Postmortem studies in schizophrenia

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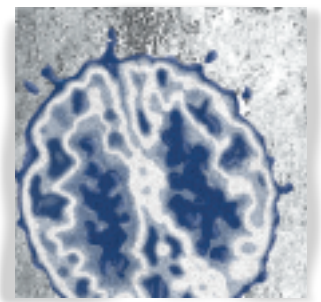

For over a century, postmortem studies have played a central part in the search for the structural and biochemical pathology of schizophrenia. However, for most of this time, little progress has been made. Recently, the situation has begun to change, helped by the emergence of more powerful methodologies and research designs, and by the availability of brain imaging to provide complementary information. As a result, it can now be clearly concluded that there are structural cerebral abnormalities in schizophrenia that are intrinsic to the disorder. The neuropathological process is not primarily degenerative, but involves a change in the normal cytoarchitecture of the brain, probably originating in development. Neurochemically, there is postmortem evidence for alterations in several transmitter systems including dopamine, glutamate, serotonin, and γ-aminobutyric acid (GABA). The cardinal findings are reviewed here, together with a consideration of the conceptual and methodological issues that face postmortem studies of schizophrenia.

Just over 100 years ago, Kraepelin, convinced that schizophrenia was an organic brain disease, persuaded Alzheimer to carry out the first neuropathological investigation. However, no robust findings emerged from this or any other postmortem study for over half a century, leading, in 1972, to the oft-quoted aphorism that schizophrenia is the "graveyard of neuropathologists,"[1] a statement which, together with critical reviews,[2,3] marked the nadir of the field. Over the past 30 years, unequivocal signs of life have appeared in the graveyard, allowing Ron and Harvey[4] to charge that "to have forgotten that schizophrenia is a brain disease will go down as one of the great aberrations of twentieth century medicine," and Weinberger[5] to state "20 years ago, the principal challenge for schizophrenia research was to gather objective scientific evidence that would implicate the brain. That challenge no longer exists." The current challenge is to establish the characteristics of the pathological changes, which remain far from clear.[6,7] Attempts to elucidate the neurochemistry of schizophrenia from postmortem studies have also proved difficult, but progress is being made in this area too. This review summarizes the key recent neuropathological and neurochemical findings. It also considers the main issues affecting the field, and its prospects for the future.

Macroscopic brain changes in schizophrenia

Although early postmortem studies and pneumoencephalography had provided some relevant data, it was the advent of computed tomography (CT) and magnetic resonance imaging (MRI) that led to the clear demonstration of macroscopic brain changes associated with schizophrenia. There have now been a large number of increasingly sophisticated and detailed imaging studies, and recently several meta-analyses and systematic reviews, which allow the cardinal changes to be identified.[8-11] These are summarized in *Table I*, together with some of the other findings that are of current interest, but that have not

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Established by systematic reviews
• Enlargement of lateral and third ventricles (+25%–40%)
• Smaller brain volume (-3%)
• Smaller cortical volume (-4%)
• Smaller gray matter volume (-6%)
• Relatively smaller medial temporal lobe volume (-5%)
• Relatively smaller thalamic volume (-4%)
• Larger basal ganglia (especially the globus pallidus)*
Other replicated findings
• Greater involvement of heteromodal association cortex
• Decrease (or loss) of cerebral asymmetries

Table I. Macroscopic brain changes in schizophrenia.
* Due to antipsychotic medication.

been substantiated to the same extent.[12,13] Because the focus of this paper is on postmortem studies, the imaging literature is not discussed in detail. However, it is noteworthy that it is the incontrovertible in vivo imaging evidence that there is a pathology of schizophrenia to be found which has driven the ongoing neuropathological studies.

The imaging data have also allowed other important conclusions to be drawn, which inform and bolster postmortem research *(Table II)*.[14-18] In particular, since the structural changes are present at the time of disease onset and are, by and large, not progressive thereafter (although there may well be exceptions to this rule[17,19]), it is reasonable to assume that the corresponding histological abnormalities share this property, even though it is in practice impossible to prove this in postmortem studies. Instead, the latter can now focus on the microscopic and molecular aspects of the pathology, which remain out of reach of any imaging modality.

Differences are readily apparent in discordant monozygotic twins[14]
Differences are present in first-episode, untreated patients, and in high-risk and unmedicated individuals[15]
No convincing evidence of heterogeneity (eg, subtypes or gender differences), or clinicopathological correlations (eg, progression of changes), although this remains controversial[16,17]
The alterations are not seen in bipolar disorder to the same extent, if at all[19]

Table II. Characteristics of structural imaging findings in schizophrenia.

