

Ethical, legal and social issues raised by human brain banks

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Abstract. – Based on the research methods of literature review and philosophical reflection, this article points out the deficiencies and problems in the current research of brain banks: lack of nature analysis of brain banks and human brains; insufficient discussion of ethical, legal and social issues (ELSI) in the process of brain bank implementation – which has become the main research goal of this article. The article firstly clarifies the formation process of modern brain banks and briefly introduces the current development status of brain banks in the UK, the US and China, as well as the different types of modern brain banks. Next, the nature of brain banks and human brain samples are analyzed through an analogical model. Then, the ELSI issues at different stages are analyzed according to three stages: recruitment of donors, acquisition and storage of human brain tissue samples, and release and use of human brain tissue samples. Last, in the conclusion section, the main ideas of this paper are reiterated and questions for further reflection are presented.

Key Words:

Brain banks, Human brain, Ethical issues, Legal issues, Social issues.

Introduction

According to statistics, nearly one billion people worldwide suffer from mental disorders¹. Among various mental diseases, depression is estimated to affect 350 million people², and schizophrenia also affects about 21 million people worldwide³. The number of people suffering from neurodegenerative diseases (such as Alzheimer's, Parkinson's, Huntington's, etc.) is also yearly increasing under the global ageing trends. Since the beginning of the 21st century, the world's major pharmaceutical companies have successively invested lots of money to develop drugs for Alzheimer's disease, but the failure rate is still as high

as 99.6%⁴. One of the important reasons is that so far, our knowledge of the human brain, especially related to memory, perception, reasoning, and self-awareness, is still limited. Because of this, brain science has been hailed as the final frontier of the 21st century⁵.

In recent years, with the development of neuroimaging, molecular biotechnology and liposome expression techniques, post-mortem human brain tissue study has received increasing attention from neuroscientists and pathologists in various countries. Through the comparative study of isolated human brain samples (diseased brain and healthy brain), scientists can understand the biological causes of brain diseases, and reveal the relationship between specific diseases and heredity and environment. Today, the study of human brain tissue is crucial for discovering therapeutic targets and is important for the development of diagnostic tools, validation and epigenetic studies⁶. Thus, as an essential primary resource facility to promote the development of brain science and overcome various neurological and psychiatric diseases, brain banks have been flourishing in recent years, and countries have invested significant amounts of funds, workforce and material resources in building complete and professional modern brain banks. Currently, 142 brain banks have been built worldwide⁷, and a communication network of brain banks based on samples and data sharing has also been formed in the UK, US and Australia. China has also started the preparation of modernized professional brain banks in recent years.

With the development of brain banks around the world, the academia began to pay more attention to various issues in brain banking. Obviously, the ethical, legal and social issues are a problem domain that needs to be focused. However, due to the different development stages and situations of the brain bank in different countries, the discussion on the ELSI of brain banks

is not comprehensive and sufficient. These studies have discussed related issues from the perspective of brain banks' operation and management, the history and development of brain banks, the value and significance of brain banks, the donation of human brain samples, and the classification of brain banks. A review of these papers shows that, on the one hand, such a research method cannot comprehensively cover the ethical, legal and social issues in the brain bank. On the other hand, those research methods mix many issues in different problem domains, making it difficult to comprehensively analyze the ELSI, including the causes, specific manifestations and results of the issues. Therefore, based on combing existing research materials, this paper divides the implementation process of brain bank into three stages, and discusses the ELSI respectively, which can clearly and effectively analyze the issues and help to better study the solution of the issues.

Formation and Development of Brain Banks

Thousands of years have passed since the human brain was historically dissected and used for medical research. The long period from Hellenistic Alexandria in the 3rd century BC to the beginning of the modern brain bank in the mid-20th century, the collection and study of human brain tissue samples was a somewhat grey area and mostly personal behavior, with the human brain even becoming part of the private collection of influential people for a time⁸. An important difference between modern brain banks and past human brain collections lies in the shift from small, private collections to large, regulated, and systematic public infrastructures and in the fact that the collection practices of modern brain banks are distinct from clinical brain autopsies for diagnostic purposes in hospitals, or brain tissue collection during surgery.

