.

INTRODUCTION

In aggregate, recent functional neuroimaging studies indicate that processing the meaning of words and objects involves a complex matrix with three primary parameters that influence the pattern of brain activation for any given word or object. These parameters are as follows: the processing modality of the object, usually either visual or verbal (e.g., Thompson-Schill, Aguirre, D’Esposito, & Farah, 1999; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996); the semantic category of the word or object (e.g., Chao, Haxby, & Martin, 1999; Ishai, Ungerleider, Martin, Schouten, & Haxby, 1996; Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Martin, Wiggs, Ungerleider, & Haxby, 1996); and the defining attributes of the word or object (e.g., Pulvermüller, Härlé, & Hummel, 2000; Crosson et al., 1999, 2002). Emotional connotation is conceptualized as a semantic attribute conveying, often implicitly, the pleasant or unpleasant nature of an object or experience. The current study addressed processing emotional connotation within the verbal modality.

Recent literature implicates two cortical areas in verbal processing of the emotional connotation of words. First, Maddock and Buonocore (1997) reported unique activity in the left posterior cingulate gyrus for processing threat-related words. In a later review, Maddock (1999) suggested that the retrosplenial cortex, in particular Brodmann’s area (BA) 30 and neighboring posterior cingulate cortex (BA 23, 31), may be involved in processing the emotional significance of words and objects. This cortical region was the most commonly activated area in experiments when an emotional condition (words or pictures) was compared to a closely matched neutral condition. Second, Crosson et al. (1999, 2002), with two separate paradigms, found left rostral frontal cortex (BA 9, 10) activation associated with processing the emotional connotation of words. In one paradigm, subjects engaged in semantic monitoring of words with emotional connotation, and in the other task, subjects generated words either to categories with emotional connotation or to emotionally neutral categories. Activation of this rostral frontal area (BA 9, 10) has also been reported in a number of studies examining processing of visual stimuli.

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(i.e., slides, film clips) with emotional connotation, positive or negative (e.g., Paradiso et al., 1999; Lane, Reiman, Ahern, Schwartz, & Davidson, 1997; Lane, Reiman, Bradley, et al., 1997; for a review, see Teasdale et al., 1999). No studies that examined processing the emotional connotation of words have reported both rostral frontal and retrosplenial activations. Further, it is not known whether retrosplenial and rostral frontal cortices are involved in similar or dissimilar aspects of processing emotional connotation.

Given what is known about the connectivity and function of the retrosplenial/posterior cingulate cortex and about the connectivity and function of the rostral frontal cortex, we might hypothesize that these two regions play different roles in evaluation of the emotional connotation of words. While both regions are connected to other cortical regions that have strong connectivity with the limbic system (Pandya & Yeterian, 1986), the posterior cingulate cortex has connections with polymodal and supramodal cortices involved in sensory processing. Thus, it has been suggested that the posterior cingulate cortex is involved in evaluating the motivational significance of sensory stimuli (Heilman, Watson, & Valenstein, 1993). On the other hand, prefrontal cortex can be seen as "motor cortex of the highest order in that it supports the cognitive functions that coordinate the execution of the most novel and elaborate actions of the organism" (Fuster, 1999, p.187). Limbic inputs to the frontal lobe are thought to have motivational significance (Fuster, 1999). Rostral frontal cortex is a rich interface between the limbic system that has access to emotional experience and other areas of the frontal lobes that organize and plan behavior. Thus, one function of the rostral frontal cortex may be to evaluate the emotional and motivational significance of behavior as it is planned. To summarize, the retrosplenial/posterior cingulate cortex is likely to be involved in evaluating the emotional significance of incoming information, but the rostral frontal cortex may evaluate the emotional significance of actions. If this conceptualization of retrosplenial/posterior cingulate and rostral frontal functions is correct, then these regions should be differentially engaged when an activity involves the comprehension of incoming information with emotional significance versus when the activity involves actions with emotional significance, respectively.

Another question is laterality of findings when processing words with emotional connotation. While left-hemisphere dominance for processing language may always bias processing in the verbal modality toward the left hemisphere, the two previous studies by Crosson et al. (1999, 2002) examining the emotional connotation of words did not image right-hemisphere function, and thus, the role of the nondominant hemisphere in processing the emotional connotation of words was not evaluated. In addition, these two previous studies did not examine effects of valence (i.e., positive vs. negative). Indeed, the relative contribution of the two hemispheres may vary by valence when processing words with emotional connotation. Although some data suggest the right hemisphere is dominant for processing emotions (e.g., Gainotti, 1997; Ross, 1997; Heilman, Bowers, Speedie, & Coslett, 1984; Tucker, 1981), the valence hypothesis posits that emotional valence determines which hemisphere, particularly frontal structures, processes emotional stimuli. Specifically, greater left- than right-hemisphere regions are thought to process emotionally positive stimuli, and greater right- than left-hemisphere regions are thought to process emotionally negative stimuli (e.g., Davidson, 1995; Sackeim et al., 1982). Canli, Desmond, Zhao, Glover, and Gabrieli (1998) found support for the valence hypothesis using picture stimuli and functional magnetic resonance imaging (fMRI) when rated arousal of the stimuli were equated across positively and negatively valenced pictures. In a tachistoscopic study of written words, Ali and Cimino (1997) also provided support for the valence hypothesis, despite a large bias for left-hemisphere processing for both words of positive and negative emotional valence.

