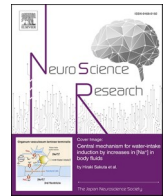


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Review article

## The way forward for neuroethics in Japan: A review of five topics surrounding present challenges

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## ARTICLE INFO

## Keywords:

Neuroethics  
Informed consent in psychiatric research  
Global environment for neuroscience research  
Neuromodulation technologies  
Neuroenhancement  
Do-it-yourself use of neurotechnologies

## ABSTRACT

Neuroethics is the study of how neuroscience impacts humans and society. About 15 years have passed since neuroethics was introduced to Japan, yet the field of neuroethics still seeks developed methodologies and an established academic identity. In light of progress in neuroscience and neurotechnology, the challenges for Japanese neuroethics in the 2020 s can be categorized into five topics. (1) The need for further research into the importance of informed consent in psychiatric research and the promotion of public-patient engagement. (2) The need for a framework that constructs a global environment for neuroscience research that utilizes reliable samples and data. (3) The need for ethical support within a Japanese context regarding the construction of brain banks and the research surrounding their use. It is also important to reconsider the moral value of the human neural system and make comparisons with non-human primates. (4) An urgent need to study neuromodulation technologies that intervene in emotions. (5) The need to reconsider neuroscience and neurotechnology from social points of view. Rules for neuroenhancements and do-it-yourself neurotechnologies are urgently needed, while from a broader perspective, it is essential to study the points of contact between neuroscience and public health.

### 1. Introduction: history of neuroethics in Japan and its agenda

Research on neuroethics in Japan began in the mid-2000 s and has a history of approximately 15 years (Fukushi et al., 2017). At that time, a number of research groups on neuroethics emerged simultaneously and several visionary and leading monographs were published (Fukushi et al., 2017). In 2007, Hidenao Fukuyama and colleagues published a comprehensive report on neuroethics in Japan (Fukuyama, 2007). Osamu Sakura and colleagues made a significant contribution to the establishment of neuroethics, while introducing international trends in neuroethics to Japan. Yukihiro Nobuhara and colleagues adopted philosophical approaches in neuroethics research. The results were

compiled in the book *Noushinkei-rinrigaku no Tenbo* [Prospects of neuroethics], edited by Nobuhara and Hara (Keiso Shobo, 2008). Takao Takahashi translated Judy Illes' *Neuroethics: Defining the Issues in Theory, Practice and Policy* (Shinohara Publishing, 2008) and introduced cutting-edge discussions from around the world to Japan. Yoshinori Hayashi and associates conducted research emphasizing a traditional ethics-based approach, leading to the publishing of a special issue on neuroethics in the *Journal of Practical Philosophy* (2007).

In addition, considerable publications in various academic disciplines have made significant contributions to the development of neuroethics in Japan. For example, Tatsuya Mima's book *Nou no Ethics: Noushinkei-rinrigaku Nyumon* [Brain Ethics: An Introduction to

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<https://doi.org/10.1016/j.neures.2022.07.006>

Received 23 December 2021; Received in revised form 20 June 2022; Accepted 20 July 2022

Available online 23 July 2022

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Neuroethics] (2010, Jinbun-shoin) has led the discussion of neuroethics in Japan from an early stage and Tetsuya Kono's booklet *Boso-suru Nokagaku* [Brain science runs amok] (2008, Kobunsha Shinsho) is a pioneering and monumental work in neuroethics in Japan. In addition, bioethicist Jiro Nudējima has published a book titled *Seishin wo Kiru Shujutsu* [Surgery of cutting the mind] (2012, Iwanami Shoten), an elaborate historical study on the ethics of lobotomies and psychiatric medicine. These publications have contributed to the introduction of neuroethics to the public and increase their interest.

There was much debate on topics such as the ethics of neuro-modulation, including the ethics of brain-machine interfaces and deep-brain stimulation (DBS; [Fukushi and Sakura, 2007](#); [Nakazawa et al., 2016](#); [Takagi, 2012](#)), the ethics of enhancement ([Kato, 2005](#)), and human free-will ([Suzuki, 2009](#)). Later, efforts were made to address pressing practical issues from neuroscience research, such as managing incidental findings (secondary findings) from neuroimaging ([Fujita et al., 2014](#); [Seki et al., 2010](#); [Takashima et al., 2017](#)). These past 15 years have brought progress in neuroscience and related fields like imaging, tissue engineering, and genetics. Fears that were dismissed in the 2000s as mere science fiction are considered real concerns today. It is crucial to astutely understand the advances in neuroscience and the associated societal changes and modify the topics used in neuroethics research.

Neuroethics in Japan was launched with the funding of several research projects ([Fukushi et al., 2017](#)), but most of these projects were terminated due to changes in funding policy for neuroscience research and development. This is due to the fact that the neuroethics research projects had started and operated with relatively large research funds for neuroscience research, and the funders had also invited research proposals on ethical issues. Nevertheless, neuroethics in Japan have made steady progress in line with the progress of brain science research, although they seem to have lost some of the enthusiasm of the pioneering period. In this context, the issues of neuroethics in Japan need to be organized according to current neuroscience research. By setting the agenda appropriately, research activities in neuroethics should be facilitated with renewed vigor. What, then, are the current neuroethical questions that should be asked in Japan? What methodologies should neuroethics use to solve these questions?

