ORIGINAL ARTICLE

Decrements in Volume of Anterior Ventromedial Temporal Lobe and Olfactory Dysfunction in Schizophrenia

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Context: Patients with schizophrenia exhibit olfactory deficits, but it is unclear whether these represent a specific abnormality. The link between olfactory impairments and regional brain abnormalities has yet to be established.

Objectives: To determine whether patients with schizophrenia exhibit volumetric deficits in the anterior ventromedial temporal lobe, the target for neuronal inputs from the olfactory bulb, and whether these are related to olfactory performance deficits.

Design: A cohort study of patients and healthy control subjects who underwent both 1-mm spoiled-gradient echo magnetic resonance imaging and behavioral tests of olfaction and memory.

Setting: Schizophrenia Research Center at the University of Pennsylvania, Philadelphia.

Participants: Fifty-two patients with a *DSM-IV* diagnosis of schizophrenia and 38 healthy control subjects. Individuals were excluded for history of head trauma, significant substance abuse, and medical conditions affecting brain function or olfactory capacity.

Main Outcome Measures: Gray matter volumes of the left and right temporal poles and the perirhinal and entorhinal cortexes; olfactory threshold detection sensitivity and identification test scores; composite indexes of verbal and spatial memory ability.

Results: Patients had reduced volumes, relative to cranial size, in left ($P=.003$) and right ($P=.01$) perirhinal and left ($P=.002$) and right ($P=.002$) entorhinal cortexes, but not in the temporal pole. Perirhinal, but not entorhinal, cortical volume decrement was associated with decreased olfactory threshold sensitivity. Neither region was associated with impaired memory performance.

Conclusions: Patients with schizophrenia have reduced cortical volumes in brain regions that receive afferents directly from the olfactory bulb. Behavioral olfactory deficits are related to structural brain abnormalities in these regions.

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THERE IS increasing evidence that patients with schizophrenia are impaired in their ability to detect and identify odors.[1] These deficits are present early in the disease course and are unrelated to symptom severity, medication use,[2] or smoking. However, it remains unclear whether they represent a specific impairment or merely reflect the global cognitive impairment seen in this disorder. The link between olfactory behavioral impairments and regional brain abnormalities in schizophrenia has yet to be established. A recent finding from our laboratory—that both patients and their healthy first-degree relatives have reduced olfactory bulb volumes—would suggest that structural abnormalities of the olfactory system underlie these impairments.[3,4] Whether comparable abnormalities exist in the cortical areas that receive neuronal inputs directly from the olfactory bulbs, and whether these are related to olfactory performance deficits, are questions that remain unanswered.

Olfactory processing is mediated by many of the same medial temporal lobe areas of the brain that have been implicated in schizophrenia. Olfactory afferents travel via the olfactory tract to the ipsilateral anterior ventromedial temporal lobe (AVMT), where they synapse with pyramidal cells. The bulk of these afferents terminate in the piriform cortex, which is located at the rostral uncus and is thought to be responsible for initial olfactory perception. Some fibers terminate posteriorly in the entorhinal cortex (EC), the gateway to the hippo-

Table 1. Patient Clinical Measures*

Characteristic	Men	Women
Age, y	28.5 (7.2)	36.3 (9.3)†
Age at onset, y	20.2 (5.5)	28.0 (9.9)†
Duration of illness, y	8.2 (7.0)	7.6 (6.7)
Illness ≤2 y, No.	10	5
Deficit, No.		
Present	4	3
Absent	23	22
Medicated, No.		
Yes	19	18
No	8	7
Brief Psychiatric Rating Scale score	35.2 (16.3)	32.8 (15.9)
Negative Symptom Scale score		
Total (items 1-22)	30.0 (24.4)	22.8 (17.1)
Affective Flattening (1-8)	9.1 (8.0)	6.8 (6.2)
Alogia (9-13)	3.6 (5.1)	2.4 (2.8)
Avolition (14-17)	6.1 (5.3)	2.9 (5.0)‡
Anhedonia (18-22)	9.8 (6.4)	9.1 (6.8)
Attention (23-25)	2.3 (3.6)	1.4 (2.6)
Positive Symptom Scale score		
Total (items 1-34)	19.2 (17.0)	15.0 (16.4)
Hallucinations (1-7)	6.2 (6.6)	5.4 (5.6)
Delusions (8-20)	9.5 (8.8)	7.8 (8.9)
Bizarre Behavior (21-25)	0.6 (1.5)	0.5 (1.6)
Formal Thought Disorder (26-34)	2.8 (6.2)	1.3 (3.5)

*Data are mean (SD) unless otherwise indicated.
†Difference between men and women, $P = .001$.
‡Difference between men and women, $P = .03$.

campus. Piriform cortex and EC also connect to the amygdala, thereby providing a neuroanatomic basis for the linkage of olfaction to emotion and memory, 2 processes known to be impaired in schizophrenia. Cytoarchitecturally, the AVMT may be subdivided into temporopolar cortex (TP) (Brodmann area 38), perirhinal cortex (PC) (Brodmann areas 35 and 36), and EC (Brodmann area 28),[5] with the piriform cortex included as part of the PC. While the latter 2, which are considered to be part of the limbic cortex, have been implicated in olfaction and memory, the TP is generally considered to be developmentally and functionally distinct. Although it connects to the amygdala, hippocampus, and basal forebrain, it does not receive direct olfactory afferents.

