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Published in:
Proceedings of the National Academy of Sciences of the USA
vol. 98, no. 20:11650-11655, September 25, 2001.

Major & Minor Subject Classification: Biological Sciences (Neurobiology)

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ABSTRACT

Neurodevelopmental models for the pathology of schizophrenia propose both polygenetic and environmental risks, as well as early (pre/perinatal) and late (usually adolescent) developmental brain abnormalities. Using novel brain mapping algorithms, we detected striking anatomical profiles of accelerated gray matter loss in very early-onset schizophrenia; surprisingly, deficits moved in a dynamic pattern enveloping increasing amounts of cortex throughout adolescence. Early-onset patients were re-scanned prospectively with MRI, at two-year intervals at three time-points, to uncover the dynamics and timing of disease progression during adolescence. The earliest deficits were found in parietal brain regions, supporting visuo-spatial and associative thinking, where adult deficits are known to be mediated by environmental (nongenetic) factors. Over 5 years, these deficits progressed anteriorly into temporal lobes, engulfing sensorimotor and dorsolateral pre-frontal cortices, and frontal eye fields. These emerging patterns correlated with psychotic symptom severity, and mirrored the neuromotor, auditory, visual search and frontal executive impairments in the disease. In temporal regions, gray matter loss was completely absent early in the disease but became pervasive later. Only the latest changes included dorsolateral prefrontal cortex and superior temporal gyri, deficit regions found consistently in adult studies. These emerging dynamic patterns were (1) controlled for medication and IQ effects, (2) replicated in independent groups of males and females, and (3) charted in individuals and groups. The resulting mapping strategy reveals a shifting pattern of tissue loss in schizophrenia. Novel aspects of the anatomy and dynamics of disease are uncovered, in a changing profile that implicates genetic and non-genetic patterns of deficits.

Introduction

Little is known about the profile of brain change in adolescence, and its modulation in diseases with adolescent onset. Schizophrenia, for example, has typical onset in late adolescence or early adulthood. Cases occurring in childhood or early adolescence, however, present unique opportunities to study disease development during adolescence. Childhood-onset schizophrenia is a severe form of the disorder that appears to be clinically and neurobiologically continuous with the later onset illness (1). The causes of schizophrenia are not known, but it is increasingly considered a neurodevelopmental disorder (2,3). Both early (prenatal) and later abnormalities of brain development have been proposed (4,5,6). However, neither the anatomical pattern nor the timing of these developmental events has been established.

In response to these challenges, we designed a novel brain mapping strategy to uncover deficit patterns as they emerged in populations imaged longitudinally through adolescence for 5 years. Because gray matter loss is implicated in schizophrenia, and is also known to occur in adolescence (7-15), we set out to create detailed spatio-temporal maps of these loss processes. Their timing and anatomical profile is fundamental to understanding how the disease emerges; so far it has been difficult to test hypotheses about genetic and environmental triggers of schizophrenia because the topography and dynamics of the disease, especially at the cortex, are not well-understood. In a recent cross-sectional genetic study based on a cohort of 80 adult twins discordant for schizophrenia (16), we isolated a genetic continuum in which cortical deficits were found in gradually increasing degrees, in individuals with increasing genetic affinity to a patient. By controlling for common genotype, we isolated discrete regions of cortex whose deficits were attributable to genetic and to non-genetic factors, although the emergence and timing of these deficits could not be evaluated.

The current study aimed to chart the emergence of these deficits in a severely-affected cohort followed for 5 years, revealing an unsuspected developmental trajectory in these schizophrenic adolescents. This technique uncovered a dynamic wave of accelerated gray matter loss, spreading from parietal cortices at disease onset to encompass temporal and frontal regions later in the disease. The rates and temporal sequencing of cortical gray matter loss was mapped in the teenage years, and was found to

be greatly accelerated in disease relative to healthy teenagers matched for age, gender, and demographics. The final profile was consistent with the loss pattern in adult schizophrenia. We also correlated loss rates with symptom severity, and controlled for potential medication and IQ effects. Local changes were examined in relation to genetic and non-genetic deficit patterns found in adults. This study is therefore the first 3D visualization of the timing, rates and anatomical distribution of brain structure changes in adolescents with schizophrenia. It suggests a dynamic structural basis for early prodromal symptoms, and for the positive and negative deficit symptoms observed clinically (17).