In the current study, male and female subjects generated words from categories with positive, negative, and neutral emotional connotation. We found significant activity bilaterally in both rostral frontal and retrosplenial/posterior cingulate cortices associated with processing the positive or negative emotional connotation of words. Given the above analysis of retrosplenial/posterior cingulate versus rostral frontal functions, time courses of activity in these two regions were compared as an indicator of their different functions. Regarding these differences, we hypothesized that the rostral frontal cortex would be active during the generation of words with emotional connotation while the retrosplenial/posterior cingulate area would be involved more with processing externally presented words with emotional connotation (i.e., the category cues). Regarding left- versus right-hemisphere activity in these two areas, we entertained three competing hypotheses: First, the verbal nature of the task would bias processing toward the left hemisphere. Second, the emotional nature of stimuli would bias processing toward the right hemisphere for words with positive or negative emotional connotation versus emotionally neutral words. Third, for structures that process emotional connotation, emotionally positive words would be processed more in the left hemisphere, whereas emotionally negative words would be processed more in the right hemisphere.

To evaluate the function and laterality of the rostral frontal cortex and retrosplenial/posterior cingulate cortex in processing words with emotional connotation, a word generation paradigm and whole-brain fMRI were used with 26 healthy adult participants (15 male, 13 female). Blocks of silent generation of words to categories with positive, negative, or neutral emotional connotation alternated with blocks of silent repetition of
words with neutral emotional connotation (Figure 1). As was done in the Crosson et al. (1999) study, a baseline task of neutral word repetition, rather than rest, was selected to control for linguistic aspects of auditory word recognition and silent word production, and to control for automatic semantic processing that is associated with the “resting state” (Binder et al. 1999). Deconvolution of the time series was used to isolate hemodynamic response functions (HRFs) for each of the three valence types. Region-of-interest (ROI) analyses were used to examine the HRFs in both rostral frontal and retrosplenial/posterior cingulate areas.

RESULTS

Behavioral Results

Because participants performed the language task silently while in the scanner, behavioral testing using overt word production immediately followed scanning sessions. Participants performed one additional run with overt word generation outside the scanner to determine the average generation rate for categories belonging to each valence. Participants also rated valence and arousal for categories with positive, negative, and neutral emotional valence. As in the Canli et al. (1998) study, we aimed to equate arousal ratings for positive and negative categories. The behavioral results, including the mean number of words generated and mean valence and arousal ratings of the categories within each valence, are listed in Table 1. From the acquired behavioral data, it did not appear that the sex of the fMRI participants significantly influenced the number of words generated, \( F(1,24) = 3,3, p = .57 \), the valence ratings, \( F(1,24) = 3.02, p = .1 \), or the arousal ratings, \( F(1,24) = 2.88, p = .1 \).

Collapsed across sex of participants, number of words generated in a 16.5-sec period did not significantly vary by valence type, \( F(2,48) = 1.05, p = .36 \). As expected, valence ratings did significantly differ among positive, negative, and neutral categories, \( F(2,48) = 193.13, p < .001 \), in the assumed directions, with ratings for positive categories the highest and ratings for negative categories the lowest (Table 1). Also as expected, arousal ratings differed significantly among categories, \( F(2,48) = 85.22, p < .001 \). Post hoc comparisons revealed significantly higher arousal ratings for positive and negative categories than for neutral categories and no significant difference between arousal ratings of positive and negative categories. In short, categories functioned as they were designed; that is, they evoked the expected levels of rated valence and emotional arousal, and rated emotional arousal was equated between positive and negative categories. Further, since there were no differences in number of words generated for categories of different valence, generation rate is unlikely to have influenced fMRI comparisons for emotional valence.

Functional Imaging Results

Brain regions associated with emotional connotation were identified with direct comparisons of the three word generation tasks, positive, negative, and neutral. These comparisons, collapsed across sex of participants, were performed with a voxelwise one-way repeated measures ANOVA for valence with area under the curve of the HRF as the dependent variable. In addition, because sex effects have been reported in two previous fMRI paradigms involving viewing pictures (Lang et al., 1998) or faces (Schneider, Habel, Kessler, Salloum, & Posse, 2000) with positive or negative emotional connotation the effect of sex of participants and its interaction with valence was investigated using a two-way voxelwise ANOVA. These analyses were conducted with a statistical threshold of \( p < .005 \) and a cluster threshold of volume \( >200 \mu l \). For the one-way repeated measures ANOVA for valence, collapsed across sex of participants, significant activity was found in both rostral frontal and retrosplenial/posterior cingulate cortices (Figure 2). The cluster in the rostral frontal cortex extended bilaterally, with the maximum intensity (MI) in the left hemisphere, with Talairach coordinates (Talairach & Tournoux, 1988) of \(-2,60,12\). The cluster was located primarily in medial BA 10 but also extended to the anterior most portions of BA 9. The retrosplenial/posterior cingulate

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**Figure 1.** Silent word generation task (white intervals) alternated with silent word repetition as a baseline task (black intervals) during scanning. Baseline intervals varied in length (9.9, 16.5, and 23.1 sec) and number of items repeated (4, 7, and 10 words, respectively), and were pseudorandomly interspersed in the 9.5 cycles of the imaging runs. Silent word generation alternated between generating words with positive emotional connotation (e.g., vacations), generating words with negative emotional connotation (e.g., weapons), and generating emotionally neutral words (e.g., buildings).

