# Ventricular Enlargement in Schizophrenia
## A Meta-analysis of Studies of the Ventricle:Brain Ratio (VBR)

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Multivariate meta-analysis was performed on 39 studies of ventricular size in schizophrenia which used the ventricle:brain ratio (VBR). The size of the VBR was dependent both upon the date when studies were carried out (more recent studies showing a reduction in the difference between schizophrenics and controls), and upon the diagnostic criterion used in the studies. Methodological factors in study design seemed more important than the characteristics of the schizophrenic subjects, in determining the VBR. Our analysis suggests that there is a difference in VBR between schizophrenics and controls which would seem to be an indisputable characteristic of schizophrenia. However, the difference is smaller than has previously been thought, so that, although of undoubted theoretical interest in accounting for the aetiology of schizophrenia, it is probably too small to be of practical significance in diagnosis, or in the differentiation of subtypes.

Ventricular size in schizophrenia was first investigated by Johnstone and her colleagues (Johnstone *et al*, 1976) using computerised tomography (CT) scanning, in a much-cited study where they noted significant ventricular enlargement in a group of chronic schizophrenics. That study clarified those earlier studies which had used lumbar encephalography (e.g. Haug, 1962; Storey, 1966) and had often found conflicting evidence for ventricular enlargement. The results of Johnstone *et al* (1976) were replicated by Weinberger *et al* (1979) who confirmed in their sample that the lateral ventricles of schizophrenics were significantly larger than those of controls. Since those two papers were published there have been many studies attempting to identify the aetiological factors responsible for ventricular enlargement in schizophrenia, and to correlate psychological deficits with what has been presumed to be an indicator of neuronal loss or brain atrophy (Reider *et al*, 1983; Reveley *et al*, 1984; Reveley, 1985; Goetz & van Kammen, 1986; Farmer *et al*, 1987).

The prevalence of ventricular enlargement varies between studies, perhaps in part due to measurement differences, differing diagnostic criteria, or the choice of control subjects. Maser & Keith (1983) cite prevalence rates of between 3% and 62% of schizophrenics in the studies they reviewed; however, in better-controlled studies prevalence rates vary from 18.6% to 40% (see Okasha & Madhour, 1982; Nasrallah *et al*, 1982; Weinberger *et al*, 1983). Such variation in prevalence requires further study and explanation.

Although lateral ventricular size has been measured in many ways (e.g. linear, area, or volumetric measures), the most widely used is the ventricle:brain ratio (VBR), which can be measured using either a CT scan or a magnetic resonance image (MRI). The area of the ventricles is conventionally expressed as a percentage of the total area of the brain scan, at the level on the scan at which the ventricles appear largest. This method of assessing VBR was first proposed by Synek & Reuben (1976) and Synek *et al* (1976), and is typically performed manually, by using planimetry, or by computerised procedures.

Although apparently straightforward, the assessment of VBR is not without problems. Roberts & Caird (1976) observed that VBR did not correlate any better with visual ratings of ventricular size on pneumoencephalograms than did ventricular area alone. Reveley *et al* (1982) found that in adult dizygotic twins, ventricular area correlated better in twin pairs than did VBR, which they interpreted as evidence that using VBR rather than ventricular area might decrease the sensitivity of studies, and therefore she and her colleagues (Reveley *et al*, 1984) have derived their own measure called the total ventricular volume (TVV), calculated by counting voxels (volume elements) from the computerised scan (1 voxel = $0.15 \times 0.15 \times 1.0 \, cm^3 = 0.0225 \, cm^3$). This method does appear to give a better estimate of ventricular size (Reveley, 1985) and has been used in a study of the heritability of ventricular size (Reveley, 1984). Nevertheless, TVV is little used in comparison with the more popular VBR (Reveley & Reveley, 1983).

Different methods for determining the areas of brain structures and of the ventricles from CT or MRI scans can produce some problems when comparing different studies. Problems such as the 'partial volume effect' have been discussed

comprehensively by Jacobson *et al* (1985). In manual planimetry, the scan image is projected onto a flat surface and traced using a mechanical device to calculate area; this technique typically results in greater measurement error than computerised methods, since distortion may occur when the scan is photographed, enlarged and projected. Such problems are partly avoided by methods in which the scan is viewed directly on the computer screen, and a light-pen or other interactive device is used to indicate areas of interest. Nevertheless, even with such techniques, different settings of contrast and brightness may modify image clarity and result in a reduced reliability. Similar machines may require different settings in order to produce an optimal image (Isherwood, 1979). In reviewing the validity of the VBR measure, Zatz & Jernigan (1983) argue that available methods for computing VBR from CT scans cannot produce absolute values of the VBR.

As well as considering the technical methods involved in the measurement of VBR, it is also necessary to consider the subjects in whom the measurements are made. Naturally, it is important that schizophrenic patients are diagnosed according to recognised and uniform criteria, and that groups of schizophrenics are as homogeneous as possible. However, a less obvious consideration concerns the nature of the control subjects with whom the schizophrenic patients are compared. Smith & Iacono (1986) (see also Smith *et al*, 1988) found that volunteer controls had larger ventricles than did medical patient controls, resulting in a smaller apparent difference between schizophrenics and controls. They suggest that this result may be because medical patient controls who happen to have larger ventricles are systematically excluded from analysis, thereby biasing the observed difference between groups. However, Raz *et al* (1988), using a somewhat larger series of studies, have argued that effect size is not related to the type of controls, and that "there is no need to avoid using patients free of gross neuropathology as controls". Certainly, it seems to us that the use of patient controls may well be vulnerable to bias, since by selecting scans from radiological files of individuals who have received CT or MRI scans as part of a medical work-up, there may well be an inadvertent tendency to select those scans that 'look normal', thereby biasing the control population to those with smaller ventricles. Sampling from medical files is not a random sampling method, and the practice is probably better avoided in order to eliminate bias.

