Ventricular Enlargement, Neuropsychological Status, and Premorbid Function in Schizophrenia

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Ventricular enlargement is one of the most consistently documented neurobiological abnormalities in schizophrenia. The timing of the development of this abnormality in the course of schizophrenic illness and its relationship to neuropsychological dysfunction and premorbid adjustment is, however, unclear. To address these questions, we examined the relationship between ventricle-brain ratio (VBR), premorbid adjustment, and neuropsychological function, in 23 acutely exacerbated chronic schizophrenic inpatients. We observed that larger ventricles were associated with better current neuropsychological test performance, better premorbid cognitive ability, greater cognitive deterioration, better childhood premorbid social function, and greater decline in social function from premorbid levels. These data suggest that at least two developmental processes may operate in the genesis of cognitive and social dysfunction in schizophrenia: (1) childhood onset associated with poor premorbid childhood function, low educational achievement, lower intelligence quotient (IQ) and variably with VBR; and (2) adolescent onset associated with relatively normal childhood social function, higher academic achievement and IQ and increased VBR. Ventricular enlargement may reflect a late developmental or degenerative pathological process in schizophrenia.

Key Words: VBR, premorbid function, schizophrenia, neuropsychology, negative symptoms

Introduction

Enlargement in the size of the cerebral ventricles is one of the most frequently replicated neurobiological findings in schizophrenia (Shelton and Weinberger 1986). This abnormality has been demonstrated by in vivo structural brain imaging techniques, including pneumoencephalography (Haug 1962), computerized axial tomography (Shelton and Weinberger 1986 for review), and magnetic resonance imaging (Coffman and Nasrallah 1986 for review). Ventricular enlargement (VBR) is a sensitive indicator of central nervous system pathology as it reflects volume of the ventricular system (Penn et al 1978). Knowledge about when ventricular enlargement occurs in the course of schizophrenic illness could provide information about the nature, timing, and progression of structural brain abnormalities in schizophrenia. The issue of timing is pivotal in the controversy concerning the developmental versus degenerative nature of schizophrenic illness (DeLisi and Lieberman 1991). When ventricular enlargement occurs in the course of schizophrenic illness has, however, not been resolved.

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A definitive way of addressing this question of timing would be to obtain sequential measures of ventricular size in schizophrenic patients from infancy to onset and then through the course of the illness, and to compare these measures to those of normal controls. Such a study has not been (and probably logistically cannot be) systematically conducted. Although a few case reports have documented ventricular enlargement in patients who have subsequently developed schizophrenia, there have been no controlled studies. The published studies of high-risk patients (Cannon et al 1989, 1993) have yielded no definitive information on timing of ventricular enlargement. A second strategy for resolving this question would be to determine whether ventricular enlargement is present at the onset of schizophrenia and whether it progressed during the course of the illness. Findings in the literature are controversial, with evidence for (Miller 1989; Kemali et al 1989; Woods et al 1990) and against progression (Nasrallah et al 1986; Illowsky et al 1988; Vita et al 1988; Sponheim et al 1991). Ventricle size appears to be unrelated to duration and treatment of schizophrenic illness (Farmer et al 1987; Lawson et al 1988). Data suggest that ventricular enlargement is probably not an ongoing process throughout the course of schizophrenic illness; however, it is unclear whether or not progressive ventricular enlargement occurs during the initial years of illness. Longitudinal studies of first-break schizophrenic patients have, hitherto, not provided definitive information on this issue (DeLisi et al 1991; Degreef et al 1991).

