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Olfactory Loss in Alcoholics: Correlations With Cortical and Subcortical MRI Indices

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SHEAR, P. K., N. BUTTERS, T. L. JERNIGAN, T. L., G. M. DiTRAGLIA, M. IRWIN, M. A. SCHUCKIT AND L. S. CERMAK. *Olfactory loss in alcoholics: Correlations with cortical and subcortical MRI indices.* ALCOHOL 9(3) 247-255, 1992. — The relationship between olfactory identification ability and MRI volumetric indices of specific cortical and subcortical brain regions was investigated in 36 recently detoxified male alcoholics. The results of correlational analyses between MRI indices and score on the University of Pennsylvania Smell Identification Test (UPSIT) revealed that impairment in olfactory identification was associated with elevated cortical and ventricular CSF volumes as well as with reduced tissue volumes in the cortical and subcortical grey matter. The volume of the thalamus was found to be a significant unique predictor of UPSIT score, even after accounting for variance shared with other MRI indices. These findings provide the first empirical support for existing hypotheses that olfactory loss in alcoholic subjects may be mediated by both cortical and subcortical structures.

Alcohol Olfaction UPSIT Magnetic resonance imaging

SEVERAL investigations have now shown that alcohol abuse may be associated with olfactory loss, not only in individuals with Korsakoff's syndrome (12,18-20,23,27), but also in non-amnesic alcoholics (2,27). In a recent study, DiTraglia et al. (2) reported that detoxified male alcoholics were impaired, relative to control subjects, on a multiple-choice test of odor identification. This olfactory deficit was apparent even after controlling for smoking and did not resolve after 3 to 4 months of abstinence. When the alcoholics' olfactory performance was correlated with CSF volumes derived from Magnetic Resonance Imaging (MRI), a significant moderate association ($r = 0.476$) was found between the sulcal fluid volume and the sensory index.

This MRI finding is consistent with reports that several anterior cortical areas are important projection sites for the processing of olfactory information. Neuroanatomical studies have revealed ipsilateral connections between the olfactory bulb and the pyriform cortex (primary olfactory cortex) in the medial temporal lobe (24). This cortical region then projects

to the dorsomedial nucleus of the thalamus (29) as well as to the entorhinal cortical area (35), both of which in turn have extensive connections with the orbitofrontal cortex. (25,36).

Both animal and human lesion studies have confirmed the importance of anterior association cortices in olfactory functions. Ablation of the orbitofrontal region of both rats (9) and primates (34) is associated with deficits in olfactory discrimination. Hippocampal damage also compromises olfactory discrimination in rats, but only if the task includes the simultaneous presentation of two stimuli (5-7,26). Human studies have indicated that patients with focal brain lesions involving orbitofrontal (21,28,37) or anterior temporal cortex (8,10,21,30,37) are impaired on odor identification and discrimination tasks. In contrast, those patients with cortical lesions confined to occipital or parietal regions demonstrate intact olfactory abilities (37).

The present investigation represents an attempt to identify the specific cortical and/or subcortical brain structures associated with the olfactory deficits of nonamnesic, chronic alco-

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holics. In addition to measuring cortical and subcortical CSF volumes, MRI-derived volumetric indices of multiple cortical and subcortical structures are correlated with performance on a standardized olfactory identification test. It was anticipated that, consistent with the focal lesion data, odor identification deficits in the alcoholics would be strongly associated with decreases in orbitofrontal and temporal pole tissue volumes. Also, since the dorsomedial nucleus of the thalamus has major afferent and efferent connections with the olfactory system (25), a significant relationship between the volume of the thalamus and olfactory ability was expected.

To address these hypotheses, a series of recently detoxified alcoholics and normal control subjects were administered the University of Pennsylvania Smell Identification Test (UPSIT) (3,4), along with a battery of cognitive tasks and an MRI brain scan. The MRI results were analyzed according to a standardized protocol developed by Jernigan et al. (13-17) to generate volumetric estimates of specific brain structures.

METHOD

Subjects

Thirty-six male alcoholics and 21 male normal controls served as subjects for the present study. UPSIT and/or MRI data for 28 of the alcoholics have been reported in earlier investigations (2,14). An additional ten alcoholics and six controls were accepted into the study, but were excluded from the present analyses because their MRI scans were technically flawed.

