

Memory-Delineated Subtypes of Schizophrenia: Relationship to Clinical, Neuroanatomical, and Neurophysiological Measures

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Memory performance was examined in patients with schizophrenia to determine whether subgroups conforming to cortical and subcortical dementias could be identified and, if so, whether subgroups differed on clinical, neuroanatomical, and neurophysiological measures. A cluster analysis of California Verbal Learning Test performance classified patients into 3 subgroups. Two groups exhibited memory deficits consistent with the cortical–subcortical distinction, whereas 1 group was unimpaired. Cortical patients tended to be male, and they had earlier illness onset, reduced temporal lobe gray matter, and hypometabolism. Subcortical patients had ventricular enlargement and more negative symptoms. Unimpaired patients had fewer negative symptoms and dorsal medial prefrontal hypermetabolism. The authors conclude that categorizing patients on the basis of memory deficits may yield neurobiologically meaningful disease subtypes.

There is increasing consensus that Kraepelin's conceptualization of schizophrenia as a disorder characterized by disturbed cognition rather than psychotic symptomatology was fundamentally correct (see Sharma & Harvey, 2000, for review). Studies in our laboratory and elsewhere have demonstrated that cognitive abnormalities are evident in patients at the onset of their illness and that these deficits persist following the amelioration of clinical symptoms (Calev, 1984; McKenna et al., 1990; Saykin et al., 1994). Against a background of general cognitive impairment, verbal learning and memory appear to be especially compromised (Binks & Gold, 1998; Heinrichs & Zakzanis, 1998; Saykin et al., 1991). Typically, reduced information encoding and retrieval capacity is the predominant finding, with storage degradation or significant forgetting being less prevalent (Gur, Moelter, & Ragland, 2000; Paulsen et al., 1995). These deficits have been linked to specific physiological abnormalities (Mozley, Gur, Gur, Mozley, & Alavi, 1996), and a similar pattern of impairments has been seen in the unaffected siblings of schizophrenic patients, suggesting that this may be a trait indicator of genetic susceptibility to the illness (Cannon et al., 1994; Lyons et al., 1995).

Schizophrenia is a heterogeneous disorder, however, and the degree of cognitive, clinical, and social dysfunction

varies in different subgroups of patients. Efforts to understand this heterogeneity have led to the development of various schemas to divide patients into subtypes with similar presentations of illness that presumably denote homogeneous pathophysiological processes. Subtyping procedures have included clinical approaches, with patients characterized according to profiles of symptomatology and longitudinal course (Carpenter, Heinrichs, & Wagman, 1988; Castle, Abel, Takei, & Murray, 1995; Crow, 1985; Hill, Ragland, Gur, & Gur, 2001), and cognitive techniques, with patients grouped according to neuropsychological profiles (Goldstein, Allen, & Seaton, 1998; Heinrichs & Awad, 1993; Palmer et al., 1997; Paulsen et al., 1995). To be valid, any subtyping scheme should reflect pathophysiological salient elements of the disorder. The profile of verbal learning and memory performance may therefore be an especially important dimension along which to classify patients.

It is well-known that different neurologic and neuropsychiatric disorders manifest different patterns of learning and memory impairment. Patients with Alzheimer's disease, for instance, exhibit impaired immediate recall, limited retention over time, intrusion errors, and poor recognition performance, suggesting a primary encoding and storage impairment (Kramer et al., 1988). Huntington's patients, in contrast, show comparable deficits in immediate recall but better retention over time, fewer intrusion errors, and improved performance on recognition testing, consistent with a primary retrieval deficit (Kramer, Levin, Brandt, & Delis, 1989; Massman, Delis, Butters, Levin, & Salmon, 1990). These differing profiles of relatively spared and compromised memory components, characteristic of the so-called "cortical" and "subcortical" dementias, respectively, are thought to reflect the different neuroanatomic substrates that are damaged in each case: hippocampal–thalamic areas in Alzheimer's disease and the neostriatal region in Huntington's disease (Massman et al., 1990; Squire, 1992). The validity of this cortical–subcortical distinction is reinforced

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This research was funded in part by the National Institutes of Mental Health Grants MH43880 and MH51117.

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by the fact that other neuropsychiatric disorders that damage these structures also produce similar patterns of memory impairment. Thus, Korsakoff's disorder, which affects the thalamus, produces a memory disturbance similar to that of Alzheimer's disease (Delis et al., 1991), whereas Parkinson's disease produces cognitive impairments resembling those of Huntington's disease (Massman et al., 1990). Similar profiles of impairment are also produced by traumatic lesions to these same brain regions (Crosson, Novack, Trenerry, & Craig, 1988).

The heterogeneity of schizophrenia also extends to the memory domain, and there is evidence to suggest that patients differ in both the severity and the character of their deficits (Paulsen et al., 1995). Using a discriminant function derived from a study of Huntington's and Alzheimer's disease patients (Massman, Delis, Butters, Dupont, & Gillin, 1992), Paulsen and colleagues (Paulsen et al., 1995) found that 50% of their large schizophrenia sample exhibited learning and memory profiles similar to those of patients with a subcortical dementia (i.e., moderately to severely impaired free recall, inconsistent retrieval across learning trials, normal retention across a delay interval, and disproportionate improvement on recognition testing). Another 15% exhibited impairments more characteristic of a cortical dementia (i.e., impaired learning, elevated cued-recall intrusions, and limited ability to benefit from recognition testing). About one third of the sample was relatively unimpaired, a finding that has since been confirmed for a broader range of cognitive domains (Palmer et al., 1997).