This review article summarizes neuroethical topics shared overall in the field based on previous debates in international contexts. Following this, we conduct a detailed examination of the inquiries that need to be made in the Japanese context. As discussed below, authors recognize that the methodology of systematic review appropriate for neuroethics is urgent to be studied. However, this review uses five topics formulated in the Global Neuroethics Summit in Daegu 2017 as a framework for analysis. This makes our review deductive and systematic in the sense that it facilitates international comparisons. Our review is also the product of group discussions among experts involved in neuroethics theory research and practice. In this way, we have attempted to maximize the validity of the analysis.

## 2. What is neuroethics? Definitions and methodologies

Neuroethics is the study of the ethical, legal, and societal implications of neuroscience. Neuroscience and neurotechnology have developed rapidly in recent years in Japan, and neuroscience has had a significant impact on humans and society. Progress in neuroscience will require anticipating its effects, assessing the value of these effects, and reaching a social consensus on them. Neuroethics is an academic field that analyzes neuroscience based on a meta-view consisting of three elements: "what" are its goals, "how" will it proceed, and the "consent" surrounding it, with regards to social consensus.

[Roskies \(2002\)](#) divided neuroethics into two categories: the ethics of neuroscience and the neuroscience of ethics. The ethics of neuroscience comprises philosophical and theoretical studies and sociological research that use quantitative and qualitative methods, scientific and

social approaches with specific practices, regulatory science, and legal studies. Neuroscience of ethics is the scientific exploration of the neural basis of morals and ethics, which are functional characteristics of human beings. The results of research on the neuroscience of ethics recursively affect the ethics of neuroscience. The rapid developments in neuroscience in recent years have also accelerated this cycle between ethics and science.

Since its earlier stages, meta-studies have examined the uniqueness of neuroethics in Japan ([Hayashi, 2007](#); [Kagawa, 2006](#); [Sakura and Fukushi, 2007](#)). Meta-neuroethics examines the academic nature of neuroethics in advancing neuroscience research and its social implications from a meta-perspective. It reviews and organizes past research findings, describes the intellectual characteristics of neuroethics, and explores its potential. It is indispensable while considering the future of this field. The central question is whether neuroethics possesses novelty as an academic field. If so, what should the subjects of research be and what methodologies should be adopted? A recent international trend in meta-neuroethics has been to highlight the normative implications of the recursive relationship between ethics of neuroscience and neuroscience of ethics as the third aspect of neuroethics ([Holtzman, 2018](#)). Neuroscience and its technological application can alter humans themselves, the subjects of ethical deliberation. Monitoring and predicting the impact of such neuroscience and technologies on ethical subjects constitutes an essential problem in this area.

### 2.1. Short-term challenges

Various methods can be adopted to study neuroethics, including humanities approaches centered on literature reviews, social science approaches focused on surveys and interviews, and natural science approaches such as interventional studies. Papers on neuroethical research often appear in journals open to applied ethics and natural science publications. Still, they do not tend to be accepted by journals that focus on the humanities. Therefore, academic methodologies leaning more towards the natural sciences are often adopted. Further, because this is a cross-over field, in addition to researchers who study medicine, neuroscience, philosophy, and ethics, those with backgrounds in psychology, sociology, public policy, and military research have participated in creating this academic discipline. Under these circumstances, the first task is to identify the topics and methodologies of neuroethical study within this interdisciplinary field. Systematic reviews, which are frequently used in the health sciences, are a strong candidate for this ([Thomas and Harden, 2008](#)).

A systematic review may appropriately integrate research findings from humanities, social sciences, and natural sciences fields and help clarify neuroethics methodologies. However, in neuroethics and applied ethics, systematic reviews are still in their infancy. It is necessary (1) to collect literature on a specific theme and to extract the ethical issues discussed in each piece of literature and (2) to establish a methodology for systematic reviews of neuroethics, referring to qualitative research methods in sociology and social medicine and sometimes incorporating quantitative research methods.

### 2.2. Long-term challenges

As different countries have different research cultures, Japan must define the role of neuroethics going forward and how it will contribute to science and society considering Japan's history of research and development, its current situation, and its research climate. Identifying topics and methodologies through such a review will help describe the academic characteristics of neuroethics and explore future possibilities. In so doing, a system will need to be established to deploy researchers from the fields involved in neuroethics and to organize research projects that make use of their expertise through collaborative interactions. Worldwide, there is a lack of scientific historical research that continuously summarizes the results of neuroethics; therefore, there is a need

for such continuous efforts to contribute to neuroscience and society through the development of neuroethics.

### 2.3. Five topics of neuroethics today

Neuroethics bridges neuroscience and ethics and reexamines ethical issues based on recent neuroscience findings that warrant discussion in international frameworks. At the 2017 Global Neuroethics Summit (GNS) in Daegu, South Korea, neuroethical topics shared by major neuroscience projects in countries such as the United States, the European Union, South Korea, Australia, China, and Japan were identified in a bottom-up manner. The results were summarized as the following five questions (Global Neuroethics Summit Delegates et al., 2018).

1. What is the potential impact of a model of neuroscientific accounts of mental disease on individuals, communities, and society? (The social implications of neuroscientific accounts on mental disorders)
2. What are the ethical standards of biological material and data collection, and how do local standards compare to global collaborators? (The ethics of biological material and data sharing)
3. What is the moral importance of the neural systems currently being developed in the neuroscience laboratory? (The ethics of moral status of human brain)
4. How might brain interventions impact or reduce autonomy? (The ethics of interventions)
5. In which contexts might a neuroscientific technology/innovation be used or deployed? (The industrial applications of neuroscientific technology; Global Neuroethics Summit Delegates et al., 2018) (NB: The summaries in parentheses were added by the authors.)

