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CT Scans in Schizophrenia

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The term 'dementia praecox' was used by Kraepelin to emphasise the tendency towards deterioration to a state of impairment resembling a dementia. Early studies looked for structural brain lesions post mortem, and later using pneumoencephalography; there were positive findings (Haug, 1962), but they were not always replicated (Storey, 1966). The risks and limitations of pneumoencephalography gradually led to its being abandoned. However, studies showing minor neurological abnormalities (Rochford *et al*, 1970) and cognitive impairment (Malec, 1978) continued to suggest an organic component to schizophrenia.

The advent of computerised tomographic (CT) scanning has led to a new freedom in examining the brain in schizophrenia. The cerebral structures examined have included principally the lateral ventricles, but also the third and fourth ventricles, and cortical structures such as sulci, as well as the Sylvian and inter-hemispheric fissures. The size of the cerebellar vermis and asymmetry of the width of the cerebral hemispheres have also been examined. As the CT scanner reconstructs the image from digital data which reflect the degree to which X-rays are attenuated by the tissues in their path (expressed as Hounsfield Units), brain tissue density can also be estimated. It seems clear from the more than 60 studies of CT in schizophrenia that subgroups of schizophrenics have structural brain changes, but a number of questions still remain unanswered, such as the prevalence and specificity of the abnormalities, their clinical significance, and their aetiology.

Prevalence

Considerable interest was aroused when Johnstone *et al* (1976) found lateral ventricular enlargement in a small group of elderly, chronically hospitalised schizophrenic patients (mean duration 32 years) compared to age-matched normal controls. This finding was confirmed by Weinberger *et al* (1979a) in a controlled study of a younger group of 58 chronically hospitalised schizophrenics, all under age 50, and all meeting Feighner and Research Diagnostic Criteria; 40% of the patients were outside the control range for ventricular size and 53% were beyond two standard deviations of the control mean, suggesting a very high prevalence of lateral ventricular enlargement. Subsequent controlled reports from independent samples (Tanaka *et al*, 1981; Pearlson & Veroff, 1981; Moriguchi, 1981; Andreasen *et al*, 1982a; Nasrallah *et al*, 1982a; Okasha & Madkour, 1982; Nyback *et al*, 1982; Weinberger *et al*, 1982; Schulz *et al*, 1983; Kling *et al*, 1983; Reveley *et al*, 1982, 1984a; Williams *et al*, 1985) found ventricular enlargement, with wide variation in prevalence from 6% to 60%, depending on the definition of enlargement (Andreasen *et al*, 1982a). Further, enlargement of the third ventricle (Tanaka *et al*, 1981; Nyback *et al* 1982; Okasha & Madkour, 1982) and of the cerebral sulci and fissures (Weinberger *et al*, 1979b; Moriguchi, 1981; Tanaka *et al*, 1981) were reported. However, other controlled studies found no evidence of ventricular enlargement at all (Gluck *et al*, 1980; Jernigan *et al*, 1982; Benes *et al*, 1982).

The study by Jernigan *et al* (1982) aroused particular attention because the methods used were far more sophisticated than the usual linear or area measurements made with mechanical instruments from photographic film. Most previous studies had expressed ventricular size as a ventricular-brain ratio (VBR), which is the area of the lateral ventricles on the slice showing them at their largest, divided by the intracranial area, and multiplied by 100. Jernigan *et al* used a semi-automated computer programme to measure the total central fluid volume (comprising ventricles and cisterns) and total peripheral fluid volume (comprising fissures and sulci); no difference was found between schizophrenics and controls on any of the measures. Further, photographic films of the scans were sent to two other groups to estimate VBR. One estimate was similar to that derived from the method of Jernigan *et al*, but the other estimate differed by almost two-fold, demonstrating that differences in measurement technique, even with the same scans, may result in substantial discrepancies.