Brain banks are large-scale collections of potential brain tissue donors identified through donor recruitment programs⁹. Through active communication to obtain consent from the patients and their relatives, the whole brain is obtained after death, sorted by pathology for storage, and then distributed to research groups or individuals applying for the sample.

The development of modern brain banks has accompanied the rise of neuroscience. Early neuroscience research focused on vertebrates with simple nervous systems (e.g., monkeys, cats, and

rats) and invertebrates (e.g., lobsters, sea slugs, and squid). There were few systematic studies on the human brain due to the lack of *in vivo* brain imaging techniques. More importantly, it was widely believed at that time that human brain tissue after death was affected and damaged by diseases and post-mortem decay of the body, and therefore was not valuable for research. Thus, until the 1970s, few neuroscientists studied the post-mortem human brain. Nevertheless, the situation changed with the publication of a research paper⁹ from the United Kingdom that reported a statistical correlation between the histopathological changes in the brain of Alzheimer's disease and the deterioration of its memory during life. As a result, more and more neurochemists and neuropharmacologists became interested in understanding the neurobiological basis of such changes. By the mid-1970s, brain banks had begun to be developed in Canada, the United Kingdom, and Germany, and an increasing number of relevant research papers had appeared.

The earliest brain banks in Britain were established by John Arthur Nicholas Corsellis, a neuropathologist at Runwell psychiatric hospital. From 1951, he collected over 8,000 brains affected by epilepsy, tumors, dementia, and psychiatric disorders, and about 1,000 healthy human brains as controls, these human brain tissues were also matched with medical records, neuropathology reports, and neuropsychiatric records. Corsellis not only collected human brain samples, but also distributed them to other researchers, so as to assist other researchers in publishing their achievements. His collection has been transformed into the earliest brain bank in Britain¹⁰.

The first brain banks in the United States consisted of samples of human brain tissue relevant to neuropathology. They were used primarily to teach residents, medical students, and those interested in the subject, with some of the tissue fixed in labelled jars filled with formalin¹¹. Edward D. Bird, one of the most important pioneers in the field of brain banks, created a brain bank at Cambridge University in England. Later, in 1978, he came to McLean Hospital, a teaching hospital affiliated with Harvard Medical School, where he established a similar facility for the study of Huntington's disease and schizophrenia patients' brains. To this day, this facility is still arguably the largest in the world, providing brain tissues for researchers not only in the United States but in many other countries, such as South America, Europe, Asia and Australia¹².

After decades of development, the United Kingdom, the United States, Australia, and the Netherlands have built brain banks of considerable scale and influence, including not only physical brain banks but also virtual brain banks based on modern big data networks. The virtual brain bank in the United Kingdom (BRAIN UK) integrates data information and samples, so that each brain bank data platform can maximize the utilization of samples (including scarce human brain tissue) and provide research for brain diseases that cannot attract funding (such as stroke, rare diseases, etc.). Australia's virtual brain bank maximizes the potential value of brain donations by expanding the core database to include existing clinical tissue and data repositories¹³.

In April 2014 and May 2016, China held the first and second "International workshop on Human Brain Banking in China" respectively. After the meeting, the "Chinese Brain Tissue Bank Collaboration Alliance" was established, which was jointly formed by ten medical schools in China, including Xiangya Hospital, PUMCH, Zhejiang University, and then released the first version of the "Standardized operational protocol for human brain banking in China¹⁴" in 2017. In the same year, the Human Brain Banking Branch of the Chinese Society for Anatomical Sciences was established, and the Ministry of Science and Technology of China approved the establishment of the National Human Brain Bank for Development and Function and the National Human Brain Bank for Health and Disease, relying on PUMCH and Zhejiang University. In 2018, with clinical neurology as the core, China National Clinical Research Center for Neurological Diseases established the brain bank community⁷. These all indicate that China has begun to join the team of global modern brain banks construction.

