

Neuroethical Issues of the Brain/MINDS Project of Japan

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The Brain/MINDS project aims to further understand the human brain and neuropsychiatric disorders through “translatable” biomarkers. Here, we describe the neuroethical issues of the project that have arisen from clinical data collection and the use of biological models of neuropsychiatric disorders.

Introduction

Despite significant research into neuropsychiatric disorders, linking data from genetic, neurophysiological, and neuroimaging studies with the real-world behaviors and distress experienced by individuals remains limited. The Brain/MINDS (brain mapping by integrating neurotechnologies for disease studies) project of Japan aims to better understand the human brain by integrating research on the marmoset with clinical research on neuropsychiatric disorders (Okano et al., 2016).

The research organization of the Brain/MINDS project involves four major groups. Three of these groups are related to the structural and functional mapping of the marmoset brain and the development of brain-mapping-related technologies. Macroscopic-level mapping using structural and functional MRI-based techniques, mesoscopic-level mapping using tracer injections and light microscopy, and microscopic-level mapping using serial electron microscopy are being developed and utilized in marmoset research. The fourth group focuses on human brain mapping and clinical research (Figure 1A).

The clinical research group conducts human brain mapping of neuropsychiatric disorders. Its missions include: (1) the exploration of disease-related neural circuits using neuroimaging, neurophysiological, and behavioral data obtained

from large-scale clinical data; (2) the discovery and development of “translatable” biomarkers that can be measured using techniques common to both nonhuman primates and humans from these neural circuits; (3) the application of these candidate translational biomarkers to the neural circuits of marmoset models; and (4) the application of these findings to establish neural-circuit-oriented re-classification strategies for neuropsychiatric disorders and to develop innovative treatments for these disorders (Figure 1A).

Thus far, research has been conducted in three teams focusing on neurodegenerative diseases, psychiatric disorders, or cerebrovascular diseases and neurorehabilitation. Example projects include neurophysiological studies in schizophrenia, early detection of a change in neurocircuits of Alzheimer’s disease and diffuse Lewy body disease, and the identification of impaired and compensatory circuits in Parkinson’s disease (Okano et al., 2016). The clinical research management team aimed to encourage close cooperation between the groups through meetings and the development of guidelines for responsible conduct of research (RCR). Neuroethics was one of the key matters discussed in the Brain/MINDS project by the central institutes and the clinical research management team. The strategic research program for brain sci-

ences (SRPBS, launched in 2008), which preceded the Brain/MINDS project, has addressed general RCR issues, and the bioethics project of the SRPBS has been managing RCR issues specific to the neuroscientific research encountered in the clinical research group (Figure 1B).

Ethical Questions Raised By the Brain/MINDS Project

The translational research approach taken by the Brain/MINDS project to establish biological models of neuropsychiatric disorders has two main aspects relevant to the Neuroethics Questions for Neuroscientists that were agreed on at the Global Neuroethics Summit in Daegu, South Korea (NeQN; Rommelfanger et al., 2018): (1) data collection with research participants and (2) the social and individual impacts of the neuroscience disease model.

Clinical Data Collection and Handling

NeQN 2: What Are the Ethical Standards of Data Collection and How Do Local Standards Compare to Those of Global Collaborators?. In Japan, discussions and early legal efforts concerning personal information started in the early 2000s, but the actual development of legislation regarding personal information handling as data was established in 2016 (the Act on the Protection of Personal



