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# Morphological Brain Abnormalities in Schizophrenia Determined by Computed Tomography: A Problem of Measurement?

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**Abstract.** The size of the cerebral ventricles was estimated from computed tomographic (CT) scans of 14 young patients with schizophrenia and 12 medical controls. The subjects were a representative subsample from a larger sample studied by Boronow et al. (1985). Although no CT abnormalities were detected in the psychiatric patients using traditional measures (mechanical planimetry for the lateral ventricles and a linear measure for the third ventricle), a volumetric analysis of the same 26 scans revealed enlargement of the lateral and third ventricles in the schizophrenics. The effect revealed by volumetric measures of the lateral ventricles was 58% greater than that obtained with digital planimetry and 96% greater than the effect found using mechanical planimetry. No differences were found between volumetric and digital planimetric measures of the third ventricle, but the effect revealed by the latter measure was 114% greater than that obtained by a linear index. It is suggested that volumetric measures of lateral ventricles based on information from several CT slices may be more sensitive to group differences in ventricular size than planimetry. Likewise, area measures of the third ventricle may be more sensitive to group differences than linear measures.

**Key Words.** Schizophrenia, computed tomography, cerebral ventricles.

Numerous computed tomographic (CT) studies in schizophrenia have been published since Johnstone et al. (1976) first observed morphological brain abnormalities on CT scans in this psychiatric population. The evidence accumulated since indicates that enlargement of the lateral ventricles is a frequent finding in schizophrenia (Weinberger, 1984). Ventriculomegaly has been documented by investigators using planimetric measures (ventricle-brain ratio, or VBR) and linear indices. Never-

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theless, Jernigan et al. (1982), using a sophisticated volumetric estimate of ventricular size, had failed to confirm this finding. This was attributed subsequently to sampling differences which could have resulted in a milder form of illness in the schizophrenic group studied by Jernigan et al. (Luchins, 1982).

Reveley (1985) attempted to determine the relative efficacy of linear, planimetric, and volumetric measures for detecting ventricular enlargement in schizophrenia. The differences in ventricular size between the schizophrenics and the controls in his study were sufficiently large to be revealed even by simple linear measures. Reveley did demonstrate, however, that volumetric measures of the ventricles of monozygotic twins produced significantly greater intraclass correlations than planimetric or linear measures. He interpreted this result as evidence of superior validity of volumetric measures.

In this study we reexamined the relative efficacy of volumetric and planimetric approaches for investigating structural brain abnormalities in schizophrenia. For this purpose we used a computer-assisted volumetric technique to analyze CT scans from a sample of severely ill schizophrenic patients (Boronow et al., 1985) in whom only enlargement of the third ventricle had been found using linear measures.

## Methods

**Subjects.** From the study of Boronow et al. (1985), in which only dilation of the third ventricle had been found, 26 of 56 scans were available for reanalysis. As will be shown below, this subsample was representative of the larger sample, with almost identical group means for the width of the third ventricle and for the VBR.

Of the 26 available CT scans, 14 belonged to schizophrenics (four females) from a group of 30 schizophrenics consecutively admitted to a research ward at the National Institute of Mental Health. All patients had been diagnosed according to Research Diagnostic Criteria (RDC) (Spitzer et al., 1978). The age range of the patients was 18-30 (mean = 23.6), the average length of illness was 5.4 years, and the average duration of hospitalization was 14.1 months.

The other 12 subjects were drawn from a group of 26 medical patients whose scans had been judged to be normal by a clinical radiologist at the National Institutes of Health Clinical Center (Boronow et al., 1985). Exclusionary criteria were: presence of diagnosed central nervous system disease or gross neurological abnormalities as cited in the chart, evidence of dehydration, past treatments with neurotoxic drugs, brain exposure to radiation, use of systemic steroids at the time of CT scanning, history of drug or alcohol abuse, and history of psychiatric problems. Six controls were cancer patients, four of whom had received chemotherapy. There were 2 women and 10 men in the control group. The age range of these patients was 17-37 with a mean age of 28 years. The controls in this subsample were older than the patients ($t = 2.41$, $df = 24$, $p < 0.05$, two-tailed). Although ventricular size increases with age, this phenomenon becomes prominent only after the fifth decade of life (Barron et al., 1976). Thus, age-related ventricular enlargement is unlikely to be observed in persons of the age range represented in our sample. Furthermore, any such enlargement would probably result in a bias against our hypothesis, for the controls were older and, therefore, at a greater risk for age-related ventriculomegaly than the schizophrenics.

