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Quantitative Brain Measurements in Chronic Schizophrenia

By RANDALL ROSENTHAL and LLEWELLYN B. BIGELOW

Despite extensive gross and microscopic scrutiny, no consistent pathological findings have emerged from studies of autopsy material from schizophrenic patients. Dunlap (1924) carried out the first controlled study involving schizophrenic and control brains and concluded that 'there was not even a suspicion of consistent organic brain disease as a basis for the psychosis of schizophrenia'. More recently both Wolf and Cowen (1952), and Weinstein (1954), reviewed the neuropathological literature and concluded that there were no consistent findings at autopsy that could be construed as characteristic of schizophrenia. These authors felt that earlier claims were based on failure to appreciate the range of normal variation in the brain as well as a failure to include an adequate control population in the study.

All previous gross anatomical studies of brain material have been based on visual inspection. Only brain weight has been measured quantitatively. In this study we measured quantitatively and on a blind basis both linear dimension and absolute volume of various brain structures in schizophrenic and matched control brains. After obtaining the measurements for 10 schizophrenic and 10 control brains, the code for identifying the clinical status of each brain was broken and comparisons were made between each category. We measured: (1) brain weight, (2) total cortical volume, (3) temporal lobe volume, (4) hippocampal volume, (5) average cortical mantle width, (6) average cingulate gyrus height, (7) average corpus callosum width, (8) thalamic volume, and (9) lenticular nucleus volume.

Description and Selection of the Sample

The clinical and pathological records of all patients autopsied at Saint Elizabeth's Hospital between 1968–70 carrying the diagnosis of schizophrenia were reviewed. In order to be selected for further study, a patient had to meet the 'bad prognosis' category of Langfeldt (1937) by history. Each selected patient had a history of at least five years of continuous illness characterized by prominent thought disorder and the reported presence of hallucinations and delusions. Evidence of a remitting disorder, neurological signs, or prominent affective colouring eliminated a patient from the sample. In addition, the reported presence of gross or microscopic abnormalities in the brain at autopsy excluded any subject. The autopsy report for each included subject carried a specific comment that there was no gross evidence for cortical atrophy or ventricular dilatation. In the period 1968–1970, 23 patients carrying a chart diagnosis of schizophrenia were autopsied at Saint Elizabeth's Hospital. Of these, 10 met the criteria for inclusion in this study. Diagnostically, 6 were regarded as chronic undifferentiated schizophrenics, 2 were called chronic paranoid schizophrenics, and there were one each diagnosed as chronic catatonic and hebephrenic schizophrenia.

Controls were drawn from autopsy material obtained during the same period, 1968–1970. For inclusion as a control the chart could carry no evidence of a functional psychosis or of any neurologic disturbance. Like the schizophrenics, there had to be no gross or microscopic evidence at autopsy of central nervous system disease. These criteria were met by 13 patients; 3 were eliminated for matching purposes. Clinical psychiatric diagnoses of this group were as follows: 5 were diagnosed as sociopathic personality disorder, and of these 3 had secondary diagnoses of alcoholism; one was diagnosed as a hysterical personality disorder, and the remaining 4 had no psychiatric diagnosis. Other aspects of the schizophrenic and control samples are given in Table I. It is evident from the table that the groups were well matched in terms of major characteristics.

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TABLE I
Characteristics of schizophrenic and control groups

	Schizophrenic	Control
Sex—number		
Male	4	5
Female	6	5
Age at death (years)		
Mean	56	50
Range	30–65	29–64
Race		
Caucasian	7	7
Negro	3	3
Cause of death (autopsy diagnosis)		
Myocardial infarction	5	3
Pulmonary embolus	1	3
Acute tracheobronchitis	2	1
Pulmonary oedema	1	0
Aspiration	1	0
Abdominal carcinoma	0	1
Acute septicaemia	0	1
Unexplained	0	1
Duration of terminal illness		
Less than 7 days	9	8
Greater than 7 days	1	2

At the time of autopsy, the brains were routinely cut in serial coronal section, 10 to 12 cuts per brain with about 1 cm. in thickness for each section. Gross and microscopic examinations were then made with sections being taken from the left side of the brain for microscopic examination. Both the dissected left side and the sectioned right hemisphere were then routinely stored in 10 per cent formalin. The measurements considered in this study were taken from the undissected right side of the brain.

Decision as to whether or not to include a given brain in the study was made solely on the basis of the clinical and autopsy information furnished by the chart. Once ten schizophrenic and control brains were found suitable for inclusion these specimens were coded and measured at random, with the examiner unaware of the clinical status of any specimen until the entire study was completed.

