Longitudinal Assessment of Gray and White Matter in Chronic Schizophrenia: A Combined Diffusion-Tensor and Structural Magnetic Resonance Imaging Study

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Abstract: Previous studies have reported continued focal gray matter loss after the clinical onset of schizophrenia. Longitudinal assessments in chronic illness, of white matter in particular, have been less conclusive.

We used diffusion-tensor and structural magnetic resonance imaging in 16 healthy subjects and 49 chronic schizophrenia patients, subdivided into good-outcome (n=23) and poor-outcome (n=26) groups, scanned twice 4 years apart. Fractional anisotropy, gray matter and white matter volumes were parcellated into the Brodmann's areas and entered into multiway ANCOVAs.

At baseline, schizophrenia patients had 1) lower anisotropy in frontoparietal white matter, 2) larger posterior frontal white matter volumes, and 3) smaller frontal, temporal, and parietal gray matter volumes. On follow-up, healthy subjects showed a more pronounced 1) decline in anisotropy, 2) expansion of regional white matter volumes, and 3) reduction in regional gray matter volumes than schizophrenia patients. Good-outcome patients showed a more pronounced decline in white matter anisotropy and a less pronounced increase in white matter volumes than poor-outcome patients. Poor-outcome patients displayed a greater gray matter loss throughout the brain than good-outcome patients.

In the chronic phase of the illness, longitudinal changes in both gray and white matter are in the direction of an effacement of between-group differences among schizophrenia patients and healthy subjects. Similarly, preexisting white matter differences between good-outcome and poor-outcome patients diminish over time. In contrast, gray matter volumes in poor-outcome patients continue to decline more rapidly than in patients with good outcome. These patterns are consistent with earlier onset of aging-associated changes in schizophrenia.

Key Words: Kraepelinian schizophrenia, poor outcome, anisotropy, white matter, illness progression.

INTRODUCTION

Illness progression remains a debated topic in schizophrenia neuroimaging research [1, 2]. It has been convincingly demonstrated that there is a continuing loss of gray matter volume for a period of perhaps several years leading to and immediately following the first outbreak of psychotic symptoms (reviewed in [3, 4]). Yet, further changes in gray matter and the white matter dynamics over the later course of the illness are not as well understood. Although some authors reported a similarly progressive decline in gray matter volumes in chronic schizophrenia patients as had been shown after the first psychotic outbreak [5], the interpretation of these results gained a degree of controversy when Weinberger and McClure [6] proposed that these findings in fact may be epiphenomenal, reflecting the methodological and/or physiological vicissitudes rather than a true tissue loss. This claim sprang from a rather obvious conjecture that by extrapolating the reported rate of excessive gray matter loss early in the illness (2-7% per year in various studies) in due time schizophrenia patients risk being left void of gray matter altogether. The possibility of a nonlinear volumetric change with age in patients with schizophrenia had been largely dismissed in the authors' initial argumentation as was already pointed out by Mathalon *et al*. [7] in their earliest response to the criticisms of Weinberger and McClure. A more recent review of the still rare longitudinal MRI studies in chronic schizophrenia patients, however, concludes that this indeed may be the case and that, unlike normal aging, the rate of regional changes in both gray and white matter volumes in patients with schizophrenia slows down with age [8].

Brain tissue changes during the course of normal aging include decline in gray matter volumes and corresponding

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increase in white matter volumes, but the timeframes of these changes are different for each tissue type (reviewed in [9, 10]). Thus, while gray matter loss with age follows a linear course, longitudinal white matter volume changes follow a reversed U-curve, expanding through the fifth decade of life and shrinking in the later years [11, 12]. Further, Bartzokis *et al*. point to a differential lobar topography of the longitudinal white matter dynamics: the volumes peak at age 44.6 years in the frontal lobe and at the age of 47 years in the temporal lobe [11]. Fractional anisotropy in the white matter shows similar but more linear anteroposterior dynamics (see [13] for review). Thus, while global white matter fractional anisotropy decreases with age [14], frontal regions appear to be affected first, followed by the temporal regions with sparing of the parietal and occipital lobes [15]. There is a suggestion that changes in fractional anisotropy precede coterritorial and apparently correlated volumetric changes in normal aging, hence may represent a more sensitive index of white matter aging [16-18].

