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Atrophic and Static (Neurodevelopmental) Schizophrenic Psychoses: Premorbid Functioning, Symptoms and Neuroleptic Response

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The question of whether schizophrenic-like disorders are neurodevelopmental or degenerative in origin has been argued since the time of Kraepelin. The authors provide evidence for the existence of two etiologically distinct endophenotypes of the psychoses contained within the rubric of familial non-affective psychosis (schizophrenia), one atrophic and the other neurodevelopmental. The atrophic psychosis, identified by progressive ventricular enlargement throughout adult illness, evidences progressive impairment of interests, relationships, and withdrawal from latency through adolescence, with emergence of trait-like negative symptoms which are only marginally responsive to conventional neuroleptics. This psychosis also exhibits delayed response of positive symptoms during neuroleptic treatment, and may also proceed to a praecox dementia in later life. In contrast, a putative neurodevelopmental psychosis, associated with static ventricles during the course of adult illness, also demonstrates preadolescent impairments, but impairments which do not progress to marked negative symptoms. Conventional neuroleptics appear to have little effect (except sedation) on positive symptoms, but appear to induce negative symptomatology and partial disengagement from the burden of persistent psychotic thought processes in such static ventricle psychoses. Thus, separate patterns of illnesses with different prodromal features, different treatment response patterns, and different patterns of residual (negative) symptoms appear to characterize patients with psychosis who have expanding as opposed to stable cerebral-ventricles at doses of neuroleptic at 10 mg haloperidol equivalents/day.
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The view that multiple etiologic factors contribute to the emergence of schizophrenic-like disorders is becoming increasingly plausible. Indeed, it has been difficult to view schizophrenia as a single disorder when so much variability persists in important features of the illness (such as age of symptom onset, symptomatology, neuroleptic response, and ultimate course of illness). Major differences in a variety of biologic domains are now clustering to make sense of such variability of clinical features. Distributions of such biologic data suggest that delineation of discrete, etiologically distinct disease processes within schizophrenic-like disorders may be appropriate. The value of understanding separate etiological processes which contribute to schizophrenic-like

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symptoms is obvious: once a particular etiologic process is understood, the opportunity exists to devise more specific treatment. Reliable detection of a specific disease process before onset of psychosis followed by early intervention designed to prevent symptom onset is clearly an even more desirable goal.

Brain imaging techniques provide anatomical information which can be used to better understand the schizophrenias. Many post-mortem and imaging studies have documented abnormalities of brains of patients with schizophrenia, but only rarely have serial in vivo studies been performed which can confirm whether these abnormalities are static (and thus suggestive of a remote developmental anomaly) or progressive (suggesting an ongoing atrophic process) during the course of clinical illness. Brain atrophy can most reasonably explain the progressive increase in ventricular volume (exceeding the increase found in the normal population) and loss of brain volume, documented in a few studies of patients with schizoprhenia. Moore et al. (1935) and Haug (1962) (both using pneumoencephalography), and Kemali et al. (1989) and Woods et al. (1990) (using computerized axial tomography [CAT]), all reported a high rate of ventricular expansion in many patients with schizophrenia. Other serial CAT studies (Nasrallah et al. 1986; Illowsky et al. 1988; Vita et al. 1988; Jaskiw et al. 1994), although often finding ventricular volume increases in some subjects, did not find a significant mean change over time.

Only three published studies have reported the rate of change in total brain or cerebral ventricular volume in patients with schizophrenic-like illness as compared to normal controls. DeLisi et al. (1997), using serial magnetic resonance imaging (MRI), found a more rapid decrease in total brain volume in a group of first-break patients with schizophrenia compared with normal controls. Nair et al. (1997) found a more rapid increase in the rate of ventricular expansion in patients with schizophrenic-like illness than in normal controls. Moreover, the Nair et al. (1997) study, as well as a reanalysis of the DeLisi et al. (1997) data by Garver et al. (1998), provided evidence for a two-cluster (bimodal) distribution of rates of ventricular expansion: the first group of patients showed ventricular expansion similar to controls and the second group showed ventricular expansion greater than four times that of the first patient group.

The purpose of this report is to characterize clinically two of the psychotic illnesses previously delineated anatomically by the bimodal clustering of ventricular expansion rates in patients with schizophrenia-like illnesses (Nair et al. 1997). The clinical characterization is based on 17 of the initially reported patients with serial ventricular studies (Nair et al. 1997), plus six additional patients who have since completed serial scans. The a priori hypotheses were: (1) there would be two groups of patients with respect to rate of ventricular change (Nair et al. 1997; Knoll et al. 1998); (2) changing ventricle patients would have a "delayed" response to neuroleptics (Kaplan et al. 1990); (3) there would be a strong relationship between total ventricular volume and age in patients with rapidly expanding ventricles (evidence for a continuous process of expansion); and (4) alcohol and drug use between ventricular volume assessments would be associated with more rapid ventricular expansion. An exploratory analyses was designed to assess interactions of conventional antipsychotics and symptoms, including differential symptom change in the two putative psychotic illnesses delineated by the two ventricular expansion rates. A secondary "exploratory" analysis examined symptoms prior to onset of psychosis for consistency with post-treatment symptoms. Finally, because age of onset is often an important parameter in defining syndromes, we explored possible differences in age of first psychosis.

