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Review

A review of MRI studies of progressive brain changes in schizophrenia

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Introduction

In the early twentieth century, when Kraepelin first described 'dementia praecox' which eventually evolved into the concept of schizophrenia, he proposed that dementia praecox was probably an unknown organic brain disease. However, in contrast to the case of Alzheimer's disease and Huntington's disease, subsequent pathological studies of the brain failed to establish the neuropathology of schizophrenia. As a result, it had been generally accepted that schizophrenia would be a functional psychosis with neurochemical aberrations but without organic abnormalities. In 1976, Johnstone et al[1] first reported the computer-assisted tomography (CT) finding of lateral ventricular enlargement in patients with schizophrenia. This finding has been replicated in a number of CT studies and has been recognized as representing brain structural abnormalities in schizophrenia.

Magnetic resonance imaging (MRI) enables more detailed and quantitative assessments of the fine brain structures, providing considerable evidence for the view that schizophrenia is a brain disorder with structural brain abnormalities.

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Cross-sectional MRI studies of schizophrenia

Since the first MRI study was done by Smith et al[2] in 1984, there have been at least 200 MRI studies of schizophrenia[3–5]. In addition to replication of the CT finding of ventricular enlargement, MRI studies of schizophrenia have shown specific gray matter volume reductions that are most prominent in the amygdala, hippocampus, parahippocampal gyrus and superior temporal gyrus. Although less consistent findings, some volume reductions have also been reported in the frontal lobe, parietal lobe and cerebellum. A recent meta-analysis[4] of 58 MRI studies that included 1,588 independent patients with schizophrenia reported that, assuming a volume of 100% in the comparison group, the mean cerebral volume of the subjects with schizophrenia was smaller (98%), but the mean total ventricular volume was greater (126%). Further, the regional volume of the schizophrenics was 94% in the left and right amygdala, 94% in the left and 95% in the right hippocampus/amygdala, and 93% in the left and 95% in the right parahippocampus.

Neurodevelopmental hypothesis

Kraepelin believed that dementia praecox was caused by a new form of progressive neuronal degeneration characterized by earlier onset than that seen in previously described entities, such as Alzheimer's disease. In recent years, however, the original Kraepelinian pathogenetic theory of premature progressive neuronal degeneration has come to be opposed by a pathogenetic model that postulates that schizophrenia results from a non-progressive pre- or perinatal derangement of development[6]. The essence of the case against a neurodegenerative mechanism is that gliosis, which is regarded as a necessary neuropathological hallmark of neuronal degeneration, has not been found in postmortem studies of brains of schizophrenics[7]. Furthermore, the hypothesis that schizophrenia is a disorder caused by early and static damage has been supported by CT studies.

Longitudinal CT studies of schizophrenia

The major evidence suggesting early and static brain damage in schizophrenia came from early CT studies that failed to find a correlation between ventricular enlargement and illness duration[8]. Subsequently, several longitudinal CT studies denied the existence of progressive ventricular enlargement in schizophrenia[9–14]. However, those early CT studies had methodological limitations such as a lack of control data and difficulties in controlling scan protocols over time. Recently, a CT study by Davis et al[15] investigated the enlargement of ventricular size over an average of 5 years in 53 patients and 13 healthy controls, and demonstrated marked longitudinal increase in ventricular size only in patients with poor prognosis.

Longitudinal MRI studies of schizophrenia

MRI has several advantages over CT in spatial resolution, discrimination between gray and white matter, easiness in controlling scan protocols, and the non-use of radiation. Thus, MRI is considered more suitable for longitudinal studies, and there have recently been several longitudinal MRI studies of progressive brain structural changes in schizophrenia.

Cortical volumes

Ten longitudinal MRI studies[16–25] investigating cortical changes over time in schizophrenia are listed in Table 1. Among these studies, Delisi and colleagues[17–19] investigated the same group of patients over different follow-up periods up to 4 years or more, and Rapoport and colleagues[20,22,24] followed the same patients repetitively up to 4 years. Although both research groups found no structural differences over the first two years[17,20], Delisi et al[19] noted a greater volume decrease in the left and right hemispheres, right cerebellum and corpus callosum, and Rapoport et al[24] found a greater volume decrease in gray matter of frontal, temporal, and parietal lobes in patients. There have been two other extensive studies that investigated progressive cortical changes over time in schizophrenia. Gur et al[21] found frontal and temporal lobe volume reduction in patients but only temporal lobe volume reduction in controls. However, Lieberman and colleagues[25] rescanned relatively larger groups of subjects, 107 patients and 20 controls, and failed to demonstrate a greater volume decrease in patients.

