
REVIEW

**IS BRAIN BANKING OF PSYCHIATRIC CASES
VALUABLE FOR NEUROBIOLOGICAL RESEARCH?**

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It is widely accepted that neurobiological abnormalities underlie the symptoms of psychiatric disorders such as schizophrenia and unipolar or bipolar affective disorders. New molecular methods, computer-assisted quantification techniques and neurobiological investigation methods that can be applied to the human brain are all used in *post-mortem* investigations of psychiatric disorders. The following article describes modern quantitative methods and recent *post-mortem* findings in schizophrenia and affective disorders. Using our brain bank as an example, necessary considerations of modern brain banking are addressed such as ethical considerations, clinical work-up, preparation techniques and the organization of a brain bank, the value of modern brain banking for investigations of psychiatric disorders is summarized.

KEYWORDS: Brain Banking. Post Mortem. Schizophrenia. Bipolar Disorder. Neurobiology.

INTRODUCTION

There is currently a high demand for neuropsychiatric brain banks to support neurobiological research with *post-mortem* tissue obtained from psychiatric patients with schizophrenia, bipolar disorder and depression. Based on a comprehensive literature search, we identified brain regions such as the hippocampus, prefrontal cortex and other heteromodal association cortices, which are presumably involved in the pathophysiology of psychiatric disorders. These investigations included functional and structural MRI studies as well as *post-mortem* studies of patients with schizophrenia and depression^{1,2}, which pointed to neuronal regions and networks affected in psychiatric disorders. Modern structural and molecular biology techniques in *post-mortem* tissue allow for the identification of the affected regions. Moreover, these approaches reveal alterations on the cellular and molecular level, such as a decreased number or volume of

different cell types (neurons and glial cells), and alterations of pathway-related genes and proteins. Since the brain tissue consists of heterogenous cell types, further *post-mortem* investigations should differentiate between molecular alterations in different cell populations in order to define more specific pathophysiological hypotheses. The psychiatric brain bank in Goettingen, Germany organized by Brain Net Europe II (www.brainnet-europe.org) may serve as an example for brain bank organization, even though brain banks in other countries will have to comply with the requirements of their own national legal and ethical framework.

In Europe, the Netherlands brain bank represents one such prospective collection of brain tissue from patients with psychiatric disorders.^{3,4} In Germany, the Brain Net provides researchers with brain tissue of psychiatric patients from several centers.⁵ The University of Magdeburg, for example, stores a collection of serially cut paraffin embedded and fresh frozen tissue samples from patients with schizophrenia and affective disorders, which facilitate stereology as well as gene and protein expression studies.^{6,7} Funded by the European Commission, Brainnet Europe II provides formalin-fixed and frozen brain tissue blocks from patients with Alzheimer's disease, Parkinson's disease, motoneuron disease,

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prion diseases, multiple sclerosis, schizophrenia (brain bank Goettingen) and affective disorders.^{1,8} Examples of well run, large scale neuropsychiatric brain banks in the USA that ship tissue to many centers include the Stanley Foundation brain collection, which provides paraffin-embedded and frozen brain tissue blocks, and the Harvard Brain tissue resource center, comprising schizophrenic, major depressive and bipolar cases.⁹⁻¹¹ The Mount Sinai School of Medicine Medical Center Brain Bank provides a large collection of fixed and frozen tissue from elderly schizophrenic patients,¹² and the Autism brain tissue bank is collecting rare tissue from children and adults with autism.¹³ In Brazil, there is a large brain bank situated in Sao Paulo.¹⁴ All these brain banks fulfill the modern criteria of brain banking such as ethical standards, proper collection of clinical data, and neuropathological investigations.