METHODS

Twenty-two patients with psychotic disorders of the schizophrenia spectrum (Farmer et al. 1987; Kendler et al. 1993) who (1) met DSM-IV (American Psychiatric Association, 1994) criteria for the diagnoses of schizophrenia, schizoaffective disorder, schizophreniform disorder, psychotic affective disorder, or psychosis, not otherwise specified (NOS), and (2) were members of multiplex pedigrees of which other members were also affected with schizophrenia and/or other spectrum disorders were selected for admission to the Clinical Research Unit of the Dallas Veterans Administration Medical Center (DVAMC). Patients with a history of chronic medical illness, head injury, seizure disorder, or DSM-IV Substance Dependence were excluded from the study. Excluded also were patients who belonged to a previously delineated endophenotype, a "dopamine psychosis" characterized by elevated plasma homovanillic acid (>85 pmol pHVA/ml) at drug-free baseline, a rapid antipsychotic response following initiation of neuroleptics, and a "good prognosis" course (Garver et al. 1997). Five controls without a history of psychiatric illness in themselves or in their family members, and having no significant medical illness or alcohol or recreational drug abuse were selected as a reference group for baseline evaluation and serial imaging studies.

After giving written informed consent for protocol participation, each patient had a baseline (time 1) 3D-MRI brain scan performed during the index admission to the DVAMC. A repeat scan was performed on a second date (time 2) 14 to 46 months later. The five reference normal control subjects also underwent MRI studies within the same period as the patient population. MR imaging was performed at the DVAMC using a 1.5

Tesla Siemens SP scanner (Siemens Medical Systems, Inc., Iselin, NJ). 3D-MRI data, consisting of 128 contiguous slices covering the entire head were acquired using the MP-RAGE pulse sequence with the following imaging parameters: flip angle = 10°, TR = 12.5 sec, TE = 5 msec, TI = 300 msec, slice thickness = 1.95 mm, field of view = 250 mm.

The digital images were transferred to a UNIX workstation (Silicon Graphics, Inc., Mountain View, CA) for volumetric analysis of the complete data set (not individual slices) using ANALYZE software (CNS Software, Inc., Stewartville, MN). Segmentation of the brain was achieved by thresholding the image (removing voxels whose gray-scale value falls outside a specified range), then performing steps of conditional erosion (removing surface layers of voxels from the brain which have gray-scale values within a threshold range) and 3D connection (growing a region from a specified seed voxel by successively adding voxels that are connected to the region until all connect voxels are separated from unconnected voxels) (Rosenfeld and Kak 1982; Serra 1988; Torowaki and Yokoi 1986), in order to to remove layers of non-brain tissues including scalp, skull, and muscle. The brain was then segmented from the ventricles by further threshold and conditional erode operations at the brain/ventricle boundary, and the separate brain and ventricle volumes were calculated by automated voxel counting. The analyses were performed with operator feedback and supervision in steps outlined in a flowchart. A few cases required manual 3D tracing to remove a small number of extraneous voxels from the ventricles.

Total ventricular volume (TVV) is the volumetric sum (in cc) of lateral, third and fourth ventricles. The rate of ventricular volume expansion (RVE) (cc/yr) was calculated as:

$$\mathrm{RVE} = \frac{\mathrm{TVV}_2 - \mathrm{TVV}_1}{\Delta t}$$

Where:
TVV_i = total ventricular volume at $time_i$
Δt = the interval between scans in years.

All volumetric measurements were performed by a single investigator who was blind to the subject's identity, age, sex, and other clinical characteristics, as well as the scan date or order. The reproducibility of the volumetric analyses was determined by repeating the analysis of four of the scans five times. These analyses were also performed blindly and were randomly interspersed among other images.

The Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al. 1992) was administered during hospitalization, using information from patients, from families, and from clinical records, and was finalized at the time of discharge. It was the data base for patient diagnostics, for history, and for premorbid adjustment assessments (CASH-modified Phillips scale [excluding sexual interests during adolescence so that preadolescent and adolescent scores could be compared]). Alcohol and/or cocaine use, both preadmission and between MRIs (assessed at approximately 6-month intervals), was assessed categorically for each patient [0 = no use; 1 = use or abuse (DSM-IV)]. Patients with dependence (DSM-IV) were excluded from the protocol.

Symptoms were assessed with the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1982a) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1982b). Preadolescent and adolescent functioning scores from the CASH were also collected from controls.

For the patients who were treated with neuroleptics between scans, the mean daily dose of haloperidol (or haloperidol equivalent) was estimated from prescription records, pill counts, and from patient and collateral reports of compliance. Neuroleptic compliance was calculated as:

$$\frac{(\text{weeks taking} \geq 5 \text{ mg haloperidol equivalents}) \times 100}{\text{number of weeks between scans}}$$

Fourteen of the original 22 patients consented to systematic trials with oral neuroleptic at fixed doses of 10 mg/dfor 4 weeks, and adjusted thereafter to $\geqslant$ 5 mg/d of haloperidol or neuroleptic equivalents for the 6-month period of treatment. Initial SAPS and SANS ratings were performed at 2- week drug-free baseline. To control for the sedative (as opposed to antipsychotic) effects of the neuroleptic, the time course and extent of response were monitored using serial SAPS and SANS ratings beginning 24 hours following the first 5-mg dose of haloperidol. Ratings occurred periodically thereafter over the course of 6 months of treatment. Scores were then plotted and extrapolated (if necessary) at 2-week intervals.

Statistical analyses were performed with SYSTAT (SYSTAT for Windows 1996) and SigmaStat (SigmaStat for Windows 1995) software. Normality of the distribution of RVE was assessed with the Kolmogorov-Smirnov one-sample test using a standard normal distribution (Lilliefors test). K-means splitting methods (cluster analyses) were used to estimate the means $\pm$ SD and range of each of the normally distributed clusters. Analyses of variance (ANOVA) followed by Bonferroni's post-hoc tests were used to compare the two patient groups and controls. Between-patient group comparisons of data with normal distributions were assessed using separate or pooled variance, as necessary, by Student's *t*-test. Comparisons of between-group data failing to conform to a normal distribution were analyzed by the Mann-Whitney Rank Sum Test. Analysis of covariance (ANCOVA) with age as a covariate was used for comparisons of control vs. patient data. Multiple time points of SAPS or SANS

scores were assessed with repeated measures analysis of variance (RM ANOVA). For categorical measures, the Pearson chi-square (χ^2) or Fisher's exact was used. Pearson correlations (r_p) were used to examine relationships between the RVE and demographic or illness features. Between-group differences of correlation coefficients were assessed with z scores (Ferguson 1971). Regression analysis was used to estimate slopes (and 95% confidence intervals, CI) of rates of ventricular expansion on age.

