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The Concept of Progressive Brain Change in Schizophrenia: Implications for Understanding Schizophrenia

Lynn E. DeLisi[1–3]

[2]New York University School of Medicine, 650 First Avenue, New York, NY 1006; [3]Center for Advanced Brain Imaging, The Nathan S. Kline Institute for Psychiatric Research, 140 Old Orangeburg Road, Orangeburg, NY 10962

Kraepelin originally defined dementia praecox as a progressive brain disease, although this concept has received various degrees of acceptance and rejection over the years since his famous published textbooks appeared. This article places an historical perspective on the current renewal of Kraepelin's concept in brain imaging literature that supports progressive brain change in schizophrenia from its earliest stages through its chronic course. It is concluded that a great deal of future research is needed focusing on the longitudinal course of change, the extent to the regions of change within each individual and the underlying mechanism and implications of brain change through functional and neurochemical imaging, combined with structural studies in the same individuals.

Historical Background

The idea that schizophrenia is a progressive brain disease was a prominent aspect of the disease concept when defined as *Dementia Praecox* by Kraepelin at the end of the 19th century (1896–1899).[1] While hallucinations, delusions, formal thought disorder, and disturbances in affect have been described since ancient times,[2] thinking about their origins did not seem to occur in the literature until close to Kraepelin's time. As he wrote in his 1899 textbook: " …. In view of the clinical and anatomical facts known so far I can not doubt we are dealing with serious … and only partially reversible damage to the cerebral cortex … 75% of cases reach higher grades of dementia and sink deeper and deeper …."[1] He then further described what he considered the neuropathology of schizophrenia and illustrated it in his 1919 volume, as "nerve cells diseased in high degree filled with lipoid products of disintegration."[3]

On the other hand, Eugen Bleuler, also an influential thinker about the psychoses, who coined the term "schizophrenia" during this same era, only partially supported this notion and considered the possibility that these were not conditions due to brain damage, rather a "splitting of the mind" that could recover and that there were several possibilities for outcome, not only a progressive deteriorating one.[4] Another contemporary of Kraepelin and Bleuler, Karl Jaspers, seemed to adopt the concept that this was a biological brain disorder, but did not address the issue of progression because his interest was more in the phenomenology itself.[5,6] Thus, the concept of progression was focused on mainly by Kraepelin at that time and was certainly controversial from its beginnings.

Kraepelin's writings were followed in the early 1900s by a few large pneumoencephalographic studies[7–11] describing evidence of brain ventricular enlargement in chronic schizophrenia. The few patients who had second follow-up studies a few years later also appeared to have further ventricular enlargement and thus evidence of a progressive brain disease (see table 1).

Later in the 1900s, however, because the infectious and neoplastic disorders of the brain were separated from "psychiatric illness," schizophrenia became a diagnosis of exclusion that was by definition thought to have no "organic" cause and thus related to the psychological environment that one was born into. It was acceptable in the mid-1900s for these patients to be treated with long-term psychoanalysis[12–14] and family therapy[15–17] and described as having schizophrenigenic mothers and bad family communication, despite the accumulation from twin and family studies that an inherited component increased risk for illness more substantially. There were 2 main discoveries that seemed to turn the tide back toward uncovering biological origins to schizophrenia, ie, the large effect of neuroleptics in suppressing symptoms of illness and the family adoption studies that showed it was not the environment, but rather inheritance that determined who did or did not develop schizophrenia.

It was not, however, until the 1970s when schizophrenia began again to be considered a biological disorder, that the previous pneumoencephalographic studies were confirmed using computerized tomography (CT). In initially a small cohort by Johnstone et al[18] in 1976

[1]To whom correspondence should be addressed; tel: 212-263-3406; fax: 212-263-3407; e-mail: DeLisi76@AOL.com.

Table 1. Pneumoencephalographic Evidence of Progressive Ventricular Brain Enlargement in Chronic Schizophrenia

Study	No. Of Patients	Follow-up Time	Results (Change over time)
Moore et al[8]	6	2–3.5 y	Increased ventricular size[a]
Huber[9]	27	3 wk–5 y	Increased ventricular size in 8 patients[a]
Haug[10,11]	24	2 mo–4.5 y	Increased ventricular size in 4 patients[a]

[a]Associated with clinical deterioration.

and then a considerably larger one in 1978 by Weinberger et al[19], significantly increased ventricular size was reported in people with chronic schizophrenia compared with age-corrected controls that did not appear to be associated with years of illness or pharmacologic treatment. This is perhaps the most replicated finding in schizophrenia research today, more than 30 years later.