As can be seen, factors associated with schizophrenia as well as factors associated with the methods of the study are likely to affect the reported size of the VBR measurements. Therefore, with this in mind, we felt that a closer look at the studies employing exclusively the VBR was needed. We therefore report a meta-analysis which assesses how a number of factors that differ between studies are contributing to the magnitude of the ventricle:brain ratio. Our study differs from more conventional reviews (e.g. Smith & Iacono (1988) who did not use any formal meta-analytic method, and Raz *et al* (1988) who carried out only a univariate meta-analysis). In this study, like that of Raz & Raz (1990), we carried out a multivariate meta-analysis, which allows us to distinguish the effects of a number of correlated moderator variables; however, our study differs in that we have studied different moderator variables, and in particular have looked at the date on which studies were carried out.

## Method

From the literature, thirty-nine studies were identified in which the VBR of schizophrenics was compared with that of controls. Details of the studies are shown in Table 1. Studies were found principally by computerised literature searches, and additionally one of us (JVH) searched manually through the indices of prominent journals such as the *British Journal of Psychiatry*, the *Archives of General Psychiatry*, and *Biological Psychiatry*. Studies were included if they were published before October 1990, reported sufficient data for our study, and in particular gave the mean and standard deviation of the VBR in schizophrenia and controls; this latter criterion meant that a few studies, such as that of Turner *et al* (1986), were omitted from the meta-analysis as they reported only median values.

Each study was classified in terms of eleven separate characteristics. It should be noted that some measures refer to the study as a whole (e.g. method of brain area measurement), and hence refer both to schizophrenics and controls; others refer separately to schizophrenics and controls (e.g. the mean age of the schizophrenics and the mean age of the controls); and others refer only to one group of subjects or the other (e.g. the diagnostic criterion used for the schizophrenics, or the nature of the controls), but can nevertheless be used as a predictor variable for the other type of subject (e.g. diagnostic criterion in schizophrenics can be used as a predictor of VBR in control subjects in the same study). In practice, this potential complication should not result in too much confusion.

(a) *Method of brain area measurement*. The methods of brain area measurement were grouped into two types: planimetry (manual tracing around a projected image) and computerised methods (usually involving an interactive device for identifying the ventricles and measuring their area).

(b) *Diagnostic criterion in schizophrenic subjects*. Four groups were recognised: studies using DSM–III (American Psychiatric Association, 1980); studies using the Research Diagnostic Criteria (RDC; Spitzer *et al*, 1975); studies in which patients met both the DSM–III

criteria and the RDC; and a single study by Benes *et al* (1982) which used only the Washington University Criteria (WUC; Feighner *et al*, 1972). For the purposes of multiple regression, the three degrees of freedom in the four groups were coded as three dummy variables, one representing the presence or absence of the DSM–III criterion, a second representing the presence or absence of the RDC criterion, and the third representing the interaction between the two criteria, being scored only if both criteria were used.

(c) *Description of schizophrenic population.* Patients were classified into three groups according to whether they were described as 'chronic schizophrenics' (i.e. chronic schizo- phrenics only), 'mixed sample' (i.e. described as a mixed group of different types of acute and chronic schizo- phrenia), or 'schizophrenia' (i.e. insufficient information given to allow further classification). For the multiple regression, the three groups were represented by two dummy variables, one each for the presence of 'mixed sample' and 'schizophrenia' groups.

(d) *Type of control subjects.* Control groups were classified as 'patients' (i.e. individuals being scanned as a part of unrelated medical investigations) and 'volunteers' (i.e. presumably healthy individuals who were being scanned only as part of a research study).

(e) *Mean age of subjects.* In almost all studies, controls and schizophrenics were closely matched in age; where possible, separate values of the mean age of subjects were recorded for schizophrenics and controls. Not all studies gave sufficient information, and in some studies only the age of schizophrenics was given, in which case it was also used as the mean age for the control subjects.

(f) *Standard deviation of age of subjects.* The standard deviation of the age is a straightforward measure of the range of ages of subjects. As for mean age of subjects, separate values were recorded, where possible, for schizo- phrenics and controls.

(g) *Age of onset of illness in schizophrenic subjects.* Where this information was available it was recorded as the mean age in years at the onset of first symptoms.

(h) *Duration of illness in schizophrenic subjects.* The mean duration of illness in years was recorded from the study, if reported, or was calculated in some cases by subtracting mean age at onset of illness from mean age at the time of the study.

(i) *Proportion of males among subjects.* The proportion of males in the schizophrenic and control subjects was noted where possible; the proportion was sometimes the same in schizophrenic and control subjects since matched controls were used. In a substantial number of studies, the proportion of males was not stated for either the patients or the controls. This situation was coped with by entering two variables into the analysis. One variable gave the proportion of males among the subjects, and if it was missing then the population mean for that group was sub- stituted. Following the recommendation of Cohen & Cohen (1983) for handling missing variables in multiple regression we also created a second, dummy, variable, which assessed the adequacy of reporting of sex ratios. This variable noted the presence or absence of adequate data on the sex of subjects (scored as 1 if the sexes of patients and controls

were fully reported, and 0 if either or both groups did not have full information reported on their sex). This method allows one to detect whether data are missing randomly or whether the absent data perhaps reflects some systematic underlying bias.

(j) *Number of subjects in the study.* The total number of schizophrenic and control subjects in the study.