The current study examines profiles of memory performance in patients with schizophrenia to determine whether, in fact, patient subgroups that conform behaviorally to cortical and subcortical dementia subtypes can be empirically delineated. If so, are there differences in clinical, neuroanatomical, and neurophysiological measures across these cognitively defined subgroups? Given that different memory deficits are seen in behaviorally and pathologically distinct neuropsychiatric illnesses, our hypothesis was that patients with different profiles of memory impairment would also differ on these other measures. If true, then characterizing patients on the basis of such learning and memory deficits could represent a pathophysiologically meaningful approach to schizophrenia subtyping.

Method

Participants

The sample consisted of 116 patients (67 male, 49 female) with *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; American Psychiatric Association, 1994) diagnoses of schizophrenia and 129 normal controls (72 male, 57 female) enrolled in research protocols at the University of Pennsylvania Mental Health Clinical Research Center. Patients were recruited from both outpatient and inpatient settings and received medical, neurological, and psychiatric evaluations, including the Structured Clinical Interview for *DSM-IV*—Patient version (First, Spitzer, Gibbon, & Williams, 1996). To ensure diagnostic accuracy, we clinically reassessed patients at 6-month intervals following initial intake. There was no history of any disorder or event, other than schizophrenia, that could potentially affect brain function. Healthy

participants were recruited by newspaper advertisement and underwent medical, neurological, and psychiatric (Structured Clinical Interview for *DSM-IV*—Nonpatient version) evaluation (First, Spitzer, Gibbon, & Williams, 1995). Controls were excluded for any history of Axis I psychiatric illness; Axis II diagnosis of schizotypal, schizoid, or paranoid personality disorder; or any medical condition or occurrence, including substance abuse, that could compromise brain function. Informed consent was obtained from all participants at time of enrollment.

Demographically, the two groups differed in their age, $t(243) = 5.18, p < .01$, and education, $t(243) = 7.10, p < .01$; patients were older ($M = 31.6$ years, $SD = 8.6$) than controls ($M = 26.6$ years, $SD = 6.4$) and had fewer years of formal education (patients: $M = 12.7$ years, $SD = 2.3$; controls: $M = 14.7$ years, $SD = 2.0$). However, there was no difference in parental education ($p > .10$), which is a more appropriate measure because schizophrenia may itself affect educational attainment (Resnick, 1992). Gender distribution was the same for the schizophrenia (58% male) and control (56% male) groups ($p > .10$). Handedness evaluation (Raczkowski, Kalat, & Nebes, 1974), however, revealed increased frequency of left- or mixed-handedness (20%) among the patients relative to the controls (3%), $\chi^2(1, N = 190) = 12.77, p < .01$.

The Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1980), the Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1983), and the Scale for Assessment of Positive Symptoms (SAPS; Andreasen, 1984) were completed for all patients at the time of neuropsychological assessment. All ratings were completed by investigators trained to a criterion reliability of .90 (intraclass correlation). BPRS items were summed to form an index of overall psychiatric symptom severity. SANS global items provided summary ratings for five standard subscales: Affective Flattening, Alogia, Avolition–Apathy, Anhedonia–Asociality, and Attention. A summary negative symptom measure averaged all SANS subscale ratings except Attention. SAPS global item ratings were averaged to yield a total positive symptom score in addition to the four subscale measures: Hallucinations, Delusions, Bizarre Behavior, and Formal Thought Disorder. Patients were also subtyped into deficit and nondeficit categories (Carpenter et al., 1988).

Patient Subgroup Formation

Verbal learning and memory were assessed using the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987). In this task, immediate free recall of a 16-item list (List A) is tested over five learning trials. This is followed by a different interference list (List B), after which recall of List A is again tested (short delay). Recall is tested again after a 20-min interval (long delay), followed by a recognition test in which the 16 List A items are interspersed with 28 distracters. The format of the test permits assessment of multiple aspects of learning and memory, including overall recall ability, rate of learning over repeated trials, ability to retain learned material over time, and subsequent item recognition. CVLT performance was used to separate patients into subgroups using a *k*-means cluster analysis. The cluster analysis sorts cases into groups that have the least possible variability within each cluster and the maximum variability between clusters. We examined the three CVLT indices that have been shown to most reliably discriminate among cortical and subcortical dementia patients, patients with affective disorders, and healthy controls (Massman et al., 1992) and that have also been used to differentiate schizophrenia patients (Paulsen et al., 1995). These three CVLT indices were the total number of items correctly recalled over five learning trials, the number of intrusion errors during category-cued recall, and the difference between recognition discriminability and recall

on Learning Trial 5. As noted above, cortical dementia patients have been found to exhibit poor total recall, high numbers of intrusion errors, and impaired recognition relative to healthy controls, whereas subcortical dementia patients exhibit poor recall but with fewer intrusion errors and relative sparing of recognition performance (Massman et al., 1992).

The three CVLT indices were converted to standardized z scores based on our control sample, and the number of clusters was set a priori to three to reflect the theoretical distinction between cortical dysfunction, subcortical impairment, and normal performance. Importantly, no constraints were imposed on the numbers of participants, the mean values of the individual variables, or the profiles of CVLT performance across the three subgroups. That is, nothing was done to yoke the three subgroups to the expected patterns of memory performance. Rather, the data were allowed to empirically define the subgroups to address the question of whether the memory disturbances exhibited by patients with schizophrenia do or do not segregate into theoretically meaningful subsets. If theoretically consistent profiles emerged for the different groups, it would provide further validation of the memory subtyping strategy.