RESULTS

Patient Demographics

Twenty-two patients with schizophrenic-like illness and a reference group of five normal controls participated in the serial 3D-MRI studies. Seventy-seven percent of the patients were DSM-IV schizophrenics, 14% were schizoaffective-depressed, 5% each were schizoaffective-bipolar or psychosis not otherwise specified. Table 1 provides demographic, baseline, and TVV_2 data on the patients and controls. At time 1, patients ranged in age from 19.5 to 46.2 years; the reference group of five controls had an age range from 27.6 to 56.4 years. There was a trend toward the controls being older (40.6 ± 10.9 years) than the patients (32.5 ± 8.8 years) ($t = 1.78$, df = 25, $p = .09$).

Table 1. Demographic Data for Patients and Controls

	Patients ($n = 22$)	Controls ($n = 5$)
DSM-IV diagnosis (No. patients)		
Schizophrenia	17	
Schizoaffective, depressed	3	
Schizoaffective, bipolar	1	
Psychosis, not otherwise specified	1	
Sex (M/F)[a] (No. Patients)	18/4	2/3
Age at first MRI[b] (Mean years ± SD)	32.5 ± 8.8	40.6 ± 10.9
Years between MRIs (Mean years ± SD)	2.5 ± 0.8	2.6 ± 0.7
TVV_2 (Mean volume [cc ± SD])	27.4 ± 10.6	22.8 ± 5.4
Preadolescent Premorbid Adjustment[c] (Mean score ± SD)	3.5 ± 2.8	2.0 ± 1.2
Adolescent Premorbid Adjustment[c, d] (Mean score ± SD)	4.4 ± 27	0.5 ± 1.0
Age at onset of psychosis (Mean years ± SD)	22.2 ± 6.2	
Duration of illness at first MRI (mean months ± SD)	122.8 ± 87.6	
Baseline SAPS (Mean score ± SD)	53.4 ± 24.2	
Baseline SANS (Mean score ± SD)	35.1 ± 19.1	

[a] $\chi^2 = 3.7$, df = 1, $p = .05$.
[b] Student's $t = 1.78$, df = 25, $p = .09$.
[c] Sum of CASH scores: withdrawal, peer relations, and interests.
[d] Mann-Whitney U = 10.5, $p < .01$.

There was a preponderance of males among the patients (82%) and a preponderance of females among the controls (60%) ($\chi^2 = 3.7$, df = 1, $p = .05$). Comparisons of the 4 female and 18 male patients reveal a trend in males toward greater lifetime use of alcohol (Mann-Whitney U = 54.0, $p = .08$). There were no significant differences in cocaine use (Mann-Whitney U = 48.0, $p = 0.19$), nor in preadolescent adjustment (Mann-Whitney U = 18.5, $p = .13$). There were no other sex differences within other domains reported herein (e.g., adolescent adjustment, age of psychosis onset, duration of illness at first MRI, current age, TVV_1, TVV_2, RVE, or baseline SAPS or SANS scores [all Mann-Whitney U < 47, $p > .30$]).

The patients (both males and females) and controls did not differ in preadolescent adjustment ($t = 1.13$, df = 25, $p = .27$). By adolescence, however, patients showed significantly poorer adjustment (Mann-Whitney U = 10.5, $p < .01$).

Mean TVV_2 of the 22 patients was 27.4 ± 10.6 cc (ranging from 12.4 to 51.4 cc) and 22.8 ± 5.4 cc in the five reference controls (ranging from 17.1 to 29.5 cc) (ANCOVA with age as covariate F = 3.363, df = 1, $p = .078$). The failure to detect significant differences previously reported between patients and controls may be due in part to the paucity of controls and to the greater variance (112.7) in the patients than in the controls (28.9).

Serial Ventricular Volume Changes

Assessment of the reliability of ventricular volumetric analyses, estimated by five blind reassessments of two scans each from two patients and two control subjects, resulted in a coefficient of variation (CV) of 0.011 (1%).

The time interval between scans was 2.5 ± 0.8 years (mean ± SD) for patients and 2.6 ± 0.7 years for controls. A timeline of TVV_1 and TVV_2 measurements for patients and controls is provided in Figure 1.

The annual rate (or slope) of ventricular expansion was computed from the ventricular change between the two scans, as noted in Methods. These rates were plotted for each patient and for each reference control (Figure 2)[. Following z-score transformations, the distribution of RVE in the patients differed significantly from normality (Kolmogorov-Smirnov one-sample test using standard normal distribution: Lilliefors max diff = 0.216, 2-tailed $p < .01$). The distribution of ventricular expansion of patients fit a two-cluster model (K-Means Splitting: F = 88.93). The distribution within each cluster did not differ from that expected of a normal distri-

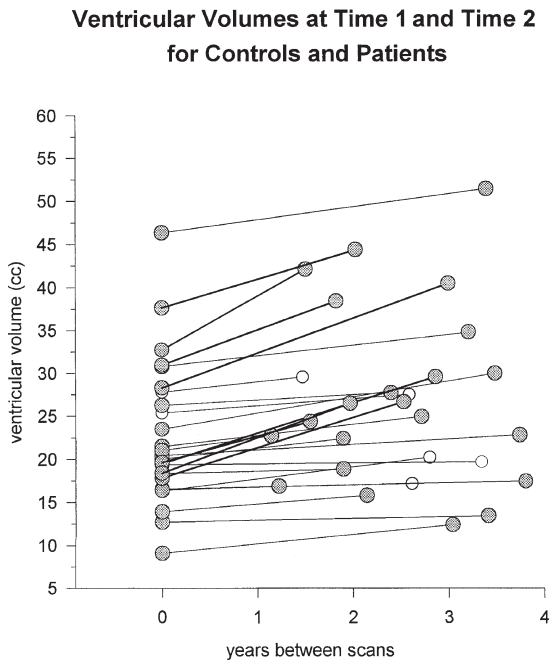

Figure 1. Timeline of TVV_1 and TVV_2 for controls (○) (n = 5) and patients (●) (n = 22).