Early studies of histological abnormalities in the brains of schizophrenia patients revealed focal demyelination, neuronal atrophy, metachromatic bodies and lacunae. However, fixation and staining techniques were not standardized and the analysis was only qualitative, as techniques for quantification were lacking.¹⁵⁻¹⁷ Accordingly, further studies were not able to confirm these findings.¹⁸⁻²⁰ In 1952 during the first neuropathological conference in Rome, most neuropathologists agreed that no neuropathomorphology of schizophrenia exists. Thus, psychiatric disorders were considered to be functional psychoses with neurotransmitter changes and no neuropathological basis. In the 1970s, after the publication of enlarged ventricles in brains of schizophrenia patients by the first computer tomographic study,²¹ there was a revival of post-mortem studies in psychiatric disorders such as schizophrenia and affective disorders.^{22,23} These data led to the conviction that psychiatric disorders are brain diseases.

However, both the etiology and pathophysiology of psychiatric disorders are elusive and not well understood.²⁴ *In-vivo* MRI investigations of the brain point to dysfunction in distinct brain regions and neuronal networks, but cannot elucidate subtle neuropathological changes or alterations at the molecular level. Post-mortem research in recent decades using improved technology, such as statistical morphometric and molecular biology techniques²⁵ as well as computer-assisted quantification techniques which can be applied to the human brain, are causing an increased demand for post-mortem tissue for research. However, modern brain banks face the challenge of declining autopsy rates in all affluent countries.^{26,27} Additionally, such brain banks must meet certain criteria, such as standardized tissue handling and collection of clinical data, which again should enable the comparison of data from different laboratories.

The following paper presents modern techniques of post-mortem investigation in human brains, along with a

selective literature review of recent post-mortem findings in psychiatric disorders of interest such as bipolar and unipolar affective disorders as well as schizophrenia. Studies were selected according to the primary field of relevance and whether the results were replicated elsewhere in the literature. Then, demands on modern brain banking are described, such as ethical considerations, clinical work-up, preparation techniques and the organization of a brain bank. Finally the value of modern brain banking for investigations of psychiatric disorders is assessed.

Frequently used standardized techniques in post-mortem investigations

Structural methods

Stereological investigations represent some of the best validated morphological methods, and they allow for the assessment of the area and volume of a defined brain structure such as different brain regions, subregions or cell types. Moreover, total cell numbers and volumes as well as their distance in a defined structure can be investigated. With the rater blinded to diagnosis, total counts are obtained by the optical fractionator method²⁸ using a stereological workstation, consisting of a modified light microscope, Uplan Apo objectives (1,5x, 20x, 50x oil, 100x oil), a motorized specimen stage for automatic sampling, an electronic microcator, a CCD color video camera, PCs with frame grabber boards, stereology software and a television screen monitor. Boundaries of layers and regions are traced on video images displayed on the computer and calculated using Cavalieri's principle. Cell numbers are estimated with the optical fractionator.²⁸⁻³⁰ In addition to histological staining methods, immunohistochemical staining of cellular proteins allows for quantitative differentiation of cellular subgroups. Different cells (pyramidal neurons, interneurons, oligodendroglia, astrocytes) that come into focus within unbiased virtual counting spaces distributed in a systematic-random fashion throughout the brain regions of interest are counted. Estimated cell numbers per section and estimated total numbers per region are calculated from the numbers of counted cells per section and the corresponding sampling probabilities. Volumes of pyramidal neurons and interneurons are estimated using the nucleator probe of the appropriate software.

Schizophrenia is a devastating brain disorder with unknown etiology. Meta-analyses of structural magnetic resonance imaging (MRI) studies reveal gray matter volume deficits in different brain regions in schizophrenic patients. The affected regions are structures within the medial temporal lobe such as the hippocampus and parahippocampal gyrus (limbic system), the heteromodal association cortices such as the prefrontal and parietal cortices, and the superior temporal

gyrus.^{31,32} Atrophy rates up to 5-10% have been described in the frontotemporolimbic network. Moreover, the asymmetry of the temporal and prefrontal cortices has been reported to be disturbed in schizophrenia.³³⁻³⁵ In schizophrenic patients, positron emission tomography (PET) studies reveal dysfunction of the cortico-cerebellar-thalamic-cortical neuronal circuit which contributes to “cognitive dysmetria,” i.e., impaired cognition and other symptoms of the disease.³⁶ The small amount of tissue volume reduction in schizophrenia patients suggests that some cellular subfractions within these structures might be lost, reduced in volume or have an altered ratio between different cell types (e.g., neuron to glia ratio). Only post-mortem studies at the microscopic level are able to clarify which cells are disturbed and contribute to the findings described above. Limbic structures may be disconnected from both the prefrontal and temporal cortices in schizophrenia. This may be due to disturbances of the microcircuitry in subsets of neurons and glial cells in the laminar organization of glutamatergic pyramidal neurons and GABAergic interneurons, in concert with oligodendroglia and astroglia in cortical and limbic regions.