Many longitudinal studies have recorded progressive decline in frontotemporal gray matter volumes in patients with schizophrenia over time. The vast majority of these studies, however, have specifically focused on the adolescent or young adult first-episode schizophrenia patients for a period of time up to 5 years following the symptomatic onset of the disease [19-30]. Longitudinal assessments in more chronic patients have been relatively few and less conclusive: one reporting significant volume loss [5], another - focal gray matter density loss [31], and 3 others - no progressive changes [32-34]. van Haren *et al*. [35], by studying a longitudinal cohort of schizophrenia patients aged 16 to 56 years, divided into subgroups based on the duration of illness, conclude that progressive gray matter volume loss in excess of normal aging slows down with age and is discernable only up to approximately 45 years of age (or ~20 years into the illness); this volume loss is more pronounced in patients with poor clinical outcome. Still scanter are the longitudinal assessments of white matter volumes in schizophrenia. Ho *et al*. [23] documented reductions in the frontal white matter and Whitford *et al.* [36] in the posterior temporal white matter volumes over the 3-year period following the first psychotic outbreak. van Haren *et al.* in the above-cited study [35] report that white matter volumes in their patients were expanding with age at an ever-slowing rate until the expansion was no longer detectable by the age of 51 years. Finally, no longitudinal follow-up reports of the white matter anisotropy changes in patients with schizophrenia have yet been published, but two cross-sectional studies [37, 38] conclude that widespread decreases in fractional anisotropy with age are more pronounced in schizophrenia and are related to the duration of illness.

The goal of the present study was to investigate the progression of changes in gray and white matter volumes, as well as white matter fractional anisotropy, in a group of middle-aged patients with chronic schizophrenia. We strived to determine whether the illness remains uniformly progressive in its chronic phase (as it appears to be around the first psychotic outbreak) and hypothesized that the morphometric evidence of the illness progression will only be evident in the more severe schizophrenia patients with poor clinical outcome. To this end, patients were divided into those with good and poor outcomes and an identical parcellation scheme was applied to both gray and white matter. This approach has previously been used in our cross-sectional studies on the large original sample which served as the recruitment base for the present follow-up [39-41], thus providing directly comparable longitudinal data.

MATERIALS AND METHODOLOGY

Subjects

Follow-up Sample

The follow-up cohort comprised 49 patients with schizophrenia (age at baseline scan 42.69±12.29 years; 7 women; 2 left-handed) and 16 healthy subjects (age at baseline 41.63±12.23 years, t_{63}=0.30, p=ns; 7 women; no left-handed), scanned approximately 4 years apart (4.10±0.54 years for schizophrenia patients and 4.22±0.52 years for healthy subjects, t_{63}=0.76, p=ns). Schizophrenia patients had significantly lower baseline Mini-Mental State Examination (MMSE) scores than healthy subjects (t_{56}=4.17, p=0.0001), but did not significantly differ in major demographic characteristics (Table **1**). These 65 participants underwent morphometric analyses for regional gray and white matter volumes. A smaller sample of 49 participants was available for the diffusion-tensor imaging (DTI) analyses: this DTI sample comprised 13 healthy subjects and 34 schizophrenia patients (17 with good outcome and 17 with poor outcome). All participants were administered a semi-structured diagnostic interview with the Comprehensive Assessment of Symptoms and History [42]. 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 comprised a history of substance abuse, head trauma, neurological illness, average body weight that exceeded upper 25th percentile, significant abnormalities on screening physical examination and laboratory tests (including urine toxicology screen, thyroid function, VDRL, B_{12} and folate levels). The project was approved by the institutional review board of the Mount Sinai School of Medicine and informed consent was obtained from each participant.

Patients with schizophrenia were classified into the good-outcome (n=23) and poor-outcome (n=26) subgroups based on the criteria by Keefe *et al.* [43, 44]. In brief, these required that poor-outcome patients met the following criteria for at least five 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. Patients classified as poor-outcome (age 47.35±11.9 years; 1 woman) were significantly older at baseline scan than patients with good outcome (37.44±10.68 years, t_{47}=3.05, p=0.004; 6 women), but did not differ in length of between-scan interval (3.98±0.4 years vs. 4.24±0.65 years, respectively, t_{47}=1.76, p=0.09). PANSS assessments at baseline showed that patients with poor outcome, as compared to those with good outcome, had significantly more severe positive (22.4±6.64 vs. 15.39±4.92, t_{47}=4.12, p=0.00015), negative (22.36±7.40