The alcoholics were drawn from patients admitted to the inpatient Alcohol Treatment Program at the Department of Veterans Affairs Medical Center, San Diego. The majority of these patients had undergone detoxification prior to their admission to the hospital, with a mean of 11.5 days (SD 11.5) between their last drink of alcohol and their initial assessment. A small number of subjects were prescribed Librium during their detoxification; however, no subjects for the present study were tested until at least 48 hours following their final dosage of this medication.

All alcoholic subjects were administered the Alcohol Research Center Intake Interview (33); additionally, one resource person (family member or friend) was interviewed for corroborative diagnostic information. Subjects were accepted into the study only if these interview data supported a DSM-III diagnosis of alcohol abuse or alcohol dependence. In cases where the resource person and the patient provided discrepant information, the more severe of the two histories was coded (i.e., the more recent date of last drink or the more protracted disease course).

Prospective alcoholic subjects were excluded for polysubstance abuse, primary psychiatric disorders other than alcohol abuse (e.g., schizophrenia or bipolar affective disorder), Antisocial Personality Disorder, history of serious neurologic insult or injury (e.g., stroke, closed head injury with prolonged loss of consciousness), liver disease, or metabolic disturbance (such as insulin-dependent diabetes). In addition, patients were excluded for conditions which would preclude the completion of an MRI brain scan. Specifically, subjects were not enrolled in the study if they reported claustrophobia, pacemaker placement, metal pins or clips in the upper body, or a history of metal fragments in the eye.

Normal control subjects were recruited from the community. They were all administered the Alcohol Research Center Intake Interview and were excluded if they met diagnostic

criteria for abuse or dependence on alcohol or other drugs. The controls met all of the medical, psychiatric, and neuroimaging criteria described above for the alcoholics.

Demographic data for the two subject groups are presented in Table 1. As is evident from this table, the two diagnostic groups were statistically similar in terms of age, but the control group had a significantly higher level of education than did the alcoholics, $F(1, 55) = 5.76, p < 0.03$. Indices of the alcoholic subjects' drinking histories are also provided in Table 1.

Procedure

Within 48 hours of admission (or, if applicable, within 48 hours of discontinuing Librium), alcoholic subjects were administered a brief neuropsychological battery comprised of the WAIS-R Vocabulary subtest as well as four tests with demonstrated sensitivity to the neurocognitive effects of alcohol (Trails A and B, WAIS Digit Symbol, and Visual Search) (31). Approximately 3 weeks following admission, the alcoholics completed an MRI brain scan (described in detail below) and a 3-hour neuropsychological assessment. Control subjects received both the brief and the extended neuropsychological batteries, together with the MRI scan, at intake into the study. The extended neuropsychological battery included, among other measures, the Booklet Category Test (1), Stroop Color Word Test (11), and the Rey Auditory Verbal Learning Test (22) to assess the presence and severity of memory impairment and generalized cognitive dysfunction.

As part of the 3-hour assessment, subjects were administered the UPSIT (3), a standardized, microencapsulated test of olfactory identification. This task is composed of 40 individual items, on each of which the subject is required to scratch a textured strip with a pencil, releasing an odorant (e.g., bubble gum). The subject must decide in a multiple-choice format which of four items (e.g., dill pickle, bubble gum, wintergreen, or watermelon) the odorant most resembles and then darken a corresponding circle on a response card. The subjects were also asked questions about past and present smoking, since increased incidence of this behavior has been found to be associated with poorer performances on the UPSIT (3).

MR scans were performed with a 1.5-T super-conducting

TABLE 1
MEAN AGE, EDUCATION, AND DRINKING HISTORIES
OF ALCOHOLIC AND NORMAL CONTROL SUBJECTS

	Alcoholics (<i>n</i> = 36)	Normal Controls (<i>n</i> = 21)
Age	48.3 (9.7)	49.8 (10.1)
Education	13.9 (1.9)	15.1* (1.4)
Years of problem drinking	12.2 (9.5)	N/A
Mean drinks per day in 3 months prior to admission	13.8 (9.2)	N/A
Days since last drink (baseline cognitive testing)	11.5 (6.7)	N/A

* $p < 0.03$.

magnet (Signa; General Electric, Milwaukee, WI) at the UCSD/AMI Magnetic Resonance Institute. Brain images were collected according to a standard protocol and were analyzed in the Brain Image Analysis Laboratory of the Department of Psychiatry, UCSD. Proton-density weighted (PDW) and T2-weighted (T2W) images were obtained simultaneously for each section, using an asymmetrical, multiple-echo sequence (TR = 2000 ms, TE = 25, 70 ms) to obtain images of the entire brain in the axial plane. Section thicknesses were 5 mm with a 2.5-mm gap; a 256×256 matrix was selected, with a 24-cm field of view. The subjects did not receive sedation during the scans.