The types of modern brain banks can be broadly classified into comprehensive brain banks and specialized brain banks. The comprehensive brain bank covers a variety of brain samples with related diseases, such as neuropsychiatric brain banks. Neuropsychiatric brain banks are focused on a group of neurological disorders and are currently the world's most important type of brain bank. This kind of brain banks mainly recruit patients with bipolar disorder, schizophrenia, major depression, and autism, just like the Netherlands Brain Bank and the Stanley Foundation Brain Collection. Comprehensive brain banks also focus on neurodegenerative diseases, such as the Harvard Brain Tissue Resource Center, Mayo

Clinic, and Sydney Brain Bank, all of which focus on Alzheimer's disease, Parkinson's disease, frontal-temporal lobe dementia, amyotrophic lateral sclerosis, and other diseases¹¹. Specialized brain banks are dedicated to collecting human brains of certain neurological or psychiatric diseases, such as the National Prion Disease Pathology Surveillance Center, Autism Brainnet, Alzheimer's Disease and Schizophrenia Brain Bank, Sinai School of Medicine Medical Center Brain Bank, etc.

ELSI of Brain Banks

The primary function of a brain bank is to collect, store, and distribute isolated human brain tissue to facilitate research into the normal function of the human central nervous system and the etiology of disease^{14,15}. The tissues collected by the brain bank include the brain (including pituitary gland), cerebellum, brainstem, spinal cord, cerebrospinal membrane, spinal fluid, etc¹³. Different processing methods are applied to take and preserve the material depending on different research purposes and needs. With the combination of big data technology, modern brain banks store physical samples and build information platforms to provide researchers with complete and correlated sample data and research data. However, due to the particularity of the recruited subjects and the uniqueness of human brain tissues, brain banks face many ethical, legal and social issues in the construction and operation process. The Brain Net Europe Consortium has issued a unified Brain Net Europe Code of Conduct to harmonize the differences in practice, policy and legal regulation among brain banks in different countries and regions, which all members adopted in 2009⁶. However, with the development of brain banks around the world, the original norms obviously cannot meet the requirements of brain banks anymore, and new problems keep emerging.

At present, brain bank research focuses more on the history of its generation, the discussion on the ethical, legal and social issues is insufficient, and there is a lack of discussion on the relevant basic concepts, such as the nature of brain banks and human brain tissue samples, which are the prerequisites for discussing the ethical, legal, economic and social issues. Therefore, this paper will first define the nature of brain banks and human brain samples and then discuss the ethical, legal, and social issues involved in each stage of brain bank operation separately.

Nature of Brain Banks and Human Brain Tissues

Perhaps, since the definition “brain banks” includes the word “bank”, it is a natural analogy for discussing the nature of brain banks as a bank. The original intention of comparing brain banks to banks is simply to capture the basic process of “store-and-acquire” in the operation of both, which increases the association with them as financial institutions. However, human biological samples and financial currencies are completely different, so the bank analogy is not an appropriate analogical model. There has been much debate around the patenting and commercialization of human tissue worldwide, and the Convention on Biomedicine’s “Non-profit principle” that the human body or its parts should not generate financial gain per se has been adopted as a critical principle by The Brain Network Europe Consortium and set out in a code of conduct for brain banks and their users¹⁶. Therefore, a brain bank should not be understood as a financial institution, should not be owned by any investor, and should not seek to maximize profits, but should aim at promoting scientific progress, improving the health of populations, and enhancing human well-being by providing samples of human brains.

Rather than defining brain banks in an institutional model, this paper argues that the uniqueness of brain banks can be better captured by interpreting their nature in terms of role function. According to Klioueva et al⁶, the brain bank is “an important link between donors, their relatives, clinicians, pathologists, and scientists”. In other words, the brain bank plays an important role as an “honest broker” between the providers and users of the samples, acting as a caretaker of the samples, managing them and their information, and providing a transparent and fair platform for information exchange and peer monitoring among researchers.

