Understanding structural brain changes in schizophrenia

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Schizophrenia is a chronic progressive disorder that has at its origin structural brain changes in both white and gray matter. It is likely that these changes begin prior to the onset of clinical symptoms in cortical regions, particularly those concerned with language processing. Later, they can be detected by progressive ventricular enlargement. Current magnetic resonance imaging (MRI) technology can provide a valuable tool for detecting early changes in cortical atrophy and anomalous language processing, which may be predictive of who will develop schizophrenia.

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It has long been known that the disorder we currently call schizophrenia is characterized by progressive clinical and cognitive change, as well as structural brain anomalies. Kraepelin himself in his series of textbooks[1] (particularly documented in 1919) illustrated his own views of what the cellular damage to the cortex must look like, although there is no evidence that this was actually based on any research findings. However, as early as the late 1920s, a few fairly large pneumoencephalographic studies had been conducted, which showed on a more macroscopic level that large ventricles were characteristic of patients with chronic schizophrenia.[2-7] At the time, this was assumed to represent a degenerative process.

To date, numerous other structural brain differences between chronic patients with schizophrenia and controls have been reported from computed tomography (CT) and magnetic resonance imaging (MRI) studies. These include nonlocalized reduced gray-matter and white-matter changes, temporal lobe volume reductions, and, particularly, anomalies of the superior temporal gyrus and temporal and frontal lobe white-matter connections, ie, arcuate, uncinate, and fornix.[8,9]

Some of the early pneumoencephalographic studies repeated the evaluations of patients a few years later and clearly a showed progressive change that correlated with clinical deterioration, but only present in some patients.[3,4,6] It should be noted that, while there were certainly other treatments available at the time of these studies, neuroleptics had not yet been introduced. This is important, since recently there has been much interest in the idea that neuroleptics might be responsible for certain progressive brain changes (see below), but clearly this cannot be the complete explanation.

Beginning in the late 1980s, we conducted a longitudinal study of individuals who had a first psychotic episode

and were admitted to hospital, and were then reevaluated in the community as part of a 10-year longitudinal study of brain changes in schizophrenia.[10-14] While *Figure 1* illustrates an extreme example of what was observed when subjects from this study were rescanned, it was clear from these longitudinal data that ventricular enlargement is progressive, and not a developmentally fixed parameter as previously thought.[15]

Despite this, it is likely that the progression begins early and can be detected even before the onset of clinical symptoms. At the first hospitalization, we and others could already detect many differences, although not all differences were reported in chronic patients and, also, not to the same extent as they were seen in the chronic patients.[8,10,11]

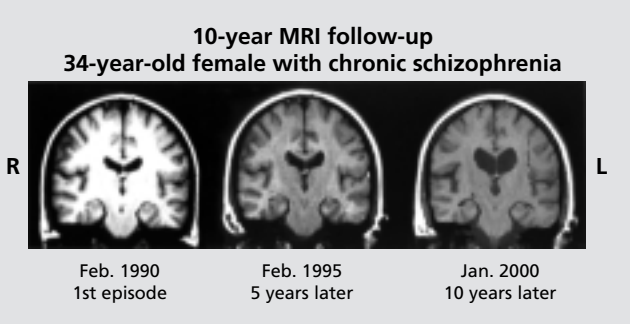

Figure 1. Magnetic resonance imaging (MRI) of a female patient who initially was scanned at the time of hospitalization for a first episode of schizophrenia. At the tenth year of follow-up, at age 34, she was an outpatient with a diagnosis of chronic schizophrenia stabilized with predominantly negative symptoms. She also had a brother with chronic schizophrenia, but he did not participate in the longitudinal study.

Over the past decade, there have been several short-term longitudinal studies. First, there are the studies beginning with an initial scan at the first episode *(Table I)* with varying results.[10-14,16-26] In the studies from our own cohort, we found ventricular enlargement over time and whole hemispheric volume decreases over a 5- to 10-year period[12-14]; some independent investigative groups support this as well *(Table I),* while other studies support variable regional changes. However, whether these progressive changes are correlated with outcome, and are thus clinically relevant, remains unclear.

Interestingly, the studies of chronic patients more consistently show ventricular increases over time, particularly in the more severely ill patients *(Table II)*.[27-38] This discrepancy could be explained if ventricular enlargement is secondary to underlying changes in the cortex that may begin earlier *(Table III)*[39-42] and, when they are extensive enough, are detected indirectly by progressive ventricular enlargement. Thus, ventricular enlargement would more consistently be seen later in the course of the illness. We further hypothesize that the cortical brain regions most affected are those involved in language processing (ie, superior temporal gyrus and its connections) and that the symptoms of schizophrenia develop on the basis that these pathways are anomalous.