**Table 1.** Behavioral Results of the fMRI Participants \( (N = 26) \) Collapsed Across Sex

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
<th>Neutral</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Words generated</td>
<td>6.44</td>
<td>1.42</td>
<td>6.29</td>
</tr>
<tr>
<td>Valence rating</td>
<td>8.00</td>
<td>.99</td>
<td>2.28</td>
</tr>
<tr>
<td>Arousal rating</td>
<td>6.11</td>
<td>1.94</td>
<td>4.99</td>
</tr>
</tbody>
</table>

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This cluster also extended bilaterally, with the MI at midline, 0, −48, and 30. This cluster, which centered upon the same region as that reported by Maddock and Buonocore (1997), was located primarily in BA 30 as well as the portion of BA 23 superior and posterior to the splenium of the corpus callosum.

To further examine areas of activity found to be significant on the one-way ANOVA, a mask of the significant clusters was generated and subjected to follow-up voxelwise t tests for positive versus neutral emotional connotation, for negative versus neutral emotional connotation, for neutral versus emotional connotation, and for positive versus negative emotional connotation with a statistical threshold of \( p < .005 \) and a cluster threshold of volume >200 \( \text{mm}^3 \). Table 2 shows all clusters of significant activity for positive versus neutral and negative versus neutral \( t \) tests that were consistent with significant areas of activity on the ANOVA. For positive versus neutral emotional connotation, significant clusters of bilateral activity were noted for both rostral frontal and retrosplenial/posterior cingulate cortices. Likewise, for negative versus neutral emotional connotation, significant clusters of bilateral activity were noted for both rostral frontal and retrosplenial/posterior cingulate cortices. Other than these areas of a priori interest, additional regions of activation were circumscribed to the left middle frontal gyrus and areas along the left temporal lobe and left temporoparietal junction (Table 2).

Brain regions more involved in the generation of words to neutral than emotional connotation were examined with a follow-up voxelwise \( t \) test in which activity associated with words to positive and negative emotional connotations was collapsed. Table 3 reveals all clusters of significant activity for the neutral versus emotional \( t \) test that were consistent with significant areas of activity on the ANOVA. Brain regions more active during generation of words with neutral emotional connotation included a posterior cingulate region lateral and inferior to the retrosplenial region associated with positive and negative emotional connotations. This region of activity extended back to the peristriate cortex (BA 19). The two other clusters of activation identified with the neutral versus emotional \( t \) test were circumscribed to the occipital cortex suggesting relatively more visualization during neutral word generation compared to emotional word generation. Two other brain regions were relatively more active during neutral word generation, one centering in the left precentral gyrus and the other centering in the left middle temporal gyrus. Thus, generation of neutral words engaged a different region of the left retrosplenial/posterior cingulate cortex that was lateral and inferior to the area involved in processing words with positive or negative emotional connotation. The rostral frontal area that was engaged during generation to words with positive and negative emotional connotation was not active during generation of neutral words. While the lateral frontopolar cortex has

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Table 2: Clusters of significant activity for positive versus neutral and negative versus neutral \( t \) tests that were consistent with significant areas of activity on the ANOVA.

Table 3: Clusters of significant activity for the neutral versus emotional \( t \) test that were consistent with significant areas of activity on the ANOVA.
been activated during generation of neutral information in other paradigms (for a review, see Christoff & Gabrieli, 2000), we did not find a similar pattern of activity increase during neutral word generation in this region. As neutral word generation was directly compared to other word generation tasks (also involving complex processing of internally generated information), this area of activity may have been cancelled by comparable activity associated with the comparison tasks.

**Time Course Analysis**

Activation in rostral frontal and retrosplenial/posterior cingulate cortices was found when comparing generation of words with emotional connotation (positive or negative) versus generation of emotionally neutral words (Figure 2). To further determine the time course associated with these differences, a mask of each region was generated, and averaged HRFs for each valence were entered into a repeated measures two-way Valence x Time (image number) ANOVA to examine differences in HRF signal amplitudes in the time domain between the three valence types. To model the entire HRF associated with the 5 images of blocked word generation, we specified 11 images (beginning at the onset of the first image of word generation) to be modeled in order to capture the entire HRF from onset to return to baseline.

For the rostral frontal cortex, the Valence x Time interaction was significant, $F(20,500) = 10.37, p < .0001$. In the case of this cortex, contrasts revealed that from Images 3 through 8, the HRF amplitudes for positive and negative emotional connotation were significantly greater than the HRF amplitude for neutral emotional connotation. For the retrosplenial/posterior cingulate cortex, the Valence x Time interaction was also significant, $F(20,500) = 13.78, p < .0001$. Contrasts revealed that during Images 3 through 7, the HRF amplitudes for positive and negative emotional connotation were significantly greater than the HRF amplitude for neutral emotional connotation. For both ROIs, the courses for positive and negative emotional connotation did not significantly differ at any time point other than during Image 7 in the retrosplenial/posterior cingulate cortex.