First of all, the brain banks specifically build communication channels of mutual trust between donors and researchers. By signing informed consent with donors and their relatives, the brain bank protects the personal information security and privacy of donors and their relatives, ensure their autonomy, and respects their right to choose. Second, it circumvents unscrupulous trading and private collection and use of human brain samples, guarantees the industry’s reputation, and protects donors from commercial exploitation. The contradiction between the need

for research and effective sample acquisition has led researchers and clinicians to sometimes take risks in obtaining human brain samples by unconventional means. Professional brain banks allow researchers to obtain human brain samples legally, reasonably, and compliantly. In addition, brain banks, as intermediaries, can prevent direct contact between users and donors and avoid infringement of donors’ interests. Third, it relies on big data technology to maximize the utilization of brain sample resources. On the one hand, unlike the acquisition of other biological samples (e.g., saliva, blood, urine), the acquisition and preservation of human brain samples require more financial, intellectual and material resources; on the other hand, the amount of human brain samples obtained worldwide is insufficient. Therefore, good quality-controlled human brain samples are scarce and precious to researchers. Through professional operation and big data technology, the brain bank allows researchers worldwide to access human brain samples and share research data, so that human brain samples can be fully utilized. Fourth, to reduce the burden on researchers. To fully explore the pathological mechanisms of neurological and psychiatric disorders, we need not only good quality-controlled diseased human brain samples, but also equally good healthy human brain samples, both of which need to be accompanied by complete clinical diagnostic data and treatment histories. The vast data collection and the tedious follow-up work are the prerequisites to ensure the quality of the samples. By formulating a recruitment plan and segregating duties, a professional modern brain bank can help researchers focus on their study projects, reducing the time of preliminary work. Fifth, to reassure relatives and provide psychological guidance. The acquisition of human brains is associated with death, and relatives need to control their inner grief to cooperate with the brain bank staff to retrieve brain samples quickly. Professional brain banks have trained psychological counselling teams to provide professional psychological counselling for relatives, helping to calm and take care of their emotions so that the human brain can be obtained in a timely manner while respecting individuals. Sixth, to increase citizens’ awareness of the value of donating human brains and increase the number of diseased and healthy human brain samples available for research. As mentioned above, there is a severe shortage of human brain sample resources worldwide; therefore, increasing public awareness of

the value of human brain research is critical to increasing willingness to donate brains after death. As a professional institution, the brain bank also undertakes to educate the public about brain science research. By planning various activities, it also makes the public understand the value of donating brains for overcoming neurological and mental diseases and increasing public trust in scientific research.

Based on the role of the brain bank as an “honest broker”, it is clear that human brain tissue samples cannot be understood as entities of financial currency in the “banking” model. Current academic theories of human tissue include the biological property, the gift, the waste, the commodity or natural resource, and the theory that “human being is identical with their living body”²¹. The biological property considers human tissues to be property with a “link” to the individual, and the link is reflected in the consistency of DNA¹⁷. The gift theory emphasizes altruism, considering human biological tissue as gifts to help organ donation and promote community solidarity¹⁸. The waste theory can be found in the “Human Tissue: Ethical and Legal Issues¹⁹” published by the Nuffield Council on Bioethics in the UK, which states that human biological tissue, such as urine, faces, sweat, peeled nails and cut hair, can be considered as waste. The commodity or natural resource theory indicate that human biological tissue has economic value, autonomy, and risks²⁰. The theory which affirms that “human being is identical with their living body”²¹ considers that the sale of human organs or tissues is an act of human trade, not a possession of something, and that organ transplantation or donation for therapeutic purposes should be seen as sharing in another human being’s misfortune, rather than as giving owned objects²¹.

The above arguments are justified for specific purposes and human tissues. However, since the human brain is a unique organ and human brain tissue for post-mortem research needs the whole brain, the nature of brain tissue needs to be analyzed based on consideration of the unique characteristics of the human brain. First, we biologically define the human brain as the core organ of the human nervous system, which, together with the spinal cord, forms the central nervous system that directs the activities of the body by processing, integrating, and coordinating the information received from the senses. At the same time, the human brain is the most complex organ in vertebrates, containing about 1.4-1.6 billion neuronal

cells in the adult cerebral cortex. Nevertheless, our understanding of how neuronal properties are generated through local and long-range loops is still minimal. As for the understanding of how neural information in the loops generates various brain cognitive functions, such as perception, emotion, thought, choice, consciousness, and language, is even more rudimentary²². Second, in the philosophical tradition, the classical issues of the mind-body relationship have gradually become naturalized with the progress of science, manifesting itself as the issue of the mind-brain relationship, which also reflects that the human brain has become the most promising beacon for reconciling dualism, and arguing that consciousness is a brain process has become a new task for philosophers and neuroscientists. Some philosophers of science agree that the internal mental states of human beings identify with the neurophysiological states of the brain and present arguments from their perspectives. Third, the human brain also plays a crucial role in different cultures and religions, and some argue that the human brain is part of the essence of the human being²³.