Histological and molecular pathology of schizophrenia

Contemporary histological studies have addressed two main areas: first, to clarify the frequency and nature of neurodegenerative abnormalities in schizophrenia; and, second, to investigate the cellular organization (cytoarchitecture) of the brain. A summary of the most established and the most often cited findings is given in *Table III*.

Gliosis and neurodegeneration

The two most robust and important findings concerning the neuropathology of schizophrenia are both negative: there is no excess of gliosis, or of Alzheimer's disease or other neurodegenerative pathology.

The issue of gliosis (reactive astrocytosis) has been extensively investigated since a report that gliosis was common in schizophrenia, especially in the diencephalon around the third ventricle.[20] As gliosis is a sign of past inflammation, this invoked scenarios for schizophrenia involving infective, ischemic, autoimmune, or neurodegenerative processes. However, over a dozen subsequent investigations using more quantitative methods have not replicated this observation, and the consensus is now that gliosis is not a feature of schizophrenia.[21] The issue is complicated by the excess of nonspecific and focal abnormalities, including gliosis, seen in brain series of schizophrenia; however, this is likely to be an epiphenomenon not an intrinsic finding[21,22] and, importantly, decreased brain size is still seen after omission of all such brains.[23]

Given the pathological implications of gliosis, its absence in schizophrenia implies that none of the processes mentioned above are likely to be relevant to its pathogenesis. Equally, the absence of gliosis has been attributed a particular positive significance: the gliotic response does not begin until the second trimester in utero, and hence an absence of gliosis is taken as prima facie evidence of a disease process occurring before this time—and therefore is important support for prenatal neurodevelopmental models of schizophrenia.[24] Unfortunately, both the absence of gliosis and its interpretation are less clear than often assumed. First, detecting gliosis is surprisingly difficult, and it can be argued that the data do not wholly rule out its occurrence. Second, despite the widely cited time point at which the glial response is said to begin, the matter has not been well investigated

	Weight of evidence
Lack of neurodegenerative lesions (eg, Alzheimer changes)	+++++
Lack of gliosis	++++
Smaller cortical and hippocampal pyramidal neurons	+++
Decreased cortical and hippocampal synaptic markers	+++
Decreased dendritic spine density	++
Loss of neurons from dorsal thalamus	++
Abnormalities of white matter neurons	+
Entorhinal cortex dysplasia	+
Disarray of hippocampal neuron orientation	+/-
Loss of hippocampal or cortical neurons	0

Table III. Histological findings in schizophrenia.
0: no good evidence; +/-: equivocal data; + to +++++: increasing amounts of supportive data.

and it is prudent not to use this to time the pathology of schizophrenia with spurious accuracy. Third, it is a moot point whether the subtle kinds of morphometric disturbance described in schizophrenia, whenever and however they occurred, would be sufficient to trigger detectable gliosis.

It has been asserted that Alzheimer's disease is commoner than expected in schizophrenia. This may have arisen from the assumption that it explains the cognitive impairment which is seen throughout the course of schizophrenia[25] and which is both common and severe in elderly patients.[26] However, a meta-analysis shows that Alzheimer's disease is not commoner, and may even be rarer, in schizophrenia.[27] This applies even in elderly schizophrenics with prospectively assessed severe dementia, who show no evidence of any other neurodegenerative disorder either.[28]

Neural cytoarchitecture in schizophrenia

If neurodegenerative abnormalities are uncommon in, or epiphenomenal to, schizophrenia, it begs the questions as to what the pathology is and how the macroscopic findings are explained microscopically. The answer has been sought in the cytoarchitecture of the cerebral cortex, with measurements of parameters such as the size, location, distribution, and packing density of neurons and their synaptic connections *(Table III)*.

Three cytoarchitectural alterations have generated particular interest: abnormal neuronal organization (dysplasia) in lamina II (pre-alpha cells) and lamina III of the entorhinal cortex[29]; disarray of hippocampal neurons[30]; and an altered distribution of neurons in the subcortical white matter.[31] These findings are important because they almost certainly reflect impairment of neuronal migration and formation of the cytoarchitecture, and hence strongly support the hypothesis of an early neurodevelopmental anomaly underlying schizophrenia.[24,32] However, none has been unequivocally replicated; for example, entorhinal cortex dysplasia has been seen in some studies[33-35] but not others,[36-38] undermining attempts to date the pathology of schizophrenia, as was the case regarding interpretation of the lack of gliosis.

