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# A comprehensive assessment of gray and white matter volumes and their relationship to outcome and severity in schizophrenia

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**Preliminary data suggest an association of posterior cortical gray matter reduction with poor outcome in schizophrenia. We made a systematic MRI assessment of regional gray and white matter volumes, parcellated into 40 Brodmann's areas, in 104 patients with schizophrenia (51 with good outcomes, 53 with poor outcomes) and 41 normal comparison subjects, and investigated correlations of regional morphometry with outcome and severity of the illness. Schizophrenia patients displayed differential reductions in frontal and to a lesser degree temporal gray matter volumes in both hemispheres, most pronounced in the frontal pole and lateral temporal cortex. White matter volumes in schizophrenia patients were bilaterally increased, primarily in the frontal, parietal, and isolated temporal regions, with volume reductions confined to anterior cingulate gyrus. In patients with schizophrenia as a group, higher illness severity was associated with reduced temporal gray matter volumes and expanded frontal white matter volumes in both hemispheres. In comparison to good-outcome group, patients with poor outcomes had lower temporal, occipital, and to a lesser degree parietal gray matter volumes in both hemispheres and temporal, parietal, occipital, and posterior cingulate white matter volumes in the right hemisphere. While gray matter deficits in the granular cortex were observed in all schizophrenia patients, agranular cortical deficits in the left hemisphere were peculiar to patients with poor outcomes. These results provide support for frontotemporal gray matter reduction and frontoparietal white matter expansion in schizophrenia. Poor outcome is associated with more posterior distribution (*posteriorization*) of both gray and white matter changes, and with preferential impairment in the unimodal visual and paralimbic cortical regions.**


*Keywords:* Schizophrenia; Poor outcome; Gray matter; White matter; Illness severity; MRI

## Introduction

Schizophrenia is a complex diagnostic entity characterized by a multitude of dauntingly variable and often subjective signs and symptoms. The broad clinical picture of schizophrenia is arguably paralleled by a like diversity of pathological and neuroimaging findings. Indeed, practically every brain region has at some point been implicated in its pathophysiology (Harrison, 1999; Shenton et al., 2001). Not surprisingly, there have been ongoing efforts to narrow this protean semiotics into more inclusive syndromes and readily identifiable endophenotypes — efforts that date back to Kraepelin and reached apotheosis with Karl Leonhard's meticulous, if counterproductive, classification of endogenous psychoses (Jablensky, 2006). The thinking goes that based on the relative preponderance of these diverse clinical manifestations, several more homogeneous schizophrenic subtypes would be delineated and genetically affixed. Longitudinal outcome and severity of the illness have not been eschewed by this classificatory attention, leading to narrower, partially overlapping (Nakaya and Ohmori, 2006) categories of deficit/nondeficit and "Kraepelinian" schizophrenia (Roy et al., 2001). The latter, very poor outcome "Kraepelinian" subtype is defined by a complete existential dependence on others for maintaining basic necessities of life and thus may represent the majority of chronically institutionalized patients with schizophrenia (Keefe et al., 1987, 1988; Bralet et al., 2002).

In comparison to schizophrenia patients with more favorable outcomes, the course of the poor-outcome schizophrenia is characterized by severe dysfunctions in self-care (Keefe et al., 1996), limitations in premorbid sociosexual functioning (Keefe et al., 1989, 1990), more severe negative symptoms and formal thought disorder (Stephens, 1978; Keefe et al., 1989), poorer response to antipsychotic treatment (Harvey et al., 1991), lower association with affective symptomatology (Kilzieh et al., 2003; Rieckmann et al., 2005), excessive summertime clustering of birthdates (Bralet et al., 2002), and more extensive family history

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of schizophrenia spectrum disorders (Keefe et al., 1991). Some of these poor-outcome characteristics are in turn interrelated, e.g. nonresposiveness to antipsychotic treatment and increased familiality of the illness (Joober et al., 2005) or poor premorbid sociosexual functioning and severity of the negative symptoms (Salokangas, 2003). Clinical studies suggest rather significant and apparently multilobar neuropsychological impairments in this group of patients, including high incidence of age disorientation (Tapp et al., 1993; Manschreck et al., 2000), impaired performance on visual–motor processing, abstraction/flexibility (Albus et al., 1996), fine motor dexterity, and executive functioning tests (Roy et al., 2003).