The questions that then remain are:

Study	Number of patients/ number of controls	Years of follow-up	Findings
DeGreef et al,[16] 1991	13/8	1-2	No change in ventricles, change
Lieberman et al,[17] 2001	51/13	1-2	associated with poor outcome
DeLisi et al,[10-14] 1991, 1992,	50/20	4-5	**Decreased hemisphere**, cerebellum, **increased ventricles**
1995, 1997, 2004	26/10	10	and associated with good outcome, no decrease in superior temporal gyrus
Gur et al,[18] 1998	20/17	2-3	Decreased **frontal lobe**, associated with good outcome
Kasai et al,[19] 2003	13/14	1.5	Decreased left **superior temporal gyrus and planum temporale**
Jaskiw et al,[20] 1994 (CT)	7/0	5-8	No ventricle change
Sponheim et al,[21] 1991 (CT)	15/0	1-3	No ventricle change
Vita et al,[22] 1994 (CT)	9/0	2-4	No ventricle change
Wood et al,[23] 2001	30/26	0.5-4.2	**Decreased whole brain**
Cahn et al,[24] 2002	34/36	1	Decreased gray metter, increased ventricle, associated with poor outcome and medication
James et al,[25] 2002	16/16	2.7/1.7	No change
Ho et al,[26] 2003	73/23	3.0	Decreased **frontal white matter** and increased cerebrospinal fluid

Table I. Brain changes over time in first-episode schizophrenia.

- Is the progression is an artifact of neuroleptic medication or some other physiological process unrelated to the illness pathology; or is it central to the process and begin prior to the clinical syndrome?
- Is the progression due to decreased myelination or a faulty pruning process during adolescence?
- Is the progression sufficient to explain all the brain changes seen in schizophrenia?

Neuroleptics and progressive brain change

Lieberman and colleagues recently published a paper in the *Archives in General Psychiatry* from a study comparing olanzapine with haloperidol in first-episode patients and comparing any brain changes to control changes over time.[43] They claim that, over a 2-year period, whole gray matter volume decreases significantly more in patients administered haloperidol than in controls or patients on olanzapine. However, the time of the follow-up MRI scans was short; there were many dropout subjects in this study and disproportionately among the groups; and some time periods were missing in one group entirely, thus hampering interpretation of these results.

There have now been several other studies attempting to examine the question of neuroleptic effects on brain structure. While it appears consistently in most, but not all, studies that the caudate enlarges with typical neuroleptics, the changes seen with respect to other cortical

Study	Number of patients/ number of controls	Years of follow-up	Findings
Davis et al,[27] 1998 (CT)	53/13	5	**Increased ventricles**, poor outcome only
Illowsky et al,[28] 1998 (CT)	13/0	7-9	No change in ventricles
Kemali et al,[29] 1989 (CT)	18/8	3	**Increased ventricles** (1/3 patients)
Mathalon et al,[30] 1998	24/25	0.7-7.5	Decreased gray matter, **increased cerebrospinal fluid**, decreased superior temporal gyrus
Nair et al,[31] 1997	18/5	1.1-3.8	**Increased ventricles**, poor outcome only
Nasrallah et al,[32] 1986 (CT)	11/0	3	No change in ventricles
Rapoport et al,[33] 1997; Jacobsen et al,[34] 1998; Thompson et al,[35] 2001; Keller et al,[36] 2003	16-24 50/101	1.5-4	**Increased ventricles**, decreased hemispheres, temporal lobe, superior temporal gyrus, hippocampus, thalamus, and striatum
Vita et al,[37] 1988 (CT)	15/0	2-5	No change in ventricles
Woods et al,[38] 1990 (CT)	9/0	1-4.5	**Increased ventricles** (8/9 patients)

Table II. Brain changes over time in chronic schizophrenia.

