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The Emotional Modulation of Cognitive Processing: An fMRI Study

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Abstract

■ The functional neuroanatomy of visual processing of surface features of emotionally valenced pictorial stimuli was examined in normal human subjects using functional magnetic resonance imaging (fMRI). Pictorial stimuli were of two types: emotionally negative and neutral pictures. Task performance was slower for the negatively valenced than for the neutral pictures. Significant blood oxygen level dependent (BOLD) increases occurred in the medial and dorsolateral prefrontal cortex, midbrain, substantia innominata, and/or amygdala, and in the posterior cortical visual areas for both stimulus types. Increases were greater for the negatively valenced stimuli. While there was a small but significant BOLD decrease in the subgenual prefrontal cortex, which was larger in response to the negatively valenced pictures, there was an almost complete absence of other decreases prominently seen during the performance of demanding cognitive tasks [Shulman, G. L., Fiez, J. A., Corbetta, M., Buckner, R. L., Miezin, F. M., Raichle, M. E., & Petersen, S. E. (1997). Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. *Journal of Cognitive Neuroscience, 9,* 648–663]. These results provide evidence that the emotional valence and arousing nature of stimuli used during the performance of an attention-demanding cognitive task are reflected in discernable, quantitative changes in the functional anatomy associated with task performance. ■

INTRODUCTION

It has long been recognized that cognitive and emotional processes are closely intertwined. Cognitive activity can attenuate emotional states and conversely, emotional and motivational factors can significantly affect cognitive performance (for a recent review, see Drevets & Raichle, 1998). Although the existence of an interrelationship between cognition an emotion is intuitively appealing, as is commonly manifest in human behavior, few empirical data exist to characterize its neural basis.

The neural correlates of these interactions in humans have largely been studied in patients with brain injury, beginning with the landmark case of Phineas Gage (Damasio, 1994; Bigelow, 1850; Harlow, 1848, 1868). While the studies of Gage and like patients (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999; Bechara, Damasio, Damasio, & Anderson, 1994; Bechara, Tranel, Damasio, & Damasio, 1996; Bechara, Damasio, Tranel, & Damasio, 1997; Benton, 1991; Saver & Damasio, 1991; Damasio, Tranel, & Damasio, 1990; Eslinger & Damasio, 1985) have strongly implicated areas within the orbital and medial prefrontal cortex and their connections with the amygdala, hypothalamus, and brainstem, little is known directly about the neural instantiation of cognition–emotion interactions in the normal human brain.

Clues concerning the normal interaction of cognition and emotion come from studies of the neural correlates of human cognition with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). From these studies have emerged observations that are consistent with a dynamic interplay between cognition and emotion (for reviews, see Bush, Luu, & Posner, 2000; Mayberg et al., 1999; Drevets & Raichle, 1998). Areas consistently implicated in emotional processing, such as the amygdala and a variety of areas within the ventral medial prefrontal cortex decrease their activity during the performance of attentionally demanding cognitive tasks (e.g., see Figure 1A and B).

More recently, it has been demonstrated that the degree to which these reductions occur reflects a combined effect of the attentional demands of the task, which cause reductions, and accompanying performance anxiety, which attenuate those reductions (Simpson, Drevets, Snyder, Gusnard, & Raichle, 2000; Simpson, Snyder, & Raichle, 2000). Reductions appear greatest when attentional demands are high and performance anxiety is minimal. Reduction are least when

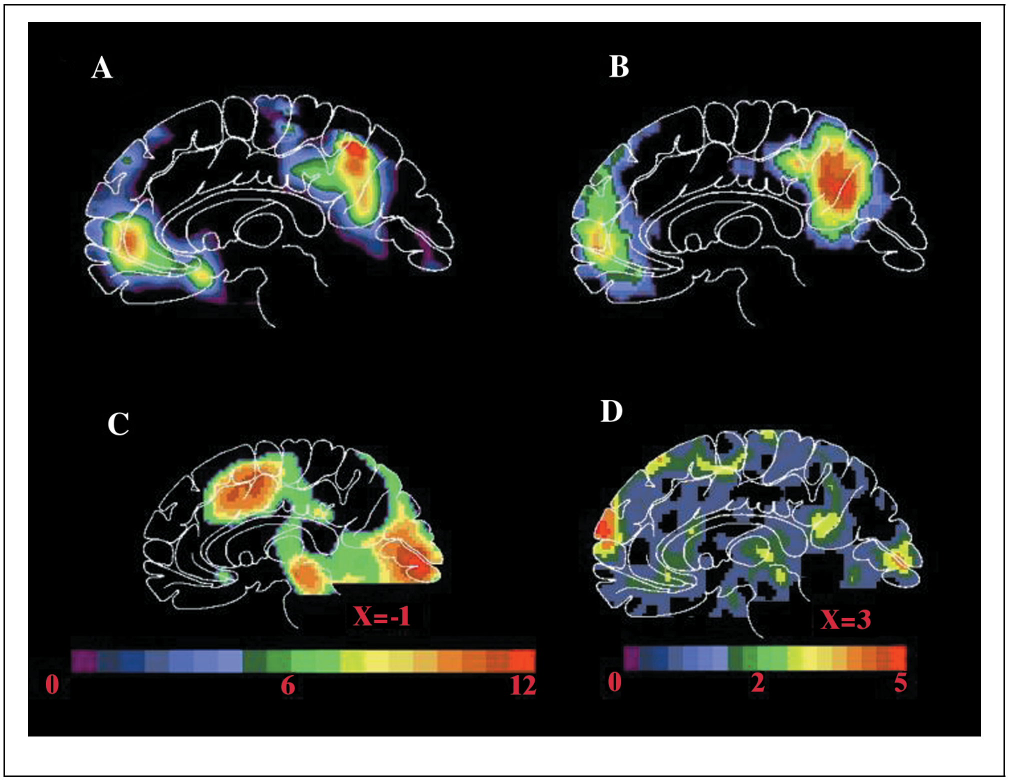

Figure 1. Midline sagittal images obtained with PET (upper left) and fMRI (upper right, lower left and lower right). (**A**) Decreases in blood flow measured with PET while practiced subjects generated verbs for visually presented nouns (these data are adapted from Raichle et al., 1994). The control state was passive visual fixation. The data illustrate decreases regularly seen along the midline during the performance of attention-demanding cognitive tasks (Shulman et al., 1997). (**B**) The same experiment depicted in the upper left image now performed using fMRI (unpublished data four subjects) to illustrate the ability of fMRI to detect responses when present in ventral medial prefrontal cortex despite the presence of significant susceptibility artifacts in the area (Ojemann et al., 1997). (**C**) An fMRI image of the main effect of time (Table 2) demonstrating the prominent changes in the dorsal anterior cingulate, visual cortex, and brainstem. The color bar indicates *z* scores. (**D**) An fMRI image of the effect of picture valence (Table 2) demonstrating a prominent response along the anterior midline in BA 9 as well as smaller responses in the posterior cingulate and brainstem. All changes represent increases in activities that were greater for the negatively valenced pictures. The color bar indicates *z* scores.

attentional demands and performance anxiety are both either high or low.