Earlier computerized tomography and MRI studies observed that in comparison to patients with good outcomes, poor-outcome patients exhibited relatively larger ventricular asymmetry (Losonczy et al., 1986), as well as size (Pearlson et al., 1984; Katsanis et al., 1991; Rossi et al., 2000), and the latter not only was predictive of poor outcome (DeLisi et al., 1992) but continued to show progressive enlargement over a 5-year follow-up period (Davis et al., 1998). More recently, our group found that poor-outcome schizophrenia patients registered lower frontal/occipital metabolic ratios and regional metabolic rates in the temporal lobe, cingulate gyrus, and striatum as assessed by PET, as well as lower volumes of the putamen, especially in the right hemisphere, which may perhaps be associated with differential responsiveness to antipsychotic pharmacotherapy among the two patient groups (Buchsbaum et al., 2002, 2003). Pilot morphometric analyses on a subsample from the current investigation suggested a pattern of *posteriorization*, or more posterior distribution of cortical gray matter deficits in patients with poor outcomes. So while all patients with schizophrenia showed dorsolateral prefrontal gray matter deficits regardless of outcome, it were more posterior – temporal, parietal, and occipital – changes in gray matter volumes that differentiated between patients with varying outcomes (Mitelman et al., 2003, 2005a).

Consilient evidence for changes in white matter volumes and connectivity patterns in the poor-outcome patients group has also been recently obtained. Lower white matter volumes in poor-outcome than in good-outcome group were noted in a subsample of subjects from the current study beneath the temporal Brodmann's area 42, parietal Brodmann's area 31, and occipital Brodmann's area 19 (Mitelman et al., 2003, 2005a). Differential prefrontothalamic (Mitelman et al., 2005b) and reduced prefrontotemporal (Mitelman et al., 2005c, 2005d) regional volume associations, larger decreases in ventral thalamic (Brickman et al., 2004) and anterior capsular (Brickman et al., 2006) volumes, and more extensive anisotropy reductions in the widespread white matter regions and fiber tracts (Mitelman et al., 2006, 2007) in the sample of patients with poor clinical outcomes used in the current study clearly implicate white matter changes in the prognostic subtyping of schizophrenia.

Changes in white matter volumes, however, are notoriously more difficult to appreciate because of the less clear-cut partitioning schemes and because of the relative subtlety of these changes in comparison to decreases in the co-territorial gray matter volumes (Mitelman et al., 2003). In this study, we utilized a large sample of schizophrenia patients with different outcomes, well-powered to detect these subtle morphological changes, and a Brodmann parcellation scheme aimed at a systematic and comprehensive assessment of both gray and white matter morphometry across the brain. Our goal was to confirm and extend the *posteriorization* in poor outcome hypothesis for gray matter from our own preliminary investigations in a much larger sample and supplement it with the analogous exploratory assessment of the regional white matter. To this end, analysis of variance (ANOVA) was done to contrast select assortments of Brodmann's areas that reflect differential pathophysiological role accorded to anatomical regions or architectonic and information-processing supraregional divisions of the brain by various authors. Regional morphometry was then evaluated in relation to illness severity as reflected by the Positive and Negative Syndrome Scale (PANSS) general psychopathology scores (Kay et al., 1987) and in relation to longitudinal outcome of the illness by means of comparing patients with very poor outcomes (Kraepelinian schizophrenia) to those with more favorable outcomes. Finally, the use of the identical sample of participants and identical parcellation of the whole-brain white matter by its association with cortical Brodmann's areas in the assessment of fractional anisotropy (Mitelman et al., 2006) and volumetric measures (in the current study) affords us a unique opportunity for their direct comparison.

## Materials and methods

### *Participants*

Participants of the study comprised 41 normal subjects and 104 patients with schizophrenia, divided into those with good outcomes ($n=51$) and with poor outcomes ($n=53$) based on the criteria by Keefe et al. (1987, 1988). In brief, these required that poor-outcome patients met the following criteria for at least 5 years prior to study contact: 1) continuous hospitalization or complete dependence on others for food, clothing, and shelter; 2) no useful employment; and 3) no evidence of symptom remission. All other schizophrenia patients were considered good-outcome. Since multiple clinical factors were considered by Keefe and colleagues (1996) in subdividing patients into the two groups, a single number to represent a severity continuum was not developed. Instead these authors emphasized naturalistic longitudinal course differences and argued "subtypologies based on differences in longitudinal course classify schizophrenic patients by criteria that are more likely than cross-sectional criteria to remain consistent throughout a patient's illness". For this reason, in our analyses we treated the good-outcome and poor-outcome subgroups in a dichotomized manner, rather than as a continuum of severity. See Table 1 for demographic and clinical details.

All participants were administered a semi-structured diagnostic interview with the Comprehensive Assessment of Symptoms and History (Andreasen et al., 1992) and those meeting DSM-IV criteria for a psychotic disorder were classified into the paranoid ($n=25$), disorganized ($n=4$), residual ($n=5$), catatonic ($n=3$), and undifferentiated ($n=56$) schizophrenia subtypes, or schizoaffective disorder ($n=11$). Patients with schizophrenia were recruited from the inpatient and outpatient services at Pilgrim State Psychiatric Center, Mount Sinai and Bronx VA Medical Centers, all in New York metropolitan area. The matched normal comparison subjects were recruited through advertisement. The exclusion criteria consisted of a history of licit or illicit substance abuse, head trauma, neurological illness, more than 25% exceedance of average body weight, as well as significant abnormalities on screening physical examination and laboratory