Previous examinations of medial temporal lobe structures in schizophrenia, using volumetric magnetic resonance imaging (MRI) techniques, have focused on the amygdala-hippocampal complex, with few studies considering the surrounding cortical areas that mediate olfaction. The principal motivation for emphasizing these 2 subcortical structures has been their link to memory and emotion processing. Memory impairments are extremely robust and selective trait abnormalities in schizophrenia[6,7]; emotion processing disturbances are gaining new prominence.[8-11] In a recent review of the literature, Shenton and colleagues[12] identified 34 (71%) of 48 studies that reported significant volume reductions in the amygdala and/or hippocampus in patients. Despite the role of the hippocampus in memory processing and the MR imaging findings supporting hippocampal abnormalities in schizophrenia, studies[13-16] of structure-function relationships have generally failed to find an association between hippocampal volume reduction and memory impairment. In contrast to the large number of studies examining the hippocampus and amygdala, only 13 studies[13,17-28] examined the adjacent parahippocampal gyrus, with 8 (62%) reporting reductions of this cortical gray matter area. Only 2 studies[29,30] examined the EC, despite its role as a critical relay between the hippocampus and associational cortexes.[31] One of these found bilateral volume reductions in patients,[29] while the other reported no difference.[30] Hence, it is still unclear to what extent AVMT cortical gray matter is reduced in schizophrenia. No studies, to our knowledge, have looked specifically at the cortical regions responsible for olfactory processing and their relationship to olfactory performance. Perhaps one reason for the relative dearth of such investigations is the problem of selecting appropriate MRI landmarks to guide region-of-interest (ROI) identification in this area. Boundaries between AVMT subregions are based on cytoarchitectural distinctions, rather than gross anatomic features.

In this investigation, we applied volumetric MRI methods to quantify the cortical gray matter volumes of cytoarchitecturally distinct areas of the AVMT in a large sample of patients and healthy control subjects. We used transitional landmarks derived from histologic analysis[5] to parse the region into discrete TP, PC, and EC. Participants were assessed on olfactory and memory performance to investigate the relationship between cortical volume abnormalities and behavior.

METHODS

PARTICIPANTS

The sample consisted of 52 patients (27 men, 25 women) with a *DSM-IV* diagnosis of schizophrenia and 38 healthy volunteers (21 men, 17 women). Patient age ranged from 19 to 53 years (mean±SD, 32.3±9.1 years); healthy control age ranged from 18 to 56 years (mean±SD, 28.2±9.4 years). This represented a small but significant group difference ($t_{88} = 2.07$, $P = .04$). There was also a difference in smoking habits: 5 of 38 controls and 19 of 52 patients were active smokers ($\chi^2_1 = 6.14$, $P < .05$). Mean numbers of packs per day were 0.13±0.30 for controls and 0.38±0.51 for patients ($t_{87} = 2.73$, $P = .008$). There was no difference between the groups in sex distribution.

Patients were consecutively referred from both outpatient and inpatient settings and received medical, neurologic, and psychiatric evaluations, including the *Structured Clinical Interview for* DSM-III-R–*Patient Version*.[32,33] To ensure diagnostic accuracy, they were clinically reassessed at 6-month intervals after intake. There was no history of any disorder or event other than schizophrenia that could potentially affect brain function. All patients who met inclusion criteria and were willing and able to provide informed consent were included. Healthy volunteers were recruited by newspaper advertisement and underwent medical, neurologic, and psychiatric (*Structured Clinical Interview for* DSM-III-R–*Nonpatient Version*) evaluation.[34,35] They were excluded for any history of Axis I psychiatric illness; Axis II diagnosis of schizotypal, schizoid, or paranoid personality disorder; family history of psychosis; or any medical condition or occurrence, including substance abuse, that could compromise brain function. Informed consent was obtained from all participants at the time of enrollment.