Magnetic Resonance Imaging (MRI)

MRIs were available for a subset of 75 patients (38 male, 37 female) and 74 controls (36 male, 38 female). Axial spin-echo images were acquired on a 1.5-Tesla scanner (GE Signa, Milwaukee, WI) with a repetition time of 3,000 ms and echo times of 30 and 80 ms. Slice thickness was 5 mm, with no interslice gap. Images were processed using methods that have been described previously in detail and will be summarized here. The three-dimensional brain volume was first extracted from surrounding voxels using an automated algorithm (Yan & Karp, 1994a) followed by interactive editing. An adaptive Bayesian algorithm, in which "shading" effects are overcome by modeling the slowly varying mean intensities of different tissue types as cubic B-spline functions, was then iteratively applied to segment gray, white, and cerebrospinal fluid tissue compartments (Yan & Karp, 1994b; Yan & Karp, 1995).

Segmented brains were realigned in three dimensions and resliced in a standard plane parallel to the anterior commissure–posterior commissure (AC-PC) axis. The borders of the left and right whole brain and frontal and temporal lobes were drawn by two investigators using previously described methods (Cowell et al., 1994; Turetsky et al., 1995). Interrater reliabilities (intraclass correlation) for regional brain volumes ranged from .92 to .95. Comparable intrarater reliabilities ranged from .85 to .93. The total number of voxels corresponding to each tissue type within each region-of-interest was multiplied by the voxel size to yield volumetric measures. All image analyses were conducted with raters blind to participant diagnosis, sex, and age.

Positron Emission Tomography (PET) Measures

Contemporaneous ^{18}F -labeled 2-fluoro-2-deoxy-D-glucose (FDG) PET scans were acquired from 47 patients (33 male, 14 female) and 64 controls (37 male, 27 female), permitting assessment of regional cerebral metabolic rate (CMRglu). Details of the PET methodology were presented in Mozley et al. (1996). Briefly, approximately 185 MBq (5 mCi) of FDG were administered intravenously while participants lay with eyes open and ears unoccluded. Arterial samples (250 μl) were taken every 15 s initially and at progressively increasing intervals thereafter. Activity was measured in a dose calibrator after a 3–4 hr decay interval. Image acquisition began after 40 min of FDG uptake. The PET scanner

(UGM Medical Systems, Philadelphia, PA) had a 9-cm axial field of view and average spatial resolution of 5.5 mm near the center of the field. An average of 30 million counts were collected over 50 min, and the data were sorted into 45 transaxial slices with a voxel size of 2 mm³. Projection data were corrected for nonuniform sensitivity, attenuation, and scatter.

PET image analysis procedures were described in detail in Resnick, Karp, Turetsky, and Gur (1993). A set of templates composed of 42 regions of interest (ROIs) was custom fitted to each participant's resliced and reoriented MRI scan by operators who were blind to diagnosis. PET images were resliced along the AC-PC line to correspond with MRI images. MRI-based ROIs were then transposed onto the resliced PET images. The mean counts per pixel in the ROIs were measured automatically, region by region. Counts per pixel for each region, volume averaged across all slices, were computed with interrater reliability greater than .85 (intraclass correlation).

The following ROIs were selected, a priori, for analysis: dorsal lateral prefrontal cortex (DL), dorsal medial prefrontal cortex (DM), superior temporal gyrus (ST), midtemporal gyrus (MT), parahippocampus (PH), hippocampus (HP), amygdala (AM), anterior cingulate gyrus (AC), caudate nucleus (CN), putamen (PT), thalamus (TH), and cerebellum (CB). For each region, the average region-to-whole brain counts per pixel was computed across left and right hemispheres.

Statistical Analysis

Following the memory-based k -means cluster analysis, the resulting patient subgroups were examined for differences on demographic, clinical, neuroanatomic, and neurophysiologic measures. Group differences in descriptive characteristics and clinical symptomatology were assessed by analysis of variance (ANOVA), with paired contrasts between individual patient clusters. For MRI and PET measures, the patient sample was first compared with the control sample, with separate paired contrasts between each patient subgroup and the control group. The different patient subgroups were then compared with each other. All analyses were conducted both with and without age and sex as covariates. Except as noted, the results were the same and are reported only for the model including covariates. Total cranial volume was an additional covariate for the regional MRI analyses. A two-tailed .05 significance level was used throughout, and analyses were limited to the contrasts described here.

Results

Description of Patient Clusters

The cluster analysis produced patient groups containing 21, 36, and 59 participants. The mean values by cluster for the three discriminating variables are presented in Figure 1. Importantly, the profiles of memory performance of the different clusters conformed to expectations concerning the existence of cortical, subcortical, and unimpaired groups. That is, one group ($n = 59$) performed significantly better than either of the other two on free recall ($p < .01$). The patients in this group resembled controls in both their cued-intrusion error rate and their difference score between recognition discriminability and Learning Trial 5. The other two groups were equally impaired on free recall, but one ($n = 21$) made more intrusion errors than the other ($n = 36$; $p < .05$) and was more impaired on the Discriminability