The nature of what is heritable is currently being investigated worldwide applying the newly emerged methods now available in molecular biology. What most investigators agree upon is that the inherited component has an effect on brain development and homeostasis. Although, specific genes or genetic pathways have not yet been definitively elucidated, a new field of "imaging the genome" has arisen from studies recently combining an examination of brain structure and function with genetic variation in such interesting brain-expressed genes as brain-derived neurotrophic factor (BDNF) and catechol-O-methyl transferase.[20] Certainly, if there is a progressive component to the disorder, this could also be a characteristic of the genetic pathology, as is with other neurodegenerative disorders, such as Huntington Chorea or Alzheimer disease. One recent preliminary report even provides data suggesting that variation in the BDNF gene contributes to progressive brain change in schizophrenia.[21] While if true, this could be an important finding that leads to considerable progress in understanding schizophrenia, it will need clear replication before time is invested further in a focused attempt to develop treatments that will combat the effects of inheriting this variation.

Once definitive genes for schizophrenia are established, it will be important to determine whether and how they could produce progressive brain changes. This will only be relevant, however, if the observed progressive component is central to the illness process, rather than due to secondary environmental effects (treatment or stress that accompanies the chronic illness course). Even if progression is central to the illness process, some investigators may propose that it is separate from the genetic vulnerability and represents a second so-called "hit" that leads to illness that could be environmentally or epigenetically induced (ie, such as stress, substance abuse, and hormonal disregulation, eg, Pantelis et al[22]).

The evidence that currently exists for progressive brain change is thus discussed in the following review; the where, why, and when of progression are suggested based on existing knowledge; and future research needed to clarify the concept of progressive change and its relevance for understanding and treating schizophrenia are proposed.

The Published Evidence for Brain Change in Schizophrenia

The Evidence

Since the CT study performed by Johnstone et al in the 1970s,[18] vast improvement in imaging technology capable of precisely viewing the brain has led to numerous more extensive and precise studies on schizophrenia. Magnetic resonance imaging (MRI) quickly replaced CT for detection of many conditions and has enabled gray and white matter abnormalities to be distinguished and volumes of anatomical structures to be measured. Parallel to the development of the hardware by physicists, computer scientists have been able to devise software to detect change that otherwise would not be visible. Thus, the field quickly went from hand measurement with planimeters of the 1970-80s for tracing of ventricles and other anatomical boundaries on CT scans, to automated computer programs for stripping tissue into its components and determining structural volumes more exactly. In sum, these studies have produced an extensive literature on deviation in brain structural size in people with chronic schizophrenia and those at the first episode of illness.[23–25] The major findings have included lateral ventricular enlargement (left > right), nonlocalized bilateral gray matter reductions, reduced white matter integrity as seen by diffusion tensor imaging (DTI),[26] regional volume reductions (frontal, temporal total, and superior temporal gyrus [STG], as well as middle and inferior,[27,28] hippocampus, and other limbic regions), loss of normal asymmetries, miscellaneous developmental abnormalities (ie, cavum septum presence, corpus callosal size, and shape changes), and caudate enlargement (thought to be a consequence of medication).[29–34] In 2 recent meta-analyses of the data on first-episode cases,[24,25] some of the findings were shown to be already distinguishable at the first episode (lateral and third ventricular volume increase, whole-brain and hippocampal reductions), while others were not (such as in temporal lobe or amygdala), possibly suggesting that the others appear later on in illness chronicity or only in people destined to have a more severe form of illness.

The Theories to Explain the Observations

When one puts all the findings in perspective with the above past history, it would appear obvious that the

most likely first explanation is that progressive degeneration has taken place, but many investigators have been reluctant to reach that conclusion. The predominant view of the 1980s and early 1990s was that because there was no gliosis detected in postmortem brain, because findings were detected as early as during a first psychotic episode, and because no study showed a correlation of years of illness with degree of change, the changes seen were most likely formed early on in brain development. Several variations of the developmental hypothesis by senior thinkers in the field influenced the accepted views about the accumulating brain structural observations. For example, Feinberg in 1982[35] proposed, based on his electroencephalography studies in psychotic adolescents, that schizophrenia was caused by an abnormality in programmed synaptic elimination during adolescence. He wrote that the "Converging evidence indicates that a profound reorganization of human brain function takes place during adolescence …. A reduction in cortical synaptic density has recently been observed and might account for all of these changes. Such synaptic 'pruning' may be analogous to the programmed elimination of neural elements in very early development. A defect in this maturational process may underlie those cases of schizophrenia that emerge during adolescence …."