A less well-known yet somewhat more robust cytoarchitectural feature of schizophrenia is that many neurons are decreased in size (ie, have a reduced cell body area or volume). This has been shown in three studies of pyramidal neurons in the hippocampus,[39-41] and has also been reported in dorsolateral prefrontal cortex[42] and cerebellar Purkinje cells.[43] Some studies found that the neurons are also more closely packed. Outside the cerebral cortex, extensive cytoarchitectural data are limited to the thalamus, for which there are reports of a loss of neurons from the dorsomedial and anterior nuclei, though the matter remains controversial.

Synapses and dendrites

Synapses and dendrites represent a potential site for pathologies that are undetectable using standard approaches. Because they are hard to visualize directly, proteins localized to these parts of the neuron are used as markers for them.[44]

Markers of presynaptic terminals are generally reduced in the hippocampus in schizophrenia.[44,45] The magnitude of the loss varies according to the individual synaptic proteins (and hippocampal subfields) studied, implying that the synaptic pathology is not uniform. There is some evidence for preferential involvement of excitatory connections.[46] Presynaptic markers may also be reduced in prefrontal cortex, but in this region it is a subset of inhibitory neurons and terminals which appears most affected.[47] Complementing these changes, alterations in dendrites have been shown in the neocortex and in the subiculum, with a decreased density of dendritic spines seen in three studies.[48] Although unproven, the usual and simplest interpretation is that these changes together reflect fewer (or otherwise aberrant) synaptic contacts being formed and received.[44,45,49]

There is an encouraging convergence between these synaptic findings and the cytoarchitectural alterations. In particular, the decreases in presynaptic and dendritic markers are in keeping with the smaller neuronal cell bodies, since the size of the latter is proportional to the dendritic and axonal spread of the neuron.[50] It is also consistent with an increased neuronal density, in that dendrites and synapses comprise most of the neuropil and, if this is reduced, neurons will pack more closely.[51] Moreover, it also corresponds with the results of proton magnetic resonance studies, which have shown reductions in the neuronal marker *N*-acetylaspartate (NAA), as one would predict if the neurons are on average smaller and have less extensive projections.[52]

Where and what is the pathology?

Most of the positive findings reported in schizophrenia are in the hippocampal formation, dorsolateral prefrontal cortex, and cingulate gyrus.[6,7] However, this may be merely a sign that these areas have been the most intensively studied. Few studies have included a comparison region (eg, striate cortex), and those which have do not provide a clear picture as to the uniformity versus selectivity of cerebral involvement in schizophrenia. Neither are any of the individual histological abnormalities specific or pathological in the sense that a neurofibrillary tangle or Lewy body is. Rather, at present, the favored interpretation is that it is a quantitative deviation of normal neuronal parameters in schizophrenia, probably arising at least partly during development, and putatively affecting functional connectivity between various brain regions. These hypotheses are elaborated further below. However, it is important to remain critical of the empirical data, which could equally lead to the conclusion that, though brain structure is clearly altered in schizophrenia, its location, nature, and consequences remain largely unknown.[53]

Neurochemistry of schizophrenia

A wide range of neurochemical parameters have been investigated in schizophrenia, both postmortem[54,55] and in vivo.[56,57] Among a multitude of findings, four major neurochemical systems have been most implicated: dopamine, serotonin (5-HT), glutamate, and γ-aminobutyric acid (GABA).

Dopamine

The dopamine hypothesis of schizophrenia has been neurochemically preeminent for 40 years.[58,59] It received support from various postmortem findings of increased dopamine content and higher densities of dopamine D_2 receptors in schizophrenia.[60] However, despite its longevity, there is still no consensus as to precisely what the dopamine hypothesis explains, nor the nature of the supposed abnormality. There are two main difficulties. First, antipsychotics have effects of their own on dopaminergic parameters (eg, receptor densities), confounding studies of medicated subjects. Second, molecular biology has revealed a large and complex dopamine receptor family, increasing the potential sites and mechanisms of dysfunction.