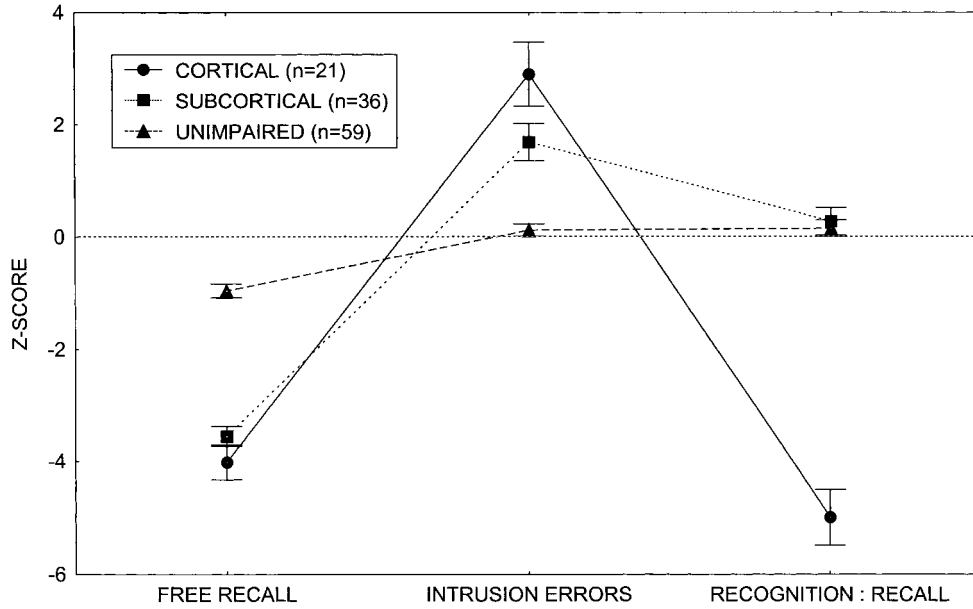


Figure 1. Mean (\pm SE) scores on each of the three cluster-defining variables for each of the three resulting patient clusters. Values are standardized z scores relative to the control sample, which has a mean of 0 and a standard deviation of 1.

Trial 5 difference score ($p < .01$). The two impaired groups were thus distinguished by profiles characteristic of the cortical ($n = 21$) versus subcortical ($n = 36$) memory deficits observed in patients with Alzheimer’s versus Huntington’s disease. The performances of the three patient groups and controls on primary CVLT indices are presented in Figure 2. It is apparent that the cortical patients rapidly forgot the learned material, whereas the subcortical patients

retained what they learned and achieved near-normal recognition performance, despite their recall deficits.

Differences in Demography and Clinical Symptomatology

Demographic information for the three patient clusters are presented in Table 1. Male and female patients were not

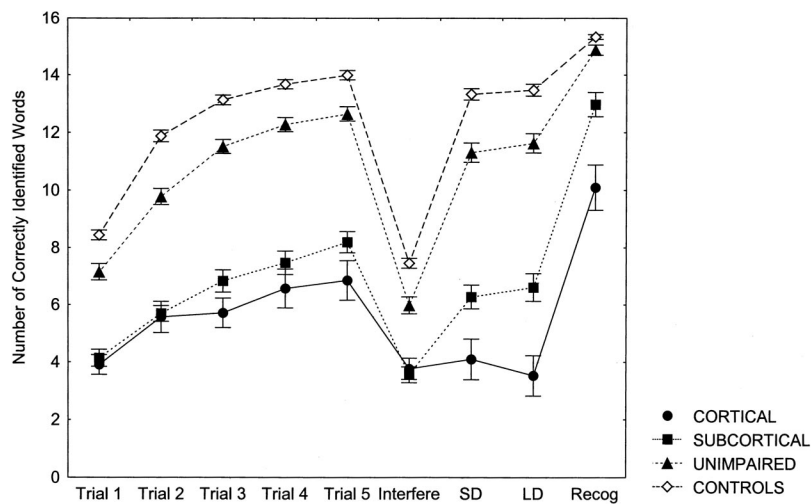


Figure 2. Mean (\pm SE) California Verbal Learning Test performance scores across trials. Both cortical and subcortical patients are impaired on immediate recall (Trials 1–5), but only cortical patients have worse recall following a delay and poor recognition (Recog) performance. Interfere = interference; SD = short delay; LD = long delay.

Table 1
Clinical-Demographic Characteristics of Schizophrenia Patients With Cortical, Subcortical, or Unimpaired Profiles on the California Verbal Learning Test

Variable	Cortical (n = 21)		Subcortical (n = 36)		Unimpaired (n = 59)	
	M	SD	M	SD	M	SD
Sex (% male)	81 ^{a,b}		53		53	
Age	28.1 ^b	8.4	33.1	8.2	32.0	8.6
Age of onset	21.2 ^a	5.7	23.5	6.1	25.1	7.7
Duration of illness (years)	7.0	6.3	9.6 ^a	6.7	6.9	6.3
% medicated	60		67		61	
Dosage (cpz mg equivs)	245.6	319.0	273.5	397.2	219.9	311.4

Note. cpz mg equivs = chlorpromazine milligram equivalents.

^a Contrast versus unimpaired group, $p < .05$. ^b Contrast versus subcortical group, $p < .05$.

equally distributed across the clusters. Rather, the cortical group had a greater proportion of male patients than either the subcortical, $\chi^2(1, N = 164) = 4.5, p = .03$, or the unimpaired group, $\chi^2(1, N = 187) = 5.2, p = .02$. The cortical group was also significantly younger than the subcortical group, $F(1, 55) = 4.70, p = .03$, and developed schizophrenia at an earlier age than the cognitively unimpaired patients, $F(1, 78) = 4.51, p = .04$. Because men typically develop schizophrenia at a younger age than women, this earlier age of onset might simply reflect the greater preponderance of men in the cortical group. We therefore repeated the analysis for male patients only. In this smaller subsample, the cortical group still had a mean age of onset that was 2.8 years earlier than the unimpaired group, but this was now reduced to a statistical trend, $F(1, 46) = 2.78, p = .10$. Subcortical patients had a longer duration of illness than the unimpaired patients, $F(1, 93) = 4.06, p = .04$. However, there were no differences in the relative proportions of new onset, unmedicated, or left-

handed patients across the groups, or in average lifetime medication dosage in chlorpromazine equivalents.