(k) *Year of publication of the study.* In order to assess secular changes in the effects of changing diagnostic or technical processes, the year of publication of the study was recorded.

It should be noted that some of these classifications (such as the diagnostic criterion being used) can be used both for assessing differences between schizophrenic subjects *and* for assessing differences between control subjects; that is, for instance the mean VBR in control subjects may be assessed according to whether the schizophrenic subjects in that study were diagnosed according to DSM– III or RDC; etc.

## Statistical testing

The statistical analysis of meta-analytic studies is not entirely uncontroversial (see Hunter & Schmidt, 1990, for a recent review). A problem with any meta-analysis is that studies vary in sample size (and hence differ in their accuracy or reliability), and that independent (or moderator or predictor) variables are not uncorrelated. We have used an unweighted multiple regression analysis to assess the independent effects of correlated predictors, and have made no attempt to weight the various studies according to their sample sizes. In so doing, we are aware of the problem emphasised by Hunter & Schmidt (1990; p. 86) that in examining meta-analytic data for effects of moderator variables the crucial characteristic is the number of *studies* and not the number of *subjects*, which paradoxically can sometimes mean that their statistical power is surprisingly low, despite apparently large subject numbers. In using univariate and multivariate analysis of studies we have followed Glass (1977) in not attempting to take any account of the differing sample sizes in studies (and hence their different sampling errors and variance heterogeneity), since, despite the concerns of Hedges & Olkin (1985), we have accepted the argument of Hunter & Schmidt (1990; p. 408) that such problems pale into insignificance in comparison with the problems posed by low power in such studies. In assessing the effects of moderator variables we have therefore used unweighted population estimates from individual studies (i.e. irrespective of study sample size) and compared them by univariate statistics and by multiple regression.

In meta-analysis it is conventional to use measures of effect size, which are typically dimensionless numbers summarising a difference between group means in terms of such measure of the variability of the groups (such as the standard deviation) (e.g. Pearson's $r$ or the $d$- statistic, calculated as (Mean$_1$-Mean$_2$)/(Combined standard deviation) – see Rosenthal (1984) for a discussion of these and other related measures). Such an approach is sensible if studies are heterogeneous in their absolute units of measurement (and in the study of Raz & Raz (1990) such

