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Brain banking in low - and middle - income countries: *Raison D'être* for the Ibadan Brain Ageing, Dementia And Neurodegeneration (IBADAN) Brain Bank project

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Abstract

Brain Banks are biorepositories of central nervous system (CNS) tissue including fixed and frozen whole brains, brain biopsies and spinal cord, as well as body fluids comprising the cerebrospinal fluid (CSF) and blood stored for research purposes. Though several independent brain banks exist in high income countries, only five low- and middle - income countries (LMIC) have brain banks. The African continent is yet to establish a formalized brain bank despite its huge human genomic diversity, ageing of her populations with concomitant increases in ageing – associated brain disorders and differential phenotypic expression and outcomes of brain disorders. Cellular and molecular clinicopathological studies are vital to shape our understanding of the interaction between racial (genetic) and geographical (environmental) factors in the natural history and mechanisms of disease, and unravelling frameworks of diagnostic biomarkers, and new therapeutic and preventative interventions. The Ibadan Brain Ageing, Dementia And Neurodegeneration

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Conflict of Interest

None

Disclosures

None.

(IBADAN) Brain Bank, the first organized brain tissue biorepository in sub - Saharan Africa, is set up to accrue, process and store unique brain tissues for future research into a broad spectrum of neurological and psychiatric disorders. The potential unique discoveries and research breakthroughs will benefit people of African ancestry and other ancestral populations.

Keywords

Brain Banking; Brain disorders; Nigeria; Africa; LMIC

1. Introduction

Brain Banks are important biorepositoriesof central nervous system (CNS) tissue. They store research samples of whole brains, spinal cord, brain and spinal cord biopsies, and body fluids including cerebrospinal fluid (CSF) and blood. (Nussbeck et al., 2015) Brain banking is a rapidly developing field of science with a promising future of enabling research to bring on board creative solutions to CNS disorders through collection, characterization, management, and accessibility of human brain tissue for research (Kliouеva et al., 2017).

Brain banks have become important global resources in the last three decades. (Kliouеva et al., 2017) Majority are established in high - income countries (HIC) with well-connected networks in North America, Europe, Australasia and Asia/Pacific (Palmer-Aronsten et al., 2016). Among low - and middle - income countries (LMICs), formalized brain banks have been established in only Brazil, Argentina, Mexico, India and China (Kliouеva et al., 2017). The emergent international collaboration among brain banks fosters networking, interactions among researchers, standardization of criteria and protocols and access to diverse tissue samples for robust research (Ravid and Park, 2014). This ultimately strengthens the field, fosters knowledge generation and exchange as well as builds skills and expertise.

There are different types of brain banks. (Hulette, 2016) Some accrue brains with specific types of neuropathologies and healthy control brains while others are disorder - specific, focusing on single diseases or syndromes such as Alzheimer’s disease, Parkinson’s disease, stroke, depression or schizophrenia (Palmer-Aronsten et al., 2016). Subject recruitment and funding are major challenges facing the establishment, consolidation and sustenance of brain banks (Nussbeck et al., 2015; Hulette, 2016). Emerging ethical, legal and societal issues (ELSI) are also increasingly encountered by biobanks because of regional differences in cultural and religious beliefs and changing dynamics of societies (Bledsoe, 2017).

2. Biobanking and Brain Banking in Africa

Africa was, hitherto, under-represented in the biobanking revolution with the few available biobanks serving mainly as conduits of samples to the developed countries. (Vaught, 2016) Recent organized biobanking efforts include those of the MalariaGen Network and those reported in the LMIC Biobank and Cohort Network (BCNet) (Mendy et al., 2014; Akinyemi et al., 2018).Although there are no formal reports of organized human brain tissue biorepositories in Africa, there are published reports of previous autopsy studies on brain tissue which were accrued over time but probably not stored away systematically for future

use (Osuntokun et al., 1995, 1994; Jendroska et al., 1994; Ogeng'o et al., 1996). These well – intended early efforts suffered from discontinuity because of the huge challenges of lack of infrastructure, inadequate manpower, paucity of research funding and declining autopsy rates (Abimiku et al., 2017; Cottler et al., 2015). However, given the Human, Heredity and Health in Africa (H3Africa) initiative, biobanking science has been bolstered, regional biobanks are springing up and awareness about biobanks is growing on the continent (Abimiku et al., 2017; Mayne et al., 2017; Schneider et al., 2016). A stroke biobank was recently established in West Africa. It has huge resources including relevant clinical information, neuroimages, blood fractions (serum, plasma, red cell concentrates, buffy coat) and DNA extracts accrued from over 3000 case – control pairs of stroke patients and age, gender and ethnicity matched stroke -free healthy controls (Akinyemi et al., 2018).