These findings are consistent with the hypothesis that cognitive activity can attenuate emotional states in infants (Harman & Fox, 1997), normal adults (Derryberry & Rothbart, 1988), and patients with mood disorders (Posner & Rothbart, 1998). Further, they may provide us with a means to understand the neural instantiation of concepts such as "self-regulation" (Posner & Rothbart, 1998) and "emotion regulation" (Gross, 1999; Levenson, 1999), thereby providing a theoretical basis for clinical treatments such as cognitive behavioral therapy (Beck & Clark, 1997; Rachman, 1997).

While the above observations support the view that an interaction between cognition and emotion is reflected in discernable changes in normal brain functional anatomy, further tests of this hypothesis are needed. In most functional imaging work to date (e.g., for a review, see Shulman et al., 1997) stimuli have been devoid of intended impact. An exception is the study by Whalen et al. (1998) in which they performed a modification of the classic Stroop interference task using neutral and negative words as stimuli. Their results are consistent with other cognitive studies showing reductions in the medial prefrontal cortex at the level of the genu of the corpus callosum. Additionally, they noted a greater reduction in activity with neutral than negative words anticipating subsequent work by us (Simpson, Snyder, et al., 2000).

Following on the work of Whalen et al. (1998), we wished to explore further whether the emotional valence of stimuli employed in a cognitive task could influence the subject's behavior as well as the functional anatomical changes associated with cognitive-task performance.

Therefore, an fMRI study of normal subjects performing a cognitive discrimination task involving the surface features of pictorial stimuli from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1997), with neutral and negative valences, was performed. In this manner, the emotional valence of stimuli could be manipulated systematically in the setting of an attention-demanding cognitive task and its resulting influence on the subject's performance and the functional brain activity evaluated.

In this study, normal young adult subjects viewed pictures selected from the IAPS (Lang et al., 1997) during fMRI. Two-thirds of the pictures were neutrally valenced and considered minimally arousing while the remaining one third were negatively valenced and considered significantly arousing. Pictures were presented for 2 sec in a fixed-interval, single-trial design separated by a gap of 16.52 sec (seven functional

frames). Visual fixation was maintained between pictures on a crosshair. The subjects' task was to determine how many humans, or parts of humans, appeared in each picture. They were instructed to press one key if there were one or less and a second key if there were two or more. In addition to reaction times and the accuracy of responses, behavioral monitoring included the measurement of skin conductance responses (SCR).

RESULTS

Behavioral Performance

Reaction Time

A 2 × 2 × 2 ANOVA (with factors of emotional valence, target response, and presentation order) was performed on the reaction time data. Only reaction times for correct answers were included in the primary analysis. This ANOVA on correct responses showed a significant main effect of valence ($F(1, 16) = 17.4$, $p < .001$); the subjects were slower to respond to the negative pictures. There was also a significant main effect of target response ($F = 14.9$, $p = .001$); the subjects were slower to respond when answering "two." There was a trend for a significant main effect of presentation order ($F = 3.9$, $p = .07$); the subjects tended to be slower to respond the first time that a picture was shown.

There was a significant interaction between valence and presentation order ($F = 4.8$, $p < .05$); the improvement in reaction time on repeat presentation was greater for negative than for neutral pictures.

One-tailed, paired t tests showed a significant slowing in reaction times for incorrect compared to correct responses, both for negative ($p < .0005$) and for neutral ($p < .05$) stimuli.

The reaction time data are summarized in Table 1.

Accuracy

A 2 × 2 × 2 ANOVA with factors as above was used to determine the significance of differences in accuracy. There was a significant main effect of target response ($F = 18.2$, $p < .001$); the subjects were more accurate in responding to both the neutral and the negative pictures when the correct response was "one." There was also a significant main effect of presentation order ($F = 12.0$, $p < .005$); the subjects were more accurate with repeated presentation. This effect of repeated presentation was driven primarily by an improvement in performance for the "two" pictures, as reflected by an interaction between target response and presentation order ($F = 9.1$, $p < .01$).

There was a significant crossover interaction between target response and valence ($F = 6.4$, $p < .05$). While the subjects performed more accurately for negative than neutral pictures when the target response was "two," they were less accurate for the negative than the neutral pictures when the target response was "one." It is noteworthy that this crossover interaction parallels the conditional probabilities of the responses (see Materials and Methods, Experimental Design). There was no significant valence-by-order interaction ($F = 1.5$, $p > .1$).

The accuracy data are summarized in Table 1.

Skin Conductance Responses

Skin Conductance Responses (SCRs) were observed in 7 of the 17 subjects. In the other 10 subjects, no physiological responses were observed. In the 7 subjects for whom responses were observed, SCRs occurred to both negative and neutral stimuli. A repeated-measures ANOVA with valence and run as factors indicated significant main effects of valence, SCRs were greater for negative pictures ($F(1, 6) = 9.9$, $p = .02$); and run, SCRs decreased across runs ($F = 2.5$, $p = .02$).