Table 1
Details of 39 VBR studies of schizophrenics and controls

| Source | Schizophrenics Age: years mean (s.d.)[1] | n²[1] | Duration of illness: years mean (s.d.)[1] | Age of onset: years mean (s.d.)[1] | Subject type | Control type[3] | Controls Age: years mean (s.d.)[1] | n²[1] | VBR of controls mean (s.d.) | VBR of schizophrenics mean (s.d.) | Difference between VBRs (t-test) (d.f.) | Effect size (r) | Method of brain area measurement[4] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Andreasen et al (1982) | 29.96 (10.61) | 52 | 4.62 (3.40) | 25.34 – | (Sub)Chronic schizophrenia (DSM-III, RDC) | P | 29.96⁵ (10.61) | 52 (27:25) | 4.46 (3.05) | 6.00 (3.91) | 2.17(97) P=0.015 | r=0.215 r_c=0.160 | C |
| Benes et al (1982) | 21.20 (5.50) | 52 (30:22) | 4.50 (4.30) | 16.70 – | Schizophrenic (WUC) | P | 29.00 (6.30) | 26 | 8.80 (3.50) | 8.50 (3.10) | –0.45(35) P=0.672 | r=0.075 r_c=0.0736 | HP |
| Bishop et al (1983) | 28.10 (7.72) | 24 | – | – | Chronic schizophrenia (DSM-III, RDC) | P | 33.60 (8.29) | 25 | 5.22 (3.60) | 8.36 (3.54) | 1.83(47) P=0.035 | r=0.258 r_c=0.255 | HP |
| Boronow et al (1985) | 24.90 (4.40) | 30 (20:10) | 5.50 – | 19.40 – | Schizophrenics & schizoaffectives (RDC) | P | 24.90⁵ (4.40) | 26 | 4.90 (1.70) | 5.70 (2.00) | 1.60(54) P=0.056 | r=0.213 r_c=0.210 | HP |
| Buckman et al (1987) | 36.91 (8.25) | 35 (35:0) | 13.78 (7.73) | 22.73 (7.19) | Schizophrenia (paranoid, residual) & schizoaffectives (DSM-III) | P | 36.00 (7.76) | 14 (14:0) | 8.95 (4.71) | 10.30 (5.59) | 0.79(47) P=0.217 | r=0.114 r_c=0.113 | C |
| DeLisi et al (1986) | 32.50 (6.00) | 25 (10:15) | – | – | Schizophrenics (DSM-III, RDC) | P | 30.70 (7.00) | 20 (12:8) | 2.09 (1.10) | 2.82 (7.00) | 2.00(43) P=0.025 | r=0.290 r_c=0.285 | HP |
| Dewan et al (1986) | 28.10 (5.30) | 23 (23:0) | 7.10 (5.30) | 21.09 – | Chronic schizophrenics | V | 34.00 (20–40) | 23 (23:0) | 3.48 (2.50) | 5.40 (5.10) | 1.62(44) P=0.054 | r=0.230 r_c=0.226 | C |
| Harvey et al (1990) | 31.30 – | 37 | – | – | Schizophrenics (RDC) | V | 31.00 (15–59) | 50 | 4.68 (2.70) | 6.83 (2.90) | 3.56(85) P=0.0005 | r=0.360 r_c=0.348 | C |
| Iacono et al (1988) | 22.80 (5.70) | 36 (31:5) | – | – | Schizophrenics (DSM-III) | V | 23.20 (2.59) | 44 (29:15) | 6.39 (2.76) | 6.74 (2.59) | 0.55(73) P=0.292 | r=0.064 r_c=0.063 | HP |
| Jernigan et al (1982) | 32.40 (8.20) | 29 (29:0) | 10.20 (7.00) | 22.00 (4.40) | Chronic schizophrenics (DSM-III, RDC) | V | 43.20 (10.70) | 13 (13:0) | 5.00 (2.00) | 5.20 (2.00) | 0.29(40) P=0.387 | r=0.050 r_c=0.048 | C |
| Kaiya et al (1989) | 32.10 (8.30) | 80 (41:39) | 8.50 (6.30) | 23.60 (6.60) | Chronic schizophrenics (DSM-III) | P | 34.60 (10.30) | 45 (16:29) | 6.28 (2.50) | 7.21 (2.50) | 1.99(123) P=0.023 | r=0.177 r_c=0.173 | HP |
| Kelsoe et al (1988) | 29.00 (1.00) | 27 (22:5) | 8.40 (0.80) | 21.00 (0.70) | Schizophrenics (DSM-III) | V | 31.00 (1.00) | 14 (10:4) | 2.00 (0.20) | 3.10 (0.30) | 12.33(39) P=7×10⁻¹⁴ | r=0.89 r_c=0.88 | C |
| Kemali et al (1987) | 27.10 (6.50) | 50 (22:28) | 5.90 (4.50) | 21.20 – | Schizophrenics (DSM-III) | V(?) | 26.80 (8.00) | 25 (9:16) | 3.37 (1.50) | 4.52 (2.25) | 2.30(73) P=0.012 | r=0.261 r_c=0.258 | C |
| Kling et al (1986) | 36.16 (5.49) | 6 | – | – | Chronic schizophrenics (DSM-III) | V | 36.80 (8.70) | 20 | 4.75 (2.00) | 9.58 (3.30) | 4.45(23) P=0.00011 | r=0.670 r_c=0.658 | C |
| Losonczy et al (1986) | 36.00 (10.00) | 28 (28:0) | 12.20 (8.80) | 23.80 – | Chronic and schizoaffectives (RDC, WUC) | V | 34.20 (10.00) | 21 (21:0) | 4.40 (2.20) | 6.17 (2.48) | 2.59(47) P=0.006 | r=0.350 r_c=0.341 | C |
| Luchins et al (1984) | 29.00 (7.40) | 45 | – | – | Chronic, sub-chronic, acute, subacute (RDC) | P | 33.90 (11.50) | 62 | 3.00 (2.30) | 4.10 (2.70) | 2.26(105) P=0.012 | r=0.216 r_c=0.208 | HP |
| Luchins & Meltzer (1986) | 28.60 (5.60) | 11 | 8.20 (4.60) | 20.40 – | Chronic schizophrenics (DSM-III) | P | 36.10 (9.20) | 11 | 2.10 (2.30) | 7.30 (3.10) | 4.67(20) P=0.000138 | r=0.706 r_c=0.696 | HP |
| Moscarelli et al (1989) | 29.20 (4.60) | 19 (14:5) | 10.60 – | 18.60 (3.40) | Chronic schizophrenics (DSM-III) | P | 25.80 (7.70) | 23 (17:6) | 3.40 (1.70) | 5.10 (2.60) | 2.54(40) P=0.007 | r=0.370 r_c=0.358 | HP |
| Nasrallah et al (1982) | 29.90 (20–45) | 55 (55:0) | 9.35 – | 22.89 – | Chronic schizophrenics (DSM-III) | P | 29.7 (20–45) | 35 (15:20) | 3.86 (3.22) | 8.70 (4.00) | 1.31(89) P=0.095 | r=0.137 r_c=0.122 | C |
| Nasrallah et al (1990) | 32.24 (7.51) | 56 (41:15) | – | – | Chronic schizophrenics (DSM-III) | V | 27.85 (7.84) | 27 (27:0) | 4.50 (2.60) | 4.56 (1.85) | 4.96(80) P=0.000046 | r=0.480 r_c=0.470 | HP |