A summary of the image analysis procedure will be provided here, to allow accurate interpretation of the data that follow. Detailed information about this method have been published previously (13–17). Each axial image was first digitally filtered to reduce signal drift due to magnetic field and gradient inhomogeneities. Briefly, each pixel location within a section of the imaged brain was classified on the basis of its signal values in both original images (TE = 25, TE = 70) as most resembling CSF, grey matter, white matter, or signal hyperintensity (tissue abnormality). This was accomplished in two steps. First, two new linear combinations of the pixel values were computed to optimize tissue contrast (CSF/brain and grey/white). Then, classification criteria that were adjusted separately for each section were applied to these computed values. The full series of axial images was analyzed, beginning at the bottom of the cerebellar hemispheres and extending through the vertex.

These "voxel-classified" images were manipulated further, to derive specific structural measures. Trained operators, blind to subject identification, used a stylus-controlled cursor on the computer-displayed images to manually separate infratentorial (cerebellar) from supratentorial areas, left from right hemispheres, and cortical from subcortical regions of the supratentorial cranium. Fluid volumes, cortical structures, and subcortical structures were defined as described below.

To delineate subcortical structures, the operators circumscribed voxels that had been classified as subcortical grey matter and that were visually determined to be in one of the three predesignated subcortical regions: caudate nuclei, lenticular nuclei, or diencephalic grey matter structures (including mammillary bodies, other hypothalamic grey, septal nuclei, and thalamus). The operators did not trace the edges of the structures but rather defined polygons which included all grey matter voxels within the regions and excluded those grey matter voxels associated with other structures. In those instances where subcortical nuclei were contiguous with other areas classified as grey but clearly distinct from these other grey matter structures, boundaries were manually constructed using the filmed images as a guide. It should be noted that areas within the lenticular nucleus containing significant iron deposits, particularly in globus pallidus, do not meet the signal criteria for grey matter, and are thus not included in this region.

The inclusion of several small grey matter structures in the diencephalic region was necessary because there are no white matter or CSF landmarks which can be used to reliably separate these structures from the thalamus or from each other. Estimates of the volumes of the three subcortical regions (caudate, lenticular, and diencephalic) were made by summing the designated grey matter voxels across all axial sections. The diencephalic region was further subdivided into its anterior and posterior aspects, as described later.

Within the subcortical white matter, some voxels were present which had signal values falling into the range characteristic

of grey matter or signal hyperintensities (i.e., they demonstrated lengthened T2 relative to other white matter voxels). These voxels were coded separately and summed to create an Abnormal White Matter Index.

To define anatomically consistent cortical regions, a method was adopted to subdivide the supratentorial cranium relative to the locations of the centromedial structural midline and two consistently identifiable points: the most anterior midline point in the genu and the most posterior midline point in the splenium of the corpus callosum. Using these landmarks to calculate rotation angles, it was possible to perform a three-dimensional rotation of the images, thus correcting each individual's image data for rotation out of the optimal imaging plane. This procedure allowed the consistent demarcation of regional boundaries, relative to gross anatomical landmarks.

The true midsagittal plane was considered to pass through the two corpus callosum points. The orientation of this plane, relative to the imaging plane, was then determined by computing a regression line through a series of manually selected brainstem midline points. Two additional planes were delineated to allow the subsequent subdivision of the cerebrum: (1) an axial plane, perpendicular to the midsagittal plane and passing through the two corpus callosum points; and (2) a coronal plane, perpendicular to the midsagittal and axial planes, and passing through the midpoint between the two corpus callosum points. All further references to planes of section in the present discussion refer to these novel coordinates and not to the original imaging plane.