A recent post-mortem study of hippocampal grey matter using a gray-level-index (GLI) showed no cytoarchitectural alterations, suggesting no changes in the neuronal perikaryaneuropil ratio.³⁷ Earlier quantitative studies in the hippocampus and entorhinal cortex described reduced glial cells as well as unchanged neuron-glia ratios.³⁸⁻⁴⁰ According to these findings, astrogliosis has not been detected in schizophrenia.^{41,42} The entorhinal cortex is closely connected to the hippocampal formation, linking cortical areas to the hippocampus.⁴³ In the entorhinal cortex, abnormalities in the positioning of neuronal clusters (pre-alpha-cells) have been reported and support the hypothesis of migrational disturbances in schizophrenia,^{6,44,45} while other studies have not confirmed these findings.⁴⁶⁻⁴⁸ Additionally, in the entorhinal cortex, an immunohistochemical study demonstrated decreased density of tyrosine-hydroxylase labelled axons, pointing to alterations in the dopaminergic system.⁴⁷ However, the number and volume of neurons in pre-alpha-cell clusters or other layers of the entorhinal cortex remain unknown. The density of interneurons has also been reported to be decreased in CA2.⁴⁹ Additionally, neurons have been shown to be smaller in schizophrenic patients.⁵⁰ However, two-dimensional cell counting in only a few sections, without consideration of the total hippocampus volume, may have some methodological limitations through the influence of volume differences (e.g., mediated by neuropil degeneration) and tissue shrinkage due to fixation procedures. Two stereological estimates of total cell number reported no differences in the hippocampus of schizophrenic patients. However, one study investigated only the total numbers of neurons,⁵¹ whereas the subdivision

of parvalbumin-positive interneurons has been reported to be decreased.⁵² The second study also did not differentiate between different cell types, and included schizophrenic as well as schizoaffective patients.⁵³



Figure 1- Dissection of the prefrontal cortex (BA46).

In the prefrontal cortex BA (Brodmann area) 10 and BA 9, no change and an increase of GLI, respectively, points to a circumscribed disturbance of cytoarchitecture was found in schizophrenia.^{54,55} Along these lines, neuronal density has been reported to be increased in BA9.^{56,57} In this region in layer III, pyramidal neurons and neuronal cells showed reduced somal size.^{58,59} Astrocyte density has been reported to be decreased in layer V.⁵⁸ A stereological study of total cell numbers described decreased numbers of oligodendrocytes in layer III of BA9 in schizophrenia.^{60,61} Stereological studies of the anterior cingulate cortex (BA24) measuring the total number of neurons and glial cells reported a reduced number of glial cells and a reduced volume of pyramidal cells in schizophrenia.^{62,63}

On the cellular level, the densities of parvalbumine-immunoreactive varicosities in the middle layer of the prefrontal cortex in schizophrenia patients were lower, sug-

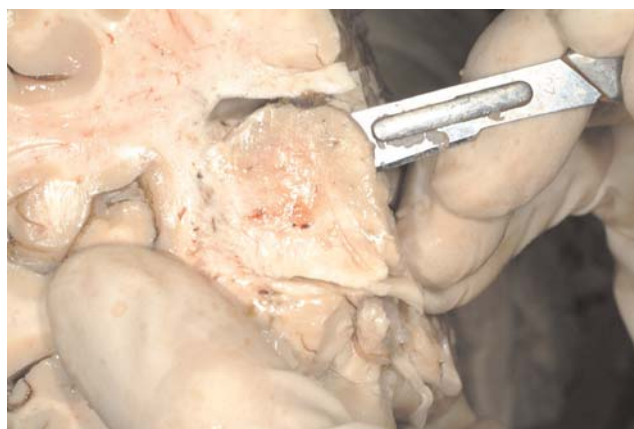


Figure 2 - Dissection of the thalamus (mediodorsal nucleus).

gesting fewer projections from the thalamus to the prefrontal cortex.⁶⁴ *Post-mortem* findings of reduced volume, neuron number, and size of the entire thalamus,⁶⁵ mediodorsal nucleus and the pulvinar and ventral posterior thalamic nuclei^{66,67} support the hypothesis of disturbed function and disconnection of different thalamic nuclei in schizophrenia.