Methods

Summary

3D maps of brain change were derived from high-resolution magnetic resonance images (MRI scans) acquired repeatedly from the same subjects over a 5-year time span. 12 schizophrenic subjects (aged 13.9±0.8 years at first scan) and a parallel group of 12 healthy adolescents (aged 13.5±0.7 years at initial scan) were imaged repeatedly for 4.6 years (the combined groups were scanned every 2.3 years ± 1.4 months (SD); for clarity this is referred to as 5 years). Patients and controls were matched for age, gender and demographics, and were scanned identically on the same scanner at exactly the same ages and intervals. The 3-dimensional distribution of gray matter in the brain was computed, as in previous studies of Alzheimer's disease(18), and was compared from one scan to the next using a novel computational cortical pattern matching strategy that aligns corresponding locations on the cortical surface, across time and across subjects. This allowed us to pool maps of individual gray matter loss over time. Average rates of gray matter loss were computed for each group and compared across corresponding regions of cortex (Fig. 1), prior to a more detailed analysis of nonlinear and age-dependent effects. Both the amount of loss, and the rate of loss, were separately evaluated. Findings were also examined in relation to genetic and non-genetic patterns found in recent studies of adult patients.

Subjects and Imaging

Subjects were recruited as part of an ongoing NIMH study of childhood-onset schizophrenia (1), and evaluated prospectively over a 5-year time period. Twelve patients (6 males/6 females) and 12 healthy volunteers (6 males/6 females), as well as an additional medication-matched group (see below) were followed longitudinally. All patients satisfied DSM-III-R diagnostic criteria for schizophrenia (19), with onset of psychotic symptoms by age 12. All patients had a history of poor response to, or

intolerance of at least two typical neuroleptics. They had a mean full-scale IQ at study entry of 70.4±12.9 SD and no other active neurological or medical disease. Diagnosis was determined from clinical and structured interviews with the adolescents and their parents based on portions of the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Epidemiologic Version (20) and of the Diagnostic Interview for Children and Adolescents Revised (21), as well as from previous records. Psychopathological symptoms were evaluated using the Scales for the Assessment of Positive and Negative Symptoms (SAPS/SANS; (22)) and the Brief Psychiatric Rating Scale (BPRS; (23); see (1) for details). Normal adolescent controls were screened for medical, neurologic and psychiatric illness and learning disabilities as described previously (1). We rigorously matched the cohorts for age (see below), gender, follow-up interval (which was identical), social background, and height.

Medication and IQ-Matched Group

Medication effects were assessed by analyzing a second group of non-schizophrenic medication-matched subjects. The 10 age- and gender-matched psychosis NOS patients (NOS=Not Otherwise Specified; (1,24)) received the same medication as the schizophrenic group at baseline and follow-up, but did not satisfy DSM-III-R criteria for schizophrenia. They were also IQ-matched with the COS patients (mean IQ: 76±10 SD), and matched for age, gender, and demographics with the healthy controls. These children had very transient psychotic symptoms, emotional lability, poor interpersonal skills, normal social interest, and multiple deficits in information processing (1). They were less severely impaired than the COS group, but continued with a mixture of mood and behavior problems. None at follow-up was schizophrenic but rather exhibited chronic mood disturbance and lack of behavioral control; they were treated with neuroleptics for these symptoms (at doses similar to that used for COS; *see below*), which were quite effective in controlling these behaviors.

Of the 10 psychosis NOS patients, 2 patients received 300 and 450 mg clozapine (mean dose 375 mg/day), 6 received risperidone (2-8 mg; mean dose 5.25±2.4 mg/day) - four in combination with valproic acid (mean 1025 mg/day) and one in combination with olanzapine (20 mg/day), and two were drug-free.

Magnetic Resonance Imaging

3D ($256^2 \times 124$ resolution) T_1-weighted fast SPGR (spoiled GRASS) MRI volumes were acquired from all 34 subjects. All images were acquired on the same 1.5 T Signa scanner (General Electric, Milwaukee, Wisc.) located at the National Institutes of Health Clinical Center, Bethesda, Md. Imaging parameters were: time to echo, 5 milliseconds; time to repeat, 24 milliseconds;

flip angle, 45 degrees; number of excitations, 1; and field of view, 24 cm. The same set of 12 healthy controls were scanned at baseline (aged 13.5±0.7 years), and ultimately after a 5-year interval (mean interval: 4.6±0.2 years; age: 18.0±0.8 years). In parallel, the 12 age- and gender-matched schizophrenic subjects were identically scanned at the exact same ages and intervals (mean age at first scan: 13.9±0.8 years; 18.6±1.0 years at final scan; mean interval: 4.6±0.3 years). All subjects (controls, schizophrenic subjects, and the medication controls) were scanned 3 times, first at baseline, then a mean of 2.3 years later, and then again 4.6 years later. The combined groups were scanned every 2.3 years ± 1.4 months (SD).

