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Psychiatric Brain Banking: Three Perspectives on Current Trends and Future Directions

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Abstract

Introduction—The study of postmortem human brain tissue is central to the advancement of the neurobiological studies of psychiatric illness, particularly for the study of brain-specific isoforms and molecules.

Methods—The state-of-the-art methods and recommendations for maintaining a successful brain bank for psychiatric disorders are discussed, using the convergence of viewpoints from three brain collections, the National Institute of Mental Health Brain Collection (NIMH), the Harvard Brain Tissue Resource Center (HBTRC), and the Mt. Sinai School of Medicine Brain Bank (MSSM-BB), with diverse research interests and divergent approaches to tissue acquisition.

Results—While the NIMH obtains donations from medical examiners for its collection, and places particular emphasis on clinical diagnosis, toxicology, and building lifespan control cohorts, the HBTRC is uniquely designed as a repository whose sole purpose is to collect large-volume, high quality brain tissue from community-based donors based on relationships across an expansive nationwide network, and places emphasis on the accessibility of its bank in disseminating tissue and related data to research groups worldwide. The MSSM-BB collection has shown that, with dedication, prospective recruitment is a successful approach to tissue donation, and places particular emphasis on rigorous clinical diagnosis through antemortem contact with donors. The MSSM-BB places great importance on stereological tissue sampling methods for neuroanatomical studies, and frozen tissue sampling approaches that enable multiple assessments (RNA, DNA, protein, enzyme activity, binding, etc.) of the same tissue block. Promising scientific approaches for elucidating the molecular and cellular pathways in brain that may contribute to schizophrenia and/or bipolar disorder, such as cell culture techniques and microarray-based gene expression and genotyping studies are briefly discussed.

Conclusions—Despite unique perspectives from three established brain collections, there is a consensus that (1) diverse strategies for tissue acquisition, (2) rigor in tissue and diagnostic characterization, (3) the importance of sample accessibility, and (4) continual application of innovative scientific approaches to the study of brain tissue are all integral to the success and future of psychiatric brain banking. The future of neuropsychiatric research depends upon in the

availability of high quality brain specimens from large numbers of subjects, including non-psychiatric controls.

INTRODUCTION

Postmortem investigation of psychiatric and neurological illnesses using human brain tissue is a well-established approach for elucidating the molecular pathways that may contribute to disease, and offers a singular avenue for exploring brain-specific isoforms and molecules not permitted by *in vivo* studies. Postmortem studies in schizophrenia and mood disorders have led to an improved understanding of the structural and molecular neuropathology of these complex psychiatric diseases (Schmitt et al 2008), paving the way in more recent years toward the discovery of a number of candidate susceptibility genes and pathways that may play a contributory role for these illnesses (Dean et al 2009; Mirnics et al 2006). As new molecules and pathways are uncovered, new approaches for diagnosis and treatment may be forthcoming. Since neuropsychiatric illnesses are self-defined as disorders of the central nervous system, there is no substitute for brain tissue analyses for the ultimate understanding of their pathogenesis.

Postmortem neuropsychiatric brain research has shifted from using postmortem samples primarily for case-control comparisons, to increasingly complex uses such as transcript characterization and the neurobiological effects of allelic variations in disorder-associated susceptibility genes. With the advent and application of genome-wide association studies, copy number variation (CNV) measurements, and other high through-put molecular genetics techniques to the study of psychiatric disease (Williams et al 2009), the field of postmortem molecular genetics has evolved considerably over the past several years. As a result, researchers utilizing brain tissue are being held to a much higher standard with regard to sample sizes and clinical characterization. Moreover, a wide range of scientific approaches are now being employed for the study of this tissue, ranging from DNA to RNA and on to proteins.

Developing a steady source of well-characterized brain tissue donations has been a major barrier for postmortem brain studies of schizophrenia. While “living donor” or prospective recruitment has been effective in some tissue banks, and has gained momentum recently in some countries (Sheedy et al 2008), recruitment through autopsy centers remains one of the most common sources of tissue donation. Yet, with the worldwide autopsy rates declining (Xiao et al 2009), an increasing demand for samples as seen by some brain banks (Dedova et al 2009), and an apparent shortage of healthy control tissue for case-control studies (Bell et al 2008), alternate approaches to collecting tissue need to be explored in order to preserve this important resource. Furthermore, collection of brain tissue clearly requires a long-term investment, not only financial (with published cost estimates of \$10,000–\$30,000 US dollars, 10,000 – 15,000 Euros for the BrainNet Europe Consortium, or \$15,000 Australia dollars per case (Dedova et al 2009; Hulette 2003; Kretschmar 2009)), but also a considerable time-investment to establish methods, build up a supply of well-characterized specimens, optimize long-term tissue storage to take advantage of evolving analytical methods, evaluate tissue requests, disseminate tissue, and maintain data collection.