bution. The first patient cluster (n = 14) showed a rate of expansion of 0.9 ± 0.5 cc/yr (similar to the rate of expansion found in controls: 0.7 ± 0.6 cc/yr) (ANCOVA with age as covariate: F = 1.394, df = 1, $p > .25$). A second patient cluster (n = 8) expanded at the rate of 4.0 ± 1.0 cc/yr. The RVE of the second cluster was significantly greater than the RVE of the controls (ANCOVA with age as covariate: F = 32.871, df = 1, $p < .001$). The patient cluster with significant ventricular expansion will hereafter be designated as the EXP group; the cluster with expansion similar to controls will be referred to as the normally expanding (NOR) group.

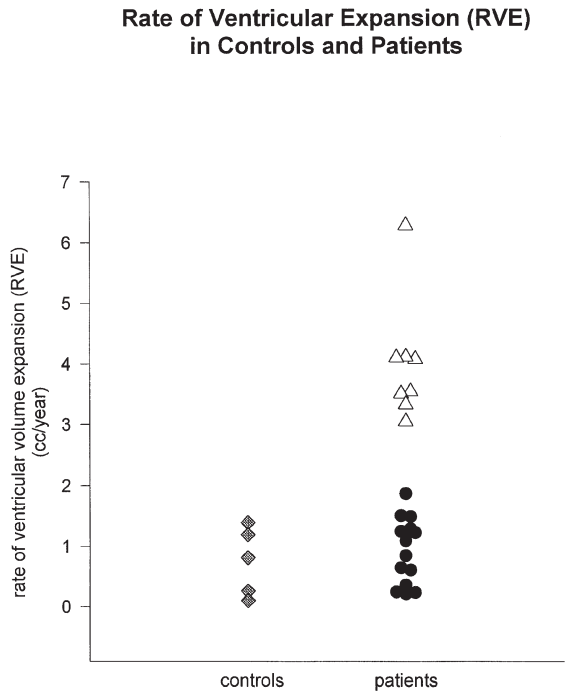

Figure 2. Rate of ventricular volume change in controls (◆) (n = 5) and patients with NOR (●) (n = 14) and EXP (△) (n = 8) ventricles.

Potential Association of Ventricular Expansion with Between-Scan Alcohol and/or Cocaine Use

Because previous reports have suggested that the rapid rate of ventricular expansion in EXP patients might be the consequence of between-scan use of drugs (particularly alcohol and/or cocaine) (Pfefferbaum et al. 1993), we examined the data to determine whether such associations might account for the ventricular expansion in the EXP patients. If 60% of the eight EXP patients and 0.00% of the 14 NOR patients were using drugs between scans, the present cohorts of patients have a power of 0.798 to detect such effects at $\alpha = 0.05$. However, 1 in 8 (12.5%) of the EXP patients used drugs between scans, compared with 6 of 14 (42.9%) of the NOR patients (Table 2). Clearly the hypothesized positive association between a greater rate of ventricular expansion in the EXP patients (hypothesis 4) was not supported by the data. In the years prior to the index admission, 3 of 8 (37.5%) of EXP patients and 7 of 14 (50%) of NOR patients reported a history of alcohol or cocaine use of abuse (Fisher's exact $p = .67$). The findings, although statistically insignificant, were in the direction opposite to that hypothesized. (It should be noted that patients with previous alcohol or cocaine dependence had been excluded from participation in this protocol.)

Age and RVE

Because other authors (Lieberman et al. 1996; DeLisi et al. 1997) have suggested that rapid ventricular expansion in schizophrenics might be limited to a period in the late teens or early 20s (near to or within the first few years following initial onset of psychosis), we assessed the relationship of age and RVE in the present cohort of patients (age 19 to 46 years). In the total cohort of patients, age was poorly correlated with RVE ($r_p = 0.12$, $p = .59$). If such rapid ventricular expansion were limited to the late teens and early 20s, the slope of RVE on age would be expected to be negative, with greatest ventricular expansion in younger patients and less expansion in older patients. However, in the present total cohort of patients (n = 22), although age correlated poorly with RVE ($r_p = 0.12$, $p = .59$), the rate of ventricular expansion as a function of age (RVE/age) had a mildly positive slope (+0.060; CI = +0.038 to +0.082). In the subgroup of patients for which the question is