Table 1. Behavioral Results

Category	*Reaction time, correct (mean ± SD)*	*Reaction time, incorrect (mean ± SD)*	*Percent correct (mean ± SD)*
First presentation, negative, target response = one	2,155 ± 710	2,574 ± 629	96.2 ± 4
Second presentation, negative, target response = one	2,037 ± 819	2,183 ± 700	96.4 ± 6
First presentation, negative, target response = two	2,213 ± 625	2,588 ± 1,067	79.8 ± 16
Second presentation, negative, target response = two	2,013 ± 542	1,996 ± 704	85.1 ± 14
First presentation, neutral, target response = one	1,929 ± 602	3,920 ± 1,951	99.4 ± 1
Second presentation, neutral, target response = one	1,773 ± 613	2,161	99.9 ± 0.5
First presentation, neutral, target response = two	2,048 ± 590	2,313 ± 1,340	72.6 ± 18
Second presentation, neutral, target response = two	1,978 ± 503	2,146 ± 1,004	83.7 ± 25

Reaction time is in milliseconds. Note: 33 percent (20 presentations per subject) of the negative stimuli and 8 percent (10 presentations per subject) of the neutral stimuli had a target response of two.

Table 2. Peak Coordinates of Significant BOLD Responses (Main Effect of Time)

Region	*Brodmann's area (BA)*	*x*	*y*	*z*	*z score*
Increases					
1. R fusiform gyrus	37	37	−55	−16	14.36
2. L fusiform gyrus	37	−29	−57	−14	13.54
3. R extrastriate cortex	18	23	−71	−10	13.47
4. L extrastriate cortex	18/19	−23	−77	−12	13.23
5. L primary motor cortex	4	−41	−29	2	13.04
6. L extrastriate cortex	18	−29	−87	12	12.41
7. R inf. parietal lobule	7	27	−57	48	12.33
8. L primary visual cortex	17	−9	−93	2	12.24
9. R ant. insula	–	31	17	8	12.05
10. SMA[a]	6/32	−9	3	46	12.02
11. R extrastriate cortex	18	17	−95	12	11.78
12. L thalamus	–	−19	−33	2	11.74
13. L ant. insula	–	−31	17	8	11.65
14. R inf. frontal gyrus	44	43	3	32	11.54
15. R extrastriate cortex	19	31	−79	16	11.43
16. medial frontal gyrus	32	3	17	36	11.22
17. L sup. parietal lobule	19	−21	−71	38	11.21
18. Midbrain	–	7	−27	−6	11.14
19. L fusiform gyrus	20	−31	−33	−16	10.64
20. L inf. parietal lobule	7	−29	−53	46	10.50
21. R fusiform gyrus	20	33	−35	−14	10.40
22. R SI/amygdala	–	21	−7	−10	10.27
23. L SI/amygdala	–	−21	−9	−10	10.25
24. R precentral gyrus	4	37	−5	50	9.67
25. L inf. frontal gyrus	44/6	−45	1	30	9.66
26. L posterior insula	–	−45	−9	8	9.41
27. L inf. parietal lobule	40	−55	−29	32	9.32
28. L sup. cerebellum	–	−7	−51	−2	9.30
29. R thalamus	–	19	−13	12	9.07
30. L cerebellum	–	−19	−45	−40	9.03
31. L cerebellar peduncle	–	−7	−29	−24	9.01
32. L cuneus	19	7	−75	32	8.92
33. R posterior insula	–	41	−3	8	8.71
34. R sup. frontal gyrus	9	29	41	32	8.57
35. L posterior cingulate	31	−11	−31	40	8.42
36. L sup. frontal gyrus	10	−27	59	−4	8.05

(continued)

Table 2. *(continued)*

Region	*Brodmann's area (BA)*	*x*	*y*	*z*	*z score*
37. Cerebellum	–	3	−59	−28	7.98
38. R sup. frontal gyrus	6	7	1	66	7.98
39. L precuneus	7	−5	−67	60	7.96
40. R cerebellum	–	23	−43	−38	7.34
41. L cerebellum	–	−25	−69	−44	7.30
42. R orbital cortex	11	27	57	−10	7.18
43. R middle frontal gyrus	10/46	41	47	14	7.04
44. L medial frontal gyrus	45/46	−45	27	22	7.01
45. L orbital cortex	47	−45	45	−6	7.00
46. R sup. temporal gyrus	22	53	−43	22	6.90
47. R inf. temporal gyrus	20	31	−5	−36	6.09
Decreases					
48. R lateral cerebellum	–	51	−65	40	9.29
49. R posterior cingulate	30	23	−45	16	8.48
50. L extrastriate cortex	19	−51	−69	36	8.22
51. SGPFC	24/25	3	19	−8	7.55
52. L middle temp. gyrus	20	−59	−29	−12	6.34

Coordinates (x, y, z) correspond to the atlas of Talairach and Tournoux (1988), where x = distance in mm to the right (+) or left (−) of the midline, y = distance anterior (+) or posterior (−) to the anterior commissure (AC), and z = distance superior (+) or inferior (−) to a horizontal plane through the AC and posterior commissure (PC). The z scores are converted from the F ratios output by the voxel-by-voxel ANOVA. A z score of 5.88 corresponded to a p value of .001, corrected for multiple comparisons. Abbreviations: ant. = anterior, inf. = inferior, L = left, R = right, SI = substantia innominata, SGPFC = subgenual prefrontal cortex, SMA = supplementary motor area, sup. = superior, temp. = temporal.

[a]The supplementary motor area activation extended inferiorly into the dorsal anterior cingulate cortex.

Functional MRI

Voxel-by-Voxel ANOVA: Main Effect of Time (Table 2)

In posterior cerebral cortex blood oxygen level dependent (BOLD) increases were identified bilaterally in occipital, temporal, and parietal cortices including the posterior cingulate; and in subcortical structures including the thalamus and substantia innominata/amygdala bilaterally, the midbrain/brainstem (Figure 1C), and the cerebellum (Table 2).

In the frontal lobe there were increases along the midline in dorsal anterior cingulate cortex and supplementary motor area (Figure 1C); symmetrical responses in the anterior insula; and bilateral responses, more striking on the right, in the dorsolateral prefrontal cortex. There was a highly significant response in the left primary motor cortex undoubtedly related to the right hand key press. There was also a small but significant BOLD decrease along the midline in the subgenual prefrontal cortex (SGPFC; predominantly BA 24/25) (Figure 1C).

Conspicuous by their almost complete absence were decreases in activity along the midline of the prefrontal cortex and in the posterior cingulate and adjacent precuneus as seen regularly in cognitive activation paradigms (compare Figure 1A and B to C and D) (Shulman et al., 1997). This was true for both the negative and neutral pictures when analyzed separately. In fact, there was an actual increase in activity in the posterior cingulate as noted above. The only exception was the SGPFC, also described above.

