CHRONIC PHRENIC A COMMON AND often incapacitating disorder that is characterized by a varied group of symptoms that encompass multiple mental domains. The symptoms of schizophrenia include abnormalities in perception (hallucinations), language (disorganized speech), inferential thinking (delusions), motor activity (disorganized behavior), and emotion (blunted or inappropriate affect and anhedonia).1 Explaining the neural basis of these diverse symptoms is a major challenge to contemporary psychiatry. Many of these symptoms have been studied with functional neuroimaging techniques, but studies to date have focused primarily on cognitive components, such as hallucinations and working memory.2 Emotion has been extensively studied with neuroimaging techniques in healthy individuals and people with classic emotional disorders, such as anxiety and mood disorders.3-11 However, to date the neural basis for emotional abnormalities in schizophrenia has not been explored in depth with neuroimaging techniques.

Anhedonia, the loss of the capacity to subjectively experience pleasure, is a core clinical feature of schizophrenia. Although functional imaging techniques have been successful in identifying the neural basis of cognitive impairments in schizophrenia, no attempts to date have been made to investigate neural systems underlying emotional disturbances.

**Context** Loss of the capacity to experience pleasure (anhedonia) is a core clinical feature of schizophrenia. Although functional imaging techniques have been successful in identifying the neural basis of cognitive impairments in schizophrenia, no attempts to date have been made to investigate neural systems underlying emotional disturbances.

**Objective** To study the neural basis of emotional processing in schizophrenia by exploring the pattern of brain responses to olfactory stimuli in patients and healthy volunteers.

**Design** Positron emission tomographic study of patients with schizophrenia and healthy volunteers. Positron emission tomographic data were collected between July 21, 1995, and September 11, 1997, and data analyses were conducted in 1999-2001.

**Setting** The Mental Health Clinical Research Center at the University of Iowa, Iowa City.

**Participants** Sixteen healthy volunteers with a mean age of 29.5 years and 18 patients with schizophrenia and a mean age of 30.0 years.

**Main Outcome Measure** Areas of relative increase or decrease in regional cerebral blood flow, measured using positron emission tomography and the [15O]water method while participants performed an emotion-induction olfactory task to determine response to pleasant (vanillin) and unpleasant (4-methylvaleric acid) odors, compared between patients and healthy volunteers.

**Results** Patients with schizophrenia subjectively experienced unpleasant odors in a manner similar to healthy volunteers but showed impairment in the experience of pleasant odors. The analysis of the regional cerebral blood flow revealed that patients failed to activate limbic/paralimbic regions (eg, insular cortex, nucleus accumbens, and parahippocampal gyrus) during the experience of unpleasant odors, recruiting a compensatory set of frontal cortical regions instead.

**Conclusion** Abnormalities in the complex functional interactions between mesolimbic and frontal regions may underlie emotional disturbances in schizophrenia.
neural mechanisms of anhedonia in schizophrenia

pairment in both the subjective experience of pleasure and the ability to express emotion, with a pattern of abnormal features that differs from mood disorders. It has been proposed that anhedonia may be the result of a basic neurophysiological dysfunction and a vulnerability marker that precedes and contributes to the liability of developing schizophrenia. The inability to experience pleasure may lead, in turn, to idiosyncratic social functioning and social withdrawal.

In humans, the ability to experience potentially pleasant or unpleasant nature of stimuli and situations has evolved beyond immediate survival to support a variety of social behaviors. Consequently, social interactions in humans are dependent on hedonic processing. The exposure to pleasant (positive hedonic affect) and unpleasant (negative hedonic affect) odors has been shown to elicit positive or negative emotions and behaviors in healthy volunteers. The olfactory and the limbic systems share a substantial portion of neural substrates that have been implicated in the pathophysiology of schizophrenia. Moreover, abnormalities in olfactory identification ability have been proposed as a marker of cerebral dysfunction in schizophrenia. Abnormalities in olfactory identification in patients with schizophrenia do not seem to be influenced by sex or medication status.

We present the first functional neuroimaging study to date that examines the biological basis of hedonic appraisal in schizophrenia. The capacity to subjectively experience pleasure and unpleasantness is explored, using odors as stimuli to study the pattern of brain responses associated with the emotional experiences evoked through the olfactory system.