There are three reasons why we employ the five questions of the GNS to analyze the issues in Japanese neuroethics: First, the GNS framework is comprehensive as it organizes contemporary issues in neuroethics. In the GNS, neuroethics issues were addressed in a bottom-up manner. The GNS framework is comprehensive as it organizes contemporary issues in neuroethics. The second is the ease of international comparison. The GNS outcome was hoped that each country would present its own specific neuroethics issues based on cultural, institutional, and neuroscientific situations, and that these issues would be shared and compared internationally. The GNS five-question framework could serve as a common format conducive to this. The third is the consideration of Eastern culture: the five questions of the GNS are basically designed from a global perspective, but since a certain proportion of the GNS participants are from East Asia (Japan, China, Korea, Taiwan), Buddhism and Confucianism in East Asian countries were also taken into consideration when the five questions were set (Global Neuroethics Summit Delegates et al., 2018). For these three reasons, we believe that it is at least possible to look at and organize the current situation in Japan in light of these five questions, even though they may not be totally equally applicable in Japan.

In response to the five fundamental questions summarized in the 2017 Global Neuroethics Summit, it is important to understand advances in neuroscience and associated societal changes and determine what research topics are adapted flexibly. In this paper, we describe the themes that should be considered by Japanese neuroethics based on international trends in neuroethics debates.

### 2.4. Topic 1: the social impact of neuroscientific accounts on mental disorders

#### 2.4.1. Background

Neuroscience research on mental disorders is unique in that the participants are patients who experience disability in interaction with society. First, the individual and social effects on the research participants need to be analyzed. Then, in addition to examining the relationship between patients and clinicians under regular medical

frameworks, it is crucial to clarify the relationships between patients, researchers, and clinicians premised on the autonomy of research participants. Further, because neuroscience seeks to understand humans, in addition to patient involvement, the public's involvement as stakeholders and the responsibilities of neuroscience research to society need to be examined as well.

#### 2.4.2. Core ethical issues

In neuroscience research on psychiatric disorders, the people involved should suffer no harm from participating in the study and enjoy benefits in the future. Therefore, in this area, it is vital to consider the social impact of research and decision-making at various stages of research.

#### 2.4.3. Previous work

Various ethical issues are raised with regard to neuroscientific accounts on mental disorders. The first problem we will focus on is the issue of stigma. It has been shown that biomedical knowledge on mental disorders may exacerbate stigma (Schomerus et al., 2012). In general, patients with neuropsychiatric disorders such as schizophrenia and dementia are more likely to be victims of prejudice and cognitive injustice due to the specificity of their conditions (Crichton et al., 2017). It is important for researchers to pay scrupulous attention to prejudice and employ a co-creative perspective. Contrastingly, a Japanese randomized controlled trial found that education on the biomedical knowledge of mental disorders does not necessarily increase stigma (Ojio et al., 2019). Thus, what to include and how to convey it are essential issues in science communication.

Second, there are ethical concerns regarding returning research results to individuals, which are linked to the issue of stigma. Social consequences should be kept in mind when returning results. There was early discussion about brain imaging research in Japan and some consensus has been reached on the condition and criteria of returning results to participants or family members when health risks, such as brain tumors, are detected incidentally in MRI studies (Takashima et al., 2017). This consensus was groundbreaking because it called for returning results based on the screening of physicians for the entire research agenda of the Strategic Research Program for Brain Sciences, a Japanese national project. However, the returning of individual findings on the biological basis of mental disorders has not yet been sufficiently investigated (i.e., Christensen et al., 2016). In particular, the gold standard debate on returning genetic test results related to mental disorders has not yet evolved. In this situation, individual studies have attempted their own measures to protect study participants regarding the return of genetic research results to participants and occasionally their family members, especially, if no effective treatment has been established for the findings. For example, the DIAN study, an observational study of dominantly inherited Alzheimer's disease conducted mainly in the United States and also in Japan, requires genetic counseling prior to study participation. The results of genetic testing are blinded to both researchers and participants and individual results are not returned (DIAN, no year). Conversely, for some types of intervention studies in which study participants are recruited on the basis of genetic testing, the return of genetic information is unavoidable under the study protocol.

Third, is the issue of informed consent, which can be considered a classic issue. One of the features of mental disorders is that the pathology may limit a patient's ability to make judgments or give consent. Therefore, a Japan's scientific community, Japanese Society of Psychiatry and Neurology, independently released a code of ethics in 1997 before the government took action, which addressed obtaining consent from people with mental disorders (Japanese Society of Psychiatry and Neurology, 1997). However, efforts to objectively assess and evaluate the ability to consent to research are still scant in Japan. The intentions of the people participating in the study are not fully reflected.

Fourth, we review public and patient involvement. Research so far has been investigator-initiated or researcher-centered, but the way

forward calls for all parties involved and the public to play more active roles. These roles will extend to things from the allocation of funding to the selection of papers (Hickey et al., 2018). There is a vigorous patient involvement movement among dementia researchers overseas (Miah et al., 2019). In Japan, similar attempts have been made to carry out studies in collaboration with caregivers of 22q11.2 deletion syndrome, a condition known for multimorbidity including psychiatric symptoms (Tamune et al., 2020). These movements aim to bring greater transparency to the research process, generate active dialogue between the parties involved and the researchers, and help create better neuroscience research.