Image Processing and Analysis

Images acquired across the multi-year time-span were processed as follows. Briefly, for each scan pair, a radio-frequency bias field correction algorithm eliminated intensity drifts due to scanner field inhomogeneity. The initial scan was then rigidly aligned (registered) to the target (25) and resampled using chirp-Z (in-plane) and linear (out-of-plane) interpolation. To equalize image intensities across subjects, registered scans were histogram-matched and a supervised tissue classifier generated detailed maps of gray matter, white matter, and CSF. Briefly, 120 samples of each tissue class were interactively tagged to compute the parameters of a Gaussian mixture distribution that reflects statistical variability in the intensity of each tissue type (26). A nearest-neighbor tissue classifier then assigned each image voxel to a particular tissue class (gray, white or CSF), or to a background class (representing extracerebral voxels in the image). The inter/intra-rater reliability of this protocol, and its robustness to changes in image acquisition parameters, have been described previously (15). Gray matter maps were retained for subsequent analysis.

3D Cortical Maps

To compare and pool cortical data across subjects, a high-resolution surface model of the cortex was automatically extracted (27) for each subject and time-point. This software creates a mesh-like surface which is continuously deformed to fit a cortical surface tissue threshold intensity value from the brain volume. The intensity threshold was defined as the MRI signal value that best differentiates cortical CSF on the outer surface of the brain from the underlying cortical gray matter. Based on the cortical models we created for each subject at different time-points, a 3D deformation vector field was computed capturing the shape change in the brain surface across the time interval. This allows us to accommodate any brain shape changes when comparing cortical gray matter within a subject across time. The deformation reconfigures the earlier anatomy into the shape of the later scan, matching landmark points, surfaces, and curved anatomic interfaces in the pair of 3D image sets. As described previously

(18), this algorithm also matched cortical regions across all the subjects in the study so that data could be averaged or compared across corresponding cortical regions. Given that the deformation maps associate cortical locations with the same relation to the primary folding pattern across subjects, a local measurement of gray matter density was made in each subject and *averaged across equivalent cortical locations*. To quantify local gray matter, we used a measure termed 'gray matter density' which has been used in prior studies to compare the spatial distribution of gray matter across subjects (28,29,15,18). This measures the proportion of gray matter in a small region of fixed radius (5 mm) around each cortical point. Given the large anatomic variability in some cortical regions, high-dimensional elastic matching of cortical patterns (30,18) was used to associate measures of gray matter density from homologous cortical regions across subjects and across time. Annualized 4D maps of gray matter loss rates within each subject were elastically realigned for averaging and comparison across diagnostic groups. Statistical maps were generated indicating locally the degree to which gray matter loss rates were statistically linked with diagnosis, gender, and with positive or negative symptoms (SAPS/SANS; (22)). To do this, at each cortical point, a multiple regression was run to assess whether the gray matter loss rate (Fig. 1) at that point depended on the covariate of interest (e.g. diagnosis). The *p*-value describing the significance of this linkage was plotted on at each point on the cortex using a color code to produce a statistical map (e.g., Fig. 2). Maps identifying these linkages were computed pointwise across the cortex and assessed statistically by permutation. We preferred this to using an analytical null distribution to avoid assuming that the smoothness tensor of the residuals of the statistical model were stationary across the cortical surface (a technical issue discussed in (31)). In each case, the covariate vector was permuted 1,000,000 times on an SGI *RealityMonster* supercomputer with 32 internal R10000 processors, and a null distribution was developed for the area of the average cortex with statistics above a fixed threshold in the significance maps. An algorithm was then developed to report the significance probability for each map as a whole (31,18), so the significance of the loss patterns could be assessed after the appropriate correction for multiple comparisons. Separate maps were made to show average rates of loss (Fig. 1(a)) and the significance of this loss in patients relative to controls (Fig. 2).

