Progressive Brain Change in Schizophrenia: A Prospective Longitudinal Study of First-Episode Schizophrenia

Nancy C. Andreasen, Peg Nopoulos, Vincent Magnotta, Ronald Pierson, Steven Ziebell, and Beng-Choon Ho

Background: Schizophrenia has a characteristic onset during adolescence or young adulthood but also tends to persist throughout life. Structural magnetic resonance studies indicate that brain abnormalities are present at onset, but longitudinal studies to assess neuroprogression have been limited by small samples and short or infrequent follow-up intervals.

Methods: The Iowa Longitudinal Study is a prospective study of 542 first-episode patients who have been followed up to 18 years. In this report, we focus on those patients ($n = 202$) and control subjects ($n = 125$) for whom we have adequate structural magnetic resonance data ($n = 952$ scans) to provide a relatively definitive determination of whether progressive brain change occurs over a time interval of up to 15 years after intake.

Results: A repeated-measures analysis showed significant age-by-group interaction main effects that represent a significant decrease in multiple gray matter regions (total cerebral, frontal, thalamus), multiple white matter regions (total cerebral, frontal, temporal, parietal), and a corresponding increase in cerebrospinal fluid (lateral ventricles and frontal, temporal, and parietal sulci). These changes were most severe during the early years after onset. They occur at severe levels only in a subset of patients. They are correlated with cognitive impairment but only weakly with other clinical measures.

Conclusions: Progressive brain change occurs in schizophrenia, affects both gray matter and white matter, is most severe during the early stages of the illness, and occurs only in a subset of patients. Measuring severity of progressive brain change offers a promising new avenue for phenotype definition in genetic studies of schizophrenia.

Key Words: First episode, longitudinal studies, neurodevelopment, neuroprogression, schizophrenia, structural magnetic resonance imaging

Schizophrenia is one of the most important public health problems in the world, ranking as the fourth leading cause of disability among people aged 18 to 45 in developed countries (1). It is a brain disease that typically first manifests itself in young people during their late teens to late 20s, with ongoing signs and symptoms usually occurring throughout the remainder of their lives (2,3). Because the illness begins early but tends to persist throughout life and sometimes worsens, one of the central questions in schizophrenia research is whether the disorder should be conceptualized as a neurodevelopmental disorder, a neuroprogressive disorder, or a combination of the two (4–9).

Structural magnetic resonance (sMR) imaging provides an opportunity to examine these questions using quantitative measures of brain tissue. One strong piece of evidence indicating that schizophrenia is a neurodevelopmental disorder derives from the fact that many types of brain abnormalities are present in patients who are assessed at the time of their first episode of illness (10–14). These include decreased cerebral size, decreased frontal and temporal lobe size, decreased thalamic size, decreases in gray matter (GM) and white matter (WM) volume, and increased cerebrospinal fluid (CSF) on the brain surface and in the ventricles. These observations support the likelihood that the illness arises because of aberrations in the complex neurodevelopmental processes that modulate brain maturation during the adolescent and young adult period.

One of the important remaining questions about the nature of the brain abnormalities that characterize schizophrenia concerns their course after disease onset. Do the brain processes that trigger the illness stabilize after onset or does the brain disease continue to progress, producing an additional loss of brain tissue? If changes continue to progress after onset, what is the pattern of change? Is it more severe during early years of the illness or during later years of the illness or does it proceed at the same rate over time? To address these questions, a prospective longitudinal design of long duration with frequent sampling of time points is necessary. Although a few studies have been completed using longitudinal designs, their sample sizes are too small and the follow-up periods too short or infrequent to reach a definitive conclusion about the long-term course of brain changes in schizophrenia (15–23). This report addresses these questions using sMR data collected in the Iowa Longitudinal Study of first-episode schizophrenia, which comprises the largest sample of prospectively followed patients and control subjects collected to date and the longest surveillance period ever examined.

Methods and Materials

Subjects

The Iowa Longitudinal Study was initiated in 1987 and includes a total cohort of 542 first-episode schizophrenia patients who were recruited after their initial presentation for a schizophrenia spectrum disorder. These patients were drawn from consecutive admissions to the University of Iowa Psychiatry Inpatient Service at a rate of 20 to 30 per year; intake into the study ended in 2007. Exclusion

From the Psychiatric Iowa Neuroimaging Consortium, The University of Iowa Carver College of Medicine, Iowa City, Iowa.

Address correspondence to Nancy C. Andreasen, M.D., Ph.D., The University of Iowa Carver College of Medicine, Department of Psychiatry, 200 Hawkins Drive, Room W278 GH, Iowa City, IA 52242; E-mail: luann-godlove@uiowa.edu.

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criteria included an IQ < 70, history of a significant head injury, or presence of metal implants. They were followed at 6-month intervals after initial intake, with assessment of clinical symptoms, psychosocial function, and treatment received. Intensive assessments (sMR and cognitive testing) were done at intake and at 2, 5, 9, 12, 15, and 18 years. For a study of this length, attrition is remarkably low. Attrition is due to a variety of factors: death by suicide, 15; death because of other factors, 7; being in jail, 2; administrative drop because of change in diagnosis, 29; lost or moved out of the area, 61; refusal to remain in the study, 126. True attrition is probably best defined by those who have been lost or who refused, $n = 187$, or a rate of 34.5%. Our retention rate is thus a remarkable 65.5% over 19 years. We have compared the subjects who were lost or refused with those who remain in the study, using a variety of variables (e.g., age at onset, age at intake, severity of symptoms at intake, IQ at intake, magnetic resonance [MR] measures at intake). We find no significant differences between those who are in the attrition group and those who continue to participate in the study, suggesting that the sample that we are following is representative of the illness.

