Emotional Activation of Limbic Circuitry in Elderly Normal Subjects in a PET Study

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Objective: *This study was undertaken to identify brain structures associated with emotion in normal elderly subjects.* *Method:* *Eight normal subjects aged 55–78 years were shown film clips intended to provoke the emotions of happiness, fear, or disgust as well as a neutral state. During emotional activation, regional cerebral blood flow was measured with the use of $[^{15}O]H_2O$ positron emission tomography imaging, and subjective emotional responses were recorded. Data were analyzed by subtracting the values during the neutral condition from the values in the various emotional activations.* *Results:* *The stimuli produced a general activation in visual pathways that included the primary and secondary visual cortex, involving regions associated with object and spatial recognition. In addition, the specific emotions produced different regional limbic activations, which suggests that different pathways may be used for different types of emotional stimuli.* *Conclusions:* *Emotional activation in normal elderly subjects was associated with increases in blood flow in limbic and paralimbic brain structures. Brain activation may be specific to the emotion being elicited but probably involves complex sensory, association, and memory circuitry. Further studies are needed to identify activations that are specific for emotion.*

(Am J Psychiatry 1997; 154:384–389)

Positron emission tomography (PET) has been used to examine the changes in cerebral blood flow (CBF) associated with emotion (1–4). While experimental designs have varied from study to study, results suggest that a variety of limbic, paralimbic, and cortical regions mediate human emotion (1–4).

All of these previous studies have examined young normal volunteers, typically in their early 20s. CBF changes associated with emotion have not been studied in the elderly. Age-related neurobiological changes (5), metabolic changes (6), and blood flow changes during cognitive tasks (7) provide a rationale for studying brain circuitry activated by emotions in elderly persons. We examined changes in regional CBF as determined by $[^{15}O]H_2O$ PET imaging in normal elderly subjects. In order to standardize the stimuli, we selected film clips that would elicit positive emotion (happiness) or negative emotion (fear/disgust). These were then compared with reactions to clips containing a neutral stimulus. We hypothesized that the emotional stimuli would produce activations in limbic and paralimbic regions and that the degree and region of activation would vary according to the type of stimulus presented.

METHOD

Eight nonsmoking, elderly subjects (two male and six female; mean age=62.6 years, SD=6.8, range=55–78), seven of whom were right-handed, were recruited from the community. They had no history of psychiatric/neurological disorder, alcohol/substance abuse, or current use of psychotropic medications. Their mean full-scale IQ was 111 (SD=11, range=99–130), their mean verbal IQ was 108 (SD=11, range=99–124), and their mean performance IQ was 110 (SD=11,

Presented in part at the annual meeting of the Society of Biological Psychiatry, Miami, May 17–20, 1995, and at the Second International Conference on Functional Mapping of the Human Brain, Boston, June 17–21, 1996. Received Dec. 5, 1995; revision received July 26, 1996; accepted Oct. 1, 1996. From the University of Iowa College of Medicine and the University of Wisconsin, Madison. Address reprint requests to Dr. Paradiso, University of Iowa Hospitals and Clinics, Department of Psychiatry Administration, Number 2887 J.P.P., 200 Hawkins Dr., Iowa City, IA 52242.

Supported in part by NIMH Research Scientist Awards MH-00163 to Dr. Robinson, MH-00875 to Dr. Davidson, and MH-00625 to Dr. Andreasen; grants MH-52879, MH-31593, MH-40865, MH-43454, MH-40747, and Clinical Research Center grant MH-43271 from NIMH; NIMH grant MH-52354 to the Wisconsin Center for Affective Science; The Nellie Ball Trust Fund; and an Established Investigator Award from the National Association for Research on Schizophrenia and Affective Disorders to Dr. Andreasen.

The authors thank Gene Zeien and Jim Bailey for image analysis; Jo Clark, Julie Koeppel, and John Richmond (nurse and magnetic resonance technicians); Alane Tranel for neuropsychological assessment; and Ted Cizadlo and Stephan Arndt for insight and guidance.

range=100–130). No gross brain abnormalities were found in the subjects' T_2- and T_1-weighted magnetic resonance imaging (MRI) scans by a neuroradiologist who was blind to the aim of the study. Several subjects, however, showed leukoaraiosis and état criblé of the basal ganglia. The University of Iowa institutional review board approved the project. After complete description of the study, written informed consent was obtained from the subjects.