To examine the extent to which differences of method might account for the discrepancies across studies, Reveley (1985) examined all methods for estimating ventricular size, including the linear Evans ratio, VBR from mechanical planimetry (as used by Weinberger and others), planimetry from a video display unit curve digitiser (as used by Andreasen), Jernigan's central fluid volume method, and Reveley's total ventricular volume method. All methods distinguished schizophrenics

with enlarged ventricles from controls, at approximately the same level of significance. But it was shown that partial volume artefact (the 'grey zone' on CT scan images where CSF and brain are mixed together), could lead to more than a two-fold discrepancy in VBR, and that linear measurements and mechanical planimetry were particularly liable to give variable results. Thus, while much of the variance in absolute values across studies is due to method, the discrepancies in the prevalence of abnormalities across carefully controlled studies are probably due to sample differences.

Yet it is still not clear what particular attributes of the samples are most associated with enlargement. The negative reports, (Jernigan *et al,* 1982; Benes *et al,* 1982) have come from samples of younger patients with a less severe illness and a good response to treatment, but there have been reports of ventricular enlargement from apparently similar samples (Weinberger *et al,* 1982; Nyback *et al,* 1982; Schulz *et al,* 1983). Studies are markedly heterogenous for the age, in-patient status, duration and severity of illness, response to treatment, and family history of patients, as well as diagnostic criteria, method of measurement and selection of controls. Some factors are rarely considered, such as birth complications or exact lifetime medication dosage. Thus, comparison across studies is likely to be misleading, as there are many different variables which might account for the disparate CT findings. The controversy could be clarified by a single large study of patients, representing the full range of disability from out-patients to chronic in-patients. Standardised clinical and radiological assessment could then be used for all subjects.

Clinical significance

The clinical implications of ventricular enlargement remain to be fully explored. Crow's (1980) hypothesis of type I and type II syndromes, with type II having irreversible structural changes in the brain, while attractive in its simplicity, has received only partial support. Ventricular enlargement and/or cortical atrophy have been associated with the defect state, as shown by cognitive (Johnstone *et al,* 1976) and neuropsychological impairment (Golden *et al,* 1980; Donnelly *et al,* 1980), poor treatment response (Weinberger *et al,* 1980a; Kling *et al,* 1983), unfavourable outcome (Williams *et al,* 1985), poor premorbid adjustment (Weinberger *et al,* 1980b; Williams *et al,* 1985), and negative symptoms (Andreasen *et al,* 1982b; Williams *et al,* 1985). However, these findings have not always been replicated. Johnstone *et al* (1976) failed to find a statistically significant association between ventricular size and negative symptoms, thus failing to support their own hypothesis. Other investigators (Nasrallah *et al,* 1982a, 1983; Boronow *et al,* 1983; Frangos & Athanassenas, 1982) have failed to relate ventricular size to type II syndrome, or to the hebephrenic sub-type, which might be expected to have type II syndrome characteristics. These discrepancies are likely to be due to both variance between samples and differences in clinical assessment.

Ventricular enlargement is a non-specific finding, and has also been found in DSM-III bipolar patients and psychotic depressives (Pearlson & Veroff, 1981), manic males (Nasrallah *et al,* 1982b) and delusional depressives (Targum *et al,* 1983). It may therefore be related to psychosis in general. Of course, ventricular enlargement is present in many organic cerebral disorders, including alcohol addiction (Ron *et al,* 1982; Gurling *et al,* 1984), and its significance and aetiology may be expected to vary with the clinical disorder. Most, but not all (Moriguchi, 1981; Tanaka *et al,* 1981) studies have found no correlation between structural abnormalities and duration of illness, so it has been assumed that treatment is not responsible for ventricular enlargement or cortical atrophy. The only study to examine the precise lifetime dose of neuroleptics (Lyon *et al,* 1981) found that dose was significantly correlated with decreasing brain tissue density in the posterior half of each hemisphere, although ventricles and sulci were not examined. The effect of treatment is obviously an important question, deserving further research.

