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## Brain research and clinical psychiatry: establishment of a psychiatry brain bank in Japan

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### ABSTRACT

The Japan Agency of Medical Research and Development (AMED) has approved the budget for the 5-year project called Establishment of the JAPAN Brain Bank Network, which commenced in 2016. This project was established with the aim of storing brain tissue samples to enable research on the etiologies and mechanisms of psychiatric diseases, which would eventually improve standards of clinical treatment for these diseases.

Japanese researchers in the field of biological psychiatry have historically depended on Western brain banks, particularly from Europe and the United States, which is regrettable. To remedy this situation and improve the Japanese research standards, attempts for establishing an autonomous Japanese brain bank are ongoing.

Reviews of the previous attempts on elucidating the etiopathology of neuropsychiatric diseases reveal that rapid advances result from studies on tissue samples from diseased brains. For example, in the Kraepelin era, i.e. in 1900 years before and after, long-term, resolute research on diseased brain specimens ultimately led to the discoveries of entities such as Alzheimer disease and Lewy body disease. The recent advances in techniques of neuroimaging and molecular biology have resulted in a shift of interest from brain tissue analysis. However, the integration of findings of all these techniques is recommended going forward, with a shift in focus back to brain tissue analysis.

The JAPAN Brain Bank Network project was launched under this setting. The success of this project largely depends on the will of patients and family members (for donating samples) as well as cooperation among many clinicians.

In this paper, we provide a brief overview of the history of biological psychiatric research and related perspectives, which will hopefully encourage further studies that will help bridge the gap between clinical and biological research on psychiatric diseases.

**Keywords:** neuropathology, brain research, clinical psychiatry, psychiatric disease, brain bank

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### INTRODUCTION

The term ‘brain bank’ is not familiar to many medical professionals, even in the psychiatric setting, unless they are involved in brain research. An online search for the term returns the

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names of organizations and associated institutions from the West. Although repositories for brain tissue samples are the most important and elementary asset for supporting brain research on psychiatric diseases, Japan has procrastinated in comparison to Western countries in relation to the accumulation of brain resources.

A detailed discussion on the various background factors that have contributed to this desperate situation is beyond the scope of this paper. However, it is evident that the establishment of a Japanese brain bank to provide easy access to brain tissue resources is essential.

In clinical settings, listening to the issues of patients and their family members and the appropriate management of their care are considered essential attributes. At the same time, clinicians should also aim to contribute to research with the aim of clarifying the etiology of diseases. Hence, Japanese psychiatrists started JAPAN Psychiatric Brain Bank Network. The success of this project will largely depend on the understanding and cooperation of many clinicians performing autopsies because they alone can build bridges between patients, families, and brain researchers.

Some cases are referred to psychiatry clinics without any neuroimaging evaluations. In most such cases, neuroimaging examinations are deemed unnecessary with the exclusion of organic diseases from differential diagnoses. However, neuroimaging information essential in clinical psychiatric diagnosis. For example, some patients with organic neurological diseases, such as Lewy body disease, anti-N-methyl-D-aspartate encephalitis, Creutzfeldt–Jakob disease, and Huntington disease, only show psychiatric symptoms in the early stages of the disease. Some of these patients are initially diagnosed with so-called functional psychoses, such as schizophrenia or bipolar disorder, and neuroimaging data is necessary to enable accurate diagnosis and early intervention. Thus, the possibility of organic disease should be considered in the clinical practice of managing psychiatric cases.

## THE HISTORY OF BRAIN RESEARCH IN PSYCHIATRY

During the Meiji era (late 1800s and early 1900s), which is considered the dawn of modern medicine in Japan, Japanese clinicians followed the German medical model. The German model was selected for psychiatry as well, primarily because of the huge archives of German medical history.

Prof. Griesinger is a founder of German psychiatric medicine. In his psychiatry text book, he claimed that psychiatric diseases consisted of both organic and physiological disorders. This statement is considered to mark the beginning of biological psychiatry. In the same textbook, he discussed a range of topics, including the organs in which psychosis-related phenomena originate and the organs showing pathological changes in psychiatric diseases. Overall, these concepts have played a fundamental role in psychiatric medicine. Since then, the identification of neuropathological changes in the brains of patients with psychosis has provided physiological and pathological evidence of the role of brain in psychiatric diseases. This promoted interest in biological psychiatry. Griesinger advocated the idea of *Einheitspsychose* (unitary psychosis). He stated, “Although psychiatric diseases can manifest with varying psychosomatic symptoms, they are essentially a unitary disease. Future progress in brain neurology (neuropathology) will guide the appropriate and effective treatment of psychiatric diseases.” He emphasized the importance and validity of detailed clinical evaluations and the employment of the scientific approach in psychiatric medicine.