Table 2. Demographic, Scan and Response Data for NOR and EXP Ventricle Groups

	NOR (n = 14)	EXP (n = 8)
Demographic and between scans		
Diagnosis (No. patients)		
Schizophrenia	12	5
Schizoaffective, depressed	1	2
Schizoaffective, bipolar	0	1
Psychosis, not otherwise specified	1	0
Sex (M/F) (No. patients)	11/3	7/1
Age at first MRI (mean years ± SD)	32.8 ± 8.1	31.8 ± 10.5
TVV_1 (mean cc ± SD)	21.2 ± 9.1	25.6 ± 7.7
TVV_2[a] (mean cc ± SD)	23.7 ± 1.0	34.0 ± 8.0
Years between scans (mean years ± SD)	2.7 ± 0.9	2.2 ± 0.6
RVE[b] (mean ± SD cc/year)	0.9 ± 0.5	4.0 ± 1.0
Preadolescent premorbid adjustment (mean ± SD)	3.4 ± 2.8	3.5 ± 2.9
Adolescent premorbid adjustment[c] (mean ± SD)	3.3 ± 2.6	6.4 ± 1.8
Age at onset of psychosis (mean years ± SD)	21.4 ± 5.2	23.8 ± 7.7
Duration of illness at first MRI (mean months ± SD)	137.6 ± 90.0	96.8 ± 82.2
Pre-Admission alcohol and/or cocaine use (yes/no)	7/7	3/5
Between MRIs alcohol and/or cocaine use[d] (yes/no)	6/8	1/7
Neuroleptic compliance (percent time ± SD)[e]	75.0 ± 31.6 (N = 7)	92.1 ± 9.2 (N = 7)
Response: 6 month haloperidol or equiv.		
Day 1 SAPS[f] (mean ± SD)	25.6 ± 14.5	49.7 ± 17.7
Day 1 SANS[g] (mean ± SD)	20.1 ± 13.2	40.7 ± 12.8
Week 26 SAPS[h] (mean ± SD)	24.7 ± 18.9	9.57 ± 13.7
Week 26 SANS (mean ± SD)	23.6 ± 12.0	30.0 ± 11.4

[a] Student's $t = 2.46$, df = 20, $p = .02$.
[b] Student's $t = 9.43$, df = 20, $p < .01$.
[c] Student's $t = 2.91$, df = 20, $p = .01$.
[d] Fisher's exact $p = 0.19$.
[e] Student's $t = 1.89$, df = 16.5, $p = .08$.
[f] Student's $t = 2.79$, df = 12, $p = .02$.
[g] Student's $t = 2.96$, df = 12, $p = .01$.
[h] Student's $t = 1.72$, df = 12, $p = .11$.

most germane, the group of EXP patients (n = 8, age 19 to 45 years), there was again a modest (r_p = 0.32, p = .45) yet mildly positive relationship of age and RVE (RVE/age slope = +0.117, CI = +0.083 to 0.151). Such positive slopes of RVE/age is opposite in direction of that which would be expected if ventricular expansion were limited to the late teens and early 20s. Patients with more rapid rates of ventricular expansion were found not solely at an early age, but appeared throughout the age spectrum in the EXP patients.

Ventricular Volume and Age in Expanding Ventricle Psychotics

In patients whose ventricles are progressively expanding, ventricular volumes could be expected to be correlated with the duration of the expansion. Because signs of psychopathology were documented in preadolescence (see below), long before onset of overt psychosis, age (rather than duration of psychotic illness) would likely be the appropriate parameter relating to "duration of expansion." Within the EXP subgroup, age was highly correlated with ventricular volume (TVV_2) (r_p = 0.94; $p < .01$), indicating that 88% of the variance in ventricular volume in the EXP subgroup could be accounted for by age. The data supports hypothesis 3, which suggests a strong relationship between age and ventricular volume in EXP patients.

In the five controls, age and TVV_2 were modestly, although insignificantly (likely due to small sample size) correlated (r_p = 0.66, p = .23). A similar, albeit slightly lower correlation (r_p = 0.56) of age and ventricular volume was found in the NOR patients, but the size of the group of NOR patients (n = 14) provided sufficient power to disclose a significant relationship (p = .04) between age and TVV_2 in the NOR group. However, a significant difference was found between the correlation coefficients (r_p) relating age and ventricular volumes in the EXP pa-

tients ($r_p = 0.94$) and the NOR patients ($r_p = 0.56$) ($z = 2.20$, $p = .028$). In contrast to the strong relationship between age and ventricular volume in the EXP patient, where 88% of the variance in ventricular volume could be accounted for by age, only 31% of the variance in ventricular volume could be accounted for by age in the NOR group. The majority of the variance in ventricular size in the NOR patients appeared to be due to factors other than age, such as genetic factors, nutrition, anomalies of neurodevelopment, or natal or post-natal injury.

Characteristics of Patients with Normally Expanding (NOR) and More Rapidly Expanding (EXP) Ventricles

Demographic data, TVV_1, TVV_2, RVE, number of years between scans, preadolescent and adolescent adjustment scores, the extent of alcohol and/or cocaine use, and day 1, and week 26 SAPS and SANS scores for NOR and EXP patient groups are provided in Table 2. There were no significant differences between the two patient groups regarding diagnosis ($\chi^2 = 3.93$, df = 4, $p = .42$), sex ($\chi^2 = 0.27$, $p = .60$), age at first MRI ($t = 0.25$, df = 20; $p = .80$), TVV_1 ($t = 1.15$, df = 20, $p = .27$), years between scans ($t = 1.47$, df = 20, $p = .16$), age of psychosis onset ($t = 0.873$, df = 20; $p = .393$), or duration of illness ($t = 1.05$, df = 20, $p = .31$). There was a trend toward better neuroleptic compliance among the patients with EXP ventricles ($t = 1.89$, df = 16.5, $p = .08$) (Table 2).

Premorbid Adjustment Patterns

Preadolescent psychopathology (from the modified Phillips scale: interests, peer relationships, withdrawal) did not significantly differ between the NOR (3.4 ± 2.8), EXP (3.5 ± 2.9), and control groups (2.0 ± 1.2) (ANOVA F = 0.620, df = 2,24, $p = .55$). By adolescence, however, there were significant differences in psychopathology (ANOVA F = 11.6; df = 2,24; $p < .01$), with both NOR (3.3 ± 2.6) and EXP (6.4 ± 1.8) patients having significantly higher scores than the controls (0.4 ± 0.9) (each Bonferroni's post hoc $p < .05$), and with EXP patients showing poorer adjustment than NOR patients (Bonferroni's post hoc $p < .05$). The EXP patients showed significant deterioration in psychopathology from preadolescence to adolescence (paired Student's $t = -2.67$, df = 7, $p = .03$). NOR patients showed no such further deterioration.