A third approach to resolving this question of timing would be the study of clinical and neuropsychological correlates of ventricular enlargement in schizophrenic patients and extrapolate the timing of ventricular enlargement from the presumed timing of its clinical/neuropsychological correlates. Correlates of particular relevance in this regard include premorbid psychosocial and neuropsychological (dys)function, and cognitive/psychosocial deterioration from baseline function. If ventricular enlargement was found to be associated with poor premorbid function, this would suggest a premorbid (possibly early developmental) occurrence; conversely, if ventricular enlargement was found to be associated with deterioration but not premorbid dysfunction, this would suggest a later time of occurrence. Ventricular enlargement has been found to be associated with poor premorbid adjustment in some studies (Weinberger et al 1980; Pearlson et al 1985). With regard to neuropsychological function, several investigators have observed that ventricular enlargement is related to poor current neuropsychological test performance (Donnelly et al 1980; Golden et al 1980; Andreasen et al 1982; Lawson et al 1988); this finding has not been replicated in other studies (Rossi et al 1987; Bilder et al 1988). The relationship of ventricular enlargement to premorbid neuropsychological function and deterioration is not well-delineated.

In an effort to shed light on some of these issues, we investigated the relationships between VBR, neuropsychological function, and premorbid adjustment in a sample of acutely exacerbated chronic schizophrenic patients. Based on our findings, a hypothesis relating structural brain changes to onset of illness, premorbid function, and deterioration in schizophrenia is presented.

Methods

Twenty-three inpatients (17 men, 6 women; mean age [± SD] 29.3 ± 9.5) admitted to the Schizophrenia Program at the University of Michigan Hospitals with an acute exacerbation of their illness participated in this study. Each individual gave informed consent to participate in the research protocol. Demographic data from interviews with the patient and family, and from medical records, included age, gender, age of first symptoms, age of first hospitalization, duration of illness, and substance abuse. All patients were evaluated by a staff psychiatrist and by a trained research nurse using the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer 1978); all met DSM III-R (American Psychiatric Association 1987) and Research Diagnostic Criteria (RDC) (Spitzer et al 1978) criteria for schizophrenia. All patients were free of medical and neurological disease (based on screening history and physical exam), history of corticosteroid treatment, recent substance abuse, and treatment with electroconvulsive therapy. Patients were nutritionally intact and well hydrated throughout the course of the study. Each person was assessed globally and in terms of positive symptoms via the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962) and in terms of negative symptoms via the Scale for Assessment of Negative Symptoms (SANS) (Andreasen 1983). Ratings were carried out at baseline (at least 2 weeks medication-free) by a psychiatrist who was blind to neuropsychological test results, estimated premorbid adjustment, and head computed tomography (CT) scan data.

Premorbid social adjustment was quantified via the Cannon-Spoor Premorbid Adjustment Scale (Cannon-Spoor et al 1982) using data gathered from interviews with family members (at least one parent or elder sibling) and all available patient records. This assessment was carried out by a staff social worker trained in the use of the Cannon-Spoor instrument and blind to the neuroanatomical, neuropsychological, and symptom data. Standard methods for quantifying premorbid social function at each age were employed (Cannon-Spoor et al 1982); in each section, all the items were summed and then divided by the maximum possible total score to yield the premorbid social function score (0–1 scale) for that age with higher scores indicating poorer function. Deterioration in premorbid social function was quantified as the difference between the last score for a

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Table 1. Neuropsychological Test Battery

WAIS-R (intelligence)
Selective Reminding Test (memory)
Ravens Colored Matrices (visual spatial ability)
Reaction Time (attention span)
Wisconsin Card Sorting Test (executive functioning)
Wechsler Memory Scale (memory)
Trail Making Test (attention span)
Tactual Performance Test (haptic spatial ability)

given patient (which differed between patients because of differences in age of onset) and the childhood score for that patient.

A comprehensive neuropsychological assessment (see Table 1 for neuropsychological battery) was performed on each patient prior to treatment. This combination of tests was selected to assess language, memory, attentional, motoric, executive, and general intellectual functioning. The neuropsychologist was aware of the patient's diagnosis but was blind to clinical ratings, premorbid adjustment scores, and CT scan findings.

Premorbid intellectual functioning and deterioration were estimated using the formulas developed by Bilder et al (1988), which are based on the assumption that some WAIS-R subscales are sensitive to organic disease ("don't hold" tests) and others are relatively insensitive ("hold" tests). Information and Vocabulary are two subscales identified as "hold" subscales by Wechsler (1958); the Digit Symbol subscale was chosen as the "don't hold" subscale as it has been shown to be sensitive to cognitive impairment from a number of causes (McFie 1975; Bilder 1985). Premorbid intellectual ability was measured as the mean of the age-corrected Vocabulary and Information subscales; intellectual deterioration was calculated as the premorbid score minus the age-corrected Digit Symbol subscale score.