Voxel-by-Voxel ANOVA: Time-by-Valence Interaction (Table 3)

In all regions the BOLD responses were greater for the negative than for the neutral pictures (see Figure 2 for representative time courses; time courses for all remaining areas have been deposited in the database). The largest differences were again seen bilaterally in the inferior occipital cortices in the vicinity of the fusiform gyrus. In posterior cortices there were also significant

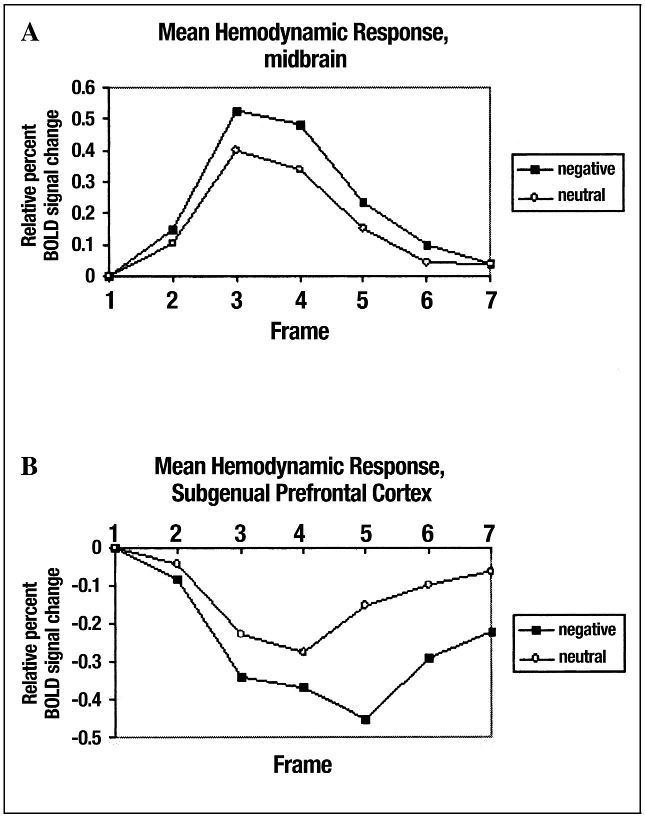

Figure 2. Representative fMRI time courses for two selected regions. Time courses for other regions listed in Tables 2 and 3 are available in the database.

differences in other striate and extrastriate visual areas and in the right superior parietal lobule (Table 3).

All of the limbic and related areas identified in this analysis had larger responses for the negative pictures. These areas included the medial frontal gyrus (BA 9 and 10; Figure 1D), the left posterior cingulate gyrus (BA 23/31; Figure 1D), the midbrain (Figure 1D), the left substantia innominata/amygdala, and the right posterior orbital cortex.

Conspicuous by its absence from this analysis was the SGPFC, although its presence was noted in the main effect of time image (Figure 1C and Table 2). Because of our long-standing interest in the behavior of this area (Öngür, Drevets, & Price, 1998; Drevets et al., 1997) we elected to test this area using a regional ANOVA (see Table 1, region 51 for coordinates). The results of this analysis indicated a significant effect of valence (z = 3.17, p = .002) with greater decreases observed for the negative pictures.

Areas more active for the neutral than the negative pictures were largely confined to the right side of the brain (see Table 3).

Additional Post Hoc Analyses

The picture sets used in this experiment differed in a few ways other than in their emotional valence. As noted above, a higher proportion of negative pictures had a correct answer of "two" (33%) than the neutral pictures (8%). The picture sets also differed in the proportion of pictures containing faces and human figures. While essentially all of the negative pictures contained human figures (i.e., a torso or more complete figure—of 30 negative pictures, 2 contained only hands and 1 depicted the inside of a chest cavity) and 90% of them contained human faces, 37% of the neutral pictures contained human figures, and 28% contained faces.

In an effort to separate out the effects of these differences, additional regional ANOVAs were performed on subsets of the data using regions defined on the time-by-valence interaction image (Table 3) and in the SGPFC. Because these analyses were performed on previously identified regions, and used less than all of the available data, a liberal statistical threshold of $p < .05$ ($z = 1.96$) was used.

A post hoc analysis was performed in which the proportion of "two" answers was matched between the negative and neutral stimuli by removing some of the negative "two" trials from the analysis. With two exceptions, all regions listed in Table 3 exceeded the significance threshold. The exceptions were the right inferior frontal gyrus (region 26 in Table 3; $z = 1.61$) and the midbrain (region 33; $z = 1.85$). A significant difference also remained in the SGPFC region where the magnitude of the response to the negative pictures (i.e., decreased BOLD signal) remained greater than the response to the neutral pictures.

Matching the stimuli for faces resulted in a large data reduction (from 180 "events" (trials) to less than 90 per subject). Nevertheless, in this comparison, where the number of stimuli containing faces was matched for the neutral and negative pictures, many regions exceeded the criterion of $z > 1.96$. The following regions from Table 3 were significant in this analysis: 1–8, 11, 14, 15, 18, 19, 24, 27–30, 32, 34, and 37–39. It is especially noteworthy that the prominent responses in the fusiform gyrus remained significant. Changes in the SGPFC were no longer significant.

An additional one-factor, voxel-by-voxel ANOVA was performed in which the subjects were separated into two groups based on the presence or absence of SCR responding. No significant effects of this between-groups factor were observed.

DISCUSSION

Behavioral Responses

The negative pictures in the IAPS have been shown to produce robust psychophysiological responses (reviewed in Lang, Bradley, & Cuthbert, 1998). Our psychophysiological data, both reaction times and SCRs, are in agreement with these earlier findings and demonstrate an effect of picture valence on the subjects'

Table 3. Peak Coordinates of Significant BOLD Responses (Time-by-Valence Interaction)