3. Ibadan Brain Ageing, Dementia And Neurodegeneration (IBADAN) Brain Bank Project: Raison D'être

3.1. Population ageing and racial disparities

African populations are gradually accruing older people. By the year 2050, 212 million older persons above 60 years of age will be domiciled on the continent in keeping with trends in other LMICs. (Dotchin et al., 2013) Concomitant with this, increased prevalence of ageing – associated disorders of the brain such as stroke and neurodegenerative diseases like Alzheimer's and Parkinson's diseases (PD) is projected (Prince et al., 2013; Akinyemi et al., 2014; Mensah et al., 2015).

In multiracial populations of North America, racial disparities have been reported both in the epidemiology and neuropathology of brain disorders. In a report from the RUSH Study, black subjects were less likely to have Alzheimer pathology as a single dementia pathology compared to white subjects (19.5% vs 42.0%), and more likely to have Alzheimer pathology mixed with an additional pathology (70.7% vs 50.6%), particularly Alzheimer pathology and Lewy bodies, with or without infarcts. Furthermore, black subjects also had more severe arteriolar sclerosis and atherosclerosis (Barnes et al., 2015). The differences described above may explain in part the reasons behind the differential treatment response and outcomes of brain diseases in people of different races/ethnicities. Outcomes of these disorders are often worse in people of African ancestry (Ruland and Gorelick, 2005; Douiri et al., 2013).

Clinicopathological studies are, therefore, critical in shaping our understanding of the aetiology, natural history and mechanisms of diseases and often provide the framework for the discovery of new therapeutic and preventative interventions (Kalaria and Ihara, 2013; Kalaria, 2012; Kalaria et al., 2012). Such approaches led to discoveries in Newcastle, UK in the 1960's that Alzheimer disease (AD) was the most common cause of dementia (Tomlinson et al., 1970) and the cholinergic and vascular basis of cognitive deficits in AD and vascular dementia in the 1970's and 1990's respectively (Akinyemi et al., 2013).

3.2. Lessons from the past

In Africa, seminal clinico – biochemical studies led to the disentanglement of the aetiology of Tropical Ataxic Neuropathy (Osuntokun, 1968; Osuntokun et al., 1968) and the Seasonal

Ataxic Neuropathy (Adamolekun and Ibikunle, 1994; Adamolekun and Ndububa, 1994) providing translational channels that eventually led to the public health interventions that controlled the disorders (Adamolekun, 1995). In the same vein, previous post-mortem studies in the 1990s on neurologically normal Nigerian Africans showed incidental Lewy body pathology burden similar to figures that were then reported from the UK and USA (Jendroska et al., 1994). The significance of this finding was the implication that the similarity of the frequency of PD-related pre-symptomatic neuropathology (and indirectly the risk of PD) in Nigerian Africans and Caucasians in the UK and USA suggested similarity of predisposition to Parkinson's disease, but the low life expectancy of Nigerian Africans explained the lower incidence rates (Akinyemi, 2012). This also implied that as African populations age, the incidence of PD might rise in concomitance. However, in an autopsy survey of 198 brains of Nigerians aged 40 years and above (including 45 patients (23%) who were above 65 years of age) to determine the occurrence of pathological hallmarks of AD, findings showed mild cortical neuronal loss and absence of neurofibrillary tangles, senile plaques and amyloidangiopathy– characteristic pathological features hallmarks of AD (Osuntokun et al., 1995, 1994). Clinically at that time, dementia was considered to be rather rare in Nigerians (Ogunniyi et al., 1992). However, an autopsy study from the Morbid Anatomy Department at the University of Nairobi indicated that AD type of pathology was almost equally present in a collection of brains from older Nairobi dwellers compared to those from the coroner's office in USA (Ogeng'o et al., 1996).

With the ongoing epidemiological transition, the scenario has changed in tandem with the growing burden of cardiovascular risk factors (hypertension, diabetes mellitus and atherosclerosis) and a recent autopsy report of carotid and intracranial atherosclerosis in Ibadan (Nigeria) showed a marked increase in the prevalence of carotid atherosclerosis (Erete et al., 2012) compared to forty years ago (Williams et al., 1975). Although the incidence of AD appears to be declining in western societies, there are no recent correlative neuropathological studies from Africa to examine whether there is a change from the earlier findings of Osuntokun and colleagues three decades earlier (Osuntokun et al., 1995, 1994; Ogeng'o et al., 1996).