Activation Stimuli

Five soundless video excerpts from commercial movies (about 60 seconds long) were used to visually elicit happiness or fear/disgust (8). After each video, subjects verbally rated their emotional feelings (happiness, amusement, sadness, fear, disgust, and anger) on a 0- to 8-point analog scale. The video sequence was randomly presented, but in reversed order of positive and negative emotional presentations. The neutral film was shown after any two emotional film clips. The video clips were viewed on a 12-inch color video monitor in full view 18 inches from the subjects' eyes while they were lying in the PET camera. The room was darkened; eye movements were not restricted. Autonomic nervous system indexes were not recorded.

On the basis of the ratings by the subjects, the film clips were classified into four categories: happiness, fear, fear/disgust, and neutral. Two of the film clips were given mean ratings of 6 or higher on the analog happiness scale and ratings of 0 for sadness, fear, disgust, or anger. These were designated "happiness 1" and "happiness 2." Happiness 1 is a clip from *On Golden Pond* and portrays a proud New England woman (Katherine Hepburn) dancing happily while rejoicing in the beauty of the woods. Happiness 2 is from *An Officer and a Gentlemen* and shows Richard Gere going back to the factory for an emotional reunion with his girlfriend. One of the fear clips received a mean rating higher than 6 on both the fear and disgust analog scales and ratings of 0 on the other scales. It was designated "fear/disgust." It portrays a man in a seedy hotel with a rat crawling into his mouth (from the movie *Cujo*). The final emotion-induction clip produced a mean rating higher than 6 only on the disgust scale and was therefore designated as "disgust." It is from *The Godfather* and shows the scene when a man awakens to find the head of his decapitated horse in his bed. The neutral scene (a fire in a fireplace) received 0 ratings on all scales apart from happiness, for which it was given a mean rating of 3.

Since novelty and familiarity appear to affect CBF (9, 10), the subjects were questioned concerning their familiarity with the film clips. Eighty-five percent of the subjects had previously seen *On Golden Pond*, 50% *An Officer and a Gentleman*, and 83% *The Godfather*; none of them had seen *Cujo*.

PET and MRI Data Acquisition

MRI scans, to be used for anatomic localization of functional activity, were obtained with a 1.5-T GE scanner. Scanning parameters of the T_1-weighted three-dimensional SPGR sequence have been described in previous papers (11, 12).

PET images were obtained with a GE 4096 Plus whole-body tomograph capable of producing 15 slices with an interslice separation of 6.5 mm (11, 12). The PET acquisition details have also been described elsewhere (11, 12).

Injections of the radioactive water were timed so that the radioactive bolus reached the brain 10 seconds before the emotion-activating film clip was completed (13). PET imaging data were analyzed by creating a parametric flow image from 40 seconds of summed data starting immediately after the bolus of $[^{15}O]H_2O$ had transited the brain (i.e., approximately 30 seconds after injection).

TABLE 1. Neural Substrates of Emotion: Happiness Stimulus Conditions

Region	t_{max}[a]	Volume (cc)	Voxels	Coordinate[b] x	y	z
Relative increased blood flow						
Right entorhinal cortex	3.96	0.2	120	32	8	–23
Right middle posterior temporal/fusiform gyrus	6.71	12.5	6209	51	–55	5
Left fusiform gyrus	6.36	10.2	5041	–39	–57	–17
Left middle posterior temporal gyrus	4.70	0.8	398	–43	–69	14
Left superior temporal gyrus	3.81	0.1	59	–53	3	–14
Left parietal operculum	4.29	0.3	136	–37	–31	18
Primary and secondary visual cortex	6.18	2.6	1266	–2	–87	2
Cerebellum	4.95	0.5	254	–3	–55	–38
Relative decreased blood flow						
Left anterior cingulate	–4.11	0.3	145	–10	18	23
Left orbital frontal cortex	–6.60	4.5	2226	–39	32	–19
Inferior medial frontal cortex	–4.25	0.3	130	2	39	–26
Right parietal operculum	–4.85	1.0	491	38	–23	17
Left middle cingulate	–5.95	3.4	1684	–7	–26	29
Left precentral cortex	–4.55	0.8	345	–39	–31	39
Left inferior temporal cortex	–5.52	1.9	942	–51	–31	–29
Left precuneus	–4.00	0.1	60	–6	–69	37
Cerebellum	–4.40	0.8	415	43	–74	29

[a] df≈1694.