Prof. Shuzo Kure, a founder of the Japanese Society of Psychiatry and Neurology (known “Japanese Society of Neurology” then), wrote the following note at the foreword of Volume 1 in official Journal of its society; “Some say psychiatric disease, others neurological disease, but

there is only a subtle difference. There is no boundary at all. However, it is deplorable that clinicians tend to see imaginary differences, especially between so-called ‘functional psychoses’ and ‘neurological disease’ without detailed scientific investigations.” He was largely influenced by Prof. Griesinger, who emphasized the importance of viewing psychiatric diseases as neuropsychiatric diseases.

Prof. Theodor Meynert (1833–1892) was a psychiatrist, anatomist, and neuropathologist influenced by Griesinger. He discovered the basal nucleus of Meynert and attempted to reveal the etiology of psychiatric diseases biologically through studies of brain neuropathology and brain anatomy (i.e., analysis of the layer structure and the nerve fiber pathways in the cerebral cortex). These biological studies offered new methodologies for investigating the correlation between clinical syndromes and brain function.

Some of Prof. Meynert’s disciples were also eminent scientists. They included Prof. Sergei Korsakoff (1854–1900), after whom Korsakoff’s syndrome is named; Prof. Josef Breuer (1842–1925) and Prof. Sigismund Schlomo Freud (1856–1939), who were great psychoanalysts; and Prof. Julius Wagner-Jauregg (1857–1940), who developed treatment for neurosyphilis and won a Nobel Prize. In this period, the work of Prof. Emil Kraepelin (1856–1926), who was considered the leader of European psychiatrists, formed the basis of German psychiatry, the so-called “Kraepelin Empire.” Apart from establishing a classification system for neuropsychiatric diseases, he made several outstanding achievements in psychiatry. He expanded on the ideas proposed by Prof. Griesinger and Prof. Meynert. He described the etiology of dementia praecox (now known as schizophrenia) as follows: “Partial disorder or destruction of neurons may occur in the cerebral cortex of patients with dementia praecox. Compensation for these deficits may occur in some cases, but most cases show permanent symptoms.” This emphasized the possibility that psychiatric diseases could have underlying pathological involvement of the brain.

Under Prof. Kraepelin’s guidance, his followers, including Prof. Alzheimer, continued the research on the brain pathology of patients with psychiatric disease. Prof. Alzheimer is renowned for discovering presenile dementia, which was later named Alzheimer disease after him. In addition to this, he actively performed neuropathological examinations on the brains of patients with *psychose* (psychosis). At that time, schizophrenia was referred to as dementia praecox, because it was considered closely related to dementia according to clinical symptoms. However, Prof. Alzheimer demonstrated the absence of neural gliosis in the brain of schizophrenia cases and hypothesized that prognosis of such cases was better than that of dementia cases. This showed that neuropathological findings are clear and scientific indicators, and these indicators can be used for classifying separate groups of clinical entities.

These viewpoints are the most important in the approach to psychiatric diseases themselves. In other words, a biological–medical approach (e.g., neuropathology), which is based on the detailed description of clinical symptoms, is deemed necessary to understand and elucidate the etiology of psychiatric diseases. The 1900s marked the beginning of a prosperous period for German psychiatry, and research on psychiatric diseases was based on neuroanatomical methods. Although this approach flourished with the discovery of abnormal protein accumulation in dementia patients, clarification of the mechanisms of endogenous psychosis remained too difficult.

Prof. Gaupp (Robert Gaupp, 1870–1953), another disciple of Prof. Kraepelin, claimed that applying the biological approach to psychiatric diseases had limitations, emphasizing the importance of “internal psychological observation.” instead. During this period, the application of scientific and biological approaches in psychiatry declined, and the so-called “dynamic psychiatry” attained prominence. Following Prof. Meynert, Prof. Freud started his career in the study of neuropathology (focusing on spinal nerves) and aphasia. He would later get influenced by Prof. Charcot and Dr. Jung, and his subsequent psychiatric research had a psychological focus, instead of a

physiological one.

Prof. Kure, a Japanese researcher, studied in Europe in 1896–1901, when Prof. Kraepelin and Prof. Nissl were enjoying great success and brought German psychiatry back to Japan. He also established the Japanese Society of Neurology (which later became Japanese Society of Psychiatry and Neurology) and founded the related official journals. He introduced the Nissl staining technique, a significant development in brain neuropathology that contributed to the expansion of psychiatry in Japan. The website of the Japanese Society of Psychiatry and Neurology has a portrait of him standing in front of a microscope.