**Table 2.** Volumes of Tissue (>200 µl) Showing Significant Activity Changes ($p < .005$) for Positive and Negative versus Neutral Word Generation

<table>
<thead>
<tr>
<th>Location</th>
<th>Positive &gt; Neutral Anatomic Area (max $t$ loc) max $t$, volume in µl</th>
<th>Negative &gt; Neutral Anatomic Area (max $t$ loc) max $t$, volume in µl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rostral frontal cortex</td>
<td>L and R BAs 9, 10 ($-3, 60, 12$), $t = 6.12$, 3035 µl</td>
<td>L and R BAs 9, 10 ($-4, 60, 29$), $t = 5.17$, 1807 µl</td>
</tr>
<tr>
<td>Retrosplenial/posterior cingulate cortex</td>
<td>L and R, BAs 23, 30, 31 ($0, -48, 30$), $t = 5.53$, 3422 µl</td>
<td>L and R BAs 23, 30, 31 ($0, -47, 29$), $t = 4.50$, 1042 µl</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>L BA 9 ($-22, 42, 31$), $t = 3.83$, 244 µl</td>
<td>L BA 22, 40 ($-54, -44, 23$), $t = 3.96$, 300 µl L BAs 22, 39 ($-40, -55, 26$), $t = 4.84$, 872 µl</td>
</tr>
<tr>
<td>Temporoparietal junction</td>
<td>L BAs 22, 40 ($-57, -51, 24$), $t = 4.44$, 772 µl, L BAs 22, 39 ($-48, -63, 16$), $t = 4.52$, 595 µl</td>
<td>L BA 21 ($-50, -30, 1$), $t = 4.16$, 413 µl</td>
</tr>
<tr>
<td>Superior and middle temporal gyrus</td>
<td>L BAs 21, 22 ($-50, -24, 0$), $t = 4.25$, 518 µl</td>
<td></td>
</tr>
</tbody>
</table>

BA = Brodmann’s area (according to Talairach & Tournoux, 1988); max $t$ = maximum $t$ value within given cluster of activity. Other abbreviations are as follows: L = left, R = right.

**Table 3.** Volumes of Tissue (>200 µl) Showing Significant Activity Changes ($p < .005$) for Neutral versus Emotional (Positive and Negative Categories Collapsed) Word Generation

<table>
<thead>
<tr>
<th>Location</th>
<th>Anatomic Area (max $t$ loc) max $t$, volume in µl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior cingulate/occipital cortex</td>
<td>L BA 30, extending to BA 19 ($-12, -55, 12$), $t = -4.83$, 1021 µl</td>
</tr>
<tr>
<td>Precentral and middle frontal gyrus</td>
<td>L BA 6 ($-43, 4, 36$), $t = -4.23$, 586 µl</td>
</tr>
<tr>
<td>Middle and superior temporal gyrus</td>
<td>L BA 37 ($-59, -49, -9$), $t = -5.13$, 1667 µl</td>
</tr>
<tr>
<td>Lingual gyrus/other visual areas</td>
<td>L BAs 19, 17 ($-29, -68, 32$), $t = -5.63$, 970 µl</td>
</tr>
<tr>
<td></td>
<td>BAs 18, 19 ($-15, -74, 7$), $t = -4.15$, 439 µl</td>
</tr>
</tbody>
</table>

BA = Brodmann’s area (according to Talairach & Tournoux, 1988); max $t$ = maximum $t$ value within given cluster of activity. Other abbreviations are as follows: L = left, R = right.
Thus, in both rostral frontal and retrosplenial/posterior cingulate cortex, HRF amplitudes for words with positive and negative emotional connotation were consistently greater than the HRF amplitude for emotionally neutral words. Furthermore, visual comparison of the HRF curves between rostral frontal and retrosplenial/posterior cingulate cortex revealed different time courses within valence across these areas. To confirm these observable differences, for each valence, the averaged HRF for each of the two brain regions was entered into a repeated measures two-way Brain Region × Time (image number) ANOVA to determine if the signal amplitudes within valence differed as a function of brain region down the time domain.

For positive valence, the Area × Time interaction term was significant, $F(10,250) = 12.02, p < .0001$. Contrasts revealed that from Images 4 through 7, the amplitude of the HRF to positive valence in the rostral frontal cortex was significantly greater than that of the HRF in the retrosplenial/posterior cingulate cortex. Thus, after Image 3, the HRF in the retrosplenial/posterior cingulate cortex begins to decline whereas that in the rostral frontal cortex continues to rise to peak. This difference in courses carries out to Image 7, after which both HRFs in both cortices fall to near-baseline levels. Therefore, in response to positively valenced categories, the HRF in the retrosplenial/posterior cingulate cortex peaks much earlier (Image 3) and follows a much shorter time course than the HRF in the rostral frontal cortex, which appears to peak at Image 4 and return to baseline at Image 8. Indeed, the time course in the retrosplenial/posterior cingulate cortex is approximately what would be expected from a response to a single event, the presentation of the positively valenced category at the beginning of word generation trials. In contrast, the rostral frontal HRF seems representative of the entire generation epoch, returning to baseline levels a few seconds after termination of the generation trial.