Results

In schizophrenic patients, a striking accelerated loss of gray matter (peak values >5% loss/yr.; Fig. 1(a)) was observed in a broad anatomical region encompassing frontal eye fields, supplementary motor, sensorimotor, parietal, and temporal cortices in both brain hemispheres (see Figs. 1(a) and (b)). Average loss rates were significantly faster in patients in superior parietal

lobules (*left hemisphere mean ± standard error*: 2.9±0.5 %/yr., *right hemisphere*: 2.9±0.5 %/yr.; *in controls*: 1.1±0.4 and 1.4±0.5; *group difference*: $p<0.005$ and 0.01), in superior frontal cortices (*L/R*: 2.6±0.5 and 2.7±0.4 *in patients*; 0.9±0.3 and 1.0±0.3 *in controls*; *group difference*: $p<0.003$ and 0.002), and in lateral temporal cortices (*L/R*: 2.3±0.9 and 2.4±0.4 *in patients*; 0.7±0.2 and 1.1±0.3 *in controls*; *group difference*: $p<0.003$ and 0.005). Subtle but significant changes were detected in normal adolescents (0.9-1.4% average loss/year; all regions showed significant loss, at $p<0.02$). The schizophrenia group exhibited a region of intense, severely progressive loss, terminating anteriorly in the frontal eye fields and encompassing the temporal cortices.

Significance of the Progressive Loss. To understand whether these changes could be normal fluctuations, the variability in both the anatomical distribution and loss rates for gray matter were computed locally across the cortex and the significance of the changes established. Again, schizophrenic subjects underwent a significant, pervasive and unrelenting loss of gray matter ($p < 0.00002$, *all p-values corrected*), with progressive deficits throughout superior frontal, motor, and a parietal brain regions, and a separate loss pattern observed in temporal cortices. Normal adolescents also lost tissue ($p<0.05$, in parietal regions) even after accounting for normal variability (Fig. 2(a)). A subtraction map was created to emphasize the fundamental loss pattern specific to the disease (Fig. 2(c)). Regions of progressive loss, in both anterior frontal and temporal cortices, were anatomically circumscribed in both the percent loss and significance maps, and appeared to terminate anteriorly in the frontal eye fields (Figs. 1,2). These figures show regions where tissue loss is faster in disease than in normal adolescents. The same anatomically-specific, dynamic profiles of tissue loss were replicated in independent samples of male and female schizophrenic patients (Fig. 3), suggesting that a similar profile and degree of progressive gray matter loss may operate in schizophrenia, irrespective of gender.

Nonlinear Loss. We further hypothesized that loss rates would be relatively greater in younger patients, possibly reflecting a more severe neurodevelopmental abnormality, that may have led to an earlier illness onset, and/or a disease-related exaggeration of non-linear normal developmental processes. In case change occurred sporadically or in a nonlinear fashion across the time-interval, we assessed which brain regions exhibited a nonlinear change, or variable rates of loss throughout adolescence. Right parietal and sensorimotor cortices (Fig. 4) underwent significantly faster loss in the younger adolescents, consistent with recent findings of overall volume reductions specific to parietal lobes in younger patients (32). In other brain regions, the rates of gray matter loss were not strongly affected by age, corroborating the use of annual averages to describe the

dynamic pattern. While nonlinear effects in other brain regions may be detectable in a much larger cohort, similar annual rates of loss were observed consistently in subjects throughout our sample, and across independent samples (Fig. 3).