New coordinates were computed for each voxel, relative to the three defined planes, which allowed classification into one of the four cerebral zones illustrated in Figure 1: (1) inferior to the axial plane and anterior to the coronal plane; (2) inferior to the axial plane and posterior to the coronal plane; (3) superior to the axial plane and anterior to the coronal plane; and (4) superior to the axial plane and posterior to the coronal plane. Anterior temporal, orbitofrontal, and some dorsolateral and mesial frontal cortex lie in the inferior anterior zone. Posterior temporal and inferior occipital cortices fall into the inferior posterior zone. The remainder of the frontal lobes

FIG. 1. Points A and B in the corpus callosum represent the most anterior midline point in the genu and the most posterior midline point in the splenium, respectively. The cerebrum is divided into four zones based on the defined axial and coronal planes shown.

fall into the superior anterior zone. The superior posterior zone contains primarily parietal areas, along with a small portion of the superior occipital cortex.

The coronal dividing plane consistently intersects the amygdala and falls between the column of the fornix and the mammillothalamic tract. It reliably divides the mammillary bodies from the more anterior hypothalamic grey areas. Since this plane passes through the diencephalic grey matter region and divides the anterior hypothalamic and septal structures (lying anteriorly) from the bulk of the thalamus (lying posteriorly), the corresponding anterior and posterior diencephalic areas were examined separately. In order to differentiate between mesial and peripheral cortical regions, an ellipsoid volume was defined within the supratentorial cranial vault. This volume was constructed to include 30% of the supratentorial volume and to have cardinal dimensions proportional to those of the supratentorial vault (i.e., the z-axis extent of the ellipsoid was proportional to the maximum z-axis extent of the supratentorial cranium, the y-axis extent of the ellipsoid to the maximum y-axis extent, and the x-axis to the maximum x-axis extent). The ellipsoid was centered in the same axial plane as the origin of the defined coordinate system but slightly posterior to that origin (at a point 60% of the distance between the genu and the splenium reference points). The size and center point of the ellipsoid volume was chosen empirically to isolate as accurately as possible the medial cortical surfaces of the limbic lobe, excluding the more lateral neocortical surfaces. The area designated as mesial consistently included the most posterior parts of the orbital frontal lobe, the amygdala, the hippocampus and most of the parahippocampal gyrus, the insula, and most of the cingulate gyrus. The ellipsoid defined mesial and peripheral zones within each of the four original cerebral zones, creating a total of eight regional cortical volumes.

Summary indices were created by totaling voxels that shared specified signal characteristics or that fell into defined cranial regions. In order to estimate ventricular and cortical fluid volumes, the subcortical and cortical CSF voxels were each summed over all sections. Similarly, the grey matter voxels were summed separately within each of the subcortical structures and within each of the eight cortical zones. Total

UPSIT SCORES

FIG. 2. Frequency distributions of total UPSIT scores for 36 alcoholic (ETOH) and 21 normal control (NC) subjects.

regional volumes were also computed for each of the eight cerebral regions (i.e., the volume resulting from the summation of all voxels, including CSF, grey matter, white matter, and hyperintensities).

To facilitate direct comparisons between diagnostic groups as well as comparisons of the magnitude of group effects across different brain structures, the MRI indices were converted to z-scores that corrected for age and cranial size, using formulae derived from control data in 107 normal volunteers (17). These values, by definition, have an expected mean of 0 and SD of 1 in controls.

TABLE 2

PERFORMANCE ON NEUROPSYCHOLOGICAL MEASURES:
ALCOHOLIC AND NORMAL CONTROL SUBJECTS

	Alcoholics (n = 36)	Normal Controls (n = 21)
WAIS-R Vocabulary (scaled score)	9.9 (2.0)	11.9 (1.9)†
Trails A (seconds)	30.8 (9.7)	24.3 (6.1)†
Trails B (seconds)	107.4 (64.4)	71.7 (29.8)*
Visual Search (seconds)	13.2 (12.5)	14.6 (5.9)
Digit symbol (total correct)	48.5 (11.2)	59.8 (10.7)†
RAVLT trial 1 (# correct)	5.7 (1.4)	7.8 (2.6)†
Delay (# correct)	9.4 (2.5)	10.4 (3.0)
Booklet Category Test (total errors)	62.4 (26.1)	36.8 (17.4)†
Stroop Interference (age-adjusted Z-score)	-0.15 (0.58)	-0.31 (1.02)

* $p < 0.05$.

† $p < 0.01$.

