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Does an Increase in Sulcal or Ventricular Fluid Predict Where Brain Tissue Is Lost?

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ABSTRACT

Quantitative volumes of cerebrospinal fluid (CSF) and brain tissue were measured on magnetic resonance images (MRIs) of 287 individuals from 5 diagnostic groups: Alzheimer's disease (AD), chronic alcoholics (ALC), individuals positive for human immunodeficiency virus (HIV), schizophrenia subjects (SZ), and normal comparison subjects (NC) older than 50 years of age. Within each group, mean volumes were calculated for ventricular CSF, cortical (sulcal) CSF, cortical gray matter, total white matter, basal ganglia gray matter, and thalamic gray matter. Correlations of CSF measures with brain tissue measures were determined, and multiple regression analyses were performed to try and predict volume of gray matter or white matter region from volume of CSF compartment. Results indicated the following:

1. Enlarged cortical fluid volume significantly predicts cortical gray matter deficits for subjects with AD and those who are ALC and SZ but not for subjects with HIV or NC.
2. Enlarged cortical fluid volume also significantly predicts white matter deficits in all five groups.
3. Enlarged ventricular fluid volume significantly predicts basal ganglia deficits in AD, HIV, and NC but not in SZ or ALC.
4. Enlarged ventricular volume has no predictive value for thalamic volume for any of the groups. This study supports the clinical practice of predicting brain tissue volume loss from CSF enlargement but not for all brain regions in all diagnoses.

Key words: cerebral spinal fluid, ventricle, sulcal fluid, MRI, gray matter, degeneration.

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Neuroimaging studies of neurologic and psychiatric diseases often have described enlargements in the estimated volumes of cerebrospinal fluid (CSF)-filled spaces. In psychiatry, Johnstone et al[1] were the first to show that in some patients with schizophrenia, there was an apparent enlargement in the cross-sectional area of the lateral ventricles on computerized tomography (CT) slices. Their finding initiated the search with neuroimaging tools for the location of brain tissue, assumed to have been lost in these patients. Other reports of enlarged ventricles or cortical sulci on magnetic resonance (MR) or CT images followed for other diagnoses, including Alzheimer's disease,[2,3] chronic alcoholic abuse,[4,5] as well as for those infected with the human immunodeficiency virus (HIV).[6,7]

Reasons for the focus on CSF are largely practical: CSF is readily visualized in some imaging protocols, particularly T1- and T2-weighted MR images. In addition, the large volumes of structures such as the lateral ventricles render them relatively easy to measure.

In addition to methodologic considerations, CSF volumes are also assumed to have clinical importance because in adult humans, there often is a direct relationship between an increase in CSF volume and a decrease in brain tissue. This assumption lies at the heart of rating scales of ventricular enlargement and sulcal dilation that are used to assess cerebral atrophy.[8–10] Longitudinal observations of ventricular enlargement, for example, are considered by many clinicians to be reliable measures of disease progression in patients with Alzheimer's disease.[11]

Perhaps the most common and intuitive assumption one makes on seeing an enlargement of CSF-filled spaces is that tissue nearby has decreased in volume as either a consequence or a cause of the greater CSF volume. Enlarged lateral ventricles suggest a decrease in subcortical gray matter, and larger cortical sulci suggest a decrease in volume of cortical gray matter (i.e., central vs. cortical volume loss).[12]

There have been examples, however, in the neuropsychiatry literature of apparent dissociations between CSF compartment size increases and nearby brain tissue decreases. For example, in a 1985 study, Coffman and Nasrallah[13] used CT scans and found little relationship between either ventricular enlargement or sulcal dilation and density measurements in the same brain slices. These results call into question the basic assumption that greater

volume of CSF is associated with less volume of nearby tissue.

Similar questions have arisen informally in our laboratory. During weekly review sessions, all anatomists inspect fully processed MRI brain scans before diagnoses of the subjects who have been scanned are revealed. Widened cortical sulci appear to be accompanied by reductions in adjacent gray matter, but such impressions are subjective, and it is not at all clear whether the relationship holds across all diagnoses. Even more problematic is the issue of volume loss in the white matter. White matter volume is very difficult to assess qualitatively yet may account for much of the tissue lost in some diagnoses, such as in chronic alcoholism or HIV infection.[14,15]

Spurred in part by these questions, the current study describes the quantitative pattern of volume differences in CSF, gray matter, and white matter for four separate neurologic/psychiatric diagnoses. We chose to focus on diagnoses for which we had greater than 50 subjects and in which we expected to see an enlargement of CSF. Our analyses included the following diagnoses: Alzheimer's disease, HIV infection, schizophrenia, and chronic alcoholism, as well as a group of older normal comparison subjects. Specifically, we wanted to know the following:

1. What are the patterns of CSF volume enlargements and gray matter and white matter deficits in the four separate patient groups?
2. For the patient groups, as well as for the normal control subjects, are enlargements of fluid volume in the ventricles accompanied by deficits in subcortical tissue volume? Are enlargements of cortical sulcal volume accompanied by deficits in cortical gray matter or white matter or both?
3. Within a diagnosis, does an enlargement of either cortical or ventricular fluid significantly predict whether there are deficits in cortical gray matter, subcortical gray matter, or white matter?