Study	No of subjects	Follow-up diagnosis	Initial findings	Change in follow-up
Pantelis et al,[39] 2003	21	1 year: 10 psychotic 11 nonpsychotic	Decreased **right temporal**, right inferior frontal, **cingulate** bilaterally	Decreased left **parahippocampal gyrus**, **left fusiform**, left orbitofrontal, left cerebellum, **cingulate** bilaterally, left temporal
Wood (unpublished data)	75	23 psychotic 52 nonpsychotic		
Lawrie et al,[40] 2002 Job et al,[41] 2005	66	2 years: 19 psychotic 47 nonpsychotic	Decreased left and right anterior **cingulate**, left parahippocampal gyrus, left temporal lobe gray, right prefrontal, thalamus	Decreased **right and left temporal**, right and left superior temporal gyrus, left **cingulate**, left and right uncinate, **left fusiform**, left uncus, left and right **parahippocampal gyrus**, right amygdala; **no ventricle change**
Johnstone et al,[42] 2002	65	1.5 years: 18 psychotic		

Table III. Studies of brain changes in prodromal patients.

regions and ventricular enlargement have yet to be shown to be due to medication *(Table IV)*.[43-51]

How early do the brain changes begin?

There are two large and interesting independent studies of people with a prodromal syndrome that is high likely to lead to schizophrenia—one in Scotland[42] and another in Melbourne,[39] Australia *(Table III)*. Both these studies have performed very parallel investigations. Initially during the prodrome, a change in brain structure seems to be present in the temporal lobe volume and cingulated. On follow-up in those who have gone onto a psychotic episode, further changes can be seen in the cingulate, temporal lobe, and parahippocampal gyrus. These two independent studies have results that are not entirely consistent with each other, but it is interesting that neither show ventricular enlargement or its progression at this stage. In general, while both research groups see initial changes in temporal and frontal lobes in people who later develop schizophrenia *and* progressive change in the time interval from prodrome to onset of clinical illness, the specific changes that are clearly predictive of illness need to be further delineated.

What is the cause?

The underlying basis for the changes detected by imaging could be related to abnormalities in axonal integrity and organization that begin to take place during the normal adolescent neuronal pruning and reorganizational process, and continue through out the lifetime of the individual during aging and brain response to normal stresses.[52,53] In some individuals, it may even begin prenatally,[54] but last a lifetime. Perhaps examining white matter integrity will give clues. We now have the techniques in MRI, ie, diffusion tensor imaging (DTI) and magnetization transfer (MT). DTI[55] focuses on the diffusion of water in the brain. Two measurements based on DTI images are the apparent diffusion coefficient (ADC), which measures the water content and reflects the amount of cerebrospinal fluid (CSF),[56] and fractional anisotropy (FA), which measures the direction of flow or, indirectly, the lining up of fibers. The FA is high when fibers are orientated in one direction and low when there is diffusion and the fibers are more disorganized. The ADC is high when the water content is high and low when the water content is low. Magnetization transfer (MT) is a proton-weighted MRI image that can give information about the integrity of myelin, in particular with the quantification of the magnetization transfer ratio (MTR).[57]

The most recent focus of our research group has been to extend the previous longitudinal studies back in time from the first episode to the study of individuals at high genetic risk for schizophrenia who are in the age range for peak incidence of developing the disorder. Current preliminary data are illustrated on 15 such adolescents,

Study	Patients	Treatment	Duration	Findings
Dazzan et al,[44] 2005	84 first-episode	Typical antipsychotic versus atypical antipsychotic versus no treatment	36 months	Increased thalamus (atypical), increased right ventricle (typical), decreased frontal (typical)
Garver et al,[45] 2005	19	Typical antipsychotic versus atypical antipsychotic versus no treatment	1 month	Increased cortical gray (atypical), no change (typical)
Lieberman et al,[43] 2005	161	Haloperidol versus olanzapine	Maximum 24 months	Decrease in gray matter, no change with haloperidol or olanzapine
Massana et al,[46] 2005	11 first-episode	Risperidone	3 months	**Increased caudate**
Lang et al,[47] 2001	30 first-episode	Risperidone	12 months	No change in caudate
Scheepers et al,[48] 2001	28 nonresponders	Clozapine	5 months	Decreased left caudate in clozapine responders only
Corson et al,[49] 1999	23 male	Typical antipsychotic versus atypical antipsychotic	24 months	Increased caudate (typical), decreased caudate (atypical)
Chakos et al,[50] 1994	29 first-episode	Typical antipyschotic	18 months	Increased caudate
Keshavan et al,[51] 1994	?	Typical antipyschotic	?	Increased caudate

Table IV. Neuroleptics and brain morphology over time.