In this report, we focus on those subjects for whom we have adequate sMR data to provide a relatively definitive determination of whether progressive brain change occurs over a time interval that is up to 15 years after intake. These comprise a total of 202 patients for whom we have a minimum of 2 scans and a maximum of 5; the total number of scans analyzed is 640; the mean interval between first scan and last available scan = 7.2 years (SD = 3.79; maximum = 15). Their mean age at intake was 24.56 (SD 7.14). One hundred forty-eight were male and 54 were female. Their mean parental education was 13.38 years. Nearly half the patients, or 92, were neuroleptic naive at the time of entry into the study. These patients are compared with a group of healthy normal volunteers ($n = 125$), recruited from the community by newspaper advertising or word of mouth, and matched to the patients on parental education. The total number of control scans analyzed is 312, with a minimum of 2 and a maximum of 5. Control subjects were screened to rule out a past history of any major psychiatric, neurologic, or general medical disorder, as well as a family history of schizophrenia. Their mean age at intake was 29.69 years (SD 8.37); 66 were male and 59 were female (Supplement 1). Their mean parental education was 13.27 years.

All subjects provided written informed consent, as approved by our Institutional Review Board.

sMR Data Acquisition

In this study, we used two scanning protocols, which we refer to as MR5 and MR6 (Supplement 1). Both are multimodal (i.e., acquire T2 or proton density [PD] sequences in addition to T1), thereby providing optimal discrimination between GM, WM, and CSF. For MR5 subjects, each participant's data included T1-, T2-, and PD-weighted images collected on a 1.5-T GE Signa scanner (GE Healthcare, Waukesha, Wisconsin). MR6 was acquired on a 1.5-T Siemens Avanto scanner (Siemens AG, Muenchen, Germany) using T1 and T2 sequence. Subjects continued in the same sequence throughout the study; those that began with an MR5 protocol remained in it for all scans, and those that began with an MR6 protocol remained in it as well. The two sequences differ primarily in slice thickness and in-plane resolution; both are acquired in the coronal plane. Voxel size for MR5 is 1.0 × 1.0 × 1.5 mm (T1) and 1.0 × 1.0 × 3 mm (T2); voxel size for MR6 is .625 × .625 × 1.5 mm (T1) and .625 × .625 × 1.8 mm (T2). Both are multimodal; MR5 acquires T1, T2, and PD sequences, while MR6 uses only T1 and T2. Our multimodal approach permits us to measure surface CSF and delineate the CSF/GM and GM/WM borders more precisely.

Image Analysis

The MR scans were analyzed using BRAINS2 software (created at The University of Iowa Carver College of Medicine by Dr. Andreasen's IPL staff, Iowa City, Iowa), a locally developed program that now yields automated quantitative measures of multiple brain regions and tissue types (24–28). Although BRAINS2 analysis was semiautomated for many years, we have recently introduced advanced image processing algorithms that eliminate the need for manual intervention at the stages of image realignment, tissue sampling, and mask editing. In addition, inhomogeneity correction, intensity normalization, and mask cleaning routines have been added to improve the accuracy and consistency of the results. This fully automated image processing routine is known as AutoWorkup (29). To eliminate any measurement artifacts that might be due to rater drift over time and to reduce any that might be due to scanner upgrades, we recently reanalyzed all 952 scans used for this report using this new AutoWorkup program.

Determining the Feasibility of Pooling the Two Sequences

Ensuring that findings are not because of scanner artifacts is a major challenge in sMR research and especially in longitudinal research. To test for comparable reliability and validity of MR5 and MR6, we acquired both types of scans back-to-back in 60 subjects to verify our ability to combine the data from both sequences in our longitudinal analyses. Through the use of minor preprocessing before application of our workup, we are able to process both MR5 and MR6 scans to extract brain measures that are essentially identical. To assess the feasibility of combining data from the two scan sequences, only the modalities common to both (T1 and T2) were used in the analysis. To further reduce the differences, a preprocessing step was included to down-sample the raw images from the MR6 sequence to the same resolution as the raw images from the MR5 sequence. Using AutoWorkup, all scans underwent field inhomogeneity correction and signal intensity normalization, which removes scanner-dependent variation over time and between the two sequences. We found that, using AutoWorkup, the intraclass correlation coefficients were consistently > .96 and usually .98 to .99 for all brain regions, apart from occipital cortex (which is reported in Supplement 1). Therefore, we have concluded that we can pool data that use the two different scanning sequences. Figure 1 illustrates a typical MR5 and MR6 scan from the same individual, as well as a difference map indicating the areas where the two scan types differ.

Cognition. All subjects were evaluated with a comprehensive cognitive battery administered by trained neuropsychologists. To provide comprehensive measurements of cognitive functioning, 36 neuropsychological test variables were grouped into six cognitive domains: verbal learning, attention, problem solving, working memory, verbal fluency, and motor speed (12).

Statistical Analysis

Analyses were performed using SAS (version 9.2; SAS, Cary, North Carolina). General linear mixed models were used to compute changes over time. Intracranial volume at initial MR scan, gender, imaging protocol (MR5 vs. MR6), and age at initial MR scan were included as covariates. To take into account within-subject correlations in brain volumes, subject was entered as random effects (PROC MIXED REPEATED statement). Compound symmetry covariance structure for repeated subject measures was used because its fit statistics were most consistently superior to unstructured correlation matrix. Relationships between brain measures and cognitive and clinical measures were examined using Pearson correlation coefficients; a two-sided p value < .05 was used to