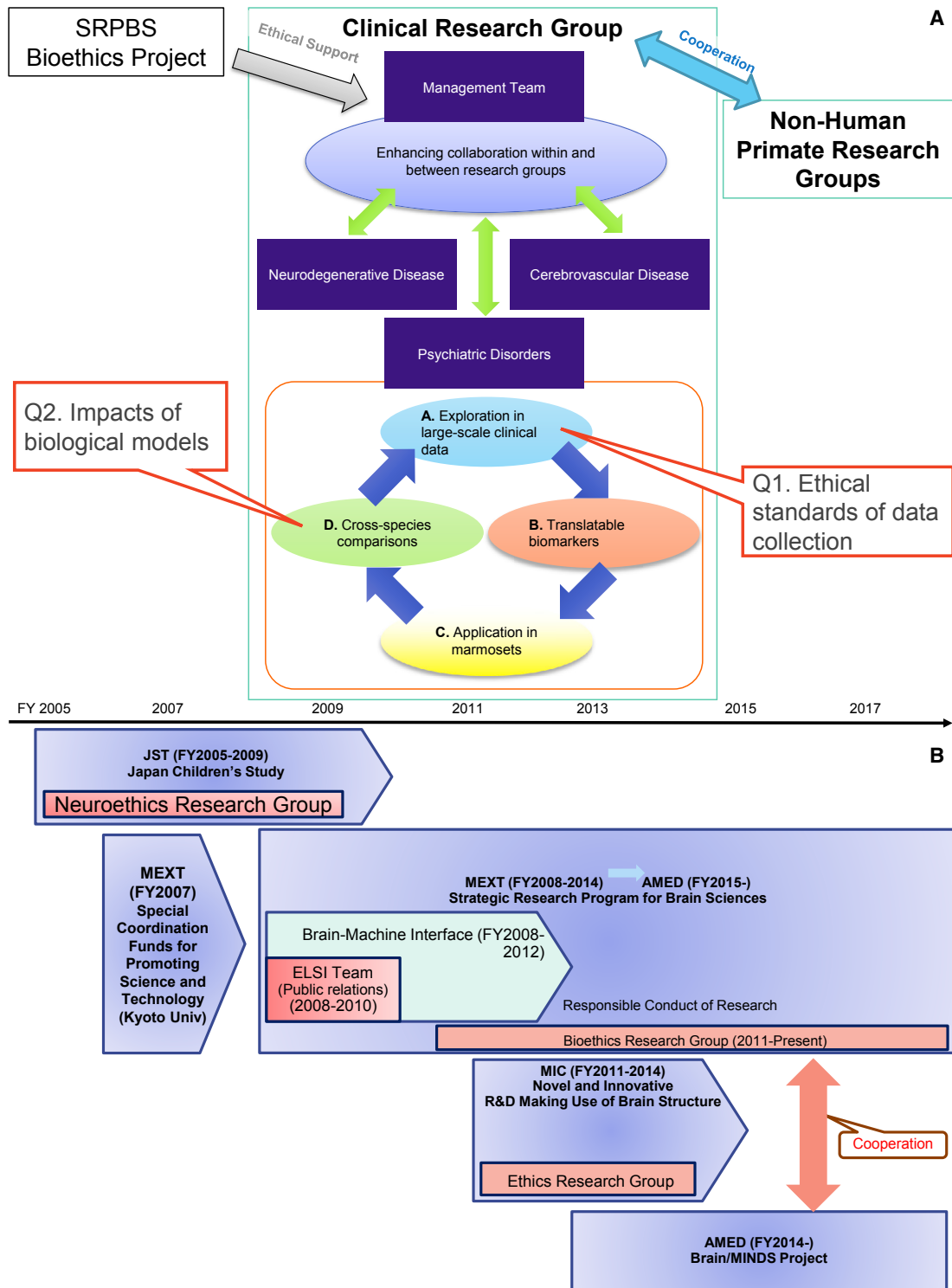


Figure 1. The Ethical Concerns of the Clinical Research Group of Brain/MINDS

(A) The workflow and ethical issues of the clinical research group. Key ethical concerns that arose from the Brain/MINDS project were: (Q1) ethical standards concerning clinical data collection and (Q2) the social and individual impact of the disease model. SRPBS, Strategic Research Program for Brain Sciences. (B) The relationship between brain science R&D projects (blue) and neuroethics (orange) in Japan since 2005. MEXT, Ministry of Education, Culture, Sports, Science and Technology; MIC, Ministry of Internal Affairs and Communications; JST, Japan Science and Technology Agency; AMED, Japan Agency for Medical Research and Development.

Information). In the Brain/MINDS project, two types of personal information are associated with the clinical research group: (1) “the individual identification code” and 2) “special-care-required personal information” as outlined in the 2016 act. Individual identification codes are specified as any type of information sufficient to identify the individual. This includes information on facial features, such as the position of the eyes, mouth, and nose, which would be reconstructable from 3D structural MRI data. Special-care-required personal information is anything ranging from race to criminal records that requires special care so as not to cause discrimination or any other harms to the individual. Clinical information shared among researchers of this project in order to conduct clinical research is an important example of special-care-required personal information. The Brain/MINDS project focuses on connecting translatable biomarkers such as MRI data (individual identification codes) with clinical and functional features specifying neuropsychiatric disorder phenotypes (special-care-required personal information). Thus, both types of data are required. Yet handling both types of data at once increases the risk of unintentionally revealing personal information such as medication use and the severity of the neuropsychiatric disorder to the public, which can lead to discrimination. Data management in the Brain/MINDS project needed to facilitate data sharing while protecting the individual’s personal information.