| Study | Group | Patient age (s.d.) n (M:F) | Duration of illness (range) | Age of onset (s.d.) | Control type | Control age (s.d.) n (M:F) | Control VBR mean (s.d.) | Patient VBR mean (s.d.) | $t$ (df) P | $r$ / $r_c$ | Method |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Obiols-Llandrich et al (1986) | Chronic schizophrenics (DSM–III) | 24.90 (6.30) 33 (11:22) | 4.50 (0.5–20) | 20.40 | P | 28.90 (6.20) 33 (11:22) | 5.82 (1.67) | 7.42 (2.17) | 3.06(56) P=0.002 | $r$=0.370, $r_c$=0.358 | C |
| Obiols et al (1987) | Chronic schizophrenics (DSM–III) | 24.00 (6.40) 42 (30:12) | 5.00 (1–17.5) | 19.00 | P | 28.80 (6.20) 42 (30:12) | 5.80 (1.67) | 7.20 (2.00) | 5.80(64) $P=4\times10^{-6}$ | $r$=0.338, $r_c$=0.333 | C |
| Owen et al (1989) | Schizophrenics (RDC) | 32.30 – 95 | – | – | V | 34.30 – 95 | 6.22 (2.34) | 7.81 (4.25) | 2.41(141) P=0.008 | $r$=0.198, $r_c$=0.196 | HP |
| Pandurangi et al (1984) | Chronic schizophrenics (DSM–III) | 28.00 (4.47) 23 (23:0) | – | – | P | 34.00 (4.47) 23 (23:0) | 3.48 (2.00) | 5.40 (4.40) | 1.906(44) P=0.03 | $r$=0.276, $r_c$=0.272 | C |
| Pearlson et al (1981) | Schizophrenics (DSM–III) | – – 22 (11:11) | – | – | P | – – 35 | 3.60 (2.60) | 7.50 (2.90) | 5.27(55) $P=2.7\times10^{-6}$ | $r$=0.579, $r_c$=0.560 | HP |
| Pearlson et al (1984) | Schizophrenics (DSM–III) | 28.80 (5.80) 19 (11:8) | – | – | V | 29.70 (5.30) 19 (11:8) | 4.5 (1.90) | 6.20 (2.60) | 2.30(36) P=0.013 | $r$=0.358, $r_c$=0.353 | C |
| Rossi et al (1987) | Chronic schizophrenics (DSM–III) | 42.44 (12.65) 18 (18:0) | 19.50 (9.50) | 22.94 | P | 34.30 (14.86) 17 (17:0) | 7.46 (1.40) | 8.71 (2.42) | 1.85(33) P=0.035 | $r$=0.300, $r_c$=0.290 | C |
| Rossi et al (1988) | Schizophrenics (DSM–III) | 33.20 (19–47) 15 (15:0) | 8.00 (2–13) | 25.20 | V | 32.6 (19–45) 15 (15.0) | 3.83 (0.81) | 5.56 (2.43) | 2.62(28) P=0.007 | $r$=0.440, $r_c$=0.420 | C |
| Rossi et al (1989) | Chronic schizophrenics (DSM–III) | 31.50 (6.30) 12 (8:4) | 7.91 (3.94) | 23.59 | V | 30.66 (6.38) 12 (8:4) | 4.05 (0.99) | 5.90 (2.15) | 2.70(22) P=0.006 | $r$=0.490, $r_c$=0.480 | C |
| The Scottish Schizophrenia Research Group (1989) | Schizophrenics (RDC) | 27.40 (9.70) 17 | – | – | V | 28.00 (9.30) 20 | 10.6 (3.20) | 9.50 (3.30) | –1.03(35) P=0.845 | $r$=0.171, $r_c$=0.166 | C |
| Shima et al (1985) | Schizophrenics (DSM–III) | 36.60 (6.70) 46 (24:22) | 13.30 (6.70) | 23.00 (5.80) | V[6] | 36.90 (6.60) 38 (19:19) | 7.60 (1.80) | 8.20 (2.30) | 1.39(90) P=0.082 | $r$=0.145, $r_c$=0.143 | C |
| Shelton et al (1987) | Schizophrenics (DSM–III) | 28.70 (5.30) 71 (49:22) | 9.70 (4.20) | 19.10 (3.90) | V | 28.70 (7.80) 71 (49:22) | 3.82 (2.65) | 5.46 (3.09) | 2.54(99) P=0.006 | $r$=0.240, $r_c$=0.237 | HP |
| Schulz et al (1983) | Schizophrenia & schizophreniform (DSM–III) | 16.50 (1.55) 15 (9:6) | 1.08 (0.416–2) | 15.42 | P | 15.90 (2.19) 18 (9:9) | 2.70 (2.35) | 8.40 (5.00) | 4.30(31) $P=9.9\times10^{-5}$ | $r$=0.610, $r_c$=0.600 | HP |
| Smeraldi et al (1986) | Schizophrenics (DSM–III) | 25.80 (7.30) 33 (28:5) | – | – | V | 24.70 (7.30) 53 (34:19) | 3.40 (2.04) | 6.30 (3.70) | 4.68(84) $P=5\times10^{-5}$ | $r$=0.455, $r_c$=0.440 | HP |
| Smith et al (1985) | Mixed sample (DSM–III, RDC) | 30.70 (7.60) 39 (16:23) | 6.60 (5.40) | 24.10 | P | – – 17 | 6.40 (1.90) | 6.20 (2.40) | –0.10(54) P=0.54 | $r$=0.0144, $r_c$=0.0003 | C |
| Smith et al (1988) | Chronic schizophrenics (DSM–III) | 28.30 (19–36) 30 (21:9) | – | – | P | 23.60 (5.60) 30 (13:17) | 6.38 (2.43) | 7.16 (2.03) | 1.42(58) P=0.079 | $r$=0.180, $r_c$=0.176 | HP |
| Weinberger et al (1979) | Chronic schizophrenics (RDC, WUC) | <50 58 | 10.60 | – | P | <50 56 | 3.50 (2.30) | 8.70 (3.90) | 8.81(112) $P=1.9\times10^{-12}$ | $r$=0.640, $r_c$=0.630 | HP |
| Weinberger et al (1982) | Chronic and schizophreniform (DSM–III) | 23.18 (7.50) 52 (30:22) | – | – | P | 30.30 (6.90) 26 (13:13) | 2.90 (2.90) | 5.52 (3.40) | 3.36(76) P=0.00068 | $r$=0.360, $r_c$=0.350 | HP |
| Williams et al (1985) | Schizophrenics & schizoaffectives (RDC) | 32.00 (6.80) 40 (30:10) | 8.90 (5.70) | 23.10 | P | 32.00[5] (6.80) 40 (30:10) | 3.37 (1.96) | 4.58 (2.55) | 2.379(78) P=0.009 | $r$=0.260, $r_c$=0.257 | C |

1. s.d. or range where available.
2. Male:female ratio is given in parentheses where available.
3. P=patients, V=volunteers.
4. C=computerised, HP=hand planimetry.
5. Age-matched control group.
6. Group specified as normal.