Subcortical structures

There have been five studies[18–20,25,26] of rescanning the subcortical structures in patients with schizophrenia (Table 2). Four[18–20,26] of them investigated only the caudate nucleus, which is the major site of antipsychotic action. Past cross-sectional MRI studies[27–30] have reported a volume increase in the caudate nucleus, in contrast to the usual pattern of neuropathological findings in schizophrenia, in which volume reduction of brain structures and ventricular enlargement are characteristically seen. The finding of caudate enlargement has been speculated to be a consequential activation and hypertrophy due to dopamine blockage by antipsychotic drugs. Chakos et al[26] observed that caudate volume increased in patients with neuroleptic treatment for 18 months but not in controls, and greater amounts of antipsychotic medication received by patients before their first scan as well as younger age at the time of the first scan were associated with a larger increase in caudate volume. Although Liberman et al[25] also reported a caudate volume increase, Delisi et al[18,19,25] and Rapoport et al[20] did not replicate this finding.

Ventricles

As shown in Table 3, 6[18-20,25,31,32] of 9 studies demonstrated greater volume increase in patients with schizophrenia compared with controls. However, the other three studies[16,17,21] failed to find ventricular volume increase in schizophrenia. These follow-up studies

Table 1. Logitudinal MRI studies of cortical volume changes in schizophrenia

Authors	year	Schizo-phrenia	Control	Stage of illness	Follow-up interval	Structures	Findings in patients compared with controls
DeGreef et al.[16]	1991	13	8	First episode	1-2	total cortical volume	No difference
Delisi et al.[17]	1992	50	33	First episode	2	temporal lobes	No difference
Delisi et al.[18]	1995	20	5	First episode	4	cerebral hemisphere, temporal lobe, superior temporal gyrus, medial temporal lobe, cerebellum, corpus callosum	No difference
Delisi et al.[19]	1997	20	20	First episode	> = 4	cerebral hemisphere, temporal lobe, superior temporal gyrus, medial temporal lobe, cerebellum, corpus callosum	Greater decrease in left and right hemisphere, right cerebellum, corpus callosum
Rapoport et al.[20]	1997	16	24	Childhood onset	2	total cerebral volume	No difference
Gur et al.[21]	1998	40	17	First episode 20 chronic 20	2-3	whole brain, frontal and temporal lobes	Reduction in frontal lobe only in patients
Jacobson et al.[22]	1998	10	17	Childhood onset	2	temporal lobe, superior temporal gyrus, medial temporal lobe	Greater decrease in right temporal lobe, bilateral superior temporal gyrus, posterior superior temporal gyrus, right anterior superior temporal gyrus, left hippocampus
Keshavan et al.[23]	1998	11	12	First episode	1	superior temporal gyrus	Increase in right side only in patients
Rapoport et al.[24]	1999	34	15	Childhood onset	4	frontal, temporal, parietal, occipital lobes	Greater decrease in gray matter of frontal, temporal, and parietal lobes
Lieberman et al.[25]	2001	107	20	First episode	1.5	cortex, hippocampus	No difference

Table 2. Logitudinal MRI studies of subcortical volume changes in schizophrenia

Authors	year	Schizo-phrenia	Control	Stage of illness	Follow-up interval	Structures	Findings in patients compared with controls
Chakos et al.[26]	1994	21	10	First episode	1.5	caudate nucleus	Increased volume with typical neuroleptics.
Delisi et al.[18]	1995	20	5	First episode	4	caudate nucleus	No difference
Delisi et al.[19]	1997	20	20	First episode	> = 4	caudate nucleus	No difference
Rapoport et al.[20]	1997	16	24	Childhood onset	2	thalamus, caudate nucleus, putamen, globus pallidus	Greater decrease in thalamus and caudate
Lieberman et al.[25]	2001	107	20	First episode	1.5	caudate nucleus	Greater increase

with negative findings were conducted for only a few years. It stands to reason, then, that longer follow-up periods are needed to reliably evaluate progressive structural changes.