METHODS

Subjects

Between July 21, 1995, and September 11, 1997, 18 patients (16 male and 2 female) were included in the study with a diagnosis of schizophrenia (Diagnosis and Statistical Manual of Mental Disorders, Fourth Edition), based on evaluation with an extensive structured interview using the Comprehensive Assessment of Symptoms and History (CASH). Their mean (SD) age was 30.0 (8.94) years and their mean (SD) educational achievement was 12.9 (3.35) years. Three had comorbid substance abuse (1 with amphetamine dependence, 1 with cannabis abuse, and 1 with amphetamine abuse and cannabis dependence); there were no other comorbid diagnoses. Thirteen were right-handed, 2 were left-handed, and 3 were ambidextrous.

On the day of the positron emission tomographic (PET) scan, patients were either drug naive (n=6) or were medication free for 3 weeks before undergoing PET imaging (n=12). The patients who were drug naive were referred by clinicians throughout the state of Iowa for evaluation in our ongoing study of The Iowa Longitudinal Study of First-Episode Schizophrenia. They underwent PET imaging within a few days after a diagnosis of schizophrenia was confirmed and thereafter were treated with medications, usually while inpatients at the Mental Health Clinical Research Center, Iowa City, Iowa. The patients who were medication free for 3 weeks were recruited through the same referral network or were recent admissions to the clinical inpatient service at the University of Iowa Hospitals and Clinics, Iowa City. They were either medication free because their medications had been discontinued by their previous physician, because they had discontinued them themselves, or because they agreed to medication withdrawal for PET imaging research studies while under careful nursing and medical supervision as inpatients at the Mental Health Clinical Research Center. After being informed about the risks of discontinuation, all those who were withdrawn from medication gave written informed consent to undergo the withdrawal procedure.

Clinical symptoms were rated weekly and also on the day of the PET scan, using the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms. Symptoms on the day of the scan, as summarized by the mean (SD) ratings on the 3 major symptom dimensions, were in the mild-to-moderate range: negative, 2.53 (1.19); psychotic, 2.55 (1.43); and disorganized, 1.26 (1.24). A score of 2 is equivalent to a mild level of symptoms and a score of 3 is considered moderate. While undergoing PET imaging, 2 subjects reported experiencing auditory hallucinations during both olfactory PET tasks, as determined by post-study debriefing. All patients were able to comply with the study instructions. Sixteen healthy volunteers, recruited from the community by newspaper advertising, were evaluated. They were screened using an abbreviated version of the CASH to rule out psychiatric, neurologic, or general medical illness, including substance abuse. Nine healthy volunteers were female and 7 were male. All were right-handed. Their mean (SD) age was 29.5 (7.56) years and mean (SD) educational achievement was 14.25 (1.7) years.

The patients and healthy volunteers also were chosen based on equivalent smoking history (using total pack-years as the measure of smoking history), to avoid confounding generated by differences in olfactory sensitivity due to smoking. All but 3 healthy volunteers (81%) and all but 4 patients (78%) were smokers. The University of Pennsylvania Smell Identification Test (possible total score of 40) was used to assess the olfactory identification ability of the subjects. Subjects with a score of 30 or less were excluded from the study.

All subjects gave written informed consent to protocols approved by the University of Iowa human subjects institutional review board.

Activation Stimuli

We examined 2 closely matched olfactory stimuli that were similarly extreme in intensity valence and differed only in hedonic direction (ie, the stimuli were either extremely unpleasant or pleasant). This strategy matches the PET olfactory tasks on their olfactory component and permits us to iso-
late the extremes of hedonic response to obtain a relatively pure measure of regional cerebral blood flow (rCBF) response to pleasant and unpleasant olfactory stimuli.

Subjects were told to evaluate their experience of the odor, and they were informed that there was no correct or incorrect answer. They were presented with 100 µL of the odorant applied on a cotton ball and were instructed to keep their eyes closed and to breathe through their noses. Timing of the activation was such that odors were presented 10 seconds before the arrival of the [15O]water bolus to the brain, assessed individually for each subject. Following the PET scan, subjects rated the valence and intensity of the odors by pointing to a specific value on a visual analog scale, specifically designed for this study. The intensity scale ranged from 0 (undetectable) to 7 (very strong). The valence scale ranged from −7 (extremely unpleasant) to +7 (extremely pleasant).