## Table 2
### Descriptive statistics for the independent variables and for VBR in schizophrenics and controls by diagnostic group

| | Schizophrenics | | | Controls | | |
|---|---|---|---|---|---|---|
| | Mean | s.d. | n | Mean | s.d. | n |
| Age[1] | 29.37 | 4.76 | 37 | 30.45 | 4.52 | 36 |
| Age at onset of illness | 21.50 | 2.59 | 23 | – | – | – |
| Duration of illness | 8.17 | 4.14 | 24 | – | – | – |
| Percentage males in sample[2] | 0.73 | 0.22 | 29 | 0.67 | 0.24 | 27 |
| Year of study | 1985.59 | 2.65 | 39 | – | – | – |
| *Mean VBR by diagnostic group* | | | | | | |
| DSM-III | 6.698 | 1.72 | 25 | 4.574 | 1.76 | 25 |
| RDC | 6.674 | 1.91 | 8 | 5.113 | 2.42 | 8 |
| DSM-III/ RDC | 5.716 | 1.99 | 5 | 4.634 | 1.58 | 5 |
| WUC | 8.500 | 0.00 | 1 | 8.800 | 0.00 | 1 |

1. Paired *t*-test *t*(35 d.f.) = – 1.82, *P* = 0.077 (two-tailed).
2. Paired *t*-test *t*(26 d.f.) = 2.37, *P* = 0.026 (two-tailed).

a method was necessary, because a range of different types of measure of brain morphology were used). However, in the present case all of the studies use VBR as the dependent variable and, therefore, it is sensible to carry out a meta-analysis in terms of that specific variable; the logic here is precisely akin to that arising in structural modelling in which typically (dimensionless) correlation matrices are used, but in which, if units of measurement are homogeneous, it makes more sense to use covariance matrices (see Kenny, 1979, for an account). Although we here present only analyses of absolute VBR measures, it should also be pointed out that re-analysis of our data using *d* as an effect size statistic results in identical conclusions.

## Results

Table 2 summarises descriptive statistics, averaged across studies (but not weighted by sample size), for the independent variables. It should be noted that some refer to subjects whereas others refer to studies.

Figure 1 shows for each study the mean VBR of the schizophrenics and the controls, with different symbols indicating the type of measurement that was used and the diagnostic criterion that was used. It should be noted that 36 (92.3%) of the studies lie above the main diagonal, compared with only three below the diagonal ($\chi^2 = 27.9$, 1 d.f., $P < 0.001$), indicating that, in general, schizophrenic subjects have higher VBR measures than do controls.

### Multivariate analysis

Three separate hierarchical multiple regressions were carried out, in which the 11 predictor variables (represented by a total of 15 variables and dummy variables) were entered at step 1 and then backward elimination used until all remaining variables were significant at the 0.05 level of
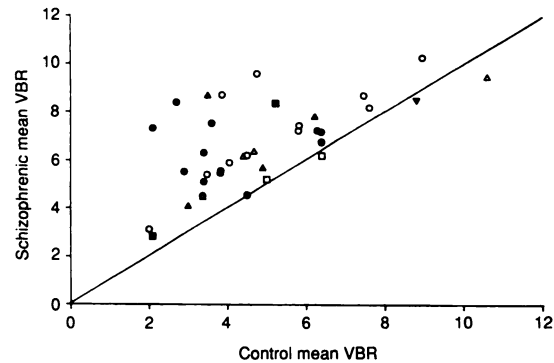


Fig. 1　Schizophrenic mean VBR in each study plotted against the VBR of controls for the same study. (Diagnostic criteria and methods of measurement: planimetry (DSM–III (●), RDC (▲), DSM–III/RDC (■), WUC (▼); computerised, DSM–III (○), RDC (△), DSM–III/RDC (□).) The diagonal line indicates the line of equality.

significance. The first analysis used the VBR of schizophrenic subjects alone as its dependent variable, and assessed which predictors were related to it. The second analysis used the VBR of control subjects as the dependent variable and assessed which predictors were related to measures of control VBR. The third analysis was effectively an analysis of covariance, assessing the difference between schizophrenics and controls by using schizophrenic VBR as the dependent variable, and then on the first step of the analysis entering the control VBR as a predictor. This analysis is therefore broadly equivalent to carrying out an analysis of unstandardised difference scores.

Missing values throughout were replaced by population means, as recommended by Cohen & Cohen (1983).

### Multiple regression of schizophrenic VBR scores

Three variables were significant after backwards elimination, resulting in an overall $F(3,36) = 5.53$, $P = 0.0031$. Significant variables were: the dummy variable indicating whether studies had adequately reported the numbers of male and female subjects ($t(36) = -3.620$, $P = 0.0009$) – studies reporting the sex of subjects adequately having lower VBRs; the duration of illness in the schizophrenic subjects ($t(36) = 2.437$, $P = 0.0199$) – studies using a sample that had been schizophrenic longer having larger VBRs; and the RDC diagnostic criterion ($t(35) = -2.171$, $P = 0.0366$) – studies using the RDC criteria having lower VBR scores.