3.3. Low autopsy rates

Laboratory-based studies of neurological disease mechanisms and patterns are sparse and hampered in Sub-Saharan Africans (SSA) by lack of relevant skills and infrastructure as well as declining availability of tissue resource due to low autopsy rates. In a study by Oluwasola and colleagues, (Oluwasola et al., 2007, 2009) on the subject of declining autopsies in Nigeria, they explored perspectives of both decedent relatives and medical doctors. Barriers to autopsy acceptance identified included fear of mutilation of the body, religious beliefs, concerns about delays to the funeral, and objections by the patient prior to death. Low educational status with incomplete understanding of the respondents was also associated with refusal to consent to autopsy (Oluwasola et al., 2007, 2009). These findings were in tandem with findings among African Americans in the United States who had low participation rates in brain donation programmes on account of familial objection, concerns about funeral delay, fear of disfigurement, mistrust of the health system as well as issues of religious belief (Lambe et al., 2011). Among clinicians, a waning clinical interest in the

autopsy as a quality control of clinical diagnosis and therapy has also been identified as one of the factors responsible for declining autopsy rates(Kretzschmar, 2009; Oluwasola et al., 2007, 2009). However, greater efforts in community education on the need for postmortems and specifying the need for better understanding of brain, its disorders and public health should increase brain donations.

3.4. Aim of the IBADAN Brain Bank Project

The aim of the IBADAN Brain Bank Project is to explore awareness and willingness to donate brain for research purpose, establish a brain bank and undertake a pilot study to evaluate the profile of ageing – associated degenerative Alzheimer and vascular pathologies in a sample of Nigerian African brains.

3.5. Protocol

3.5.1. Brain tissue collection and selection criteria—Brain tissue will be collected from subjects with consent from the next-of-kin and pre-enrolled consenting donors. Criteria for selection include age (over 40 years of age) and no history of substance abuse (except for alcohol and nicotine use). Subjects who die from significant head injury, received assisted ventilation for more than 24 h or who have a poor agonal status due to other causes are excluded from the collection (White et al., 2018). Antemortem factors that lead to prolonged agonal state include seizure, coma, respiratory illness and hypoglycemia. Such cases that do not meet the clinical diagnostic screening criteria are not used in research cohorts but are retained in the collection as such tissue could be useful for testing protocols and exploring new research topics.

3.5.2. Clinical and laboratory data—A well-structured brain bank is designed to provide high quality material and comprehensive clinical information. Data available on each brain include: demographic, clinical, laboratory, radiological and pathological data, comprehensive overview of lifestyle, neuropsychometric assessment and family history of donor. Additional details such as liver pathology, blood alcohol levels at the point of death, head injury if any are also provided where available.

Data on specimens are stored in a computer database with relevant backups in password - protected external hard drives. Each specimen will be allotted an identification number for confidentiality. Confidentiality of information given by donors is highly essential to avoid ethical misconduct (Martinez et al., 2008). Even though donor and family members have given consent, confidentiality is still important and shall be respected (Igbe and Adebamowo, 2012). Access to information is restricted to core staff of the brain bank. Preservation of confidentiality is a must and a criterion to good practice in tissue banks (Bell et al., 2008). All sensitive data are protected from easy access. The brain bank database is provided with a secure back up in a fully encrypted and password - protected form. Data are coded such that they are not linked to the donor’s person or family. Data set are divided into three basic sets (Nacul et al., 2014) viz:

First set: Comprehensive clinical history including cognitive data accrued from neuropsychological assessments of subjects.

Second set: Autopsy data: clinical details at the time of death, macroscopic brain analysis, documentation of slice and block nomenclature, information from routine neuropathological screening and microscopic analyses of tissue.

Third set: The imaging dataset containing digital images of the whole and slices of the brain from individuals with specific brain disorders as well as disease – free controls. Fixed and frozen sets of brain tissue will have at least four images each.

3.5.3. Brain dissection—At autopsy, the brain weight is determined and digital photographs of the lateral, inferior and superior views of the intact brain are taken. (Nacul et al., 2014) The whole brain is bisected by a sagittal cut. The cerebellar hemisphere and brainstem are removed from each cerebral hemisphere by transversely sectioning the brainstem through the rostral midbrain at the level of the superior colliculi (Sheedy et al., 2008). One set of randomly selected but alternate cerebral hemisphere with its cerebellar hemisphere and brainstem is stored fresh for further molecular studies. The other half is fixed for further histopathological studies. Digital photographs of the dissected hemispheres are taken and further dissection is performed in accordance with the Newcastle Brain Map (Perry and Oakley, 1993; Kalaria, 2016).