We have conducted a longitudinal MRI study[32] with 10-year follow-up period which is perhaps the longest follow-up term to date, in which 15 schizophrenics and 12 controls were investigated (Fig. 1). The results showed that a significant lateral ventricular enlargement was found only in patients (mean, 22.9%) but not in controls (5.1%). Exploratory correlation analysis suggested that there was a trend for lateral ventricular enlargement and worsening of negative symptoms (Fig. 2). These findings support the idea that schizophrenia is a disease with progressive structural changes, and may be a direct consequence of schizophrenia's underlying pathophysiology and characteristics of the disease process itself.

Table 3. Logitudinal MRI studies of ventricular volume changes in schizophrenia

Authors	year	Schizo-phrenia	Control	Stage of illness	Follow-up interval	Structures	Findings in patients compared with controls
DeGreef et al.[16]	1991	13	8	First episode	1-2	total ventricular volume	No difference
Delisi et al.[17]	1992	50	33	First episode	2	lateral ventricles	No difference
Delisi et al.[18]	1995	20	5	First episode	4	lateral ventricles	Greater increase in left ventricle
Delisi et al.[19]	1997	20	20	First episode	> = 4	lateral ventricles, sylvian fissure	Greater increase in left ventricle
Nair et al.[31]	1997	18	5	Chronic	2-3	total ventricular volume	Greater increase
Rapoport et al.[20]	1997	16	24	Childhood onset	2	lateral ventricles	Greater increase
Gur et al.[21]	1998	40	17	First episode 20, chronic 20	2-3	cerebrospinal fluid	No difference
Lieberman et al.[25]	2001	107	20	First episode	1.5	lateral ventricles	Greater increase in patients with poor outcome
Saijo et al.[32]	2001	15	12	Chronic	10	lateral ventricles	Greater increase

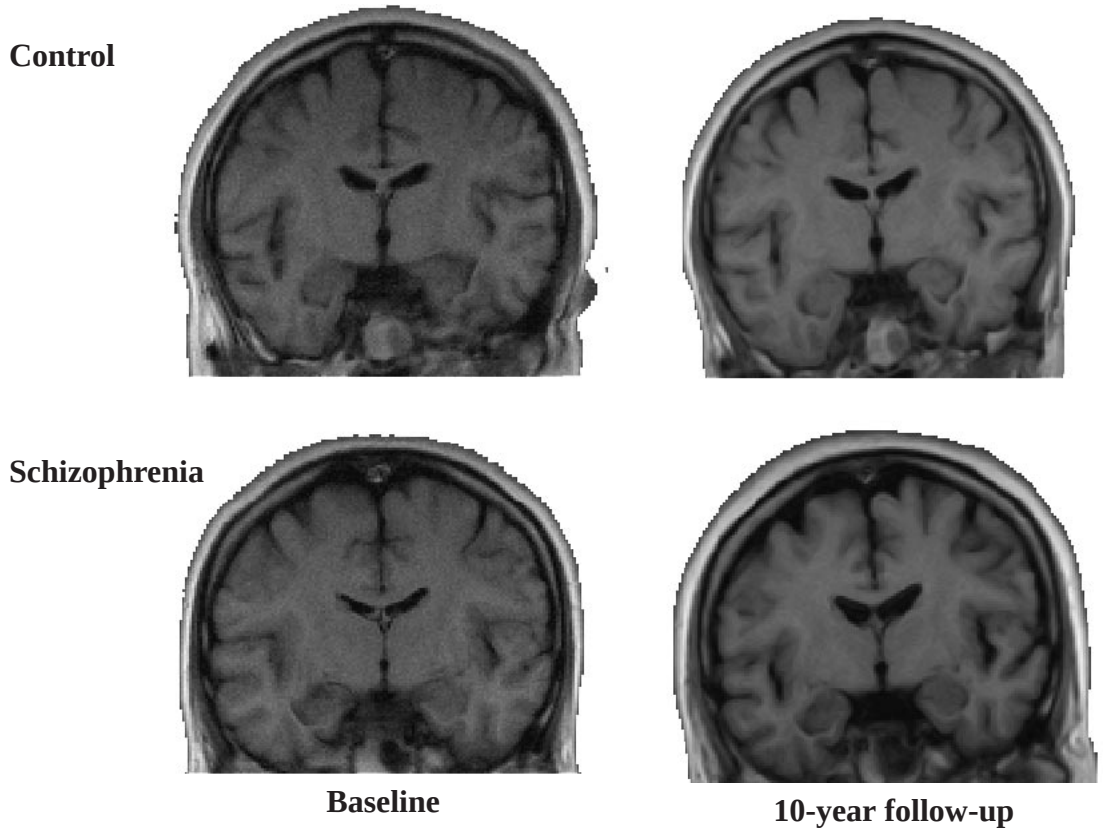

Fig. 1. An example of comparison of ventricular volume changes for 10 years (left column: baseline, right column: 10-year follow-up) between a patients with schizophrenia (lower row) and a control (upper low).