Database Construction. The construction of a human MRI database that could harmonize ethical personal information management and the sharing of clinical data among multiple research sites is a priority issue in the Brain/MINDS project. The neuroethical framework constructed by the preceding national brain projects (Figure 1B) in Japan needed to be extended (Fukushi et al., 2017). We constructed an MRI database that allowed multiple levels of information access. At the highest security level, information including clinical data (i.e., “special-care-required information”) linked to the individuals’ MR images was stored. These data were primarily used within the research institutions by the clinical research group or by close joint research

facilities with consent from the individual study participants as well as approval from both research facilities’ research ethics committees. De-identified data could be used by applicants with a relatively simple registration. In February 2018, structural MRI data obtained from 20 individuals with schizophrenia, 21 individuals with major depression, 16 individuals with bipolar disorder, and 97 healthy controls have been uploaded to this database (<https://www.brainminds.riken.jp/>). These data also include simple demographic information such as age and gender, but information about facial features was completely removed in advance.

To fully utilize the multilayered structure of this database, both database users and database contributors face different types of ethical issues regarding storage and handling of data containing personal information. In the Brain/MINDS project, the clinical research organizing team summarized important points of transferring, analyzing, and presenting clinical data within the group. The clinical research organizing team has also created guidance for any necessary modifications needed in ethical protocols due to revisions of research guidelines and related legislation concerning personal information handling, which also included recent changes regarding data sharing with international institutions. The guidance is necessary because ethical approval should be obtained from the ethics committee of each research institute. This guidance provides information about considerations regarding clinical and MRI data sharing for non-clinical basic research institutes using this kind of data collected within the Brain/MINDS project.

The Impact of a Biological Model of Neuropsychiatric Disorders

NeQN 1: What Is the Potential Impact of a Biological Model or Neuroscientific Account of Disease on Individuals, Communities, and Society? The Brain/MINDS project’s integration of clinical and basic research aims to find translatable disease biomarkers. These will be used to establish a biological basis of neuropsychiatric disorders. However, the etiology behind neuropsychiatric disorders remains unknown, and many neuropsychiatric disorders either include heterogeneous syn-

dromes or exist on a continuum between normal and disease. Thus, it is difficult to draw a line between risk factors or traits (which may or may not lead to disease onset) and occult signs of illness. While such an endeavor promises great strides for clinical diagnosis and care, potential biomarker candidates gleaned from clinical data should be carefully interpreted given the potential impact that a neuropsychiatric diagnosis may have for the individual and society.

When studying biomarkers for neuropsychiatric disorders, special care must be taken not to create “labels of risk” (Ando et al., 2013). An example is the at-risk mental state (ARMS), which was originally created for early detection and treatment of psychosis. However, it is now known that the transition rate from ARMS to full-blown psychosis within the first few years is about 10%–30%, resulting in high false positives. Many guidelines, such as the UK-based National Institute for Health and Care Excellence (NICE), now recommend against the preventive use of antipsychotics because the high risk of side effects outweighs potential benefits. This is also recognized in Japan, and the Japanese Society for Prevention and Early Intervention in Psychiatry is currently working on a Japanese version of the guidance. Furthermore, psychosis is not associated with functional outcomes, whereas symptoms of depression and anxiety cause significant distress. Thus, at present, broad cross-diagnostic and/or trans-diagnostic interventions for symptoms and for mental wellbeing in general are believed to be a more efficient strategy for functional outcome and personal recovery in individuals “labeled” as ARMS than a focus on early psychosis-based interventions, improving quality of life and recovery (McGorry et al., 2018).

Discovery of the biological correlates of neuropsychiatric disorders might also have strong social impacts. In Japan, like many parts of the world, stigma is a major obstacle to seeking help from a mental health professional. Some people still believe that individuals with mental illness do not recover (Ando et al., 2013). Research into neuropsychiatric disorders may affect public understanding of neuropsychiatric disorders in both positive and negative directions. Evidence suggests

that increased public understanding of the biological basis of neuropsychiatric disorders does not change the amount of stigma and may sometimes even increase stigma (Schomerus et al., 2012).