[b] Coordinates correspond to those from the Talairach and Tournoux atlas (20); x, y, and z represent spatial coordinates with respect to a point located in a horizontal plane through the anterior and posterior commissures (z=0), at the midline of this brain slice (x=0), and at the midpoint between the anterior and posterior commissures (y=0). The x coordinate is the distance in millimeters to the left (positive) and to the right (negative) of the midline. The y coordinate is the distance in millimeters anterior (positive) or posterior (negative) to the midpoint between the anterior and posterior commissures. The z coordinate is the distance in millimeters above (positive) or below (negative) a horizontal plane through the anterior and posterior commissures.

Image Analysis

The BRAINS software (14–18) and an adaptation of the Montreal method (18, 19) were used for image processing and analysis. Spatial and signal normalization was performed according to the method described by Worsley et al. (19).

Results were calculated by subtracting the data obtained in the neutral condition from the data in the emotion-eliciting condition. Data reported in tables 1–3 show the location of peaks (with anatomic localization based on visual inspection of coregistered MRI and PET images rather than on Talairach and Tournoux [20]) coordinates); the x, y, and z Talairach and Tournoux coordinates; the t_{max} value (highest t test value identified in the peak); and the volume of the peak in cubic centimeters that exceeds the t=3.61 (df≈1694) threshold. This threshold, which has been consistently used by our center, corresponds to an uncorrected significance level of <0.0005 per voxel. There were about 300,000 gray matter voxels in our images, representing approximately 242 resolution elements (19). After filtering, the three-dimensional image resolution is 2.5 cc. The degrees of freedom were extremely large for the t tests: df≈1694=number of resolution elements × (number of subjects – 1). Only areas that exceeded 30 contiguous voxels were described, so as to omit isolated outlying values.

RESULTS

In the happiness 1 condition, the subjects showed relatively higher blood flow in the calcarine fissure, the cuneus, bilaterally in the fusiform gyrus and posterodorsal temporal lobe (right greater than left), and in the right

TABLE 2. Neural Substrates of Emotion: Disgust Stimulus Condition

Region	t_{max}[a]	Volume (cc)	Voxels	Coordinate[b] x	y	z
Relative increased blood flow						
Bilateral thalamus	6.76	0.8	409	–2	–18	8
Right inferior middle temporal/fusiform gyri	7.48	18.8	9350	38	–54	–16
Left inferior middle temporal/fusiform gyri	6.87	15.8	7851	–41	–76	6
Visual cortex	4.50	0.5	252	–4	–84	9
Cerebellum	4.32	0.3	150	–10	–70	–42
Relative decreased blood flow						
Inferior medial frontal cortex	–3.73	0.1	30	0	20	–28
Right dorsolateral frontal cortex	–4.23	0.4	211	26	24	35
Right retrosplenial cingulate	–4.12	1.3	660	4	–51	32

[a]df≈1694.
[b]See footnote b, table 1.

TABLE 3. Neural Substrates of Emotion: Fear/Disgust Stimulus Condition

Region	t_{max}[a]	Volume (cc)	Voxels	Coordinate[b] x	y	z
Relative increased blood flow						
Left orbital frontal cortex	3.99	0.1	55	–23	8	–17
Right posterior middle temporal/fusiform gyrus	6.90	14.8	7352	50	–65	6
Left posterior inferior temporal/fusiform gyrus	5.73	12.3	6103	–36	–74	–10
Right secondary visual cortex	4.10	0.2	80	24	–82	29
Primary visual cortex	3.90	0.1	30	–3	–87	14
Relative decreased blood flow						
Inferior medial frontal cortex	–4.47	0.4	215	2	39	–22
Right dorsolateral frontal cortex	–3.81	0.1	40	36	45	2
Right parietal operculum	–4.25	0.3	162	39	–24	20
Bilateral retrosplenial cingulate	–4.49	5.1	2508	–2	–31	27
Visual cortex	–4.21	0.3	156	7	–97	–2

[a]df≈1694.
[b]See footnote b, table 1.

entorhinal cortex (table 1 and figure 1, part A). Additional smaller areas of activity were seen on the left in the inferior parietal lobule and the superior temporal gyrus. Activation was also seen in the medial cerebellum.