15 controls, and 15 of their siblings with chronic schizophrenia *(Figures 2 to 6)*. *Figure 2* shows a DTI comparison of FA in high-risk subjects with controls illustrating evidence of reduced FA (or directional axonal organization) already taking place in the left posterior superior temporal gyrus. *Figure 3* shows evidence of higher ADC (or water content, ie, CSF) already evident in the left parahippocampal gyrus and right superior temporal gyrus in the high-risk patients. This is more widespread in those with schizophrenia, suggesting that atrophic changes occur early and could be progressing into later stages of illness. *Figures 4 and 5* show that MT changes are also present, ie, changes in fiber membranes in the superior frontal gyrus and posterior cingulate. In addition, we have been performing functional MRI (fMRI) lexical decision task, as previously developed,[58] which has the ability to show lateralized activation in the supe-

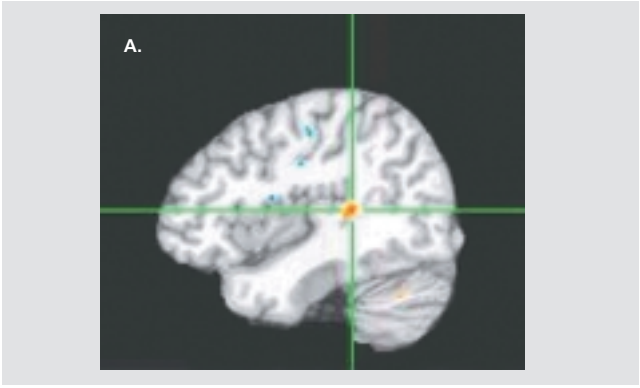

Figure 2. Diffusion tensor imaging (DTI). Fractional anisotropy (FA) of 15 subjects at high genetic risk for schizophrenia. Sagittal view showing FA reduced in the left posterior superior temporal gyrus in high-risk subjects compared with controls (P<0.01, minimum cluster size =100). Talairach coordinates of cluster peaks: x=-41, y=-36, z=9.