Head CT scans were performed on each patient, (GE 9800 scanner, GE Medical Systems, Milwaukee, WI) with a matrix size of 512 by 512. Slices were taken relative to the orbito-meatal line with angles of 9.0 ± 7.0 degrees; slice thickness was 10 mm. Ventricle-brain ratio was measured on the cut that demonstrated the ventricular system at its largest. Measurements were performed by digitizing the films using computer-based image analysis software and displaying them on a computer monitor. The program used to calculate area ("Image" software program, developed at NIMH, Bethesda, MD) allowed the operator to magnify the image size and enhance contrast selectively. Ventricle areas were hand-traced using the computer mouse, and two measurements were performed on each cut, the mean of which was used for analysis. Total brain area was measured by maximizing the image contrast between brain and bone, and having the computer determine the area of the nonbone structures within the skull; this measurement was exclusively computer-determined. VBR was calculated by dividing the ventricle area by the total brain area for each slice. This procedure produced a measure of maximum VBR which was used in subsequent statistical analyses. The investigator measuring VBR was blind to clinical ratings, estimated premorbid adjustment, and neuropsychological test data.

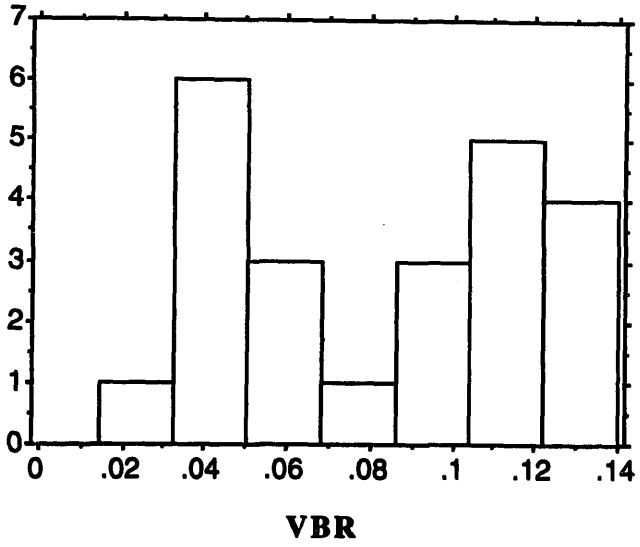

Figure 1. Frequency of distribution of VBR.

Statistical analyses included Spearman's Rank-Order correlations of CT data with clinical, premorbid adjustment, and neuropsychological data. This nonparametric statistic was used because the distribution of the CT scan data was nonnormal (see Figure 1) and could not be made to approximate normality by log transformation. Clinical, neuropsychological, and premorbid adjustment variables were compared between patients with larger ventricles and those with smaller ventricles by rare point-split analysis (utilizing *t*-tests), as the frequency distribution suggested clear subgroups of patients in terms of VBR (see Figure 1). Pearson's correlation coefficients were used to analyze relationships between neuropsychological, clinical, and premorbid data.

Results

Descriptive clinical, neuropsychological, and premorbid social function data for the sample are presented in Table 2. Clinical ratings, premorbid ability, neuropsychological test results, and CT scan data were unrelated to patient age, gender, handedness, age of first symptoms, duration of illness, and prior history of substance abuse. VBR (8.0 ± 3.6%) showed a trend toward a positive relationship with age of first hospitalization (Rho = 0.38, $p < 0.08$). All other comparisons between demographic and clinical ratings and

Table 2. Descriptive Data (Mean + SD)