Standard clinical rating scale measures for the three groups are shown in Table 2. The two memory-impaired groups both contained a greater proportion of deficit subtype patients than the unimpaired group, which was composed almost entirely of the nondéficit subtype. They both also had elevated ratings on the Alogia and Attention subscales of the SANS and on the Formal Thought Disorder subscale of the SAPS. However, they differed on other clinical measures. Subcortical patients exhibited the greatest overall psychiatric impairment, as indicated by their BPRS scores, which were significantly higher than those of unimpaired patients. They also exhibited more pervasive negative symptomatology, having elevated ratings on all five SANS subscales, relative to unimpaired patients, and greater Affective Flattening than the cortical group.

In contrast to these robust differences in negative symptomatology, there was a relative paucity of group differ-

Table 2
Clinical Rating Scale Profiles of Schizophrenia Patients With Cortical, Subcortical, or Unimpaired Profiles on the California Verbal Learning Test

Variable	Cortical (n = 21)		Subcortical (n = 36)		Unimpaired (n = 59)	
	M	SD	M	SD	M	SD
% with primary deficit symptoms	43 ^a		39 ^a		14	
Brief Psychiatric Rating Scale	39.7	12.1	44.0 ^b	8.5	38.9	9.8
Negative Symptoms Scale						
Global	2.2 ^a	1.3	2.5 ^a	0.8	1.6	1.0
Affect	1.9 ^c	1.7	2.6 ^a	0.8	1.7	1.3
Alogia	2.5 ^a	1.4	2.1 ^a	1.3	1.3	1.3
Avolition–Apathy	1.9	1.5	2.5 ^a	1.2	1.5	1.5
Anhedonia–Asociality	2.9	1.4	3.2 ^b	0.9	2.7	1.3
Attention	1.9 ^a	1.6	1.9 ^a	1.1	0.8	1.1
Positive Symptoms Scale						
Global	1.9	1.1	1.9	0.9	1.7	0.9
Hallucinations	2.0	1.5	1.7	1.6	2.0	1.6
Delusions	2.1 ^{b,c}	1.4	2.9	1.4	3.0	1.4
Bizarre Behavior	1.2	1.4	1.1	1.2	0.7	1.2
Formal Thought Disorder	2.2 ^a	1.5	1.9 ^b	1.5	1.3	1.3

^a Contrast versus unimpaired group, $p < .01$. ^b Contrast versus unimpaired group, $p < .05$. ^c Contrast versus subcortical group, $p < .05$.

ences on measures of positive symptomatology, aside from the increase in Formal Thought Disorder among the cognitively impaired patients. There were no differences in total SAPS score, and the cognitively impaired patients were not rated higher on any of the other individual subscales. Surprisingly, the only other significant difference was a relative absence of Delusions among the cortically impaired patients compared with both the subcortical and unimpaired patient groups.

Neuroanatomic Differences

Consistent with numerous previous investigations, the schizophrenia patients in this sample had enlarged ventricles, independent of age, sex, or cranial volume, $F(1, 144) = 5.68, p = .02$. However, in separate paired contrasts with the control group, significant ventricular enlargement was seen for the subcortical, $F(1, 91) = 5.20, p = .02$, and unimpaired $F(1, 110) = 4.54, p = .04$, subgroups, but not for the cortical, $F(1, 81) = 1.22, p = .27$, subgroup. Mean ventricular volume was largest, overall, for subcortical patients (see Figure 3).

The pattern of effects was different when brain parenchymal measures were examined. For the whole brain, right- and left-hemisphere gray- and white-matter volumes were entered as dependent variables in a single multivariate analysis of variance (MANOVA), with tissue type (gray vs. white) and hemisphere as within-subject factors and age, sex, and cranial volume as covariates. Although there was no overall reduction in brain volume among patients, there was a significant diagnosis by tissue type, $F(1, 147) = 8.86,$

$p < .01$, and hemisphere, $F(1, 147) = 5.13, p = .02$, interactions. Patients had relatively less gray matter than controls, with volume reduction being more pronounced on the left side. This gray matter deficit, however, was not apparent across the three patient subgroups. In individual contrasts with the control group, it was most prominent for the cortical subgroup, $F(1, 84) = 9.59, p < .01$, with a smaller but still significant abnormality evident in the unimpaired group, $F(1, 113) = 5.76, p = .02$. The subcortical group, though, was no different than the control group, $F(1, 94) = 1.54, p = .22$.