METHOD

Brain weight was taken from the autopsy report. Volumetric measures were obtained as follows:

An exact tracing of the cross-sectional outline of a given structure, as seen on the complete coronal cross section, was made on tracing paper. Since a given structure was usually seen on both the anterior and posterior surfaces of the coronal cross section, a separate tracing was made for each side. A planometer (Keuffel and Esser #620000) was then used to outline the tracing in order to obtain its area. For each brain slice an average area for the anterior and posterior face of the structure being considered was found from the planometer readings and multiplied by the measured thickness of the slice (in the region of the structure) to find the volume of the structure for that section of brain. The total volume of a structure was determined by adding all the volumes from all the sections in which that structure appeared. Planometric measures covering an area of 4 cm.^{2} carry a standard deviation of $\pm 0{\cdot}15$ cm., and for a 40 cm.^{2} area carry a standard deviation of $\pm 0{\cdot}40$ cm. based on ten repeated measures of the same outline.

When the anterior or posterior boundary of a structure was reached, the structure would often appear on one side of the coronal section but not on the other. In this case, one of the areas was considered as zero, the average area being calculated by dividing the other area by two. The actual boundary was found by dissection so that an accurate perpendicular depth for that structure could be ascertained.

The thickness of a structure was found with a caliper calibrated to $\pm 0{\cdot}01$ cm. The planometer was calibrated to 0·1 sq. cm. When a planometric reading was obtained below 2·0 sq. cm. four separate readings were obtained on each tracing and averaged to increase accuracy.

The anterior and posterior boundaries for the volumetric measures are given as follows:

Thalamus—
- anterior: Appearance of the anterior ventral thalamic nucleus.
- posterior: Disappearance of the pulvinar.

Lenticular nucleus—
- anterior: Appearance of complete separation of the caudate from the lenticular nucleus by the anterior limb of the internal capsule.
- posterior: Complete disappearance of the lenticular nucleus.

Hippocampus—
- anterior: First appearance of the hippocampal laminations directly posterior to the amygdaloid nucleus.
- posterior: The disappearance of the hippocampus (usually at the same level of pulvinar disappearance).

Temporal Lobe—
- anterior: Anterior pole of the temporal lobe.

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posterior: Disappearance of bifurcation of the lateral cerebral fissure.

Total Cortex—

Anterior and posterior poles of the entire right hemisphere (including temporal lobe).

The measuring techniques and boundaries for the remaining structures are given below:

Average cortical mantle width. Four random cuts were made on the periphery of each coronal section. The perpendicular thickness of the cortical gray matter underlying each of these cuts was then measured. All such measurements (40–50) from all the sections were then averaged to give the average cortical mantle width for that brain.

Average corpus callosum width. The perpendicular thickness of the corpus callosum (superior to inferior) was taken in every coronal section in which this structure appeared as a band of white matter running from one hemisphere to the other. Measurements were not made in sections in which the genu or splenium of the corpus callosum appeared. Both anterior and posterior measurements were made on each section and all the measurements (approximately ten) from all the sections were averaged to give the average corpus callosum width for that brain. Because of a slight bulge in the band in the area of the septum pellucidum the measurement was uniformly made ·5 cm. to the right of the midline.

Average cingulate gyrus height. This measurement consisted of the perpendicular height of the superior aspect of the cingulate gyrus in relation to the superior aspect of the corpus callosum. It was obtained in every section in which the cingulate gyrus appeared (8–10) and averaged to obtain the final value for that particular specimen.

After the code was broken, the measurements obtained on each structure were segregated into the schizophrenic and control category and analyzed with a standard t-test (two tailed). A Pearson Product Moment correlation table was prepared to look for relationships between structures within each group.

Results

There were no significant differences between the schizophrenic and control groups in any of the parameters measured, with the exception of the average corpus callosum width (see Table II); this measurement was significantly larger in the schizophrenic group with a $p < 0{\cdot}001$. The range of the measurement in the schizophrenic group was ·558 to ·638 cm., with a mean of ·611 cm. and a standard deviation of ·023; in the control group the range was ·454 to ·571 cm., with a mean of ·518 and a standard deviation of ·037. Of interest is the fact that all the other measurements were slightly though non-significantly higher in the schizophrenic group.

When the average corpus callosum width from all twenty specimens was ranked in a descending quantitative order the first nine measurements were seen to come from the schizophrenic specimens. There were two control values that were higher than the lowest schizophrenic measurement. On the non-parametric Mann-Whitney test this was also significant ($p < 0{\cdot}001$).