Early Deficits. Due to the apparent sparing of inferior frontal cortices in the dynamic maps (Fig. 1,2), and their appearance in our recent cross-sectional studies of adult schizophrenia (16), we were concerned that earlier (perinatal or pre-pubertal) nonprogressive maldevelopment may not have been observed in the dynamic maps, as these maps only capture loss that intensifies over time. To detect earlier loss, we compared gray matter profiles across all 24 subjects at their first scan (Fig. 5(a), *top row*), and at their last scan 4.6 years later (Fig. 5(a), *bottom row*). Two striking features emerged. Fig. 5(b) shows the significance of these effects. First, the severe progressive lateral temporal and dorsolateral pre-frontal cortex (DLPFC) deficit observed later (Fig. 5(a), *bottom row*), was not apparent at age 13 (*top row*), even a mean of 3 years after the onset of psychotic symptoms. These deficits, which are characteristic of adult and childhood schizophrenia (16,33,1) were severely progressive after illness onset (on average 5% lateral temporal attrition per year), but were absent in the early phase of the disease. In evaluating the power of the approach, we would have been likely to detect an early temporal and DLPFC deficit, if present, but the near identity (to within 0-1%) of average normal and patient gray matter distribution at first scan, combined with the high rate of progression and significant deficit observed later (Fig. 5(b)), jointly suggest that the process of temporal and prefrontal gray matter attrition is a later developmental event. Second, parietal and motor cortices showed a severe early deficit (up to 20% loss; $p<0.0005$) with diffuse loss in other (but not temporal) cortical regions. This early (pre-pubertal) parietal deficit (Fig. 5(a),(b); *top rows*) is consistent with the faster parietal loss found in younger patients (Fig. 4), while the dynamics of loss in other regions is more uniform with age. The initial parietal deficit, which is also progressive (Fig. 1), also occurs in regions where normal adolescents lose gray matter, although in disease this loss process is significantly accelerated (Fig. 2). While it is unclear whether the normal and aberrant processes have a similar mechanism or are independent, it remains clear that the parietal and motor cortical deficits are progressive, and are the earliest to develop. We recently found that the parietal regions, specifically, are also in deficit in adult patients relative to genetically identical controls (their monozygotic discordant twins). This indicates that environmental, and not purely genetic, factors are implicated in triggering this deficit, at least in adults (16). In the present study, a dynamic wave of progression from parietal cortices occurs later, into superior frontal, dorsolateral prefrontal, and temporal cortices (including superior temporal gyri; Fig. 5). These regions comprise a specific band of cortical territory in which adult deficits are thought to be strongly influenced by genetic factors (16,34), as deficits here [1] are found in unaffected relatives and [2] significantly covary with an individual's degree of genetic affinity to a

patient. In our adolescent cohort, the temporal and DLPFC deficits were among the most severe, but began in late adolescence and were observed only after symptom onset (Fig. 5(a),(b)).

Medication-Matched Subjects. To address the possibility that neuroleptic exposure and/or lower IQ could have determined differential gray matter loss in the schizophrenics, we mapped 10 serially imaged subjects referred to the childhood schizophrenia study who did not meet diagnostic criteria for schizophrenia (labeled Psychosis NOS - Not Otherwise Specified - in DSM terms; (24)). These subjects received identical medication to the patients in this study through adolescence, primarily for control of aggressive outbursts, and at follow-up, none had progressed to schizophrenia (35) but all continued to exhibit chronic mood and behavior disturbance. While medication is unlikely to be responsible for a loss profile that moves across the brain, clozapine, for example, may increase Fos-immunoreactivity in the thalamus (36), and might, logically, modulate rates of cortical change. (In addition, brain regions important for motor function, including the basal ganglia, show increased volumes in response to some older, conventional neuroleptics, although these effects are renormalized after treatment with the atypical antipsychotics used in this study). As seen in Figure 6, while the non-schizophrenic group did show some subtle but significant tissue loss, this was much less marked than for the schizophrenics. Moreover, no temporal lobe deficits were observed in the PNOS group (Fig. 6), suggesting that the wave of disease progression into temporal cortices may be specific to schizophrenia, regardless of medication, and also regardless of gender or IQ. Intriguingly, the psychosis NOS subjects, who share some of the deficit symptoms but do not satisfy criteria for schizophrenia, exhibited significantly accelerated gray matter loss in frontal cortices relative to healthy controls, in approximately the same, but a less pervasive, region than schizophrenics (a significant loss of 1.9%±0.7%/yr. was detected in both left and right superior frontal gyri; $p<0.03$). Groups of healthy controls, psychosis NOS and schizophrenic patients therefore lost frontal gray matter at successively increasing rates, i.e. in a statistical hierarchy with loss rates significantly faster in the non-schizophrenic control group than in healthy controls, and even faster in schizophrenia. In the region where the medication controls were affected (superior frontal cortices), their deficits at follow-up averaged 7.5%±1.6% relative to healthy controls ($p<0.006$). This was significantly less severe ($p<0.05$) than the 13.0%±3.2% deficit in the schizophrenic group ($p<0.001$, relative to healthy controls), whose global functioning was more greatly impaired at follow-up ($p<0.05$; *cf*. *CGAS scores*, Table 1).