### Multiple regression of control VBR scores

Four variables were significant after backward elimination, resulting in an overall $F(4,35)$ of 2.2673 ($P = 0.0816$). Three of the four significant variables were the dummy variables related to the diagnostic criterion used in the schizophrenic subjects (note that here we are analysing the control subjects). The three dummy variables were significant with $t(35) = -2.674$, $-2.296$ and 2.292, giving probabilities of 0.0113,
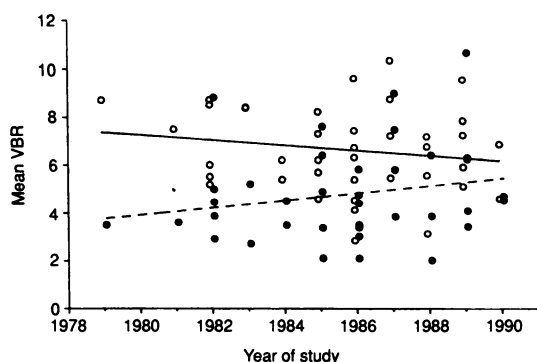
Fig. 2 The mean VBR for schizophrenics (o) and controls (●) for each study, plotted against the date of publication of the study (in order to avoid confusing overlap a few data points have been shifted laterally by a small amount). The solid line is the least squares regression for the schizophrenics and the dashed line is the regression line for controls.
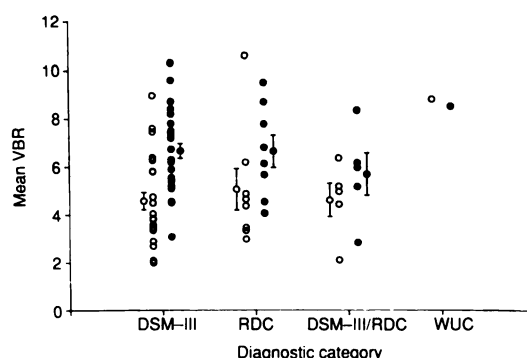


Fig. 3 The mean VBR either for schizophrenics (●) or controls (o) in a particular study, according to the diagnostic criterion used. Neighbouring symbols represent the mean VBR ($\pm$ 1 standard error of the mean) for that criterion.

0.0278 and 0.028 respectively. Taken together, these results indicate that mean VBR scores were less in studies using the RDC or the DSM–III criteria than in those using other methods of assessment; however, there was also an interaction between usage of RDC and DSM–III criteria so that studies using both criteria did not have as extreme a VBR as might have been expected. Table 2 summarises the mean VBR of both control and schizophrenic subjects according to the diagnostic criteria used. The fourth significant variable was the year in which the study was carried out ($t(35) = 2.055$, $P = 0.048$), with more recent studies showing larger values of VBR for the control subjects.

### Multiple regression of schizophrenic subjects using control subjects as covariate

The control VBR was entered at the first step of the regression and was highly significant ($F(1,38) = 28.739$, $P < 0.0001$), accounting for 43.1% of the total variance in schizophrenic VBR. Addition of the predictor variables, followed by backwards elimination, showed that four predictor variables were significant, resulting in an overall significance level of $F(5,34) = 14.257$, $P < 0.0001$, and an improvement in fit of $F(4,35) = 6.487$, $P < 0.001$. The four significant variables were: the year of publication ($t(34) = -2.884$, $P = 0.0068$), indicating that the difference between schizophrenic and control subjects is less in the later studies (the decreasing size of the difference being shown graphically in Fig. 2); the dummy variable indicating the use of DSM–III, indicating a large difference between schizophrenics and controls in the studies using this criterion ($t(34) = 2.881$, $P = 0.0068$); the dummy variable indicating the use of both RDC and DSM–III criteria ($t(34) = -2.866$, $P = 0.0071$), indicating that the difference between schizophrenic and control VBRs was less in those studies which had used both criteria (see Table 2); and the dummy variable indicating whether studies had

adequately reported the sex ratio of their subjects ($t(34) = -3.213$, $P = 0.0029$), indicating that those studies which adequately reported the sex ratio of the subjects had a smaller difference between the VBR of schizophrenics and controls.

Scrutiny of Fig. 3 might suggest that the interaction between diagnostic criterion and the size of the VBR could be the result of a single outlying study in the RDC control group (in fact the Scottish Schizophrenia Research Group, 1989, mean VBR = 10.6). That this is not in fact the case is shown by repeating the regression analysis omitting that single study. The interaction between RDC and DSM–III criteria is still significant ($t(32) = -2.767$, $P = 0.0093$).

### Multiple regression of estimates of standard deviation of VBR measures

In the previous multiple regressions we have considered the way in which the mean VBR differs between studies. Studies also differ, however, in the standard deviation (s.d.) of the VBR which is reported, a high s.d. meaning that subjects are more variable in their VBR than a low s.d. Meta-analysis can also assess differences between studies in s.d. of VBR as well as in mean of VBR, using the s.d. as the dependent variable in the multiple regression, and the same predictor variables used earlier.

### Standard deviation of schizophrenic VBR

Multiple regression with backwards elimination found that only two variables were significant at the 0.05 level (duration of illness, $t(37) = 2.194$, $P = 0.034$; mean age of schizophrenics, $t(37) = -2.448$, $P = 0.019$). However, the fact that neither of these variables showed a significant simple correlation with the s.d. of VBR, coupled with their signs being in opposite directions to those which might have been predicted, suggests strongly that these two variables are only significant due to multicolinearity, and may be ignored.

## Standard deviation of control VBR

Multiple regression with backwards elimination found that the only significant predictor was the type of control used ($t(38) = 2.212$, $P = 0.033$), studies with patient controls having higher variability in the controls' VBR than those using volunteer controls.

## Standard deviation of schizophrenic VBR using control VBR as a covariate

Multiple regression with backwards elimination, after forced entry of the control VBR at the first step, showed that no predictor variables were significant. The highly significant effect of the control VBR s.d. in predicting the schizophrenic VBR s.d. ($t(38) = 3.595$, $P = 0.0009$, $r = 0.504$) does, however, suggest that differences in s.d. between studies are systematic rather than random.