The relative successes and longevity of established brain banks throughout the world at securing larger, non-aged sample sizes for postmortem study of schizophrenia and bipolar disorder have led to a shift in the field whereby larger sample sizes are becoming increasingly common. While previous studies with sample sizes of 20 or less per cell in case-control studies were acceptable just a decade ago (e.g., (Holt et al 1999; Karson et al 1999)), studies in the past few years reported an average of more than double those numbers for controls, with two recent papers on postmortem control samples in the hundreds recently

being published (Myers et al 2007; Nakata et al 2009), with similar increases in postmortem psychiatric samples (Sartorius et al 2008; Uriguen et al 2009). Thus, the demand for well-characterized postmortem human brain tissue already exceeds the supply, and this imbalance is bound to worsen without a renewed and reinvigorated investment in tissue acquisition.

Rather than reiterate what many researchers have previously described as the potential pitfalls, as well as the considerable advantages, to the collection and study of postmortem human tissue, we instead provide three unique perspectives on the current practices in psychiatric brain banking from the NIMH Brain Collection (NIMH), the Harvard Brain Tissue Resource Center (HBTRC), and the Mt. Sinai School of Medicine Alzheimer's Disease and Schizophrenia Brain Bank (MSSM-BB), as well as their recommendations for the immediate future of psychiatric brain banking.

The NIMH Brain Collection Perspective – Current Practices

Tissue Acquisition

The NIMH Brain Tissue Collection was founded by Dr. Joel E. Kleinman in 1977, and currently maintains approximately 1,026 brain tissue samples (generally acquired from 1992-present; with previously acquired tissue depleted or discarded). The NIMH Brain Tissue Collection is funded by the NIMH Intramural Research Program, and is maintained by the Section on Neuropathology in the Clinical Brain Disorders Branch, NIMH. Cases are collected from the Offices of the Chief Medical Examiner of Northern Virginia and of the District of Columbia, and consent is obtained and audiotaped with the legal next-of-kin at the time of autopsy. Usually, 25–30% of families approached are likely to consent to tissue donation, which results in approximately 67 cases donated annually.

The NIMH Brain Tissue Collection contains over 150 cases with a DSM-IV diagnosis of schizophrenia, 226 adult controls (non-psychiatric, non-substance abuse), 50 cases with bipolar disorder, and 107 cases with major depression (data from 1992-present; see Table 1). Cases donated to NIMH are on average 43 years old at time of death, with an average postmortem interval (PMI) of 34 hours, and are roughly 48% Caucasian and 48% African-American. NIMH cases include suicides (22%), but the majority died by natural causes (49%), and in general, comorbid substance abuse is high (34%). Although the NIMH Brain Tissue Collection was not designed as a “core facility” whose primary focus is to dispense tissue, and the Section on Neuropathology conducts many diverse research studies using this tissue, the NIMH tissue is used by many other NIH institutes (e.g., NIA, NIAAA, NICHD, NIDA, NIDCR, and NINDS) as well as by numerous outside research groups worldwide (e.g., Allen Institute for Brain Science, Oxford University, University of Alabama at Birmingham, University of Miami, Yale University).

At NIMH, as with any brain bank, the importance of brain pH, neuropathological examination, postmortem interval, agonal state, and freezer storage methods cannot be overlooked as absolutely critical to ensuring quality postmortem tissue samples for every incoming case, but these tissue characteristics have been previously well-described (Durrenberger et al 2010; Harrison et al 1995; Tomita et al 2004) and tissue processing protocols have been published (Vonsattel et al 2008). Our own work and that of others have demonstrated that RNA integrity (RIN) may be one of the single most important indicators of tissue quality and hence gene expression in postmortem human brain (Lipska et al 2006; Stan et al 2006; Webster 2006). Thus, all incoming cases are screened region by region for RIN to determine their viability for studies.

Clinical Characterization

The reliability of psychiatric diagnoses for subjects is an absolute necessity in postmortem research. However, the diagnosis of subjects retrospectively, particularly those collected through medical examiners without antemortem study contact, has been an ongoing challenge. A detailed screening questionnaire at the time of donation has proven to be a valuable resource in the initial characterization process at NIMH, and often gives important information about other potential sources of clinical information. The team at NIMH, along with many other banks collecting tissue through medical examiners, has shown that acquisition of clinical information from multiple sources is the best way to accurately make/confirm postmortem diagnoses. These data sources include psychological autopsy interviews with family informants, interviews with treating professionals, semi-structured diagnostic assessment tools such as the SCID, medical examiner information, review of psychiatric records, and/or use of a semi-structured tool such as the DIBS or DEAD to review available clinical histories. Efforts must also be made to demonstrate both inter-rater reliability and ante-mortem and postmortem agreement for psychiatric diagnoses determined retrospectively (Deep-Soboslay et al 2005; Kelly and Mann 1996; Sundqvist et al 2008). Moreover, this process must be initiated quickly after brain donation in order to optimize the amount of information available for review.