Aetiology of the abnormalities

Cerebral ventricular size has been shown to be normally under a high degree of genetic control (Reveley *et al,* 1984b), and thus similar to other anthropomorphic characteristics, such as height. Even using an elderly CT 1010 scanner, less than 20% of the variation was due to environmental factors, which may have included head position and measurement artefact. However, among a group of identical twins discordant for schizophrenia, the schizophrenic twins tended to have larger ventricles than both their own co-twins and normal control twins (Reveley *et al,* 1982). Similar observations were made in a family study of singletons (Weinberger *et al,* 1981). Further, the intra-pair variation within the twins who were discordant for schizophrenia was significantly greater than that among normal twins, suggesting an environmental effect which appeared to be related to the development of schizophrenia. This hypothesis was further supported by the finding that ventricular enlarge-

ment in a group of schizophrenic twins was confined to those without a family history of major psychiatric disorder (Reveley *et al*, 1984a). This suggests that when the genetic liability to schizophrenia is reduced, environmental trauma, perhaps reflected by increased ventricular size, becomes more important for aetiology. This finding has been supported by Oxenstierna *et al* (1984), and by Lewis (1984), but the nature and timing of the postulated environmental events have not been established. While Reveley *et al* (1984a) found a history of birth complications to be predictive of ventricular enlargement in controls, there was not such a simple relationship in schizophrenia. Studies finding enlargement in young schizophrenics support the concept that it antedates the illness in at least a subgroup (Weinberger *et al*, 1982; Schulz *et al*, 1983).

Environmental causes such as infection, perinatal injury, periventricular haemorrhage, other trauma, or a variety of non-specific events could lead to primary brain atrophy. Depending on the location of the damage, there might be a secondary ventricular dilatation or enlargement of the cortical fissures or sulci. Alternatively, environmental or genetic causes (Reveley & Reveley, 1983) could lead to mild hydrocephalus as the primary event (Lishman, 1978), with partial obstruction to flow within the ventricular system (obstructive hydrocephalus) or in the extraventricular subarachnoid space or villae (communicating or normal-pressure hydrocephalus). This hypothesis has just begun to be explored. Using isotope cisternography, Oxenstierna *et al* (1984) found evidence of reduced CSF flow in the subarachnoid spaces over the hemispheres in ten out of 30 schizophrenic patients, though there was no relationship of flow abnormalities to CT scan abnormalities. Clearly, further work with larger samples would be of great interest.

Further clues to pathogenesis may come from follow-up studies which examine the natural history of structural abnormalities. Progressive atrophy would suggest an active process, such as degeneration, or obstructive or communicating hydrocephalus, for which specific intervention might be indicated. Static atrophy would implicate discrete traumatic events as the likely causes. Further, relating treatment in the follow-up period to changes between baseline and follow-up scans would answer the question of whether large ventricles lead to more treatment, or whether more treatment leads to large ventricles, in at least a subgroup of patients.

Other measures

Ventricular size, while the most obvious, is not the only area of investigation. Functional laterality may be reflected by anatomical disproportion, and post mortem and CT studies demonstrate that in normal people, the frontal lobe is larger on the right than left, while the occipital lobe is larger on the left than right. The initial finding of Luchins *et al* (1979) of a substantial reversal of the normal pattern in schizophrenics was replicated in none of five subsequent independent reports for frontal asymmetry, and in only one of five studies for occipital reversals (Tsai *et al*, 1983). In addition to sampling variation, there are substantial methodological problems with the definition of the midline and the use of linear measurements. The use of area or volume measurements of hemispheric size in future studies of asymmetry might clarify these issues.

Recently, increasing attention has turned to brain absorption density, which has been found to be lower in the left frontal regions (Golden *et al*, 1981) and increased in diencephalic regions (Dewan *et al*, 1983) in schizophrenics. While this technique offers considerable promise for localising areas of brain damage, the density abnormalities reported are small, and well within the range of scanner drift and partial volume artefact. It is not surprising, therefore, that contradictory reports are already emerging (Largen *et al*, 1983).