Region	*BA*	*x*	*y*	*z*	*z score*
Increases, negative > neutral					
1. R extrastriate cortex	19	43	−69	−8	7.11
2. R fusiform gyrus	37	41	−55	−16	6.95
3. L fusiform gyrus	37	−41	−55	−18	6.76
4. R middle temp. gyrus	19	37	−71	20	6.30
5. L extrastriate cortex	19	−43	−75	−2	6.18
6. L sup. parietal lob.	19	−25	−77	36	6.09
7. R sup. parietal lob.	7	21	−65	54	5.98
8. L medial temp. gyrus	39/19	−41	−77	16	5.53
9. medial frontal gyrus	9	−5	59	34	5.31
10.R inf. frontal gyrus	45/46	47	33	16	5.31
11. medial frontal gyrus	10	1	59	18	5.20
12. L primary vis. ctx.	17	−5	−89	0	4.67
13. R sup. Frontal gyrus	10	27	63	20	4.64
14. L cerebellum	–	−27	−81	−32	4.59
15. L inf. parietal lob.	40	−43	−37	46	4.39
16. L post. cingulate	23/30	−1	−51	22	4.36
17. L inf. frontal gyrus	46	−53	23	16	4.23
18. Cerebellum	–	1	−83	−38	4.18
19. R extrastriate cortex	18/19	37	−87	10	4.18
19. SMA	6	−5	1	48	4.15
21. R primary vis. ctx.	17	15	−93	4	4.08
22. L extrastriate cortex	18	−29	−91	−4	4.07
23. L mid. temp. gyrus	28	−29	1	−26	3.86
24. L sup. temp. gyrus	22	−55	−57	12	3.85
25. L SI/amygdala	–	−17	−11	−6	3.84
26. R inf. frontal gyrus	47	43	17	−2	3.80
27. R inf. frontal gyrus	44	47	3	32	3.72
28. Sup. frontal gyrus	8	1	33	52	3.69
29. L mid. frontal gyrus	6/9	−41	−5	42	3.69
30. Sup. frontal gyrus	8	−1	49	48	3.59
31. R sup. Frontal gyrus	6	27	−5	62	3.54
32. L inf. frontal gyrus	47	−47	19	0	3.52
33. Midbrain	–	−5	−27	−4	3.52
34. R post. orbital gyrus	47	23	9	−20	3.51
35. L caudate	–	−13	−13	20	3.48
36. R inf. parietal lob.	40	47	−37	28	3.48

(continued on next page)

Table 3. *(continued)*

Region	*BA*	*x*	*y*	*z*	*z score*
Increases, neutral > negative					
37. R mid. temp. gyrus	39	57	−27	12	5.19
38. R postcentral gyrus	1	47	−21	46	4.20
39. L precentral gyrus	4	−25	−23	66	3.82
40. R sup. temp. gyrus	22	41	−35	20	3.80
41. R postcentral gyrus	2/5	25	−41	64	3.79
Decreases, negative > neutral					
42. L med frontal gyrus	24	−15	29	0	3.69

Coordinates (x, y, z) correspond to the atlas of Talairach and Tournoux (1988). A z score of 3.48 corresponded to a p value of .0005, uncorrected for multiple comparisons. Abbreviations: inf. = inferior, L = left, lob. = lobule, mid. = middle, post. = posterior, R = right, SI = substantia innominata, SMA = supplementary motor area, sup. = superior, temp. = temporal, vis. ctx. = visual cortex. No significant BOLD decreases were identified in the voxel-by-voxel ANOVA with time and valence as factors. Note: Increases and decreases are relative to visual fixation.

psychophysiological state in the context of performing a cognitive task. It should be noted that in our experiment SCRs occurred to both the neutral and negative pictures, indicating that performing a cognitive task involving analysis of the surface features of complex pictorial stimuli elicited a measurable autonomic response even to neutrally valenced pictures.

Neuroimaging: Task-Associated Responses

Task performance, independent of picture type, elicited robust changes in neural activity. Consistent with the experience of others (Lang, Bradley, Fitzsimmons, et al., 1998; Lane, Reiman, Bradley, et al., 1997), viewing IAPS pictures produced large responses in striate and extrastriate visual cortices. Of particular interest were the changes observed in limbic regions. There were significant increases bilaterally in the substantia innominata/amygdala and anterior insula and in the midbrain/brainstem for both negative and neutral pictures (see below).

Importantly, considering the frequency of their occurrence in most cognitive activation paradigms (Shulman et al., 1997), there was an almost complete absence of decreases in activity in the medial prefrontal cortex (Figure 1C). The only remnant of these decreases was a small but significant decrease in the SGPFC, an area previously identified in imaging studies of mood disorders (Todd, Heath, Raichle, & Botteron, 1999; Öngür, Drevets, et al., 1998; Drevets et al., 1997). It should be noted that these decreases, when present, have been accompanied by decreases in activity in the amygdala (Shulman et al., 1997). In the present study increases in the "extended amygdala" (i.e., the region comprising the substantia innominata and/or the superior amygdala) were observed.

One possible explanation for the absence of decreases in the ventral medial prefrontal cortex is that they are simply missed by fMRI due to susceptibility-induced loss of signal, which is particularly severe in the ventral medial prefrontal cortex (Ojemann et al., 1997). However, an examination of the signal-to-noise ratio throughout the brain across the subjects in this study indicates that in the vicinity of the reported deactivation in the subgenual anterior cingulate, the signal-to-noise ratio was reduced by approximately a factor of two relative to more superior regions. Thus, the signal-to-noise ratio was still quite high, and given the fact that the voxel-by-voxel ANOVA identified a region of BOLD response in the SGPFC with a very high z value, well above the value corresponding to a p value of .001 corrected for multiple comparisons, this response is unlikely to be significantly altered by magnetization susceptibility artifacts. Furthermore, typical reductions in this area observed with PET during the cognitive task of verb generation are quite nicely reproduced with fMRI (compare Figure 1A and B).

Another area, which commonly exhibits large decreases in cognitive paradigms, is the posterior cingulate and adjacent precuneus (Figure 1A and B; Shulman et al., 1997). Changes in this area, which is not subject to any degradation of fMRI signal, are conspicuous by their absence in the present study (Figure 1C and D). We will return to a brief discussion of this finding below.

Neuroimaging: Effects of Picture Valence

Picture valence had a significant effect on responses in a subset of regions. The largest differences (i.e., greater responses to the negative pictures) occurred outside of limbic cortices, in the occipital and temporal lobes, primarily in the area of the fusiform gyrus bilaterally. The fusiform gyrus is thought to be involved in the processing of faces (Kanwisher, McDermott, & Chun, 1997; Haxby et al., 1994). This finding prompted an additional analysis to determine whether the difference we observed was a function of the significantly larger

number of faces in the negative pictures. Our analysis, while tentative, suggests that this was not the determining factor. Rather, the increased response in fusiform gyrus was related to the emotional valence of the pictures themselves. This conclusion is supported by a PET study that used IAPS pictures matched for the presence of human faces. Greater activations for negative than for neutral pictures in the occipito-temporal region were seen in this study as well (Lane, Reiman, Bradley, et al., 1997).