#### 2.4.4. Short-term challenges

There is a need to continue the examination of scientific communication to reduce social discrimination and stigmatization of mental and neurological disorders. The current situation in Japan warrants investigation regarding how to disseminate secondary findings from research and the use of human participants whose ability to consent may be limited or variable as research subjects. In addition, the involvement of stakeholders and citizens needs to be considered, such as understanding and giving opinions on the characteristics of diagnostic imaging using AI and in patient-public involvement in accumulating cases and requesting surveys for research.

#### 2.4.5. Long-term challenges

Based on the survey described above, concrete methods of science communication and patient-public involvement need to be developed, and their related proposals, implementation, and feasibility call for continuous examination.

#### 2.4.6. Examples of research questions

According to preceding studies, research on the handling of incidental findings related to brain imaging has been promoted in Japan. It is promising to develop this direction and promote research on secondary findings in genetic studies and studies using big data, which have made remarkable progress in recent years. In addition, the establishment of a framework for public involvement in mental disorder research is in line with the needs of our society, which is based on the principles of diversity and inclusion. Therefore, we propose the following examples of specific research questions regarding the neuroethics of mental disorders.

- In genetic studies of psychiatric and neurological disorders, how exactly should individual results, including secondary findings, be returned?
- What social stigmas may arise from the results of genetic tests for neuropsychiatric disorders? How can these be avoided?
- What are the appropriate methods for returning incidental findings from brain imaging research?
- How do big data and AI change the problems of returning individual results from brain imaging or brain wave research?
- How can the autonomy of research participants be protected in studies whose subjects are patients with mental disorders, such as assessing the capacity to make judgments, the criteria for proxies, and advocacy, etc.?
- What are the appropriate relationship between patient associations, researchers, and clinicians in research on neuropsychiatric disorders?
- What are the frontiers of clinical ethics in neurological diseases? Such as end-of-life decision-making and care or relational and narrative autonomy?
- How should patient-public involvement and responsible research innovation look in neuroscience?

## 2.5. Topic 2: the ethics of biological material and data sharing

### 2.5.1. Background

In addition to conventional retrospective studies analyzing medical records from a single institution, a notable international trend in recent observational studies features more comprehensive approaches using large databases and biobanks (Boyer et al., 2012; Henny et al., 2020; Jang et al., 2019; Langner et al., 2020). Large databases of brain images, genome databases, and postmortem brain banks are valuable resources for the future development of neuroscience (Lewis et al., 2016). This is an area where a proactive approach to ethical issues is needed due to the rapidly changing research environment, which includes the entry of private-sector players through industrial applications, significant developments in digital technology, and the acceleration of joint international studies (Anderlik, 2003; Baker et al., 2016; Coppola et al., 2019; Thompson and McNamee, 2017).

### 2.5.2. Core ethical issues

Ethical issues related to research studies that examine human samples and data to understand diseases and human beings themselves include problems with donor consent, risk assessments for the common use of data, risk-based regulatory issues, and fairness in the handling of data (Bernasconi et al., 2020; Li et al., 2019; Liyanage et al., 2018). Such issues are complicated and have emerged recently due to research developments in neuroscience and related fields. Brain banks also need to be sensitive to the donors who leave their bodies to science and their families. The social acceptability of brain banks is a prominent issue in this field (Reymond et al., 2002; Kaye et al., 2015; Global Neuroethics Summit Delegates et al., 2018; Sadato et al., 2019).

### 2.5.3. Previous works

The ethics of neuroscience using big data have been developed mainly through researchers associated with the EU's Human Brain Project (Kaye et al., 2015; Ong et al., 2017). The philosophy and ethics of AI, or the exploration of the impact of AI on humans and society using methods from the humanities, have been gradually established (Benke and Benke, 2018; Johnson, 2020). In addition, a study of the ethical issues involved was conducted when an all-Japan brain bank network was established (Kaye et al., 2015).

### 2.5.4. Short-term challenges

Creating rules to promote the joint international use of biobanks and databases is considered an urgent issue (Kiehltopf and Krawczak, 2011; Schinder et al., 2016). To collectively comply with the adequacy decision of the EU General Data Protection Regulation (2016), Japan is moving towards unifying its laws and ordinances regarding personal information under the Personal Information Protection Act (2016), which was revised in 2020 (Nikkei, 2020). Because of this, it is essential to investigate the status of regulations on the common international use of samples and data in Asian countries where joint research has accelerated recently. Based on this, analyzing the circumstances and formulating feasible rules will be possible.

The expansion of brain banks will contribute to the stable and sustainable development of neuroscience. Therefore, a macro-perspective on brain banks in Japan is needed. The current situation of pathological autopsies in Japan must be taken into consideration when discussing issues related to brain banks. In fact, the number of pathological autopsies is decreasing compared to previous years due to medical financial issues (Sadato et al., 2019). Financial issues create problems for the sustainable operation of brain banks, such as the stable management of freezers. Such financial problems are likely to jeopardize the maintenance of the cooperation of the brain bank network.

