Brain Activity During Transient Sadness and Happiness in Healthy Women

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Objective: *The specific brain regions involved in the normal emotional states of transient sadness or happiness are poorly understood. The authors therefore sought to determine if $H_2{}^{15}O$ positron emission tomography (PET) might demonstrate changes in regional cerebral blood flow (rCBF) associated with transient sadness or happiness in healthy adult women.* *Method:* *Eleven healthy and never mentally ill adult women were scanned, by using PET and $H_2{}^{15}O$, during happy, sad, and neutral states induced by recalling affect-appropriate life events and looking at happy, sad, or neutral human faces.* *Results:* *Compared to the neutral condition, transient sadness significantly activated bilateral limbic and paralimbic structures (cingulate, medial prefrontal, and mesial temporal cortex), as well as brainstem, thalamus, and caudate/putamen. In contrast, transient happiness had no areas of significantly increased activity but was associated with significant and widespread reductions in cortical rCBF, especially in the right prefrontal and bilateral temporal-parietal regions.* *Conclusions:* *Transient sadness and happiness in healthy volunteer women are accompanied by significant changes in regional brain activity in the limbic system, as well as other brain regions. Transient sadness and happiness affect different brain regions in divergent directions and are not merely opposite activity in identical brain regions. These findings have implications for understanding the neural substrates of both normal and pathological emotion.*
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Although most agree that the pathological states of depression and mania are brain based, relatively little is known about the precise regions that are important in inducing and regulating normal mood and whether these are also involved in producing affective illness (1–3). Early in this century Papez (4), MacLean (5–7), and others formulated the concept of the limbic loop and made the association between this primitive part of the brain and human emotion. More information about the functional neuroanatomy of emotion has been gleaned from patients with strokes (8–13), multiple sclerosis (14), or other destructive lesions in the frontal or temporal lobes who then develop depression or mania (15). In addition, there is a substantial literature on the role of the temporal lobes in modulating affect in health and disease states such as focal epilepsy (16–21). Recently, new technologies have emerged, such as positron emission tomography (PET) (2, 22, 23), single photon emission computed tomography (24, 25), and functional magnetic resonance imaging (MRI) (26–29), which can probe the functional neuroanatomy

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TABLE 1. Tasks Performed by 11 Healthy Women During Mapping of rCBF

Task Name	Number of Runs	Order	Eyes	Stimuli	Cognitive Tasks			
					Introspection	Remembering Specific Events	Looking at Faces	Mood Change
Rest/introspection	1	Initial	Closed	None	Yes	No	No	No
Neutral emotion	2	Semirandom	Open	Faces	Yes	Yes	Yes	No
Happy emotion	2	Semirandom	Open	Faces	Yes	Yes	Yes	Yes
Sad emotion	2	Semirandom	Open	Faces	Yes	Yes	Yes	Yes

of affective illness and the normal regulation of human emotion.

Our group and others have employed PET to delineate the neuroanatomic regions involved in experiencing different emotions (30–35). An important question is whether the functional brain changes associated with clinical depression are similar to those that accompany transient sadness in normal subjects. Many persons commonly, and possibly mistakenly, link clinical depression with the state of transient sadness that is part of healthy normal psychological experience. However, there is only limited phenomenological overlap and scant scientific justification for linking these two emotional states. Although some depressive episodes follow psychosocial stressors that normally produce grief, others are unrelated to life events, particularly late in the course of the illness (36). The difference between clinical depression and sadness is most vivid in patients, especially those with bipolar illness, who are significantly depressed but who claim that they can no longer feel sadness ("emotional numbing"). Thus, the differences and similarities between sadness and clinical depression are of major interest in understanding the neural networks involved in mood dysregulation. Are transient sadness and clinical depression related to the same neurobiological substrates but to a different degree of sensitivity or persistence, or do they occupy different substrates with or without some overlap? To address this question, we carried out the current PET study designed to activate central nervous system regions that accompany transient sadness or happiness.

METHOD

Subjects

Eleven healthy paid female volunteers (mean age=33.3 years, SD=12.3) participated in the study. This initial investigation was limited to women in order to avoid confounds due to gender. Another study has involved men and explored possible gender differences in both the induction procedure and regional cerebral blood flow (rCBF). All subjects gave written informed consent and were healthy as established by physical and neurological examinations, medical and psychiatric histories, and routine laboratory tests including drug screen, testing for HIV, and an MRI of the head. Subjects were also screened for psychiatric illness and were deemed never mentally ill following the structured Schedule for Affective Disorders and Schizophrenia—Lifetime Version Modified for the Study of Anxiety Disorders (SADS-LA) interview (37). All subjects except one were right-handed (38).