Subjects first were exposed to the olfactory task during an initial scout injection study (using lemon extract as the odor) to avoid novelty effects that might confound the results. Both groups experienced the lemon extract as pleasant; the mean (SD) score for this odor for healthy volunteers was 4.40 (1.75), and for patients it was 1.67 (3.55) (t22 = 2.70; P = .009). During data acquisition of the PET scans, subjects then were exposed to 1 of 2 well-documented odors, pleasant (vanillin) and unpleasant (4-methylaleric acid), and asked to judge how pleasant or unpleasant the odors were. These odorants do not have confounding components of cranial nerve V stimulation. To avoid possible carryover of the more enduring effects of the unpleasant stimulus (as determined by pilot behavioral evaluation of a group of patients with schizophrenia and healthy individuals not included in the PET study), the scan for the pleasant odor was always obtained first. These 2 stimuli presented herein were part of a larger ongoing 8-condition study designed to use multiple sensory modalities to examine hedonic response in schizophrenia.

Data Acquisition and Image Analysis
Quantitative data of CBF from the PET images were acquired (GE 4096-plus whole-body scanner; GE Medical Systems, Milwaukee, Wis) following the administration of an intravenous injection of the [15O]water bolus. To acquaint subjects with the imaging conditions and to ascertain stimulus timing, the time from the arrival of the bolus to the brain was individually measured by delivering a 15-mCi bolus during the initial scout injection study. For all subsequent scans, subjects were administered an intravenous dose of 50-mCi [15O]water bolus. Imaging began at the time of injection (t = 0) and continued for 100 seconds in the form of twenty 5-second frames. Manual sampling and analysis as previously described or analysis via autosampler were used for arterial blood sampling (t = 0 to 100 seconds).31,32 Data from the first 40 seconds immediately after the arrival of the bolus transit were summed and reconstructed into 2-mm voxels (128 × 128 matrix) using a Butterworth filter (order = 6, cut-off frequency = 0.35 Nyquist). Using this summed image and the measured arterial input function, the rCBF was calculated on a pixel-by-pixel basis using the autoradiographic method33 and normalized by dividing by the global CBF. To reduce anatomical variability, an 18-mm Hanning filter was applied. Imaging was repeated at approximately 15-minute intervals.

Magnetic resonance imaging (MRI) scans were obtained for each subject with a standard T1-weighted, 3-dimensional, spoiled gradient-recalled echo pulse sequence on a 1.5-T GE Signa scanner (GE Medical Systems) (echo time = 5 ms, time to repeat = 24 ms, flip angle = 40°, number of excitations = 2, field of view = 26 cm, matrix = 256 × 192, slice thickness = 1.5 mm). The normalized quantitative images from the PET scans for rCBF and the MRI scans were analyzed using the locally developed software package BRAINS.34,35 The outline of the brain was identified on the MRI scans by a combination of edge detection and manual tracing. Magnetic resonance imaging scans were volume-rendered; the anterior commissure–posterior commissure (AC–PC) line was identified and used to realign the images of the brains of all the subjects to a standard position to place each image in standardized Talairach coordinate space.36 The PET image of each individual was then fit to that individual’s MRI scan using a surface-fit algorithm.37 After the delivery of each injection of [15O]water bolus, head movement was checked and the PET image was individually refit as needed. The results of the MRI scans of all the subjects were averaged so that the data obtained with PET imaging could be localized on coregistered MRI scans and PET images.38 The coregistered images were resampled and simultaneously visualized in all 3 orthogonal planes.