Descriptive clinical information and standardized rating scale measures for patients are presented in **Table 1**. Male patients were younger than female patients ($t_{50} = 3.4$, $P = .001$) and were significantly younger at illness onset, as defined by the

earliest evidence of psychotic symptoms in the context of functional decline (t_{50}=3.5, P=.001). There were no differences in duration of illness or medicated vs unmedicated status. Fifteen cases were of relatively new onset, with illness duration less than or equal to 2 years. Fifteen patients were not taking antipsychotic medications. The Brief Psychiatric Rating Scale (BPRS),[36] *The Scale for Assessment of Negative Symptoms (SANS)*,[37] and *The Scale for Assessment of Positive Symptoms (SAPS)*[38] were administered at the time of MRI. Ratings were completed by trained investigators, with interrater reliability greater than 0.90. The BPRS items were summed to form an index of overall symptom severity. The *SANS* items were combined to form 5 standard subscale scores: Affective Flattening, Alogia, Avolition, Anhedonia, and Attention. A summary Negative Symptom Scale score combined all *SANS* subscales except Attention. The *SAPS* items were summed to yield a total Positive Symptom Scale score and 4 subscale measures: Hallucinations, Delusions, Bizarre Behavior, and Formal Thought Disorder. Patients were also subtyped into deficit and nondeficit categories.[39] Total BPRS, *SANS*, and *SAPS* scores suggest that global symptom severity in this sample was relatively mild. Male patients scored higher on the avolition-apathy subscale of the *SANS* (t_{50}=2.21, P=.03); otherwise, there were no sex differences in symptoms.

MR IMAGE ACQUISITION

Magnetic resonance images were acquired on a 1.5-T system (GE Signa; General Electric Co, Milwaukee, Wis) with the following acquisition parameters: spoiled-gradient echo sequence; flip angle, 35°; repetition time, 35 milliseconds; echo time, 6 milliseconds; field of view, 24 cm; 1-mm slice thickness without gaps; and transaxial images with 0.9375×0.9375-mm in-plane resolution. Images were realigned to correct for head tilt and resliced into coronal sections orthogonal to the anterior commissure–posterior commissure line. Brain volume was extracted semiautomatically and segmented into gray matter and white matter by means of the optimal thresholding and morphologic operations described previously.[40-42]

ROI IDENTIFICATION

The ROIs were traced on coronal images for 3 cortical gray matter areas within the temporal lobe: EC, TP, and PC. The EC encompasses Brodmann area 28. The PC is composed of Brodmann areas 35 and 36 and includes the piriform cortex. The TP represents Brodmann area 38. **Figure 1** illustrates the approximate boundaries of these cortical areas on the surface of the AVMT. Precise boundaries are defined histologically on the basis of the identification of cytoarchitectonic transition zones.

Operational criteria for defining ROI boundaries on coronal MRIs were adapted from Insausti and colleagues,[5] who validated the MRI landmarks through a histologic analysis of brains that underwent autopsy. All MRI boundaries were traced by individuals familiar with these neuroanatomic landmarks, and interrater reliability exceeded 0.85 for all regions. Specific MRI-guided criteria for each region were as follows (**Figure 2**).

Temporopolar Cortex

The TP covers the anterior portion (first 6-8 mm) of the temporal lobe. Proceeding in a rostral-caudal direction, the entire temporal lobe parenchyma was included until the appearance of the superior and/or inferior temporal sulci (Figure 2A). Typically, the superior temporal sulcus appears slightly rostral to the inferior temporal sulcus. From this point on, the dorsolateral border was defined as the lateral border of the temporopolar sulcus (delineating the gyrus of Schwalbe) or, if this was absent, by the midpoint of the dorsal aspect of the pole. The ventrolateral border was located at the medial edge of the inferior temporal sulcus or, if not present yet, then along the medial edge of the superior temporal sulcus (Figure 2B). Caudally, the TP terminated with the appearance of the collateral sulcus, usually approximately 2-4 mm rostral to the limen insulae.

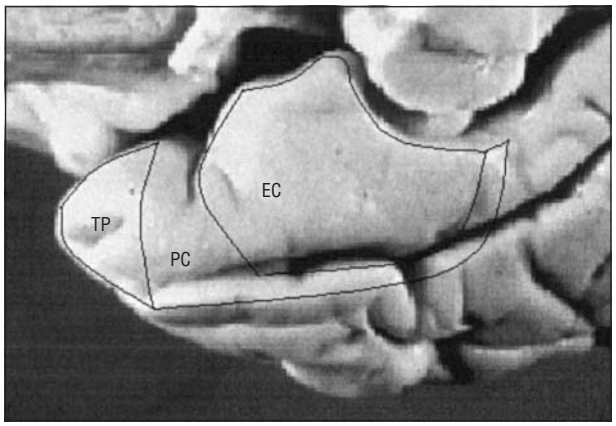

Figure 1. Medial view of the right hemisphere, depicting the approximate boundaries of the 3 cortical subdivisions of the anterior ventromedial temporal lobe. Precise boundaries are defined histologically on the basis of cytoarchitectonic transition zones. TP indicates temporopolar cortex; PC, perirhinal cortex; and EC, entorhinal cortex.