For negative valence, the interaction term was again significant, $F(10,250) = 9.44, p < .0001$. Contrasts revealed that from Image 1 to 2, the HRF for the retrosplenial/posterior cingulate cortex has a significantly steeper rise than that of the rostral frontal cortex, or that the rostral frontal cortex exhibits a lag or delay, whereas the retrosplenial/posterior cingulate cortex does not. From Image 3 to 4, the courses again significantly diverge: the HRF in the rostral frontal cortex rises to peak while that of the retrosplenial/posterior cingulate cortex descends towards baseline. Similar to the differences found for positive valence, the HRF in the retrosplenial/posterior cingulate cortex follows a much shorter time course and the HRF amplitude is significantly greater for the rostral frontal cortex for Images 4 through 6.

Finally, for neutral valence, the interaction term was significant, $F(10,250) = 9.57, p < .0001$. Contrasts revealed that from Image 3 to 4, trajectories of the HRFs in the two cortical areas diverge due to a sharp drop of the retrosplenial/posterior cingulate HRF to below baseline levels. From Images 4 to 6 where the retrosplenial/posterior cingulate HRF is at below baseline levels, the amplitude of the rostral frontal HRF was significantly greater than that of the retrosplenial/posterior cingulate HRF. The sharp rise of the HRF curve in the retrosplenial/posterior cingulate cortex back to baseline levels from Image 6 to 8 also resulted in significant differences in trajectories of the neutral HRF in the retrosplenial/posterior cingulate area versus that of the neutral HRF in the rostral frontal area.

**Laterality Analysis**

For the rostral frontal and retrosplenial/posterior cingulate regions, where activity extended across the midline, it was important to examine lateralization in the context of valence. As noted previously, there were three competing hypotheses regarding lateralization and valence: (a) that the left hemisphere would dominate processing because the stimuli were verbal, (b) that the right hemisphere would dominate processing because of emotional content, and (c) that the left hemisphere would be more involved in processing positive emotions, and the right hemisphere would be more involved in processing negative emotions. The clusters were divided into right and left hemisphere components (Table 4). In comparisons to neutral emotional connotation, both positive emotional connotation and negative emotional connotation demonstrate a clear majority of the cluster in the left hemisphere. These data are incompatible with the right-hemisphere hypothesis of emotional processing. Because negative emotional connotation showed an even greater left-hemisphere bias

<table>
<thead>
<tr>
<th>Location</th>
<th>Positive &gt; Neutral</th>
<th>Negative &gt; Neutral</th>
</tr>
</thead>
<tbody>
<tr>
<td>L rostral frontal (BAs 9, 10)</td>
<td>2366 µl; 78% total cluster</td>
<td>1726 µl; 96% total cluster</td>
</tr>
<tr>
<td>R rostral frontal (BAs 9, 10)</td>
<td>669 µl; 22% total cluster</td>
<td>81 µl; 4% total cluster</td>
</tr>
<tr>
<td>L retrosplenial/posterior cingulate cortex (BAs 23, 30, 31)</td>
<td>2211 µl; 65% total cluster</td>
<td>858 µl; 82% total cluster</td>
</tr>
<tr>
<td>R retrosplenial/posterior cingulate cortex (BAs 23, 30, 31)</td>
<td>1211 µl; 35% total cluster</td>
<td>184 µl; 18% total cluster</td>
</tr>
</tbody>
</table>
than positive emotional connotation for both rostral frontal and retrosplenial/posterior cingulate cortices, the data are also incompatible with the hypothesis that negative emotional connotation would show a right-hemisphere bias. Thus, at least for these two cortical regions, data are most consistent with a left-hemisphere bias due to the verbal nature of the stimuli.

As mentioned earlier, other regions of the stimuli that were significant on the one-way valence ANOVA and subsequent positive versus neutral and negative versus neutral t tests were circumscribed to the left hemisphere (Table 2) for both positive emotional connotation and negative emotional connotation. Again, these data are consistent with a left-hemisphere bias because of the verbal nature of the stimuli and are inconsistent with other hypotheses.

Also with respect to laterality, the voxelwise t test for generating words with negative versus positive emotional connotation revealed only two significant clusters of activity. In both cases, activity either favored the left hemisphere or was located entirely within the left hemisphere. Activity for the retrosplenial/posterior cingulate region was greater for positive than negative emotional connotation. This region centered in the left hemisphere (MI = 50, 22), with some activity crossing over to the right hemisphere. The second area showed greater activity for negative than positive emotional connotation and was located in the left inferior frontal sulcus (MI = 46, 18, 28). Thus, activity differences in generating words with positive versus negative emotional connotation are located primarily in the left hemisphere regardless of valence.

Finally, a Sex × Valence ANOVA with repeated measures on valence was also performed to assess sex differences and the interaction of sex with valence. Two clusters for the sex main effect survived the statistical threshold of p < .005 with a cluster threshold of volume >200 μL. The first was in the right precentral gyrus (MI = 50, −4, 27), and the second was in the left cerebellum (MI = −28, −42, −22). In both cases, the clusters were more active for men than for women. Thus, regardless of valence, men showed more activity in the right precentral gyrus and the left cerebellum than women. The interaction of sex of participants and valence of words generated showed no significant areas of activity.