Additionally, public interest in brain banks and the use of brain banks by private companies (e.g., pharmaceutical companies) need to be discussed. In particular, publicly funded brain banks are required to supply samples to a wide range of research institutions. Social consensus

is also required regarding the use of the agreed-upon samples by companies and the creation of intellectual property and profits from such use.

The approval and cooperation of the general public is essential for the operation of the brain bank. Studies on the social acceptability of postmortem research and brain banks and how to approach donors and their families on topics such as lifetime consent should be conducted while maintaining the allocation and industrial uses of research funds and medical resources in mind (Matsushita, 2017).

#### 2.5.5. Long-term challenges

In the medium- to long-term, literature studies, theoretical research, and comprehensive research using sociological methods should be promoted to examine problems related to the interactions between AI and human brains/minds. This research has already begun in Europe and the United States through studies investigating how the use of big data in neuroscience affects humans and society (Birney, 2012; Nature, 2016; Kalkman et al., 2019; Wolf, 2018). Recently, there has been a demand for needs surveys on the applicability of dynamic consent, which is a form of consent that has attracted attention in biobanks and databases, and for examining basic designs for biobanks that use feasible forms of dynamic consent (Budin-Ljøsnøe et al., 2017).

#### 2.5.6. Examples of research questions

The ethics of data sharing is a global issue. In Japan, the law on the protection of personal information is being revised, and it is crucial to explore the issue from the perspective of neuroethics. In particular, data sharing with (or including) Asian countries should be considered as a future research topic. In such cases, appropriate consent for participation in research, including dynamic consent, should be considered. The ethics of brain banking, an ongoing endeavor, will undoubtedly form a central area in ethical issues surrounding consent. We therefore offer the following several examples regarding the ethics of biological material and medical data sharing.

- Continuous investigation of regulations and standards for transferring samples and data in joint international studies: How should collaborative research systems be built not only in the United States and Europe but also in areas geographically closer to Asia such as China, South Korea, India, Taiwan, and the Philippines?
- The need for studies investigating the use of big data in neuroscience from the perspectives of consent, risk, and fairness: How to go from ethical norms to social norms (legal systems) regarding issues related to the collection and use of big data?
- Constructing ethics for postmortem brain donors: What are the ethical relationships regarding lifetime consent, withdrawal of consent by family members, and donor candidates? What are social perceptions of the brain and other organs?
- How effective is dynamic consent in neuroscience, and what are the practical problems of its implementation?
- How do neuroethics and AI research impact the human mind and brain?

### 2.6. Topic 3: The moral significance of the neural system

#### 2.6.1. Background

The brain is an organ that executes the mind's intentions, and therefore, it has a moral value that differs from other organs. Many believe human brains have different moral values than animal brains. In addition, the level of ethical discussion on animal research varies depending on whether the subjects are primates or other animals. Much research on tissue engineering is being conducted using techniques such as brain organoids created from human stem cells, animal chimera, and ex vivo brain tissue as alternatives to living human brains.

#### 2.6.2. Core ethical issues

The core ethical concerns are whether the brain or its parts have a different moral status than other tissues of the human body and whether human brains have a different moral status than the brains of other animals. These questions about the moral status of the brain can open up unique realms of brain ontology and metaphysics. In the theories of this field, moral status must be considered for whole and partial living brains, total and partial deceased brains, neural networks that mimic brain functions, the brains of non-human primates, and the brains of other animals. Each of these must be compared to other organs of the human body, other natural objects, and artificial objects.

#### 2.6.3. Previous works

When investigating the moral status of the brain, it is useful to refer to ethical arguments concerning brain death. The United States adopted a unified law for assessing death in 1981, with most parties agreeing that brain death represents the person's death. In Japan, there has been a fierce debate on whether brain death is human death or not. Today, organ transplantation from cadavers has become a common practice in Japan. While we accept the concept of brain death, we have not yet reached a point where we are ready to use the brain for research purposes because of the lack of progress in donating the brain itself.

Debates over the moral status of the brain have also manifested in ethics surrounding the development of the nervous system. Research using human embryos is based on the Warnock (1984), which proposed a "14-day rule" limiting the duration embryos could be cultured after fertilization. Based on this report, the Ethical Guidelines for Research on Assisted Reproductive Technology Treatment Producing Human Fertilized embryos (2021) was formulated by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare of Japan. According to these guidelines, the biological basis for this 14-day rule lies in what is considered the appearance of a primitive streak or the early signs of the development of the nervous system. This was also used to draw the line for restricting its use for research purposes. However, under some conditions, the International Society for Stem Cell Research's guidelines (2021) proposed the allowance of research using fertilized embryos beyond the 14-day limit. Different countries are also expected to review their guidelines going forward. Depending on where these changes lead the field, academic societies related to neurobiology may be forced to respond.

Ethical discussions have progressed alongside rapid developments in research using living human brain tissue (Greely, 2021; Sawai et al., 2019). The transplantation of cultured or processed living brain tissue into humans has already sparked debate regarding ethical issues related to its effects on personality and the possible collapse of the uniqueness of the human species. There has also been criticism from the field of animal ethics about the creation of chimera animals that contain human-derived cells in their brain tissue. Although animals are used widely in neuroscience research, the preferred method for creating animal models for mental disorders is to establish genetic modification techniques for primates, as they are closer to humans than animals such as mice (Sasaki, 2013).

