5-HT REUPTAKE INHIBITORS, EPILEPSY AND MYOCLONUS

which may explain the apparent difference in proconvulsive activity between these agents (Squires 
& Saederup, 1988).

Depression is a common complication of epilepsy, and while the product manufacturers urge caution, there is a paucity of clinical research on the use of 5-HT reuptake inhibitors in patients with seizure disorders. Further studies are needed to establish whether these compounds may have a place in the treatment of depression in epilepsy. The widespread use of highly specific 5-HT reuptake inhibitors will also enable the role of serotonin in seizure disorders to be further explored as their effects on seizure frequency are of considerable theoretical interest.

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References


Head Circumference in Elderly Long-Stay Patients with Schizophrenia

GARETH H. JONES and JOHN E. LEWIS

The head circumference of a long-stay population with schizophrenia was compared with that of a population with dementia, matched for sex and year of birth. Schizophrenics had a smaller head circumference, even after correction for height and weight. This confirms earlier but inconclusive and controversial reports, and might be taken as supporting a neurodevelopmental hypothesis of the aetiology of schizophrenia. British Journal of Psychiatry (1991), 159, 435-438

Andreasen et al (1986) concluded that schizophrenics had smaller brains than a group of normal controls on the basis of measurements performed on a mid-sagittal scan of a magnetic resonance image (MRI). Decreased cranial and cerebral sizes were associated with prominent negative symptoms, and with impairment on certain cognitive tests, findings which the authors state are consistent with some type of early developmental abnormality that might retard brain growth and subsequently skull size.

The July 1987 correspondence columns of Archives of General Psychiatry were filled almost exclusively with comments and criticisms about head size and
schizophrenia. For example, DeLisi et al (1987) stressed the importance of matching patients adequately with controls for variables such as sex, body build, and economic and nutritional status. Weinberger et al (1987) questioned the reliability of using MRI scanning to measure cranial size, and thought that the use of a high-quality tape measure would be more appropriate. In their own series, slightly larger heads were found in the schizophrenics, in contrast to what would be expected from Andreasen et al's results. However, it is difficult to make any meaningful interpretation of Weinberger et al's findings, not only from the point of view of adequate matching of patients with controls, but also because their patients were undergoing regional cerebral blood flow and computerised electroencephalographic mapping studies. They might, therefore, be assumed to be more motivated and intelligent subjects, this not necessarily being true of schizophrenics as a whole. Also, if early developmental abnormalities were thought to be important, then these highly selected subjects might already have been screened and excluded if they had had a history, for example, of birth injury.

Reveley et al (1987) commented that, in their computerised tomography (CT) studies, there was no significant difference in intracranial area on the largest supra-orbital cuts between the schizophrenic monozygotic twin and his/her unaffected co-twin, nor between healthy control monozygotic twins. However, their studies were limited to a comparison of twins, who are in themselves not representative of the population as a whole, most of whom are not twins. Multiple births are more prone to environmental effects such as placental insufficiency, prematurity and difficult births, all factors which could have considerable bearing on brain development, and which might mask smaller differences between schizophrenics and normals.

We felt that this debate was far from conclusive, and decided to look at the head circumference of the old long-stay patients in Whitchurch Hospital.

**Method**

All the in-patients resident for more than one year in Whitchurch Hospital, Cardiff, and who were born during or before 1939, were recruited for the study. This population was chosen as they would be more prone to display diminished head size from neurodevelopmental abnormalities in early life, being subject to borderline nutrition, and increased risk of perinatal morbidity because of the high proportion of home births at that time. One obviously microcephalic lady with a subsidiary diagnosis of mental subnormality was excluded. Patients were asked for, and gave, informed consent. This produced a total of 39 individuals, who satisfied DSM-III-R criteria for schizophrenia (American Psychiatric Association, 1987), 23 female, and 16 male. Head circumference was measured with a high-quality tape measure. The patient sat while the tape was passed around the head, just above (but not including) the brow ridges, and the maximum circumference was recorded. All measurements were made by one of us (JL), as a pilot study of 20 patients and controls had found rather better test–retest reliability (Spearman's $r = 0.998, P < 0.001$) than inter-rater reliability ($r = 0.979, P < 0.001$).