Statistical Analysis
Data analyses were conducted in 1999-2001. Sample sizes for both groups were based on a previous methodological study designed to determine optimal sample size for functional imaging studies of mental activity.39 The results of this method indicated that maximal sensitivity and power are obtained by a sample size greater than 15. Specific between-group differences in neural activation were examined by a direct statistical comparison between patients and healthy volunteers, using nonparametric statistical techniques that are particularly appropriate to complex between-group comparisons in PET imaging studies.40,41 Statistical techniques that rely on the general linear model for between-group comparisons make many assumptions about the data. Randomization analysis is a nonparametric statistical technique that makes no assumptions about variance and is not affected by between-group differences in variance. Our specific methods for conducting randomization analysis have been described elsewhere.40,42

The randomization analysis was based on an initial subtraction of the 2 experimental conditions from one another for all study subjects (ie, the rCBF data for the pleasant stimulus were sub-

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NEURAL MECHANISMS OF ANHEDONIA IN SCHIZOPHRENIA

The difference in mean rCBF in each peak, based on the subtraction of pleasant from unpleasant odors, is shown to indicate the differences in direction in each group. Negative vs. positive values indicate lower and higher rCBF, respectively. The overall size of the area of the peak indicates the number of voxels that exceed the preset significance threshold.

Comparison of PET imaging data from prior studies indicated that the peaks produced through randomization were relatively smaller than those produced by the Montreal-Worsley method, which we use for within-group comparisons. Areas where statistical analysis showed specific regional differences were identified as "peaks." This threshold closely approximates the sizes of peaks defined by a t = 3.61 (uncorrected) using the Montreal-Worsley method.

Every peak has been described by the number of adjacent pixels that comprise the peak and by Talairach atlas coordinates. The Talairach coordinates shown in the Table are based on 2 reference lines that create planes in a 3-dimensional grid system. Distances from these planes then can be measured in millimeters. For the coronal plane (the y dimension), the reference point is the midline and is used to identify the right (positive value) and left (negative value) hemispheres. The z dimension is defined by a vertical line that traverses the posterior margin of the anterior commissure and separates the front (positive values) from the back (negative values) of the brain. The AC-PC line creates a horizontal plane that defines the z dimension, with positive values being above the plane. For example, a region such as the left anterior insula (shown in the Table, with x, y, z coordinates of −34, 24, 1) is located 34 mm to the left of the midline, 24 mm anterior to the anterior commissure, and 1 mm above the plane defined by the AC-PC line. The region name given to each peak in the Table is based on direct visual inspection of coregistered MRI scans and PET images, which provide a more accurate localization than the use of Talairach coordinates alone. We report all significant peaks that contain more than 50 adjacent voxels.

Interpretation of the direction of rCBF change in each group was determined by examining the quantitative rCBF data for each peak identified as significantly different in the 2 groups by the randomization analysis. The voxels from the location with the highest significance level (as defined by the Talairach coordinates) were averaged for each condition within each group.

Table. Brain Regions Showing Relative Decreased and Increased rCBF in Patients With Schizophrenia During Exposure to the Unpleasant Odor Compared With the Pleasant Odor