RESULTS

Cognitive Performances of Alcoholics Versus Controls

Group means for the alcoholic and control subjects on the neuropsychological tests in the battery are presented in Table 2. Four of the alcoholic subjects could not complete the Stroop or the Booklet Category Test because of colorblindness; therefore, all statistical analyses that include these tasks are based on a group of 32 (rather than 36) alcoholic subjects. As anticipated on the basis of previous reports of cognitive dysfunction secondary to alcohol abuse, one-way ANOVAs revealed that the alcoholic group was significantly impaired, relative to the controls, on many of the neuropsychological measures. Since these group differences were not ameliorated when analyses of covariance were computed with education as the covariate, the relative cognitive impairment of the alcoholic group is evident even after educational differences have been accounted for statistically.

TABLE 3
PEARSON CORRELATIONS AMONG UPSIT AND COGNITIVE MEASURES: ALCOHOLIC SUBJECTS ($n = 32$)

	UPSIT	Tr A	Tr B	V Srch	D Sy	RAV #1	RAV-D	BCT	Stroop
UPSIT	1.00								
Trails A	-0.11	1.00							
Trails B	-0.18	0.58†	1.00						
Visual Search	0.08	0.14	-0.06	1.00					
Digit Symbol	0.17	-0.57†	-0.46†	-0.04	1.00				
RAVLT-Trial 1	-0.10	-0.10	-0.29	0.02	0.28	1.00			
RAVLT-Delay	0.23	-0.25	-0.43†	-0.05	0.29	0.45*	1.00		
Booklet Category Test	-0.26	0.29	0.25	-0.15	-0.17	-0.15	-0.19	1.00	
Stroop	0.06	0.27	0.12	0.12	-0.30	-0.08	-0.03	-0.13	1.00

* $p < 0.05$.

† $p < 0.01$.

Olfactory Functioning

The distributions of UPSIT scores (out of a maximum of 40 possible correct) are shown in Figure 2 for the alcoholic and normal control groups. The normal controls (mean 37.6, SD 2.0) performed significantly better, $F(1, 55) = 8.20$, $p < 0.01$, than did the alcoholics (mean 34.1, SD 5.4).

Supplemental analyses were performed to determine the degree to which certain factors other than olfactory integrity per se may have contributed to the relatively reduced UPSIT scores in the alcoholic group. Since 28 of the 34 alcoholic subjects reported current smoking, the correlation between the average number of packs of cigarettes smoked per day (mean 1.03, SD 0.68) and UPSIT scores was computed for the alcoholic group. The resulting Spearman correlation coefficient did not reach statistical significance ($r = -0.122$). Thus, from the available smoking data, there is little evidence to suggest that the UPSIT scores within the alcoholic group were influenced by the frequency of the patients' current smoking behavior. A similar correlational analysis could not be performed for the normal controls, because only four of these subjects smoked.

A second important consideration in interpreting the UPSIT results is that the alcoholics' relative deficit on this task may potentially be reflective of generalized cerebral dysfunction that compromises these patients' ability to accurately complete cognitive aspects of the task demands (e.g., difficulty maintaining task set, making multiple-choice discriminations, etc.). To evaluate this issue, the intercorrelations between UPSIT and the other neuropsychological tests in the battery were examined. The presence of multiple significant correlations between the olfactory and cognitive measures would be interpreted as suggesting that UPSIT scores may be affected by the presence of neuropsychological dysfunction or that a single pathological process may be mediating both olfactory and cognitive performance decrements. Alternatively, the lack of such intercorrelations would suggest that the UPSIT scores are reflective of sensory loss that is relatively independent of disturbance in other cognitive domains.

Table 3 shows the Pearson product-moment correlation matrix for the UPSIT and the other neuropsychological tests in the battery. Although there are multiple significant correlations among the various cognitive measures, the UPSIT does *not* correlate significantly with any of the other tests in the battery.