From the above, it is clear that the human brain has a unique moral perception compared to other human organs, and even as a part of a corpse, the brain that has lost its “vitality” still has a moral value. As the most extraordinary and vital organ in the human body, the brain is closely related to human beings and their nature. Although the isolated human brain removed from a cadaver no longer has sentience and consciousness, it cannot be ignored that the brain is still a common organ for human beings – the brain is both universal and special, everyone has a brain, all with similar structures and functions, and it distinguishes people from other life forms. Yet, each brain belongs to a certain person and is only connected to that person and plays an important role in defining who they are during their whole life. The brain contains the reasons why we all have a different personality and also contains the reasons for people to be human. Thus, from the perspective of virtue ethics, we should not take the human brain as an ordinary object that can be disposed at will, since it is both a matter of respect for the deceased person and the human being. As Daniel Dennett mentions when describing the respect for human corpses – “how we handle this corpse now has repercussions for how other people, still alive, will be able to imagine their own demise and its aftermath. Our

capacity to imagine the future is both the source of our moral power and a condition of our vulnerability²⁴, which is the same for the human brain. The fear of imagining that one's brain might be treated in a certain way gives people the virtue of maintaining respect for the human brain.

ELSI at the Stage of Donor Recruitment

First of all, the days of body snatching, black market trading, and taking advantage of one's position to obtain human brain tissue for research through clinical and forensic autopsy have passed. At present, brain banks around the world mainly seek potential brain donors through donor programs. According to the donor programs, brain banks worldwide generally need to recruit individuals with certain neurological or psychiatric disorders, but also healthy human brains without a history of neurological or psychiatric disorders, drug abuse or alcoholism²⁵, and of suitable age and sex to serve as controls. Thus, one of the most controversial questions is how to make a reasonable and valid distinction between healthy and unhealthy brains. Due to the definition of "healthy" is still very controversial¹², and some unhealthy people do not consider themselves psychiatric patients and do not consider themselves "abnormal". Then, a reasonable and effective definition standard is very important for recruitment. Meanwhile, how to avoid violating the human dignity of the patients in the recruitment process needs to be guaranteed by professional recruitment procedures and well-trained staff.

Second, patients with mental diseases and their relatives may suffer social discrimination due to disclosing personal information and privacy during recruitment, which may cause distress and trouble in their lives. Patients with mental disorders and their relatives are often accompanied by a strong sense of stigma, which makes the issue of privacy and confidentiality in brain banks even more important. A survey from the United Kingdom showed that 56% and 51% of people with mental disorders experienced discrimination from family and friends, respectively, and 44% experienced discrimination from GPs working in primary care, in addition to 37% of people with mental illness experienced discrimination when seeking employment and 47% experienced discrimination in the workplace²⁶. Therefore, there is a need for strict confidentiality of personal information obtained during the recruitment stage. In addition, when patients pass away, although the

leakage of their personal information does not directly affect them personally, we need to be alert to the possible effects of information leakage on their relatives and descendants, as well as the negative effects on the public and society. Thus, ensuring the security of patient information is a responsibility that cannot be ignored. The process of release and use faces similar issues, which will be discussed later.

Third, the recruitment process may result in the exploitation of vulnerable groups and the infringement of their interests. Patients with mental disorders are vulnerable, many of whom may be incapable of decision-making. It is challenging to ensure that patients and their relatives fully understand the agreement's content, especially when it comes to professional and profound research content. Moreover, they may not be aware of their legitimate rights in the study, so that some patients may be blackmailed or even threatened and deceived by financial gain and thus make choices against their will.