DISCUSSION

The major finding of the current study is that generating words with positive or negative emotional connotation led to unique activity bilaterally in rostral frontal and retrosplenial/posterior cingulate cortices when directly compared to generating words with neutral emotional connotation. In addition, examination of time courses in these two areas revealed differences that may correspond to unique roles during processing of emotional connotation. With respect to laterality, activation in these areas, while bilateral, showed consistently greater lateralization to the left hemisphere. The relative proportion of these sizable clusters in the right hemisphere did not indicate any support for either the valence hypothesis or the right-hemisphere hypothesis. Rather, it appears that the verbal nature of the task led to a strong left-hemisphere bias regardless of valence. In addition, the sex of participants did not further influence differences in brain activation associated with word generation to positive, negative, and neutral categories.

An examination of the hemodynamic response curves in the rostral frontal cortex and in retrosplenial/posterior cingulate cortex (Figure 2) provides clues to their respective functions in mediating processing of emotional connotation. First, it is apparent that generation to positive and negative emotionally valenced categories, but not neutral categories, led to significant activation in these areas. Despite this common pattern, the time courses between these areas are quite different. The functional activity in the retrosplenial/posterior cingulate cortex begins to increase immediately after the stimulus presentation, peaks relatively early after stimulus presentation, and then returns to baseline before the end of word generation, much like an event-related response. We suggest that the role of this cortex is in the evaluation of an external stimulus with emotional salience, which in this case was the category cue. This hypothesis is consistent with the assessment of Heilman et al. (1993) that the posterior cingulate cortex evaluates the motivational significance of external stimuli.

In the case of the rostral frontal cortex, the response is slightly delayed, remains throughout the active generation period, and then lingers for an additional 4 to 5 sec after word generation has ended before falling to baseline. Therefore, the rostral frontal cortex is implicated in the process of generation of words with emotional connotation. This finding raises two interesting questions. First, is the rostral frontal cortex involved in evaluating emotional connotation only relative to some kind of behavioral output (e.g., word generation) or does it have a more general function of processing emotional connotation in any circumstance? In addressing this first question, it should be noted that this is the third demonstration of rostral frontal activity in processing words with emotional connotation. In the first instance (Crosson et al., 1999), generation of words with emotional connotation was compared to generation of emotionally neutral words, similar to the current study. However, Crosson et al. (1999) did not distinguish between positive and negative connotation. By contrast, the current study establishes that the rostral frontal cortex is active during word generation for both words with positive emotional connotation and words with negative emotional connotation. In the second instance (Crosson et al., 2002), semantic monitoring of words with emotional connotation was...
compared to semantic monitoring of sensory stimuli (i.e., auditory presentation of words with emotional connotation vs. emotionally neutral words). Subjects in this experiment were not just listening to words but were actively involved in making semantic decisions about the words. Thus, it can be argued that all studies that have shown rostral frontal activity in processing words with emotional connotation have involved active output of some kind. A future direction would be to evaluate whether this area of activity occurs during processing of emotional connotation when no behavioral output is required.

The second question regarding the sustained activity in the rostral frontal cortex is whether activity in this area only occurs in the presence of some level of sustained mood change (positive or negative). Indeed, at least two previous imaging studies using visual stimuli and mood induction procedures also reported brain activity in this rostral frontal area (Teasdale et al., 1999; Lane, Reiman, Ahern, et al., 1997). Unfortunately, as this particular experiment involving word generation was not intended to serve as a mood induction procedure (MIP), we did not assess whether mood changes occurred during participation in the experiment. Generally, MIPs in imaging experiments have involved sustained exposure (typically longer than 16 sec) of emotionally evocative material (almost always with a visual component) of one valence. The Teasdale et al. (1999) study and the Lane, Reiman, Ahern, et al. (1997) study, both of which were attempting mood induction, involved longer stimulus exposures (30 and 120 sec, respectively) within valence than the current study involving only 16.5-sec periods of within-valence exposure. Also during MIPs, in most previous imaging experiments (e.g., Schneider et al., 2000; Lane, Reiman, Ahern, et al., 1997) and otherwise (e.g., the Velten MIP; for a review, see Gerrads-Hesse, Spies, & Hesse, 1994), the participant is instructed to attempt to experience the desired mood state. In contrast, we did not provide any suggestions or directions regarding mood induction. Thus, our procedures differed from typical MIPs. It is possible that the rostral frontal cortex (BA 9, 10) is involved both in experiencing mood and in processing emotional connotation, in much the same way that the premotor cortex is involved in both action planning and in processing action semantics (i.e., action verb and tool knowledge; see Kellenbach, Brett, & Patterson, 2003; Pulvermüller, 2001; Chao & Martin, 2000; Pulvermüller et al., 2000). Nonetheless, we must concede that we did not attempt to measure if changes in mood occurred during our experiment. Therefore, future studies of emotional processing should assess self-ratings of mood in addition to valence and arousal ratings along with psychophysiological measures to further explore this question.