Increased D_2 receptor densities occur in patients with schizophrenia, but it is unclear what proportion, if any, is not attributable to antipsychotic medication.[61] Statistical methods have been used to argue that there is a schizophrenia-associated elevation, but this must be balanced against positron emission tomography (PET) studies of D_2 receptors in drug-naive and first-episode cases, all but one of which are negative. Recently, it has been suggested that the "clustering" of D_2 receptors is altered in schizophrenia, with more of the receptors existing as monomers rather than oligomers.[62] This situation has two implications: it complicates interpretation of the imaging data, since different ligands have differential selectivity for these receptor states; and it means that there could be alterations in the functional activity of D_2 receptors even without an increase in total receptor number (eg, via G protein coupling). Expression of D_1 and D_3 receptors has also been reported to be changed in schizophrenia in postmortem or in vivo studies, but these reports are either unconfirmed or contradicted by other studies.[63] Particular controversy has surrounded the D_4 receptor following a report that it was upregulated several-fold in schizophrenia.[64] However, the result appears to have been due to a D_4-like site (perhaps related to the D_2 monomer/oligomer issue), not the true D_4 receptor, and the status of the latter in schizophrenia is unknown.[63]

In contrast to the equivocal and hard-to-interpret data concerning dopamine receptors in schizophrenia, there is emerging good evidence for alterations in dopamine neurons. Several PET and single photon emission computed tomography (SPECT) studies have shown ele-

vated striatal dopamine release in response to amphetamine in untreated, acutely psychotic patients, implying a dysregulation and hyperresponsiveness of dopamine neurons.[65] There is also recent evidence that D_2 receptor occupancy is higher in schizophrenia, implying an increased synaptic dopamine concentration; interestingly, the magnitude of the elevation predicts response to antipsychotic medication.[66] Although the state-dependent nature of the changes mandates in vivo rather than postmortem studies, the latter can provide independent and corroborative support; for example, an altered dopaminergic innervation in schizophrenia may be an anatomical correlate.[67]

Serotonin (5-HT)

There are two well-replicated postmortem findings concerning the 5-HT system in schizophrenia: a loss of the serotonin 5-HT_{2A} receptor expression from the frontal cortex; and an increased density of 5-HT_{1A} receptors.[63] Changes in the 5-HT transporter have also been reported. Both of the receptor alterations have been found in medication-free patients and are not reproduced in rats by antipsychotics, suggesting that, unlike the dopamine receptor findings, they are not primarily caused by drug treatment. The 5-HT_{2A} receptor data illustrate how postmortem studies suggest targets for in vivo ligand-based imaging, since the data have led to three PET studies of younger and unmedicated subjects, and also how postmortem data can clarify their interpretation. Only one of the three imaging studies has replicated the decrease in 5-HT_{2A} receptors in the frontal cortex,[68] but this may reflect methodological problems. That is, the cerebellum is used as the reference region for the PET analysis, which presupposes an absence of cerebellar 5-HT_{2A} receptors, but this may not be the case.[69] Hypotheses to explain the role of 5-HT in schizophrenia include the trophic functions of the 5-HT system in neurodevelopment, interactions between 5-HT and dopamine, impaired 5-HT_{2A} receptor–mediated activation of prefrontal cortex, and 5-HT_{2A} receptors as candidate genes.[70-72]

Glutamate

The observation that phencyclidine and other noncompetitive antagonists of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor produce a psychosis resembling schizophrenia has driven hypotheses of glutamatergic dysfunction in the disorder.[73] There are now some postmortem data in schizophrenia to support this proposal. For example, in the temporal lobe, glutamatergic markers are decreased,[74] with reduced expression of non–NMDA glutamate receptors.[75] In the prefrontal cortex, the alterations affect NMDA receptor subunit mRNAs,[76] illustrating a regional and subtype selectivity of the findings, which precludes a simple conclusion about the nature of the abnormality.[73,77] Putative mechanisms of glutamatergic involvement in the disorder center on interactions with dopamine[78] and subtle forms of excitotoxicity.[79]

γ-Aminobutyric acid (GABA)

In addition to the excitatory pathology implied by glutamatergic abnormalities, the major inhibitory transmitter GABA has also been advocated, on the basis of alterations in receptor expression seen in the hippocampus and frontal cortex,[80-82] as well as a possible loss[81] or decreased activity[83] of GABAergic neurons and the loss of GABAergic presynaptic terminals mentioned earlier.[47] The latter studies illustrate the overlap between neurochemical and structural aspects of pathology, and emphasize that the one cannot be understood clearly without knowledge of the other. For example, consider a decrease in the density of a receptor present on the dendritic spines of pyramidal neurons in schizophrenia: does this reflect a primary disturbance of the receptor, or is it secondary to a loss of dendritic spines, a generalized dysfunction of the spines, or even a pathology of the neuron itself? Postmortem studies have the unique potential to allow all these possibilities to be addressed, and therefore the nature of the abnormalities in schizophrenia to be understood; these advantages counterbalance, and must be offset against, the many difficulties of postmortem research.