Most schizophrenia patients investigated in post-mortem studies were treated with antipsychotic medication such as haloperidol and clozapine for decades. In an animal study, we demonstrated that an increase of total hippocampal volume after chronic haloperidol treatment was not associated with alterations of stereologically measured neurogenesis.⁶⁸ In the striatum of rats, haloperidol treatment induced larger volumes after one month of treatment. This enlargement was associated with vacuous chewing movements, an animal paradigm for tardive dyskinesia.⁶⁹ Additionally, volumetric MRI studies in schizophrenic patients showed an enlargement of the nucleus caudatus after chronic haloperidol treatment and a subsequent volume reduction after treatment with clozapine.⁷⁰

The hippocampus is also a key structure affected in the neurobiology of depression.⁷¹⁻⁷³ However, structural magnetic resonance imaging (MRI) studies of the hippocampus in patients with depression show conflicting results, probably due to antidepressant treatment. A recent MRI study of drug-free depressive patients showed a reduced hippocampal volume, especially on the left side.⁷⁴ However, the hippocampus in affective disorders has not yet been studied using stereological techniques. In the entorhinal cortex of patients with bipolar disorder, the total number of parvalbumin-immunoreactive interneurons was decreased.⁷⁵ In major depression, the number of GABAergic neurons were reduced in the prefrontal cortex,⁷⁶ whereas in bipolar disorder, calretinin-stained neurons showed an increased density.⁷⁷ In a densitometry study of the prefrontal cortex, neuronal and glial cell density as well as neuronal size were reduced in depression.⁷⁸ In a stereological study of the orbitofrontal cortex, neuronal size was reduced in layer I in bipolar disorder and in layer 3 in major depressive disorder without an alteration of the cell number.⁷⁹ In bipolar disorder, major depressive disorder and schizophrenia, neuronal density was increased while neuronal size was reduced in the anterior cingulate cortex, indicating similar pathophysiological conditions between these mental illnesses.⁸⁰ In the paraventricular nucleus of the hypothalamus, a stereological post-mortem study reported a significant reduction of neuronal number in major depression and bipolar disorder.⁸¹ Thus, further structural investigations in affective disorders are warranted to define the affected cell populations in these disorders.

Gene expression studies

Altered patterns of gene expression (mRNA) are implicated in the pathophysiology of schizophrenia, depression and

bipolar disorders.^{71,82,83} The advantage of cDNA microarrays is the ability to simultaneously examine thousands of expressed genes of potential interest, without a hypothesis. Other new molecular techniques include subtractive hybridization⁸⁴, serial analysis of gene expression (SAGE)⁸⁵ and differential display of mRNA.⁸⁶ However, microarray data often require confirmation by other molecular biological techniques, such as reverse transcription-polymerase chain reaction (RT-PCR) and *in-situ* hybridization, which has the advantage of the ability to delineate anatomically defined structures.⁸⁷ Since the brain is not only organized in functionally different regions and circuits, but also in a large variety of cell types (e.g., macro- and microneurons, oligodendrocytes, astrocytes and microglia), which express different fractions of the human transcriptome, large variations in mRNA expression levels are expected. New methods such as laser capture microdissection, fluorescence activated cell sorting (FACS) and single-cell RT-PCR with RNA amplification⁸⁸⁻⁹⁰ are promising in showing characteristic alterations of small cell populations. In the thalamus, for example, laser capture dissection of subnuclei permitted the evaluation of gene expression differences in the thalamus of schizophrenic patients.⁹¹