Differences in type and intensity of emotional stimuli across studies of emotional processing may contribute to inconsistencies in this literature in terms of the laterality of findings and the presence or absence of sex differences. In terms of laterality, while the current study did not support either the valence or right-hemisphere hypothesis, a likely explanation is that the language demands of this task outweighed any hemispheric differences that might occur in response to the valence of a stimulus. In other words, engaging language cortex in the act of word generation may have dampened right-hemisphere activity secondary to transcortical inhibition of cortices not devoted to language generation (Gazzaniga, 1998). One functional imaging study that has found support for the valence hypothesis used pictures rather than words (Canli et al., 1998). Thus, the use of words with this study, rather than pictures, may be the source of the discrepancies between the current findings and those of Canli et al. (1998) that support the valence hypothesis. In a similar vein, the use of words rather than pictures or film clips in this study may have also precluded findings of sex differences in processing positive versus negative emotional connotation that have been reported in two previous functional imaging studies (Schneider, et al., 2000; Lang et al., 1998). Future studies that attempt to disentangle these variations in methodologies would be helpful in determining what variables (e.g., processing modality, emotional valence, type of emotional stimuli, duration of exposure) influence direction of findings of hemispheric specialization and sex differences.

In closing, the current study is unique not only in showing activity of both rostral frontal and retrosplenial/posterior cingulate cortices in processing words with emotional connotation, but it also speaks of differences in the roles of these cortices in processing emotional connotation. Based on the different time courses within these areas as well as what is known about their respective functions, we are suggesting that the retrosplenial/posterior cingulate cortex is involved in processing the emotional significance of sensory stimuli, while the rostral frontal cortex may be involved in processing emotional connotation when generation of some kind of active output is required. Regarding the status of emotional connotation as a semantic attribute, this is a provocative hypothesis. We know of no other instance in which it has been suggested that the cortex that processes a specific semantic attribute depends on whether an external stimulus is being evaluated or whether some significant output is being generated. With respect to this hypothesis, future research should address two questions: First, can the hypothesis be verified in other research designs? Second, if the hypothesis can be further verified for emotional connotation, is this anterior–posterior division for response generation versus sensory processing unique to emotional connotation, or can it be applied to other semantic attributes such as visual form or object function?
METHODS

Participants

Twenty-six (13 men, 13 women) strongly right-handed [Edinburgh Handedness Inventory (Oldfield, 1971), M = 81.9, SD = 14.3] volunteers participated (age 18–49 years, M = 31.5 years, SD = 9.9; education 13–20 years, M = 16.4 years, SD = 1.7 years). Male and female participants did not significantly differ in terms of years of education, t(24) = −.56, p = .58, or age, t(24) = −.95, p = .35. Potential participants were excluded if they reported a history of neurological disease, major psychiatric disturbance, learning disability, attention deficit disorder, or substance abuse, or if they reported current use of psychoactive medications. Potential risks were explained, and informed consent was obtained from participants according to institutional guidelines established by the Health Center Institutional Review Board at the University of Florida.

Materials and Methods

Experimental Stimuli

Emotional and neutral categories were extrapolated from nouns listed in the Affective Norms for Emotional Words (ANEW, Bradley, Cuthbert, & Lang, 1988) corpus. This corpus provides words with ratings on a valence dimension from negative to positive (range, 1.00 to 9.00) and an arousal dimension from low to high arousal (range, 1.00 to 9.00). Categories were chosen to be representative of items from this corpus with positive, negative, and neutral emotional connotation. ANEW was also used to select emotionally neutral words for the repetition baseline condition. A behavioral pilot study with 12 different subjects (6 males, 6 females; age 25–34 years, M = 28.5, SD = 3.4; education 18–21 years, M = 19.0, SD = .95) was conducted to equate number of words generated in a 16.5-sec time period across the valence of categories and to equate arousal ratings across positive and negative categories. We wanted to equate arousal ratings between positive and negative categories, as laterality differences have only been found in the past when arousal has been equated (Canli et al., 1998). As a result of the pilot study, 45 of 80 piloted categories were selected for the fMRI study.

Experimental Tasks

During each of the four functional imaging runs, blocks of silently generating words to categories with positive, negative, or neutral emotional connotation alternated with a baseline task of silent repetition of emotionally neutral words (Figure 1). A blocked presentation format was used because pilot studies indicated a blocked paradigm produced hemodynamic responses of greater amplitude and consistency than an event-related paradigm. The use of a baseline of neutral word repetition, rather than rest, has also been found to increase sensitivity of comparisons between word generation tasks (Crossoen et al., 1999). During category generation, participants heard a category and silently generated as many exemplars as possible during a 16.5-sec word generation period. Categories with positive (e.g., desserts), negative (e.g., disasters), or neutral (e.g., containers) emotional connotation were presented in a pseudorandom order, such that each functional run consisted of three categories from each valence (positive, negative, and neutral). During alternating baseline periods of variable length (either 9.9, 16.5, or 23.1 sec, distributed within runs in a pseudorandomized order), participants silently repeated emotionally neutral words, with 4 words to repeat during the 9.9-sec baseline; 7 words to repeat during the 16.5-sec baseline; and 10 words to repeat during the 23.1-sec baseline. The number of words to repeat was matched with the mean number of words generated in a 16.5-sec period, determined by the behavioral pilot.