Neurodegenerative process in schizophrenia?

The findings from longitudinal MRI studies are not in disagreement with the neurodevelopmental hypothesis, but they do provide strong evidence that in schizophrenia progressive brain reduction occurs even after onset of the disease. The supposition that these findings may be a direct consequence of the underlying pathophysiology of schizophrenia and the characteristics of the disease process itself is of a speculative

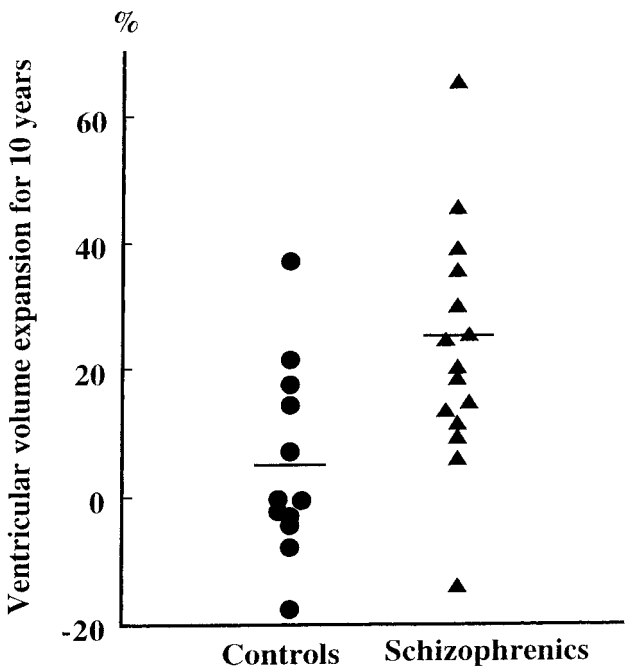

Fig. 2. Ventricular Volume Expansion in Patients with Schizophrenia (n = 15) and in Normal Controls (n = 12) for 10 Years[32].
Ventricular volume expansion (%/10 years) was calculated as: (10-year follow-up - baseline)×100 / baseline where 10-year follow-up and baseline mean the ventricular volume at 10-year follow-up and baseline, respectively.

nature. One possible pathogenetic model is that of excessive neuronal apoptosis[33]. Although cell death can occur by apoptosis, it does not lead to inflammatory changes and gliosis. If postnatal pathological neuronal loss could result from nongliotic apoptosis, the absence of gliosis would no longer limit the time of occurrence of that loss. Aberrant neuronal pruning, which increases neuronal density without cell loss, is also believed to contribute to the brain volume change[34,35].

Summary and the future

The finding of continued ventricular expansion even after disease onset seems to be especially robust, as lateral ventricular enlargement is the most robust finding in cross-sectional MRI studies of schizophrenia. Further, longitudinal MRI studies have provided evidence for progressive changes in the frontal and temporal lobes, and possibly in the hippocampus in schizophrenia. These findings of progressive changes do not contradict the neurodevelopmental hypothesis. But they do provide strong evidence that in schizophrenia, progressive changes occur even after onset of the illness, and they suggest the necessity of a “two-hit” model for progression of the pathology[3].

Most of the MRI studies reviewed here were based on classical volumetry, which involved the calculation of multiple regions of interest (ROIs) drawn manually over a series of MRI slices. However, this method has several limitations, such as that it is a time-consuming procedure, has poor intra- and inter-observer reliability, and that it is impossible to measure structures for which it is difficult to settle a landmark. Thus, only a limited number of brain structures have been measured based on preset hypothesis.