The neutral condition produced relatively higher blood flow compared to the happiness 1 condition in the inferior medial and left orbital frontal cortex, left inferior temporal cortex, anterior and posterior cingulate, precuneus, and right lateral cerebellum (table 1 and figure 1, part A). These regions have been noted to be active during "rest" or "neutral" conditions in a variety of PET studies (2, 11).

Comparison of the data from the second happiness induction with the data from the neutral condition showed virtually identical results. However, the first happiness condition activated the right enthorinal cortex (table 1), while the second happiness stimulation activated the left enthorinal cortex (t_{max}=3.83, df≈1694; x=–33, y=11, z=–28). Activation in the right enthorinal cortex did not reach significance during the second happiness stimulation (t_{max}=2.52, df≈1694; x=32, y=8, z=–23), and in the left enthorinal cortex it did not reach significance during the first happiness stimulation (t_{max}=2.74, df≈1694; x=–33, y=11, z=–28).

The disgust condition produced bilateral activations in the fusiform gyri leading down into the inferior temporal cortex and up into the supramarginal/angular cortex in a pattern very similar to that seen during the happiness condition (table 2 and figure 1, part B). The cerebellum and visual cortex were also activated. In addition, there was increased flow in the medial thalamus. The neutral condition produced activations in the inferior medial frontal, right frontal, and retrosplenial cingulate cortex and the precuneus.

The final stimulus, fear/disgust, activated the visual cortex and efferent pathways to the inferior temporal lobes through the fusiform gyri bilaterally (table 3). In addition, this task activated the left inferior orbital frontal cortex. The regions of relative higher blood flow during the neutral condition were similar to those observed in previous subtractions (table 3).

DISCUSSION

This study demonstrated that mood induction in elderly normal subjects produced a variety of changes in regional blood flow. Some of these were in limbic or paralimbic regions. The happiness film clips produced prominent activations in both hemispheres in areas thought to be active in the recognition and memory components of the stimuli. The clips eliciting happiness produced activation in the entorhinal cortex, disgust produced activation in the medial thalamus, and the fear/disgust tape produced activation in the left orbital frontal cortex. These findings are consistent with the hypothesis of a role for limbic structures in the mediation of human emotion and of regional specialization for emotion.

All three conditions produced similar activations in the primary, secondary, and tertiary visual cortex, as well as middle, inferior, and basal aspects of the temporal lobe bilaterally. This probably reflects the visual delivery of the emotional stimuli (21, 22), which activates pathways used for visual functions such as facial, object, and spatial recognition, detection of movement, and association of specific memories with facial recognition (21–26).

Some of the commonalities across the three conditions may also reflect the memory and emotional components of the stimuli. With the use of PET, the temporal inferior regions have been found active in memory (9, 10, 26). They may integrate perceptual and memory capacities (22). The type of memory involved may be more than simple recognition of a previously seen movie clip, since temporal lobes were activated by the

film clip to which they had not previously been exposed (i.e., fear/ disgust). Activation of the inferior temporal cortex during this clip probably involved accessing memory traces of a past moment of fear. There is experimental evidence that emotions are associated with memory (27).