The NIMH Brain Collection Perspective – Future Directions

Directed Toxicology Testing

One area that has received relatively little attention as part of the clinical screening and postmortem psychiatric diagnostic process is adequate toxicology testing. While reporting medical examiner toxicology results in postmortem studies has been routine, little attention has been paid to the limitations of these data, particularly when studying cases as “medication-free” vs. “on medication at time of death”. Upon review of medical examiner toxicology reports, (which are generally conducted for the purpose of ruling on cause of death), for 130 NIMH postmortem cases with schizophrenia, we recently found that while 88% of cases had toxicology screenings as part of their autopsy, just 18 cases (13.8%) were positive for antipsychotic medication. In contrast, when additional “directed toxicology testing” was conducted (i.e., supplemental toxicology testing “directed by” extensive case history reviews of last known prescribed medications in psychiatric records, medical examiner documents, and family interviews), through National Medical Services (NMS Labs, Inc., www.nmslabs.com), an astounding 68% of cases were positive for antipsychotic medication (See Supplemental Figure 1; see also preliminary data in (Deep-Soboslay 2007)).

The reason for such discrepancies in reported rates of acute antipsychotic use at time of death is simple to understand. First, the purpose of medical examiner toxicology is to determine cause of death, and in the absence of obvious overdose or known illicit drugs of abuse, screening for antipsychotic medication is irrelevant to their purposes. Second, the cost is prohibitive for medical examiners to screen for every possible psychiatric medication in the absence of a known history of a person taking such medication, particularly drugs such as Risperidone, Olanzapine, or Aripiprazole which may not be part of routine assays, and for which detection can be problematic in certain tissues. Third, even if an individual was known to be prescribed such medications, forensic toxicology laboratories may set detection limits to toxic or lethal levels, thereby leading to false negative reports of antipsychotics at therapeutic or sub-therapeutic levels.

Directed toxicology testing may be impractical for some established brain banks whose funding is limited, as average costs range from around \$250–500 per case in blood, and can be more depending on the matrix used and the number of medications tested. However,

going forward, brain banks must now be more cautious when labeling cases as “medication-free” or “antipsychotic-negative” based on medical examiner data alone. In brain banks where no toxicology data is available, this testing may be even more crucial. Since antipsychotic treatments have long been viewed as a major confound to postmortem brain research in psychosis, and since gene expression studies may necessitate data on acute antipsychotic use, directed toxicology testing is recommended. Furthermore, this testing often covers quantitation of postmortem levels of nicotine and cotinine, in turn providing valuable data on smoking in schizophrenia. In a similar manner, healthy control subjects must also be screened extensively for illicit drug use when not done so during the donation process, as the NIMH has found that approximately 10% of its potential control subjects are found to be positive for acute use of illicit drugs such as marijuana or cocaine that were not previously screened at autopsy.

Lifespan Cohort

Looking to the future of psychiatric brain banking, one of the primary goals set forth by the NIMH Brain Collection will be to increase the number of available control samples, with particular emphasis on child/adolescent control cases, so as to permit the study of large cohorts of non-psychiatric control subjects to explore candidate genes of interest that have been previously identified *in vivo* in psychosis. Recently, Myers and colleagues carried out whole-genome genotyping and expression analysis by pooling tissue of 193 “neuropathologically normal” human brain samples (≥ 65 years old) gathered from several Alzheimer's brain banks, demonstrating that understanding normal gene expression will become an increasingly important avenue for understanding the cellular mechanisms of psychiatric illness (Myers et al 2007). At NIMH, a study of a large healthy control “lifespan cohort”, comprised of 39 fetal samples, and 207 controls from birth to age 80 is currently underway, in an effort to assess normal gene expression across the pre-natal and post-natal lifespan, as well as to examine differences in age, sex, race, and single nucleotide polymorphisms (SNPs) (Huffaker et al 2009; Nakata et al 2009). Going forward, NIMH intends to focus resources on expanding its lifespan control collection.

SNP Database

Another integral advancement in psychiatric brain banking will be the use of web-interactive databases for exploring data, as has already been implemented with banks such as the Stanley Foundation (Kim and Webster 2009). The NIMH Brain Collection has internally launched its Genome Web Browser, a user-interactive SNP database used by investigators for exploratory analysis of data from microarray gene expression and genotyping analyses in its lifespan cohort. This user-interactive database will soon hold data on psychiatric cases too, and will become accessible to outside collaborators, and in the future, will be launched for eventual public use. As public genomic databases become more commonplace, this will no doubt soon become a necessary component to brain banking collections.