All of the responses in limbic areas, while present for both picture types, were larger for the negative pictures. These included greater increases in the medial frontal gyrus (BA 9; part of the medial prefrontal cortex), the left posterior cingulate gyrus (BA 23/31), the midbrain, the left substantia innominata/amygdala, and the right orbital cortex (BA 47); and a greater decrease in the SGPFC (BA 24).

These results should be contrasted with cognitive activation paradigms using quite neutral stimuli (e.g., words, word fragments, or simple visual targets where decreases in limbic areas were regularly observed, Shulman et al., 1997). The increases in limbic areas might be attributed to the increases associated with the negative pictures alone were it not for the fact that increases, while of lower magnitude, were also seen with the neutral pictures. In this regard it should also be recalled that the neutral pictures as well as the negative pictures elicited SCRs. It is possible that the cognitive task, irrespective of the picture valence, evoked a degree of performance anxiety, as was previously shown to attenuate limbic system decreases in another cognitive task, verb generation (Simpson, Snyder, et al., 2000). It is also possible that, due to the mixed nature of the presentation of stimuli (i.e., negative and neutral pictures were interspersed) there was a "carryover" effect that heightened responses to the neutral pictures. Future experiments will be needed to more directly address these questions.

As in our previous studies with verb generation (Simpson, MacLeod, Fiez, Drevets, & Raichle, 1997) and anticipatory anxiety (Simpson et al., 1997) we again observed decreases in activity in the SGPFC. The SGPFC has extensive connections with the amygdala (Carmichael & Price, 1995), hypothalamus, and periaqueductal gray (PAG) region (An, Bandler, Öngür, & Price, 1998; Öngür, An, & Price, 1998; Öngür, 1999). Neuroimaging and neuroanatomical abnormalities have been reported for the SGPFC in mood disorders (Hirayasu et al., 1999; Mayberg et al., 1999; Todd et al., 1999; Öngür, Drevets, et al., 1998; Drevets et al., 1997). Brain damage resulting in a derangement of emotional functions frequently includes the SGPFC (Damasio et al., 1990; Damasio, 1994). Thus, it seems clear that the SGPFC is important for some aspects of emotional regulation, although its precise functions have not yet been delineated.

An activity increase in medial prefrontal cortex in BA 9 (Fig. 1D) distinguished negative from neutral pictures. This response was about 2 cm (vector distance) ventral and anterior to a response seen by Lane and colleagues (Lane, Fink, Chau, & Dolan, 1997a) when subjects attended to their subjective appraisal of the IAPS pictures (i.e., deciding whether the scene was pleasant or unpleasant) compared to judging surface features of the pictures (i.e., deciding whether the scene was indoors or outdoors). Because they did not employ a simple baseline state task (e.g., visual fixation) it is not known whether their indoor/outdoor task elicited some measure of activity in this area as did our neutral pictures. In our experiment it is tempting to think that while subjects were instructed to attend to surface features of the pictures at all times, some level of appraisal was unavoidable even for the neutral pictures. This was probably aided by the long interstimulus interval and stimulus duration.

Large BOLD increases were seen in a region of the forebrain between the basal ganglia and the amygdala. The increase on the left side was significantly larger for the negative than neutral pictures. While it is not possible to precisely localize the anatomical region of this response, it is likely to be either in the superior portion of the amygdala (i.e., the central nucleus) or in what has been termed the "extended amygdala," which includes the substantia innominata and sublenticular cell groups (De Olmos & Heimer, 1999). This region has been proposed to act in concert with the amygdala, with which it is heavily interconnected, in mediating emotional processes (De Olmos & Heimer, 1999). A large body of literature points to a role of the amygdala in assigning emotional significance to sensory inputs (reviewed in LeDoux, 1996), and it is plausible that the activations identified in the present study are related to this function. Similar responses have been observed in previous imaging studies with IAPS pictures (Lane, Reiman, Bradley, et al., 1997; Irwin et al., 1996) as well as with emotional faces (Phillips et al., 1997) and emotional films (Lane, Reiman, Ahern, Schwartz, & Davidson, 1997; Reiman et al., 1997).

Changes in midbrain activity were also prominent, and were larger for the negative pictures. The resolution of the imaging technique used does not permit precise localization. However, it seems plausible, based on its connectivity and its role in emotion and visceral functions, that these changes may have included the PAG region (An et al., 1998; Bernard & Bandler, 1998; Öngür, An, et al., 1998; Bandler & Shipley, 1994). Several studies of emotion report activations in midbrain or brainstem (Tölle et al., 1999; Lane, Reiman, Bradley, et al., 1997; Rauch, Savage, Alpert, Fischman, & Jenike, 1997; Fredrikson, Wik, Fischer, & Andersson, 1995). Furthermore, autonomic responses such as the SCR are likely to be mediated, at least in part, by nuclei in the posterior hypothalamus and midbrain (for review, see Sequeira & Roy, 1993).

In the posterior cingulate and precuneus, the decreases that are typically seen in cognitive activation

paradigms (Shulman et al., 1997) were not observed (Figure 1C and D) and in fact some small but significant increases were detected. As this region has recently been proposed to play a role in emotion (Maddock, 1999), it is possible that the absence of decreases is related to the emotional content of the negative pictures, though one might then still expect to see a decrease for the neutral pictures. Another possible explanation is the large visual angle subtended by the stimuli, which ranged from 10° to 20° in horizontal visual angle. We have proposed (Raichle, 1998) that the posterior cingulate and precuneus may be critical to the monitoring of extrafoveal stimuli, and that focused attention on foveal stimuli necessitates a reduction in neural activity in this area. Thus, in the present study, where the stimuli spanned more than the central 10°, such reductions might not be expected to occur. An experiment, which examines the effect of stimulus size on posterior cingulate/precuneus activity, would be instructive in this regard.