Perirhinal Cortex

The PC borders the TP along the medial surface of the rostral temporal lobe. Rostrally, the PC replaces the TP in the dorsomedial aspect of the temporal lobe and caudally in the ventromedial temporal lobe. The rostral tip of the PC was defined as the first slice in which the collateral sulcus could be seen. On the most rostral slices, the edges of the PC were the lateral edge of the collateral sulcus ventromedially and the lateral border of the gyrus of Schwalbe dorsolaterally (Figure 2C). On the first slice in which the limen insulae appeared, the dorsomedial edge was the most medial point of the parahippocampal gyrus (Figure 2D). Caudal to this slice, the PC extended from the middle of the medial bank of the collateral sulcus to the lateral edge of this sulcus (Figure 2E-G). The PC terminated, caudally, with the disappearance of the gyrus intralimbicus.

Entorhinal Cortex

The rostral edge of the EC was one slice caudal to the appearance of the limen insulae. The medial edge of the EC was the most medial point of the parahippocampal gyrus, extending laterally to the midpoint of the medial bank of the collateral sulcus (Figure 2E). Caudally, with appearance of the hippocampal fissure, the medial edge of the EC became the inferomedial edge of the fissure (Figure 2F). The EC terminated caudally one slice after the disappearance of the gyrus intralimbicus.

OLFACTORY PSYCHOPHYSICAL TESTING

Participants underwent standardized psychophysical assessment of their olfactory abilities. A single-staircase, forced-choice odor detection task was used to estimate basal detection sensitivity to phenylethyl alcohol. Participants were asked to smell successive pairs of odorants differing in concentration and to identify which odorant "smells stronger." The geometric mean of the last 4 staircase reversals (out of 7) provided the measure of odor detection threshold sensitivity.

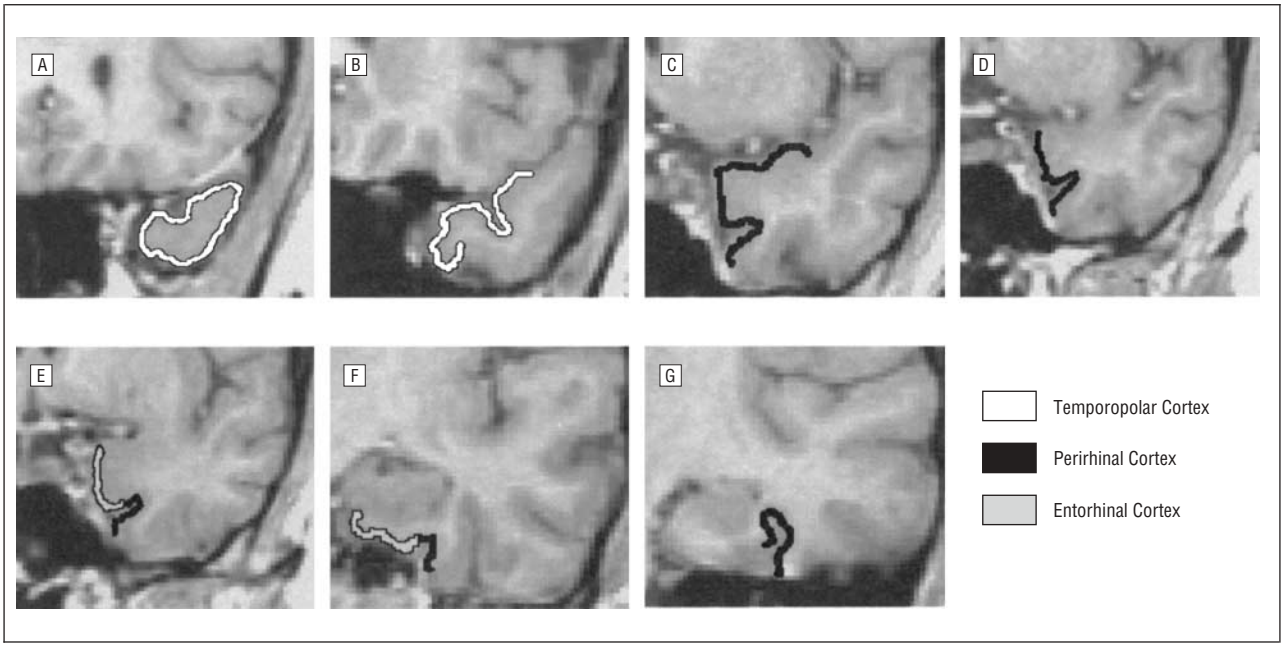

Figure 2. Examples of the regional boundaries of anterior ventromedial temporal lobe regions as operationally defined on coronal magnetic resonance images. Images A through G move progressively in a rostral to caudal direction.