Tasks

The rCBF was mapped while subjects performed four different tasks (table 1). The emotion induction tasks were initially piloted in a series of nine healthy volunteers, and the following combination of stimuli were chosen for their ability to facilitate maximal emotional changes in normal control subjects. The initial scan, done only once, was a "resting" study in which subjects were instructed to "close their eyes and concentrate on their sensory and emotional experience." Subjects were aware that they would later be questioned about their experiences during the scan. Subjects next underwent happy, sad, and neutral activation tasks, each performed twice (a combined total of seven scans per subject). Subjects performed the tasks in a semirandom order after the initial scan. The entire scanning session was divided in two (the first three tasks, second three tasks), and each task occurred randomly once within each half. Thus, for example, two sadness activations could be adjacent only if one occurred at the end of the first half (i.e., scan 4) and the beginning of the second half (i.e., scan 5). In addition, the last task of the entire session was never a sadness induction in order to avoid unintended carryover effects of sadness persisting after the scanning episode.

Before the scanning session the purpose of the study was explained, and each subject was asked to name specific events in her life that, when recalled, would make her sad (two events) or happy (two events). For the neutral control task each subject was also asked to recall two specific times in the recent past when she was emotionally neutral, that is, not experiencing any particular emotion (two events). Each memory (see results section) was then reviewed by two of us (M.S.G., P.I.P.) in order to assess whether the emotion was appropriate (e.g., not mixed happy/sad or angry), and additional specific sensory stimuli were elicited that would possibly aid in recalling the memory (e.g., exact place where the subject was at the peak moment of emotion, clothing, time of year, sights or smells).

During each task, after being reminded of the affect-appropriate event, each subject was then sequentially shown three affect-appropriate human faces from the Pennsylvania Battery designed by Drs. Raquel and Ruben Gur (39) (45 seconds per face). The faces were displayed through the use of Superlab—a Macintosh computer software program for administering neuropsychological tests (40). Stimuli were displayed on a 19-inch high-resolution computer monitor approximately 12–18 inches in front of the subject's eyes while the subject was in the PET scanner.

Thirty seconds before radiotracer injection, each subject was told of the nature of the task (happy, sad, or neutral) and then reminded of a previously agreed-upon affect-appropriate memory. Subjects were instructed to remember the emotion that they had felt during that time and to try to make themselves feel that way again. They were then reminded that to help them reexperience the appropriate emotion, they would be shown affect-appropriate faces. They were instructed to look at the face, imagine the emotion being experienced by the individual, and then to try and make themselves feel that emotion. After radiotracer injection, the faces were shown for another 105 seconds, with 10 minutes of rest between tasks. Affect rating scales (visual analog scale and the Positive and Negative Affect Schedule [41]) were completed immediately before and then retrospectively after each task. The visual analog rating scale used was 25 points (–12 to 12), with –12 representing very sad during all of the scan, –8 moderate sadness during most of the scan, 0 balanced mood, 8 moderate happiness during most of the scan, and 12 representing very happy

during all of the scan. The room was darkened, and eye movements were not otherwise restricted.

PET Image and Data Acquisition

Radiotracer uptake was measured seven times in each subject with PET by using a Scanditronix PC2048-15B scanner, with an in-plane resolution of 6.9 mm (full width at half maximum) and an axial resolution of 5–6 mm. Data were collected in 15 planes parallel to the inferior canthomeatal line and spaced 6.5 mm apart. Transmission scans were obtained by using a ^{68}germanium/^{68}gallium source rotated around the subject's head and were used to correct the emission scans for photon attenuation by cerebral tissues and skull. Head movement was restricted with a thermoplastic mask, facilitating pixel-by-pixel within-subject comparisons of rCBF during the various tasks. Between 30 and 40 mCi of $H_2{}^{15}O$ was injected intravenously 30 seconds after the subject began each task, and tomographic image acquisition began when the bolus of radiotracer arrived in the head. Each scan lasted for 60 seconds, with the subject continuing the task for another 15 seconds. Because of the near-linear relationship between rCBF and tissue counts accumulated over a brief scan interval, the images reflect relative changes in rCBF during different scan states (42, 43). The time between scans was approximately 12 minutes (i.e., more than six half-lives of $^{15}O_2$) in order to allow radioactive decay to less than 2% of peak levels.

Data Analysis

Image manipulations and calculations were performed by using PROMATLAB (Mathworks, Sherborn, Mass.) on a Sun SPARCstation 2 (Sun Microsystems, Inc., Mountain View, Calif.) with software for image display (ANALYZE, Biodynamic Research Unit, Mayo Clinic, Rochester, Minn.) (44). Image data were analyzed by using statistical parametric mapping software (MRC Cyclotron Unit, Hammersmith Hospital) (45, 46). Each scan was individually inspected for image quality and possible artifacts and was interpolated to 43 slices, and roll and yaw were corrected. The intercommissural line was identified from the rCBF images, and the images were reoriented along this line (46). The images were then resized, rescaled, and resliced to correspond to the human brain atlas of Talairach and Tournoux (i.e., stereotactically normalized) (47).