Conclusion

Complex stimuli that more closely approximate "real world" sensory experiences introduce a new level of complexity to the design and interpretation of functional imaging experiments. It is clear from our data as well as the work of others that the use of such stimuli elicits responses in areas of the brain known to be associated with processing of emotional information such as the SGPFC, amygdala, and brainstem that, while greater for arousing, negatively valenced pictures apparently can be present even with neutral pictures. Have we really produced a negative emotional response and, if so, how should it be defined? As Davidson and Irwin (1999) have cautioned, the presentation of emotional information "does not necessarily (nor even likely) elicit an emotion." Our data would only indicate that when arousing negatively valenced stimuli are confronted but incidental to the performance of a cognitive task, performance on the task deteriorates, heightened autonomic responses are elicited, and many but certainly not all structures in the brain thought to be concerned with emotion processing exhibit changes in activity. While all of these changes may constitute elements of a specific emotion such as fear and anxiety (for discussion, see Armony & LeDoux, 2000), they are likely to be only aspects of a subsystem of emotional processing related to emotional processing.

One of the most challenging features of this and other work will be to understand more clearly the role of the ventral medial prefrontal cortex in emotional processing. Functional responses were conspicuously absent from this region in the present experiment. As we have noted earlier, this area is uniquely positioned between areas receiving tertiary sensory information from the internal milieu and the external environment and areas associated with emotional responses (i.e., amygdala, brainstem, and hypothalamus). An important feature of this complex region of the brain, demonstrated in our parallel work with anticipatory anxiety (Simpson, Drevets, et al., 2000) is the fact that activity as measured with PET shows little difference between a nonanxious, resting state and a state in which significant levels of anxiety have been provoked in a particular task setting. Furthermore, activity in this area may be correlated with the level of anxiety such that those experiencing the most intense anxiety exhibit the smallest difference from the nonanxious baseline state whereas those experiencing the least anxiety exhibit the greatest reduction in activity from baseline.

The above relationships challenge us to rethink the functional significance of so-called baseline activity in areas like the ventral medial prefrontal cortex where reductions in activity are more commonly seen than increases or so-called activations. We would like to suggest that observations presently in hand including the data we report here are consistent with a hypothesis that within the ventral medial prefrontal cortex reside areas whose functionality is tonically active rather than triggered by transiently occurring events. Further, we would like to suggest that the function in question is necessary for the ongoing detection and evaluation of environmental and internal stimuli of relevance to the motivational state of the individual. Reductions, achieved during some types of cognitive activity but (e.g., see Figure 1A and B) but not seen in the present experiment (Figure 1C) reflect an attenuation of this function that may be required in the performance of some tasks requiring focused attention (cognition).

MATERIALS AND METHODS

Subjects

Eighteen subjects (nine male, nine female) between the ages of 19 and 32 (mean age 24.9) were recruited from the local Washington University community. Seventeen subjects were right-handed and one male subject was left-handed. All the subjects were without significant abnormal neurological history and were normal or corrected-to-normal in visual acuity. The subjects were paid US$25 for each hour of their participation and gave informed consent in accordance with guidelines set by the Human Studies Committee of Washington University Medical Center. One of the female subjects misunderstood the task instructions, and her data were therefore excluded.

Pictorial Stimuli

The subjects viewed full-color pictures selected from the IAPS (Lang et al., 1997). Pictures were resized such that their heights were uniform, subtending a vertical visual

angle of approximately 9°. The horizontal visual angle subtended ranged from a minimum of approximately 10° to a maximum of approximately 20°. All pictures were centered on a black background and were displayed for 2 sec.

A total of 90 pictures, 30 with an unpleasant, negative emotional valence (''negative'') and 60 with a neutral emotional valence (''neutral'') were used. This two-to-one ratio was employed to reduce possible habituation to the negative stimuli by increasing the unpredictability of negative picture occurrence. Pictures were selected based on published ratings of pleasure and arousal (Lang et al., 1997) and on pilot behavioral studies. The negative pictures had a pleasure rating (rated on a scale of 1 to 9) of 1.94 ± 0.52 (mean ± *SD*), and an arousal rating (also rated on a scale of 1 to 9) of 6.54 ± 0.61. The neutral pictures had a pleasure rating of 5.56 ± 0.87, and an arousal rating of 3.26 ± 0.76. The differences in ratings were highly significant (paired, one-tailed *t* tests, both $p < .000001$.)

Stimuli were projected with an Ampro LCD-150 projector onto a Cineplex rear-projection screen positioned at the head end of the MRI scanner bore. The subjects viewed the screen through a mirror mounted on the head coil. A fiber-optic, light-sensitive key press permitted us to record the subjects' behavioral responses.

Functional Imaging

Imaging was performed on a Siemens 1.5-T Vision System (Erlangen, Germany). Structural magnetic resonance (MR) images were acquired using a sagittal MP-RAGE three-dimensional T1-weighted sequence (repetition time [TR] = 9.7 msec, echo time [TE] = 4 msec, flip angle $\alpha = 12°$, inversion time [TI] = 300 msec, voxel size = 1.25 × 1 × 1 mm) as well as a T2-weighted spin-echo sequence with high brain/nonbrain contrast (TR = 3,800 msec, TE = 90 msec, $\alpha = 90°$, voxel size = 1.07 × 1.85 × 16 mm). fMRI images were collected in runs using an asymmetric spin-echo echo-planar sequence sensitive to BOLD contrast (T2*) (TR = 2360 msec, T2* evolution time = 50 msec, $\alpha = 90°$). During each functional run, 128 sets (''frames'') of 16 contiguous, 8-mm thick axial images were acquired (3.75 × 3.75 mm in-plane resolution), allowing complete brain coverage at a high signal-to-noise ratio (Conturo et al., 1996). Functional images were acquired parallel to the plane containing the AC–PC plane in each subject after prescribing slice position based on automatic measurements of rotation, translation, and tilt of the structural images relative to an averaged ($n = 12$) MP-RAGE anatomical image representative of the atlas of Talairach and Tournoux (1988). This procedure also centered the brain in the multislice volume and the MR scanner field of view.

Each run of functional imaging data was postprocessed to remove artifacts due to properties of the MR scanning system and subject movement. Compensation for asynchronous slice acquisition: Because approximately 130 msec separates successive slice acquisitions, these time shifts were removed using sinc interpolation. Debanding: This step removed systematic odd versus even slice intensity differences that occur with contiguous interleaved slice acquisition (see above). A single parameter, α, was computed such that intensity scaling of odd and even slices by $(1 - \alpha)$ and $(1 + \alpha)$, respectively, minimized the component of variance attributable to banding. Realignment: A six-parameter rigid-body realignment mutually registered all frames in all runs for each subject (Snyder, 1995; Friston, Jezzard, & Turner, 1994). Registration error was computed as difference image variance (Friston, Williams, Howard, Frackowiak, & Turner, 1996; Snyder, 1995). Reslicing was by 3D cubic spline interpolation, which produces results very similar to those obtained by the sinc interpolation method (Hajnal et al., 1995).