Despite methodological and sampling variation, it seems that we can accept the findings of cerebral ventricular enlargement in a proportion of schizophrenics with a fair degree of confidence. We may be able to attribute this to a 'non-genetic' pathogenesis, providing further evidence for a distinction between genetic and environmental causation. Future studies will need to examine large samples with maximum clinical heterogeneity, particularly in respect of family history and stage of illness. Prospective follow-up studies would clarify whether treatment can cause structural brain abnormalities, and whether atrophy represents a progressive degeneration or the effects of early brain injury. Finally, the development of objective radiological assessment would greatly facilitate comparisons across studies.

References

ANDREASEN, N. C., OLSEN, S. A., DENNERT, J. W. & SMITH, M. R. (1982b) Ventricular enlargement in schizophrenia: Relationship to positive and negative symptoms. *American Journal of Psychiatry*, **139**, 297–302.

—— SMITH, M. R., JACOBY, C. G., DENNERT, J. W. & OLSEN, S. A. (1982a) Ventricular enlargement in schizophrenia: Definition and prevalence. *American Journal of Psychiatry*, **139**, 292–296.

BENES, F., SUNDERLAND, P., JONES, B. G., LEMAY, M., COHEN, B. M. & LIPINSKI, J. F. (1982) Normal ventricles in young schizophrenics. *British Journal of Psychiatry*, **141**, 90–93.

BORONOW, J. J., PICKAR, D., VAN KAMMEN, D. P. & PAUL, S. M. (1983) Normal ventricles and sulci in schizophrenic patients. *Psychopharmacology Bulletin*, **19**, 581–586.

CROW, T. J. (1980) Molecular pathology of schizophrenia: More than one disease process? *British Medical Journal*, **280**, 66–68.

DEWAN, M. J., PANDURANGI, A. K., LEE, S. H., RAMACHANDRAN, T., LEVY, B., BOUCHER, M., YOZAWITZ, A. & MAJOR, L. F. (1983) Central brain morphology in chronic schizophrenic patients: A controlled CT study. *Biological Psychiatry*, **18**, 1133–1140.

DONNELLY, E. F., WEINBERGER, D. R., WALDMAN, I. N. & WYATT, R. J. (1980) Cognitive impairment associated with morphological brain abnormalities on computer tomography in chronic schizophrenic patients. *The Journal of Nervous and Mental Disease*, **168**, 305–308.

FRANGOS, E. & ATHANASSENAS, G. (1982) Differences in lateral brain ventricular size among various types of chronic schizophrenics: Evidence based on a CT scan. *Acta Psychiatrica Scandinavica*, **66**, 459–463.

GLUCK, E., RADU, E. W., MUNDT, C. & GERHARDT, P. (1980) A computed tomographic prolective trohoc study of chronic schizophrenics. *Neuroradiology*, **20**, 167–171.

GOLDEN, C. J., GRABER, B., COFFMAN, J., BERG, R. A., NEWLIN, D. B. & BLOCH, S. (1981) Structural brain deficits in schizophrenia: Identification by computer tomographic scan density measurements. *Archives of General Psychiatry*, **38**, 1014–1017.

—— MOSES, J. A. JR., ZELAZOWSKI, R., GRABER, B., ZATZ, L. M., HORVATH, T. B. & BERGER, P. A. (1980) Cerebral ventricular size and neuropsychological impairment in young chronic schizophrenics: Measurement by the standardised Luria-Nebraska Neuropsychological Battery. *Archives of General Psychiatry*, **37**, 619–623.

GURLING, H. M. D., REVELEY, M. A. & MURRAY, R. M. (1984) Increased cerebral ventricular volume in monozygotic twins discordant for alcoholism. *Lancet*, *i*, 986–988.

HAUG, J. O. (1962) Pneumoencephalographic studies in mental disease. *Acta Psychiatrica Scandinavica*, **38**, (Supplement 165) 1–104.