**CT Scan Analysis.** All CT scans were performed without contrast medium on the same GE 8800 scanner at 15° to the canthomeatal line, with 1 cm cuts. CT data were analyzed with a computer-assisted method devised to quantify volumetric parameters of the brain (Yeo et al., 1983; Bigler et al., 1985). This method has been used in the study of Alzheimer's dementia (Bigler et al., 1985), closed head injury (Cullum et al., 1986), and cognitive lateralization in

normal subjects (Yeo et al., 1987). In contrast to other volumetric methods (e.g., Jernigan et al., 1982), in this procedure CT films rather than original digital data are used as input. This allows the use of archival films for volume computations when the original CT digital data are unavailable.

The measurement procedure involved several steps. After the scans of the schizophrenics and the controls had been mixed randomly, the films were placed on an X-ray view box and the perimeters of the cranium, brain, and clearly visible ventricular areas were traced with a pencil on a sheet of tracing paper superimposed over the CT film. Special care was given in tracing the border of the brain to details of all visible sulci and fissures. The lowest slice traced was the one in which both temporal poles could be visualized. Ten consecutive slices were traced for each subject. Tracings were performed without knowledge of diagnosis by three of the authors (S.R., N.R., and E.T.). The tracings were then digitized using a Summagraphics Bitpad digitizer. A cursor was manually moved along the perimeter of each target structure recording X and Y coordinates at the rate of 5 points per sec. Areas of brain structures in each slice were computed from the digitized data using a program written in APLSF on a DEC-20 computer. The algorithm makes linear interpolations between consecutive points on the perimeter of a structure, and then uses the method of directed triangles to compute the area of relevant structures. Detailed description of the digital planimetry method may be found in Turkheimer et al. (1983).

Volumes are computed using the trapezoidal interpolation rule, so that the volume of any given structure between two consecutive slices equals the product of the mean of the areas visible on the slices and the distance between them. It is assumed that the target structure comes to a point in the slices immediately above and below the highest or the lowest slice in which it can be visualized. Interrater reliability of this procedure approaches unity (intraclass $r = 0.99$) for volume of the whole brain as well as for smaller structures (Yeo et al., 1983).

To correct for differences in head size, the volume of each of the target structures was divided by cranial volume and multiplied by 100, thereby producing percentage ratios of cerebrospinal fluid to cranial volume. Two ratios were computed: lateral ventricle-cranium ratio (LVCR) and third ventricle-cranium ratio (IIIVCR).

The VBRs of our 26 subjects were also obtained via digital planimetry, the procedure used as the first step in our volume computations (Turkheimer et al., 1983). Two planimetric indices were produced for each subject—lateral digital VBR (VBRd) and the VBR of the third ventricle (VBR-III).

## Results

The group means reported by Boronow et al. (1985) for the total sample of 56 scans (VBR = 4.9 and 5.7 in controls and schizophrenics, respectively; third ventricle width = 0.9 mm and 1.1 mm in controls and schizophrenics, respectively) were similar to the group means for the subsample of 26 (4.9, 5.9, 0.9 mm, and 1.1 mm, respectively). Thus, our subsample appears to be representative of the total sample. The correlations among all measures of ventricular size for the subsample are presented in Table 1. Although the correlation between digital volumetric (LVCR) and planimetric (VBRd) measures is quite high, inspection of the scatter plot (Fig. 1) reveals that this association is weaker in schizophrenics with large ventricles than in those with small ventricles or in controls.

The correlation between digital and mechanical VBR increased ($r = 0.81$, $p < 0.001$) when a single outlier—a schizophrenic patient with the second-ranked VBRd and the seventh-ranked VBR—was removed from the sample. Since this outlier could be a potential source of bias in favor of our hypotheses, we analyzed the data with and without this patient.

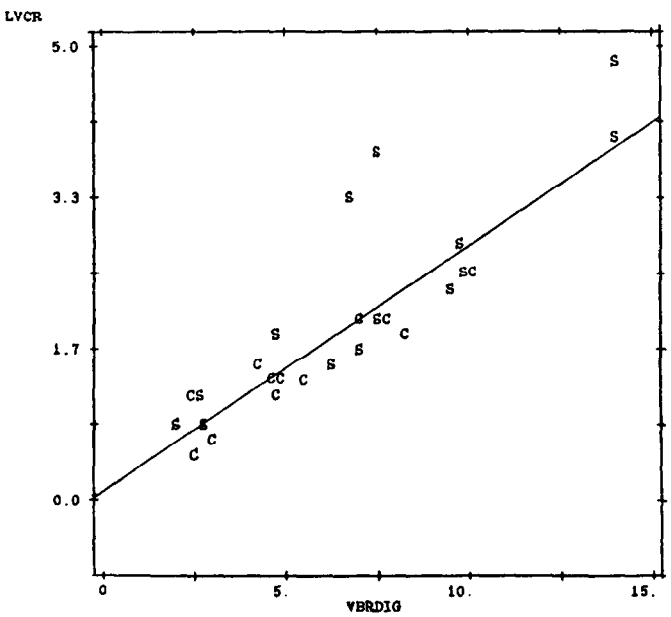
**Table 1. Correlations among measures of ventricular size[1]**