Table 2. Magnetic Resonance Imaging Measures

Cortex	Volume, Mean (SD), cm³		Odds Ratio (95% CI)*
	Patients	Controls	
Temporopolar			
Left	2.98 (1.13)	3.27 (1.11)	1.27 (0.86-1.88)
Right	3.08 (0.86)	2.91 (1.10)	0.83 (0.53-1.30)
Perirhinal			
Left	2.19 (0.71)	2.39 (1.02)	1.32 (0.81-2.17)
Right	1.94 (0.69)	2.22 (0.85)	1.65 (0.93-2.91)
Entorhinal			
Left	1.87 (0.65)	2.05 (0.67)	1.51 (0.78-2.89)
Right	1.89 (0.58)	2.02 (0.67)	1.42 (0.71-2.81)

Abbreviation: CI, confidence interval.
*Relative risk of illness associated with a 1-unit change of the variable of interest in the direction of increasing abnormality.

Sensitivity data were not obtained from 3 female patients who could not adequately comprehend the task. The ability to identify odors was assessed by the University of Pennsylvania Smell Identification Test (UPSIT),[43] a standardized 40-item forced-choice test. The UPSIT data were available for all participants.

MEMORY ASSESSMENT

Participants were administered a set of standardized neuropsychological tests. Individual test results were grouped together to form summary *z* score measures reflecting performance in different cognitive domains.[7,44,45] For this correlative analysis, we selected *z* score measures for verbal and spatial memory. Verbal memory tests included the Wechsler Adult Intelligence Scale–Revised,[46] logical memory immediate and delayed recall, and the California Verbal Learning Test,[47] trials 1 through 5. Spatial memory tests included the Wechsler Adult Intelligence Scale–Revised, design reproduction immediate and delayed recall. Neuropsychological data were unavailable for 1 male patient, 1 male control, and 2 female controls.

DATA ANALYSIS

To examine patient-control differences in brain volume, a general linear model with separate slope estimates was used. Gray matter volumes in the left and right TP, PC, and EC areas were the dependent measures, diagnosis was a grouping factor, and total cranial volume was a continuous predictor. The modulating effects of age, sex, and smoking (packs per day) were assessed by including these variables in the model. The relationship between regional brain volumes and olfactory functioning was examined by means of a separate-slopes general linear model with threshold detection sensitivity and UPSIT scores as dependent measures, diagnosis as a categorical predictor, and total cranial and regional brain volumes as continuous predictors. The relationship between brain volumes and memory performance was assessed similarly, with the verbal and spatial memory *z* scores as dependent measures. The relationship to clinical measures within the patient group was also considered. The *SANS*, *SAPS*, and BPRS scores, illness duration, medication dosage, age at onset, and deficit-nondeficit status were separate dependent measures, with regional and total brain volumes as continuous predictors. Statistical significance was based on a multivariate probability of $P<.05$ for all analyses.

RESULTS

REGIONAL BRAIN VOLUMES

The volumetric measures for each region are presented in **Table 2**. There were no significant main effects of diagnosis for any of the individual brain regions. However, multivariate separate-slope analyses of individual brain regions disclosed significant interactions between diagnosis and total cranial volume for gray matter in the PC (Wilks $\Lambda_{4,168}=0.84$, $P=.006$) and EC (Wilks $\Lambda_{4,168}=0.83$, $P=.004$), but not the TP (**Figure 3**). Post hoc univariate analyses showed significant diagnosis × cranial volume effects in both left and right hemispheres for both regions (PC: left,

$F_{2,85}=6.33$, $P=.003$; right, $F_{2,85}=4.78$, $P=.01$; EC: left, $F_{2,85}=6.72$, $P=.002$; right, $F_{2,85}=6.89$, $P=.002$). These group × cranial volume differences remained significant after accounting for age, sex, and smoking. There was a significant interaction between diagnosis and smoking for the EC (Wilks $\Lambda_{4,162}=0.79$, $P<.001$), but not for the PC or TP. Patients who smoked showed a slight volume decrement that was not seen among controls who smoked. There were no effects of sex or age on these regional volume measures and no differences between medicated and unmedicated patients.

A diagnosis × cranial volume interaction implies that the relationship between total cranial volume and ROI volume is different in the 2 diagnostic groups. As can be seen in Figure 3, gray matter volumes in the PC and EC were smaller in patients with schizophrenia, but primarily for those with larger cranial volumes. This is the type of relationship that one would expect if there were a relative percentage decrease in regional volume across subjects with different cranial volumes, as opposed to a relative magnitude decrease. The mean decreases observed here were 10.6% for the PC, 7.5% for the EC, and 1.9% for the TP.