Effects of Chronic Neuroleptic Treatment

As noted in Methods, 14 (7 NOR and 7 EXP) of the above 22 patients underwent a 6-month treatment trial beginning with 10 mg haloperidol/d for the first 4 weeks, and continuing with ⩾5 mg haloperidol or equivalents/d for a full 26-week period. SAPS and SANS rating were collected periodically during the 6-month period.

Symptomatic Presentation at Beginning of Oral Neuroleptic Trial (Day 1). Twenty-four hours following the first 5-mg dose of haloperidol, day 1 SAPS scores were significantly higher in the EXP group (49.7 ± 17.7) when compared with the NOR group (25.6 ± 14.5) ($t = 2.79$, df = 12, $p = .02$). SANS scores were also significantly higher in the EXP group (40.7 ± 12.8) vs the NOR group (20.1 ± 13.2) ($t = 2.96$, df = 12, $p = .01$) (Table 2).

Differences in Symptoms and Patterns of Response in NOR and EXP Psychotics During a 6-Month Neuroleptic Trial

Between the NOR and EXP groups there was a significant difference with respect to patterns of change in SAPS scores (RMANOVA F = 9.57, df = 13,156, $p < .01$) from day 1 throughout the 6 months of treatment. The EXP group showed greater percentage improvement of positive symptoms (76.6 ± 42.7%) than the NOR group (7.2 ± 66.2%) ($t = 2.331$, df= 12, $p < .04$). There was also a significant between-group difference in patterns of SANS scores (RMANOVA F = 4.01, df = 13,156, $p < .01$) during the extended treatment period, but this change appeared to be related to the deleterious effect of higher neuroleptic dose associated with the NOR patients' negative symptoms (see below).

Normally-Expanding Ventricle Psychotics (NOR) (n = 7). NOR psychotics showed no significant reduction of psychotic symptoms monitored with serial SAPS during the entire 6-month treatment period (RMANOVA F = 0.43, df = 13,78, $p = .95$) (Figure 3A).

In contrast, there were changes in SANS scores during the 6-month period of treatment (RMANOVA F = 7.28, df = 13,78; $p < .01$). As illustrated in Figure 3A, following an initial decrease during the first 4 weeks of neuroleptic treatment (in parallel with a modest reduction in SAPS), the SANS subsequently increased progressively until week 22 of treatment, and then fell back associated with neuroleptic dosage reduction.

The likely source of the significant increase in the SANS scores during this 6-month period appears to be the result of open clinical efforts after week 8 to treat the nonresponsive psychotic symptoms (monitored by SAPS) with increasing neuroleptic doses. During this period, mean doses of haloperidol equivalents were increased from 9 to 14 mg/d. At week 24, dosage was reduced to 12 mg/d, accompanied by a concomitant reduction of SANS scores (Figure 3B). Throughout this 18-week period of open dose adjustment, SANS scores were highly correlated positively with the neuroleptic dose in haloperidol equivalents ($r_p = 0.90$, $p < .01$).

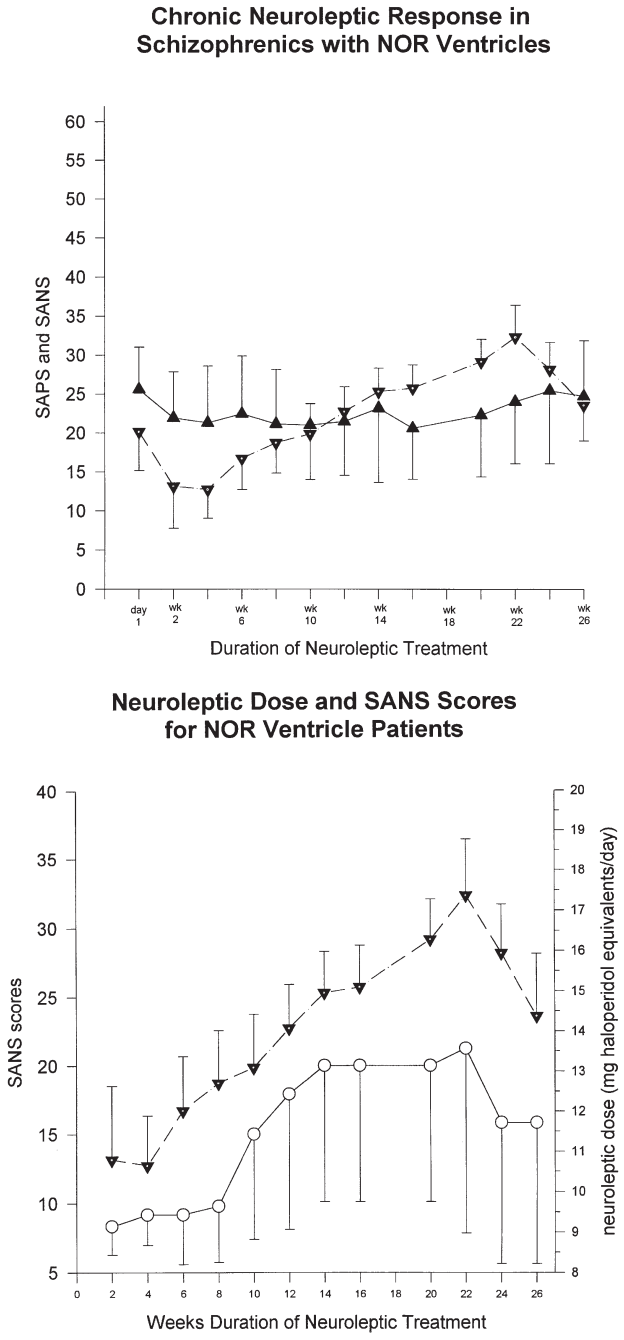

Figure 3. (Top) Chronic neuroleptic response: SAPS (▲) and SANS (▼) scores (mean ± SE) of NOR ventricle (n = 7) patients from day 1 through week 26 of haloperidol equivalent treatment. (Bottom) Correlation between increase in SANS (▼) scores (mean ± SE) and daily haloperidol equivalent dose (○) (mean ± SE) in NOR ventricle (n = 7) patients from day 1 through week 26 of haloperidol equivalent treatment.