Methodological issues

Postmortem studies of schizophrenia have an unenviable reputation of being seriously flawed because of two main sorts of artifact: those due to perimortem changes, and those due to antipsychotic medication or other treatments.

Perimortem confounders are a real but manageable problem.[84] Depending on the parameter being measured, various individual factors are important. For

example, for morphometric studies, the mode of tissue fixation and processing is important, whereas neurochemical and molecular targets are more affected by mode of death and hypoxia/ischemia. A range of experimental and statistical strategies are available to address these factors, and to allow the effects of schizophrenia to be distinguished from them.[85]

Confounding by antipsychotic drugs is unavoidable, in that virtually all schizophrenics have (and should have) received treatment during life, and the majority are on medication at the time of death. Such confounding is greatest in two areas: for dopamine and other neurochemical parameters, which are the target of the drugs; and for neuropathological studies in the striatum and substantia nigra, where there is clear postmortem and experimental evidence that antipsychotics induce neuronal and synaptic changes.[86] However, for other studies and in other brain regions, antipsychotic effects are an overemphasized problem. For example, for cortical cytoarchitectural studies, no correlations have been found with treatment, nor do the drugs have any effects upon similar parameters in rat brain.[86]

Conclusions

Postmortem studies in schizophrenia have contributed significantly to the considerable, albeit partial, progress which has been made towards understanding the neuropathological *(Tables I to III)* and neurochemical *(Table IV)* characteristics of the disorder. Although imaging modalities provide an increasingly powerful and diverse technical armamentarium, in several key areas, there is no substitute for direct examination of the brain. For instance, it is not (yet) possible to measure neuronal size, synaptic terminals, or neuronal gene expression in any other way. The important thing is to apply each method judiciously and to choose the appropriate range of techniques to allow integration of in vivo with postmortem data.

Beyond these simple issues of robustness and convergence, contemporary postmortem studies of schizophrenia are attempting to answer several questions *(Table V)*. First, what is the core neuropathology of schizophrenia and in what sense is it specific? Features such as decreased cortical volume and cytoarchitectural abnormalities are certainly not unique to schizophre-

Transmitter	Main postmortem findings	Other supporting evidence
Dopamine	• Increased density of D_2 receptors	• DA-releasing agents produce psychosis
	• Decreased cortical DA innervation	• All antipsychotics are D_2 receptor antagonists
	• Increased D_4-like receptor binding	• Increased striatal DA release in vivo
	• Alterations in D_3 receptor splicing	
Glutamate	• Decreased presynaptic markers	• NMDA receptor antagonists produce
	• Decreased HC AMPA and kainate receptor expression	schizophrenia-like psychosis
	• Minor changes in FC NMDA receptor subunits	• Roles of NMDA receptors in development
	• Altered glutamate fibers in cingulate cortex	and neurotoxicity
		• Partial NMDA receptor agonists
		have some therapeutic benefit
5-HT	• Decreased FC 5-HT_{2A} receptor expression	• 5-HT_2 agonists (eg, LSD) are psychotomimetic
	• Increased FC 5-HT_{1A} receptors	• 5-HT_2 receptor polymorphisms associated
	• Increased 5-HT transporter affinity	with schizophrenia and clozapine response
	• Developmental and trophic roles of 5-HT	• Atypical antipsychotics have high affinity
		for several 5-HT receptors
GABA	• Decreased density of FC GABAergic terminals	• Roles of GABA in stress and neurotoxicity
	• Increased $GABA_A$ receptor binding in limbic areas	
	• Altered expression of FC $GABA_A$ receptor subunits	
	• Decreased FC expression of glutamic acid decarboxylase	
	• Altered density of cingulate GABAergic cells	

Table IV. Key postmortem findings concerning the major transmitter systems implicated in schizophrenia.
AMPA: amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; DA: dopamine; FC: frontal cortex; GABA: γ-aminobutyric acid; HC: hippocampus; 5-HT: serotonin; LSD: lysergic acid diethylamine; NMDA: *N*-methyl-D-aspartate.