A correlation coefficient table for the schizophrenic and control samples is shown in Table III. There was surprisingly little correlation between the various parameters as seen in either of the groups. Unexpectedly, the brain weight in both tables did not correlate signi-

Table II

Comparison of structural dimensions in control and schizophrenic brains

Mean ± SD; N = 10 in each group

Structure	Schizophrenic	Control	P*
Brain weight (gm.)	1299·5 ± 115·7	1283·0 ± 108·1	NS
Cortical mantle width (cm.)	0·337 ± ·020	0·325 ± ·014	NS
Corpus callosum width (cm.)	0·611 ± ·023	0·518 ± ·037	< 0·001
Cingulate gyrus height (cm.)	1·49 ± ·102	1·43 ± ·234	NS
Hippocampal volume (cm.3)	4·51 ± ·979	3·74 ± 1·059	NS
Thalamic volume (cm.3)	6·01 ± ·967	5·41 ± ·475	NS
Lenticular nucleus volume (cm.3)	4·41 ± ·83	4·40 ± ·41	NS
Temporal lobe volume (cm.3)	52·3 ± 12·0	48·9 ± 13·2	NS
Total cortical volume (cm.3)	461·1 ± 36·3	445·4 ± 47·0	NS

* Student 't-test'.

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TABLE III

Correlation between structures measured in schizophrenic and control brains

	Cortical mantle width	Corpus callosum width	Cingulate gyrus height	Hippocampal volume	Thalamic volume	Lenticular nucleus volume	Temporal lobe volume	Total volume
Brain weight	C ·10	C ·18	C ·09	C −·05	C ·15	C −·28	C ·04	C ·48
	S ·11	S ·60	S −·18	S ·62	S −·34	S ·16	S ·23	S ·12
Cortical mantle width		C ·31	C ·32	C ·20	C ·14	C −·07	C ·03	C ·53
		S ·14	S −·05	S ·34	S ·03	S ·28	S −·01	S −·14
Corpus callosum width			C ·21	C ·70*	C ·18	C ·61	C ·52	C ·56
			S −·39	S ·50	S ·08	S ·13	S ·34	S ·01
Cingulate gyrus height				C ·25	C ·71*	C ·12	C ·31	C ·56
				S −·26	S ·50	S ·82*	S ·06	S ·54
Hippocampal volume					C ·44	C ·86*	C ·83*	C ·59
					S −·36	S ·04	S ·41	S ·06
Thalamic volume						C ·33	C ·25	C ·68*
						S ·41	S ·01	S −·16
Lenticular nucleus volume							C ·56	C ·32
							S ·18	S ·57
Temporal lobe volume								C ·40
								S ·51

Pearson product-moment correlation coefficient.
N = 10 each group.
* $r > .63$; $p < .05$.

ficantly with the other variables. In the control group, the total volume tended to correlate at fairly high levels with all of the other structures, but this relationship achieved significance only for the thalamic volume. This trend was not seen in the schizophrenic group. Other significant correlations in the control group were seen between the hippocampal volume compared to the temporal lobe and the lenticular nucleus volume. There was also significant correlation between the cingulate gyrus height and the thalamic volume. In the control group the only parameter that was significantly correlated with the corpus callosum width was the hippocampal volume. None of the above relationships were significant in the schizophrenic group. The only significant correlation coefficient in the schizophrenic sample was between the cingulate gyrus height and the lenticular nucleus volume.

The average corpus callosum width did not correlate with the patient's age, race, sex, or time of autopsy. This held true in both the schizophrenic and the control groups. Alcohol ingestion in three of the control patients did not appear to affect the ranking of the corpus callosum width.

DISCUSSION

The rationale for choosing a specific CNS structure for measurement in this study was based on its possible theoretical significance in the schizophrenic syndrome as well as the technical feasibility of obtaining reasonably accurate measurements on a given structure. Our finding of an increase in the average corpus callosum width in the schizophrenic sample applies only to that part of the corpus callosum appearing as a band running from one hemisphere to the other (the portion lying between

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the genu and the splenium of the corpus callosum).

Since the analysis of the data presented here involves multiple comparisons within the same sample, some might argue that the single finding of a significant difference between groups could be in part due to the fact that multiple comparisons were made. Such a criticism would be particularly valid if the measurements taken in each brain were shown to be highly correlated. This did not seem to be the case here, as the correlation tables showed significant relationships in only 6 of the 72 comparisons. It therefore seems safe to conclude that each structural measurement was reasonably independent of the other measurements in a given specimen.