OLFACTORY PSYCHOPHYSICAL MEASURES

Mean scores on olfactory psychophysical measures are presented in **Table 3**. As expected, the patient sample showed significant impairments in both odor detection (Wilks $\Lambda_{2,84}=0.88$, $P=.004$) and UPSIT identification performance (Wilks $\Lambda_{2,87}=0.90$, $P=.01$). These were not explained by sex, age, or smoking differences, and there were no performance differences between medicated and unmedicated patients. However, when the volumetric measures were included in the general linear model as explanatory variables, there were no longer main effects of diagnosis. Rather, for olfactory thresholds, there were significant interactions between diagnosis and left PC (Wilks $\Lambda_{4,144}=0.87$, $P=.05$), right PC (Wilks $\Lambda_{4,144}=0.86$, $P=.03$), and left TP (Wilks $\Lambda_{4,144}=0.86$, $P=.02$). In all cases, reduced regional gray matter volume was associated, in patients, with poorer ability to detect the presence of an odor (**Figure 4**). In control subjects, there was either no relationship or a tendency toward the opposite (ie, better detection sensitivity associated with smaller volumes, consistent with the slightly better thresholds observed normally in women compared with men). There were no associations between EC volume and detection threshold sensitivity. For odor identification (UPSIT) performance, there were significant interactions between diagnosis and right TP (Wilks $\Lambda_{4,150}=0.86$, $P=.02$) and right EC (Wilks $\Lambda_{4,150}=0.88$, $P=.047$), with decreased volume associated with poorer UPSIT performance in patients. The PC volumes were unrelated to performance on the odor identification task. These structure-function relationships were unaffected by age, smoking, or sex.

MEMORY PERFORMANCE MEASURES

The pattern of results for the memory performance measures differed from those observed for the olfaction measures. Patients were impaired on both verbal ($F_{1,82}=16.50$, $P<.001$) and spatial ($F_{1,82}=6.75$, $P=.01$) memory. There was also a significant diagnosis × age interaction for verbal memory ($F_{1,82}=5.35$, $P=.02$), with healthy individuals showing a decline with aging that was not observed in patients. However, neither of the memory performance measures was related to any of the regional brain volumes, either directly or interacting with diagnosis. Therefore, although memory performance was impaired in patients, this was not related to the extent of gray matter volume reduction in the AVMT. This was notwithstanding that these cortical regions have been implicated in memory processes.

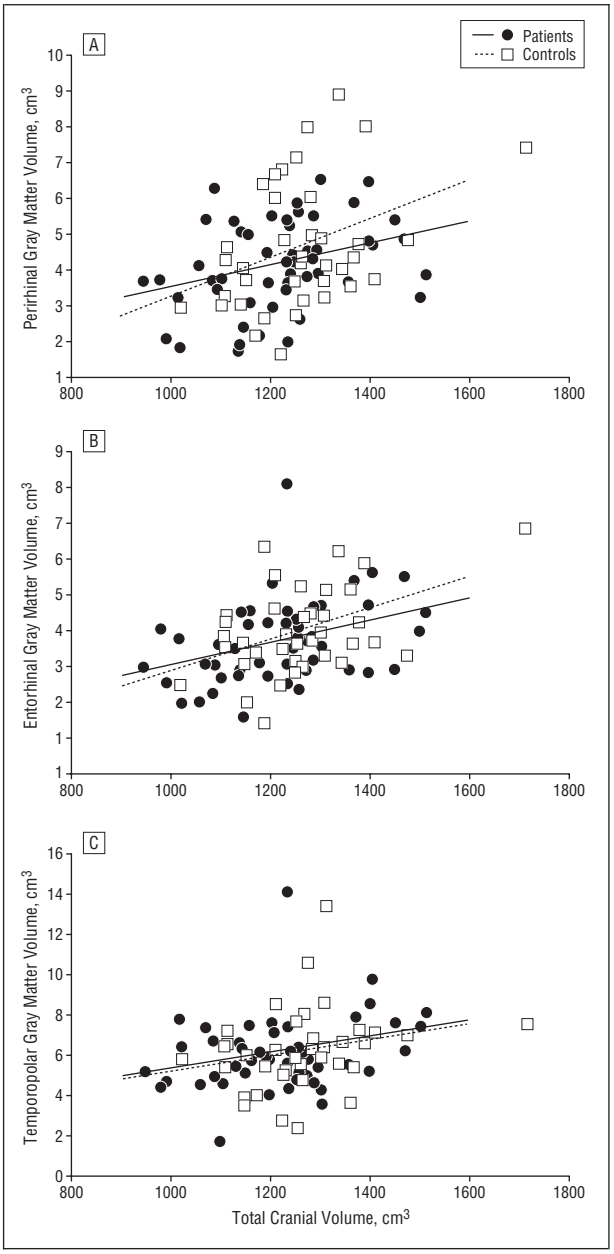

Figure 3. Relationship between cortical gray matter volume and total cranial volume for the 3 separate subdivisions of the anterior ventromedial temporal lobe. Regional volume measures are the sum of the left and right hemisphere values. Patient-control differences are significant for perirhinal ($P=.006$) and entorhinal ($P=.004$) cortexes but not for the temporopolar cortex.