For each subject, an atlas transformation was computed based on an average of the first frames of each functional run (the first frame contains the most anatomical information) and the T2 and MP-RAGE structural images. A six-parameter, rigid-body, cross-modal registration similar to the method of Andersson et al. (1995) registered the averaged first frame data to the T2 image. A similar procedure registered the T2 image to the MP-RAGE image. In both of these registrations, in-plane stretch was allowed, partly compensating for distortions (particularly in the phase-encoding [anterior–posterior] direction) inherent in echo-planar images. The MP-RAGE image was registered using a 12-parameter general affine transformation to an averaged MP-RAGE target image produced by mutual coregistration of images from the 12 normal subjects and spatial normalization (Lancaster et al., 1995) of this average to the atlas of Talairach and Tournoux (1988). Finally, all the involved images were brought into mutual register by matrix multiplication. Functional data were interpolated to 2-mm cubic voxels in the atlas space.

Psychophysiological Recording and Analysis

SCRs were recorded with the Biopac MP100 system (Santa Barbara, CA, USA) using silver/silver chloride electrodes. The electrodes were attached to the medial side of the right foot. Readings of skin conductance in microsiemens (μS) were acquired at a sampling frequency of 1000 Hz and stored in a Macintosh G3 computer coupled to the Biopac MP100. Subsequent processing involved filtering with a low-pass filter (cutoff = 3 Hz) to remove artifacts arising from radio-frequency pulses during scanning. The time of onset of each picture was also recorded with the SCR trace, allowing SCR responses to individual negative and neutral pictures to be identified. Responses with an onset in the time window from 1 to 5 sec after

stimulus presentation were measured. Response magnitude was defined as the maximum value within the time window minus the minimum value prior to the maximum within the same window. Responses were averaged within each run for the two stimulus types and a repeated-measures ANOVA with valence and run as factors was applied.

Experimental Design

Ten functional runs were acquired for each subject. Pictures were presented in a fixed-interval, single-trial design, i.e., pictures appeared one at a time, separated by a gap of 16.52 sec (seven functional frames). A fixation crosshair was displayed in the center of the screen before the first picture, between the pictures, and after the last picture of each run. Each IAPS picture was displayed for 2 sec. There were 18 pictures per run, 6 negative and 12 neutral. Each negative picture was presented once within the first five runs, and presented a second time within the second five runs. Within a run, two negative pictures could not appear in succession. Neutral pictures never appeared twice in the same run, but approximately 25% appeared twice within the same half of the study, i.e., within runs 1 through 5 or within runs 6 through 10. Subject to these constraints, picture presentation within and across runs and across subjects was randomized.

The subjects were instructed to fixate on the crosshair when it was present. They were told that they could move their eyes freely when a picture appeared. They were instructed to determine how many humans, or parts of humans, appeared in each picture. They were instructed to press one key if there were one or no humans or parts of humans (hereafter referred to as ''one'') and a second key if there were two or more (''two''). They were instructed that ''part of a human'' could refer to a body part extending beyond the edge of the picture, or to an actual severed part. Responses were made with the right hand, using the index finger to signal one and the second finger to indicate two. Responses and response times were recorded by the Tempo program. Response times were calculated from stimulus onset to the keypress response.

The conditional probabilities of a ''one'' or ''two'' response varied with picture valence. Of the 30 negative pictures, 20 should have elicited a response of ''one'' and 10 pictures should have elicited a response of ''two.'' Of the 60 neutral pictures, 55 should have elicited a response of ''one'' and 5 pictures should have elicited a response of ''two.''

Because of ambiguity of the correct response, data from one negative (IAPS catalog number 3110) and three neutral pictures (IAPS catalog numbers 2890, 7501, 7590) were not included in calculations of accuracy and response time.

A list of the IAPS catalog numbers for the pictures used in this study appears in the database.

Statistical Analysis of fMRI Data

The fMRI data were analyzed using the general linear model (Worsley et al., 1996; Friston et al., 1994; Friston, Holmes, Poline, et al., 1995; Friston, Holmes, Worsley, et al., 1995) and a voxel-by-voxel ANOVA (Braver et al., 1997) for a regional random-effects model. The general linear model employs an orthogonal set of delta functions as regressors. This set of functions is coded into the model for each stimulus presentation such that the solution of the model at each voxel yields an estimated time-course of the BOLD response to each stimulus. The time-course values for all the subjects were entered into the ANOVA. To reduce the effects of anatomical variability, a four-voxel (8 mm) full width at half-maximum (FWHM) three-dimensional Gaussian smoothing kernel was applied. The ANOVA included time as one factor and valence as a second factor. The factor of time had seven levels corresponding to the seven frames of the time course of the modeled hemodynamic response. Valence had two levels, negative and neutral. The ANOVA created two useful statistical maps: the main effect of time and interaction of time by valence. Statistical maps were computed as F statistics, which were converted to z statistics. The main effect of time statistical map was corrected for multiple comparisons using the unified theory of Worsley et al. (1996) that ensured that $p < .001$. The time-by-valence statistical map was thresholded at a z value of 3.48, corresponding to $p = .0005$, uncorrected for multiple comparisons.

A second set of voxel-by-voxel ANOVAs was performed with time and presentation order (first or second) as factors. These ANOVAs were performed for all pictures and for negative and neutral pictures separately. The time-by-order interaction statistical maps were thresholded at a z value of 3.48, as above.

The location of the peaks of BOLD responses in the statistical images created by the ANOVAs were identified using an automated peak-search algorithm (Mintun, Fox, & Raichle, 1989), based on z value and cluster size. Regions of interest (ROIs) were then defined based on these peak coordinates for use in regional analyses. These ROIs were used to extract time course information from the fMRI data to determine the average direction and magnitude of change within each ROI.

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The data reported in this experiment have been deposited in National fMRI Data Center (http://www.fmridc.org). The accession number is 2-2000-1119F.

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