| | VBRd | VBR | IIIVCR | VBR-III | Width-III |
|---|---|---|---|---|---|
| LVCR | 0.87[2] | 0.74[2] | 0.04 | 0.22 | 0.19 |
| VBRd | | 0.74[2] | -0.10 | 0.04 | -0.01 |
| VBR | | | -0.06 | 0.01 | 0.15 |
| IIIVCR | | | | 0.66[2] | 0.52[2] |
| VBR-III | | | | | 0.70[2] |

*Abbreviations.* LVCR = lateral ventricle-cranium ratio. VBR = ventricle-brain ratio. VBRd = lateral digital VBR. IIIVCR = third ventricle-cranium ratio. VBR-III = VBR of the third ventricle.

1. $n = 26$.
2. $p < 0.05$.

**Fig. 1. Scatterplot of planimetric vs. volumetric measures of ventricular size**




S = schizophrenics, C = controls. Regression equation: LVCR = 0.068 + 0.279 VBRdig.

Three one-way multivariate analyses of variance (MANOVA, Hotelling's $T^2$) were conducted using linear combinations of ventricular indices as dependent variables: digital volumetric (LVCR and IIIVCR), digital planimetric (VBRd and VBR-III), and traditional (VBR and Width-III) measures. Psychiatric status (schizophrenics vs. controls) served as a two-level grouping factor. The results of these analyses are summarized in Table 2.

The results of the MANOVAs indicate that only linear combinations of digital methods (volumetric and planimetric) yielded statistically significant differences between schizophrenics and medical controls. Group membership accounted for 39% and 32% of the variance in digital volumetric and digital planimetric measures,

respectively[1] (34% and 26% after correction for shrinkage[2]). When traditional methods were used, group membership accounted for only 10% of the variance in ventricular size (2% after correction for shinkage). No statistically significant group differences were obtained using a linear combination of mechanical VBR and the width of the third ventricle as a dependent measure. Removal of the outlier did not affect the results: the share of the variance explained by group membership changed by 2 percentage points only.

Univariate *t* tests (Table 2) demonstrated that group differences in lateral ventricular size were revealed only by digital volumetric measures. Neither traditional indices, nor the digital VBR were successful in demonstrating lateral ventriculomegaly in schizophrenics. Group differences in the size of the third ventricle were disclosed by both digital volumetry and digital planimetry.

**Table 2. Comparison of 3 indices of ventricular size for 26 scans[1]**

| | Controls | | Schizophrenics | | | Wilks' | Multivariate | |
|---|---|---|---|---|---|---|---|---|
| Index | Mean | SD | Mean | SD | *t* | lambda | *F* | $R^2$ |
| **Volumetric measures** | | | | | | | | |
| LVCR | 1.37 | 0.62 | 2.32 | 1.19 | 2.46[2] | | | |
| | | | (2.22) | (1.15) | (2.17[2]) | | | |
| | | | | | | 0.61 | 7.24[3] | 0.39 |
| | | | | | | (0.63) | (6.33[3]) | (0.37) |
| IIIVCR | 0.11 | 0.03 | 0.15 | 0.04 | 2.48[2] | | | |
| | | | (0.15) | (0.04) | (2.38[2]) | | | |
| **Digital planimetric measures** | | | | | | | | |
| VBRd | 5.43 | 2.49 | 7.43 | 3.78 | 1.59 | | | |
| | | | (6.92) | (3.39) | (1.26) | | | |
| | | | | | | 0.68 | 7.33[3] | 0.32 |
| | | | | | | (0.70) | 4.76[2] | (0.30) |
| VBR-III | 1.06 | 0.31 | 1.25 | 0.45 | 2.71[2] | | | |
| | | | (1.23) | (0.40) | (1.10) | | | |
| **Traditional measures (from Boronow et al., 1985)** | | | | | | | | |
| VBR | 4.86 | 1.77 | 5.93 | 2.58 | 1.27 | | | |
| | | | (5.94) | (2.81) | (1.19) | | | |
| | | | | | | 0.90 | 1.37 | 0.10 |
| | | | | | | (0.88) | (1.48) | (0.12) |
| Width-III | 0.93 | 0.35 | 1.10 | 0.37 | 1.25 | | | |
| | | | (1.10) | (0.36) | (1.40) | | | |

*Abbreviations.* LVCR = lateral ventricle-cranium ratio. IIIVCR = third ventricle-cranium ratio. VBR = ventricle-brain ratio. VBRd = lateral digital VBR. VBR-III = VBR of the third ventricle. Width-III = width of the third ventricle.