Weinberger in 1987 wrote that "…. The findings suggest … that the pathology occurs early in development, and that the causative process is inactive long before the diagnosis is made … a fixed lesion from early in life interacts with normal brain maturational events that occur much later …."[36]

Murray et al[37] in 1991 concluded that "… the evidence regarding structural brain abnormalities and epidemiology suggests that a significant portion of cases of schizophrenia have their origins in fetal or neonatal life. The mechanisms involved in the aberrant neurodevelopment remain obscure, but some impairment of neuronal migration is an appealing hypothesis."

Crow in 1989 wrote "…. Schizophrenia is associated with structural changes in the brain, although whether these precede onset of illness or progress with episodes is not established. In a post-mortem study we find that ventricular enlargement affects the posterior and particularly the temporal horn of the lateral cerebral ventricle … selective to the left hemisphere. The findings are consistent with the view that schizophrenia is a disorder of the genetic mechanisms that control the development of cerebral asymmetry.[38]"

While these senior investigators (Feinberg, Weinberger, Murray, and Crow) have certainly gone on to develop their theories further about the origin of brain changes in a more detailed and comprehensive fashion over recent years, these published statements represent the variety of different views that had determined the direction of subsequent research and thought in this field toward the end of the 20th century.

The Evidence for Progressive Brain Change

By the early 1990s, a few researchers had begun to question the much accepted developmental hypotheses. In December of 1990, an all-day symposium conducted by L. E. DeLisi and J. A. Lieberman as an ACNP (American College of Neuropsychopharmacology) satellite brought together many of the investigators in this field to debate the facts on neurodevelopment vs neurodegeneration. The proceedings from this day were later published in a special issue of *Schizophrenia Research* in 1991 (eg, Degreef et al[43] and DeLisi et al[44]). During the conference, Brian Woods (from McLean Hospital at that time) presented data showing an extreme case of a patient with schizophrenia who had obvious visible ventricular enlargement over time; but this was dismissed by many present as a case of a degenerative neurological disease of unknown origin with accompanying psychosis. Despite heated and at times emotional debate, no consensus was reached at this meeting because carefully collected case and control data were not yet available to confirm whether the structural brain findings were stable over time or progressed. The early CT studies either had no controls for comparison and/or were only measurements with considerable error and variation due to subject position in the scanner and thickness of slices used. At that time, the methods were not well developed to conduct such longitudinal scanning protocols.

However, during the last decade or more, a wave of new sets of carefully controlled MRI studies were performed, the first of which was a 5-year longitudinal examination of first-episode schizophrenia patients and matched controls.[45,46] In this study, scans were performed at multiple time points most annually, and thus, the data could be considered more extensive and consistent, despite limitations of MRI scanning in the time period of this study (approximately 1988–1994). A significantly greater rate of ventricular enlargement over time, as well as a reduction in cortical volume, was observed in the patients compared with controls. These findings were later confirmed by other investigators similarly scanning first-episode patients and also scanning chronic patients over time, thus obtaining time points in different stages of illness (see tables 2 and 3). There were also other studies not reporting any measurement of ventricular volume but focusing on other structures, such as those within temporal and frontal cortices and the limbic system. Thus, these studies almost all consistently show progressive brain change and are now extensively reviewed in the literature by many investigators (eg, Pantelis et al[22], DeLisi[74], and Lieberman[75])

Where Does the Progression Occur?