Forth, a further issue is the reasonableness of informed consent. That is, whether the principle of informed consent applies or should apply fully to the body of the deceased remains a less clear question⁶. Informed consent is distinguished from authorization, which is a decision by the individual donor to consent to donation, and authorization, which allows a relative or legal guardian to donate in place of an incapacitated person or child. In the case of patients with neurodegenerative diseases, the criteria for determining whether they can make autonomous decisions and what model of consent to use are issues that need further discussion. Whether the relatives have the right to overrule the patient's living decision when the patient dies is also a problem that needs further discussion. Furthermore, in brain banks, the argument against traditional informed consent is that the donor is dead, meaning that his or her rights are over, and pathologists and neuroscientists are in a better position to judge whether his or her brain is beneficial to medical progress, so the decision should be left to professionals²⁷. The opposite attitude to this utilitarian view holds that the body and its parts have significant or supreme value to the individual or relatives. Removing organs only with expert advice may violate personal will, religious beliefs, social understanding, and cultural traditions. Additional issues need to be considered may include: Should every brain bank adopt a policy of informed consent, even if the brain bank can be waived these

requirements under state law or regulation? Can the right to consent be delegated to a doctor or research committee? Is it permissible to retain and use organs for specific research purposes if an autopsy is authorized? etc⁶.

Fifth, following up and updating the clinical information of donors in real-time is a time-consuming task that requires significant human and technical support. In order to obtain samples with better research value, patient information needs to be dynamically updated on their treatment course during their lifetime. However, the average time from recruitment to donation is weeks to months for some diseases such as Creutzfeldt-Jakob disease (CJD) patients and decades for multiple sclerosis (MS) patients and healthy donors²⁸. Therefore, the cost of time and manpower resources is high, and how to balance cost and sample value requires more comprehensive consideration and advanced technical support.

Sixth, the acquisition of the human brain occurs after a person's death, and the human brain is different from other human organs, people treat it differently than other body organs, which increases the difficulty of recruitment. One of the reasons is that people consider the human brain to be part of what constitutes the essence of a person. Also, some surveys have shown that there is a tradition and belief from the Chinese Confucian and Roman Catholicism that all the body parts must be buried with the person²³. For instance, Chinese Confucian culture has always valued the body as the foundation of the present life and human being, which also implies a great respect for the body parts of the deceased.

Finally, although the use of fetal brain tissue for research is almost a century old, the use of brain tissue from post-mortem fetuses often involves abortion. Additionally, only post-abortion fetal brain tissue can be used for research. Parents must give permission instantly after the death of their child, but this is a period of extreme grief and a painful decision for the mother. So, it is likely to be an inflammatory sociopolitical issue in the United States, and there is a lack of discussion and regulation of related research in other countries.

ELSI at the Stage of Acquisition and Storage of Human Brain Tissue Samples

First, the stringent requirements of quality control (QC) may conflict with sample acquisition. QC is critical to ensure that brain banks serve as an infrastructure for neuroscience re-

search. QC encompasses two aspects, namely information and samples. Patient information can be numerous and diverse over a patient's lifetime. The value of follow-up research can only be ensured by managing the diagnosis and treatment information of patients according to the coding standards. Samples quality is the standardized sectioning, processing, and storage of brain tissue and the pathologic evaluation of the tissue. After a patient's death, it is usually required to contact brain bank staff for brain retrieval within 24-48 hours, as the RNA integrity and pH of the tissue are usually used as markers of brain tissue quality. Related studies have shown that post-mortem temperature and time significantly impact tissue quality, and tissue should be frozen immediately at -80°C to prevent protein degradation²⁸. Therefore, it is extremely critical to obtain brain tissue samples promptly after the death of a patient. However, this process contradicts the emotions of the relatives, and getting relatives in the midst of bereavement to agree to craniotomy for brain retrieval immediately is not an easy task and mishandling it can also result in relatives' refusal to donate. Which also brings up another question: do relatives have the right to override a decision made during the patient's life? It may often be emotionally appropriate to respect the patient's relatives, but the scarcity of specific samples and the potential scientific contribution should not be overlooked.