Voxel-based morphometry (VBM) on segmented MRI data volumes with spatial normalization has recently emerged as an ideal tool for whole brain analysis[36]. It will make it possible to compare structural changes over time on a voxel-by-voxel basis. Another major advantage is the almost completely user-independent data processing, thereby to a greater extent avoiding intra- and inter-observer variations (an example of application of VBM are shown in Fig. 3). In the future, large cohort studies to monitor whole brain changes on a voxel-by-voxel basis over time using up-to-date techniques will lead to a further understanding of the neuropathology of schizophrenia.

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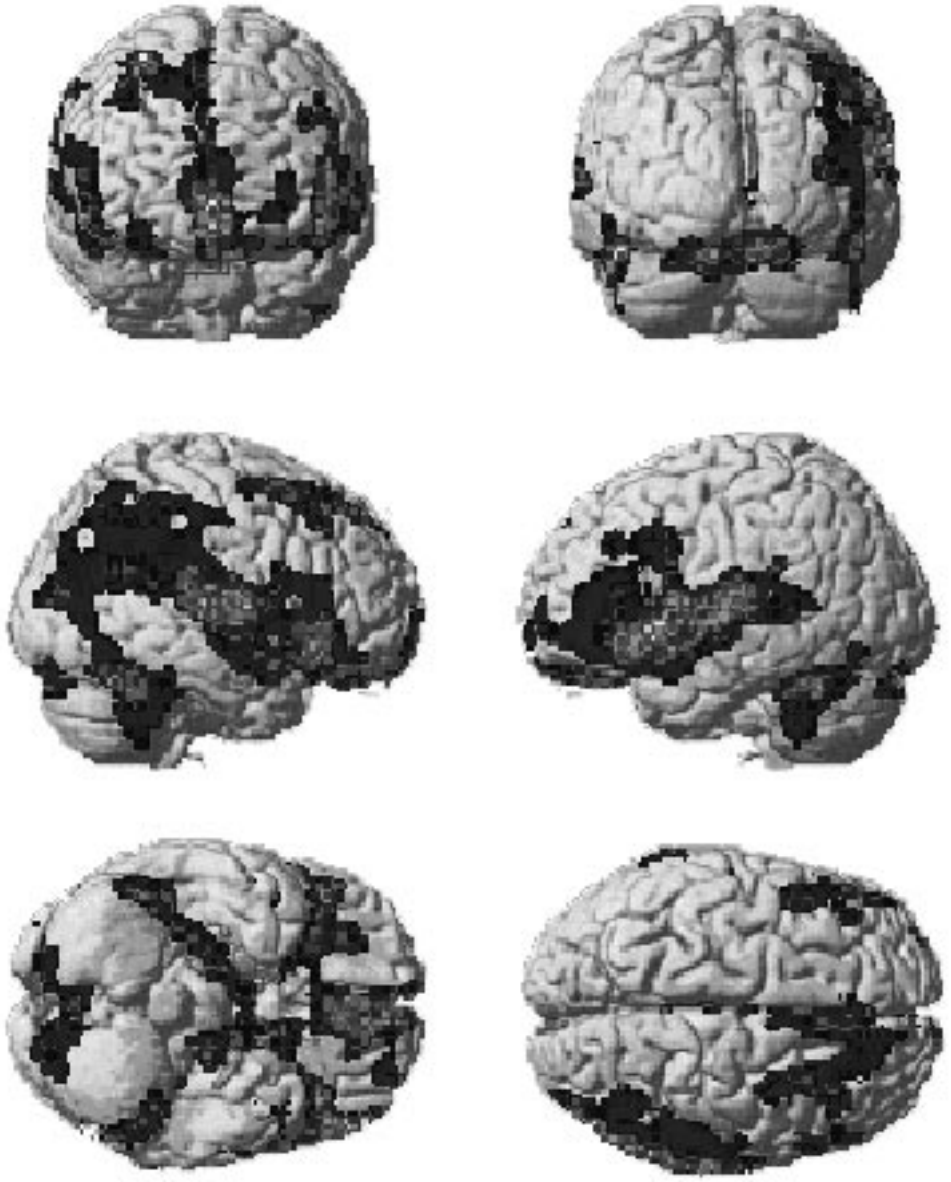

Fig. 3. An example of analysis using voxel-based morphometry (VBM). Age-related volume reduction in cortical gray matter is observed prominently in the temporal and frontal lobes on the 3-D standardized brain (SPM99 height $p<0.001$, extent corrected $p<0.05$, the subjects were 34 healthy subjects from 20 to 64 years of age).

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