The logic of asking this third question stems from a problem often faced by clinical neuroradiologists. If the MRI of a patient's brain displays an obvious enlargement of the CSF, is it possible to predict where tissue may have been lost? Although the intuitive answer may be that brain tissue has been lost nearest the CSF compartment showing the most obvious enlargement, little is known about whether this is true, and if so, if it is true for gray as well as for white matter, or whether it is true across diagnoses. This study addresses these questions in four diagnoses by using multiple regression analyses to predict various brain tissue compartment volumes from two CSF compartments, the ventricular system, and the subarachnoid fluid. This approach makes it possible to say whether one fluid compartment is a stronger predictor of tissue loss than the other compartment.

Subjects and Methods

Subjects: A total of 287 volunteers participated in this study. They were drawn from the following five populations:

1. AD group: There were a total of 58 patients from the Alzheimer's Disease Research Center of the University of California, San Diego. All were diagnosed with probable AD[16] using criteria from the National Institute of Neurological Disorders and Stroke and the Alzheimer's Disease and Related Disorders, Association, and with primary degenerative dementia according to the Diagnostic and Statistical Manual for Mental Disorders, Third Edition, Revised.[17] Mean age was 71.5 years (range, 56–84 years; standard deviation [SD], 6.1); there were 29 women and 29 men.
2. ALC group: There were a total of 52 patients from the San Diego Department of Veterans Affairs Medical Center's Alcohol Treatment Program, a 28-day program for alcoholism counseling and treatment. All patients had undergone detoxification before admission and were diagnosed with alcohol abuse or dependence using the DSM-III criteria[18] after participating in the Alcohol Research Center Intake Interview.[19] Data on drinking and medical histories also were obtained from at least one resource person such as a family member or a close friend. The majority of subjects had undergone detoxification shortly before admission to the hospital, and MRIs were obtained during the third week of hospitalization. Subjects typically had been sober for only approximately 30 days before the MRI scanning session. Mean age was 48.4 years (range, 27–68 years; SD = 9.9); all patients were men.
3. HIV group: There were a total of 52 patients from the HIV Neurobehavioral Research Center at the University of California, San Diego. All patients were HIV-positive, and the primary risk factor for HIV infection in all civilians was homosexuality; the primary risk factor for military participants was either sexual behavior or unknown. Mean age was 33.4 years (range, 24–42 years; SD = 5.0); all patients were men.
4. SZ group: There were a total of 62 patients from the San Diego Veterans Affairs Medical Center, the University of California, San Diego Psychiatry Outpatient Services, and the Geriatric Psychiatry Clinical Research Center of the University of California, San Diego. All patients were diagnosed with schizophrenia using DSM-III-R criteria after administration of the Structured Clinical Interview for DSM-III-R.[20] Mean age was 30.8 years (range, 18–49 years; SD = 8.0); there were 22 women and 40 men.
5. NC group: There were a total of 63 healthy individuals, older than 50 years of age, who were recruited as control subjects for clinical studies and studies of normal

aging. Mean age was 65.2 years (range, 51–82 years; SD = 7.8); there were 34 women and 29 men.

Exclusion criteria for all groups included significant psychiatric history (except for schizophrenia in the SZ group); significant neurologic history, including head injury with loss of consciousness for more than 30 minutes (except for Alzheimer's dementia in the AD group); and major medical conditions, including history of overt liver, metabolic, or vascular conditions. Exclusion for drug abuse or dependence differed by group. In the ALC group, subjects were excluded for history of drug abuse predating the onset of alcoholism. In the SZ group, subjects were excluded if the abuse or dependence could be causally related to the psychosis. In the HIV group, subjects were excluded if the abuse consisted of seven or more drinks per day for at least 2 weeks in the month before entering the study, or for 90 consecutive days for the previous year. In the AD and NC groups, subjects were excluded for past or current substance abuse or dependence. Most of the patients and control subjects have been reported on previously, and details of clinical assessment are contained in those publications.[15,21–23]

MRI Protocol: All scans were obtained on a 1.5-Tesla superconducting magnet (Signa, General Electric, Milwaukee, WI). Axial images were collected from the entire brain with an asymmetric pulse sequence (TR, 2000 ms; TE 25, 70 ms). Image slices were 5-mm thick with 2.5-mm gaps between slices. One multiple echo series yielded two registered images for each section, one a proton density-weighted (PDW) and the other a T_2-weighted (T2W).