Relationship to Clinical Deficits. We further evaluated the clinical specificity and functional correlates of these findings. patient group deteriorated overall; their CGAS scores, which provide a global assessment of function, deteriorated from 37.4 ± 5.7 at

study entry to 30.8 ± 3.4 at follow-up (p<0.05; Table 1). Meanwhile, the average scores for the IQ/medication control group remained stable (43.0 ± 6.5 at entry; 41.9 ± 3.8 at follow-up), and were higher (less impaired) than those of the schizophrenic patients at follow-up (p<0.05). This suggests an overall deterioration of global functioning in COS, consistent with the progressive deterioration of structure.

At an individual level, rates of temporal loss correlated strongly with SAPS total score at final scan (*Scale for Assessment of Positive Symptoms* (22); p<0.015, *left hemisphere*; p<0.004, *right hemisphere; all p-values corrected*). Faster loss in both the superior temporal gyri and the entire temporal cortices were significantly associated with a more severe clinical profile of positive symptoms (e.g., hallucinations or delusions). While tissue loss rates were not significantly linked with the rate of change in SAPS scores from baseline (p>0.05), and SAPS scores were not linked with the amount of tissue at baseline (p>0.05), loss rates were a good predictor of positive symptoms at follow-up, i.e. the remaining symptoms that were refractory to medication. In addition, those with the least overall tissue deficit had the best cognitive performance in terms of full-scale IQ at follow-up, and those with the worst deficit on MRI had lowest full-scale IQ at follow-up (r=0.62; p<0.016). Gray matter quantity at initial scan was also a good predictor of full-scale IQ in the patient group at follow-up (r=0.52; p<0.042). At baseline, this linkage did not reach significance (r=0.44; p=0.077), but a change in correlations between baseline and follow-up was not significant (r_2-r_1=0.18; z=0.54; p=0.3). Faster loss rates in frontal cortex were also strongly correlated with more severe negative symptoms (e.g., flat affect, poverty of speech; p<0.038 for total SANS score at final scan). This linkage is consistent with the physiological hypothesis that negative symptoms of schizophrenia may depend on reduced dopaminergic activity in frontal cortices (37). The tight linkage between the deficit symptoms of schizophrenia and the pervasive loss of cortical tissue suggests a disease mechanism that may only be partially opposed by neuroleptics (38).

Discussion

During the development of schizophrenia in these early adolescent subjects, a dynamic wave of gray matter loss occurred, starting in parietal association cortices, and proceeding frontally to envelop DLPFC and temporal cortices, including the superior temporal gyri (STG). The deficits spread and intensified, in the same subjects, over 5 years of disease progression and eventually engulfed parietal, motor and supplementary motor, temporal (including primary auditory) and prefrontal cortices. The dynamic pattern is intriguing, as it begins in brain regions where deficits, at least in adults, appear to be mediated by

environmental (nongenetic) factors (parietal cortices (16)). It then progresses over a multi-year time-frame into frontal and temporal regions where deficits appear, from our twin and other familial studies, to be strongly mediated by genetic factors (16,34).

Relation to Prior Findings. The dynamic pattern of loss may also suggest a structural basis for the prodromal and chronic neuromotor, sensory and associative deficits observed clinically and in studies of the functional and metabolic integrity of the cortex. Glucose metabolism is reduced in frontal cortices in chronic childhood and adult schizophrenics both at rest and while performing tasks that increase frontal lobe metabolism, such as the Continuous Performance Test (CPT; (39)). COS patients also display significantly increased metabolic rates in inferior frontal gyri with marked decreases in superior and middle frontal gyri. This profile may mirror, to some degree, the discrete pattern of accelerated gray matter loss identified here (Fig. 1). Whether or not this increased metabolism represents an adaptive or compensatory response to cell loss in superior frontal systems, a similar underlying pathophysiology may underlie these structural, metabolic and functional impairments as the disease develops.

The early parietal deficits observed here are consistent with recent functional MRI studies in adult patients showing marked parietal activation deficits in working memory tasks (40). Recent functional imaging studies using positron emission tomography (PET; (41,42)) and functional MRI (43) also show a diminished activation of the sensorimotor cortex and supplementary motor area (SMA) during motor tasks (finger-to-thumb opposition) in schizophrenia. Implication of cortical motor systems is also consistent with premorbid motor impairments, consistently noted in studies of childhood-onset schizophrenia. In frontal cortices, regions of fastest progressive gray matter loss terminated anteriorly in the frontal eye fields (FEF). Visual search tasks are thought to tap a key attentional dysfunction in schizophrenia (44), namely a deficit in the ability to hone in on the most important elements in a picture, and to stare instead of engaging in active visual search. By studying exploratory eye movements during scene perception, impairments have been observed in schizophrenic adolescents in the basic control of exploratory eye movements, suggesting that they stared more and had difficulty in the top-down control of selective attention and visual search. Continuous attrition of gray matter in frontal eye fields may underlie some of the deficit symptoms in visual attention. The marked anterior limit of the loss pattern around the anterior limit of the frontal eye fields (Brodmann area 8) may indicate an anatomically specific progression that directly impacts the systems supporting attentional dysfunction.

