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EDITORIAL

Progress in Human Brain Banking in China

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Human brain banks collect, preserve, and distribute postmortem and biopsied brain samples for histological, pathological, and molecular research. Different from the western countries, human brain banking in China has remained preliminary over decades. However, joint efforts during the past few years have substantially promoted this key frontier of neuroscience in China. This special topic brings together review and perspective articles on the ethical, administrative, and practical issues of brain banking. Several original studies report molecular and pathological characterizations based on banked human brain samples. In this editorial, we make a brief comment on the papers published, and also extend our endorsement of human brain banking to support high-quality research into major neurological, psychiatric and developmental brain diseases affecting the Chinese people.

The human brain is estimated to contain approximately 86 billion neurons interconnected by some 100–500 trillion synapses [1]. The complexity of our nervous system is even more mind-boggling when one considers the fact that each neuron is unique, no two brains are alike, and neuronal connections are constantly modulated throughout life [2, 3]. While it is obviously challenging, to understand the human brain there is no alternative to directly studying it to decode its mysteries that define the nature of humanity. Human brain studies have played a key role in the advance of modern neuroscience. The application of microscopic and histological inventions to observe human brain tissues in the late 1800s and early 1900s by Albert von Kölliker, Camillo Golgi, Franz Nissl, Santiago Ramón y Cajal, Auguste Forel, and others contributed directly to the formulation of the basic theory of the nervous system [4], which still governs today's understanding of the brain as a massive computing network of neurons interconnected by synapses. Human brain studies have also played a fundamental role in defining many neurological diseases [5]. For instance, Alzheimer's disease was initially characterized by the silver staining of two hallmark pathologies—extracellular neuritic plaques and intraneuronal neurofibrillary tangles [6]. Parkinson's disease is defined by Lewy body formation inside neurons and loss of neurons in the substantia nigra [7]. These classic neuropathologies have guided the search for the biochemical constituents of disease-defining lesions, the potential genetic/molecular links to pathogenesis, and the modeling of diseases in animals [8, 9]. Today, new pathological findings are continuously delivered by studying human brains with modern techniques, broadening the understanding of neurodegenerative changes, and reshaping the

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spectrum of clinical diagnosis of dementia and other neurological diseases [10]. Human brain studies are also revealing unprecedented neuropathologies underlying some developmental and psychiatric disorders [11].

In an era with new technologies emerging and converging into life science exploration every day, human brain studies are rapidly expanding, much more than classical pathological examination. For instance, high-throughput and multi-signal amplification provide site-specific and even the single-cell resolution detection of development, pathology, or disease-related genomic, epigenomic, transcriptomic, and proteomic changes. The use of novel and sensitive neural tracers with the aid of advancing computation technologies may visualize the human brain connectome at astonishing microscopic, mesoscopic, and macroscopic scales. Coming waves of brain research driven by high technologies are not only expected to greatly improve human life but also pave the way to power mankind's creativity and capability [9–13].

China has a population of over 1.3 billion, which imposes a great burden on the healthcare system for the diagnosis and treatment of neurological and psychiatric diseases. The life expectancy of the Chinese people has steadily increased in the past few decades, and the incidence of age-related neurodegenerative disorders is expected to rise dramatically [14]. Compared to the western countries, human brain banking has been limited in China, while consensus is building that this frontier needs to be preferentially promoted to support high-quality research in neuroscience [15].

Human brain banking involves numerous legal and ethical issues, which exist in all countries and ought to be considered while building the system in China. Huitinga *et al*. have provided a perspective on these issues [16]. The authors point out that the existing regimes still differ significantly throughout the world, and there are many uncertainties concerning the initiation and management of brain banks in different nations. Regardless, conditions *sine qua non* for the good conduct of a professional brain bank are guidelines established and strictly followed on informed consent, confidentiality, financial sustainability, accountability, and transparency. In western countries, the focus on brain banking has changed with greater emphasis on recovering brains from longitudinally-studied cohorts. Francis *et al.* update the initiative and achievements of the Brains for Dementia Research (BDR) in the United Kingdom [17]. BDR has received over 700 brains from donors with antemortem cognitive and brain imaging records. One of the key ongoing projects is to pinpoint the contribution of synaptic pathology to the clinical symptoms of various types of dementia. Kim and Webster introduce the Stanley Neuropathology Consortium Integrative Database for Psychiatric Disorders in the United States [18]. This Institute has obtained more than 6000 individual neuropathology datasets, as well as multiple microarray gene expression datasets, microRNA array data, single nucleotide polymorphism array data, proteomic data, epigenetic data, and RNA-seq data from 12 different brain regions of 60 cases. These databases are helping researchers to identify abnormal neuropathological markers for major psychiatric disorders, and the genes and biological processes associated with these markers. Shepherd *et al*. comment on the strategies to collect and store brains for different purposes in research on neurodegenerative diseases and brain aging [19]. The authors emphasize the importance of developing strategic regional and worldwide alliances to provide sufficient tissues to rapidly advance mechanistic investigations. Jonkman *et al*. highlight the applications of combined post-mortem brain MRI and histological studies in the verification of radiological biomarkers for antemortem diagnosis and drug discovery [20]. Qi *et al.* review the progress of developing human brain tissue culture to investigate brain disorders and screen drugs [21]. Human brain slice cultures may maintain more morphological and physiological characteristics than other *in vitro* modeling systems. Zhu *et al.* review the issue of activation of the brain to postpone dementia, which is related to the compelling question whether brain activity protects against ("use it or lose it") or might promote neuronal vulnerability to dementia-causing damage [22]. The authors provide an extensive review of the complex interplay between environmental stimulating factors and the risk for dementia, indicating that bilingualism/multilingualism, education, occupation, musical experience, physical exercise, and leisure activities may slow cognitive decline. In addition, Erskine *et al.* provide a perspective on the pathological changes in the subcortical visual system relevant to the visual hallucinations in dementia with Lewy bodies, by incorporating evidence from genetic as well as neuropathological and brain imaging studies [23].