The nosologic distinction between schizophrenia and bipolar disorder, which is also known as manic-depressive disorder, is an area of ongoing controversy, since both disorders share psychotic and affective symptoms as well as response to antipsychotic treatment.⁹² Accordingly, DNA microarray studies show the same up- or downregulation of genes. Furthermore, mitochondrial dysfunction has been shown in the brain samples of schizophrenia⁹³⁻⁹⁷ and bipolar disorder patients.^{96,98,99} Mitochondria produce energy, and a failure in energy metabolism has been hypothesized in these disorders. Additionally, oligodendrocyte dysfunction has been hypothesized in schizophrenia,⁶⁰ i.e., downregulation of oligodendrocyte-related mRNAs has been reported in schizophrenia.^{96,100-104} In schizophrenia, downregulation of genes associated with neurite outgrowth, cytoskeletal proteins or synaptic plasticity are in accordance with the hypothesis of disturbances of microconnectivity.⁹⁷ Apart from mitochondrial¹⁰⁵ and oligodendrocyte dysfunction,^{96,106} downregulation of genes encoding calcium channels and neurotransmitter receptors has been reported in bipolar disorder, while the expression of heat shock proteins was upregulated.¹⁰⁴ In major depression, oligodendrocyte proteins,¹⁰⁷ fibroblast growth factor related genes and glutamate transporters have all been reported to be downregulated.¹⁰⁸⁻¹¹⁰ Finally, alterations of the GABAergic system were related to depression and suicide.¹¹¹

Investigations of protein expression

One limitation of gene expression approaches is their ability to study only the intermediate mRNA molecule. Ad-

ditionally, protein expression should be examined. However, proteins are also vulnerable to degradation by enzymes during the agonal state and the post-mortem period. Moreover, the functions of gene products (proteins) are often highly dependent on posttranslational modifications such as phosphorylation or glycosylation.¹¹² Standard techniques to determine protein levels include Western blotting, 2D polyacrylamide gel electrophoresis (2D-PAGE), chromatographic separation, mass spectrometry and radioligand receptor binding, which also examines the functional state of neurotransmitter receptors. Immunohistochemical techniques using specific antibodies in formalin-fixed, paraffin-embedded material are often performed for in-situ investigations of specific anatomical subregions. Proteomic analysis is performed by two-dimensional gel electrophoresis (2DE) followed by MALDI-TOF/TOF mass spectrometry. This combination is one of the most potent methods of analyzing the complete proteome; it allows a rapid view of changes in multiple protein extracts. Shotgun proteomics is a new method that can overcome some of the limitations of two-dimensional gel electrophoresis. This allows for the investigation of a greater fraction of expressed proteins and for the evaluation of differential protein expression with higher precision. Quantification of shotgun-generated data is improved by the use of stable isotope labeling of the proteins, which allows for more precise comparison and quantification.¹¹³ Isotope-Coded Protein Labeling (ICPL) is a method for the accurate quantitative comparative analysis of protein regulation.¹¹³ ICPL is based on isotope labeling of free amino groups in intact proteins. After the modification, the heavy and light isotope labeled proteins are digested and analyzed by liquid chromatography (LC) followed by tandem mass spectrometry (MS/MS). Relative quantification of differential protein expression is based on the comparison of the peak intensities of the heavy- and light-labeled peptides from the mass spectra.

In accordance with gene expression studies, proteins of the mitochondrial pathway have been shown to be altered in schizophrenia, bipolar and depressive disorders,^{95,114} while there is no consensus on the direction of the expression changes. In bipolar disorder and schizophrenia, reduced expression of cytoskeletal proteins has been reported.^{95,114} In addition to these pathways, proteins related to oxidative stress, synaptic function and signaling were altered.¹¹⁵ Moreover, proteins involved in gene transcription, protein and RNA chaperoning and cellular homeostasis have been shown to be downregulated in schizophrenia and upregulated in bipolar disorder.¹¹⁶ Other immunohistochemical studies show downregulated oligodendrocyte-related proteins in the gray matter of patients with schizophrenia,^{117,118} as well as synaptic proteins in the frontal cortex and hippocampus in schizophrenia and affective disorder.¹¹⁹⁻¹²² Contrastingly,

neural stem cell proliferation was reduced in the dentate gyrus of the hippocampus in schizophrenic but not in depressive patients.¹²³ Immunohistochemical investigation of the protein expression of the candidate gene neuregulin-1 in schizophrenia⁷ revealed a decreased density of neuregulin-1-alpha splice variant expressing cells. Further proteomic and immunohistochemical studies are warranted to identify alterations of proteins which are related to specific metabolic pathways and cell systems in psychiatric disorders.