When frontal and temporal lobe volumes were considered, rather than whole brain volumes, a similar pattern of effects was seen. Diagnoses by tissue type interactions were significant in both frontal, $F(1, 146) = 11.99, p < .01$, and temporal, $F(1, 146) = 6.15, p < .01$, regions, consistent with a diffuse gray matter volume reduction among patients. Separate contrasts of each patient subgroup versus control group revealed proportional gray matter reductions in both frontal and temporal lobes for cortical and unimpaired patients. Subcortical patients also had significant deficits in the frontal lobe, $F(1, 93) = 6.08, p = .02$, but their temporal lobe gray-matter volumes were preserved, $F(1, 93) = 0.80, p = .37$. Consistent with this, there was a significant difference between cortical and subcortical patients in the relative amount of gray matter in the temporal lobes, $F(1, 29) = 4.44, p = .04$, which was not mirrored in the frontal lobes, $F(1, 29) = 1.82, p = .19$ (see Figure 3). These MRI findings suggest a double dissociation between the cortical and subcortical groups, with the subcortical group having

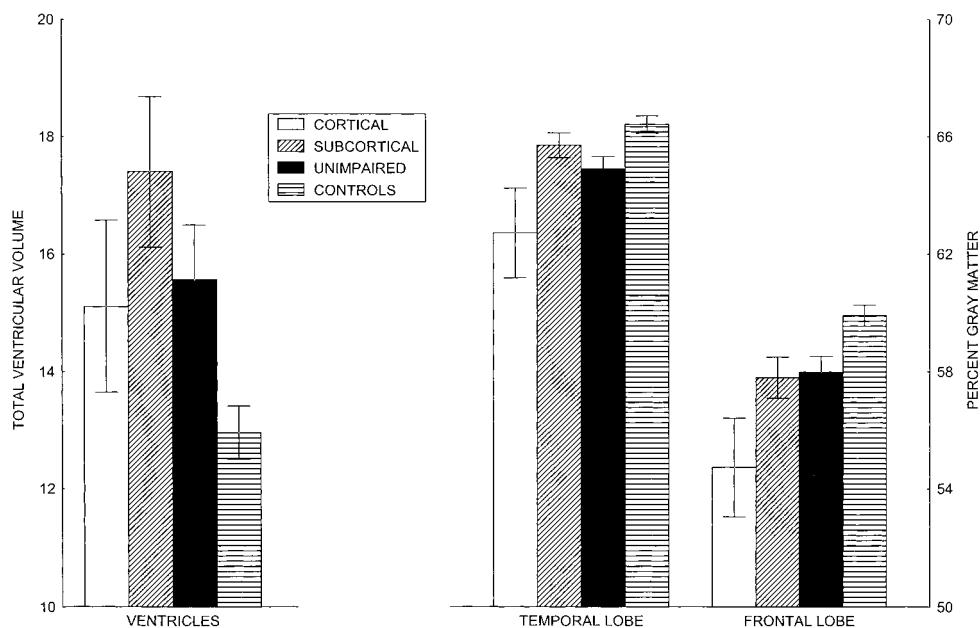


Figure 3. Left: Mean (\pm SE) ventricular volume, measured in milliliters. Right: Mean (\pm SE) percent gray matter volume in temporal and frontal lobes. Subcortical patients have largest ventricular volumes, whereas cortical patients have reduced percent gray matter.

enlarged ventricles but relatively normal gray and white matter volume distribution, especially in the temporal region, and the cortical group having the opposite pattern. Unimpaired patients exhibited both abnormalities but each to a milder degree than the significantly affected cognitively impaired patients. This suggests that the unimpaired group may, in fact, be composed of two sets of individuals who exhibit milder cortical or subcortical impairments. To test this hypothesis, we repeated our cluster analysis using only the group of 59 unimpaired patients. We observed, again, a separation into subgroups exhibiting profiles characteristic of cortical ($n = 27$) or subcortical ($n = 16$) memory deficits, with 16 patients remaining unimpaired.

Differences in Regional Cerebral Metabolism

When the patient sample was considered in its entirety, abnormal CMRglu was evident in only one region, DM, $F(1, 107) = 5.39, p = .02$. Surprisingly, patients had relatively greater resting metabolism in this area. The patterns of abnormal metabolic activity were not the same, though, across the three subgroups (see Figure 4). Although unimpaired patients exhibited an isolated increase in DM metabolism, as observed for the sample as a whole, $F(1,$

$84) = 7.46, p < .01$, neither of the two cognitively impaired groups did. Subcortical patients exhibited no significant metabolic abnormalities. Cortical patients, in contrast, exhibited abnormalities in each of the following regions: ST, $F(1, 70) = 6.99, p = .01$; MT, $F(1, 70) = 6.00, p = .02$; HP, $F(1, 70) = 7.21, p = .01$; TH, $F(1, 70) = 4.80, p = .03$; and PT, $F(1, 70) = 4.07, p = .05$. Exclusion of age and sex as covariates reduced the statistical significance of each of these findings to a trend level ($.05 < p < .10$). However, in all cases, region-whole brain metabolism remained lower in the cortical subgroup.

Discussion

These findings provide strong support for the premise that patients with schizophrenia can be meaningfully categorized into subtypes based on the profile of memory deficits that they exhibit. Those patients with memory impairments may be further grouped according to whether they exhibit a pattern of abnormalities consistent with either a cortical or a subcortical dementia, as described in other well-characterized neuropsychiatric disorders. That is, there does not appear to be a single profile of memory deficits in schizophrenia representing a continuum along which individual