The use of the common marmoset in neuroscience research in Japan has received particular focus. Following the 2005 revisions to the Humane Treatment and Management of Animals Law, an academic society issued the "Guidelines for the Care and Use of Nonhuman Primates in Neuroscience Research" (The Japan Neuroscience Society, 2021), and various research institutes established ethical screening systems based on the "3Rs" (replacement, reduction, refinement), which is an international standard for animal experiments. In addition, regulations on animal experiments using primates are becoming stricter, especially in Europe.

#### 2.6.4. Short-term challenges

Research ethics covering the use of common marmosets are urgently needed. The international community has made strong demands on

Japan concerning the ethics of research using non-human primates. Neuroscience studies that use transgenic common marmosets have become something that requires international accountability. Due to this, a consensus within Japan also must be reached. In addition, regarding the use of brain tissue from chimera animals as a form of human-derived tissue, the problems associated with creating animals with human brain tissue (such as concerns about mice with superior intelligence) must be explored at the basic research level.

Basic ways of thinking about the social and human implications of research using living human brain tissue need to be developed, along with suitable regulations in line with them. Issues related to the scope of the use of brain organoids for research and restrictions on their clinical use need to be explored, particularly regarding their safety, concerns about brain organoids possessing a mind, and how the transplantation of brain organoids into the human body may affect personality.

#### 2.6.5. Long-term challenges

Questions such as what the brain is, whether it has a moral status above other tissues, and how the general public perceives the brain need to be examined in the medium- to long term. Whether brain tissue is used for research or created to be transplanted, neuroethics needs to engage in ontological debates over whether the human brain is the basis of neuroscience as a whole.

The fundamental ideas about the moral status of the brain need to be reexamined. Although the emergence of the primitive streak nervous system has been a keyword in this area, its implications for neuroethics remain unclear. Neuroethics needs to question the validity of the 14-day rule.

Ethics regarding non-human primates need a foundation of debate and not just tentative proposals of practical solutions. Animal ethics in Japan need to be redefined, and basic ideas about animal welfare need to be proposed regarding the use of common marmosets in neuroscience studies. This should be based on the ongoing debates over animal ethics, mainly in Europe. In addition, the essence of the relationship between humans and animals in Japanese culture (traditional or modern) should be captured and incorporated into modern ethics for animal experiments so Japanese researchers can build an ethics body for the common marmosets used in research from a Japanese perspective.

#### 2.6.6. Examples of research questions

In accordance with the short- and long-term challenges described above, we can offer the following example research questions. This topic is unique in that basic neuroscience research leads to the core ethical issue of the difference in moral values between animals and humans. In this sense, it is not always easy to address these research questions. However, they are valuable and critical questions that need to be discussed extensively in collaboration with neuroscientists and ethicists, involving the public, and taking into account the Japanese context.

- Ethical implications of tissue-engineered neural systems: How should the social and human implications of research using brain organoids, ex vivo brain tissue, and chimeras be evaluated?
- What is the moral status of the brain tissue itself?
- When the brain is developing, when does it begin to possess moral significance? – Regulations and ethics for research using embryos.

### 2.7. Topic 4: ethics of interventions

#### 2.7.1. Background

Interventions on the brain are actions that artificially change the functions of the brain. Their main purpose is to treat illness, while enhancement can be considered a secondary effect. The first stage of intervention research in neuroscience entails performing interventions on the brain for research purposes. Neuroscience research that entails interventions on the brain aims to accurately estimate the risks and benefits of such interventions and treatments. The second stage entails

randomly separating populations into groups and imposing different conditions on each. Risk/benefit analyses and respecting autonomy are important ethical themes regardless of the interventions used. The intervention's ethical issues need to be considered based on their methods (e.g., pharmaceutical, deep-brain stimulation, transcranial magnetic/electrical stimulation, neurofeedback, cognitive-behavioral approaches, education).

#### 2.7.2. Core ethical issues

The ethics of intervention research on human subjects can be categorized by the effects technology has on personality and society. As for effects on personality, the issue is the relationship between autonomy and interventions on mental processes such as desire, intention, emotion, and cognition. As for the societal aspect, aversion to psychosurgery must be considered with a focus on public understanding and acceptance of manipulating the mind.

#### 2.7.3. Previous work

Since the establishment of neuroethics, ethical debates surrounding brain stimulation have been preceded by research that investigated the safety of DBS on Parkinson's disease patients, its effects on personality, and its application for mental illness (Takagi, 2012). In addition, brain stimulation methods such as Transcranial Magnetic Stimulation (TMS) and transcranial direct current stimulation (tDCS) are technologies that can be applied in various areas of research going forward, such as the development of new treatments for mental disorders and furthering the understanding of the brain functions of healthy people. In the West, the ethics of TMS and tDCS are already being debated with regards to safety (Rossi et al., 2009) and to search for modes of informed consent based on the degree of invasiveness (Illes et al., 2006; Nuttin et al., 2014; Wu et al., 2021).

Neurofeedback technology using EEG, MRI, or other tools has attracted the attention of neuroethics in that the interventions are performed with equipment usually used for observational purposes. Both EEG neurofeedback and MRI neurofeedback have been researched extensively in recent years. A certain level of understanding has already been obtained regarding their safety. On the other hand, with the development of treatments for mental disorders using neurofeedback technology, recent ethical research has been conducted to evaluate the effects of these methods on human existence and society. Further exploration of the mechanisms by which these methods improve symptoms is needed, as problems with irreversibility have already been pointed out (Nakazawa et al., 2016).