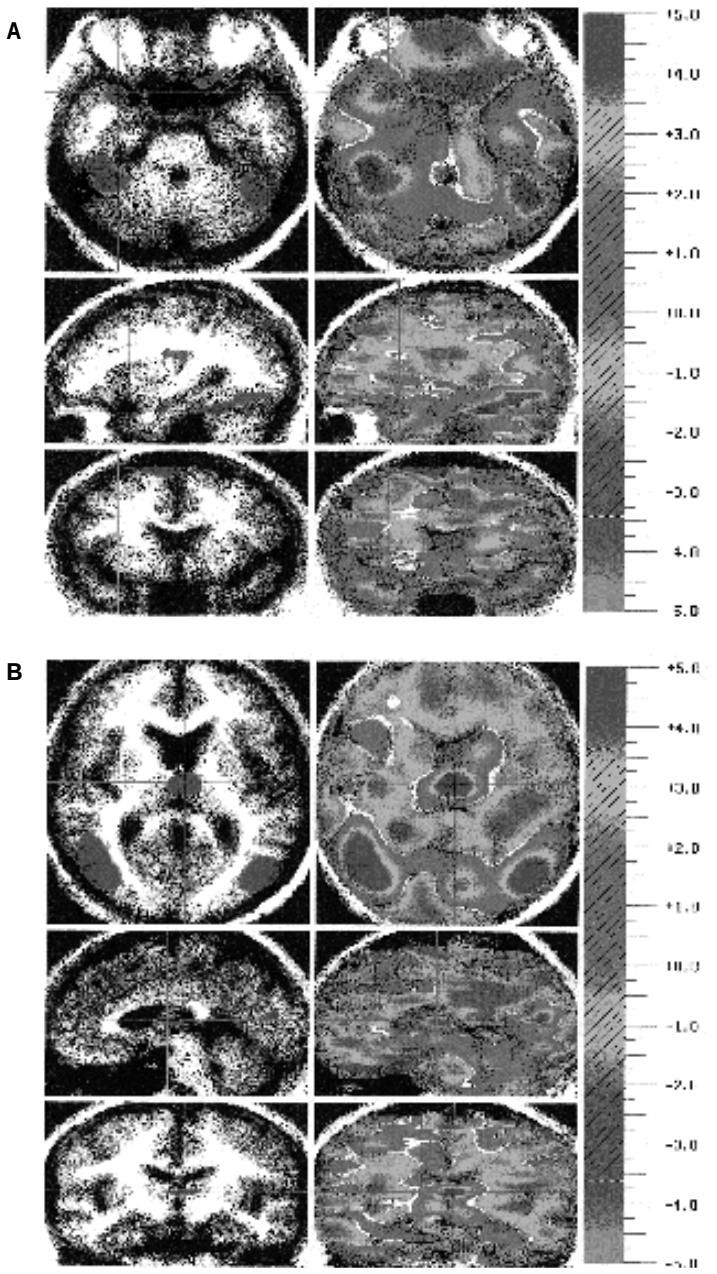
The three different emotional activations also showed specific differences in pattern of activation, which may reflect different neural pathways that are associated with these specific emotions. The subjects showed a relative increase in blood flow in the three-layered entorhinal cortex of the limbic system during the positive emotional activation. The entorhinal cortex includes the allocortical cortex and gives rise to the most prominent input to the hippocampal formation, especially to the dentate gyrus and amygdala, and receives inputs from the subiculum (28). The entorhinal cortex is reciprocally connected with the sensory visual cortex and with multimodal association areas of the temporal neocortex. The projections from primary sensory areas are very weak compared with those of the multimodal association areas. The entorhinal cortex may thus almost exclusively receive highly processed information that is committed to several modalities.

The left mesial orbital frontal cortex was more active during the fear/disgust film clip. The orbitofrontal cortex is part of the dorsolateral limbic circuit (29). Abnormality of blood flow in the left prefrontal cortex has been described in patients with major depression (30, 31).

The disgust condition activated the thalamus, a structure of the subcortical limbic system. The midline nuclei and the nucleus reuniens of the thalamus are highly connected to cortical limbic areas such as the inferior, anterior, and retrosplenial cortex of the cingulate and the prefrontal and entorhinal cortex. Thalamic activation was recently observed during emotional challenges (4). George et al. (3) reported left thalamic activation during sad stimuli.

Many PET studies use a resting condition (typically, lying quietly with eyes closed) as the reference task. Investigators using PET have begun to question the possibility of obtaining a genuinely neutral state of the brain. Subjects may engage in recall during the "resting" state (11). This hypothesis is consistent with the types of activations seen during the

FIGURE 1. Neural Substrates of Emotion in a PET Study of Elderly Individuals[a]



[a]Three orthogonal views are shown. Crosshairs are used to show the location of the slice. Images follow radiological convention. Statistical maps of the PET data are superimposed on a composite magnetic resonance image derived by averaging the MRI scans from the eight subjects. The value of t is shown on the color bar on the right. The "t map" (right side of image) shows the value of t for all voxels in the image and provides a descriptive picture of the general geography of the activations. The "peak map" (left side of image) shows areas where all contiguous voxels exceed the predefined threshold for statistical significance. The planes have been chosen to illustrate the location of the relevant activity for each specific task.