Prof. Kure, a professor of Psychiatric Medicine at the Tokyo Imperial University, enthusiastically performed autopsies in Tokyo Metropolitan Sugamo Hospital (later named Tokyo Metropolitan Matsuzawa Hospital). One of his students, Prof. Shimoda, actively studied brain neuropathology, but ultimately advocated that neuroanatomical evidence was lacking to prove the organic etiology of schizophrenia.<sup>1)</sup> His later research focused on immodithymia.

Research studies in the field of brain neuropathology yielded important results on neurodegenerative diseases and neurosyphilis (i.e., the discovery of syphilitic spirochete), but failed to generate reproducible findings in other neuropsychiatric diseases, such as schizophrenia and bipolar disorder.

At the 1st congress of the International Academy of Neuropathology held in Rome in 1952, researchers made the following official statement: “Schizophrenia does not have an underlying neuropathology.” In 1972, Dr. Plum made the following negative comment: “Schizophrenia is the graveyard of neuropathologists”<sup>2)</sup> ironically.

Despite these setbacks, some researchers continued working on brain neuropathology. Among them were two Japanese researchers, Prof. Tatetsu and Prof. Miyakawa, whose achievements<sup>3,4)</sup> should be reconsidered, considering that Miyakawa’s reports were recently validated. Their findings of neuropathology in schizophrenia have been confirmed reproducibility nowadays from the view point of newly approach.

Gaupp, Freud, and Shimoda (in Japan) are credited with great achievements in psychiatry. Furthermore, the background of each of these researchers included great knowledge and understanding of brain pathology. Prof. Kandel, who won the Nobel Prize in Physiology or Medicine in 2000, wrote, “All psychological processes, even the most complex psychological processes, derive from operations in the brain. Genes and their protein products are important determinants of neuronal connection patterns in the brain and the details of their functioning. Alterations of gene expressions, by themselves, cannot explain all the variations of a given major psychological diseases. Gene expression is altered as a result of learning, giving rise to changes in neuronal connection patterns. The long-term behavioral changes induced by psychotherapy or counseling are considered to occur via this learning mechanism, which results in both gene expression changes that alter the strength of synaptic connections and structural changes that alter the neuronal connection patterns in the brain.”<sup>5)</sup> He proposed the linking of psychological functions to biological principles. This idea is extraordinarily important in clinical psychiatry, because, regardless of pharmacological intervention, treatment may cause alterations in brain of patients. If this hypothesis is valid, both psychoanalysis and dynamic psychotherapy could cause significant alterations in brain tissue.

Capgras syndrome (also referred to as misidentification syndrome), reported in 1923 by the French psychiatrist Dr. Jean Marie Joseph Capgras, is a good example of this phenomenon. During the first half of the 20<sup>th</sup> century, this syndrome was interpreted as a defense mechanism to disguise or camouflage strong feelings toward loved ones or incestuous feelings toward parents from a psychoanalytic point of view. However, in recent years, this syndrome has been frequently reported in patients suffering from organic brain diseases, such as brain cancer, or

neurodegenerative diseases, such as Alzheimer disease or Lewy body disease. This has generated much interest in its etiology and pathophysiology. In 2001, Prof. Haydn Ellis hypothesized that Capgras syndrome is closely related to the phenomena of false recognition and the misidentification of faces.<sup>6)</sup> Although this hypothesis cannot completely explain the associated phenomena, it greatly improved the understanding of the syndrome.

Prof. Oliver Sacks (1933–2015), a neurologist and novelist, has critiqued the split of neuropsychiatry into the two specialties of neurology and psychiatry: “By the turn of the century, a split had occurred, into a soulless neurology and a bodiless psychology.” This message should not be forgotten, and treatment should be administered according to the concept of “neuropsychiatric disease” rather than the simplistic concept of “psychiatric disease.”

## RESEARCH ON THE BRAINS OF PATIENTS WITH NEUROPSYCHIATRIC DISEASE

Brain research has shifted its focus from neuropathological examination to neuroimaging and molecular biology, which have played important roles in analyzing the etiology and pathophysiology of psychiatric diseases in recent years. However, the accumulation of the results of several such studies has rekindled interest in brain tissue studies. Currently, neuroimaging can provide detailed information on the diseased brain; for example, multiple studies have reported on decreased brain volume schizophrenia patients. Such discoveries and related hypotheses should be validated by the analysis of existing brain tissue samples.