Cell Culture

While numerous scientific approaches and techniques have been and continue to be applied to the NIMH Brain Collection over the last several decades, study of postmortem tissue necessitates continual application of novel techniques. One interesting approach currently underway is the application of cell tissue culture to postmortem human scalp samples collected at autopsy. Even though the knowledge that cells could be cultured from postmortem tissue was discovered more than 40 years ago, it has only been in the last two decades that an accelerated interest in culturing cells from autopsy materials has occurred (Macpherson et al 1985; Okumura 1993; Pellett et al 1984). Of specific interest to psychiatric research, cultured fibroblasts from human postmortem tissue have been used to

study complex neurological diseases such Alzheimer's disease (Huang et al 1994), and schizophrenia (Mahadik and Mukherjee 1996; Wang et al 2010).

At NIMH, hair samples are collected as part of the brain tissue donation for segmental hair toxicological analysis. In the last year, NIMH has begun culturing postmortem fibroblasts from fresh scalp tissue, and has successfully grown cells in cases with a PMI of under 48 hours, regardless of age, sex, diagnosis, or ethnicity. To date, we have collected 65 scalp samples from which 66% have produced healthy fibroblasts, including cases with schizophrenia, depression, bipolar disorder, and non-psychiatric controls (See Supplemental Figure 2).

While challenges exist in creating viable postmortem cell culture libraries, such as confounds of infection and cell senescence, cell culturing offers a promising avenue for studying the underlying genetic architecture of psychiatric disorders. One of the most exciting new techniques is the ability to create induced pluripotent stem cells (iPS) from cultured fibroblasts (Takahashi et al 2007). Although not identical to embryonic stem cells, the characteristics of iPS cells are similar enough that these cells may be used for developmental studies, including the epigenetics and gene expression of differentiation. IPS cells, once created, can also be re-differentiated into other various cell types, such as neurons. Neurons created from iPS cells have been used to study the mechanisms of spinal muscular atrophy and amyotrophic lateral sclerosis (Dimos et al 2008; Ebert et al 2009), and are currently being applied to better understand Alzheimer's disease and schizophrenia as well.

Using postmortem tissue for iPS cell creation offers a unique advantage in that gene expression profiles and epigenetic properties of any neurons derived from iPS cells can be compared to those in the postmortem tissue of the corresponding subject, and allows for further validation of the accuracy of iPS-derived neurons, and also creates a way to study in vivo the postmortem abnormalities observed in vitro. Furthermore, this application of a new methodology capitalizes on an existing postmortem tissue resource currently being under-utilized.

The Harvard Brain Tissue Resource Center Perspective – Current Practices

Tissue Acquisition

The Harvard Brain Tissue Resource Center (HBTRC) was founded by Dr. Edward Bird in 1978 and to date, has collected postmortem brain tissue from over 8,000 individuals throughout the U.S. The HBTRC is uniquely designed, not as a research organization, but as an NIH-supported national brain tissue resource that accepts community-based donations nationwide via both pre-registered (i.e., prospective recruitment) and previously unregistered interested donors. While the HBTRC has both types of donation, pre-registration generally results in a low yield for psychiatric cases, and is more successful in neurological disorders with a high and somewhat predictable mortality rate. All psychiatric donations originate from telephone calls initiated by the family when death is imminent or immediately after the donor has been pronounced.

The HBTRC averages about 300 donations per year, a total that includes neurodegenerative disorders (Alzheimer's disease, Parkinson's disease, Huntington's disease, frontotemporal dementias), psychotic disorders, and non-neuropsychiatric controls (40–50 per year to accommodate age-matching for a variety of disorders across the lifespan—e.g., the neurodegenerative disorders have an average age at death of approximately 73 years, while for schizophrenia and bipolar disorder, it is 60 years). The HBTRC also serves as a

repository for autism and Tourette's cases, although these belong to private foundations with scientific and/or tissue advisory boards.

As a result of its unique method of tissue acquisition, the incidence of illicit substance abuse in HBTRC donations is quite low, even in the psychiatric cases (10%). About 70% of donations come from New England and the Mid-West, while the rest come from the south and west (i.e., Texas and California). The vast majority of HBTRC cases (approximately 95%) are Caucasian, while the remaining cases are either Asian or Hispanic in origin.

Residing at a world-renowned academic center, the Harvard Brain Bank has instant name recognition both nationally and internationally. Moreover, its reputation for academic excellence, especially in the field of medicine, extends an extraordinary cachet to this brain bank. The HBTRC has also cultivated an ongoing relationship with a variety of patient advocacy groups, including the National Alliance for the Mentally Ill (NAMI), the Tourette's Syndrome Association (TSA) and the Autism Tissue Program of Autism Speaks.