JERNIGAN, T. L., ZATZ, L. N., MOSES, J. A. & BERGER, P. A. (1982) Computed tomography in schizophrenics and normal volunteers: I. Fluid volume. *Archives of General Psychiatry*, **39**, 765–770.

JOHNSTONE, E. C., CROW, T. J., FRITH, C. D., HUSBAND, J. & KREEL, L. (1976) Cerebral ventricular size and cognitive impairment in schizophrenia. *Lancet*, *ii*, 924–926.

KLING, A. S., KURTZ, N., TACHIKI, K. & ORZECK, A. (1983) CT scans in subgroups of chronic schizophrenics. *Journal of Psychiatric Research*, **17**, 375–384.

LARGEN, J. W., CALDERON, M. & SMITH, R. C. (1983) Asymmetries in the densities of white and grey matter in the brains of schizophrenic patients. *American Journal of Psychiatry*, **140**, 1060–1062.

LEWIS, S. (1984) Presented to the Second Biannual Winter Workshop on Schizophrenia. Davos, Switzerland.

LISHMAN, W. A. (1978) *Organic Psychiatry: The Psychological Consequences of Cerebral Disorder*. Oxford, Blackwell.

LUCHINS, D. J., WEINBERGER, D. R. & WYATT, R. J. (1979) Schizophrenia: Evidence of a subgroup with reversed cerebral asymmetry. *Archives of General Psychiatry*, **36**, 1309–1311.

LYON, K., WILSON, J., GOLDEN, C. J., GRABER, B., COFFMAN, J. A. & BLOCH, S. (1981) Effects of long term neuroleptic use on brain density. *Psychiatry Research*, **5**, 33–37.

MALEC, J. (1978) Neuropsychological assessment of schizophrenia vs bain damage: A review. *Journal of Nervous and Mental Diseases*, **166**, 507–516.

MORIGUCHI, I. (1981) A study of schizophrenic brains by computerised tomography scans. *Folia Psychiatrica Neurologica Japonica*, **35**, 55–72.

NASRALLAH, H. A., JACOBY, C. G., MACCALLEY-WHITTERS, M. & KUPERMAN, S. (1982a) Cerebral ventricular enlargement in subtypes of chronic schizophrenia. *Archives of General Psychiatry*, **39**, 774–777.

—— MCCALLEY-WHITTERS, M. & JACOBY, C. G. (1982b) Cerebral ventricular enlargement in young manic males: A controlled CT study. *Journal of Affective Disorders*, **4**, 15–19.

—— KUPERMAN, S., HAMRA, B. J. & MCCALLEY-WHITTERS, M. (1983) Clinical differences between schizophrenic patients with and without large cerebral ventricles. *Journal of Clinical Psychiatry*, **44**, 407–409.

NYBACK, H., WIESEL, F. A., BERGGREN, B-M. & HINDMARSH, T. (1982) Computed tomography of the brain in patients with acute psychosis and in healthy volunteers. *Acta Psychiatrica Scandinavica*, **65**, 403–414.

OKASHA, A. & MADKOUR, O. (1982) Cortical and central atrophy in chronic schizophrenia: A controlled study. *Acta Psychiatrica Scandinavica*, **65**, 29–34.

OXENSTIERNA, G., BERGSTRAND, G., BJERKENSTEDT, L., SEDVALL, G. & WIK, G. (1984) Evidence of disturbed CSF circulation and brain atrophy in cases of schizophrenic psychosis. *British Journal of Psychiatry*, **144**, 654–661.

PEARLSON, G. D. & VEROFF, A. E. (1981) Computerised tomographic scan changes in manic depressive illness. *Lancet*, *ii*, 470.

REVELEY, A. M. & REVELEY, M. A. (1983) Aqueduct stenosis and schizophrenia. *Journal of Neurology, Neurosurgery, and Psychiatry*, **46**, 18–20.

—— —— & MURRAY, R. M. (1984a) Cerebral ventricular enlargement in non-genetic schizophrenia: A controlled twin study. *British Journal of Psychiatry*, **144**, 89–93.