3.6. Tissue sampling and processing

The fresh hemisphere is cut in 1 cm coronal sections and photographed. Coronal slices including core frozen samples are frozen using either brass plates or nitrogen vapour and then placed in a -80 °C freezer. Fresh frozen tissue slices will be used for mRNA, protein extraction and PCR techniques, cryo-sectioning for in situ hybridization, immunohistochemistry and cell-based adhesion assays. (Nacul et al., 2014) The other hemisphere is fixed in 10% neutral buffered formalin for four to six weeks. Coronal sections at 1 cm intervals are cut from the fixed brain tissue from the frontal to the occipital pole according to international standards (Bell et al., 2008; Nacul et al., 2014; Sheedy et al., 2008; Perry and Oakley, 1993; Kalaria, 2016; Vonsattel et al., 2008) and digitally photographed before further processing. Diagnostic blocks are taken from 15 regions of interest [frontal (BA46), cingulate (BA32/24), superior temporal (BA41/42), amygdala, anterior hippocampus, posterior hippocampus, striatum, thalamus, posterior parietal lobule (BA39), primary visual cortex (BA17), cerebellar cortex, midbrain, pons, medulla and spinal cord (cervical, thoracic, lumbar levels and dorsal root ganglia) (Perry and Oakley, 1993; Kalaria, 2016). These blocks are appropriately labelled and embedded in paraffin wax. Formalin fixed paraffin embedded (FFPE) blocks of tissue will be stored away for future research. 5 μm sections are taken from each block and stained with haematoxylin and eosin (H & E), luxol fast blue/ cresyl violet (LFB/CV), Congo red, modified Bielschowski and Bodian silver stains. Immunohistochemistry is assessed using the following antibody clones: tau (AT8); β-amyloid (4G8); α-synuclein (Novocastra) and TDP43 (TARDBP Protein Tech Group).

3.6.1. Brain tissue quality parameters—Post-mortem autolysis and putrefaction are affected by the ambient temperature and these in turn may affect brain tissue integrity. The quality of brain tissue is assessed with tissue pH and RNA integrity (Rivka, 2014).

3.6.2. Tissue pH—Brain tissue pH is a marker of brain tissue quality and is an important factor in the interpretation of molecular data (Sheedy et al., 2012). Approximately 3 g of lateral cerebellar hemisphere is taken and frozen at −80° C at the time of brain dissection. Brain tissue pH is measured with a standardized hand-held pH - meter using 1 g of cerebellar tissue homogenized in 10 vol of distilled water at neutral pH. Measurements may also be made from the cortical regions. Tissue pH is a good measure of the impact of pre - mortem conditions on the quality of post - mortem brain tissue. (Monoranu et al., 2009)

3.6.3. RNA integrity—This is a more reliable measure of the integrity of brain tissue than the pH. It is measured as an RNA Integrity Number (RIN) with a cut off value of greater or equal to 6 (range 0–10) considered optimal. RNA integrity is determined with the Agilent 2100 Bioanalyzer© (Agilent Technologies) following sample preparation using the Agilent RNA 6000 Nano Kits (Agilent Technologies, Santa Clara, CA). (White et al., 2018)

3.6.4. Histological assessment of autolytic change of cerebellar cell layer—The cerebellar cell layer is assessed microscopically to determine the degree of autolytic degradation by the experienced neuropathologists involved in the study. (Sheedy et al., 2012) This is an important consideration as the high ambient temperatures of Nigeria can introduce additional factors in the preservation and evaluation of the brain tissues. Post mortem delay and quick processing of the brain tissue are factors important to the integrity of the tissue. Therefore, human brain tissues with a postmortem interval ≤ 24 h are best for the brain bank.

3.6.5. Safety issues—All tissues are handled with “Universal Precautions” regardless of the infectious status. While tissues are tested for several pathogens, there is always the chance that new or evolving pathogens/prions could be present and potentially infectious. Thus all human tissues and body fluids are always handled as if they are potentially infectious. Laboratory safety rules will also be observed when handling or disposing tissues using ethically approved procedures. All instruments used for the dissection of brain tissue will be routinely cleaned with 70% ethanol and dried.

3.6.6. General and ethical oversight—An IBADAN Brain Bank Steering Group has been formed consisting of the key investigators, leaders in neurology, pathology, bioethics, anthropology, medical sociology, local ethics committee chair, religious leaders, community leaders and patient advocacy group leaders. The group will meet every 6 months to oversee project developments, and to deliberate on requests from researchers for tissue provision. The success of the project will be judged on the number of patients and controls recruited from regular hospital autopsy and brain donor program, number of donations, quality of post-mortem tissues, number of research projects supplied with tissue, number and quality of publications and communications resulting from such research, and feedback from users and researchers as to the level of service from the IBADAN Brain Bank.