1. Values in parentheses are results for the sample without the outlier.
2. $p < 0.05$, 2-tailed.
3. $p < 0.01$, 2-tailed.

1. $R^2 = 1$ - Wilks' lambda.
2. $R^2 = 1 - (1 - R^2)[(N-1)/(N-k-1)]$, where $R^2$ = unshrunken value, $R^2$ = shrunken value, $N$ = sample size, $k$ = number of dependent variables in MANOVA.

To examine the relative efficacy of individual measures of ventricular size, $t$ values (Table 2) were compared following conversion into product-moment correlations ($r$). Because of sizable correlations among measures of ventricular size (Table 1), the $Z_1$* statistic (Steiger, 1980) was used to test the differences among the $r$'s. This statistic has been developed for comparing dependent correlations within the same matrix, and its distribution approximates normal, permitting the use of tabulated $z$ scores for determining statistical significance. The differences between the effects obtained with different methods fell just short of the conventional 0.05 level of statistical significance, but the trend was quite clear: $Z_1$* = 1.46, 1.51, and 1.59 with $p = 0.072$, 0.066, and 0.056 (one-tailed) for LVCR vs. VBR, LVCR vs. VBRd, and VBR-III vs. Width-III, respectively.

The disadvantage of traditional methods for detecting group differences in ventricular size can be better illustrated using the concept of effect size (Cohen, 1977). The index of effect size, d, is the difference between the schizophrenic and control group means divided by the pooled standard deviation. Expressing effect size in SD units brings group differences obtained with various methods or in different laboratories to a common metric allowing direct comparison. The effect sizes for each measure of the lateral and third ventricles are presented in Table 3.

As shown in Table 3, digital volumetry revealed a large effect for the lateral ventricles (a group difference of about 1 pooled SD between group means), whereas both digital and mechanical planimetry showed only moderate effects (one-half of the pooled SD). For the third ventricle, volumetric as well as digital planimetric measures showed group differences of about 1 pooled SD, a large effect size. Indices of ventricular size used in this study produced a 58-114% increase in the effect size compared to traditional measures.

**Table 3. Comparison among measures of ventricular size**

| Index | d |
|---|---|
| LVCR | 0.98 |
| IIIVCR | 1.00 |
| VBRd | 0.62 |
| VBR-III | 1.07 |
| VBR | 0.50 |
| Width-III | 0.50 |

*Abbreviations:* LVCR = lateral ventricle-cranium ratio. IIIVCR = third ventricle-cranium ratio. VBR = ventricle-brain ratio. VBRd = lateral digital VBR. VBR-III = VBR of the third ventricle. Width-III = width of the third ventricle.

## Discussion

The main point of this study is that enlargement of the lateral and third ventricles, measured by a computer-assisted volumetric method, has been found in a sample of schizophrenic patients in which no differences were detected by traditional planimetric or linear measures. It appears that volumetric, planimetric, and linear

measures may not be equally likely to detect enlargement of cerebral ventricles. Furthermore, digital volumetric measures of lateral ventricular size were found to be more sensitive to group differences than either digital or mechanical planimetry.

In assessing the size of a relatively large irregular three-dimensional structure like the lateral ventricles, use of information from multiple sections may reduce error variance. Since the estimate of ventricular size, for each slice, is assumed to be a combination of a true value and random error, the true differences in the size of the ventricles are expected to add up when more sources of information are taken into account, while random errors stemming from various sources of unreliability should cancel out. Thus, volume measures are expected to yield a more reliable and valid estimate of the differences in lateral ventricular size than planimetry or linear indices. Greater reliability and validity of volumetric measures would increase the likelihood of finding significant group differences. The implication is that subtle group differences that may pass undetected by planimetry could be revealed by volumetric measures. Our analysis also indicates that when a small structure with an irregular shape (e.g., the third ventricle) is estimated, area may serve as an adequate index, with linear measures being too distorting, and volume estimates not adding much to the sensitivity of the measures.

The preliminary nature of this study is underscored by the relatively small number of CT scans available for analysis. Although definite conclusions about the relative efficacy of volumetric and planimetric methods for studying lateral ventricular size could not be reached, statistical analyses comparing the effects obtained by volumetric measures with those obtained by planimetry suggest that researchers using volumetric assessment may stand a better chance of discovering a significant effect than their colleagues relying on planimetry, particularly when group differences are not large.

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