Age		29.3 ± 9.5
Sex	73.9% male	26.1% female
Handedness	91.3% right	8.7% left
Age of 1st symptoms		21.0 ± 6.2
Age of 1st hospitalization		26.5 ± 8.2
Duration of illness (years)		8.3 ± 8.6
Global severity (BPRS total)		44.6 ± 7.0
Positive symptoms (BPRS "THOT")		14.1 ± 2.6
Negative symptoms (SANS total)		10.2 ± 4.0
Education (years)		12.9 ± 2.9
FSIQ		86.5 ± 16.9
PIQ		88.9 ± 17.3
VIQ		85.6 ± 15.6
Premorbid-cognitive (info + vocab)		8.9 ± 3.6
Deterioration-cognitive (info + vocab)/2 – dig. sym.		1.8 ± 3.0
PAS-childhood		0.29 ± 0.24
PAS-early adolescence		0.31 ± 0.25
PAS-late adolescence		0.35 ± 0.24
PAS-adult		0.49 ± 0.26
PAS-general		0.42 ± 0.18
PAS-deterioration		0.18 ± 0.26
VBR (%)		8.0 ± 3.6

CT scan findings were non-significant. VBR was not related to angle of the scan to the orbito-meatal line.

VBR tended to correlate positively with education (Rho = 0.35, $p < 0.10$), Full-Scale IQ (Rho = 0.42, $p < 0.06$), and Performance IQ (Rho = 0.40, $p < 0.06$). Premorbid cognitive ability, as estimated from current intellectual functioning (WAIS-R), was strongly correlated with VBR (Rho = 0.51, $p < 0.02$). Premorbid intellectual ability was also related positively to virtually all neuropsychological tests utilized in this study, as well as estimated cognitive deterioration (all $p < 0.05$), that is, better premorbid intellectual ability was associated with greater intellectual deterioration. With regards to premorbid social adjustment (PAS), childhood functioning was negatively associated with age of first symptoms ($r = -0.60$, $p < 0.01$) and VBR (Rho = −0.41, $p < 0.06$); thus patients with better premorbid adjustment exhibited a later age of onset and larger ventricles. Similarly, early adolescent functioning ($r = -0.60$, $p < 0.01$), late adolescent functioning ($r = -0.62$, $p < 0.01$), adult functioning ($r = -0.53$, $p < 0.05$) and general premorbid functioning ($r = -0.42$, $p < 0.05$) were negatively correlated with age of first symptoms. All estimates of premorbid social functioning were strongly correlated with education; this is expected given the items assessed by the Cannon-Spoor instrument. In an effort to gauge deterioration in social function, the difference between the latest premorbid functioning estimate and childhood premorbid functioning was calculated; the greater the difference, the greater the deterioration. This measure was significantly correlated to VBR (Rho = 0.58, $p < 0.01$), estimated premorbid cognitive ability ($r = 0.48$, $p < 0.05$), and Performance IQ ($r = 0.44$, $p < 0.05$). The decline in premorbid social functioning is also supported by the positive correlation between VBR and adult PAS scores, a change in direction of relationship over the premorbid period. This finding is brought about by the decline in function in patients with larger ventricles, without manifestation of overt psychotic symptoms, and the greater frequency of preadult onset of psychosis in patients with smaller ventricles (see Figure 2). Table 3 lists the correlations conducted between VBR and demographic, clinical, premorbid, and neuropsychological variables.

Table 3. VBR Correlations

Parameters	Rho	p
Age of 1st symptoms	0.28	NS
Age of 1st hospitalization	0.38	<0.08
Duration of illness (years)	0.20	NS
Global severity (BPRS total)	−0.16	NS
Positive symptoms (BPRS "THOT")	−0.29	NS
Negative symptoms (SANS total)	−0.03	NS
Education (years)	0.35	<0.10
FSIQ	0.42	<0.06
PIQ	0.40	<0.06
VIQ	0.32	NS
Memory quotient	0.15	NS
Trails-A	−0.09	NS
Trails-B	−0.26	NS
Reaction time-simple	−0.19	NS
Reaction time-choice	−0.28	NS
RCPM	0.34	NS
WCST	−0.22	NS
Premorbid-cognitive (Info + vocab)	0.51	<0.02
Deterioration-cognitive (Info + vocab)/2 – dig. sym.	0.34	NS
PAS-childhood	−0.41	<0.06
PAS-early adolescence	−0.32	NS
PAS-late adolescence	−0.09	NS
PAS-adult	0.53	<0.05
PAS-general	0.21	NS
PAS-deterioration	0.58	<0.01