<table>
<thead>
<tr>
<th>Brain Region (Brodmann Area [BA])</th>
<th>Randomization (Significance of Peak), P Value†</th>
<th>Size of Significant Peak, No. of Voxels‡</th>
<th>Difference in rCBF (mL/g/min) Between Unpleasant and Pleasant Odors§</th>
<th>Talairach Coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Lower rCBF in Patients</td>
<td></td>
<td>Patients Healthy Volunteers</td>
<td>x</td>
</tr>
<tr>
<td>Left anterior insula</td>
<td>&lt;.001</td>
<td>341</td>
<td>−0.76</td>
<td>7.88</td>
</tr>
<tr>
<td>Right nucleus accumbers</td>
<td>&lt;.001</td>
<td>806</td>
<td>−2.65</td>
<td>6.93</td>
</tr>
<tr>
<td>Left parahippocampal gyrus (BA 28/35)</td>
<td>&lt;.001</td>
<td>178</td>
<td>−3.76</td>
<td>4.08</td>
</tr>
<tr>
<td>Left superior temporal gyrus (BA 22/42)</td>
<td>&lt;.001</td>
<td>144</td>
<td>−6.00</td>
<td>2.15</td>
</tr>
<tr>
<td>Left lingual gyrus (BA 19)</td>
<td>&lt;.001</td>
<td>278</td>
<td>−5.07</td>
<td>3.42</td>
</tr>
<tr>
<td>Right lingual gyrus (BA 19)</td>
<td>&lt;.002</td>
<td>79</td>
<td>−3.15</td>
<td>4.04</td>
</tr>
<tr>
<td>Left vermis</td>
<td>&lt;.001</td>
<td>155</td>
<td>−3.47</td>
<td>3.88</td>
</tr>
<tr>
<td></td>
<td>Relative Higher rCBF in Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left and right orbitomedial prefrontal (BA 11)</td>
<td>&lt;.001</td>
<td>224</td>
<td>3.90</td>
<td>−5.31</td>
</tr>
<tr>
<td>Right dorsolateral frontal (BA 9/46)</td>
<td>&lt;.001</td>
<td>539</td>
<td>3.85</td>
<td>−5.17</td>
</tr>
<tr>
<td>Left dorsolateral frontal (BA 9/46)</td>
<td>&lt;.001</td>
<td>308</td>
<td>5.74</td>
<td>−2.42</td>
</tr>
<tr>
<td>Left medial frontal (BA 8/32)</td>
<td>&lt;.001</td>
<td>223</td>
<td>3.79</td>
<td>−4.46</td>
</tr>
<tr>
<td>Right lateral frontal (BA 10)</td>
<td>&lt;.001</td>
<td>191</td>
<td>3.70</td>
<td>−4.65</td>
</tr>
<tr>
<td>Right lateral frontal (BA 8)</td>
<td>&lt;.001</td>
<td>190</td>
<td>4.32</td>
<td>−4.10</td>
</tr>
<tr>
<td>Left lateral frontal (BA 8/9)</td>
<td>&lt;.002</td>
<td>83</td>
<td>3.96</td>
<td>−3.77</td>
</tr>
<tr>
<td>Left frontal operculum (BA 4/6)</td>
<td>&lt;.001</td>
<td>350</td>
<td>4.13</td>
<td>−5.80</td>
</tr>
<tr>
<td>Right parahippocampal gyrus (BA 28/35)</td>
<td>&lt;.002</td>
<td>86</td>
<td>2.19</td>
<td>−5.07</td>
</tr>
<tr>
<td>Left posterior cingulate (BA 23)</td>
<td>&lt;.001</td>
<td>80</td>
<td>1.66</td>
<td>−5.93</td>
</tr>
</tbody>
</table>

* rCBF indicates regional cerebral blood flow.
† The randomization analysis is a nonparametric statistical test that indicates the significance of the differences between patients and healthy volunteers. It is based on an initial within-group subtraction of the response to the unpleasant odor minus the pleasant odor, followed by a between-group comparison of the differences in response. The P values indicate the magnitude of the significance level for each peak, indicating between-group differences in response.
‡ The overall size of the area of the peak indicates the number of voxels that exceed the preset significance threshold.
§ The difference in mean rCBF in each peak, based on the subtraction of pleasant from unpleasant odors, is shown to indicate the differences in direction in each group. Negative values indicate lower rCBF and positive values indicate higher rCBF during exposure to the unpleasant odor.
The mean voxels for the pleasant condition then was subtracted from the mean voxels of the unpleasant condition. This difference (positive or negative values in milliliters per gram per minute) is a direct indication of the regions in which rCBF is increased or decreased in response to the unpleasant and pleasant odors.

RESULTS

Patients with schizophrenia and healthy volunteers rated the intensity of odors (scale 0-7) at the same level. For the pleasant odor, patients reported a mean (SD) intensity of 4.16 (1.33) and healthy volunteers reported 3.84 (1.92). For the unpleasant odor, patients reported 4.47 (1.94) and healthy volunteers, 4.05 (1.50). The 2 groups also did not differ in their rating of subjective experience of the hedonic valence value (scale, –7 to +7) of the unpleasant odor (patients, –4.19 [1.80]; healthy volunteers, –4.00 [1.28]). In contrast, patients had modest difficulty in attributing the appropriate hedonic valence value to pleasant stimuli. Patients’ mean (SD) ratings of the pleasant odor were lower than that of the healthy volunteers (patients, 1.33 [3.79]; healthy volunteers, 3.41 [2.31]; F1,33=3.77; P =.03, 1-tailed). A finding that occurred in this study was that some individuals may experience vanillin as unpleasant rather than pleasant; but this finding was limited only to patients, 5 of whom gave vanillin negative valence ratings. All healthy volunteers rated vanillin as pleasant.