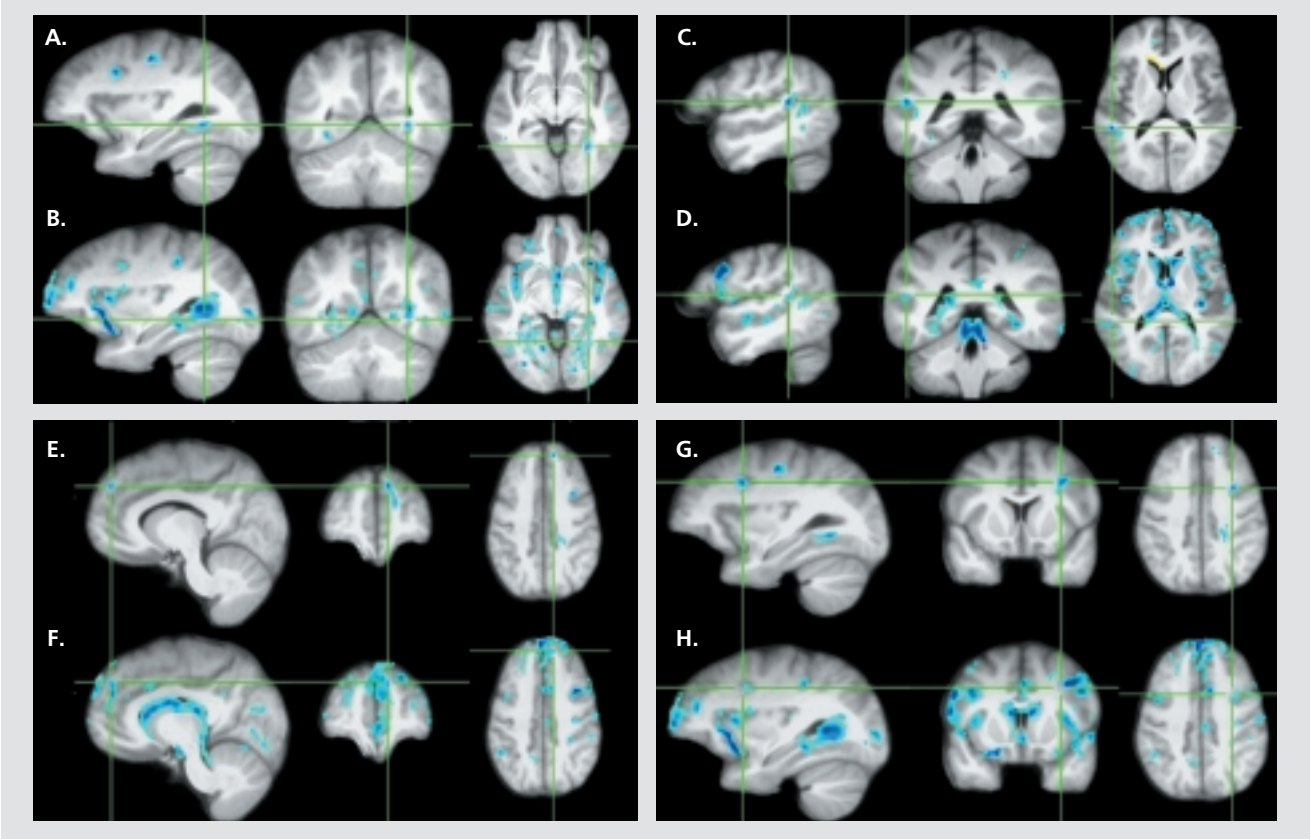

Figure 3. Sagittal, coronal, and axial views of the region in the vicinity of the left parahippocampal gyrus and right superior frontal gyrus, where the apparent diffusion coefficient (ADC) was higher both in (**A**, **C**) subjects at high genetic risk for schizophrenia and (**B**, **D**) the patients with schizophrenia P<0.01, cluster size >200 mm^3 as compared with controls. Sagittal, coronal, and axial views of the region in the left superior frontal gyrus and left middle frontal gyrus shows that subjects at high genetic risk for schizophrenia (**E**, **G**) and patients with schizophrenia (**F**, **H**) had higher ADC compared with controls: P<0.01, cluster size >200 mm^3 in these regions as well.

rior temporal gyrus in normal individuals. In our preliminary analyses, less lateralized activation is seen in the individuals at high-risk for schizophrenia than controls, similar but to a lesser extent than what is seen in the patients with chronic schizophrenia *(Figure 6)*. These studies taken together indicate that changes are occurring early in the brains of people who are likely to later develop schizophrenia, and that these changes are relevant to those regions of the brain that are involved in language processing.

Figure 4. Magnetization transfer (MT): Coronal (**A** and **C**) and sagittal (**B**) views showing a greater magnetization transfer ratio (MTR) in controls compared with subjects at high genetic risk for schizophrenia bilaterally in the superior frontal gyrus (P<0.05, minimum cluster size =100). Talairach coordinates of cluster peaks: **A** and **B**, *x*=-10, *y*=14, *z*=52; **C**, *x*=10, *y*=15, *z*=51.

Conclusion

It appears that brain structural change is detectable in both gray and white matter prior to illness onset, that active progression of the changes may also begin prior to the onset of clinical symptoms, that progressive brain changes may account for the brain structural anomalies seen in chronic schizophrenia, and that the structures involved in language processing are affected. White-matter anomalies in the anatomical connections relevant to language and/or

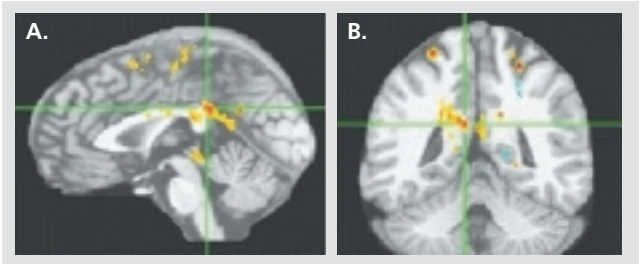

Figure 5. Magnetization transfer (MT). Greater magnetization transfer ratio (MTR) is shown in controls versus subjects at high genetic risk for schizophrenia in the posterior cingulate gyrus (*P*<0.05, minimum cluster size =100). Talairach coordinates of cluster peaks: **A**, *x*=-0, *y*=-36, *z*=27; **B**, *x*=8, *y*=-45, *z*=22.