Pathologic Studies. Recent neuropathological studies (45), evaluating regional neuronal density *post mortem*, have found altered cell packing of pyramidal and nonpyramidal neurons in the schizophrenic cortex, with a disproportionate reduction in layer V of prefrontal area 9. Pathologic and *in vivo* MRI studies jointly suggest that neuronal atrophy may be one anatomic substrate for deficient information processing in schizophrenia. Altered laminar density of cells in the schizophrenic cortex, and moderate reductions in cortical thickness, may be a major contributor to the intense dynamic processes of gray matter loss that are imaged here *in vivo*, and mapped as they spread from parietal to frontal and temporal regions.

Developmental Implications. Neurodevelopmental theories of the onset of schizophrenia posit disturbances, either pre- or post-natally, in the processes of neuronal migration (3,46), or in synaptic pruning, which intensifies around the age of 5 years (47-49,15). Our data indicate that structural changes clearly progress after psychosis onset and well into adolescence, consistent with earlier reports of ventricular expansion and overall lobar reduction (7,9,50). Cross-sectional studies of this COS population have also found a failure of normal maturation in neurological test performance during adolescence (51). This is also consistent with several recent brain structure studies showing more subtle but significant progressive cortical gray matter loss in adult onset schizophrenia (52,8,53,11). Perhaps surprisingly in this cohort, while parietal and frontal/motor deficits precede puberty, temporal deficits do not. It is probable that early neurodevelopmental abnormalities and later gray matter loss are related, as genes affecting prenatal development may also have roles in later brain maturation (47,54,55). Intriguingly, the earliest deficits occur in a regions of parietal cortices where progressive cortical change occurs significantly in both healthy and schizophrenic subjects in the teenage years. In adults, parietal deficits appear to be mediated by environmental (nongenetic) factors, as the mathematical pattern of these deficits distinguishes schizophrenic adult twins from their healthy, genetically-identical, monozygotic co-twins. Finally, the frontal and temporal territories, which were spared when our cohort were first scanned, are later engulfed by the wave of tissue loss. In these regions, deficits in adult patients appear to be highly heritable (16,34). By dissociating early brain structure deficits that pre-date psychosis onset, those that progress, and those that begin in adolescence, dynamic and genetic brain mapping may shed light on the triggers of schizophrenia. These findings are consistent with the notion that activation of some non-genetic trigger contributes to the onset and initial progression of the illness (56,57).

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Acknowledgments: Grant support was provided by a P41 Resource Grant from the National Center for Research Resources (P.T., C.V. and A.W.T.; RR13642) and by National Institutes of Health intramural funding (J.N.G., P.G., J.B., R.N., J.L.R.). Additional support for algorithm development was provided by the National Library of Medicine (LM/MH05639), NINDS (NS38753), the National Science

Foundation (BIR 93-22434), and by a Human Brain Project grant to the International Consortium for Brain Mapping, which is funded jointly by NIMH and NIDA (P20 MH/DA52176). Special thanks go to our colleagues for their support. Please address correspondence to Paul Thompson, e-mail: thompson@loni.ucla.edu.

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Figure Legends

Fig. 1. Average Rates of Gray Matter Loss in Normal Adolescents and in Schizophrenia. (a) 3D maps of brain changes, derived from high-resolution magnetic resonance images (MRI scans) acquired repeatedly from the same subjects over a 7-year time span, reveal profound, progressive gray matter loss in schizophrenia (*right column*). Average rates of gray matter loss during the 5-year period from 13 to 18 years of age are displayed on average cortical models for the group. Severe loss is observed (*red and pink colors*; up to 5% annually) in parietal, motor and temporal cortices, while inferior frontal cortices remain stable (*blue colors*; 0-1% loss). Dynamic loss is also observed in the parietal cortices of normal adolescents, but at a much slower rate. The significance of group differences and nonlinearities in these changes are further explored in Figs. 2-4. (b). Average gray matter loss rates were computed for all 24 subjects in superior frontal gyri (SFG), lateral temporal cortices (LTC), and superior parietal lobules (SPL) in both brain hemispheres. Error bars indicate the standard error of the sample means, by region, in controls and patients. Individual loss rates (in percent per year) are plotted (*patients, filled squares, controls, white squares*), showing significant group separation despite some outliers.