A) Happiness stimulus condition 1. The transaxial (top) view shows a large area of activity presumed to reflect emotion components of the task: the left entorhinal cortex. The sagittal plane (placed laterally on the right side) indicates prominent activity reflecting visual recognition and memory in the fusiform and inferior temporal gyrus both anteriorly and posteriorly. Areas of relative decreased activity (blue-purple) in the medial inferior frontal lobes (transaxial plane) and in the parietal operculum presumably reflect the free-association component of the neutral task.

B) Disgust stimulus condition. The cognitive components of this task are nearly identical to those seen in part A. The emotional nature of the task is probably reflected in prominent and bilateral thalamic activity.

neutral task, which occur in regions activated in studies of memory, such as the frontal regions, cingulate, precuneus, and cerebellum. The interaction between memory and emotion may explain the relative decreases in blood flow observed in these regions in PET studies of emotion (2, 3, 32).

Most studies of emotion induction have used recall of past emotional experiences and have reported results similar to those observed in the present study, such as activations of the inferior frontal, thalamic, and temporal regions. Although these regions share a common association in inducing emotional changes, the tasks were usually not comparable. Both George et al. (3) and Lane et al. (4) used visually induced emotion, however, and the activations observed in their work differ in some respects from those seen in our subjects. For example, George et al. (3) noted that happy memories were associated with increased flow in left temporal and right frontal regions, while our results place this emotional state in the right entorhinal cortex.

To our knowledge, this is the first study to examine the effects of emotional stimulation on CBF in elderly individuals. The differences between the findings in this study and those of prior investigations may reflect the examination of an elderly study group. Prior work by Grady et al. (7) has shown that visual processing, which was the primary mode of stimulation in the present study, activates different regions in elderly individuals in comparison with younger individuals. Brain metabolism has been shown to decline in elderly adults compared to younger adults (6). The phenomenology of altered emotional states such as depression and depressive disorders in the elderly has proven to be quite distinct from that of youthful subjects (33). Elderly depressed patients experience more somatic symptoms (e.g., weight loss) and fewer psychological symptoms (e.g., feelings of worthlessness and guilt) (34, 35). This may reflect the different recruitment of neuronal circuitry in older persons and is in keeping with the neurobiological and metabolic changes found with increasing age (5, 36–38).

Several studies have posited that the cerebellum may also perform cognitive functions (12, 39–44). Cerebellar activity was reported by George et al. (45) during a task of facial emotion recognition compared to a spatial-position matching task. Reiman and colleagues (44) reported increased cerebellar activity during visually generated emotions similar to those reported in this study. We found higher cerebellar blood flow during two of the three emotion-activating conditions. There was no motor component in any of the challenges. Cerebellar midline structures (i.e., the vermis) were activated. These structures, together with other older cerebellar regions including the flocculonodular lobe and fastigial nuclei, have been considered as the equivalent of the limbic cerebellum (46).

This study had a variety of limitations. Because of the relatively small size of the study group and because our method of analysis does not allow quantitative interhemispheric comparisons of blood flow, conclusions about lateralized activity should be drawn cautiously (47). Emotional activations were not "pure." Film clips provide a "standardized" emotional challenge of "real-life" complexity, but they also make results more difficult to interpret, since several different types of emotion (e.g., fear and disgust) are combined within a single film clip. Further, on-screen duration, color, luminance, and motion may not be equal across the films. The group studied was predominantly middle-class, white, and female. Although the results in the two male subjects did not appear to be grossly different, the results reported here may be most clearly applicable to females (1). Data from one left-handed patient were included in the analyses, and this may have affected some of the findings. The timing of data acquisition was determined by using the method from previous work done by our group (13); it was based on cognitive activation studies. We do not know whether earlier or later PET acquisition would have produced different results. We did not rescan subjects during viewing of the same clip to assess reproducibility of results. However, the results obtained while subjects viewed happiness videos 1 and 2 were virtually identical. We also did not have physiological measures of emotions. Although autonomic nervous system measures have been used to record emotional arousal, there is a question about whether they may be helpful in distinguishing emotions of a different type and valence (48, 49, and personal communication from D. Fowels).

In summary, visual emotional stimulation activates in the elderly several limbic and paralimbic regions as well as modality-specific and memory regions. Some limbic areas of activation seem to be specific to the emotions studied.

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