Handling Biomarkers

Two strategies taken in the Brain/MINDS project turned out to be advantageous in confronting the obstacles overlaid in the research of neuropsychiatric disorders. One is the approach of using translatable biomarkers and the other is the collection of cross-diagnostic and/or trans-diagnostic data.

Although most clinical research projects are based on clinical diagnoses, having a brain-biomarker-based approach might enable faster and more efficient translation between the laboratory and the clinic. Neuropsychiatric diagnoses are based on the phenotypes of behavior and cognition, most of which are difficult to study in nonhuman animal models. Brain biomarkers enable us to look for neurophysiological or neuroimaging “endophenotypes” that are measurable and comparable between humans and non-human primates. This approach is similar to that of the research domain criteria (RDoC) initiative (<https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml>) of the US National Institute of Mental Health and holds the advantage of being able to conduct more neurobiologically oriented research in the field of neuropsychiatric disorders.

Our clinical research team also focused on collecting data from individuals with different diagnoses. Cross-diagnostic and/or trans-diagnostic data enables the exploration of the findings throughout the spectrum of neuropsychiatric disorders. There has been much debate on the consequences of categorical diagnoses, yet at the moment, drifting too far from the categorical system would be disadvantageous in terms of clinical application. A difficult aspect of studying neuropsychiatric disorders is that, while the etiology lies within the brain, the disability experienced by the individual is embedded in a psychosocial environment. Much of the clinical science, treatment, and social support available in this field are still based on the categorical diagnosis. Therefore, the introduction of a new diagnostic system will require a gradual transition to avoid a problematic

“gap” between research and clinical practice. A similar argument has also arisen in the framework of the RDoC initiative. Emphasis has been placed on the need for interdisciplinary engagement in the field of science as well as its political, commercial, and public counterparts. This leaves much to be worked on before clinical implementation. However, regardless of the diagnostic system utilized, research participants deserve a thorough explanation of the research project and its motives upon recruitment, as well as careful interpretation and non-declarative presentation of the findings.

The next step will be a focus on the clinical implications of the findings. The clinical research teams are focusing on the relationships between brain circuit biomarkers and everyday functioning in individuals with neuropsychiatric disorders. Examples would be the associations between eye movement characteristics and work hours or between subcortical volume differences and socio-cognitive function in schizophrenia. Both eye movements and subcortical volumes are key focuses as translatable biomarkers and are currently being researched in marmosets as well. Non-human primate models, with appropriate ethical consideration, will be necessary for this step to improve our understanding of the neurobiological aspects of neuropsychiatric disorders and, in light of the recent advances in genetics and regenerative medicine, may lead to new targets for novel treatments such as precision medicine. Further research linking “micro-level” neurobiological findings to everyday life in individuals with neuropsychiatric disorders would thus provide a significant advance in the field of neuropsychiatry.

Brain/MINDS Project as Infrastructure: Medical Big Data and Brain Bank

The increasing trend of collection and analysis of “big data” has led to the enactment of legislation governing the systematic and government-led de-identification of medical data in Japan, which will enable the use of medical big data for non-medical users and researchers by 2020. Along with the change of medical big data regulation, R&D projects in Japan, including the Brain/MINDS project, will need to adjust their own data management plans and explain them to

patients and public, since there is less awareness of that change. The R&D community will also need to promote understanding of the utilization of medical big data to the public. On the one hand, the collection of large, heterogeneous, and longitudinal data may allow for more accurate predictions of life course and more personalized intervention approaches, which could provide value to healthcare even beyond neuropsychiatric diagnosis. On the other hand, such big data analysis may enable re-identification of the initial participants in the disease database (Rommelfanger et al., 2018). If de-identification procedures are transparent and strictly defined, Japanese citizens who are concerned about information leakage and privacy (Nakazawa and Tsuchiya, 2018), particularly around brain imaging data, will feel more secure. However, to ensure the ethical legitimacy of consent (by opt-out), appropriate information disclosure is required. Even if the connection between data and individuals is de-identified, some disenfranchised groups in society may become further stigmatized and unintended biases may occur if study design and analyses are not done carefully. This potential is highlighted by NeQN 1b: *Is it possible that social or cultural bias has been introduced in research design or in the interpretation of scientific results?*