Manipulation of the brain using optogenetics has now been actively adopted in experiments featuring animals. Optogenetic techniques for manipulating the brains of macaque monkeys to induce movement have been reported (Watanabe et al., 2020) and there are aspirations for applications in humans (National Institute for Physiological Sciences, 2020). This extends not only to motor functions but to cognitive functions, with the ethics of memory manipulation using optogenetic technology being a hot topic of discussion (Zawadzki and Adamczyk, 2021).

#### 2.7.4. Short-term challenges

While considering the expectations for clinical applications of neuromodulation technologies such as neurofeedback, TMS, and tDCS, a social context is critical. The social acceptance of neuromodulation in Japan must be discussed while keeping in mind the history of Japan where psychosurgery has been socially contraindicated. Above all, it is essential to explore the ethics of techniques that intervene in the more fundamental parts of the human mind. The effects of emotional interventions on human autonomy and personality need to be examined in addition to their social implications.

#### 2.7.5. Long-term challenges

The development of technology for interventions on neurological functions needs constant monitoring, and there should be a proactive

investigation of ethical issues. Presently, the ethical issues involved in brain manipulation using optogenetic technology in humans are the topic of preliminary discussions. So far, these techniques have only been used on animals.

#### 2.7.6. Examples of research questions

It is necessary to examine how the development of brain intervention technologies will affect our personality and, by extension, what kind of changes it will bring about in Japanese society. While urgent consideration is needed for technologies that have already been applied, such as TMS, tDCS, and fMRI neurofeedback, we also believe it is necessary to examine the impact of optogenetic technologies and other technologies in the future, which are somewhat more distant. With this in mind, we present the following three research question examples.

- How does neurofeedback on emotions affect personality, and what are its social implications?—The purposiveness of the mind and issues surrounding manipulation
- How can the effects of brain stimulation methods such as TMS and tDCS on autonomy be evaluated?
- What ethical issues need to be solved before applying optogenetic technologies for brain manipulation on humans?

### 2.8. Topic 5: industrial applications of neurotechnology

#### 2.8.1. Background

The development of neurotechnology now touches human social activities outside the scope of medical and academic research. Various technologies enable non-invasive approaches to modify human brain functions, such as enhancing brain functions by drug intake, electrical and magnetic stimulation, and advancement of brain activity measurement and analysis technologies into marketing, politics, education, and other fields. This development has brought ethical issues related to widening social disparities, increasing conflicts, and military applications. These issues are closely linked to the ethics of human brain intervention research discussed in *Topic 4* (e.g., the right to self-actualization and regulation of the exercise of that right). They also include clues to Japanese society's structural problems, such as accepting diversity and securing the public interest.

#### 2.8.2. Core ethical issues

While neuroscience and neurotechnology can be used for human self-actualization, correcting social inequalities, and accepting diversity, they may also help widen inequalities, eliminate (or reject) diversity, and promote conflicts between different social groups. The question persists then how to handle/balance these two aspects, incorporate neuroscience and neurotechnology in the real world, and achieve harmonious use.

#### 2.8.3. Previous work

In Japan, neuroenhancement has been discussed since the nascent stages of industrialization and the social dissemination of neuroscience and neurotechnology. This discussion has covered topics including the transformation of moral concepts (Tachibana, 2017), the effects on the existing educational system, and changes to the concept of mental disorders due to industrialization (Tachibana, 2018a, 2018b). However, systematic research efforts have been lacking, and the dissemination of findings internationally has been sporadic. This is because neuroethics has not been incorporated into the frameworks of public research funding as an independent field of academic research. Instead, it has been treated as a sub-field of bioethics and the philosophy of science. Research has been conducted on an individual basis or single team in national neuroscience research projects to provide ethical support for neuroscience. Within these frameworks, the emphasis has been on providing ethical support for neuroscience. Together, all of these factors have delayed the development of venues for training neuroethics

specialists and reflecting their findings in the educational system (Fukushi et al., 2017). As for the government, the Japanese Ministry of Internal Affairs and Communications (2011) discussed the ethical issues involved in the industrialization and social implementation of brain information and communications technology in its "Final report of the advisory panel on brains and ICT – Further development of ICT using brain frameworks." In addition, although the Science Council of Japan (2012) has been investigating matters related to military and security research, discussions specific to neuroscience have not made much progress.

#### 2.8.4. Short-term challenges

As authors introduced in previously, The Japanese Ministry of Internal Affairs and Communications (2011) and the Science Council of Japan (2012) are milestones in the discussion regarding safe and peaceful use of neurotechnologies. Given the importance of documents, continuous re-examination and further updating are required. These include a survey on the actual status of neuroenhancement and do-it-yourself (DIY) use of neurotechnologies in Japan; an analytical study of ethical cases based on the activities of domestic ventures related to brain information and communication technology, etc.; a follow-up to the report of the Ministry of Internal Affairs and Communications (verification of dissemination and effectiveness in the field of brain science research and development), and a follow-up to the study by the Science Council of Japan (validation of the response of the brain science community). In addition, it is urgent to establish a prospective cohort research system to study the impact of social disparity on human brain function and mental health, which has been pointed out to be becoming more prominent in the wake of COVID-19 (Holmes et al., 2020).