Image Analysis: Details of the image analysis procedure can be found in several articles[21,24,25] and are described briefly here. All identifying information, including diagnosis, was removed from the MR images. Digital images were processed by trained image analysts using software developed in the laboratory on a DOS-based personal computer platform. First, all nonbrain pixels (e.g., skull) were excluded. Images then were digitally filtered to reduce inhomogeneities caused by nonbiologic signal drift across the images. Next, all pixels were classified into one of four categories: gray matter, white matter, CSF, and signal hyperintensity. This segmentation procedure was accomplished in two steps. First, two new linear combinations of pixel values (PDW/T2W) were computed to optimize distinctions between gray and white matter, and CSF and brain, respectively. Second, classification criteria, which were based on the optimized pixel values, and adjusted section by section based on white matter signal values, were applied to individual images. Image analysts then designated anatomic regions, blind to subject age or diagnosis. A stylus-controlled cursor on the displayed image was used to manually separate cerebellar from cerebral areas, left from right hemispheres, and cortical from subcortical regions. Because the segmentation procedure described above had already separated gray matter, white matter, and CSF pixels from one another, separate estimates were therefore yielded for four of the seven measures in this study: cortical gray matter, cortical (sulcal) CSF, subcortical (ventricular) CSF, and total white matter. The remaining three brain regions measured in this study were all subcortical gray matter structures: caudate nucleus, lenticular nucleus, and the thalamus. To delineate these three regions, the image analysts did not trace the edges of the structures but defined polygons that included all gray matter pixels within the structures and excluded those gray matter pixels associated with other structures. In some cases, when the subcortical nuclei were contiguous with other areas classified as gray matter, but clearly not in the structures, boundaries were manually constructed using the filmed images as a guide. Finally, the thalamus measure in this study largely excludes hypothalamus and septal structures stereotactically by defining the thalamus only posterior to a coronal plane halfway between the most anterior and posterior points of the corpus callosum (for further details, see the previous articles[24,25]). Two image analysts independently processed a set of 20 full sets of axial images from 20 different individuals to determine interrater reliability. Spearman rank order correlations were between 0.84 and 0.98.

Volume estimates for each region of interest were made by summing all pixels for a given measure across all sections and transforming the values to z-scores normalized to a sample of age-matched and cranium size-matched healthy control subjects.[26] These z-score computations were based on data from a large sample of normal volunteers ranging widely in age. The z-scores were derived from each normal control subject as follows (see also reference[26]). First, measures of CSF and brain tissue volumes were computed that expressed the original values (voxel counts) as derivations from the values predicted from the subjects' ages and cranial sizes. Then, similar analyses were done to estimate any age-related change in the variance of the new derivation scores. Finally, formulas were constructed for estimating a subject's volume scores relative to those of age peers with similar cranial volume. By definition, these z-scores should have a mean of 0 and an SD of 1 in groups of normal control subjects and should produce volume measures that are independent of cranium size and age.[26]

Measures of interest for this study were cortical (sulcal) CSF, subcortical (ventricular) CSF, total cortical gray matter, total white matter (including normal white matter and white matter with signal hyperintensities), and three separate subcortical gray matter regions: the thalamus, the caudate nucleus, and the lenticular nucleus, the latter consist-

ing primarily of the putamen. The caudate and lenticular nuclei were combined into one measure for this study by taking the mean of the two z-scores, a procedure justified by the fact that the two nuclei are very close in actual pixel totals. Figure 1 shows a series of three processed brain sections with segmented gray matter, white matter, and CSF for a 64-year-old male normal control subject.

Statistical Analysis: The mean volumes for each of the five groups were computed. In each of the four patient groups, the six regions of interest were compared to the means of those regions in the normal control subjects using two-tailed Student's *t*-tests. Pearson product–moment correlations were calculated in each of the five subject groups to compare each of the four tissue volumes with each of the two CSF volumes. The mean comparison analysis was performed primarily to confirm that the subject groups had increased fluid volumes relative to age- and head-size comparable to normal control subjects. The pairwise correlation was performed as a first step in building the multiple regression models. Therefore, corrections for multiple comparisons were not made in either of these analyses. Four separate multiple regression models were run in each of the five groups. In each regression analysis, the two CSF measures were the predictor variables, and one of the brain tissue volumes (i.e., cortical gray matter, total white matter, thalamus, or basal ganglia) was the outcome variable. Additional post hoc standard multiple regression analyses were run in some diagnostic groups to determine the extent to which the association between predictor variables and outcome variables was mediated by other brain regions.