## Discussion

It is clear from this meta-analysis that schizophrenics seem to have a higher VBR than do controls. However, the size of the difference between schizophrenics and controls is affected by the diagnostic criterion that is used. The inclusion of subjects in almost all investigations is contingent upon them meeting a specific diagnostic criterion for schizophrenia, or a subcategory of schizophrenia, as determined by a recognised diagnostic system. DSM–III is both a clinical and a research tool for use in psychiatric evaluation, whereas the RDC are geared more specifically towards research purposes. Because of this difference between the methods, it is possible that patients who are included under one criterion may be excluded under another. Our analyses found that in those studies where DSM–III alone was used the difference between schizophrenics and controls was largest, that the difference was less in studies using the RDC alone, and smallest in those studies in which patients met *both* the DSM–III criteria and the RDC. The latter result is surprising, since it might be expected that if one criterion is stringent, then two criteria will be yet more stringent; patients who, therefore, meet both criteria should be more severely affected, and hence should show a larger effect rather than a smaller effect.

Two possible explanations for the result may be hypothesised. Firstly, the stricter criterion of satisfying both DSM–III and RDC may exclude a number of subjects who happen to have the largest ventricles, possibly because they are severely demented, or suffer from alcohol or other substance abuse. Alternatively, it may be that using the RDC or DSM–III criteria alone allows into the study a number of subjects who are not only schizophrenic but also suffer from conditions such as alcohol abuse, which are known to result in increased VBR size even when signs of dependence are not present (see for example Ron, 1983). Although apparently similar, these explanations are not the same: under the first hypothesis the single criterion group contains just schizophrenics, and the double criterion group has certain severe schizophrenics excluded from it, whereas under the second hypothesis it is the double criterion group which has a representative selection of schizophrenics and the single criterion group which contains individuals suffering from other conditions that affect the VBR. If the second hypothesis is correct then it is only those studies with dual criteria which are valid, and the size of the effect is even smaller than is conventionally estimated.

There was no indication that studies with a lower proportion of schizophrenic males have a lower VBR, which is inconsistent with previous findings by Bridge *et al* (1985), who observed that normal males have larger VBR scores than do normal females. In addition, they found that there was a relationship between VBR and height that was stronger in their female sample. The height of subjects was not routinely reported for the studies in our analysis, and, therefore, we cannot confirm this finding. The observations that, in general, schizophrenics are taller and thinner than controls (for instance Sheldon, 1940; Kretschmer, 1945) may represent a possible artefact accounting for some of the difference in VBR between schizophrenics and controls (see Harvey *et al*, 1990). That VBR is related to height is possible given that simple allometry might predict that brain and ventricle would scale proportionately, and therefore cancel out in a ratio measure such as VBR.

Although our analysis did not find any difference in VBR between studies having higher or lower proportions of female subjects, we did, however, find the somewhat surprising result that studies which had not adequately reported the sex of their subjects tended to show larger VBRs in schizophrenics and a larger difference between the VBRs of schizophrenics and controls. Although not easy to interpret, we suggest that this is best seen as evidence that studies carried out more meticulously (and, therefore, reported more precisely) had taken greater care over the matching of patients and controls, or had used better procedures for ensuring the blindness of assessment of VBRs by raters. The dummy variable is thus best interpreted as a proxy for overall study quality. The importance of the care with which subjects and controls are selected is also

seen in the finding that studies using non-volunteer subjects as their controls had a higher s.d. of the VBR than did those studies using patients as controls.

Our observation that the difference in mean VBR between schizophrenics and controls has decreased during the past decade may be explained by a number of factors. It probably partly represents an indication of the increasing awareness by researchers of the problems associated with computed imaging studies, and in particular the greater care in choosing control groups. The effect cannot be readily explained as a result of better selection of schizophrenic subjects since there was no trend in the size of the VBR in schizophrenics themselves (only in controls). A similar argument would suggest that although CT scanners are known to show secular trends (e.g. the study of Jacobson et al, 1985), it is unlikely to account for our finding since the effect should then be present in both schizophrenics and controls.

Figure 2 clearly shows that the difference in VBR between schizophrenics and controls is decreasing. Although a wild extrapolation of the figure might suggest that within a few years the difference in VBR between schizophrenics and controls might be nullified or even reversed, we do not actually believe that will be the case. There seems little doubt of the overall reality of the phenomenon, albeit of a somewhat reduced magnitude compared with that originally claimed. Probably the best single piece of evidence that schizophrenics indubitably have larger ventricles and smaller volumes of grey matter than controls is the magnetic resonance imaging study of discordant monozygotic twin pairs, by Suddath *et al* (1990), in which the schizophrenic twins were compared with their non-schizophrenic co-twin. Additional support for the reality of the phenomenon is shown by the finding in this and other analyses that schizophrenics with a longer duration of illness have a greater VBR (Raz & Raz, 1990). Nevertheless, the difference between the VBRs of schizophrenics and controls may well be generally smaller than is often reported, and more vulnerable to methodological problems than is conventionally realised.

That the difference in VBR between schizophrenics and controls is smaller than had initially been reported has practical consequences. To be useful as a screening test in practical diagnosis a difference between two groups should be large relative to the variances within the groups. Our data show that although the mean difference in VBR between schizophrenics and controls has decreased in the past decade, there is no similar trend in the variances. The result is that the specificity and sensitivity of any test using VBR as a criterion of schizophrenia (or of schizophrenic subtypes) has diminished, such that it is unlikely to be of any practical use in diagnosis.

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