Expanding Ventricle Psychotics (EXP) (n = 7). The delayed responsiveness (Garver et al. 1988) of this new cohort of expanding ventricle psychotics (EXP) over the course of the first 26 weeks of neuroleptic treatment is illustrated in Figure 4, and is supportive of hypothesis 3. Following the initial 5-mg dose of haloperidol, significant further reduction of SAPS scores continued until at least week 8 (RMANOVA F = 16.05, df = 4,28, $p < .01$).

In contrast, SANS scores showed an initial trend toward decrease (day 1 to week 4) (RMANOVA F = 23.0, df = 2,12, $p = .09$), which paralleled the delayed reduction of SAPS scores. Thereafter, SANS scores showed no further decrease from weeks 4 to 26 (RMANOVA F = 0.19, df = 11,66, $p = .99$); the EXP patients evidenced a persistent "trait-like" negative symptomatology. The mean dose of medication administered to the drug-responsive EXP psychotics from week 4 to 26 was lower than that received by the neuroleptic-resistant NOR psychotics, ranging from 6 to 9 mg/d during the 5-month period. Mean open label haloperidol equivalent dose during week 5 to week 26 was 6.2 ± 1.7 mg/d in the EXP patients and 11.0 ± 8.8 mg/d in the NOR patients. Dose and SANS symptoms failed to show meaningful correlations ($r_p = -0.46$, $p = .14$) in the EXP psychotics during this extended treatment period.

DISCUSSION

A large number of cross-sectional studies have contrasted ventricular brain ratio (VBR) or ventricular areas of patients with schizophrenic-like illness to that of

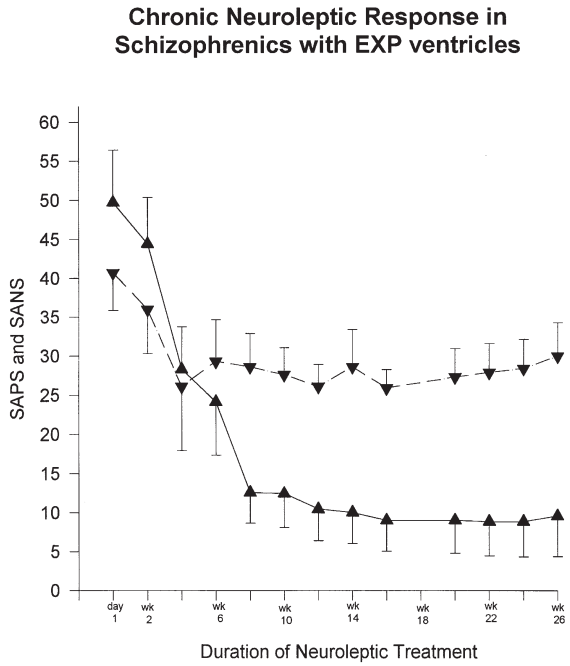

Figure 4. Chronic neuroleptic response: SAPS (▲) and SANS (▼) scores (mean ± SE) in EXP ventricle (n = 7) patients from day 1 through week 26 of haloperidol equivalent treatment.

control comparison groups. Virtually all comparisons which had sufficient power to detect differences found that schizophrenic VBRs or areas of ventricular size were significantly larger in the schizophrenics than in controls. A recent meta-analysis of such cross-sectional studies by Daniel et al. 1991 found the distribution of VBR or ventricular size was indeed different in patients and controls, but that the distribution of VBR size in each population was not inconsistent with that which would be expected of a normal (Gaussian) distribution. It is clear that ventricular size alone cannot discriminate two or more patient populations within the schizophrenic-like psychoses.

However, several investigations have utilized serial VBR measurements in order to determine whether there might be differences in the rate of brain loss and/or ventricular expansion in patients with schizophrenic-like psychoses. Nasrallah et al. (1986), Kemali et al. (1989), Woods et al. (1990), and Jaskiw et al. (1994) reported apparent progressive ventricular enlargement in some, but not in all schizophrenics. Although most of the studies have shown at least a few patients with rapidly changing areas/volumes, the mean change in VBRs or ventricular volumes has only twice (Kemali et al. 1989; Woods et al. 1990) been greater than the error of the method. A meta-analysis of such data however, reveals that the rate of VBR increase (not the VBR itself) does not fit a normal distribution pattern, but resembles a bimodal pattern, with one group of patients showing a rate of change within the error of the method, and another group of patients showing a excessive rate of increase substantially outside of the method's error. Thus, there appears to be a bimodality of the rate of change of VBR (Knoll et al. 1998).

The error of the method has been reduced by at least a magnitude with the recent use of serial MRI evaluations of patients and controls. The recent report of Nair et al. (1997), demonstrates that an error of less than 2% in the estimate of ventricular volume is now feasible. Such reduction of error has set the stage for serious reevaluation of brain and ventricular change during schizophrenic-like illnesses. Nair et al. (1997) described the distribution of ventricular rate of change in schizophrenic-like patients to be significantly different than would be expected from a normal (Gaussian) distribution. Using cluster analysis (also used in this expanded sample), Nair et al. (1997) determined that there were two clusters or two groups, each normally distributed. Two such clusters or groups suggest two separate patient populations: one with a rate of ventricular expansion considerably greater than the other. A rapidly expanding ventricle subgroup of schizophrenic-like patients could be delineated for study from the relatively non-expanding ventricle schizophrenias studied here. Furthermore, a recent reanalysis of the DeLisi et al. 1997 data indicates that non-normal distributions are present for rates of change of the right and left cortexes and for right ventricle (and a trend for left ventricle), with ~20% of patients showing a brain atrophic, ventricular expansive psychotic disorder (Garver et al. 1998).