On rare point-split analysis, the subgroup of patients with larger ventricles tended to perform better than those with smaller ventricles on Performance IQ ($t = 1.99$, df = 20, $p < 0.07$). Patients with larger VBR performed better on Trails B ($t = 2.03$, df = 16, $p < 0.06$) and had faster choice reaction time ($t = 1.76$, df = 18, $p < 0.10$). Individuals with larger ventricles had significantly higher cognitive premorbid scores ($t = 2.20$, df = 20, $p < 0.05$). Patients in the larger VBR group had better childhood premorbid functioning ($t = 1.72$, df = 20, $p = 0.10$), but by the adult premorbid period this relationship had reversed ($t = 2.23$, df = 15, $p < 0.05$) reflecting the greater frequency of early onset in the smaller ventricle group. The changing nature of premorbid social function in the two groups is also reflected by the signifi-

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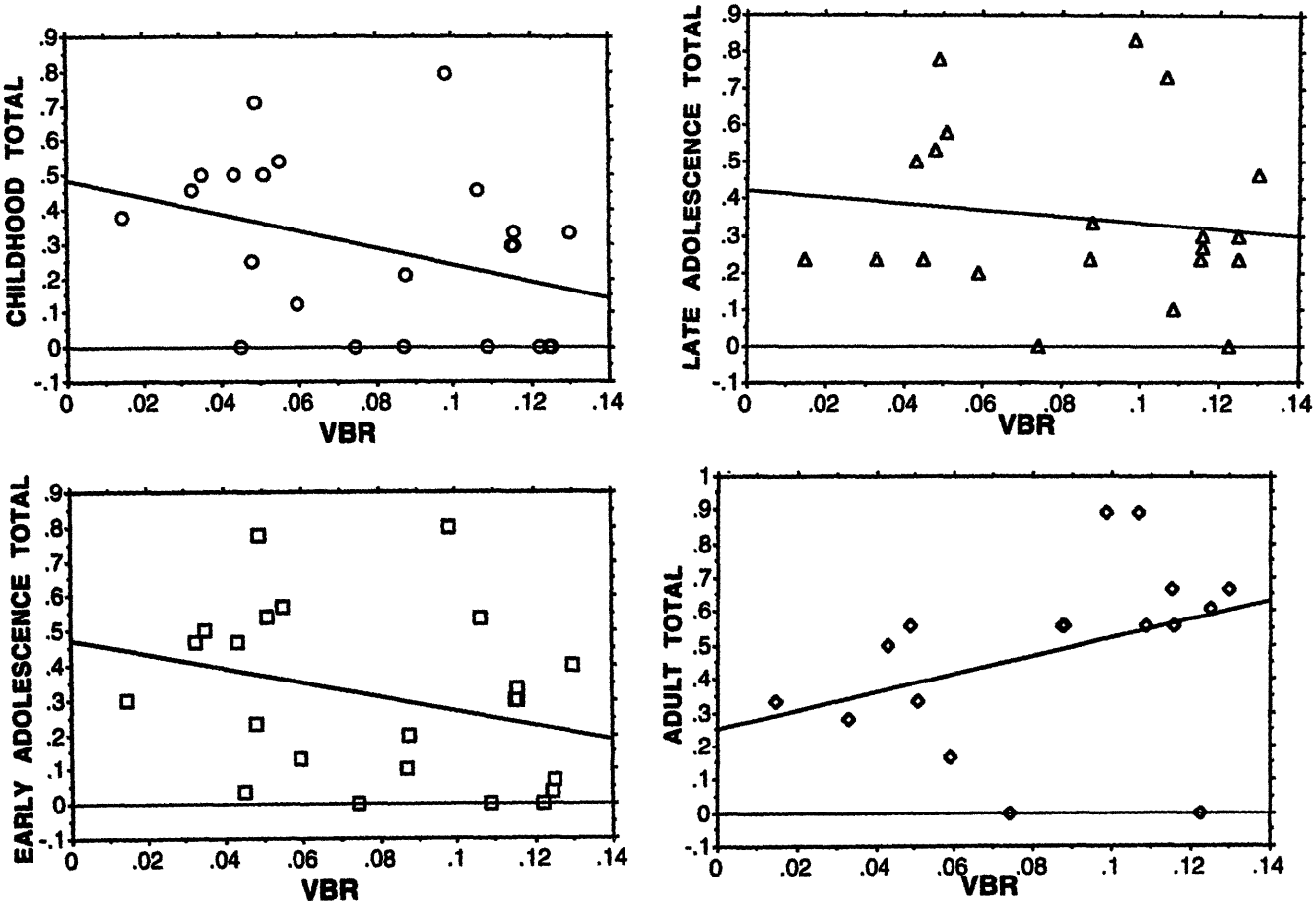