Ventricular enlargement has been the most frequently studied longitudinal study and clearest finding from

Table 2. Studies Examining Lateral Ventricular Brain Size Longitudinally in Schizophrenia in Chronological order

Study	Scanner	No. of Patients	No. of Controls	Stage of Illness at Baseline	Years of Follow-up	Findings
Nasrallah et al. (1986)[39]	CT	11	0	Chronic schizophrenia	3	No change
Vita et al. (1988)[40]	CT	15	0	Chronic schizophrenia	2–5	No change
Kemali et al. (1989)[41]	CT	18	8	Chronic schizophrenia	3	Increased ventricles in one-third of patients
Woods et al. (1990)[42]	CT	9	0	Chronic schizophrenia	1–4.5	Increased ventricles in 8/9 patients
Degreef et al. (1991)[43]	MRI	18	8	First-episode schizophrenia	1–2	No change
DeLisi et al. (1991, 1992, 1995, 1997, 2004)[44–48]	MRI	50 26	20 10	First-episode schizophrenia	4–5 10	Increased ventricles Increased ventricles
Sponheim et al. (1991)[49]	CT	15	0	First-episode schizophrenia	1–3	No change
Jaskiw et al. (1994)[50]	CT	7	0	First-episode schizophrenia	5–8	No change
Vita et al. (1994)[51]	CT	9	0	First-episode schizophrenia	2–4	No change
Nair et al. (1997)[52]	MRI	18	5	Chronic schizophrenia	1.1–3.8	Increased ventricles—poor outcome only
Davis et al. (1998)[53]	CT	53	13	Chronic schizophrenia	5	Increased ventricles—poor outcome patients only
Rapoport et al. (1997)[54]	MRI	16	24	Chronic childhood schizophrenia	1.5–4	Increased ventricles
Illowsky et al. (1998)[55]	CT	13	0	Chronic schizophrenia	7–9	No change
Lieberman et al. (2001)[56]	MRI	51	13	First-episode schizophrenia	1–2	Increased Ventricular size associated with poor outcome
Mathalon et al. (2001)[57]	MRI	24	25	Chronic schizophrenia	0.7–7.5	Increased CSF
Saijo et al. (2001)[58]	MRI	15	12	Chronic schizophrenia	10	Increased ventricles
Cahn et al. (2002)[59]	MRI	34	36	First-episode schizophrenia	1	Increased ventricles
James et al. (2002)[60]	MRI	16	16	First-episode childhood schizophrenia	1.7–2.7	No change
Ho et al. (2003)[61]	MRI	73	23	First-episode schizophrenia	3	Increased CSF

Note: CT, computerized tomography; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid.

longitudinal studies (see tables 1 and 2). It also appears that the progressive change takes place and may even originate unilaterally in frontal and temporal lobes but eventually appears throughout the cortex and seen as overall cortical reduction. However, the studies suggesting this need more consistent replication, and thus, the "where" question cannot be answered with certainty and is also associated with the timing of these events because "where" it is taking place may very well be determined by when in the course of illness individuals are studied.

The studies from Edinburgh and Melbourne using MRI in prodromal cases are reviewed in table 3.[70–72] These are only preliminary findings that again need replication in larger samples by other investigators, as well as replication in high-risk cases before they have any symptoms of the disorder. Nevertheless, these studies so far show that some structures appear abnormal at the first sign of any symptoms (reviewed in Pantelis et al[76]), while others progress over time and thus at further follow-up appear abnormal. While both cohorts show abnormalities in either left or right regions of the temporal, medial temporal, and frontal lobes and then some progressing over time, the specific structural abnormalities initially present and those that emerge later are not the same in both studies. This could be due to cohort differences in when during the time course of illness development study participants are ascertained. However, these data are also not completely consistent with the literature as a whole in defining what specific structures are abnormal very early on and which are detectable by the first hospitalization. For example, while the Melbourne ultra-high risk studies implicate the medial temporal lobe as detectably abnormal during the prodrome,[76] Razi et al[77] fail to find any medical temporal lobe structures to be abnormal at the first episode but do see differences in these structures in chronic patients. At present, there is not enough consistent data accumulated to definitively say which specific structures are involved in this process. Furthermore, whether the structures affected are the same and the entire process the same in ALL individuals

Table 3. Studies Reporting on Anatomical Changes in Other Structures Longitudinally in People at a Prodromal Stage of Schizophrenia, With a First Episode of Schizophrenia or Diagnosed With Chronic Schizophrenia