Human brain samples are crucial to the investigation of human neuropsychiatric disorders. Based on the tradition of autopsy research in Japan, the Japan brain bank net (JBBN) was launched in 2016 and is supported by SRPBS by the Japan Agency for Medical Research and Development (AMED); it is a network of brain banks of Japanese universities and research centers (<https://www.jpbrain.net/>, in Japanese). JBBN contributes to the neuroscience community, including research for the Brain/MINDS project, by providing human brain samples donated by deceased Japanese people with a high-quality diagnosis. Its activity follows the ethics guidelines of brain banks established by the Japanese Society for Neuropathology and the Japanese Society of Biological Psychiatry in 2015 (<http://www.jsnp.jp/pdf/brainbank.pdf>, in Japanese), which states that the banking should be based on a pathological autopsy. The percentage of pathological

autopsies in Japan, which had been high in the past, has recently declined. This may be caused by re-allocation pressure of medical resources, in part due to the belief that medical imaging data might be sufficient to establish etiology (Iritani et al., 2018). In addition to neurologists and psychiatrists, biostatisticians and bioethicists are also participating in the JBBN to promote the project in a scientifically and ethically sound manner. Key issues are the promotion of donor registrations by individuals with neuropsychiatric disorders during their lifetime and the construction of close relationships to promote mutual communication with bereaved family members. The effort is ongoing, with a promising response. International collaboration to share expertise into handling these issues would be helpful.

Neurofeedback: The Brain/MINDS Project Will Provide Empirical Data for New Treatment of Neuropsychiatric Disorders

NeQN 4b: What Measures Can Be in Place to Ensure Optimal Autonomy and Agency for Participants and Users?. Research into human brain function and mechanisms of neuropsychiatric disorders for the Brain/MINDS project and other national brain projects may lead to the development of new treatments for neuropsychiatric disorders. One distinct example is neurofeedback using real-time fMRI (Watanabe et al., 2017, for review) largely funded by SRPBS. Neurofeedback is an innovative technique that uses fMRI not only for observation but also for intervention. Targets of fMRI neurofeedback interventions are conditions such as refractory depression and neurodevelopmental disorders. The Brain/MINDS project aims to play an important role in developing fMRI neurofeedback treatment by supplying biologically defined connectome information. Neurofeedback technology could be an intervention tool to enhance cognitive capacity and social communication skills by controlling the plasticity of the neural network system. In 2015, the research ethics consultation team at SRPBS

created a project, which is still ongoing, about the ethics of fMRI neurofeedback. It required that the clinical trials of fMRI neurofeedback, in their early phase, should be performed with a limited number of participants and in appropriate research settings, with monitoring by the safety review committee established by SRPBS specific to fMRI neurofeedback research. Since fMRI neurofeedback is an innovative treatment for patients with neuropsychiatric disorders and one that could undermine patient autonomy and agency, additional consideration is needed for potentially vulnerable research participants. The SRPBS ethics working group recommended that institutional review boards review considerations of autonomy and agency that could be compromised by such an intervention. The shortage of pre-clinical data and the uncertainty surrounding the mechanism of fMRI neurofeedback treatment for neuropsychiatric disorders are ethical concerns. Potential irreversibility of neurofeedback is a drawback as an enhancement tool, and the ethical implications of neuroenhancement are still being explored in Japan (Nakazawa et al., 2016). However, more research in this area is needed, and we will be exploring NeQN 5—*In which contexts might a neuroscientific technology/innovation be used or deployed?*—as we develop this technology.

Brain/MINDS Beyond

Brain/MINDS Beyond is a new brain science project launched in September 2018 and built upon the framework of Brain/MINDS. In this project, studies using translatable biomarkers in human and non-human primate research continue, but with further extensions. One such extension is to advance international collaborations with other brain science projects such as the Human Connectome Project; research will also be conducted on the harmonization of heterogeneous MRI data collected from different scanners and vendors. As we expand our collaborations, we are dedicated to deeply exploring the ethical issues, particularly with a cross-cultural

lens through collaborations with the International Brain Initiative's neuroethics workgroup, as an integral part of our research program. In so doing, we hope to develop better treatment and related technologies for individuals with neuropsychiatric disorders and society more broadly with high ethical standards.

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