The measurement was made with firm but not strong pressure to the nearest millimetre, and the average of two values recorded. The patient's weight was then recorded in stockinged feet and light indoor clothes, using a beam balance, measurements being taken twice to the nearest 0.1 kg. Height was measured in stockinged feet using a wall ruler, measurements being taken twice to the nearest 0.5 cm.

The subjects were then matched for sex, and as near as possible for year of birth, with a group of patients from a population suffering from primary dementia. We decided to use this diagnostic category as sufficient patients with affective illness could not be found. The patients with dementia were mostly in-patients, although their length of stay was much shorter than that of the schizophrenics. Thus they shared mostly a similar environment and diet to the schizophrenics, and also had the advantage of accessibility. All had a dementia acquired late in life, and had no significant previous medical, psychiatric or neurological history. All patients satisfied DSM-III-R criteria for dementia arising in the senium and presenium, and included people with Alzheimer's, multi-infarct dementia, or a mixed pathology, but not specific disorders such as Huntington's or Korsakoff's. However, we found difficulty in obtaining males to match for the youngest schizophrenics. Thus, three of our controls had year of birth differing by up to 2.8 years, but all the other subjects were matched to within six months. There was also a slight mismatch for place of residence: nine of the controls (five women and four men) lived in their own homes in the community, although all, except two of the men, attended regularly at the day hospital.

Informed consent was obtained from the patients with dementia, and the same measurements carried out in an exactly similar fashion to the schizophrenic subjects. Neither the schizophrenic nor dementia groups contained any subjects thought at any time to be mentally handicapped. Indeed, all subjects had at one time led independent lives, as judged by their having held a job or run a household.

**Results**

The difference of head circumference of about one standard deviation in men with schizophrenia v. those with dementia achieves statistical significance on a paired $t$-test, and would not at first sight seem to be accounted for by marked differences in body build (Table 1). The matching for year of birth was less than perfect, up to 2.8 years in one instance, owing to a difficulty in obtaining males with presenile dementia. The male population estimate is based on measurements of 58 industrial workers in west Wales, who were of a roughly comparable racial background, although
Table 1  
Measurements of male (n = 16) and female (n = 23) schizophrenics and male (n = 16) and female (n = 23) controls (dementia patients)

<table>
<thead>
<tr>
<th>Population estimate</th>
<th>Schizophrenia</th>
<th>Dementia</th>
<th>P</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean head circumference: cm (s.d.)</td>
<td>56.16 (1.40)</td>
<td>57.79 (1.71)</td>
<td>&lt;0.01</td>
<td>57.17 (2.23)</td>
</tr>
<tr>
<td>Mean height: cm</td>
<td>169.81 (7.03)</td>
<td>170.44 (7.08)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Mean weight: kg</td>
<td>66.89 (10.06)</td>
<td>69.14 (11.48)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Mean year of birth</td>
<td>1922.17 (8.68)</td>
<td>1922.70 (9.21)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean head circumference: cm (s.d.)</td>
<td>54.03 (1.20)</td>
<td>54.76 (1.05)</td>
<td>0.05 &lt; P &lt; 0.1</td>
<td>55.42 (1.35)</td>
</tr>
<tr>
<td>Mean height: cm</td>
<td>153.70 (9.00)</td>
<td>156.91 (6.73)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Mean weight: kg</td>
<td>56.90 (15.78)</td>
<td>56.68 (9.37)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Mean year of birth</td>
<td>1916.35 (8.58)</td>
<td>1916.20 (8.53)</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

The difference of 1.04 cm in head circumference between patients with schizophrenia and those with dementia is much greater than is likely to have been accounted for by any unreliability of measurement, as the standard deviation of repeat measurement was only 0.08 cm. It also survived correction for the obvious possible confounding variables of height and weight; our full model accounts for 56% of the total variance of head circumference. At first sight this seems to be consistent with Andreasen et al's finding of smaller cerebral size in schizophrenia. A similar finding of a 1.1 cm difference was reported by Betz (1942), in a study limited to females, that only reached the 6% level of significance, with no correction for age or height. One other study (Price, 1969) found no difference in maximum head breadth between 29 schizophrenics and their siblings of the same sex, but in this instance the control group was obviously not matched for year of birth, and the whole group was much younger than ours.