Results

Patterns of CSF Volume Enlargements and Gray Matter and White Matter Deficits: Figure 2 illustrates for each diagnosis the mean volumes of cortical (sulcal) fluid, ventricular fluid, cortical gray matter, total white matter, thalamic gray matter, and basal ganglia. As predicted, in all four disease diagnoses, there was a significant mean enlargement of sulcal fluid and ventricular fluid, although *t*-tests for paired data of the differences between the two fluid compartments indicated that the pattern among diagnoses was somewhat different. For example, the enlargement of ventricular fluid volume was much greater than for sulcal fluid volume in the Alzheimer disease group (mean difference = 1.78, $p < 0.0001$). The alcoholic group, conversely, had greater enlargement of sulcal fluid than ventricular fluid (mean difference = 0.60, $p = 0.0017$). Sulcal and ventricular enlargements were similar in the HIV group and the SZ group (mean differences 0.16 and 0.18; $p = 0.4787$ and 0.4314, respectively). In all four of the patient groups, there were significant deficits in one or more of the tissue compartments under consideration. With confirmation of fluid enlargement and gray matter or white matter deficits in each of the patient groups, we next asked whether enlargement of sulcal or ventricular fluid was specifically related to deficits in cortical or subcortical tissue.

Relationship of Sulcal and Ventricular Fluid to Gray Matter and White Matter: Table 1 illustrates Pearson product–moment correlations for the tissue volumes in each of the four patient groups and normal control groups. Cortical gray matter, white matter, and basal ganglia vol-

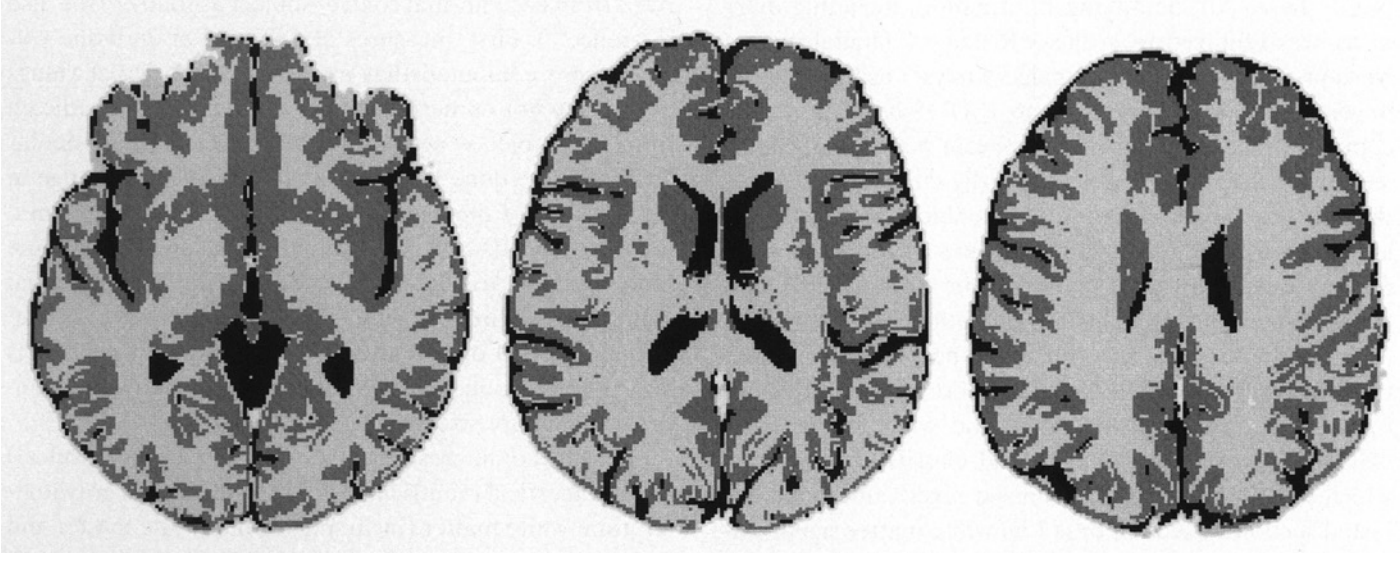

Fig 1. Fully processed anatomic images from a magnetic resonance imaging of a 64-year-old male normal control subject. In these axial slices from three superior-to-inferior levels (image on left is most inferior, image on right is most superior; anterior is at top), cerebrospinal fluid appears black, gray matter appears dark gray, and white matter appears light gray.