Such bimodal distributions of data relevant to psychosis clearly suggest separate patient populations or endophenotypes related to ventricular stability/instability nested within the schizophrenia syndrome. We have previously described still another endophenotype of psychosis, a "dopamine psychosis": a group of patients with schizophrenic-like illness occupying an upper mode of a bimodal distribution of the metabolite of dopamine (homovanillic acid) in the plasma of drug-free psychotic patients, and have characterized their illness course, their responsiveness to medication, and their family patterns of illness (Garver et al. 1997).

Herein, we have characterized differential aspects of illness course, and of responsiveness to medication in these non-dopamine psychotics, themselves separated on the basis of rate of ventricular expansion. The atrophic psychosis with expanding cerebral ventricles has shown a pattern of progressive early adolescent impairment of interests, of peer relationship and of withdrawal (negative symptoms), differentiating the future atrophic psychosis endophenotype from a more static ventricle psychosis with relative stability of ventricular volumes and clinical impairments. In the atrophic endophenotype, such negative symptoms appear to progress as the illness progresses and are resistant to amelioration by conventional psychotics. Using serial VBRs, Davis et al. (1998) has recently reported that such an expanding ventricle psychosis is also associated with a profound impairment of the will to self-care in chronic schizophrenic patients in their 60s and 70s, who required continuous custodial care, and evidence a non-Alzheimer's dementia at post-mortem examinations.

There is no evidence that the rapid increase in ventricular size found in atrophic patients is limited to a period surrounding onset of the illness, as suggested by some investigators (Lieberman et al. 1996). The slope of the RVE and age is not negative, as would be anticipated if ventricular expansion occurred primarily at an early age at the onset of psychosis, but mildly (although insignificantly) positive in the EXP psychoses. Cross-sectionally, it is striking that 88% of the variance in ventricular volume TVV_2 can be accounted for by an age-associated, apparently continuously active atrophic process in the EXP psychosis group. In the NOR group, only 31% of the variance in TVV_2 could be accounted for by age. For the NOR group, the greater part of the variance in ventricular size must arise from other sources, such as genetic factors, diet, anomalies of neurodevelopment and/or injury.

There is as yet no direct evidence of frank degeneration in the EXP psychosis. A series of investigations are presently underway to determine the etiology(ies) of

the atrophic process, including studies of lipid peroxidation, of neurotrophic deficiencies, and of autoimmune phenomenon (Knoll et al. 1998). It remains possible that there is simply a progressive packing of neuropile associated with progressive volumetric reduction of brain and with ventricular expansion. It is also possible that the actual rates of ventricular enlargement in the EXP patients may be exaggerated in association with state changes in the brain and ventricles. Apparent rates of ventricular expansion between periods of acute psychotic decompensation and during a subsequent period of partial remission could be exaggerated if acute decompensations were themselves associated with brain expansion. Such increases in cerebral volumes might be associated with inflammatory immunologic reactions, with brain edema, and with compression of ventricles during acute psychotic reactions in EXP patients. Such state-associated changes in ventricular volumes could account for the relatively unsustainable rates of ventricular expansion estimated from index admissions (in decompensated states) to periods of partial recovery in EXP patients. Investigations concerning the nature of the process(es) which may result in both acute state-related changes and in sustained, progressive brain and ventricle changes are clearly necessary.

With respect to the normally expanding ventricle psychosis (NOR), the striking clinical feature is the relative absence of major negative symptoms. Our sample also demonstrated a relative paucity of positive symptoms, but this may be a skew derived from our relative inability to enter such positive symptom psychotics who are more severely ill into systematic studies. We have observed that highly psychotic patients without prominent negative symptoms are much less likely to agree to participate in research studies. Their active paranoid stance often precludes their ability to trust staff, physicians and hospitals, and renders them hesitant to sign consent for research. Thus, we believe that there is no real indication that NOR, probably neurodevelopmental psychotics, have fewer positive symptoms than atrophic psychotics. We would expect all levels of pathologic severity associated with neurodevelopmental psychosis to depend quantitatively upon how much neuronal migration has failed, and qualitatively upon what circuits (locations) are poorly formed as a consequence of such failure.

The apparent sensitivity to negative symptom development associated with medication increase (in an attempt to treat a treatment-resistant psychotic illness) is also striking in the non-expanding psychosis patients. This sensitivity may contribute to the trend toward the observed greater neuroleptic non-compliance and greater alcohol and/or cocaine use in the non-expanding and compared to the expanding ventricle psychotics.

Limitations of this study are related to the small reference group of controls with respect to ventricular changes, the relative paucity of patients who fully participated in both serial MRIs and systematic (6-month) trials of medication, and in the potential confounds to the rate of ventricular change in the EXP patients potentially introduced by state changes in brain volumes.

In summary, we have provided herein evidence supporting the concept of two separate psychotic illness process related to the ongoing changes (or lack thereof) in ventricular volumes. It is likely that the putative expanding ventricle endophenotype is associated with a degenerative process (Knoll et al. 1998), although the evidence at this point is circumstantial. Another putative endophenotype of psychosis appears to occur without such ventricular expansion, and may be indicative of anatomical anomalies arising in the remote past, probably during neurodevelopment. Still another non-expanding putative endophenotype of psychosis (a third psychosis) is clinically very different, with elevated plasma homovanillic acid and rapid neuroleptic response: a dopamine excess, good prognosis psychosis (Garver 1997; Garver et al. 1997).

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