Ethical issues and brain bank organization

There are a number of ethical issues involved in the implementation and ongoing activities of a brain bank. Patients with severe psychiatric illnesses such as chronic schizophrenia have caregivers and are not able to appreciate all the consequences of consent in research purposes. For this reason, relatives should be informed if the patient gives his written consent before death in a donor program, and the caregiver should also provide his written consent. A physician should document that the patient has been able to understand the content of the agreement. Donor programs have the advantage of performing prospective standardized diagnostic tests, psychopathological and neuropsychological examinations and relating this information to data obtained from neurobiological measurements.

To obtain the relatives' consent, it is essential to provide them with an informational brochure about the research purposes of the brain bank as well as its organization. It is important that relatives are able to refuse consent at any time, that data protection and anonymization are declared, and that relatives are able to exempt the medical staff from professional discretion for the analysis of medical records and clinical data. If there are no relatives, autopsies for research purposes should not be carried out, since the legal position is not clear.

In our psychiatric institute, a psychiatrist is informed by the (neuro)-pathologist of an appropriate case before autopsy. He/she then calls the relatives and asks for oral consent and requests clinical information on the deceased. It is also important to organize a hotline where the coordinator of the brain bank can be reached at all times. Once informed of the autopsy, he should immediately try to get oral consent from the deceased's relatives. Then, the brain can be prepared and written consent can be obtained. Brain banks need additional manpower for the distribution of the tissue to researchers and documentation.

Clinical data and data protection

Information about clinical data can be obtained from

Table 1 - Neuroanatomical preparation protocol in Brain Net Europe II, brain bank of psychiatric diseases, Göttingen

1.	Collect the liquor cerebrospinalis after craniotomy.
2.	Divide the fresh, unfixed brain into the two hemispheres, including the brain stem and cerebellum.
3.	Put the hemispheres on the medial side to prepare the lateral samples A to L (see sample list table 2) from top to bottom according to the Brodmann-diagram.
4.	Put the hemispheres on the lateral side to prepare the medial samples M to PP (table 2) according to the Brodmann-diagram.
5.	Cut the brainstem with the cerebellum at the level of the mid brain 0.5 cm above the <i>substantia nigra</i> and place it aside
6.	Cut the hemispheres frontally through the <i>corpora mamillare</i> into an anterior and a posterior part.
7.	Take the posterior part and cut a frontal slice 2 cm behind the <i>corpora mamillare</i> .
8.	From the anterior and posterior part as well as the 2 cm slice, prepare samples Q through TA (basal ganglia, thalamus, hippocampus, nucleus accumbens).
9.	As a last step, the brain stem and cerebellar areas will be prepared (sample U until N. Dentatus, table 2).
10.	Cut samples from the musculus psoas, m. quadriceps femoris, liver, and abdominal fat for analysis of metabolic syndrome, and take one blood sample for genetic analysis.

relatives, general practitioners, psychiatrists and medical records. Clinical diagnosis should be standardized according to DSM-IV/ICD-10 criteria. It is possible to reconstruct psychiatric diagnoses according to the information obtained using the DSM-IV checklists.¹²⁴ Within Brainnet Europe II, our working group on neuropsychiatric brain banking has developed a consensus on clinical information.¹ All tissue preparations and medical data will be analyzed using code numbers, which precludes associations between data and individuals. Only the written consent form contains personal data and the names of relatives, and these personal data are stored in a separate location. In case of cancellation of consent, the data are erased. The obtained data are included in a firewalled database with access only available to the authorized brain bank assistant.