Study	Scanner	No. of Patients	No. of Controls	Stage of Illness at Baseline	Years of Follow-up	Findings
DeLisi et al. (1991, 1992, 1995, 1997, 2004)[44–48]	MRI	50	20	First-episode schizophrenia	4–5	Decreased hemispheric volume bilateral
		26	10		10	No change in STG
Gur et al. (1998)[62]	MRI	20	17	First-episode schizophrenia	2–3	[a]Frontal lobe decreased. No change in temporal lobe
Jacobsen et al. (1998)[63] Thompson et al. (2001)[64] Keller et al. (2003)[65] Sporn et al. (2003)[66]	MRI	16	24	Chronic childhood schizophrenia	1.5–4	Decreased hemispheric volume, temporal lobe, STG, hippocampus, thalamus, striatum
Mathalon et al. (2001)[57] Puri et al. (2001)[67]	MRI	24	25	Chronic schizophrenia	0.7–7.5	Whole brain gray matter and STG decreased bilaterally
Wood et al. (2001)[68]	MRI	30	26	First-episode schizophrenia	0.5–4.2	Whole brain volume, decreased bilaterally, no change in hippocampus or temporal lobe
Cahn et al. (2002)[59]	MRI	34	36	First-episode schizophrenia	1	[b]Whole brain gray matter decreased
Ho et al. (2003)[61]	MRI	73	23	First-episode schizophrenia	5	Frontal white matter decreased
Kasai et al. (2003)[69]	MRI	13	14	First-episode schizophrenia	1.5	Decreased left STG and planum temporale
Lawrie et al. (2002)[70], Job et al. (2005)[71]	MRI	19 psychotic at 2 year	49 non-psychotic at 2 years	Prodromal cases	2	[c]Decr R temporal R/L STG, L cingulate, LR uncinate, L fusiform, L uncus, LR PHG, R amygdala
Pantelis et al. (2003)[72]	MRI	10 psychotic	11 non-psychotic	Prodromal cases	1	[c]Decr L PHG, L fusiform, L orbitofrontal, L cerebellum, Cingulate bilateral, L Temporal
Whitford et al. (2006)[73]	MRI	25	26	First-episode schizophrenia	2–3	Gray matter reductions: parietal and temporal

Note: MRI, magnetic resonance imaging; STG, superior temporal gyrus; R, right; R/L, right and left; PHG, parahippocampal gyrus.
[a]Associated with good outcome.
[b]Associated with poor outcome.
[c]No change in ventricles, unpublished communication.

who develop schizophrenia is unclear and as of yet untested.

Why Does Progression Occur?

An Overview

Despite several years of accumulated data on progressive brain structural change in people with schizophrenia, an understanding of their significance continues to be elusive. While it has been suggested that both developmental deviance and progressive change could be possible,[22,78] it has been Weinberger and McClure's contention[79] that the findings being presented in longitudinal MRI studies have to be artifactual or at best, epiphenomena. In a later article, examining the effects of neuroleptic withdrawal on brain volume in a small sample of patients, they concluded that the longitudinal regional brain volume change is most likely physiological

and thus potentially reversible.[80] They argue that quantitatively the findings of progressive brain change do not make sense, given that these changes occurred in studies of patients in all stages of illness and that if taken to be continuous over a long time span, the rates of change being reported would lead to very little brain tissue remaining in later life. People do not die of schizophrenia, nor do they lose their sense of orientation and considered as cases of dementia for the most part, as people with Alzheimer disease. This argument can be countered by at least 2 studies showing that the change occurring is nonlinear and may be sporadic and/or curvilinear.[81,82] In the study of Van Haren et al,[81] detectable progressive change was occurring in a curvilinear fashion between ages 22 and 47, peaking, and then the rate of change decreasing beyond the late forties. DeLisi et al[82] also showed by graphing individual change over time during a 5-year period subsequent to the first episode that, regardless of the age of the patient, the rate of progressive change varied over time among individuals and within each individual and was clearly not linear.

More recently, the controversy over whether neuroleptics affect the brain has led to questions about how much of the reported change is medication induced and not related to the origin of disease, nor its functional outcome (see below).

Thus, the question becomes whether there is functional evidence to support the significance of progressive structural change to the disease process. For structural deviance to have any clinical meaning, one must assume that there is evidence of a resultant malfunctioning and that this can be measured. However, it has not been clearly seen that structural change is related to poorer clinical outcome, and some studies actually report the opposite.[62,82] However, because almost all patients are medicated continuously, it is difficult to separate out the associations with outcome from medication effects, whether the outcome is favorable or unfavorable. Nevertheless, more studies are needed to clarify this relationship in detail and it likely will only be resolved once the biological mechanism for the progressive change is established.

