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Cerebral ventricular size in depressed subjects

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SYNOPSIS A computed tomographic study of 101 depressed patients and 52 normal control subjects is described. Increasing age and male sex were both associated with larger ventricular size in both patient and control groups. Controlling for these effects, the depressed patients had larger ventricles than the control subjects. In the patient group there was no association between ventricular size, course of illness or exposure to drug treatment or electroconvulsive therapy.

INTRODUCTION

The initial enthusiasm generated by the demonstration of cerebral ventricular enlargement, by computed tomography, in patients with schizophrenia (Johnstone *et al.* 1976; Weinberger *et al.* 1979; Golden *et al.* 1980; Andreasen *et al.* 1982*a*) has been muted by the uncertainty of the clinical significance, aetiology and pathogenesis of the observed changes. Attempts to delineate a clinical subgroup of schizophrenic patients with these changes has met with only limited success (Crow, 1980; Andreasen *et al.* 1982*b*).

There is also a possibility that such changes are present in other 'functional' psychiatric conditions, such as the affective disorders. Rieder *et al.* (1983) compared patients with chronic schizophrenia with those suffering from schizoaffective disorder and bipolar affective disorder, and reported no difference in ventricular size between the groups, concluding that ventricular enlargement may not be specific to schizophrenia. Pearlson & Veroff (1981) reported on a mixed group of 16 patients with bipolar and unipolar depression and found that ventricular size, compared with that in control subjects with personality disorder, was increased. Nasrallah *et al.* (1982) reported similar findings on 24 manic patients, comparing them with control subjects with neurological disorders. Scott *et al.* (1983) reported increased ventricular size in 10 patients with depression, characterized by delusions, compared with an age-matched control group of medical in-patients. Jacoby & Levy (1980) in a study of elderly patients, controlled with patients without a psychiatric abnormality, demonstrated that there was a subgroup of patients with affective disorders who had ventricular enlargement. This subgroup was shown in a follow-up study (Jacoby *et al.* 1981) to have an increased mortality rate compared with those without ventricular enlargement.

All these studies suggest evidence of ventricular enlargement in some patients with affective disorder. Only Jacoby & Levy (1980) utilized a control group of subjects without any illness, but their study was based on an elderly age range. The other studies either examined patients admitted to a specialized ward for their depressive illness or used, as controls, patients who were suffering from some other illness. However, the result of this research is sufficiently consistent to indicate a further exploration of the association of CT scan abnormality (ventricular enlargement or sulcal atrophy) and affective illness but one in which a representative sample of depressed patients of mixed ages is compared with subjects without any current illness. Such a study would provide the basic information as to whether, like schizophrenia, there was a tendency for clinical depression to be associated with ventricular enlargement. If so, then it would also aim to determine whether the changes were associated with the course, type of illness, 'cognitive' impairment, or the treatment given.

METHOD

Selection of patients and controls

In order that outcome and treatment variables could be studied, patients who had had a clear cut depressive illness in the recent past were chosen as the target group.

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Patients were included in the study if they met the Research Diagnostic Criteria (RDC) for depression (Spitzer *et al.* 1978) and their age was in the range 20 to 79 years. Patients with a history of alcohol abuse, substance abuse, leucotomy, epilepsy or major physical illness (e.g. diabetes mellitus, thyroid disorders) were excluded. The patients were selected by examination of the discharge records of in-patients of the psychiatric unit at the Royal Free Hospital between 1976 and 1978 (the index admission). A second sample was obtained, using the same procedure, from discharge records of the in-patient psychiatric unit at the Whittington Hospital. Patients so selected were traced through their general practitioner. Of those considered eligible for the study, 78% were successfully traced and agreed to attend for interview, 9% could not be traced, 8% had died and 5% refused to participate.

The control subjects were healthy volunteers who were recruited from various sources, including hospital staff, hospital volunteer service and an elderly group attending a day centre. All control subjects were screened by the investigators for physical and psychiatric illness. An alcohol consumption of less than 5 units (1 unit = 1 glass of wine, half pint of beer, 1 measure of spirits) was a necessary condition for inclusion in the control group. Of those approached, 81% agreed to participate.

Methods of patient assessment

A detailed psychiatric history obtained by interview was supplemented by information from psychiatric case records. Particular attention was given to the presence or absence of a family history of depression or a major psychosis, details of medication and its type and duration and ECT application. In addition, the Present State Examination (PSE) (Wing *et al.* 1974) was administered to each patient to establish current clinical status.

Three subgroups of patients were defined according to the course of their illness since their index admission: those who had had a single episode of depression with complete recovery; those who had had recurrent episodes of depression with complete remission between these episodes; and those who had a chronic course defined as incomplete recovery with persistent symptoms or that depressive symptoms were present for at least 50% of the period since index admission. Using these criteria, three futher subgroups were defined according to the course of their illness prior to index admission.