Statistical Analysis

For PET images, statistical analysis was performed by using pixel-based analysis of covariance of tissue count images obtained over 60 seconds to adjust for differences in global flow over the different baseline and activation conditions (45). The covariation analysis first generates seven mean activity maps: one for the rest condition, two for the neutral task, and two each for both of the two experimental conditions (sadness and happiness), all normalized to a mean global CBF of 50 ml/min per 100 gm, and each with an associated error variance. The pixel values of rCBF in these maps, together with the associated error variances, were used for further statistical analysis. Statistically significant focal changes in activity, assumed to be independent of changes in global activity, can then be detected (45). The results from each time that a subject performed a specific task were then averaged for final comparison analysis across tasks. Planned comparisons between the three conditions were performed by using t statistics with a threshold set at $p<0.05$ and a correction for multiple nonindependent comparisons. The results were displayed as statistical parametric maps (48).

Four planned rCBF comparisons were made: 1) the neutral emotion task minus the passive introspection rest task to assess the regions activated by the event recall and face viewing aspects of the mood induction paradigm; 2, 3) the sad and happy tasks minus the neutral task; and 4) a direct comparison of the happy and the sad tasks. Significant increases and decreases in blood flow between the two conditions were displayed through the use of statistical parametric maps. Pixels that were significant at the given threshold of $p<0.05$ (corrected for multiple comparisons) were displayed and listed.

The significance of emotional changes across tasks was determined by using paired, two-tailed Student's t tests to compare ratings on the Positive and Negative Affect Schedule and 25-point visual analog scale before and after the emotion induction tasks.

RESULTS

Performance

The induction method outlined earlier in this article induced significant transient states of sadness and happiness in these 11 women. For the visual analog scale, the mean change during the sadness tasks (averaged) was −7.9 (SD=4.5) ($t=5.89$, $df=10$, $p<0.001$, Student's paired t test). This corresponded to most subjects reporting "moderate sadness for most of the scan." The mean change during the happiness tasks was 7.7 (SD=2.8) ($t=9.17$, $df=10$, $p<0.0001$, Student's paired t test), which corresponds to "moderately happy during most of the scan." It is interesting and important to note that although most subjects were able to induce the transient emotional state, most had also returned to a neutral state before the next task began 10 minutes later. There was no significant change in mood during the neutral emotion task according to ratings on the visual analog scale.

The significant results documented by the 25-point visual analog scale were also demonstrated by the Positive and Negative Affect Schedule (41), administered immediately before and retrospectively after each task. In our experience, the positive and negative affects rated by the Positive and Negative Affect Schedule do not necessarily correspond well to states of pure happiness or sadness. For example, low positive affect is characterized by sadness and lethargy, while low negative affect is characterized by calmness and serenity (41). During the two sadness inductions there was a mean decrease of −3.73 (SD=4.50) ($t=2.7$, $df=10$, $p=0.02$, Student's paired t test) on the positive affect scale and an increase of 3.92 (SD=3.23) on the negative affect scale ($t=4.01$, $df=10$, $p<0.01$, Student's paired t test). During the happiness induction there were nonsignificant increases of 4.45 points (SD=8.30) ($t=1.7$, $df=9$, Student's paired t test) on the positive affect scale and 0.05 (SD=0.83) ($t=0.19$, $df=9$, Student's paired t test) on the negative affect scale. During the neutral mood inductions there was a significant decrease in the positive affect score of the Positive and Negative Affect Schedule ($t=3.04$, $df=9$, $p=0.01$, Student's paired t test), due in part to lower ratings of "attentiveness" ($t=3.5$, $df=9$, $p<0.01$; Student's paired t test for all comparisons), "alertness" ($t=2.75$, $df=9$, $p<0.05$), "enthusiasm" ($t=2.9$, $df=9$, $p<0.05$), and "interest" ($t=3.5$, $df=9$, $p<0.01$) during the neutral task than immediately before.

Arterial P_{O_2}, O_2 saturation, and P_{CO_2} did not significantly change across the different emotional tasks for seven subjects who had arterial blood gas monitoring after each scan.

After completion of the study, subjects were asked to

TABLE 2. Brain Regions Significantly Activated During Transient Emotional Tasks Performed by 11 Healthy Women