As a milestone in the progress of human brain banking in China, the English version of the Standardized Operational Protocol for brain banking in China is published for the first time in this issue [24]. This is a result of extensive collaboration among domestic and international experts over several years of continuous effort. Thus, three special human brain banking conferences have been held to strengthen the scholarly consensus and coordinate multi-institutional efforts on brain banking in China. The first international workshop was held in Changsha and Beijing in 2014 (http://anatomy.sbm.pumc.edu.cn/brainbankworkshop2014/en/). At that meeting, Professor Shumin Duan proposed to set up multiple banking centers and develop shared protocols and databases accessible to all researchers. The meeting also discussed obstacles and strategies involving brain banking in China. Thus, the scientific

community should work with legislative branches to promote body/organ donation laws. Public education needs to be improved to increase social awareness and thus the resource for brain donation. Training programs should be established for professional management of brain banks, networks, and databases. More research funding should be raised to support the setup and maintenance of brain/tissue banks, as well as specific human brain research projects. Third-party evaluation should be introduced into the processes of brain banking, sample sharing, bioinformatics assembly, and output measures [15]. Following the above initiatives, a second workshop was held in Beijing at Peking Union Medical College in 2016, with a third in Hangzhou at Zhejiang University in 2018. All these meetings consisted of thematic presentations on topics covering the role of human brain banking in basic, translational, and clinical neuroscience, the status of brain banking in the world and China, and scholarly findings in the areas of dementia, Parkinson's disease, depression, schizophrenia, motor disorders, and developmental disorders. Practical workshops were provided after each meeting, with procedures for brain collection, preservation, histological preparation, and neuropathological observations provided by overseas experts to participating students. These meetings have also led to significant organizational achievements. Thus, with joint contributions from neuroscientists in China, a Chinese version of the standard operational protocol for brain banking was published following the second meeting, and more importantly, the China Brain Bank Consortium was established. The mission of the consortium is to foster basic and translational human brain research by providing donors' clinical biometrics, brain/tissue/fluid samples, and primary neuropathological documentation. The consortium also aims to function as a knowledge-integration and broadcasting organization for public education and policy-making to improve human neuroscience, brain disease research, and ultimately the brain health and life of the Chinese people.

The ultimate measure of the success of a professional brain bank is the outcome and quality of the research derived from the brain samples preserved. Human brain samples are continuously used in histopathological studies, while new approaches are developed for basic and translational research. In this special issue, Zhang *et al.* report an original finding of intraneuronal accumulation of phosphorylated 43-kDa transactive response DNA binding protein 43 (pTDP-43) along with primary age-related tauopathy, based on newly-banked brains from Chinese donors [25]. The authors suggest four sequential stages of dissemination of pTDP-43 with brain aging. Guo *et al.* demonstrate a novel method to quantify the expression of tyrosine hydroxylase and its receptor ErbB4 in the locus coeruleus of patients with mood disorder [26]. Specifically, the authors use a multispectral method to untangle the blue immunocytochemical staining and brown neuromelanin that coexist in this particular group of neurons. A team from Peking Union Medical College examines reference genes for transcriptional studies in postmortem brain tissue [27]. The CYC1 and TBP genes are the most stable among the candidate genes investigated, and therefore might serve as suitable internal references for gene transcription studies [28]. The same group also shows that APOE ε4, the ADAM10 RS2305421 GG genotype, and the RS10498633 GT genotype encoding SLC24A4, a member of the potassium-dependent sodium/calcium exchanger protein family, correlate with cognitive dysfunction and postmortem Alzheimer-type pathologies in Han Chinese [29]. Sun *et al.* from Tiantan Hospital of Capital Medical University demonstrate that diffuse intrinsic pontine glioma exhibits the cell-biological and molecular signatures of fetal hindbrain-derived neural progenitor cells [30]. The research reports included in the current special issue, together with others recently published elsewhere [31–35], clearly showcase that brain banking in China can support important original investigations for the better understanding of human brain structure and function. It can be expected that, with further progress on this front, additional discoveries will emerge and help unravel the underpinnings of major neurological, psychiatric, and developmental brain diseases affecting the Chinese people.

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