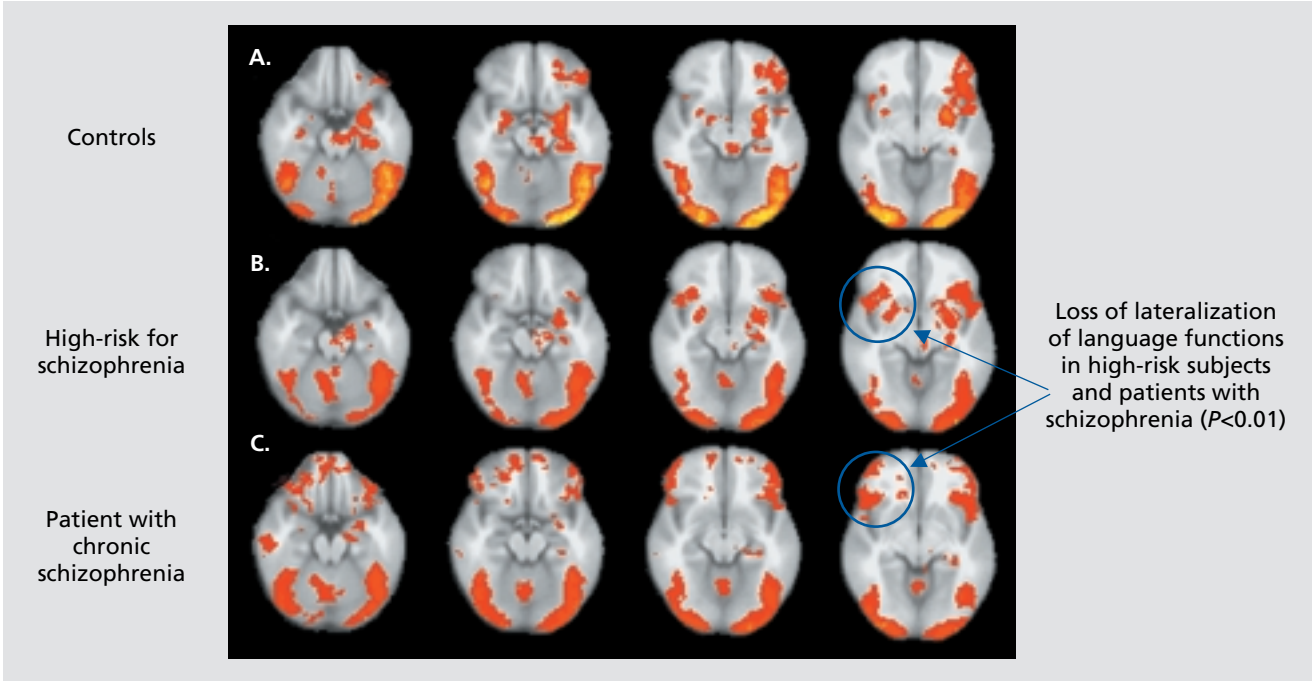

Figure 6. Functional magnetic resonance imaging (fMRI) showing brain activation during a lexical decision task (no REST contrast) in 11 controls (**A**), 9 subjects at high risk for schizophrenia (**B**), and 11 patients with chronic schizophrenia (**C**). Lateralization of activation is reduced in the schizophrenic patients compared to controls (*P*<0.01) as well as the subjects at high risk, but to a lesser extent (*P*<0.01).

myelination of these connections could be involved. The ability to have specific MRI predictors of who will develop schizophrenia among those at high risk appears hopeful for the near future. Having the ability to predict the development of illness will then lead to studies to determine whether early pharmacological treatment will prevent the cortical progressive brain cortical change and, in doing so, have a significant effect on clinical outcome. ❑

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Comprensión de los cambios estructurales del cerebro en la esquizofrenia

La esquizofrenia es una enfermedad progresiva, crónica, que se origina por cambios estructurales cerebrales, tanto de la sustancia blanca como de la sustancia gris. Es probable que estos cambios comiencen antes de la aparición de los síntomas clínicos en regiones corticales, especialmente aquéllas relacionadas con el procesamiento del lenguaje. Más tardíamente estos cambios pueden ser detectados por un progresivo crecimiento de los ventrículos. La tecnología actual de imágenes por resonancia magnética puede aportar una valiosa herramienta para detectar precozmente cambios atróficos corticales y anomalías en el procesamiento del lenguaje que podrían permitir de identificar personas susceptibles de desarrollar una esquizofrenia.

Comprendre les modifications structurales cérébrales dans la schizophrénie

La schizophrénie est une maladie progressive chronique pour laquelle on retrouve, à l'origine, des modifications cérébrales structurales des substances grise et blanche. Il est probable que ces modifications surviennent avant le début de l'apparition des symptômes cliniques dans les régions corticales, surtout celles concernées par le processus du langage. Plus tardivement, elles peuvent être détectées par un élargissement ventriculaire progressif. L'IRM (Imagerie par résonance magnétique) actuelle peut être un outil précieux pour détecter les modifications précoces d'atrophie corticale et d'anomalies de processus du langage qui permettraient d'identifier les personnes susceptibles de développer une schizophrénie.

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