Task	Talairach Coordinates x	y	z	z Score	rCBF[a] Control	Task	Region[b]
Transient sadness compared to neutral task							
Increase in sadness							
	2	44	12	4.4	63.5	65.0	Right medial frontal gyrus
	−14	30	0	3.8	45.0	46.7	Left cingulate gyrus
	26	10	−8	3.9	65.7	67.2	Right putamen
	0	12	4	4.0	47.3	49.1	Midcaudate
	−14	18	−8	3.9	57.1	58.5	Left cingulate, orbitofrontal cortex
	−18	−12	12	3.8	53.0	54.8	Left thalamus
Decrease in sadness							
	−24	−74	16	4.3	50.8	49.3	Left medial occipital gyrus
	−50	−60	−4	3.8	41.2	40.0	Left medial occipital gyrus
	50	−62	−4	4.0	37.9	36.5	Right medial occipital gyrus
	46	−50	20	3.8	56.3	54.9	Right superior temporal gyrus
	−44	−74	0	4.1	38.3	37.2	Left lateral occipital gyrus
	20	−90	0	4.1	52.8	50.3	Right occipital cortex
	46	−56	16	4.0	53.8	52.9	Right midtemporal gyrus
Transient happiness compared to neutral task[c]: decrease in happiness							
	52	−52	−4	4.6	38.7	37.6	Right midtemporal gyrus
	20	54	−8	3.7	40.6	39.5	Right superior frontal cortex
	−44	−58	8	3.7	50.5	49.1	Left midtemporal gyrus
Transient sadness compared to transient happiness							
Increase in transient sadness							
	20	36	8	4.0	41.1[d]	42.4[e]	Right anterior cingulate
	18	10	−8	4.2	63.9[d]	65.3[e]	Right putamen
Decrease in sadness[f]							
	−20	−72	16	4.5	54.5[d]	52.8[e]	Left cuneus
	−40	−80	−4	3.9	37.2[d]	35.8[e]	Left inferior occipital gyrus
	−22	−96	0	3.8	38.4[d]	36.4[e]	Left occipital cortex
	22	−88	0	3.7	53.3[d]	51.1[e]	Right occipital cortex
	−12	−96	8	3.7	.42.7[d]	40.8[e]	Left occipital cortex
Neutral task compared to passive control							
	12	−98	8	2.7	32.2[d]	39.4[e]	Right visual cortex
	−14	−98	8	2.6	31.0[d]	37.7[e]	Left visual cortex

[a]Relative rCBF normalized across subjects to 50 ml/dl per minute.
[b]Regional names are only approximations. The effective resolution of this analysis is 11 mm at full width at half maximum. This is especially true for smaller structures such as the amygdala.
[c]No significant increases.
[d]Happy.
[e]Sad.
[f]2,530 voxels divided by 66,000 total.

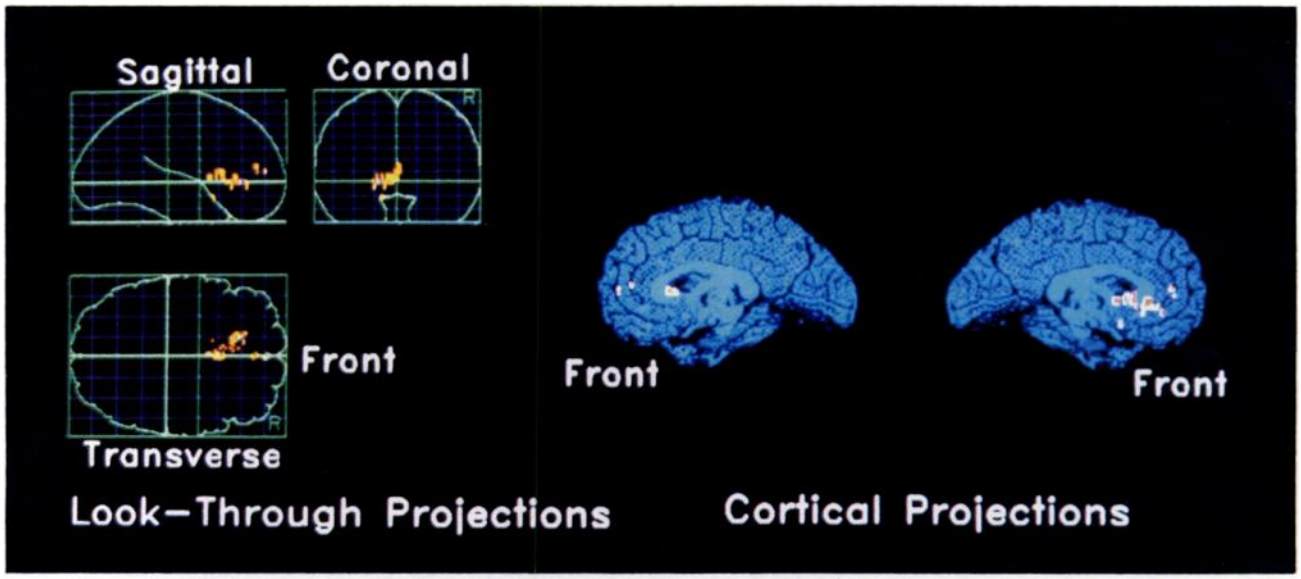
subjectively rate the difficulty of the emotion inductions. Subjects rated the neutral task the easiest, followed by happiness and then by sadness.

The types of memories used by each subject for each of the two happiness, sadness, and neutral inductions are as follows (11 subjects × 6 tasks=66 memories). For the happiness induction, subjects remembered children's births (N=2), engagements and marriages (N=4), raises, graduations, job offers (N=4), events shared with friends and family (N=7), and other (N=5). For the sadness induction, subjects remembered the death of a loved one (N=9), separations from loved ones (N=2), illness of a loved one (N=5), and other (N=6). For the neutral induction, subjects commonly remembered specific moments in the week before the scan; these included commuting (N=6), shopping (N=2), moments from work or school (N=4), performing routine chores (N=4), and other (N=6).