The analysis of rCBF revealed several differences between groups (Table, Figure 1, Figure 2, and Figure 3). Figures 2 and 3 (see Figure 1 for reference) show some of the regions for which the randomization analysis found significant differences. Areas of decreased rCBF in patients are shown in blue tones and areas of increased rCBF are shown in yellow and red tones. The differences in actual rCBF values for all significant randomization regions are shown for each group in the third and fourth columns of the Table.

Patients with schizophrenia, compared with healthy volunteers, had multiple regions with relatively decreased rCBF in response to the unpleasant odor. These regions include key limbic regions known to play a role in emotional responses. The randomization analysis showed that patients had decreased rCBF in the left anterior insula, the right nucleus accumbens, the left superior temporal gyrus and parahippocampal gyrus, the lingual gyrus, and the cerebellar vermis. The actual measurements of mean rCBF in these regions obtained during the pleasantness evaluation task were subtracted from those obtained during the unpleasantness evaluation task for interpretation of the randomization statistics. As the Table indicates, the patients have consistently negative values in 1 group of regions shown in the upper half of the Table, indicating a relative decrease in rCBF during the unpleasant odor evaluation. In contrast, patients have consistently positive values for a group of regions shown in the lower half of the table, indicating that they have increases in rCBF to these regions while evaluating the unpleasant odors.

Furthermore, patients also showed increased rCBF to a large number of regions during the unpleasant odor evaluation. In contrast to their inability to activate limbic and other subcortical regions, they showed relative increases in rCBF in extensive regions of the frontal cortex, as well as the parahippocampal gyrus and posterior cingulate gyrus. The abnormal findings in the frontal cortex are bilateral and widely distributed, including ventral, dorsolateral, and medial regions. Again, the examination of the actual measured rCBF data, using the within-group subtractions, confirms that during the unpleasant odor evaluation, the patients had relative increases in rCBF and the healthy volunteers had relative decreases in rCBF in these regions.

To determine the potential clinical implications of these results, we examined the correlations between symptom ratings and the way the patients rated the emotional valence of the odors. Scores on the positive, negative, and disorganized symptom dimensions were not significantly correlated with ratings of emotional valence for the pleasant odor (r =–0.04, P = .87; r =0.03, P =.90; r =0.25, P =.31, respectively), nor were negative or disorganized symptoms correlated with ratings for the unpleasant odor (r =0.35, P =.16; r =–0.17, P =.51, respectively). However, the psychotic dimension was negatively correlated with the rating of the unpleasant odor (r =–0.65; P =.004). That is, the more psychotic the patient, the more aversive the subjective experience of the unpleasant odor.

Because the patient group was heavily weighted with male subjects, we examined whether these results could be because of sex differences in rating the intensity or hedonic valence of the odors. The results were essentially identical to the whole sample comparisons. The male patients gave similar intensity ratings to the healthy volunteers for both the unpleasant (3.2 [2.5] vs 4.2 [1.8]) and pleasant (+4.0 [1.3] vs +6.0 [1.6]) odors. In addition, significant differences were not found between patients and healthy volunteers for the ratings of unpleasant hedonic valence (–3.2 [2.5] vs –4.2 [1.8]). The male patients did differ from the healthy volunteers in their ratings of hedonic valence for the pleasant odors (1.3 [3.8] vs 3.7 [2.5]). We also examined the ratings of the healthy male volunteers vs healthy female volunteers and found that both gave similar ratings for intensity and valence. Taken together, these results suggest that our findings are not a consequence of sex differences in the 2 groups.