Figure 2. Plot of VBR and PAS by developmental period.

cantly greater degree of decline in premorbid function in the larger VBR group ($t = 3.92$, df =20, $p < 0.001$). VBR was not related to the degree of cognitive deterioration, symptom ratings, and neuropsychological test performance on this analysis (see Table 4).

Discussion

The present study found that in acutely ill chronic schizophrenic patients, larger ventricles were associated with *better* premorbid social and estimated premorbid cognitive ability, *better* current cognitive functioning, and with greater social and cognitive deterioration. These findings raise questions about current assumptions pertaining to relationships between VBR, cognitive function, and premorbid ability in schizophrenia.

The finding that larger ventricle size is associated with greater education and higher IQ is counter-intuitive and appears to be in conflict with those of other studies (Johnstone et al 1976; Lawson et al 1988). Our study is not the first to indicate a more complicated relationship between VBR and neuropsychological function than was previously believed, however. Rossi et al (1987) and Obiols et al (1987) failed to find a negative relationship between ventricular enlargement and cognitive impairment as measured by the WAIS-R; indeed, the latter group found that increased VBR was positively correlated with performance on the Information subscale of the WAIS-R. Bilder et al (1988), in a design similar to that used in the present investigation, found VBR to be positively correlated with neuropsychological test performance, estimates of premorbid cognitive ability, and degree of deterioration. They suggested that in patients with more normal scans, cognitive impairment may reflect a failure of acquisition, whereas in the patients with enlarged ventricles, impairment reflects deterioration from a higher (normal) premorbid level of functioning.

Data from our present study support this proposition. Estimates of premorbid cognitive and social ability and the degree of deterioration were positively correlated with VBR. Patients with larger ventricles had better early premorbid social and cognitive function and greater social and cognitive deterioration than patients with smaller ventricles. Higher premorbid ability and greater deterioration seen in patients with ventricular enlargement (when com-