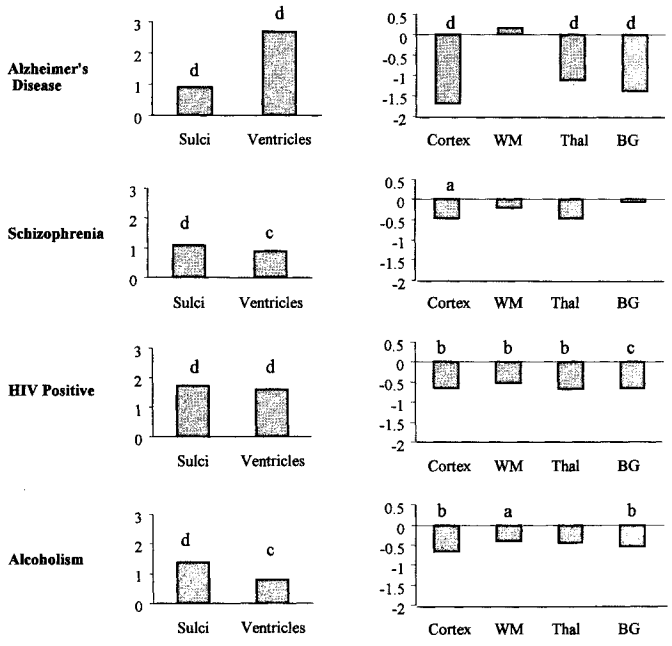

Fig 2. Bar graphs indicating mean volume in standardized z-scores for cortical CSF (sulci), ventricular CSF (ventricles), cortical gray matter (cortex), total white matter (WM), thalamic gray matter (Thal), and basal ganglia gray matter (BG). "a" = significantly different from normal comparison group at $p \leq 0.05$. "b" = significantly different from normal comparison group at $p \leq 0.01$. "c" = significantly different from normal comparison group at $p \leq 0.001$. "d"= significantly different from normal comparison group at $p \leq 0.0001$.

umes were significantly correlated with sulcal fluid and ventricular fluid in many of the diagnoses, including those for the normal control subjects. Thalamic gray matter volume was less frequently correlated with fluid volumes: smaller thalamic volume was moderately related to larger ventricular volume in SZ and strongly related to enlargement of sulcal fluid in SZ and AD. The main result illustrated in Table 1 is that fluid volume, whether sulcal or ventricular, was significantly correlated with tissue volume deficits in most brain regions measured. This was true for diagnoses in which there is a significant loss of the tissue type in question (e.g., white matter loss in HIV) as well as for diagnoses in which there was no significant mean loss of the tissue type (e.g., white matter in AD). Figure 3 contains examples of four scatterplots illustrating significant and nonsignificant correlations between fluid and tissue volume measures.

The central question of this study is whether CSF increase can significantly predict tissue loss nearby. We hypothesized that (larger) volume of cortical sulci would significantly predict (smaller) volume of cortical gray matter as well as total white matter and that ventricular volume would similarly predict subcortical gray matter volume. Simple correlations do not help much in answering the question. For example, in ALC subjects, white matter deficit was highly significantly related to enlargement of sulcal fluid ($r = -0.53$, $p = 0.0001$) and ventricular fluid ($r = -0.43$, $p = 0.0014$). The correlation analyses are not informative of whether either sulcal fluid volume or ventricular fluid volume serves as a better predictor. Therefore, for all patient groups and normal control subjects, we used multiple regression analyses to determine whether the volume of either fluid compartment significantly predicted volume deficits in white matter, cortical gray matter, or subcortical gray matter. Results of the multiple regression analyses are listed in Table 2.

Prediction of Cortical Gray Matter Loss from Fluid Volumes: When sulcal and ventricular fluid volumes were used to predict cortical gray matter volume, sulcal fluid was in general the only significant predictor for the patient groups, supporting the hypothesis for several of the groups (Table 2). Ventricular fluid shared little or no unique variance with cortical gray matter. For example, in ALC subjects, the β coefficient for sulcal fluid was −0.46 ($t = 0.004$); for ventricular fluid, the β coefficient was only −0.02 ($t = 0.88$). Similar relationships were seen for AD and SZ. For HIV, there was no significant predictive relationship between either of the fluid volume measures and cortical gray matter deficit. In normal control subjects, sulcal fluid was not predictive of cortical gray matter, but ventricular fluid volume was predictive ($\beta = -0.28$, $t = 0.04$). In general, the hypothesis was supported for AD, ALC, and SZ but not for HIV or NC.