COMMENT

This study reveals an interesting paradox that is consistent with the emotional experiences that characterize schizophrenia: patients with schizophrenia appear to have a normal ability to experience unpleasant emotions, coupled with an impairment in the ability to experience pleasant ones, and the more psychotic they are, the greater the acuity of their ability to recognize unpleasantness. At the neural level, patients with schizophrenia who subjectively rated the unpleasant odor the same as did healthy volunteers failed to recruit the subcor-
Figure 2. Statistical Maps of Brain Regions With Differences in Regional Cerebral Blood Flow Based on Between-Group Randomization Analysis Comparing the Unpleasant Minus Pleasant Subtraction in Patients and Healthy Volunteers

Two types of statistical maps of the positron emission tomographic data, showing regions that are significantly activated in the experimental condition, are superimposed on a composite magnetic resonance image (MRI) scan derived by averaging the MRI scans from the subjects. The \( t \) values corresponding to the \( P \) values generated by randomization are shown for purposes of display. The peak maps show the small areas where all contiguous voxels exceed the predefined threshold for statistical significance (\( P < 0.005 \)). The \( t \) maps show the \( t \) value for all voxels in the image and provide a general overview of the landscape of differences in regional cerebral blood flow (rCBF) between the 2 groups. Areas of relative decreased rCBF appear in blue and increased rCBF are in red. Green crosshairs are used to show the location of the slice. A, A large area of decreased rCBF is seen between the crosshairs in all 3 planes. Inspection of multiple planes in the MRI scans indicates that the center of this area is in the nucleus accumbens, although it extends into other basal ganglia regions (eg, caudate nucleus, as seen in B). In addition, a small area of decreased rCBF also is seen in the right lingual gyrus in the sagittal view. B, A large area of decreased rCBF is shown in the insula, which is marked by the crosshairs and seen in all 3 planes. In addition, an extension of the activation in the nucleus accumbens is seen in the transaxial view. Small areas of rCBF increase also are seen in frontal regions in the coronal and sagittal planes. Within the images, R indicates right; L, left; A, anterior; and P, posterior.
tical limbic and paralimbic structures that would normally be used for this task. Instead, their normal behavioral response was associated with abnormally increased rCBF in a widely distributed group of frontal cortical regions. On the other hand, these patients had difficulty identifying the positive emotional valence of the pleasant odors, despite the fact that they gave intensity ratings within the normal range. This behavioral response is consistent with the clinical observation that patients with schizophrenia frequently experience anhedonia. Thus, this study suggests that these patients have a dysfunction in the neural circuitry used to assess both extremes of hedonic experience in the olfactory domain, in addition to a dysfunction in their ability to subjectively experience the pleasurable extreme.

Their prefrontal brain regions, which would normally be used to recognize pleasurable stimuli, appear to be hijacked for the more fundamental and evolutionarily necessary task of recognizing unpleasant stimuli, as a compensation for the apparent failure of their paralimbic regions to recognize unpleasant stimuli as negative or dangerous.

These results are consistent with our current knowledge of the functions of these prefrontal regions. Extensive studies have demonstrated the importance of limbic regions for survival in the face of dangerous or aversive stimuli. The paloeocortical division of the limbic system is engaged in an unconscious affective evaluation of stimuli that occurs prior to conscious awareness of the stimulus in question.43-46 Recent functional imaging studies of odor perception in healthy volunteers have confirmed the importance of the insula and nucleus accumbens in olfaction.47-49 The amygdala, also important in olfaction, was not identified as a peak in this study, perhaps because it was active in both conditions and therefore subtracted out.

Patients with schizophrenia have decreased rCBF in 3 key limbic regions (the nucleus accumbens, the insular cortex, and the parahippocampal gyrus) in response to the unpleasant odor, as well as the cerebellar vermis. Each of these regions is known to play a role in the appraisal of the emotional valence of stimuli, and in studies of schizophrenia each also has been found to be dysfunctional. For example, animal studies have shown that the nucleus accumbens is engaged in both appetitive and aversive responses.50,51 Based primarily on phar-

Figure 3. Statistical Maps of Other Brain Regions With Differences in Regional Cerebral Blood Flow Based on Between-Group Randomization Analysis Comparing the Unpleasant Minus Pleasant Subtraction in Patients and Healthy Volunteers