Several post-mortem series have reported a loss of brain substance, as assessed by brain weight, although such studies cannot distinguish between either a failure of brain development, or neuronal loss in adult life. The series closest to ours, that of Brown et al (1986), reported a 6% loss of brain weight in a post-mortem study of a complete series of 41, old long-stay, Feighner-positive schizophrenics, compared with 29 patients with a primary affective disorder. Adjustment was made for age, sex, and year of birth, but not for height or weight. Interestingly enough, our finding of a reduction of head circumference by 2% would be compatible with a 6% reduction of brain volume, if the brain were to be regarded as a sphere (circumference = 2πr; volume = 4πr³/3, a cubic function).

A brain-weight reduction of 4.5% was described more recently by Bruton et al (1990), accompanied by a reduction of brain antero-posterior length of 0.7 cm (3.9%) in males and 1 cm (5.7%) in females. Adjustment was made for age, but not for height or weight.
Thus, our finding of a reduction in head circumference takes the argument further, by being consistent with either a failure of brain development, or of neuronal loss before maturity. The sex difference in our data is of particular interest, with males showing a difference at the 1% level, while a similar trend in the females just failed to reach statistical significance. This greater effect in male patients would be compatible with Crow’s (1990) pseudo-autosomal hypothesis that the development of schizophrenia may be associated with a failure to develop normal brain asymmetry, the latter process known to be much more prominent in males.

Alternatively, our findings might be explained by a developmental arrest in a proportion of schizophrenics, induced perhaps by an environmental insult such as an intrauterine virus or an obstetric complication. However, it should be borne in mind that our difference of 2% in head circumference is only slightly greater than that which is known to occur from the age of 18 to full adult size (Nellhaus, 1968). Thus, it is not possible to say that all patients are affected, nor exactly when it might be that such a developmental arrest occurred.

The greatest problem with our series is the lack of matching for occupational status and intelligence, the latter being known to correlate broadly with head size. It should not be forgotten that several series have found a broad epidemiological correlation between low intelligence and the eventual development of schizophrenia (e.g. Mason, 1956). Mason’s study is particularly compelling as the intelligence quotient (IQ) was measured at army entrance, many years before the onset of illness, and might well be taken as supporting the idea of a developmental arrest.

It would be especially difficult to match for pre-morbid IQ as the old long-stay population is particularly difficult to test psychometrically, as are severely demented patients. One possible way forward in the future would be to make any assessment of pre-morbid intelligence using the New Adult Reading Test in dementia (Nelson & O’Connell, 1978), although this has not, to our knowledge, been validated in a long-stay schizophrenic population.

The second problem is that our long-stay population is obviously a highly selected one (perhaps only 1% of the total lifetime at-risk group of this hospital’s catchment population), being more likely to be socially impoverished, and possibly more damaged in general. Indeed, Jones & Offord (1975) argued that a low pre-morbid IQ was genetically independent of any transmission of schizophrenia, but also tended to give poorer outcome, with perhaps a higher tendency to reach long-stay care.

In search for the causes of schizophrenia, the notion of early brain lesions during the period of development has a growing body of evidence in its support, albeit at present circumstantial. Clearly, further research is urgently needed. Ironically, the old long-stay population may yet provide vital clues. We would suggest that they be studied more closely before they either die, or become more difficult to follow, as they are rehoused away from traditional mental hospitals.

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Thanks are due to Professor Eric Sunderland, University College of North Wales, for advice on the anthropological literature, to Dr Robert Newcombe, Department of Medical Computing and Statistics, University of Wales College of Medicine, and to Professor Peter McGuffin, Head of Department, for continued support.

References


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