Prediction of White Matter Loss from Fluid Volumes: Based on the observation that the majority of white matter underlies cortical gray matter and is composed of the cortico–cortical connections among cortical areas, we hypothesized that sulcal fluid would significantly predict white matter volume loss, at least in patients with HIV, for whom there was a relatively greater loss of white matter compared to other diagnoses. The hypothesis was supported. Multiple regression analyses (Table 2) demonstrated, in fact, that sulcal fluid was a relatively strong predictor of white matter volume compared to ventricular fluid in all five diagnoses, including normal control subjects. The relationship for SZ was significant at a trend level of $t = 0.07$. The relationship was particularly strong for patients with HIV and AD, in whom volume of sulcal fluid uniquely shared 21% and 22% of the variance, respectively, in white matter volume.

Prediction of Subcortical Gray Matter Loss from Fluid Volumes: Separate nuclei and regions within subcortical gray matter suffer different fates in the diagnostic groups of this study. For example, in SZ, the basal ganglia are, on average, larger in volume,[26–28] and the thalamic volumes tend to be smaller than in normal control subjects.[29,30] To detect potential predictive relationships between subcor-

Table 1. Association Between CSF and Brain Tissue Measures

Diagnosis	CSF Measure	Cortical Grey Matter	Total White Matter	Basal Ganglia	Thalamus
NC	Ventr	−0.25*	−0.20	−0.38†	−0.19
	Sulci	−0.05	−0.62§	−0.19	−0.06
AD	Ventr	−0.30*	−0.37†	−0.58§	−0.13
	Sulci	−0.40†	−0.53§	−0.38†	−0.35†
ALC	Ventr	−0.28*	−0.43‡	−0.31*	−0.12
	Sulci	−0.48‡	−0.53§	−0.34†	−0.12
HIV	Ventr	−0.22	−0.45‡	−0.35†	−0.08
	Sulci	−0.28*	−0.60§	−0.24	−0.17
SZ	Ventr	−0.25*	−0.19	−0.18	−0.27*
	Sulci	−0.45‡	−0.28*	−0.29*	−0.44‡

* = significantly different from normal comparison group at $p \leq .05$.
† = significantly different from normal comparison group at $p \leq .01$.
‡ = significantly different from normal comparison group at $p \leq .001$.
§ = significantly different from normal comparison group at $p \leq .0001$.

tical fluid enlargements and gray matter deficits, we performed separate multiple regression analyses using either the thalamus or the basal ganglia as the dependent variable. Results are listed in Table 2. For the thalamus and basal ganglia, the hypothesis was that increased ventricular fluid would predict loss of gray matter in these subcortical structures.

Prediction of Thalamic Volume Loss from Fluid Volumes: The hypothesis was not supported for any diagnostic group in this study. Ventricular fluid increase did not significantly predict thalamic volume loss in any of the five groups. The regression models were in general very weak (R squared ranged from 0.02–0.12). In two diagnoses, however, *sulcal* fluid significantly predicted thalamic gray matter decrease: in AD, sulcal fluid volume accounted for 11% of the variance in thalamic volume, and in SZ, sulcal volume accounted for 13% (both significance at $t < 0.01$). Post hoc analyses revealed, however, that in AD and SZ, the relationship between sulcal fluid volume and thalamic volume was mediated by another variable, cortical gray matter. When sulcal fluid and cortical matter were used as the predictor variables for thalamic volume in these two diagnoses, cortical gray matter volume accounted for 26% of variance in thalamic volume for AD ($t < 0.0001$) and 34% of the variance in thalamic volume for SZ ($t < 0.0001$). Sulcal fluid no longer shared any significant unique variance with thalamic volume.

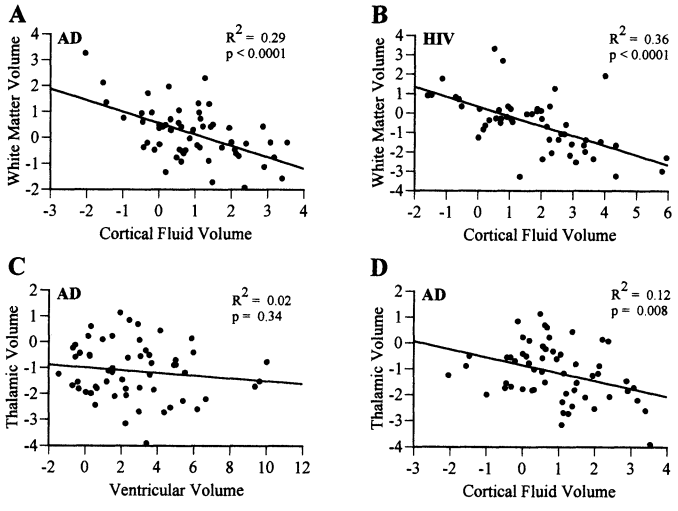

Fig 3. Scatterplots illustrating examples of the relationship between cerebrospinal fluid volume measures and brain tissue volume measures in Alzheimer's disease (AD) and human immunodeficiency virus. Units on both axes are standardized z-scores. R squared and significance values are given for each scatterplot. (A) Relationship between cortical fluid volume and total white matter volume in subjects with Alzheimer's disease is highly significant. (B) Relationship between cortical fluid volume and total white matter volume in subjects with human immunodeficiency virus is highly significant. (C) Relationship between ventricular fluid volume and thalamic volume in subjects with AD is not significant. (D) However, the relationship between cortical fluid volume and thalamic volume in subjects with AD is significant.