Computed tomography

Computed tomography (CT) was performed on patients and controls using a CT 1010 EMI scanner. Contiguous 10 mm slices parallel to the orbital–meatal line were obtained encompassing the brain stem, the ventricular system and uppermost sulci. CT scan data were coded and stored on floppy disks and magnetic tape.

For analysis, ventricular size was measured as a ratio of ventricular area to total brain area (VBR = ventricular area/brain area × 100). VBRs were measured using a method previously described by Reveley (1983). In summary, scans were displayed on a computerized video display unit (VDU) and the slices showing the largest area of lateral ventricle were selected. Using a tracker ball which controlled a VDU pointer, areas encompassing the lateral ventricles and brain were traced. The number of pixels whose absorption density was in the range 0–20 Hounsfield Units (HU) was taken as the measure of ventricular area, while the number of pixels whose absorption density was in the range 0–100 HU was taken as the measure of brain area. Each of these measures was repeated on three occasions and the mean was taken as the final reading. The repeated measures were highly correlated (Pearson correlations) for both ventricular ($r = 0{\cdot}96$) and brain ($r = 0{\cdot}98$) areas. This method of assessment has also been shown to be highly correlated with mechanical planimetric measures (Reveley, 1983).

Sulcal size was rated on a 3-point scale (0–2) from photographic negatives, using a visual grading scheme by comparison with pre-defined standards. Ratings were taken for the following areas: frontal, parietal, occipital and temporal lobes, as well as interhemispheric and sylvian fissures. Two raters (P.C. and A.M.), who were blind to diagnosis, carried out the ratings. Agreement as to the presence or absence of atrophy (0 *v.* 1 and 2) was reached on 94% of scans, while complete agreement was reached on 81% of scans (0 *v.* 1 *v.* 2).

This paper presents data on the cerebral ventricular measures in patients with affective disorder compared with controls. A companion paper will examine the sulcal appearances of the same groups.

Statistics

Statistical analyses were performed using the SPSS computer package (Nie *et al.* 1975). A logarithmic transformation of the raw VBR scores was carried out prior to the analyses; this ensured that the measurements were then approximately normally distributed with constant variance. All statistical tests were carried our on transformed data. Pearson product-moment correlations were estimated, and then analyses of variance were carried out using the SPSS procedure MANOVA (Hull & Nie, 1981). Main effects examined by means of the latter procedure were those of age, sex, diagnosis and treatment, as well as interactions between these factors. In examining the main effects of age, patients were categorized into three age groups as follows: 20–39, 40–59 and 60–79. Using the MANOVA procedure, the effect of a particular explanatory variable is adjusted for the effects of each explanatory variable in a step-wise fashion.

RESULTS

(i) Subjects and controls

108 patients (74 female, 34 male) and 52 control subjects (37 female, 15 male) were included in the study. Seven patients who were interviewed refused to have a scan. The clinical characteristics of the patients are presented in Table 1. Twenty of the patients were drawn from Whittington Hospital. There was no significant difference between the mean ages of the patients ($55{\cdot}2 \pm 14{\cdot}3$) and of the control subjects ($54{\cdot}0 \pm 14{\cdot}6$).

Table 1. *Clinical characteristics of patient group* ($N = 108$)

Mean age	55 years
Female	69%
Family history	
Depression	40%
Schizophrenia	7%
Course of illness	
Single episode	14%
Recurrent episodes	25%
Chronic illness	61%
Bipolar	25%
Unipolar	75%
Past treatment	
ECT	64%
Phenothiazines	52%
Tricyclics	81%
Lithium	35%
MAOIs	20%
Benzodiazepines	78%

(ii) Ventricular size in patients compared with controls

A scatter plot of the VBRs of patients and controls is presented in Fig. 1. The raw VBRs of patients and controls for each age range are presented in Table 2. The overall means of the VBRs of patients ($7{\cdot}24 \pm 4{\cdot}64$) and control subjects ($5{\cdot}6 \pm 3{\cdot}34$) were significantly different ($P < 0{\cdot}02$), the patients having enlarged ventricles compared with the control group. The mean VBRs of patients from Whittington Hospital ($7{\cdot}0 \pm 3{\cdot}98$) did not differ from those from the Royal Free Hospital ($7{\cdot}2 \pm 4{\cdot}81$). A highly significant correlation was found between ventricular size and age in both patients ($r = 0{\cdot}63$, $P < 0{\cdot}001$) and control subjects ($r = 0{\cdot}61$, $P < 0{\cdot}001$).

Because of the likely effect of age and sex on the apparent difference between patients and controls, an analysis of variance was carried out to discover the main effects of age-group, sex and of clinical status (i.e. being a patient or control subject and having a bipolar or unipolar illness). The results of this analysis are presented in Table 3.