Moreover, genetic research has revealed that many of the candidate genes of schizophrenia are related to neuronal maturation, differentiation, and migration. These results should be verified through histopathological examination of brain tissues. Furthermore, findings related to genetic information and protein synthesis should be validated, and structure formation could be only detected by observing the neuropathology of the brain. In conclusion, for improved understanding of disease etiology and pathophysiology, neuroimaging and molecular biological approaches should be combined with neuropathological evaluations of actual brain tissue samples.

Moreover, achievements in the field of molecular biology have made it possible to create animal models that can be used to investigate disease pathophysiology. Neuropathological research using these animal models has provided valuable clues that can be applied in human brain research. This is because pure disease phenotypes can be analyzed by excluding the impact of factors before the onset of disease, during the end stages of disease, and before post-mortem examinations including agonal factor, all of which have adverse effects on pathophysiological observation.

DISC1 knock-out animal models are considered to reflect the pathophysiology of schizophrenia in humans. Several investigations of the neuropathology of the brains of DISC1 knock-out mice have yielded useful findings, which were validated by studies on brains of human schizophrenia patients.

Recently, some studies have reported the use of molecular biological techniques for studying cerebral white matter abnormalities, particularly for evaluations glial cells in the brains of schizophrenia patients.<sup>7)</sup> Furthermore, some neuroimaging studies have used diffuse tensor imaging to investigate abnormalities in white matter connections in schizophrenia patients. In conclusion, combining neuroimaging or molecular biological findings with neuropathological findings from studies using actual brain tissue will help in understanding the precise pathophysiology of psychiatric diseases, which will subsequently help in elucidating disease etiologies.

## THE USEFULNESS AND AVAILABILITY OF PSYCHIATRIC BRAIN BANKS

At this point, attention needs to be directed on the availability of brain tissue resources for future studies. For example, the long-lost brain tissue sample of Auguste D, the first known Alzheimer disease patient, was found in Munich in 1997 and was subjected to molecular biological analyses. In 2012, the patient was found to have a presenilin-1 (*PSEN1*,  $\gamma$ -secretase) gene abnormality, which is a known cause Alzheimer disease.<sup>8)</sup> This confirmed that preserved brain tissue can be used for analyses at a much later date and that new discoveries from such analyses might reveal disease etiology and contribute to progress in psychiatry. In other words, adequately preserved brain tissue repositories will support future research in psychiatry.

The etiologies of many psychiatric diseases remain unknown despite ongoing research. Despite this, efforts should be sustained for improving psychiatric care, keeping in mind the importance of the brain in psychiatric diseases. This will enable the optimal clinical application of advancements in brain research as well as techniques from other scientific fields.

Of course, it is important for clinical psychiatrists to consider the organic basis of psychiatric diseases while administering clinical care on a day-to-day basis. Neuropathological investigation using brain tissue samples can improve the clinical skills of clinical psychiatrists, it is to say, facing sincerely to clinical medicine.

## LIMITATIONS AND FUTURE PERSPECTIVES ON PSYCHIATRIC BRAIN BANKS

Several factors need to be considered while starting and maintaining a brain bank. For example, autopsy procedures are becoming less common in Japan. Although this is a worldwide trend, it is more pronounced in Japan than in Western countries. Pathological autopsy frequency in Japan peaked in 1985, with 40,000 being performed. Autopsy frequency has rapidly declined since 1990, and <10,000 being performed currently every year (according to the data of Japanese Society of Pathology). The autopsy rate in hospitals with >500 beds is reported to be up to 9.2%, whereas the overall rate for all medical institutions in Japan is only 2% (according to the Japan Council for Quality Health Care). Such a trend is seen in clinical psychiatry as well. Autopsy frequency in psychiatric hospitals has recently declined as part of medical cost-cutting. This is partly because of the belief that neuroimaging data is sufficient to investigate brain neuropathology in patients with psychiatric diseases. Such factors indicate that starting and maintaining psychiatric brain banks will be difficult.

However, the 5-year project called Establishment of the JAPAN Brain Bank Network has commenced in 2016, under the guidance of the Japan Agency for Medical Research and Development (AMED). This is a wonderful opportunity to establish an autonomous brain bank in Japan. The success of this project largely depends on the will of patients and family members (for donating samples) as well as cooperation among hundreds of clinicians

Cooperation in the process of accumulating brain tissue repositories will greatly contribute to progress in psychiatry, potentially acting as a bridge between clinical and biological research on psychiatric diseases.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest in association with the present study.

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