A. An area of increased regional cerebral blood flow (rCBF) in bilateral inferior medial frontal regions seen in all 3 planes at the site of the crosshairs is shown. Other areas of rCBF increase also are seen in the right parahippocampal gyrus (transaxial plane) and posterior cingulate (sagittal plane). A large area of rCBF decrease is seen in the cerebellar vermis in transaxial and sagittal planes. B, Multiple areas of rCBF increase in frontal regions are shown. The crosshairs are placed on an area in the left frontal lobe, and a corresponding region also is seen on the right. Description of these statistical maps is in the legend to Figure 2. Within the images, R indicates right; L, left; A, anterior; and P, posterior.
macological evidence, the nucleus accumbens has been implicated in neural mechanisms underlying schizophrenia. Furthermore, a dysfunction in the hippocampal-amygdalar-accumbens system has been related to patients’ difficulty in interpreting stimuli based on their affective content and the context in which they occur.

Another major node of the limbic system that showed abnormal rCBF is the insular cortex. The insular cortex is a multimodal sensory integration region that aids in the association of sensory events or experiences with appropriate emotional responses. Previous functional neuroimaging studies have reported increases in activity in the insula during diverse negative emotional states, including aversive stimuli presentation, nociception, anticipatory anxiety, and negative mood-state provocation. Decreased rCBF in the insula in patients with schizophrenia is consistent with the results of previous studies that have shown functional and structural abnormalities in the insular cortex in these patients.

The third limbic node, the parahippocampal gyrus, is involved in mnemonic functions. The left parahippocampal gyrus appears to be specifically engaged during encoding experiences that are later well remembered. The right hippocampal region is involved in the response to unexpected stimuli, retrieving stored information during novelty assessment. The relative decrease in rCBF in the left parahippocampal region may reflect a dysfunction in encoding negative stimuli, whereas increased activity in the right parahippocampal gyrus may indicate a compensatory overactive retrieval of stored information prompted by unpleasant stimuli. Thus, laterality differences in hippocampal regions in patients may be the result of 2 different kinds of impairment in normal mnemonic processes triggered by sensory stimuli. The decreases in rCBF noted in the cerebellar vermis are consistent with its known connectivity to limbic regions. A growing literature also suggests that the cerebellum is crucially involved in nonmotor mental activity.

In addition to these decreases in rCBF in the subcortical regions, the patients also displayed increased rCBF in frontal cortical regions during the evaluation of an unpleasant odor. This response may be a compensatory change occurring in brain regions recruited by patients to accomplish a life-relevant emotional task. The awareness of unpleasant and potentially dangerous external stimuli may be more necessary to survival than the detection of pleasant features. Nonetheless, the use of heteromodal prefrontal cortex for such survival tasks may also lead to an aberrant tendency to attribute threatening aspects to stimuli and in turn give rise to paranoid thinking. This interpretation is confirmed by our finding in this study that those patients who were more severely psychotic experienced the unpleasant odor more averagely. There was a highly significant negative correlation between scores on the psychotic dimension and the emotional valence rating for the unpleasant odor, suggesting that their nervous system is highly tuned to recognize potential change. The orbitofrontal cortex is normally associated with the evaluation of affective aspects of stimuli in general, including olfactory stimuli, and in particular with positive affective aspects. The increases in rCBF in the frontal cortex observed in the patients parallel the behavioral rating data that show impairment in the evaluation of pleasant stimuli. Instead of using the frontal cortex to recognize a pleasant stimulus as pleasurable, the prefrontal cortex is overactivated to recognize an unpleasant stimulus. These results provide new evidence to support a role for malfunction in the frontal lobe and its connections in schizophrenia, and they also shed new light on the complex clinical implications of this malfunction.

In summary, our findings suggest that patients with schizophrenia have a decrement in their capacity to experience pleasure within the olfactory domain, reflecting of a dysfunction in distributed neural circuits used for appraisal of both the pleasant and unpleasant extremes of olfactory experience. Whether these findings reflect a generalized dysfunction in the neural circuitry used for hedonic experience and appraisal needs to be determined. Abnormalities in the complex interactions and connectivity between the mesolimbic system and other brain regions, including the insular cortex, hippocampal region, nucleus accumbens, cerebellum, and frontal cortex, may represent the neural substrates of emotional disturbances seen in patients with schizophrenia.

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NEURAL MECHANISMS OF ANHEDONIA IN SCHIZOPHRENIA


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