Prediction of Basal Ganglia Volume Loss from Fluid Volumes: The hypothesis that increased ventricular fluid predicts basal ganglia volume was supported for some of the patient groups in this study. In AD, as well as in NC, greater volume of ventricular fluid significantly predicted loss of gray matter in the basal ganglia. In HIV, the relationship was predictive at a trend level of significance. In ALC patients, neither ventricular nor sulcal fluid significantly predicted basal ganglia volume, even though the volume of the basal ganglia was significantly reduced in this group. The hypothesized prediction was therefore supported for AD, HIV, and NC but for neither ALC nor SZ.

Discussion

This study examined the relationship between volume enlargements of CSF and volume deficits in peripheral versus central brain tissue. We were interested in testing the

Table 2. Predictions of Brain Tissue Volume Measures from CSF Measures

Diagnosis	CSF Measure	Cortical Grey Matter	Total White Matter	Basal Ganglia	Thalamus
NC	Ventr	−0.28*	0.08	−0.37†	−0.20
	Sulci	0.07	−0.66§	−0.03	0.02
AD	Ventr	−0.18	−0.20	−0.51§	−0.003
	Sulci	−0.33†	−0.46‡	−0.19	−0.35†
ALC	Ventr	−0.02	−0.20	−0.18	−0.08
	Sulci	−0.46†	−0.42†	−0.24	−0.08
HIV	Ventr	−0.07	−0.12	−0.33	0.04
	Sulci	−0.24	−0.52‡	−0.04	−0.20
SZa	Ventr	−0.08	−0.09	−0.08	−0.10
	Sulci	−0.42†	−0.25	−0.26	−0.40†

* = significantly different from normal comparison group at $t \leq .05$.
† = significantly different from normal comparison group at $t \leq .01$.
‡ = significantly different from normal comparison group at $t \leq .001$.
§ = significantly different from normal comparison group at $t \leq .0001$.

assumption that loss of cortical tissue is accompanied by a differential increase in sulcal compared to ventricular fluid and that loss of subcortical tissue is directly related to enlarged ventricles. To the extent that this assumption is true, it might be possible when viewing clinical MRI films to predict with some assurance the relative magnitude of tissue loss based on the appearance of the fluid-filled compartments. For instance, larger sulci visible in T2-weighted scans of patients with AD could provide the clinician with an indication of how much cortical gray matter has been lost, and, in conjunction with previous scans, the relative rate of such loss. The current study explicitly tested this assumption in four patient groups, all with significant increases in ventricular and sulcal fluid volume. In addition, we examined the relationship between fluid volume and brain tissue volume in normal control subjects in whom age effects were statistically removed by z-scores computation.

The major results of this study are as follows:

1. Enlarged cortical fluid volume significantly predicted cortical gray matter deficits in three of the patient groups (AD, SZ, ALC, although not in HIV). In normal control subjects, the variability in ventricular fluid volume, not sulcal fluid, significantly predicted the variability in cortical gray matter volume.
2. Larger cortical fluid volume predicted total white matter deficits in all five groups.
3. Larger ventricular fluid volume predicted basal ganglia volume loss in AD, HIV, and NC groups but not in SZ or ALC.
4. Larger ventricular fluid volume had no predictive value for thalamic volume in any of the diagnosis groups.

Relationship of Thalamic Volume Loss to Fluid Increase: In this study, thalamic volume was only weakly correlated with fluid enlargement and significantly so only in AD and SZ. In addition, for these two groups, thalamic volume was more significantly predicted by sulcal than ventricular fluid. One reason thalamic volume may have such a weak relationship with fluid volumes is that the thalamus is much smaller in volume than the other gray and white matter compartments we examined. The next smallest tissue compartment measured in this study was the basal ganglia, a structure more than twice the size of the thalamus. Loss of thalamic tissue may simply have little impact on the adjacent fluid compared to loss of tissue in larger midline structures such as the basal ganglia. Alternatively, the imaging protocol used for this study, which included 5-mm-thick sections and 2.5-mm gaps, may have yielded less accurate volume estimates for smaller or irregularly shaped structures, such as the thalamus and the lenticular nucleus. Recent work in our laboratory, however, using 4-mm contiguous sections suggests that volume measures obtained in the current study are at least reproducible in another sample of patients with thinner MRI sections.[28] Why, then, would thalamic volume be more related to cortical than subcortical fluid loss? One possibility is that the thalamus is closely related to the cortex, anatomically and functionally. Virtually all nerve fibers reach the cortex from the periphery by traveling through the thalamus. Loss of cortical tissue and the concomitant increase in cortical fluid may therefore have a stronger relationship with thalamic volume than do loss of subcortical tissue and the ventricular increase. The relationship between sulcal fluid volume and thalamic volume, therefore, probably is mediated by another variable, cortical gray matter volume, at least in AD and SZ. Support for this comes from the results of the standard multiple regression analysis using the thalamus as the outcome variable and cortical fluid and cortical gray matter as the predictor variables. In this analysis, the cortical gray matter volume accounted for fully 26% and 34% of the variance in thalamic volume for the AD and SZ groups, respec-