Second, there is a problem with the standardization of acquisition procedures. Different research purposes require different methods of sample processing and storage. The human brain is a complex organ with many unique structures, and it needs to be sampled according to structural markers in different brain areas. However, processing standards may differ between regions and countries worldwide, which would reduce the usability of samples in comparative or association studies. Therefore, whether there should be unified regional or even international standards or what data-sharing models can better facilitate the transition from hypothesis-driven to data-driven research, which need to be further discussed. Human brain tissue samples are scarce and precious resources from all over the world, especially those with good morphological characteristics and accompanied by complete clinical diagnosis and treatment information, and it is a long cycle from acquisition to use. This makes it a moral imperative to make the most use of human brain tissue and give full play to its maximum value.

Finally, fresh human brain tissue may contain highly infectious agents that risk exposing others to highly infectious diseases. Some hazardous infectious agents (viruses, prions) may be present for a long time; for example, the formalin-resistant prions that cause CJD have been shown to remain infectious after many years of storage²⁹. A protocol for performing high-risk autopsies indicates that sources of infection that may harm humans include human immunodeficiency (HIV) infection, CJD, and blood-borne viruses (including hepatitis B and C) infection³⁰. Therefore, obtaining human brains requires standardized procedures and protective measures to ensure the safety of the staff involved.

ELSI at the Stage of Release and Use of Human Brain Tissue Samples

First, there is an issue of information security and sharing. The brain bank will generate a wide range of personal information data, including personal identification information, clinical treatment information, and extensive research data. We may not have to worry about the risk of leaking the personal information of the deceased donors in the brain bank. However, there is a need to be vigilant about the risks associated with using these data for research. From the nature of data, data itself contains the laws of natural intelligence³¹, and once there is enough data, the data itself will speak³². Thus, in the era of big data, there is a need to be alert to the impact and challenges of research results and algorithms based on brain bank data in social, medical and public health fields. On the other hand, there is also a need to be vigilant about data security issues arising from the brain bank's vulnerability of the data storage system to be stolen by criminals.

The second is the problem of cost and benefit in brain banks. Non-profit is the basic operating principle of human brain tissue banks, yet the collection, processing, and storage of human brain tissue are often costly. Brain banks are expensive to both establish and maintain. Estimates of running costs vary from €10,000-15,000 per brain in the Brain Net Europe Consortium to \$10,000-30,000 in the USA³³. Thus, a reasonable cost recovery plan is a condition to ensure the long-term operation of brain banks. Brain banks are either funded by private funds or may receive public funds, which may have a different impact on cost recovery strategies. One possible question is: Is it reasonable to pass on costs to users? Or is it reasonable to select or

approve brain samples in favor of future research projects with more substantial economic benefits rather than those with more scientific merit to keep the brain bank running? Further, there may be questions about whether human brain tissue can be traded as a commodity. Families may not know that their relatives' donations will be marketed and sold as medical supplies. It may be argued that selling tissue to profitable research companies can accelerate the discovery of potentially life-saving treatments because commercial groups have more social resources than academia. At the same time, with the emergence of a new bioindustry, many scientists can purchase research products made from human tissue or its biological derivatives from commercial human tissue banks. For example, blood cells that cannot be sold for profit are bioengineered into marketable blood products in blood banks. Although there is a clear distinction between the two, there is a need to be wary of using this policy to disguise organ or tissue trafficking.

The ownership of human brain tissue is another area where conflicts may arise in the use process. After the donor's death, whether the donor's relatives and descendants still have certain rights to the use of the tissue, such as withdrawal, can the brain bank refuse? Or does the human brain sample belong to the sample user? Or should the donated tissue be viewed as a gift – a public good, that will benefit all humanity? The conflict is that research datasets may have great commercial value, and researchers in commercial companies may hoard research data to obtain patents. Furthermore, if the tissues they use come from altruistic donations, does the provider of the tissue samples also get a share of the profits? Also, can brain banks be copyrighted for their role in organizing the tissues they provide? The Convention on Biological Diversity (CBD) has temporarily resolved the conflict over attributing genetic resources to all human beings in the form of “national sovereignty + intellectual property³⁴”. However, as mentioned above, the research on the human brain is still full of uncertainties and difficulties. Overcoming diseases such as Alzheimer's disease, Parkinson's disease, depression, and schizophrenia is the common goal of all countries. Sharing research results will be beneficial to the health of the world's population. Therefore, it remains to be further discussed whether we should break through national boundaries to realize resource sharing and temporarily suspend personal interests.