—— —— CHITKARA, B. & CLIFFORD, C. A. (1984b) Genetics of cerebral ventricular volume. *Psychiatry Research*, in press.

—— —— CLIFFORD, C. A. & MURRAY, R. M. (1982) Cerebral ventricular size in twins discordant for schizophrenia. *Lancet*, *i*, 540–541.

REVELEY, M. A. (1985) Ventricular enlargement in schizophrenia: The validity of computerised tomographic findings. *British Journal of Psychiatry*, in press.

ROCHFORD, J. M., DETRE, T., TUCKER, G. J. & HARROW, M. (1970) Neuropsychological impairments in functional psychiatric diseases. *Archives of General Psychiatry*, **22**, 114–119.

RON, M. A., ACKER, W., SHAW, G. K. & LISHMAN, W. A. (1982) Computerised tomography of the brain in chronic alcoholism: A survey and follow up study. *Brain*, **105**, 497–514.

SCHULZ, S. C., KOLLER, M. M., KISHORE, P. R., HAMER, R. M., GEHL, J. J. & FRIEDEL, R. O. (1983) Ventricular enlargement in teenage patients with schizophrenia spectrum disorder. *American Journal of Psychiatry*, **140**, 1592–1595.

STOREY, P. B. (1966) Lumbar air encephalography in chronic schizophrenia: A controlled experiment. *British Journal of Psychiatry*, **112**, 135–144.

TANAKA, Y., HAZAMA, H., KAWAHARA, R. & KOBAYASHI, K. (1981) Computerised tomography of the brain in schizophrenic patients: A controlled study. *Acta Psychiatrica Scandinavica*, **63**, 191–197.

TARGUM, S. D., ROSEN, L. N., DE LISI, L. E., WEINBERGER, D. R. & CITRIN, C. M. (1983) Cerebral ventricular size in major depressive disorder: Association with delusional symptoms. *Biological Psychiatry*, **18**, 329–336.

TSAI, L. Y., NASRALLAH, H. A. & JACOBY, C. G. (1983) Hemispheric asymmetries on computed tomographic scans in schizophrenia and mania: A controlled study and a critical review. *Archives of General Psychiatry*, **40**, 1286–1289.

WEINBERGER, D. R., BIGELOW, L. B., KLEINMAN, J. E., KLEIN, S. T., ROSENBLATT, J. E. & WYATT, R. J. (1980a) Cerebral ventricular enlargement in chronic schizophrenia: An association with poor response to treatment. *Archives of General Psychiatry*, **37**, 11–13.

—— CANNON-SPOOR, E., POTKIN, S. G. & WYATT, R. J. (1980b) Poor premorbid adjustment and CT scan abnormalities in chronic schizophrenia. *American Journal of Psychiatry*, **137**, 1410–1413.

—— DELISI, L. E., NEOPHYTIDES, A. N. & WYATT, R. J. (1981) Familial aspects of CT scan abnormalities in chronic schizophrenic patients. *Psychiatry Research*, **4**, 65–71.

—— —— PERMAN, G. P., TARGUM, S. & WYATT, R. J. (1982) Computed tomography in schizophreniform disorder and other acute psychiatric disorders. *Archives of General Psychiatry*, **39**, 778–783.

—— TORREY, E. F., NEOPHYTIDES, A. N. & WYATT, R. J. (1979b) Structural abnormalities in the cerebral cortex of chronic schizophrenic patients. *Archives of General Psychiatry*, **36**, 935–939.

—— —— —— —— (1979a) Lateral cerebral ventricular enlargement in chronic schizophrenia. *Archives of General Psychiatry*, **36**, 735–739.

WILLIAMS, A. O., REVELEY, M. A., KOLAKOWSKA, T., ARDERN, M. & MANDELBROTE, B. M. (1985) Schizophrenia with good and poor outcome: II. Cerebral ventricular size and its clinical significance. *British Journal of Psychiatry*, **146**, 239–246.

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