#### 2.8.5. Long-term challenges

The above-mentioned fact-finding surveys, follow-up surveys, case analyses, and other research approaches demonstrate the need to pursue research on creating rules and fostering morals in various dimensions of neuroscience and neurotechnology, including industrial applications, social implementation, and prevention of abuse. A normative examination needs to be conducted on the ethics of public health interventions using cognitive biases, which include techniques such as nudging. In particular, solving the problems related to public health applications of neuroscience and neurotechnology and DIY methods will require greater cooperation and integration of neuroscience, neuroethics, regulatory science, and health technology assessments (HTA). In addition, continuing the above-mentioned prospective cohort studies will hopefully lead to progress in neuroscientific analyses of the effects of social inequality on humans and in the correction and elimination of inequalities based on these findings.

#### 2.8.6. Examples of research questions

There are a variety of research questions that need to be addressed regarding the industrial application of neurotechnology. Focusing on the regulation of enhancement, including DIY, and social fairness, we present the following seven research questions as examples. Discussions on enhancement have been ongoing since the pioneering days of neuroethics, and in the 2020's, the social implementation of enhancement technologies should be recognized as a realistic issue, and realistic regulations should be considered in light of the social situation in Japan. It is considered essential for the development of neurotechnology that social fairness be appropriately discussed in that examination.

- Are purposeful nudges acceptable and ethical regarding public health applications of neuromarketing, neuroscience, and neurotechnology?
- What should the relationship be between Japanese neuroscience and military/defense research in a world of deepening conflict? Problems surrounding dual-use neuroscience in Japan.

- Do pathological, health, and superiority enhancement technologies help achieve the purpose of self-actualization in humans?
- Can neuro-enhancements help correct social inequalities?
- How should Japan regulate DIY methods in neuroscience?
- How can neuroscience contribute to a multi-agency society based on sexual diversity?
- What is the relationship between socioeconomic status and neuroscience?

### 3. Discussion and conclusion

Neuroethics is the study of the ethical, legal, and societal implications of neuroscience. This paper has discussed issues related to neuroethics in Japan as of 2020 s. Neuroethics is still a fledgling discipline and field, and its methodologies and academic identity require better establishment and definitions. In this paper, the ethical issues surrounding neuroscience in Japan were organized into five topics. By incorporating the perspective of patient-public involvement into informed consent and decision-making in psychiatric research, neuroethics can make ethical contributions to research on mental disorders (Topic 1). In research using samples and data, frameworks need to be created to construct a global research environment (Topic 2). The construction of brain banks and their use in research require ethical support within a Japanese context. This needs to be based on a reconsideration of the moral values of the human neural system (Topic 3). This topic is related to the similarities and differences between human and animal brains. In turn, a consideration for animal ethics must also be included. Brain intervention has been a central theme since the early days of neuroethics. At present, a major issue is neuromodulation technologies that intervene in emotions (Topic 4). In addition, neuroscience and neurotechnology, including brain interventions, need to be reconsidered from social perspectives (Topic 5). Rules for neuroenhancements and DIY use of neurotechnologies are urgently needed, while from a broader perspective, it is important to study the points of contact between neuroscience and public health. Conclusively, neuroethical issues will change dynamically along with advances in neuroscience, and this paper has clarified the tasks facing Japanese neuroethics in the 2020 s

This study organizes current issues in Japanese neuroethics in line with the international analytical framework established through the Global Neuroethics Summit ([Global Neuroethics Summit Delegates et al., 2018](#)) and thus does not offer an original analytical framework and methodology. However, this may be seen as a choice to facilitate international comparisons of neuroethics. Reports from different countries on neuroethics efforts are useful as descriptive ethics and aggregating reports allow global neuroethics.

Neuroethics in Japan is in step with the development of neuroscience in Japan, and if there are technologies and developments in neuroscience research that are unique to Japan, then neuroethics should be adapted accordingly. In addition, neuroethics in Japan should take into account not only the political system and social structure of Japan, but also Japanese customs and culture. For example, cultural and religious beliefs need to be taken into consideration regarding donation and living consent to brain banks.

What this study offers researchers engaged in neuroethics is a clarification of the research agenda that should be promoted in the 2020 s. Of course, the significance goes beyond just benefits to neuroethicists; it is important for neuroscientists and neuroethicists to share the ethical, legal, and social issues raised by neuroscience in order to develop socially acceptable neuroscience.

### Funding information

This paper is supported by the National Institute for Physiological Sciences, Japan; Research Meeting, Japan Science and Technology Agency; Research Institute of Science and Technology for Society, Japan, Grant Number JPMJRX21XX, Japan Society for the Promotion of

Science; KAKENHI, Japan, Grant Number JP20H05717, and Japan Agency for Medical Research Development, Japan, Grant Number JP20dm0307004.

### Declaration of Competing Interest

None.

### Acknowledgments

This paper is supported by National Institute for Physiological Sciences, Research Meeting, JST RISTEX Grant Number JPMJRX21XX, SPS KAKENHI Grant Number JP20H05717, and the Japan Agency for Medical Research and Development (AMED) under grant numbers JP22dm0307004, JP22dm0307005, and JP22dm0307020.

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## Glossary

*DBS*: Deep Brain Stimulation

*DIY*: Do It Yourself

*EEG*: Electroencephalography

*MRI*: Magnetic Resonance Imaging

*tDCS*: transcranial Direct Current Stimulation

*TMS*: Transcranial Magnetic Stimulation