Fig. 2. Significance of Dynamic Gray Matter Loss in Normal Adolescents and in Schizophrenia. These maps show the local significance of the dynamic brain change in normal adolescents, in schizophrenic subjects. Highly significant progressive loss occurs in schizophrenia in parietal, motor, supplementary motor and superior frontal cortices. Broad regions of temporal cortex, including the superior temporal gyrus, experience severe gray matter attrition. By comparing the average rates of loss in disease (*middle column*) with the loss pattern in normal adolescents (*first column*), the normal variability in these changes can also be taken into account and the significance of disease-specific change can be established (*last column*).

Fig. 3. Dynamic Changes in Male and Female Teenagers with Schizophrenia. A consistent pattern of progressive gray matter loss, in parietal, frontal and temporal cortices, is observed in independent groups of males and female patients. While larger studies may reveal subtle gender differences, a single pattern is observable in both boys and girls, supporting the anatomical specificity of the findings. Loss is highly significant when males and females are pooled (*bottom row*).

Fig. 4. Mapping Nonlinear Brain Changes and Age Effects. Dependencies between the rate of gray matter loss and the patient's age are mapped locally and visualized. Maps of correlation between rates and age are mapped, as is their significance. Parietal regions lose gray matter faster in younger patients (*red colors*; $r > 0.8$; $p < 0.001$), consistent with an earlier timing of deficits and a slowing of the rates of progression as adolescence continues.

Fig. 5. Mapping Early and Late Deficits in Schizophrenia. Deficits occurring during the development of schizophrenia are detected by

comparing average profiles of gray matter between patients and controls at their first scan (age 13; *top row*) and their last scan 5 years later (age 18; *bottom row*). Although severe parietal, motor and diffuse frontal loss has already occurred (*top row*), and subsequently continues (Figs. 1,2), the temporal and dorsolateral pre-frontal loss characteristic of adult schizophrenia is not found until later in adolescence (*bottom row*), where a process of fast attrition occurs over the next 5 years. The color code shows the significance of these effects.

Fig. 6. Mapping Brain Change in Medication-Matched Subjects Not Satisfying Criteria for Schizophrenia. No temporal lobe deficits are found in subjects matched for medication who do not meet criteria for DSM-III-R schizophrenia, suggesting that the progression of the deficits into temporal lobe is specific to schizophrenia, regardless of medication (and regardless of gender; *q.v.*, Fig. 3). Nonetheless, these patients share some symptoms with schizophrenics, exhibiting frontal deficits in a similar anatomical pattern. These frontal deficits (i.e., gray matter loss rates) are statistically significant relative to healthy controls, but significantly smaller in magnitude than the greatly accelerated loss rates in schizophrenia.

Table 1. *Clinical Severity of the Schizophrenic and Medication-Controlled Groups.* SANS and SAPS tests (22) of positive and negative symptom severity (as well as the Children's Global Assessment of Functioning Scale; CGAS (58)) were administered both at baseline and every 2.3 years at follow-up. Mean scores and standard errors are given for both groups, at study entry and at the follow-up 4.6 years later. This corresponds to the interval over which brain changes were mapped. SAPS and SANS scores improved in the COS group ($p < 3\times10^{-6}$ and $p < 0.005$, respectively), partly as a result of neuroleptic treatment. However, the COS group's positive and negative symptoms were initially much more severe than the medication/IQ controls ($p < 2\times10^{-5}$ and $p < 10^{-7}$ for SAPS and SANS, respectively) and they were more impaired in global functioning at follow-up (group difference: $p < 0.05$).

		Schizophrenics (COS)	Medication/IQ Controls (PNOS)
SAPS	Baseline	58.3 ± 5.3	18.4 ± 5.1
	Follow-up	18.2 ± 4.3	20.2 ± 5.4
SANS	Baseline	73.8 ± 4.7	19.3 ± 3.9
	Follow-up	49.8 ± 8.5	28.4 ± 5.8
CGAS	Baseline	37.4 ± 5.7	43.0 ± 6.5
	Follow-up	30.8 ± 3.4	41.9 ± 3.8

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