The majority (90%) of normal control specimens are obtained through the New England Organ Bank, the principle organ procurement organization (OPO) in the New England area. The NEOB receives referrals from families and hospitals through that region, but is only able to refer cases that are not on a respirator, as these are considered optimal for organ transplantation purposes. The staff at the NEOB screen all the cases by conducting a telephone interview with the legal next of kin (LNOK). This includes information regarding medical history, medications taken at the time of death, substance abuse and the presence of mental illness. The NEOB performs serological testing for hepatitis B and C, AIDS and Creutzfeldt Jakob Disease, information which becomes part of the HBTRC records for the respective cases.

Tissue Characterization

Digital images of each brain as it appears when it arrives and after it has been cut coronally are available on a User Interactive Website that is made available to investigators who have been approved for tissue disbursement. A standard set of blocks are removed from the formalin-fixed hemisphere, imbedded in paraffin, sectioned at 6 μ m and stained with hematoxylin-Luxol fast blue and the Bielchowsky method. Every case receives a complete neuropathological examination that includes detailed gross and microscopic information that is used to confirm the diagnoses of neurodegenerative disorders. In the case of normal controls and psychiatric cases, the neuropathological assessment is used to rule out the presence of inflammation, infection, infarction, trauma or tumors that could interfere with their use in scientific protocols.

Accessibility

In order to achieve the mission of the HBTRC, which is “to assist the neuroscience community in discovering the causes of debilitating diseases of the central nervous system and in developing novel and more effective strategies for treating them”, the HBTRC must maintain a large volume of specimens (2,000 – 3,000) at any given time to promote constant tissue disbursement. However, to make these specimens easily accessible, the HBTRC has found it absolutely necessary to adopt entirely web-based applications to manage tissue requests, demographic data, and gene expression data.

Tissue Disbursement

First, to facilitate prompt review of tissue requests, they are submitted through the HBTRC website (www.brainbank.mclean.org). Investigators worldwide must submit an application indicating what diagnoses, regions and tissue preparations they would like to request, must

describe the nature of the project, and provide a biosketch. The HBTRC then evaluates the timeliness of the project, the productivity of the investigator, and the availability of appropriate federal funding and other resources that will be used to undertake the project. Any research conducted by staff affiliated with HBTRC must make application for tissue to include scientific rationale, diagnoses, regions, and tissue preparation requested, just as any outside investigator must do. Generally, tissue requests are processed in less than one month, but review times may vary depending on the volume of requests in a given week.

User-Interactive Website

In addition to its use of the internet as a portal for tissue disbursement requests, the HBTRC also offers its approved investigators a User-Interactive Website to cover all donated cases, containing detailed information such as final distributive diagnoses, demographic data, neuropathological reports, and photomicrographs of the brains and histological sections (Haroutunian and Pickett 2007). The web-based access to this information greatly enhances the use of tissue from this source, as it allows investigators to factor demographic and neuropathological parameters into their research, especially their statistical analyses. By maintaining a web-based application, data requests and back-and-forth between HBTRC and approved investigators is greatly reduced, and information sharing is immediate.

Gene Expression and SNP Database

Most recently, in April 2004, the HBTRC launched the National Brain Databank (NBD), a public repository for depositing data obtained from postmortem tissues obtained through this facility (http://national_databank.mclean.org/brainbank/ApproveUser). It currently contains microarray-based gene expression profiling from the hippocampus, dorsolateral prefrontal cortex and anterior cingulate cortex from cohorts of normal controls, schizophrenia and bipolar disorder matched for age, PMI, hemisphere, sex and, to the extent possible, cause of death. There is also a Parkinson's 20 cohort consisting of gene expression profile (GEP) results from dopamine neurons of the substantia nigra obtained using laser microdissection. Most recently, the HBTRC has begun depositing data from a cohort consisting of approximately 850 cases of normal controls, Alzheimer's disease and Huntington's chorea that were processed by the Merck Corporation and its one-time affiliate Rosetta. This dataset consists of both GEP and SNPs from three different regions (i.e. the dorsolateral prefrontal cortex, inferior parietal area and cerebellum) for each case. The data deposited in the NBD are available to the public, with two levels of access. The first is the "guest" privilege that is available to the general public. Demographic and medical information is not available to "guests" using the NBD. The second level is that of "investigator". To be granted "investigator" privileges, a copy of the principal investigators NIH Biosketch must be submitted, and must demonstrate that the candidate has had experience with clinical research and understands the importance of abiding by HIPAA regulations.