Imaging Analysis

The mean age-adjusted z -scores on each of the MRI indices are shown in Table 4 for the normal control and alcoholic groups. One-way ANOVAs indicated that the alcoholics displayed significantly elevated cortical and ventricular fluid levels ($p < 0.001$ and $p < 0.05$, respectively) and diminished overall cortical grey matter volumes ($p < 0.01$), relative to the normal controls. Within the specific lateral cortical regions, the alcoholics demonstrated significantly reduced volumes in the lateral orbitofrontal/temporal pole ($p < 0.05$), dorsolateral frontal cortex ($p < 0.01$), and parietal/superior occipital cortex ($p < 0.01$). Subcortically, the alcoholics showed reduced caudate ($p < 0.01$) and lenticular ($p < .05$) nuclear volumes, relative to the controls. It is noteworthy that, although not all MRI indices in the table reveal group differences that reach statistical significance, all of the mean differences are in the direction of the alcoholic group having relatively lower grey matter volumes and relatively higher fluid volumes than the control group. Therefore, these analyses illustrate that, in our subject sample, alcoholism is associated with specific MRI abnormalities, most prominently, increases in fluid volume and reduced peripheral cortical and basal ganglia volumes. These findings are very similar to those reported in a previous report from this laboratory (14). However, Jernigan et al. (14) did identify a statistically significant elevation in the white matter abnormalities of their alcoholic group (relative to the controls) that is not evident in the present data. Comparison of the mean z -scores obtained in the two studies reveals that the relatively reduced magnitude of the group difference (alcoholics versus normal controls) in the present investigation is attributable to an increment in the white matter changes shown by our control group.

In order to explicate the relationship between olfactory loss and the observed MRI changes associated with alcoholism, Spearman correlations were computed between the UPSIT scores and each of the MRI indices for the alcoholic subjects (Table 5). Since most of the normal controls earned perfect or near-perfect scores on the UPSIT (Fig. 2), the range of their scores was too restricted to be useful in correlational analyses with MRI indices. The results within the alcoholic group showed that both cortical and ventricular fluid levels were significantly and negatively correlated with scores on the UPSIT (i.e., higher fluid levels were associated with performance decrements on the olfactory measure). In terms of cortical

TABLE 4
MEAN AGE ADJUSTED z-SCORES

	Normal Controls (<i>n</i> = 21)	Alcoholics (<i>n</i> = 36)
Fluid measures		
Cortical	0.11 (0.94)	1.56 (1.46)†
Ventricular	0.11 (1.31)	0.81 (1.23)*
Total cortical grey	0.17 (1.15)	-0.75 (1.24)†
Lateral cortex		
Lateral orbitofrontal/temporal pole	0.15 (0.97)	-0.45 (1.09)*
Lateral temporal/inferior occipital	-0.13 (1.11)	-0.44 (0.97)
Dorsolateral frontal	0.36 (1.01)	-0.66 (1.15)†
Parietal/superior occipital	0.09 (1.06)	-0.89 (1.40)†
Mesial cortex		
Mesial orbitofrontal	-0.16 (1.11)	-0.60 (1.00)
Mesial temporal	-0.26 (0.68)	-0.59 (0.79)
Anterior insula/cingulate	0.28 (0.87)	0.13 (0.93)
Posterior insula/cingulate	0.60 (1.20)	0.31 (1.26)
Subcortical grey		
Caudate	0.12 (1.07)	-0.64 (0.95)†
Lenticular	0.15 (1.22)	-0.58 (1.07)*
Diencephalon		
Anterior	0.01 (1.36)	-0.50 (0.88)
Posterior	0.07 (0.90)	-0.44 (1.14)
Abnormal white matter index	0.34 (1.16)	0.60 (1.20)

**p* < 0.05.

†*p* < 0.01.

grey matter, higher volumes were associated with higher UPSIT scores. Within specific cortical regions, correlations between UPSIT and grey matter volumes reached statistical significance for all four of the lateral cortical measures and for two of the four mesial cortical measures. Subcortically, UPSIT scores were significantly associated with values for the caudate and lenticular nuclei and for the posterior diencephalon (i.e., thalamus). In all cases, the correlations were in the hypothesized direction (i.e., greater abnormality on MRI was correlated with lower UPSIT scores).

It was of interest to determine whether the obtained simple correlations between UPSIT and specific MRI indices accurately reflected brain-behavior localization, or whether they were substantially accounted for by variance in UPSIT scores that was shared among multiple MRI measures. This issue was addressed with a series of standard multiple regressions, each of which inspected the unique contributions of individual MRI indices (i.e., the significance of the standardized regression coefficients) in the presence of other, neuroanatomically relevant, indices.