The effects of age group and sex were first entered into the analysis. Even when these variables are controlled, significant differences emerge between patients and control subjects ($P < 0{\cdot}005$), the patients having larger ventricles than the control subjects. However, no differences were apparent between patients having unipolar and bipolar illnesses. There was an independent significant effect of age group ($P < 0{\cdot}001$), indicating an increase in ventricular size with age and an independent effect of sex ($P < 0{\cdot}05$), males having larger ventricles than females.

The interactions between the main effects are shown in Table 3B. Each interaction has been examined separately after controlling for its main effect and other possible interactions. A significant interaction was observed between sex and age group ($P < 0{\cdot}05$), implying that the increase in ventricular size with age is less marked in males than in females. There was no interaction between sex and clinical status, implying that this relationship between sex and ventricular size was present in both control subjects and patients. No interaction was shown between age and clinical status, implying that the

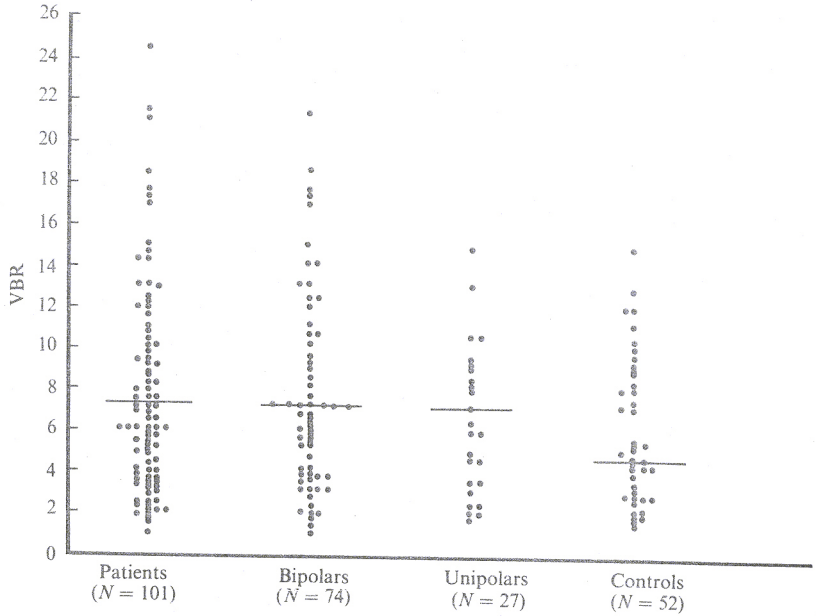

FIG. 1. Ventricular brain ratios of patients and controls.

Table 2. *Mean VBRs of patients and controls for each age group*

Age group	Patients	Controls
60–79	10·17±4·76 (*N* = 40)	8·24±3·19 (*N* = 20)
40–59	6·23±3·59 (*N* = 43)	4·31±2·41 (*N* = 23)
20–39	3·14±1·61 (*N* = 18)	3·03±1·24 (*N* = 9)

Table 3. *Analysis of variance of age, sex, clinical status by ventricular size in 101 patients and 52 control subjects*

	df	*F*	*P*
A. Main effects			
Sex	1	4·32	0·039
Age group	2	58·54	0·001
Unipolars *v.* bipolars	1	0·02	0·88
Affectives *v.* controls	1	9·54	0·002
B. Interactions			
Sex × age group	2	4·04	0·02
Sex × (unipolars *v.* bipolars)	1	0·33	0·57
Sex × (patients *v.* controls)	1	1·37	0·24
Age group × (unipolars *v.* bipolars)	2	1·6	0·18
Age group × (patients *v.* controls)	2	2·01	0·14

difference in ventricular size between patients and controls occurred throughout the age ranges. There were no interactions between age and diagnosis, indicating that patients with bipolar and unipolar illnesses had similar ventricular appearances at all ages.

(iii) Ventricular size and illness characteristics

The same statistical analysis used to provide the data shown in Table 2 was used to examine ventricular brain ratio and aspects of the depressive illness. No differences were discovered in the ventricular brain ratio of patients with a family history of depression compared with those without such a history, nor when those with a family history of any major psychosis were considered. There was no relationship between the course of the illness, the age of first onset of depression, the number of hospitalizations or the length of illness and ventricular brain ratio once the effect of current age had been controlled.

No significant relationship was found between ventricular size and previous treatment, or length of treatment with the following drugs: phenothiazines, tricyclic antidepressants, monoamine oxidase inhibitors, lithium and benzodiazepines. Similarly, there was no significant relationship between ventricular size and previous treatment

with electroconvulsive therapy (ECT) or the number of applications of ECT. Alcohol consumption, as estimated by average weekly intake in units of alcohol, was not associated with increased ventricular size.