The confidentiality of the donor and the donor's family is a critical issue and it has been necessary to anonymize the data to the extent possible. This includes using a special set of numbers that are distinct from the "B" numbers generally given by the HBTRC to each case. Additionally, the age is rounded off to the nearest decade, while the PMI is rounded off to the nearest 10 hrs. The microarray data obtained from NBD has already given rise to studies that have been published in peer-reviewed reports. Genotyping data will require even greater effort to protect the identity of the donors. One approach is to permanently anonymize the cases. The limitation of this approach, however, is that the GEP and SNP data cannot be related to other forms of data obtained from the same cases. A second approach to protecting confidentiality of genotyping data is to eliminate certain variables such as hemispheric laterality, cause of death and possibly even PMI.

The HBTRC – Future Directions

Tissue Accessibility

Accessibility to the valuable resource generated through brain collections is of utmost importance to the future of brain banking. The HBTRC's use of the internet for a three-tiered web-based database application facilitates its ability to disseminate tissue and associated data in a streamlined process. Specifically, the use of a straightforward, web-based approach for requesting tissue expedites this process, and has been advantageous to the HBTRC. Despite potentially limited resources for other brain collections, most banks likely have some form of databasing already in place, and could realistically develop a web-based application for tissue requests and reviews to simplify this process for collaborators. Secondly, granting investigators real-time access to demographic, clinical and neuropathological data via the internet, while not a simple task given confidentiality concerns, firewall issues and the like, is a second step that other brain banks need to consider going forward. Lastly, increased accessibility to gene expression profiles and SNP databases will further promote research on psychiatric disease and countless other disorders, and should be explored by other brain banks to the extent possible in the near future.

With a world-renowned reputation and a longstanding track record in psychiatric and neurological brain banking, the HBTRC emphasizes maintaining relationships with the national community as well as continued accessibility to tissue resources as integral to the future of brain research.

The Mt. Sinai School of Medicine Alzheimer's Disease and Schizophrenia Brain Bank Perspective – Current Practices

Tissue Acquisition

The Mount Sinai Department of Psychiatry received its first donation in November of 1986 and as of this writing has banked brain and other biological specimens from 1,589 donors. This brain bank is dedicated to supporting specific studies in aging, dementia and major mental illnesses. The specifically supported studies are those associated with the Mount Sinai CONTE center on White Matter Abnormalities in Schizophrenia (MH066392), Alzheimer's Disease Research Center (AG-02219), Clinical and Biological Studies of Early Alzheimer's Disease (AG-02219) and the JJ Peters VA Medical Center's Mental Illness Research and Education Clinical Center (MIRECC). Through these projects and programs, the Mount Sinai Alzheimer's Disease and Schizophrenia Brain Bank (MSSM-BB) distributes brain tissue specimens to participating laboratories within these programs and to investigators worldwide who collaborate with these research programs.

The overarching emphasis of the MSSM-BB is on high quality objective phenotypic and postmortem characterization of the specimens that are banked. Thus, every effort is made to accept donations from persons who have participated in antemortem diagnostic and neuropsychological evaluation protocols, including controls. Specifically, when subjects are recruited for antemortem studies, and at each subsequent assessment interval, they are informed that postmortem examination of the brain and clinico-pathological correlative study is among the primary goals of the research project. Of course subjects are free to opt in or out of the postmortem donation program at any time. Caregivers, whether family members or institutional representatives, are requested to contact the brain bank upon a subject's hospitalization or death. Research personnel are on-call through a manned "hot-line" telephone system at all times to either accept postmortem consent for donation from the next of kin, discuss the donation procedures and related questions and issues, or in case

of medically ill and hospitalized subjects, to be alerted to their health status. Although percentages vary from year to year, the 5 year average of pre-accessed donors is 62%.

Clinical Characterization

At MSSM-BB, emphasis is placed on donations that are free of potentially confounding factors such as dependence of alcohol and illicit substances, ambiguous or violent circumstances of death, and neurological or neuropsychiatric comorbidities. Of course not all comorbidities are apparent at the time of donation and antemortem diagnoses are not always consistent with neuropathological findings. Therefore, all donations that are accepted by the MSSM-BB undergo detailed structured neuropathological characterization and study with quantitation of neuropathologic lesions (e.g., neuritic plaques and neurofibrillary tangles, number, size, location of vascular lesions) so that distributions for research can match the intended study hypotheses/objectives as closely as possible and preclude the use of specimens with undetected comorbidities. Because postmortem neurobiology represents in part a snapshot of the biological state at the time of death, even when subjects have been directly assessed and diagnosed antemortem, the interval between the last assessment and death is a critical period. Potential changes in the neurological, cognitive and psychiatric status of donors is assessed with extensive structured reviews of medical records and semi-structured interviews of informants who have 10 hours/week or more contact with the deceased. The importance of detailed and accurate phenotyping of donors cannot be overemphasized. This is especially true for cases classified as controls, since unlike some neurological diseases like Alzheimer's or Parkinson's disease, the absence of discernable neuropathology does not indicate the absence of psychopathology (Purohit et al 1998). Similarly, multiple studies have shown that agonal events and states such as coma, hypoxia and seizures can significantly affect the integrity of cells, RNA and proteins. Thus, in addition to proxy measures such as tissue pH and measures of RNA integrity, medical record review documents the severity and duration of agonal states and events.