In other more biological functional studies, others, such as Salisbury et al[83] provide evidence that electrophysiological abnormalities (ie, the mismatch negativity amplitude) may be correlated with structural progression.

Evidence for functional change also comes from functional MRI studies. For example, in the study of Li et al,[84] we have shown that language processing is clearly different in people at high genetic risk for schizophrenia, and less lateralized, which suggests less efficiency and perhaps an indication of early vulnerability. The reduced lateralization could be due to an underlying structural anomaly in the asymmetric development or degeneration of the white matter pathways for language and their connections between hemispheres. Some preliminary evidence in the same subjects is provided that this could be the case,[85] and both studies suggest that these changes could progress because they are considerably more severe in chronic patients by comparison. Thus, although these are not longitudinal studies of progressive change, they suggest that functional change may be associated with structural deviation early on and unrelated to medication.

Is Progressive Change an Artifact of Medication?

A recent publication by Lieberman et al[86] suggests that one conventional neuroleptic haloperidol, but not one atypical neuroleptic olanzapine, may have an effect on gray matter volume. However, there were several problems with this short treatment trial/follow-up study, and while intriguing, these results need replication. Some, but not all earlier studies showed specifically caudate volumes were larger with neuroleptics, particularly conventional neuroleptics, but were not affected by the newer atypicals, a concept that was consistent with effects on the dopamine receptor rich cells of the caudate (eg, Chakos et al[29], Corson et al[30], Dazzan et al[31], Lang et al[32], Keshavan et al[33], and Scheepers et al[34]).

Two recent important publications from the David Lewis laboratory in Pittsburg deserve serious attention.[87,88] The administration of both haloperidol and olanzapine to macaque monkeys over a 2-year period resulted in a significant overall shrinkage in brain tissue in both gray and white matter across several regions on autopsy, with lower glial cell counts and corresponding increased neuronal density that was unrelated to any tissue fixation procedures. Although the numbers of monkeys in each experimental group were small ($N = 6$), only adult animals were used, only 2 of the many neuroleptics were tested, and in addition nonhuman healthy primates may be more sensitive to effects of neuroleptics. Nonetheless, these results are strikingly strong evidence for an effect of these drugs on brain tissue. This is an effect not clearly tested by pharmaceutical companies prior to obtaining approval for placing their drugs on the market. In addition, neuroleptics may have different effects on the brain during different stages of illness (reviewed in Vita and DePeri[89]). While the effects of neuroleptics on neuronal health directly need to be clarified further and the above studies independently replicated, one must be reminded that prior to the use of neuroleptics, ventricular enlargement was clearly reported with pneumoencephaplography and shown to be progressive in some patients. Other treatments could have also been the cause, but this remains unknown. In addition, the studies of prodromal cases not yet treated with neuroleptics also provide evidence of progressive change occurring in the cortex unrelated to treatment.

Is Progressive Change Due to Metabolic Change?

It is possible also that weight gain and a change in the physiological balance and general hydration of an

individual may play a somewhat reversible role in what appears to be brain volume changes. Past reports have included ventricular enlargement in alcoholism[90] that declines in abstinence and ventricular enlargement in anorexia[91] that improves with resolution of the illness. It cannot be ruled out that some of the observed progression in brain volume or ventricular size that particularly occurs in the early stages of illness, the leveling off or even resolving, may be such epiphenomena.

When Does Progression Occur?