Table 3. Behavioral Measures

Measure	Mean (SD)		Odds Ratio (95% CI)*
	Patients	Controls	
Threshold detection sensitivity (concentration), log/log units			
Left nostril	–5.21 (1.37)	–6.21 (1.50)	1.56 (1.33-2.14)
Right nostril	–5.65 (1.29)	–5.74 (1.48)	1.05 (0.77-1.44)
Odor identification, No. of items correct of 20			
Left nostril	16.81 (2.58)	17.84 (1.87)	1.25 (1.00-1.57)
Right nostril	16.96 (2.27)	18.26 (1.64)	1.42 (1.11-1.81)
Verbal memory, *z* score	–1.28 (1.07)	0.18 (1.00)	3.72 (2.11-6.56)
Spatial memory, *z* score	–1.19 (1.50)	0.07 (1.12)	2.06 (1.38-3.07)

Abbreviation: CI, confidence interval.
*Relative risk of illness associated with a 1-unit change of the variable of interest in the direction of increasing abnormality.

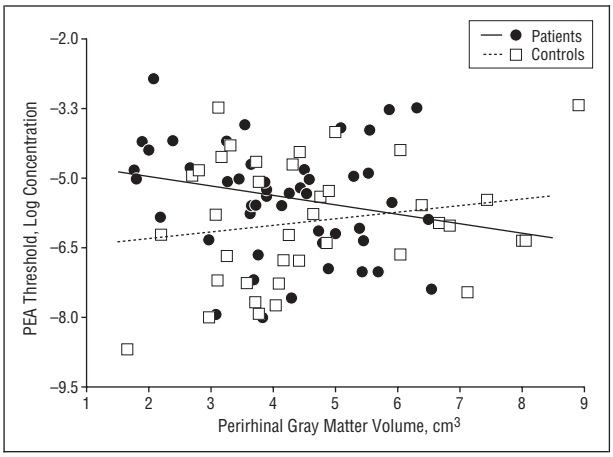

Figure 4. Relationship between perirhinal gray matter volume and olfactory threshold sensitivity. This relationship is significantly different for patients and controls. Reduced perirhinal volume results in higher threshold concentrations (ie, decreased olfactory sensitivity) in patients, but not in healthy controls. PEA indicates phenylethyl alcohol.

CLINICAL MEASURES

There were no associations between MRI measures and clinical measures of illness onset, illness duration, or negative symptom rating scores. There were also no differences between deficit and nondeficit, new-onset and chronic illness, or medicated and unmedicated patients. There was an isolated relationship between left PC volume and ratings on the Bizarre Behavior subscale of the *SAPS* ($F_{1,43}$=8.00, P=.007), with smaller volumes being associated with increasingly bizarre behavior.

COMMENT

Table 4 summarizes the basic findings of this investigation. These findings support the hypothesis that patients with schizophrenia have reduced cortical volumes in some, but not all, subdivisions of the AVMT. We observed bilateral reductions in both the PC and EC, both of which receive direct afferent inputs from the olfactory bulb, with the latter also being integrally involved with hippocampal-mediated memory processes. Not surprisingly, the magnitude of the volume loss increased with increasing head size. In contrast, the TP—which is not considered to be part of either the limbic or olfactory cortex and does not receive inputs from the olfactory bulb—did not exhibit volume reductions in patients.

Table 4. Summary of Findings by Region

Finding	Perirhinal Cortex	Entorhinal Cortex	Temporal Pole
Volume reduction in patients	Yes	Yes	No
Related to sex	No	No	No
Related to smoking	No	Yes	No
Affects odor threshold sensitivity	Yes	No	Yes
Affects odor identification	No	Yes	Yes
Affects memory performance	No	No	No

The data also support the hypothesis that olfactory deficits reflect specific structural brain abnormalities in cortical regions underlying different aspects of olfactory processing. We found an association between threshold detection sensitivity and bilateral PC volumes. This region includes the piriform cortex, the area that receives the bulk of the afferent inputs from the olfactory bulb and is primarily responsible for early odor perception.[48] No such relationship was found between these same PC volume measures and olfactory identification performance. This suggests that the link between PC volume reduction and impaired olfactory threshold detection sensitivity represents a specific structure-function relationship that is disturbed in schizophrenia, rather than a nonspecific correlation reflecting global impairments. It is significant, in this regard, that EC volume was not similarly associated with olfactory threshold detection sensitivity. Although this region had comparable bilateral volume reductions in the patients, it is not as extensively innervated by olfactory bulb afferents and receives a much more widely distributed array of inputs. This further supports the specificity of the relationship between olfactory threshold sensitivity and PC volume.