Regions of interest and neuropathological preparation

Most scientists prefer to use frozen tissue for studies of protein expression, RNA expression and receptor binding. However, post-mortem intervals (PMI) should not be longer than 48 hours for these studies. Therefore, in brains with PMI until 48 hours, we decided to collect two frozen samples from each brain region and one formalin-fixed and paraffin-embedded sample for immunohistochemistry and neuropathological staining to exclude Alzheimer-related pathology. Brains with longer PMI should be totally formalin-fixed and embedded for morphometry. An example for a neuropathological preparation protocol is given in table 1. Freezing of the samples is carried out in liquid nitrogen-cooled isopentane (n-heptane) to avoid freezing artifacts. Fixation is best in 4% buffered paraformaldehyde with consecutive paraffin-embedding after several hours. Brain sample pH is believed to be closely associated with the terminal condition of a patient, such as agonal state. Patients with low pH brain tissue exhibit a gene expression profile distinct from that seen in patients with higher pH.¹²⁵ Thus, pH measurement

Table 2 - Definition of regions of interest in psychiatric disorders according to Brodmann. (Each region: 2 frozen samples and 1 formalin-fixed, paraffin-embedded sample). Numbers represent Brodmann Areas

A:	17, 18
B:	39
C:	10
D:	9
EE:	47
E:	11
F:	44, 45
G:	46
H:	38
I:	22 a = anterior
J:	22 p = posterior
K:	21
L:	1, 2, 3, 4, 7
M:	32, 24 a = anterior
N:	23, 31 p = posterior
O:	Corpus callosum
P:	20
PP:	28 / 34
Q:	Thalamus: mediodorsal
QX:	Thalamus: medial Pulvinar
QY:	Thalamus anterior region
RX:	N. caudatus dorsalis
RY:	N. caudatus ventromedialis
S :	Putamen
T:	Globus pallidus
TT:	Substantia Nigra
TX:	Capsula interna ventralis
TY:	Capsula interna dorsalis
TT:	Hippocampus
TA:	N. accumbens
U:	Pons-Basis rostral
V:	Pons, caudal
W:	Medulla oblongata rostral
X:	Medulla oblongata caudal
Y:	Spinal cord
	Cerebellum-Vermis Lous. anterior
	Cerebellum, Vermis, Lobus medialis
	Cerebellum, Hemisphere, Lobus posterior
	Cerebellum Nucleus dentatus

is an important way to define this confounding variable in post-mortem tissue. Both hemispheres should be considered in psychiatric cases, because of laterality changes in several brain regions.³⁵ A detailed list of regions according to the atlas of Brodmann¹²⁶ is given in table 2.

Neuropathological findings in psychiatric cases such as plaques and tangles are common, and should be diagnosed carefully to eliminate confounding factors which may influence data related to the neuropathology of psychiatric disorders.^{127,128} Late-onset psychiatric symptoms such as depression, hallucinations and delusions are common even in patients at the early stages of Lewy body dementia, Alzheimer's disease, Progressive Supranuclear Palsy and Corticobasal Degeneration,¹²⁹⁻¹³² and may lead to misdiagnosed cases in a brain bank.¹³³ International standard criteria should be followed regarding clinical and neuropathological diagnosis of these dementias.^{129,134} In addition to patients with clinically assessed dementia, patients with schizophrenia and

depression may also exhibit Alzheimer's and Parkinson's related neuropathological alterations in their brains, since these changes may precede clinical symptoms by many years.¹³⁵

In summary, modern brain banking is indispensable for neurobiological investigations on mechanisms on the structural, cellular and molecular (mRNA, protein) levels. However, the neurobiological origins of the detected alterations are undetermined. Further studies in post-mortem brains, animal models and cell cultures are required to elucidate the influence of candidate genes and environmental factors during brain development. A growing number of studies identifying candidate genes in mental disorders^{136,137} demonstrate the necessity of genotyping brains of psychiatric patients in order to elucidate the relationship between gene and protein expression and risk genotypes. Finally, in animal models, the interaction between genetic and environmental risk factors, both of physical and psychological origin, must be investigated.

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