Regional Activation During Specific Tasks

Neutral task minus passive rest task (table 2). In order to determine which brain areas are activated by the general methods used to induce the emotional state (remembering events, looking at human faces) rather than as a result of feeling sad or happy, we compared the average of the two neutral emotion tasks with a different control task in which subjects had their eyes closed and were introspective. Compared to the passive control task, the neutral emotion induction task was associated with more activity in the visual cortex, consistent with the visual nature of looking at human faces, and

FIGURE 1. Regional Brain Activity of 11 Healthy Women During Sadness[a]



[a]These images are statistical parametric maps of regions that were significantly more activated during the average of the two transient sadness tasks than during the average of the two neutral emotion tasks. During sadness there was increased activity in diffuse limbic and paralimbic structures including the left prefrontal, bilateral anterior cingulate, hypothalamus, and inferomedial prefrontal cortex. All color points are pixels that were significantly more active during the sadness task at the given threshold of $p<0.05$ (corrected for multiple comparisons). The images on the left are look-through three-dimensional projections, whereas those on the right are cortical renderings with significant pixels mapped onto the medial surface of the brain.

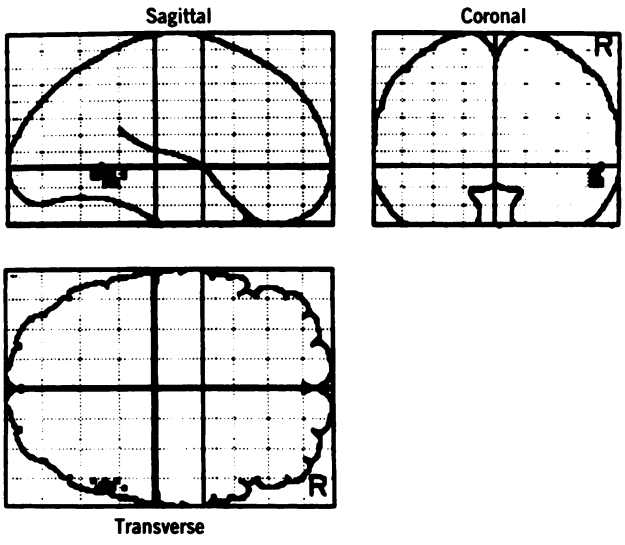
with less activity in the bilateral prefrontal, as well as anterior temporal, cortex.

Sad task minus neutral task (table 2 and figure 1). Compared to the neutral mood induction task, during the average of the two sad tasks, our subjects had significantly more activity in diffuse limbic, paralimbic, and other related structures (N=11, t test, $z>3.8$, $p<0.05$ with Bonferroni corrections, for all statistical parametric map results, effective resolution at full width at half maximum +11 mm). These included the medial prefrontal, left lateral prefrontal, bilateral anterior cingulate, fornix, insula, thalamus, midline cerebellum, and bilateral putamen and caudate. Significantly less activity during sadness than during the neutral emotion task occurred in the visual cortex (N=11, t test, $z>4.0$, $p<0.05$ with Bonferroni corrections).

Happy task minus neutral task (table 2 and figure 2). During the average of the two transiently happy tasks, the 11 subjects showed no areas of significantly increased activity. However, in contrast to the sad inductions, there were significant and widespread decreases in activity in bilateral midtemporal cortex, right prefrontal cortex, and right superior temporal gyrus (N=11, t test, $z>3.8$, $p<0.05$ with Bonferroni corrections).

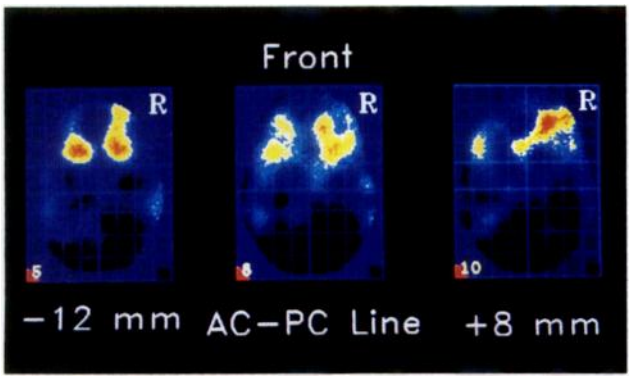
Sad task versus happy task (table 2 and figure 3). Direct comparison of the averages of the two emotional tasks revealed that during transient sadness, there was significantly more rCBF in the right anterior cingulate and bilateral prefrontal cortex, thalamus, and basal ganglia (N=11, t test, $z>3.8$, $p<0.05$ with Bonferroni corrections). There was also significantly less activity during sadness in the bilateral visual cortex (N=11, t test, $z>3.8$, $p<0.05$ with Bonferroni corrections) (table 2).