Table 4. VBR Rare Point-Split Analysis

Parameter	Smaller VBR (mean + SD)	Larger VBR (mean + SD)	*t*	*p*
Age of 1st symptoms	19.5 ± 5.1	22.0 ± 7.3	0.92	NS
Age of 1st hospitalization	23.5 ± 8.9	29.3 ± 7.3	1.66	NS
Duration of illness (years)	6.5 ± 7.7	10.0 ± 9.6	0.93	NS
Global severity (BPRS total)	44.6 ± 8.7	44.4 ± 6.0	0.06	NS
Positive symptoms (BPRS "THOT")	14.8 ± 2.9	13.6 ± 2.3	1.10	NS
Negative symptoms (SANS total)	9.6 ± 4.4	10.3 ± 3.8	0.42	NS
Education (years)	11.5 ± 2.2	13.8 ± 3.1	1.99	<0.07
FSIQ	82.7 ± 16.4	92.4 ± 14.3	1.48	NS
PIQ	81.0 ± 13.8	92.3 ± 12.6	1.99	<0.07
VIQ	85.6 ± 16.6	93.9 ± 16.5	1.17	NS
Memory Quotient	90.7 ± 20.1	92.5 ± 17.2	0.23	NS
Trails-A (sec.)	50.2 ± 30.8	44.9 ± 21.6	0.45	NS
Trails-B (sec.)	141.6 ± 87.1	83.2 ± 25.0	2.03	<0.06
Reaction time-simple (msec)	596.9 ± 516.1	379.4 ± 135.2	1.35	NS
Reaction time-choice (msec)	682.3 ± 371.4	475.1 ± 115.4	1.76	<0.10
RCPM	27.3 ± 7.8	30.5 ± 6.6	1.00	NS
WCST	24.7 ± 19.4	18.1 ± 14.2	0.73	NS
Premorbid-cognitive (Info + vocab)	7.5 ± 3.3	10.5 ± 3.2	2.20	<0.05
Deterioration-cognitive (Info + vocab)/2 – dig. sym.	0.65 ± 2.3	2.75 ± 3.3	1.69	NS
PAS-childhood	0.40 ± 0.21	0.23 ± 0.25	1.72	=0.10
PAS-early adolescence	0.40 ± 0.23	0.26 ± 0.24	1.46	NS
PAS-late adolescence	0.41 ± 0.22	0.34 ± 0.24	0.72	NS
PAS-adult	0.36 ± 0.14	0.60 ± 0.23	2.23	<0.05
PAS-general	0.41 ± 0.15	0.46 ± 0.18	0.69	NS
PAS-deterioration	0.00 ± 0.16	0.34 ± 0.23	3.92	<0.001

pared to those patients without ventricular enlargement) suggests that patients with enlarged ventricles were able to achieve greater levels of cognitive ability and subsequently "fell" to a greater extent than those patients with lower premorbid ability who started lower and declined less.

Methodological limitations necessitate caution in interpreting the study's findings. The use of estimates of intellectual premorbid ability and deterioration based on current levels (hold and nonhold tests) of functioning are suboptimal. It would be preferable to obtain school records of IQ testing and to correlate VBR with past cognitive performance and an actual measure of intellectual decline. Another possible confound is the method used to acquire the CT scan images; scans were not taken exactly parallel to the orbito-meatal line. The fact that VBR was unrelated to the angle of the scan relative to the orbito-meatal line suggests that this confound does not explain the findings of this study. Lastly, given the relatively small number and relatively high education level of the patients we studied, the generalizability of these findings may be limited.

A comment is in order concerning the number of statistical tests performed and their influence on the conclusions of this study. As can be seen in Tables 3 and 4, 25 tests were performed for rare point-split analysis (*t*-test) and correctional analysis (Spearman's Rank-Order correlation). Utilizing a Bonferroni correction (Grove and Andreasen 1982) with α set at 0.1 (to balance risk of Type I and Type II error), a p-value of < 0.004 is required; the only finding that would remain significant is the relationship between VBR and PAS deterioration found on rare-point split analysis. The Bonferroni correction would be overly conservative, particularly in light of the hypothesis-generating nature of this paper. Nonetheless, the possibility that the findings reported occurred by chance must be borne in mind; however, given that the positive results are all in the same direction makes this unlikely. The ultimate answer to this question is through replication with improved methodology, which is currently underway.

Our data are consistent with the hypothesis that multiple developmental processes are involved in the genesis of schizophrenia (i) a later onset of illness with comparatively normal early premorbid cognitive ability and social functioning, associated with ventricular enlargement and greater deterioration, and (ii) an earlier onset with relatively impaired premorbid intellectual and social functioning, associated with normal ventricles and a lesser degree of deterioration. In terms of possible underlying neuropathological processes, the hypothesis would predict that later-onset patients, with greater deterioration, would demonstrate progressive ventricular enlargement early in the course of the illness; this may relate to excitotoxic damage resulting from repeated psychotic episodes

(Miller 1989; Woods and Yurgelun-Todd 1991). In early onset patients, with normal ventricles and poorer premorbid functioning, processes unrelated to generalized cell loss, for example, aberrant hippocampal cell migration (Scheibel and Kovelman 1981; Akbarian et al 1993) may be involved. Longitudinal studies of schizophrenic patients followed through various stages of illness will be necessary to test this hypothesis.

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