Then, there is an issue of sample utilization and disposal of surplus samples. What to do with those samples that will never be used again? Is it a waste of public resources? For example, research on Alzheimer's disease may require only the hippocampus, so how should the rest of the human brain tissue be sorted and used properly? On the one hand, this question needs to consider both the demands of scientific research and ethical considerations. From the perspective of scientific research, no research value at present does not mean no value in the future; From an ethical point of view, as mentioned above, the human brain has a certain moral status and cannot be disposed of at will. On the other hand, should consideration be given to returning these samples to their relatives so they can be buried? Considering that the meaning of the brain tissue to family members may have changed after a period, if the family members refuse to accept it, does the brain bank have the right to destroy it? The public generally does not consider whether their donated tissue is disposed of properly. However, the public should be aware, especially the relatives of brain donors, of what may happen to their brain samples if tissues lose research value, whether they should remain as a "collection" or have the right to request their return. As Professor Hugh Perry, Chair of the MRC Neuroscience and Mental Health Board, says, "every day all over the UK, there are dozens of neurosurgical units discarding bits of human brain tissue³⁵". Therefore, the use of samples and the disposal of surplus samples is not only a management problem, but also an ethical problem.

The final issue is the notification of genetic information. Genetic information in brain banks may come from autopsies or the process of conducting scientific research with the tissue of deceased individuals. Providing autopsy information to relatives is a better practice to motivate other family members to participate in brain donor programs. However, autopsy or research may reveal genetic information that is detrimental to relatives or offspring. Further discussion is needed on the conditions under which genetic information should be informed or not to relatives to avoid unnecessary harm.

Conclusions

The research of this paper firstly shows that the brain bank plays an important role as an "honest broker" between the providers and us-

ers of the samples, acting as a caretaker of the samples, managing them and their information, and providing a transparent and fair platform for information exchange and peer monitoring among researchers. Secondly, human brain tissue samples should be regarded as a "common organ for human beings", which should not be disposed of at will and should be respected. Thirdly, some of the ELSI at different stages of the brain bank can be solved by formulating reasonable and effective management, laws and regulations and ethical oversight frameworks (such as privacy, quality control, security and sample utilization). Some may involve complex political and cultural backgrounds, which need to be discussed based on the actual situation (such as recruiting patients with neurological and mental diseases, using fetal samples for research, etc.). Some other issues are relatively more complex, such as recruitment strategy, informed consent, sample ownership and benefit sharing. These issues need to be combined with the social cultural, economic and political background, consider the purpose, value and results of relevant research, and carefully weigh before finding reasonable solutions.

As brain banks continue to develop, the following reflections may provide valuable references to address the ethical, legal, and social issues more efficiently: (1) What scale and types of brain banks should be built in what way? (2) What research purpose will the collected samples be used for? (3) What approaches or strategies can effectively increase the number of donors while respecting human beings? (4) How can we design a data management system that is more secure while still meeting research needs? Include sample and data acquisition-storage-extraction-use-feedback processes. (5) Should a uniform informed consent model be used for different recruitment targets, or should different models be used differently? (6) Is there a need to establish specimen and information sharing facilities at the level of regional or national? (7) Is there a need to develop regionally or nationally consistent sample and data standards? (8) Is there an obligation to provide study results to donor relatives? (9) How to maintain the sustainability of the brain bank in terms of funding, technology, human resources, and equipment? In addition, current research on brain banks is more focused on practical aspects and lacks consideration of basic conceptual and philosophical reflection. For example, what is the nature of the isolated human brain tissue used for research? Does the isolated human brain have

moral value? From the perspective of philosophy, what is the nature of the human brain? What is the relationship between the human brain and the human being, life and self? In order to better address the ELSI issues in the brain bank, it is crucial to demonstrate the relevant basic concepts from the philosophical level.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

Ruipeng Lei: financial support, article structure design. Chao Bai: manuscript writing, collection and reorganization materials. Bohua Liao: collection and reorganize materials, language proofreading.

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