The first regression examined the relative contributions of the two fluid measures to the prediction of the UPSIT score. Results indicated that, although the simple correlations were significant for both fluid measures, neither of the two indices contributed a statistically significant amount of unique variance when considered together. Similarly, when the eight cortical grey matter MRI indices were entered into a multiple regression, none of the eight indices accounted uniquely for a significant proportion of the variance in the UPSIT score. Turning to the four subcortical grey matter indices (anterior and posterior diencephalon, caudate, and lenticular nuclei), it was found that the overall regression was significant, $F(4, 31) = 2.89$, $p < 0.04$, and, more importantly, that the posterior

diencephalon made a significant unique contribution to the prediction of UPSIT score, above and beyond that of the other subcortical regions ($p < 0.02$). A final multiple regression confirmed that the posterior diencephalon contributed significant unique variance ($p < 0.05$) even when considered in combination with the total cortical grey matter volume. This analysis also revealed that the unique contribution of cortical grey matter approached significance ($p = 0.086$), suggesting the possibility that cortical damage may have an independent and additive effect on olfactory dysfunction.

Finally, it was of interest to determine whether the identified correlations between UPSIT score and regional brain volumes were specific to olfaction or, rather, were reflective of widespread and possibly nonspecific intercorrelations between MRI indices and behavioral measures. To address this issue, two correlation matrices were computed. The first was chosen to examine the relationships between the MRI indices and a cognitive measure with demonstrated sensitivity to the cognitive dysfunction of the alcoholics in our sample (Booklet Category Test). The second matrix was selected to address the associations between all of the cognitive measures in the battery and an MRI index known to differentiate alcoholics from control subjects (cortical fluid volume). Consistent with our previously reported findings (14) and, in contrast to the significant relationships between MRI indices and the olfactory measure, none of these correlations proved to be statistically significant.

DISCUSSION

The present results confirm, in a larger sample of patients, the DiTraglia et al. (2) findings of reduced olfactory identification ability in chronic, nonamnesic alcoholics. These results

TABLE 5
SPEARMAN RANK ORDER CORRELATION
COEFFICIENTS BETWEEN MRI INDICES AND UPSIT
SCORES IN THE 36 ALCOHOLIC SUBJECTS

Fluid measures	
Cortical	-0.391†
Ventricular	-0.288*
Total cortical grey	0.506†
Lateral cortex	
Lateral orbitofrontal/temporal pole	0.316*
Lateral temporal/inferior occipital	0.288*
Dorsolateral frontal	0.329*
Parietal/superior	0.423†
Mesial cortex	
Mesial orbitofrontal	0.193
Mesial temporal	0.181
Anterior insula/cingulate	0.281*
Posterior insula/cingulate	0.471†
Subcortical grey	
Caudate	0.346*
Lenticular	0.393†
Diencephalon	
Anterior	0.099
Posterior	0.477†
Abnormal white index	0.178

* $p < 0.05$.

† $p < 0.01$.

stand in contrast to other reports that alcoholic subjects perform comparably to normal controls on olfactory tests which require same/different discrimination (19), magnitude estimation (18), psychophysical scaling (20), and spontaneous naming of olfactory stimuli (12). Small sample sizes in previous studies may, in part, account for the discrepant findings with regard to the presence or absence of olfactory loss in this population (3). More importantly, however, it is clear that variations in the task demands of olfactory assessment instruments may differentially elicit patterns of normal or impaired performance (5-7,21,37). It must be borne in mind, therefore, that the present results may only legitimately be compared to other investigations which implemented a multiple-choice test of olfactory identification.

Although the alcoholics as a group were impaired, relative to the controls, on many of the neuropsychological tests in the present battery, correlational analyses indicated that the level of UPSIT impairment evident in the alcoholic group was unlikely to be due to a generalized cognitive impairment *per se*. This finding is consistent with many previous reports that olfactory dysfunction is independent of cognitive decline (2,18-21,37).

While the obtained magnitude of the group difference in UPSIT score may be mildly inflated by the higher prevalence of cigarette smoking in the alcoholics (3), correlational analyses failed to suggest that their level of current cigarette consumption was a significant mediator of their UPSIT score. This finding is consistent with previous reports of a nonsignificant relationship between UPSIT scores and the number of packs smoked per day in normals (3) and alcoholics (2). Support for the hypothesis that smoking behavior did not contribute significantly to the observed UPSIT decrement emanates also from the previously reported result (which included a subset of the present subject pool) that even nonsmoking alco-

holics showed a decrement in UPSIT performance relative to controls (2). Since it was not possible within the scope of the present study to perform a comprehensive assessment of peripheral sensory structures, we cannot completely rule out the possibility that peripheral disease or trauma may potentially have affected observed olfactory deficits in the alcoholic group. However, a peripheral contribution, if one were present, is unlikely to account substantially for the obtained central (brain-behavior) relationships.