It is very clear from the few reports and studies already conducted that cortical brain changes are present prior to clinical illness presentation (see table 3) and even before any prodromal symptoms emerge.[85] Our group has some preliminary data (Hoptman M., L.E. DeLisi, B. Ardekani, C. A. Branch, unpublished data) that shows a change in white matter fractional anisotropy within the left, but not right, STG over a 1-year follow-up in 10 genetically at-high-risk individuals. In addition, another study by Mori et al[92] recently published is consistent with this. These data need replication but are consistent with the studies reporting reduced STG volume over time subsequent to a first episode of schizophrenia more often on left than right[69] and meta-analyses mentioned earlier that show what appears to be an association with duration of illness and possibly a progressive decline[24,25]. However, there is at least one failure to replicate this STG finding in older MRI scans taken over a 10-year period.[93] While there was one anecdotal early report by Weinberger,[94] showing ventricular enlargement in an adolescent before he developed a first episode of schizophrenia, there is little evidence that ventricular enlargement can be detected in the years prior to illness. Ventricular enlargement is apparent by a first acute episode of illness leading to hospitalization, but this occurs after brain changes have been likely progressing over the years prior to overt psychosis. The prodromal brain imaging studies do not show it (personal communication with C. Pantellis and E. Johnstone). Ventricular enlargement could be secondary to brain change in the cortex; the cortical changes likely progress over time and eventually lead to detectable ventricular enlargement. Thus, it is concluded that changes in the cortex are detectable first and ventricular enlargement can be observed later. Nevertheless, the amount of tissue fluid may now be detected by more sensitive measures (ie, the Apparent Diffusion Coefficient [ADC] using DTI). The higher the ADC, the more fluid and the more presumed atrophy. In the study of DeLisi et al[85] the ADC was found to be significantly higher within the region of the left superior and left middle frontal gyri in genetically at high-risk people compared with controls. It is suggested that this method shows an early sign of atrophy that cannot be detected by overall ventricular volume quantification.

It is possible that progression occurs very early in some structures before subjects are even identified as ill and then spreads further to other brain regions because the illness process progresses, and that the timing of the progression and the structures involved may vary from person to person. Alternatively, there could be both a neurodevelopmental and a progressive degenerative process that are occurring in schizophrenia. Some structures may never have developed to their full adult capacity, while others did but are deteriorating over time.

One issue that remains, however, is whether progressive change is a result of a primary structural brain change that then when severe enough leads to corresponding functional change or the reverse, that a functional change, perhaps neurochemical in origin, leads to cellular damage and eventually detectable progressive structural change as seen on MRI scans. In the latter case, functional changes will be detectable prior to the detection of structural change. Only more longitudinal combined structural and functional studies of high-risk individuals early on will clarify these hypotheses.

Conclusions

In summary, it is clear that brain structural change is detectable in both gray and white matter prior to illness onset and before neuroleptic medication is given; active progression may occur prior to the onset of clinical symptoms; ventricular change occurs later and is a consequence of cortical change; and the progression is generally widespread. Why this occurs is still unknown. It is speculated here that the changes over time could be part of the genetically controlled disease process, but other explanations are possible, such as various environmental exposures. Although there is some evidence that neuroleptics can change brain tissue, their use is clearly insufficient to explain the several studies now reported of progressive brain change in schizophrenia. Whether progressive brain change can account for all the brain structural anomalies seen in chronic schizophrenia is also unknown.

We can only speculate on when these disturbances are likely to begin. However, it is clear from MRI studies reviewed here and elsewhere that disturbances in brain structure can be detected at least during a prodromal stage in the adolescence or early adulthood. It is highly likely that this process begins much earlier either prior to birth or during postnatal brain development because the literature is filled with studies of delayed developmental milestones and other subtle abnormalities that occur in people who eventually develop schizophrenia. The knowledge that the clinical expression of the illness rarely occurs prior to puberty suggests that the synaptic changes occurring in the cortex with advancing adolescence is crucial for this process. Given a genetic predisposition of undetermined origin, one conclusion is that the same genetic factors must be operating from prior to birth through the

aging process, at different times affecting different processes depending on the age of the individual, from the migration of neurons in early brain cortical development, to brain plasticity and apoptosis during the aging process. The observed progressive brain changes can, if primary to the illness process, be a consequence of the latter.

Regardless of its origin, whether the observed structural change and progression is clinically relevant and can be used by clinicians to guide treatment is not now certain or ready for translation to the clinic. Also, whether early treatment can prevent progression is an important question that can only be addressed once we understand the cause of progression and its connection to the central disease process.

It is suggested that future research should (1) focus on studies of high-risk people longitudinally; (2) emphasize uncovering what in the entire brain of the same person is changing and how this is related to clinical outcome, positive, negative and cognitive symptoms; (3) combine progression with functional and neurochemical studies to understand its significance; and (4) in addition, use animal models for examining the underlying process that may be occurring. For example, one interesting animal model[95] involves kainic acid administration to adult rats that produce neuronal loss over time particularly to the limbic-cortical system. Might this be the first of a series of new models that may ultimately uncover the underlying mechanism of illness?

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