Table 1. Clinical and Demographic Characteristics

Subject Group	Age at Initial Scan Date	Age at First Treatment[a]	Duration of Illness[b]		PANSS[c]		MMSE[d]
				Positive	Negative	General	
FULL BASELINE SAMPLE (n=145)							
Healthy Subjects (n=41)	44.15±14.66						29.86±9.12
Schizophrenia Patients (n=104)	42.77±12.12	24.96±9.12	18.49±12.71	18.86±6.64	18.91±7.77	37.07±9.87	26.86±2.71
Good-Outcome Patients (n=51)	40.62±12.60	26.82±7.06	14.82±12.10	16.04±4.94	16.25±5.53	32.38±7.83	27.00±2.64
Poor-Outcome Patients (n=53)	44.79±11.39	22.82±10.74	22.74±12.20	21.74±6.94	21.60±8.72	41.81±9.42	26.72±2.80
FOLLOW-UP COHORT (n=65)							
Healthy Subjects (n=16)	41.62±12.23						30.00±0.00
Schizophrenia Patients (n=49)	42.69±12.29	23.80±8.01	18.67±12.05	19.04±6.80	19.00±7.25	40.53±13.23	26.47±3.15
Good-Outcome Patients (n=23)	37.44±10.68	26.81±5.51	12.29±8.78	15.39±4.92	15.35±5.08	35.32±14.63	27.32±2.36
Poor-Outcome Patients (n=26)	47.35±11.90	20.96±9.05	24.77±11.71	22.4±6.64	22.36±7.40	45.12±10.05	25.79±3.56
DROP-OUT SAMPLE (n=80)							
Healthy Subjects (n=25)	45.62±15.75						29.77±0.53
Schizophrenia Patients (n=55)	43.19±12.37	25.38±9.88	18.40±13.08	18.38±6.20	19.00±8.46	35.52±10.14	27.20±2.43
Good-Outcome Patients (n=28)	42.21±13.25	26.46±8.10	16.54±13.66	16.96±5.53	16.52±5.98	33.27±7.83	27.36±2.08
Poor-Outcome Patients (n=27)	43.62±11.53	23.90±11.98	20.95±12.12	20.36±6.63	21.23±9.87	40.04±8.86	27.35±2.41

[a]Documented age at the time of first exposure to antipsychotic agents
[b]Time (in years) since the first illness-related exposure to antipsychotic agents to the initial scan
[c]Positive and Negative Syndrome Scale
[d]Mini-Mental State Examination.

vs. 15.35±5.08, t_{47}=3.79, p=0.0004), and general psychopathology scores (45.12±10.05 vs. 35.32±14.63, t_{47}=2.7, p=0.01), as well as a longer duration of illness (t_{41}=3.94, p=0.0003), but did not differ significantly in MMSE scores (t=1.6, p=0.12). Duration of illness at the initial scan date was conservatively constructed as time in years since the age of the first illness-related antipsychotic treatment.

Comparison with Full Baseline Sample and with Subjects Lost to Follow-up

This follow-up cohort of 65 subjects was recruited as a 4-year continuation of our baseline study of 104 patients with schizophrenia (51 with good outcome and 53 with poor outcome) and 41 healthy subjects, published elsewhere [39-41, 45-51]. In order to rule out potential sources of systematic bias in subject retention and attrition, we compared age and illness severity of the current follow-up cohort with those of the full baseline sample of 145 participants and with those of the drop-outs that were lost to 4-year follow-up (Table **1**). There were no significant differences in age or PANSS subscale scores between healthy subjects, all schizophrenia patients, and schizophrenia subgroups by outcome in the comparison of the full original sample of 145 participants and the current follow-up cohort of 65 participants. There was a trend (t_{151}=1.65, p=0.073) towards more severe general psychopathology PANSS subscale score in schizophrenia patients in the current follow-up cohort (40.53±13.23) than in the full original sample (37.07±9.87).

In the comparison of the current follow-up cohort of 65 subjects with the drop-out sample of 80 subjects, schizophrenia patients retained to follow-up (n=49) had significantly more severe (t_{102}=2.36, p=0.032) PANSS general psychopathology scores (40.53±13.23) than schizophrenia patients that were lost to follow-up (n=55, 35.52±10.14). There was also a trend towards more severe PANSS general psychopathology scores (t_{51}=2.01, p=0.056) in the poor-outcome schizophrenia patients that were retained for follow-up (n=26, 45.12±10.05) than in the poor-outcome patients that were lost to follow-up (n=27, 40.04±8.86). The healthy subjects, all schizophrenia patients, good-outcome and poor-outcome subgroups in the current follow-up and the drop-out samples were not significantly different otherwise.

Image Acquisition and Processing

T_1-weighted MR images were acquired using a 1.5T Signa 5× scanner (GE Medical Systems) with a 3D-SPGR sequence (TR=24 msec, TE=5 msec, flip angle=40°, matrix size 256×256, field of view 23 cm, slice thickness 1.2 mm, total slices 128, NEX=1). The diffusion tensor sequence acquired fourteen 7.5-mm-thick slices (TR = 10 s, TE = 99 ms, TI = 2.2 s, b = 750 s/mm, δ = 31 ms, Δ = 73 ms). Before the diffusion EPI sequence, a Turbo Spin Echo was also acquired to obtain a localizing anatomical image. In order to solve for the components of the diffusion tensor, seven diffusion EPI images were obtained: six with different non-collinear gradient weightings and one with no diffusion gradient applied. The diffusion tensor for every voxel in a slice was then computed by solving the seven simultaneous signal equations relating the measured signal intensity to the diffusion tensor. Anatomical SPGR MR images were resectioned to standard Talairach-Tournoux position using the

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