The most important new findings in the present investigation are the significant associations between performance decrements on the UPSIT and volumetric loss seen on MRI. In addition to the significant correlations of cortical and ventricular fluid volumes with UPSIT scores, the present results demonstrate several critical relationships between olfactory capacities and the volumes of cortical and subcortical grey matter regions. While the contribution of midline thalamic nuclei to olfaction in alcoholics has been proposed previously based upon known anatomical connections (18-20,27), little direct empirical support for this relationship has been observed. The present finding that the volume of the posterior diencephalon (i.e., the thalamus) contributes significantly to the prediction of UPSIT performance, even after partialing out variance shared with other cortical and subcortical grey matter structures, may represent an important verification of the role of the thalamus in olfactory experience.

The noted correlation between UPSIT score and the total cortical grey matter volume suggests that cortical mechanisms may also contribute significantly to the olfactory deficits of alcoholics. The role of frontal and temporal cortex in olfaction has been clearly demonstrated in focal lesion patients (21,28,37). Although the simple correlations in the present study indicated significant relationships between UPSIT scores and volumes of the orbitofrontal and temporal cortices, the multivariate analyses suggest that these correlations are best conceptualized as reflecting variance in UPSIT score that

TABLE 6
PEARSON CORRELATION COEFFICIENTS
BETWEEN MRI INDICES AND BOOKLET CATEGORY
ERRORS IN 32 ALCOHOLICS

Fluid measures	
Cortical	-0.131
Ventricular	0.030
Total cortical grey	0.218
Lateral cortex:	
Lateral orbitofrontal/temporal pole	0.027
Lateral temporal/inferior occipital	0.163
Dorsolateral frontal	0.151
Parietal/superior	0.215
Mesial cortex	
Mesial orbitofrontal	-0.110
Mesial temporal	-0.217
Anterior insula/cingulate	-0.073
Posterior insula/cingulate	-0.006
Subcortical grey	
Caudate	0.119
Lenticular	0.273
Diencephalon	
Anterior	-0.014
Posterior	0.201
Abnormal white index	0.051

TABLE 7

PEARSON CORRELATION COEFFICIENTS BETWEEN TOTAL CORTICAL FLUID AND COGNITIVE SCORES IN 32 ALCOHOLICS

Trails A (seconds)	0.126
Trails B (seconds)	0.126
Visual Search (seconds)	0.038
Digit Symbol (Total Correct)	0.120
RAVLT Trial 1 (# correct)	0.050
Delay (# correct)	-0.202
Booklet Category Test (Total Errors)	-0.131
Stroop Interference (age-adjusted z-score)	-0.003

is shared among the cortical indices. Thus, while our data do not support the conclusion that olfactory decrements are associated with localizable cortical volume loss in alcoholics, they do suggest a relationship between olfactory ability and generalized cortical grey matter integrity. Furthermore, there was a statistical trend suggesting that overall tissue loss in the cortical grey matter may be uniquely associated with UPSIT decrements, independent of the identified thalamic contribution to olfactory loss. Taken together, the present data and the existing anatomical and focal lesion studies provide strong support for the conclusion that both cortical grey matter and the medial portions of the thalamus serve as major projection sites for the olfactory system.

Since the present study relies on correlations between imaging and behavioral measures, several other methodological

issues deserve consideration. First, although the UPSIT scores failed to correlate with any cognitive measures in the present battery, it is still possible that this multiple-choice task requires certain functions that were not assessed or detected by our neuropsychological test battery and which may, in part, mediate the observed brain-behavior relationships (e.g., retrieval of olfactory images or sustained attention during a self-administered task). Second, both UPSIT decrements and volumetric changes in the brain structures may be mediated in part by a common factor not identified or evaluated in the present study. For instance, metabolic dysfunction and/or malnutrition, both of which are common in chronic alcoholics, may have detrimental effects on grey matter structures as well as on peripheral neural entities that mediate olfaction. If such were the case, portions of the observed correlations between MRI indices and UPSIT performance could represent secondary, noncausal relationships. Finally, while the present study indicates that at least certain alcoholics are impaired in olfaction and that this sensory loss has neurologic correlates, the specific processes underlying the deficit remains unanalyzed. That is, future studies need to explore whether the patients' deficits reflect heightened absolute thresholds for all odorants or, rather, a failure to process specific odorants.

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