FIGURE 2. Regional Brain Activity of 11 Healthy Women During Happiness[a]



[a]In contrast to sadness, transient happiness was associated with significantly less activity in secondary association cortex in the bilateral temporal-parietal and right prefrontal cortex compared to the neutral control task. All plotted points are pixels that are significantly less active during the happiness task at the given threshold of $p<0.05$ (corrected for multiple comparisons).

FIGURE 3. Regional Brain Activity of 11 Healthy Women During Sadness Compared to Happiness[a]



[a]This statistical map demonstrates those brain regions that were significantly more activated during the average of the two sadness tasks than during the two happiness tasks. Thus, direct comparison of the two emotional states demonstrates that sadness activated a larger portion of limbic cortex, particularly in the right medial inferior prefrontal cortex, anterior cingulate, and bilateral putamen. All color points are pixels that are significantly more active during the sadness task than during the happiness task at the given threshold of $p<0.05$ (corrected for multiple comparisons). (See table 2 for exact local maxima.)

Analysis of Run 1 and Run 2 for Each Task

In order to examine whether regional activity differed as a function of the novelty of the task, we directly compared the first and second runs of the neutral, sadness, and happiness tasks by using the 11 subjects with normalized data. There were no significant differences in the degree of emotion induced, the subjective rating of performance, or the degree of difficulty during the first and second runs (scores on the visual analog scale and Positive and Negative Affect Schedule, Student's paired t tests) for any of the tasks. There were, however, significant differences in regional activation between the first and second runs of the happy and sad, but not the neutral, tasks (omnibus statistic chi-square value for neutral tasks=5.92, N=11). There was more activity in the secondary visual cortex and less activity in the left mesial temporal region (hippocampus) during the first than during the second happiness task (N=11, t test, $z>3.8$, $p<0.05$ with Bonferroni corrections). Finally, there was more activity in the bilateral mesial prefrontal cortex and left thalamus in the first than in the second sadness run (N=11, t test, $z>3.8$, $p<0.05$ with Bonferroni corrections).

DISCUSSION

This study has demonstrated that $H_2{}^{15}O$ PET can detect significant changes in regional brain activity during transient emotional states in healthy adult women. Specifically, transient sadness is accompanied by significant increases in rCBF in widespread limbic and paralimbic structures—right medial frontal gyrus, left dorsolateral prefrontal cortex, bilateral cingulate gyrus, caudate, putamen, thalamus, fornix, left insula, and left midline cerebellum. During transient happiness there is a nonsignificant increase in rCBF in the left anterior cingulate and a significant and widespread decrease in rCBF in bilateral temporal-parietal and right frontal cortex. These novel findings have interesting theoretical and clinical implications.

Previous Work Localizing the Neuroanatomical Regions Important in Mood Regulation

Emerging data from clinical case reports and EEG and PET studies are beginning to implicate a *functional* loop involved in mood regulation that may operate abnormally in patients with affective illness (2, 49–55). This loop probably encompasses both temporal lobes, the anterior cingulate and the prefrontal cortex, the basal ganglia, and possibly the midline cerebellum. Numerous PET studies, conducted during the resting state, of depressed subjects with primary depression have found prefrontal lobe hypoactivity (2, 51, 54, 56, 57), with a few exceptions (58). In addition, PET studies examining patients with secondary depression have revealed decreased prefrontal lobe metabolism in depressed patients with Parkinson's disease, Huntington's chorea, bulimia nervosa, focal epilepsy, and AIDS (59–63). An unanswered question is whether this hypoactivity is state dependent and disappears after the clinical depression resolves. Some (64) but not all (65, 66) preliminary data are consistent with the notion that prefrontal hypoactivity returns to normal between episodes of clinical depression (2).

The literature on brain lesions and affective state in humans is complex, and a detailed review is beyond the scope of this article. In brief summary, however, left prefrontal damage has been associated with secondary clinical depression (8, 11, 12, 14, 67), while damage to the right side of the brain, particularly in the temporal lobe, has been implicated in cases of secondary mania (3, 9, 10, 68, 69). However, this entire area of differential hemispheric involvement in depression and mania remains in dispute (70, 71). In addition, since these studies deal with depression or mania rather than transient mild emotions such as happiness or sadness, they are difficult to compare to our study.

In contrast to the abundant emerging data on the structural and functional brain changes associated with clinical depression, there is a dearth of data on brain changes associated with sadness or grief, although several investigators are beginning to work in this area. In the initial imaging study in this field, Pardo and colleagues studied seven healthy volunteer men and women and demonstrated that during transient sadness, induced by remembering a sad event, there was significantly increased activity in the bilateral inferior and orbitofrontal cortex (31). The control condition was a passive task of closing the eyes and having no programmed mental activity. The notion that thinking

sad thoughts causes increased left prefrontal activity was also posited by Drevets and colleagues, who studied 33 depressed female subjects with O_{15} PET and found left prefrontal *hypermetabolism* (58). They hypothesized that their results conflict with the preponderance of studies that have found left prefrontal hypometabolism in depression because their subjects were not instructed to perform any task while in the scanner and were thus free to ruminate and think sad thoughts. Most other studies that have found left prefrontal hypometabolism in depression have had subjects performing some form of task.