DISCUSSION

The research has indicated that a series of patients with a history of affective disorder have significantly larger ventricles than normal control subjects. This difference is found both in patients with unipolar and with bipolar illness and is not dependent upon the age and sex of the patient. There was no specific association of size with the presence of a family history of depression, the duration of course of the depressive illness, exposure to psychotropic medication or treatment with ECT. Thus it appears that a proportion of depressed patients with major depression, both unipolar and bipolar, will display enlargement of the ventricular system on CT scan. Such changes, therefore, are not specific to schizophrenia.

However, there are possible sources of bias arising out of the design of the study. The retrospective selection of patients may have resulted in the incorporation of a more 'organic' group, for it could be that such a patient group is more refractory to treatment, thereby keeping in touch with medical services and easily traceable. However, neither length nor course of illness was associated with ventricular size. Secondly, patients were selected from the case records of those referred to a teaching hospital who could be atypical or treatment resistant and perhaps contain a more 'organic' group. To counteract this possible bias part of the cohort was selected from a district hospital population, and it was discovered that the findings applied wherever the referred site. Thirdly, it must be noted that this was a study between patients, i.e. those who identify themselves as ill, and healthy subjects. Therefore they are a selected group by virtue of this identification and referral to hospital. It could be that some feature, such as severity or disability of some depressed patients, is related to ventricular brain size and referral to hospital. This bias cannot be discounted, and would invalidate any claim that ventricular enlargement had been demonstrated in 'depression', an extra-mural study being indicated. Lastly, there is a possibility that the chosen control group could be atypical in the small size of their ventricles and therefore provide a spurious impression that the patient group had enlarged ones. The selection criteria, as regards alcohol consumption, could explain the atypicality of such a group. Patients were excluded only if there was a history of alcohol abuse. However, patients who were alcohol abstainers had larger ventricles than controls. Patients who had mild to moderate alcohol intake did not differ from abstainers in terms of ventricular size. Furthermore, the ventricular appearance of the control subjects in this study was similar to that reported in previous studies, although there are methodological problems in such direct comparisons (Barron *et al.* 1976; Haug, 1977).

As indicated earlier, ventricular enlargement has already been reported in both young patients and elderly patients with affective disorder. The present study revealed ventricular enlargement in patients of all age ranges, thereby confirming the earlier reports. Nevertheless, a visual examination of the raw data does indicate a strong tendency for the patient–control differences to be more marked in the middle and older age ranges.

The other independent association of ventricular size found here – namely, the ventricular size increase with age – is consistent with previous reports both in patient and in control subjects (Rieder *et al.* 1983; Jernigan *et al.* 1982; Gyldensted, 1977; Barron *et al.* 1976). Similarly, a sex difference in respect of ventricular size as described in the present study has previously been reported (Gyldensted, 1977; Haug, 1977). Several studies have not reported an increase in ventricular size with age (Johnstone *et al.* 1976; Weinberger *et al.* 1979). This discrepancy may have arisen because these contrasting reports have examined age homogeneous samples of patients and control subjects. An analysis of the data of the patients and controls in this study by specified age groups (e.g. 20–40) resulted in the disappearance of the significant correlation of ventricular size with age except in the over 60 age group. It was only when the total sample of patients and control subjects was analysed that a highly significant correlation was present between ventricular size and age.

Ventricular enlargement was not associated here with the duration of the depressive illness – a similar finding to the reports of CT scan investigations in schizophrenic patients (Weinberger *et al.* 1979; Frangos & Athanassenas,

1982; Golden *et al.* 1980). Weinberger *et al.* (1979) have reported a significant correlation between previous treatments with ECT and ventricular size. A significant correlation between the number of previous treatments with ECT and ventricular size in the patient sample reported here disappeared when current age was controlled for, suggesting an increased likelihood of treatment with ECT with advancing age.

The lack of an association with the duration of illness or treatment would suggest that ventricular enlargement antedates the onset of the illness. As reported in parallel studies in schizophrenia, Reveley *et al.* (1984) found no association of ventricular enlargement with a family history of illness although they reported that ventricular size was increased among schizophrenics without a family history. In the present study there was no association between the presence or absence of a family history of depression or major psychosis and ventricular enlargement. Does this suggest that these changes are not genetically determined and that some environmental event therefore leads to ventricular enlargement? Reveley *et al.* (1984) reported an association between birth complications and increased ventricular size in normal twins. Such an association was not examined in the current study. Whatever the cause, ventricular enlargement may make the individual vulnerable to psychiatric illness whose nature is perhaps determined by other factors. On the other hand, there may be more than one process at work resulting in ventricular enlargement, each process also being relevant to the onset of the specific psychiatric disorder. The meaning of these ventricular changes is, as yet, obscure.

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