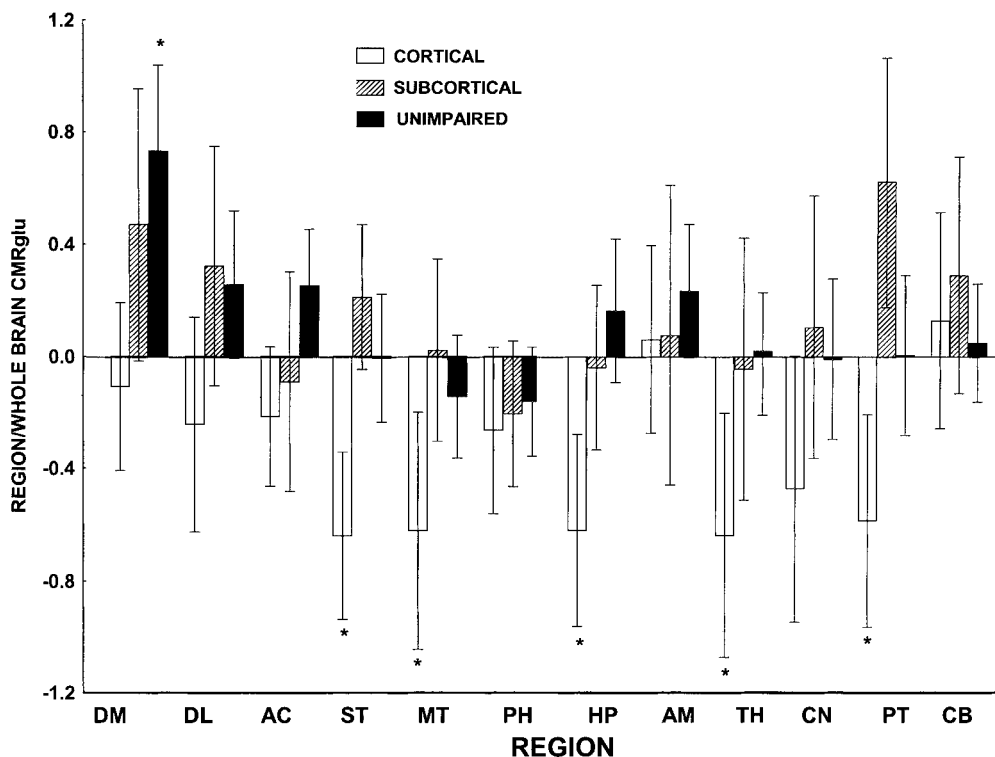


Figure 4. Region/whole brain cerebral metabolic rate ($\pm SE$) for individual brain regions of interest. Data for each patient cluster are plotted as standardized z scores relative to the control sample, which has a mean of 0 and a standard deviation of 1. Significant differences between patient groups and controls are noted by asterisks. DM = dorsal medial prefrontal cortex; DL = dorsal lateral prefrontal cortex; AC = anterior cingulate; ST = superior temporal gyrus; MT = middle temporal gyrus; PH = parahippocampal gyrus; HP = hippocampus; AM = amygdala; TH = thalamus; CN = caudate nucleus; PT = putamen; CB = cerebellum.

patients can be placed. Rather, there are categorical differences in the nature of the cognitive deficit, permitting segregation of patient subtypes. In this respect, our findings, derived empirically from the neurobehavioral data without prior constraints, provide confirmation that the suggested cortical–subcortical distinction may be appropriately applied to schizophrenia (Paulsen et al., 1995). That such a patient categorization may have much broader import is demonstrated by the consistent differences in clinical presentation, neuroanatomy, and neurophysiology observed across these cognitively derived subtypes. These differences clearly suggest that different pathophysiologic processes may underlie the observed cognitive differences.

The similarity to cortical and subcortical dementia extends to the magnitude as well as the profile of these memory deficits. In the study by Massman et al. (1992), Alzheimer's and Huntington's patients both had free-recall scores that were ~ 3.5 standard deviations below that of age-matched control participants. Huntington's patients were ~ 1 standard deviation above normal on cued intrusion errors, whereas Alzheimer's patients were ~ 3 standard deviations above normal. These are remarkably similar to the levels of impairment seen in our two cognitively impaired subgroups. Only on the third measure, the Discrimination Trial 5 difference score, do the schizophrenia patients differ. Whereas Huntington's patients performed ~ 2.5 standard deviations above and Alzheimer's patients ~ 1 standard deviation below normal on this measure, the two impaired schizophrenia groups performed at much lower levels. However, this is likely to reflect, at least in part, a ceiling effect in our data relative to Massman et al.'s. The younger control participants in our study performed at near-perfect levels on the discrimination task, making it difficult for the patients to score substantially better, even with excellent scores. What is more important is that the difference between the two impaired schizophrenia groups on this measure is again comparable with the difference between Alzheimer's and Huntington's patients.

The cortical subtype, representing 18% of our patient sample, was the most distinctive. These patients were predominantly male, younger, and with a relatively earlier age of illness onset. Their clinical profile, which included greater levels of Formal Thought Disorder, Attentional Disturbance, and Alogia accompanied by a relative absence of Delusions and less Affective Flattening, is reminiscent of the *DSM-IV* (American Psychiatric Association, 1994) disorganized schizophrenia subtype. The neuroimaging data suggest that this patient subgroup can be uniquely characterized by structural and functional pathology in the temporal lobe. They, and they alone, exhibited a relative reduction in temporal gray matter volume and hypometabolism in temporal lobe structures linked to language and memory processes (ST, HP). As these patients were younger and less chronic than the subcortical group, these deficits are unlikely to be related to any progressive neurodegeneration associated with the illness state. Nor are they likely to be nonspecific markers of illness severity, as BPRS ratings were no different for this group than for unimpaired patients. Rather, they are consistent with the idea that focal

temporal lobe pathology underlies the cognitive impairment observed in a subgroup of patients with a distinctive variant of schizophrenic illness.