Findings for the TP were more complex. This region was linked both to threshold sensitivity on the left and, with the EC, to odor identification on the right. There is an emerging understanding of the functional role of the TP as mediating recognition of familiar objects.[49] As part of a so-called paralimbic system, the temporopolar region is important in integrating the perceptual expe-

rience of external sensory stimuli with one's subjective internal state.[50] It might therefore participate in aspects of both odor perception and odor identification. However, without direct afferents from the bulb, this would appear to be an indirect association to more complex cognitive processes involving the integration of perceived odors, rather than to odor perception per se.

The specificity of the link between regional MRI measurements and olfaction is reinforced by the absence of any association between the volumes of these regions and memory performance. Memory abnormalities are relatively selective and severe deficits in patients.[7] If reduced brain volume were a global indicator of disease severity and/or chronicity, we might expect it to correlate with memory performance more than with any other neuropsychological or psychophysical measure. The fact that we find memory impairments in this patient sample, but do not see an association with AVMT volumes, suggests that the associations we do observe (eg, between olfactory threshold sensitivity and PC volume) are functionally and anatomically specific.

The absence of associations between brain volumes and clinical measures is not too surprising. Structural brain changes, which are already evident at the initial presentation of illness,[42,51,52] are relatively stable abnormalities, while clinical symptoms fluctuate over the course of illness.[53] It is particularly noteworthy that there was no relationship of MRI volumes to either negative symptoms or the interaction of negative symptoms and age. Some studies,[54-56] although not all,[57] have reported associations of olfactory dysfunction with negative symptoms. These symptoms have also been shown to increase with increasing age of patients,[53] although this is not prominent until much later in life. In this sample, with all but one patient younger than 50 years, negative symptoms were unrelated to either olfactory performance or age.

Two possible mechanisms may underlie the loss of AVMT gray matter and the associated disturbance in olfactory function. Glutamate is likely the predominant excitatory neurotransmitter acting at the synapse between afferent neurons originating in the mitral cell layer of the olfactory bulb and pyramidal cells in the piriform cortex.[58] High levels of *N*-methyl-D-aspartate (NMDA) glutamatergic receptors are found in this region.[59] Dysfunction of NMDA receptors is the cornerstone of the "glutamate hypothesis" of schizophrenia.[60] According to this model, hypofunction at the postsynaptic NMDA receptor results in excess release of glutamate, which, in turn, leads to both psychotic symptoms[61] and irreversible neuronal degeneration in corticolimbic regions.[62] If this is correct, then areas rich in NMDA receptors, such as the piriform cortex and EC, would be especially prone to structural damage and associated functional loss.

There is also evidence that abnormalities in the olfactory system extend to the most peripheral afferent neurons. Postmortem studies in our laboratory have demonstrated that there is abnormal development of olfactory receptor neurons in the nasal epithelium of patients with schizophrenia.[63] We have also noted reductions in olfactory bulb volume on MRIs of patients.[4] These findings are consistent with a model of underlying synaptic dysregulation within the olfactory bulb. Direct examination of the olfactory bulb has now provided further support for this hypothesis. Significant alterations have been found in the densities of presynaptic and postsynaptic proteins, as well as molecules important for trophic support in the bulb.[64] These peripheral abnormalities are likely to result in secondary disruptions of the afferent inputs into primary olfactory cortical regions. Such a relative deafferentation not only would result in functional olfactory impairments but also could cause anterograde degeneration of the primary sensory areas of the cortex.[65,66]

The validity of behavioral measures of olfactory dysfunction is limited by nonspecific factors such as patient motivation and global cognitive impairment. The multiple replications in the literature suggest that these factors do not, in themselves, account for the olfactory deficits seen in patients. Nevertheless, they may be influencing some of the relationships we observe. Newer methods, using olfactory event-related potentials, are now available to directly assess the physiologic responses of olfactory cortical areas. We have recently shown that patients with schizophrenia also demonstrate impairments with the use of these nonbehavioral measures.[67] It will be important to next determine whether these functional measures similarly correlate with brain volume measures. If they do, this will provide even stronger evidence of a specific structural-functional impairment of olfaction in schizophrenia.

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