Reiman and colleagues used PET to image 12 healthy women during internally generated (remembering events) and externally generated (watching silent film clips) emotional states of happiness, sadness, and disgust (34). They did not report their data separately in terms of the different emotional states but did find differences between externally and internally generated emotional states when all three emotional states were grouped together. Visually generated emotion had higher activity in the occipital-temporal and anterior temporal cortex, amygdala, hippocampal formation, hypothalamus, and lateral cerebellum. An interesting finding is that internally generated emotion had higher levels of activity in the anterior cingulate. Similarly, Downhill and Robinson recently reported pilot PET data for two elderly subjects shown video sequences containing happy, fearful, or neutral contents (35). They concluded that emotional activation produced changes in limbic areas of cortex.

On the basis of the previously cited work, our prestudy hypothesis was that transient sadness would be accompanied by a greater increase in blood flow in the left than in the right prefrontal cortex. We also hypothesized that depressed patients (either on a state or trait basis) would activate these regions differently than control subjects. We are currently testing the latter hypothesis in ongoing work.

Sadness—Limbic and Paralimbic Activation

We have demonstrated that transient sadness is associated with increased activity in diffuse paralimbic structures, including the inferior-medial prefrontal cortex and anterior cingulate cortex bilaterally, as well as the left prefrontal cortex. These findings extend and elaborate on the pilot study of Pardo and colleagues, who found more activity in inferior and orbitofrontal cortex during transient sadness than during a passive control condition (31). The present study, using a more active control condition (i.e., remembering neutral past events in addition to viewing neutral facial emotions), suggests that during transient sadness, there is more activity in many limbic structures and that prefrontal cortical activation is more medial than Pardo and colleagues reported.

This study also invites further exploration of the complex relationship among transient sadness, grief, and clinical depression. We have demonstrated that transient sadness has associated increases in medial prefrontal activity. Many of the subjects used grief memories to induce their sadness. As mentioned earlier in this article, many patients with clinical depression have associated hypometabolism in the medial prefrontal cortex (2). A tempting model for integrating these concepts is to speculate that transient sadness or grief-induced hyperactivity in medial prefrontal and limbic structures might evolve in some susceptible persons into a compensatory pattern of medial prefrontal hypometabolism. An interesting parallel may exist with another neuropsychiatric disease—complex partial seizures. During a seizure there is transiently increased activity initially, followed by postictal hypometabolism at the site of the seizure focus and surrounding tissues (72–74). One wonders whether a similar mechanism might be working in clinical depression, although the time scale of seizures (seconds to minutes) is different from that of sadness and grief (minutes to months). Further work with serial scanning of subjects with grief reactions that resolve and others that progress into a state of clinical depression may help test this formulation.

The anterior cingulate, activated in the present study during transient sadness, is an area of the brain that animals self-stimulate for pleasure (75–77) and is also part of the efferent system from the amygdala, as revealed in studies in animals (78, 79) and man (80). Finally, studies have also highlighted the role of the anterior cingulate in affiliative behavior and bonding (76, 79, 81–83), as well as attention (84–88).

Happiness—Decreases in Cortical Activity

In contrast to the marked activation in limbic structures during transient sadness, transient happiness is associated with only nonsignificant increases in anterior cingulate activity. The most significant changes during happiness are *reductions* in activity in secondary association cortex. This first demonstration of brain changes during transient happiness is interesting in the light of recent PET research into the neurobiology of euphoria. London and colleagues have demonstrated that during morphine- and cocaine-induced euphoria (89–91), there are profound reductions in regional activity in prefrontal and bilateral parietotemporal cortex. We have found that the euphoria induced by intravenously administered procaine is associated with robust mesial paralimbic (especially anterior cingulate) activation in the absence of diffuse cortical activation (30). The mild happiness induced in the present study would not likely be comparable to the profound euphoria produced by these powerful pharmacologic agents. Nonetheless, the parallel reductions in activity in secondary association cortex may be common to both transient happiness and profound euphoria, and these changes may exist on a continuum.

The current study also complements previous work by our group demonstrating that intravenously administered procaine can directly activate amygdala and

paralimbic structures and produce resultant changes in mood ranging from anxiety to euphoria, as well as psychosensory changes including visual and auditory hallucinations (30). Similar to the induction of happiness, procaine-induced euphoria is associated with secondary association cortex hypometabolism and correlates inversely with left mesial temporal rCBF. Procaine-induced dysphoria or anxiety is associated with more widespread increases in activity in the amygdala and its projections and correlates positively with right mesial temporal (amygdala) activity. The amygdala are crucial structures in determining the emotional content of normal daily experience and are intricately connected with limbic structures, as well as with higher cortex (92). Several groups have reported EEG spikes from the amygdala or surrounding regions during psychotic behavior or psychological distress in man (93–98). In animals, removal of the amygdala bilaterally often results in the Klüver-Bucy syndrome, with resultant hypoemotionality (99). Thus, the current study, as well as previous studies of both man and other animals, implicates the amygdala as crucial structures in regulating emotion.