The subcortical subtype was more prevalent (at 31%) and exhibited a clinical profile that included relatively diffuse positive symptoms, the greatest degree of total psychiatric impairment, and the highest level of negative symptomatology. This behavioral constellation of a subcortical-type dementia and more pronounced negative symptoms is suggestive of underlying frontal–striatal regional pathology. The ventricular enlargement and isolated frontal lobe gray matter reductions observed in these patients are consistent with this suggestion. In contrast to the cortical subgroup, there was a relative absence of any evidence of temporal lobe pathology in this subgroup. The idea that there are distinct schizophrenic subtypes, which differ with respect to the degree of structural and functional impairment in the temporal lobe, is consistent with previous observations that both electrophysiologic and volumetric temporal lobe abnormalities are subtype specific (Turetsky, Colbath, & Gur, 1998; Turetsky et al., 1995). This may explain some of the inconsistencies that exist in findings from aggregate studies of patients with schizophrenia.

One caveat must be noted. Although the three patient groups did not differ in either the percentage of patients who were medicated at the time of testing or their average lifetime medication dosage (see Table 1), the subcortical group did have a longer duration of illness and so may have had greater cumulative exposure to neuroleptics. We cannot, therefore, dismiss the possibility that the iatrogenic effects of antipsychotic medications may have contributed to some of these findings. In particular, the greater Affective Flattening observed in the subcortical group might be a reflection of greater neuroleptic exposure. It is unlikely, though, that neuroleptic use alone could completely explain the unique pattern of deficits observed in the subcortical group. Indeed, given that the one consistent effect of antipsychotic medications on volumetric MRI measures is enlargement of the subcortical nuclei (Gur et al., 1999), we would expect the subcortical patients to have smaller, rather than larger, ventricles. So, if anything, our estimates may be overly conservative.

A conceptual alternative to the idea of discrete patient subtypes is one that similarly posits that different dimensions of clinical and cognitive abnormality arise from different neuropathological substrates, but which assumes that these different domains of impairment can be more or less present in all patients. Such an approach has, for example, been applied to neurobiological investigations of the psychotic, negative, and disorganized domains of schizophrenic symptomatology (Liddle et al., 1992). It is interesting to note, in this regard, that the positive–negative distinction, from which this tripartite model was derived, was initially conceptualized as describing distinct subtypes of schizophrenia, rather than independent but overlapping processes. Although subsequent work altered this conceptualization, the original grouping criteria provided the initial framework for this endeavor, and the subtype distinction persists in a more refined version as deficit versus nondeficit subtypes

(Carpenter et al., 1988). Similarly, we cannot completely rule out the possibility that the cortical versus subcortical subtype distinction is really a question of the relative degrees of impairment in different processes affecting different neural substrates. This remains an issue that is open to debate and which will only be answered by further investigation.

Another alternative interpretation of the patterns of deficits seen in patients is that there is only a single dimension of memory impairment, with the cortical patients being most severely affected and the unimpaired patients being least affected. In this case, the differences in the CVLT measures across the groups might simply reflect a hierarchy in the sensitivity of the measures to different degrees of impairment; that is, recall might be more sensitive to any deviations from normal, but recognition being sensitive only to more severe impairments. A similar argument has been raised in other studies of cognitive heterogeneity in schizophrenia. In an analysis that was limited to neuropsychological data, Goldstein and colleagues (1998) suggested that differences among patients with schizophrenia reflected a combination of both distinct subtypes and a continuum of general impairment. Although it is true that the CVLT data in our study could also be seen as reflecting a continuum of ability levels, our MRI results do not support an interpretation based on a single continuum. If that were the case, we would not expect to see a double dissociation between the subcortical ventricular and cortical temporal lobe gray matter abnormalities. Moreover, we would expect the cognitively unimpaired patients to have less structural and functional deficits, overall, than either of the impaired patient groups. Contrary to these expectations, the unimpaired patients had both greater ventricular enlargement than the cortical patients and greater temporal lobe gray matter reductions than the subcortical patients. This argues strongly for the validity of the cortical–subcortical distinction in schizophrenia.

The unimpaired group, which comprised half of this patient sample, may not therefore constitute a distinct subgroup, but rather it may be a composite mixture of patients with less severe cognitive and neurobiological manifestations compared with the other two cognitive subtypes of schizophrenia. This is supported by our observation that the *k*-means cluster analysis when applied only to the unimpaired patient group also elicits two discrete profiles, consistent with mild cortical and subcortical memory impairments. In this sense, our findings are entirely consistent with those of Goldstein et al. (1998). Although we find clear evidence to support distinct subtypes, we also find evidence of heterogeneity on the basis of varying severity within each subtype. In this regard, our findings are also consistent with those of Palmer et al. (1997), who noted the existence of a large cohort of patients characterized by an absence of neuropsychological deficits and, in particular, fewer negative symptoms.

In sum, this study suggests that a subtyping strategy based on a profile of verbal learning and memory impairments may help to identify subgroups of schizophrenic patients who differ in underlying neurobiological measures.

In particular, it suggests that patients with a cortical dementia profile exhibit brain abnormalities that are preferentially localized to temporal regions, whereas those with a subcortical dementia profile have abnormalities that are restricted more to the frontal–striatal area. Such a distinction could be an important first step in efforts to elucidate the specific neural mechanisms of the disorder. Further investigation of this classification scheme appear to be warranted. Questions that remain include the longitudinal stability of the deficit profiles, the distinction between discrete subtypes and overlapping subprocesses, the relationship to symptomatic treatment response, and in particular the cognitive and neurobiological course of those patients who present initially with relatively little impairment.

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Received July 26, 2001

Revision received January 24, 2002

Accepted March 11, 2002 ■