The onset of generation blocks was marked by the cue, “generate,” while baseline repetition blocks commenced with the cue, “repeat.” All words, cues, and categories were delivered binaurally via acoustically insulated air conduction tubes connected to hollow foam earplugs using a Kenwood KR-A4070 amplifier, Realistic 31-2005 Tenband stereo frequency equalizer, and JBL 16-Ω speaker. Prior to the experiments, auditory threshold in the scanner was determined for each subject using recognition of target words during scanner operation. Volume was adjusted by adding a constant 35 dB to each subject’s auditory threshold.

Four of five possible category lists were administered to each experimental subject during the four imaging runs, with the order of these runs pseudorandomized across participants. Following scanning, a fifth category list was administered outside of the scanner to provide information about the generation rate for categories of emotionally positive, negative, and neutral valence. The list administered outside the scanner was varied between subjects in a random fashion with the constraint that each list be used approximately an equal number of times. Following completion of the fifth list, fMRI participants rated all 45 categories for valence and arousal.

Image Acquisition

Each experimental run consisted of nine 16.5-sec periods of word generation during which 5 images were acquired. The baseline state was repetition of emotionally neutral words for 9.9, 16.5, or 23.1 sec (corresponding to 3, 5, and 7 images respectively). Length of baseline periods was varied pseudorandomly to mitigate low-frequency periodic and quasiperiodic physiologic artifacts. Each length of baseline was used an equal number of times, except that an extra 16.5-sec baseline period was added to the end of each run. Thus, for each functional imaging run, there was an average of 10 images per word generation–baseline cycle, with 95 images total per functional run. By
staggering the baseline condition, the onset of the experimental task (word generation) was also aperiodic. The length of word generation blocks did not vary so that a single HDR could be modeled for each block using the deconvolution technique.

Whole-brain imaging was performed on a 1.5-T GE Signa scanner using a dome-shaped quadrature radio frequency head coil. The field was aligned such that the interhemispheric fissure was within 1° of vertical. For fMRI sequences, 22 slices (5.8–7.0 mm thick) were acquired. The plane between the eleventh and twelfth functional image slices was centered at the interhemispheric fissure for equal coverage of both hemispheres. Images were obtained using a two-spiral gradient-echo sequence with the following parameters: TE = 40 msec, TR = 1650 msec, FA = 65°, FOV = 180 mm. After functional image acquisition, structural images were acquired for 124 1.3-mm-thick sagittal slices, using a 3-D spoiled GRASS volume acquisition (TE = 7 msec, TR = 27 msec, FA = 45°, NEX = 1, FOV = 24 cm, matrix size = 256 × 192).

Image Analysis

Functional images were analyzed and overlaid onto anatomic images with Analysis of Functional Neuroimages (AFNI) software (Cox, 1996). To minimize effects of head motion, time series of images were spatially registered in 3-D space. For each subject, mean slice signal intensities were normalized to the grand mean of slice intensity across functional runs. Voxels where the standard deviation of the signal change exceeded 5% of the mean signal were set to zero to decrease large vessel effects and residual motion artifact. Images were visually inspected for gross artifacts and were viewed in cineloop 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 removed from further analyses. Data from 3 of 29 subjects who participated were eliminated because of motion artifact, leaving the 26 subjects who were described above.

Four runs of 95 images each were concatenated into a single time series of 380 images for each of the 22 functional image slices. Then, HRFs were deconvolved from the 380-image time series on a voxel-by-voxel basis. Each HRF was modeled using the 11 TR periods that directly followed each category cue. Eleven TR periods were modeled in order to capture the entire hemodynamic response from its onset to its return to baseline. For each voxel, a single HRF was deconvolved separately for positive, negative, and neutral emotional connotation. Magnitude of response for each condition was operationally defined as area under the curve of the HRF.

Anatomic and functional images were interpolated to volumes with 1-mm³ voxels, coregistered, and converted to the stereotaxic coordinate space of Talairach and Tournoux (1988) using AFNI. HRFS within the 1-mm³ voxels were spatially smoothed using a 3-mm full-width half-maximum (FWHM) Gaussian filter to compensate for variability in structural and functional anatomy across participants. A voxelwise one-way repeated measures ANOVA was performed to determine the effect of valence on the pattern of brain activation during word generation across participants. The effect of sex of participants and its interaction with valence was also investigated using a two-way voxelwise ANOVA. In both cases, area under the HRF curve was the dependent variable. Cluster analyses on resulting statistical parametric maps were conducted. Post hoc t tests were performed on significant clusters identified by each ANOVA to evaluate the direction of differences in HRFS (area under the curve) between the conditions. For both the ANOVA and the subsequent t tests, a volume threshold of 200 µl and a statistical probability threshold of p < .005 were used.

ROI analyses were performed within two clusters that exhibited visibly different temporal evolutions of the HRF according to valence and to spatial region. For the HRFS of each of these two brain areas, a two-way repeated measures ANOVA was performed for each brain region across valence type (3 levels) and number of TR periods or images modeled in deconvolution (11 levels). In addition, a two-way repeated measures ANOVA was performed for each valence type across brain regions (2 levels) and number of TR periods or images modeled in deconvolution (11 levels).

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The data reported in this experiment have been deposited in the fMRI Data Center (http://www.fmrib.org). The accession number is 2-2003-113YQ.

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