- Which of the cytoarchitectural and synaptic alterations are robust?
- Is there a single pathology or several?
- How are the structural and neurochemical findings related?
- Does the neuropathology underlie the aberrant functional connectivity?
- Does the neuropathology relate to psychotic symptoms or the cognitive deficits?
- Are the changes diagnostically specific?

Table V. Some questions for postmortem studies of schizophrenia.

nia, overlapping with those observed in a range of other conditions.[50] There could be a diagnostic lesion characteristic of schizophrenia still going unrecognized, though this is increasingly implausible. Or, it could be the precise combination of alterations, and their location and timing, which produce schizophrenia. Some clarification will emerge as other idiopathic and putatively neurodevelopmental conditions, such as bipolar disorder[87] and autism,[88] are investigated. A complete answer, however, will also likely require identification of the causative genes and a better understanding of the pathogenesis, not just the pathology, of schizophrenia. At this point, one reencounters the circular problem: the goal of the research is to find a valid endophenotype, yet without one the goal may be unattainable.

A second area to highlight concerns the relationship between the structural abnormalities and the pathophysiology of the disorder. Functional imaging and neuropsychological data have led to the view that aberrant functional connectivity between brain regions underlies schizophrenia.[89,90] The question is whether the neuropathological features represent its structural and molecular basis,[6] since such dysconnectivity does not necessarily require an anatomical substrate.[91] A related question concerns which aspect of the clinical syndrome is most related to the neuropathology. It could be argued that structural lesions are inherently more likely to relate to the cognitive (or negative) symptoms, since these are more stable and persistent than the positive psychotic symptoms—especially as many brains examined come from patients who had been in remission for many years. The neuropathology could also be a trait marker of vulnerability to schizophrenia rather than related directly to symptoms themselves, as is the case for many of the MRI findings. The ability to answer these challenging questions will require a sustained and sophisticated approach to postmortem schizophrenia research over the next decade. ❑

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Estudios post mortem en la esquizofrenia

Por más de un siglo, los estudios post mortem han tenido un papel central en la búsqueda de la patología estructural y bioquímica de la esquizofrenia. Sin embargo, a pesar de este tiempo transcurrido se han realizado escasos progresos. Recientemente esta situación ha comenzado a cambiar, facilitada por la aparición de metodologías más poderosas y mejores diseños de investigación, y por la disponibilidad de imágenes cerebrales que aportan información complementaria. Como resultado de esto, ahora se puede concluir claramente que existen alteraciones estructurales cerebrales en la esquizofrenia que son intrínsecas a esta enfermedad. El proceso neuropatológico no es degenerativo, sino que implica un cambio en la citoarquitectura normal del cerebro, probablemente originado durante el desarrollo. Existen evidencias neuroquímicas post mortem de alteraciones en algunos sistemas de transmisión entre los que se incluyen la dopamina, el glutamato, la serotonina y el ácido gama amino butírico (GABA). Aquí se revisan los hallazgos cardinales junto con una consideración acerca de los problemas conceptuales y metodológicos que afrontan los estudios post mortem de la esquizofrenia.

Données d'autopsie dans la schizophrénie

Depuis plus d'un siècle, l'autopsie a joué un rôle essentiel dans la recherche des anomalies pathologiques structurales et biochimiques de la schizophrénie. Néanmoins, peu de progrès ont été accomplis durant cette période. Cette situation a commencé à évoluer récemment avec l'émergence de stratégies de recherche et de méthodologies plus puissantes auxquelles se sont ajoutées les informations complémentaires fournies par l'imagerie cérébrale. Cette évolution a permis de conclure à l'existence d'anomalies cérébrales structurales propres à la schizophrénie et de préciser que le processus neuropathologique n'est pas dégénératif mais lié à une modification de l'architecture cytologique du cerveau dont l'origine serait précoce, intervenant au stade du développement du système nerveux. Les autopsies ont mis en évidence l'existence d'altérations neurochimiques affectant plusieurs systèmes de neurotransmetteurs tels la dopamine, le glutamate, la sérotonine et l'acide γ-aminobutyrique (GABA). Cet article passe en revue les principaux résultats tout en examinant les problèmes conceptuels et méthodologiques qui se posent au cours des autopsies dans la schizophrénie.

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