4. Implications

Tissue from brain banks facilitates clinicopathological studies and cutting edge basic brain research that can contribute meaningfully to the elucidation of neurobiology and mechanisms of neurological and psychiatric disorders. To the best of our knowledge, the

IBADAN Brain Bank will be the first organized brain bank in Africa. Brain banks also provide a platform for comparison between a diseased tissue and a normal tissue. (Bell et al., 2008) The brain bank will enable researchers undertake indepth study of brain disorders, particularly in subjects who have been studied longitudinally in life and have detailed clinical information which can be correlated with post -mortem neuropathological data. Datasets in cases are compared with data from healthy disease – free control subjects (Waldvogel et al., 2008). Collection of brain tissue from normal, age, gender and ethnicity-matched disease – free controls requires very robust public engagement and brain donation programmes using acceptable and culturally appropriate approaches. The brain bank is particularly important for the study of conditions for which suitable animal models are lacking or inappropriate (Nacul et al., 2014). Although clinical investigations and neuroimaging, transgenic animal models, have contributed significantly to the understanding of central nervous system (CNS) disorders, it is important to note that none of these approaches renders post – mortem studies needless especially in the face of ever changing research techniques (Nacul et al., 2014; Waldvogel et al., 2008).

Brain banks will ensure progress of neuroscience research. The availability of samples for research will provide teaching material for students, improve framework for discovering new diagnostic biomarkers and treatments, and enhance generation of research data for policy formulation. A brain bank with tissue from indigenous Africans, in particular, will facilitate the exploration of racial differences in the mechanisms and phenotypic expression of brain disorders with implications for appropriate control measures.

Reports from literature have already established that post mortem donation is in a decline. (Oluwasola et al., 2007, 2009; Mahdavi-Mazdeh et al., 2013) Solutions proposed from previous studies include refining the approach (Lambe et al., 2011), implementing awareness and sensitization programmes to bridge the knowledge gap in terms of the benefits of brain donation (Lambe et al., 2011; Mahdavi-Mazdeh et al., 2013),excellent communication and management of various aspect of the donation driveMahdavi-Mazdeh et al., 2013), and establishing a local donor systems. (Rivka, 2014) It is also essential to explore the barriers and facilitators unique to the African culture, language and belief systems as well as the ethical, legal and societal implications of the use of post-mortem brain tissue.

Determinants of the size and regions of the brain tissue stored are subject to change so as to meet the everchanging demands of research as the needs arise. Similarly, protocols are being harmonized across networks of brain banks such that researchers can source for samples from more than one bank with similar approaches, and assurance of tissue quality. (Palmer-Aronsten et al., 2016; Rivka, 2014)As the brain bank grows, subdivisions within the brain bank focusing on specific disorders can also be established within the main bank (de Oliveira et al., 2012; Grinberg et al., 2007).The IBADAN Brain Bank Project will partner with other brain banks in other LMICs and HICs to learn from their wealth of experience and synergize in unravelling the unique characteristics inherent in the African brain. Established collaborations will be complementary and resources, personnel and other resources will be judiciously and sustainably utilized. In order to meet the immediate infrastructural needs of the IBADAN Brain Bank, the project is collaborating with the

Department of Pathology and existing projects in the University of Ibadan and the University College Hospital Ibadan that have already acquired relevant biobanking infrastructure. Principally, the project collaborates with the SIREN Study that has already acquired at least four -80 °C freezers, solar powered inverter systems for continuous power supply, freezerworks laboratory information management systems, REDCap database for clinical data and standard operating procedures for its processes. (Akinyemi et al., 2018)

In terms of sustainability, following the seed fund from the University of Ibadan, the investigators are already applying for follow up grants (local and international). The project also enjoys the full support of the administrative leadership of the College Research and Innovation Management as well as developing mutually beneficial partnerships with sister projects in the University of Ibadan while carrying along the Nigerian government through her Federal Ministry of Health.

5. Conclusions

The Ibadan Brain Ageing, Dementia And Neurodegeneration (IBADAN) Brain Bank, the first organized brain tissue biorepository in sub - Saharan Africa, is established to accrue, process and store unique African neural tissue resources for future research into a broad spectrum of neurological and psychiatric disorders with potential unique discoveries and research breakthroughs that will benefit people of African ancestry and other ancestral populations (Rotimi et al., 2016).

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