Another possible clinical application of these findings is in the subset of patients with advanced multiple sclerosis who reach a state of inappropriate euphoria (100–108). The present study predicts that this inappropriate euphoria may result from the combined effects of multiple lesions in right prefrontal and bilateral temporoparietal regions or from damage to the left amygdala, or both. In a similar clinical vein, these results imply that patients with euphoric mania would have relatively decreased activity in these secondary cortical regions and the left amygdala, while dysphoric or irritable manic patients would have preserved activity in these cortical areas, along with bilaterally increased activity in the amygdala and limbic structures (3).

Limitations and Cautions in Interpretation

Because we were inducing a subjective change in transient emotion, this study relied on self-ratings and suffers from not having an objective measure of "performance." During the prescan explanation of the purpose of the study, we emphasized that honesty in self-reporting was more important than the actual degree of emotion induced, that subjects would be paid even if no emotions were induced, and that mild changes in emotion were also useful for correlational analysis. The self-ratings might also suffer if some people were better able to monitor and rate their internal emotional state than others (alexithymia) (40). This was not noted to be a problem in these female volunteers, and future studies should explicitly examine this issue.

Another potential problem with this type of work involves the purity of the emotional state. Many memories are emotionally mixed. Sadness and happiness are not necessarily mutually exclusive and can often be experienced at the same time. The memories were prescreened with this in mind. If mixed emotional states did occur, it would tend to diminish the differences in the direct comparison of the happy and sad states and not in the emotional states compared to the neutral control.

An additional question arises when one tries to distinguish those brain regions that are activated because of the method used to induce the emotional state from those regions activated by experiencing the actual emotion. That is, what regions are activated during sadness in particular, compared to other regions that are activated by remembering emotionally laden memories in general or seeing human faces? One can begin to answer this question from several directions. First, one can look at other published brain activation studies that used similar tasks (e.g., recalling memories [109] or looking at the emotional content of faces [110]), where emotion did not change. Different memory imaging paradigms have shown activity in the left dorsolateral prefrontal cortex with working memory (109, 111), mesial temporal structures with longer-term memory (112), and even the cerebellum with some forms of conditioning (113). Examination of the emotional content of faces involves the left prefrontal cortex, bilateral anterior temporal cortex, and right insula, as well as primary visual cortex (110). Second, one can compare the neutral activation task to a passive resting condition. The induction method in general activated the visual cortex. Thus, from two perspectives, the limbic activation seen with sadness does not appear to be due to the nonspecific aspects of the task and is more likely to be due to actually experiencing the emotion. Third, if one compares the images during sadness and happiness, almost all of the mood induction and processing components of the task should be subtracted out, and only regions differentially involved in the emotional content of the affective state should be revealed (figure 3).

In interpreting these findings one should also remember that demonstrating an *association between* regional brain activity and a transient emotional state is not necessarily the same as saying that a specific brain region and an emotional state are *causally linked* (114). The brain regions that we have demonstrated as active during transient sadness might be epiphenomenally activated and not actually serve a direct role in mood regulation. For example, one might be more attentive during a sad state and activate, indirectly, brain regions involved in attention. Further studies using different induction methods are needed, as are techniques such as transcranial magnetic stimulation that can produce "temporary lesions" and then measure the effect on emotional state, thereby implying a tighter causal connection (115).

There were changes in regional activity in both the happy and sad tasks from run 1 to run 2, although these are of unclear impact on the final results. Both runs of each task were averaged for the statistical analyses, and thus these minor differences across runs are unlikely to greatly affect the overall results. The increased visual cortex activation in the first happiness task may repre-

sent the novelty of examining faces during the first run. In addition, the increased mesial prefrontal and left thalamic activity in the first run of the sadness task may be consistent with the novelty of performing the induction and with more rCBF going to the regions active in the task. Other studies involving repeated scans of the same neuropsychological task have found that task novelty directly influences regional brain activity (84). Some brain regions, particularly the anterior cingulate, are more active during initial runs of a task, while others are consistently activated and do not change across repeated runs (84). The current study design did not allow for direct examination of these issues in this mood induction paradigm.

Finally, it should be emphasized that this study involved only healthy women. There is a growing body of evidence of gender differences in brain structure and functional neuroanatomy. In fact, healthy men do not activate these brain regions in the same fashion (George et al., unpublished manuscript).

SUMMARY

In this study, happy and sad moods in healthy women were associated with significant changes in brain regions detectable by $H_2{}^{15}O$ PET. Sadness activated limbic and paralimbic structures, while happiness was associated with temporal parietal reductions. This study begins to map the functional neuroanatomy of different transient emotional states in healthy individuals. Future studies like this one are needed to determine whether these same brain regions are associated with other common emotions such as anger, anxiety (32, 33, 116, 117), or disgust (118). Work such as this involving the regulation of affect in the normal range may then help uncover the pathological mechanisms and substrates in disorders of anxiety and mood.

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