The MSSM-BB Perspective – Future Directions

Anticipating Brain Banking Trends

Technical and conceptual advances in neurobiology have grown exponentially during the past few decades. Given the relatively slow rate of accrual of specimens by brain banks, banks must anticipate the needs that will arise in the years to come and collect, process, and store brain specimens to accommodate those yet to be determined needs, techniques, and concepts. This is, of course, an impossible task. However, some needs are invariant and some trends evident. For example, the study of gene expression is likely to continue for years to come and the use of recently developed techniques such as laser capture microscopy are likely to become more and more common. Accommodating these approaches requires a greater emphasis on aseptic techniques and better approaches to tissue preservation than those that were required previously. Similarly, neuroanatomic study approaches have become increasingly quantitative with strong emphasis on stereologic sampling techniques. Brain bank tissue dissection and sampling techniques must be adapted to accommodate these increasingly sophisticated and quantitative approaches (Perl et al 2000).

Expansion of Brain Tissue Resources

As described above, postmortem brain tissue from well-characterized donors is a scarce commodity and brain banks cannot afford to distribute whole tissue blocks for all meritorious study requests when the proposed studies require widely requested tissue needs. For example, as described above, requests for brain specimens to accommodate DNA-based studies of single nucleotide polymorphisms or copy number variants, or methylation/acetylation status are exploding. Distributing whole brain tissue blocks for each such study

can deplete banked tissues faster than they can be replenished. Brain banks may need to expand their mission by isolating and banking tissue derivatives such as DNA, RNA, and protein that can be multiply aliquoted, and stereological section series that can be separately distributed to maximize the utilization of each specimen banked. Such an expansion of mission away from traditional brain banking approaches will allow each specimen to serve many different important studies. However, this same expansion of mission will place significant financial burdens on programs that are already being forced to do more with significantly less and require “re-tooling” by the banks not only with respect to capital resources, but also technical and intellectual expertise.

The MSSM-BB demonstrates success in prospectively following and recruiting brain donations for which ample antemortem data are readily accessible. As a result, the MSSM-BB can focus extreme rigor in the area of clinical characterization on every case. Going forward, the MSSM-BB anticipates the need for increasing adaptability in how tissue is stored, preserved, dissected, and prepared for study. Brain banks may need to consider creating aliquot “banks” of DNA, RNA, protein and other derivatives, such as pre-sectioned and slide-mounted specimens in order to adapt to the increasing demand for larger sample sizes and more numerous and varied tissue requests.

DISCUSSION

NIMH, HBTRC, and MSSM offer three different approaches towards the acquisition of brain tissue for neuropsychiatric research, each demonstrating the relative successes of three very different methods for tissue acquisition, i.e., “unregistered” donations at autopsy, nationwide networking (both pre- registered and unregistered), and primarily prospective, pre- registered collection, respectively. The three tissue acquisition methods yield somewhat different samples with respect to demographics. For example, NIMH has the advantage of younger cases, but tends to have longer postmortem intervals, an increased incidence of suicide and substance abuse in its psychiatric cases, and possibly more severely ill cases given sampling from medical examiners. The HBTRC may be the most renowned and prolific bank worldwide, acquiring up to 300 cases annually. The incidence of substance abuse in the collection is quite low, many of its psychiatric cases die via natural causes (thus, it may sample less severe forms of schizophrenia and bipolar disorder, i.e., outpatients and/or those with family support who initiate brain donation); however, the HBTRC may tend towards slightly older cases. MSSM-BB has the obvious strength of being able to psychiatrically and neuropsychologically assess the majority of donors while living, which removes the confounds of retrospective clinical diagnosis; however, pre-registered donation is extremely labor-intensive with regards to tracking donors, and its yield is directly proportional to funding support and can therefore be lower than other donation methods.

Despite unique perspectives from three established brain collections, several key points and summary recommendations are mutually agreed upon. First, employment of diverse strategies for tissue acquisition are necessary, all of which rely upon strong working relationships and networking with respective tissue sources. These key relationships may start with medical examiners' offices, from the chief ME to support staff, or start with the local community, grassroots organizations such as NAMI, word-of-mouth, or by national or international reputation, but all of these relationships go back to the generosity of individual donating families who believe in the research mission of these organizations. Increasing collaborations between brain banks and organ donor networks may be useful in increasing the number of non-psychiatric control specimens, especially in younger age groups.