Ventricular dilatation secondary to obstructive hydrocephalus could conceivably lead to thinning of the corpus callosum. Such a cause for the difference observed in this study is unlikely, as each autopsy report specifically mentioned that there was no visible ventricular enlargement. Thinning of the corpus callosum in the control group secondary to ageing is also an unlikely explanation of the difference, as the control group were somewhat (though not significantly) younger than the schizophrenic sample.

Although we are not aware of any evidence suggesting it, we cannot rule out the possibility that the finding reported here is a consequence of long-term phenothiazine administration and/or chronic institutionalization. This possibility must be kept in mind in this or any other investigation involving a retrospective study of chronic schizophrenic illness.

If this observation of increased corpus callosum width in chronic 'bad prognosis' unremitting schizophrenia can be confirmed, it will raise a number of possibilities. The corpus callosum is the great band of white matter connecting the two cerebral hemispheres. Geschwind (1965) reviewed the literature and clinical findings in patients who had had surgical section of the corpus callosum for seizure disorders, and confirmed the existence of various subtle alterations in perception and integration of function in these patients. However, all these changes required careful observation and special testing to elicit. Most authors have been impressed with the lack of major findings after section of such a massive intracranial structure (Sperry, *et al.*, 1969).

In contrast to the subtle findings that are consequent to surgical section of the corpus callosum, neoplasm in this structure is characterized by 'mental and emotional deterioration' (Elliott, 1969). Also, in Marchiafava's disease mental and emotional disorders often indistinguishable from schizophrenia are the presenting symptoms. This latter illness is characterized by, but not limited to, a focal degeneration of the corpus callosum. It is not possible to say whether the psychiatric symptoms seen in tumours or degeneration involving the corpus callosum are directly related to altered function of that structure, or whether such symptoms are a reflection of damage to other C.N.S. structures. In any case, the contrast between the apparent minor sequelae of surgical interruption as opposed to the psychiatric syndromes found in disease of the corpus callosum remains striking.

At this time we cannot, of course, conclude that this finding of an increased size of the corpus callosum has any functional significance for understanding either the cause or consequences of schizophrenia. Any such hypothesis should more properly await independent verification of the finding and further study of possible variables involved.

Summary

The brain specimens of ten chronic schizophrenic and ten control patients were measured in regard to the volume of the thalamus, lenticular nucleus, hippocampus, temporal lobe, and total cortex. In addition, the brain weight, average corpus callosum width, average cingulate gyrus height, and average cortical mantle width were obtained on each specimen. Of all of these parameters only the average corpus callosum width stood out as being significantly different between the schizophrenic and control specimens ($p < 0{\cdot}001$), this measurement being larger in the schizophrenic sample.

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BIBLIOGRAPHY

DUNLAP, C. B. (1924). 'Dementia praecox: some preliminary observations on brains from carefully selected cases, and a consideration of certain sources of errors.' *American Journal of Psychiatry*, **80**, 403–10.

ELLIOTT, F. A. (1969). 'The corpus callosum, cingulate gyrus, septum pellucidum, septal area, and fornix.' In: *Handbook of Clinical Neurology*, **2**, 758–65 (ed. Vinkent and Bruyn), New York: Elsevier.

GESCHWIND, N. (1965). 'Disconnexion syndromes in animals and man.' *Brain*, **88**, Part II, 237–94; Part III, 585–644.

LANGFELDT, G. (1937). *The Prognosis in Schizophrenia and the Factors Influencing the Course of the Illness*. Copenhagen: Munksgaard.

SPERRY, R. W., GAZZANIGA, M. S., and BOGEN, J. E. (1969). 'Inter-hemispheric relationships: the neocortical commissures; syndromes of hemisphere disconnection.' In: *Handbook of Clinical Neurology*, **4**, 273–89 (ed. Vinkent and Bruyn), New York: Elsevier.

WEINSTEIN, M. R. (1954). 'Histopathological changes in the brain in schizophrenia.' *Archives of Neurology and Psychiatry*, **71**, 539–53.

WOLF, A., and COWEN, D. (1952). 'Histopathology of schizophrenia and other psychosis of unknown origin.' In: *The Biology of Mental Health and Disease* (Milbank Memorial Fund Conference), 469–86, New York: Harper.

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Randall Rosenthal, M.D.

Llewellyn B. Bigelow, M.D.

Laboratory of Clinical Psychopharmacology, National Institute of Mental Health, Saint Elizabeths Hospital, Washington D.C., 20032

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