tively, and sulcal fluid accounted for less than 2% of the unique variance. The importance of the result for clinical scans, however, is that only in the schizophrenia group is there even a relationship between ventricular fluid volume and thalamic volume (Table 1). Regression analyses suggest that for all four diagnostic groups, including SZ, it is not possible to predict a decrease in thalamic volume from an increase in ventricular fluid volume (Table 2).

Causal Relationships between Fluid Enlargements and Tissue Deficits: The assumption that CSF volume increases are accompanied by adjacent tissue loss is largely based on the fact that in adult humans, the volume of the braincase is fixed. Loss of brain tissue presumably allows the expansion of the nearby fluid compartment into the region formerly occupied by gray or white matter. Although the data in this study cannot speak directly to the tissue of causation, some of the results of this study suggest that the relationship between tissue loss and fluid increase sometimes may be more complex or at least harder to detect. The idiosyncratic relationship of thalamic volume to ventricular and sulcal fluid volume in the AD and SZ groups has been discussed above already. Normal control groups provide another example in this study of a counterintuitive relationship between fluid compartments and adjacent tissue. In this group, larger cortical fluid volume does not significantly predict smaller cortical gray matter, but larger ventricular volume does. This finding suggests that an increase in fluid volume near tissue that has been lost may not always be caused by loss of that particular tissue and can be independent of it. This is important from a clinical standpoint because any attempt to predict volume of tissue loss based on the apparent increase in fluid should be predicted on the knowledge that such a relationship is known to exist for that diagnosis. This study shows that the assumed relationship does exist for many diagnoses but is not uniformly true for all groups of subjects. In addition, although it is common in clinical practice to assume a relationship between sulcal fluid volume and gray matter volume, the results of this study suggest that, in general, enlarged sulci are more predictive of white matter deficits than gray matter deficits. This was true for the patients with AD, those who are ALC, and HIV-positive individuals. In the current study, the volume measurements were relatively inclusive: the cortical fluid measure included all the cortical sulci; similarly, the subcortical fluid measure included the third and the fourth ventricles. Quantitative measures for tissue type included all the cortical gray matter and all the white matter. The relationship between CSF increase and brain tissue decrease may, however, occur more locally. For example, the relationship between CSF and thalamus volume might be more apparent if the third ventricle had been measured separately from the rest of the ventricular system. An example of this point from the neuroimaging literature is provided by Sullivan and colleagues,[31] who found that widened cortical sulci in the temporal lobe of elderly individuals are correlated with reduced gray matter volume in the temporal lobe. It is possible that we would have seen different or stronger relationships between volumes of CSF and brain tissue in our subjects if our measures had included smaller regions of the brain. In many cases, such relationships could have direct clinical relevance. It has been suggested, for example, that wider-than-normal third ventricles could be used as an assessment tool in identifying patients with AD with cholinergic deficits secondary to volume loss in the nucleus basalis.[10]

Clinical Dectectability of Fluid Increase on MRI Films: The clinical utility of predictive relationships between CSF increases and tissue decreases rests partly on the reliable detection of fluid increase on MRI scans. Is it possible to detect by eye an enlargement of 1 SD above the mean of similarly aged healthy normal individuals? Are 2 SDs more reliably detected? When there is an increase that is reliably detected clinically, what statements can the clinician confidently make about the chance that there is a decrease in volume of nearby tissue? There are empiric questions that could be answered by future clinical studies. The data from the current study, however, do suggest that enlarged cortical sulci significantly predict smaller white matter volume in all groups studied and also predict smaller gray matter volume in patients with AD and those who are ALC and SZ. Conversely, enlarged ventricles significantly predict smaller basal ganglia volume mainly in patients with AD and are more predictive of smaller white matter volume than basal ganglia volume in those who are ALC and patients who are HIV-positive.

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