Looking to the future of psychiatric brain banking, it seems that rather than focusing on the new development of brain banks, which is costly with respect to both time and money,

North America may benefit from following the lead of Australia and Europe, where brain banking networks or “globalization” have recently been established to combine efforts and resources across countries for identifying, collecting, and sharing specimens (Falkai et al 2008; Ironside 2009; Kretschmar 2009). It would seem to be a logical next-step to network among the established banks such as NIMH, HBTRC and MSSM-BB to pool resources. While an official North American brain banking network may not be feasible given the diverse infrastructure of many of the banks within the United States and Canada (being funded privately, through the federal government, Veteran's Administration, or in universities), and even among the three collections described here, a national meeting of all key personnel managing the banks is recommended to pool resources and potentially to standardize collection and storage techniques. This would allow for reciprocity in tissue sharing, and sharing of recruitment and screening methodology. At the same time, one must also use caution before pooling tissue from varied sources such as those of NIMH, HBTRC and MSSM-BB, where cases may differ significantly in age, socio-economic background, postmortem interval, severity of illness, comorbidity and the like. Subtle differences in demographics may lead to variance and in turn Type II errors. In some studies, as was demonstrated in a recent study using microarray techniques in human brain by Oldham and colleagues, efforts can be made to offset such variance by statistically normalizing to reduce “batch effects” resulting from combined datasets (Oldham et al 2008).

The advantage of several centralized large brain banks over multiple diffuse smaller feeders is a standardization in clinical characterization, toxicology, neuropathology, and brain dissection, which reduces the ‘noise’ in any given assay by limiting the variability in these ‘controllable’ methodological variables.

Second, all three of the brain collections agree that rigor in tissue and diagnostic characterization are essential to a successful bank, whether it be detailed clinical diagnostic information gathered antemortem or postmortem, toxicological analysis of medical examiner cases, neuropathological examination of all cases to screen for neurological diseases, or adoption of stereological tissue sampling methods.

Thirdly, the importance of sample accessibility has been underscored. Accessibility can mean a number of things, beginning with access to gathering large numbers of well-characterized cases to ensure adequate tissue for dissemination, as well as individual investigators' accessibility to these tissue resources, by way of tissue disbursement. Data accessibility is also critical to postmortem brain studies, particularly through investigator databases seen at all three banks, whether for demographic or clinical data, neuropathological data, tissue tracking, or genomic data.

Lastly, the adaptability of both the brain banks collecting tissue, as well as the investigators conducting research is absolutely essential to the evolving field of postmortem human brain research, through continual application of innovative scientific approaches to the study of brain tissue (e.g., microarray techniques, cell culture, laser capture microscopy) is critical to the success and future of psychiatric brain banking in psychosis.

Conclusion

The study of schizophrenia and related disorders is actually the study of brain disease. Accordingly, although blood, urine, CSF, lymphocytes, and fibroblasts have some utility, ultimately, there is no substitution for brain tissue. Despite the divergent methods for tissue acquisition, emphasis on collection of certain psychiatric diagnoses, and research focus among the three brain collections, NIMH, HBTRC, and MSSM-BB, all three collections have a proven track record for successfully collecting well-characterized brain tissue

samples of psychotic disorders and controls subjects. What is most striking is not the differences found among the three collections but rather that the common goal among them is to apply ever-increasing rigor, not just to diagnostic determination of cases, increasing sample sizes, or screening and tissue characterization processes, but also to the forward-thinking scientific approaches in studying this tissue with the common goal of improving treatments and seeking out understanding of the causes of schizophrenia, bipolar disorder, and related illnesses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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<p>NETWORKING</p> <ul style="list-style-type: none"> -Close working relationships with tissue source (medical examiner, families of individual donors or prospective donors, grassroots community organizations and support groups) lead to increasing sample sizes, such that neuropathological abnormalities or clinically complex cases can be excluded from study
<p>RIGOROUS CHARACTERIZATION</p> <ul style="list-style-type: none"> -Dedicated trained professional to determine antemortem or retrospective diagnoses of donors through detailed clinical diagnostic review process of all available data -Directed toxicological screening of all cases in addition to medical examiner toxicology, particularly for cases donated through medical examiners' offices -Well-screened non-psychiatric controls across the lifespan (negative for psychiatric or substance abuse history, negative toxicology for all illicit drugs including marijuana) -Neuropathological examination to both confirm for and screen out neurological and neurodegenerative diseases
<p>STANDARDIZATION OF TISSUE PROCESSING</p> <ul style="list-style-type: none"> -Standardized methods and consistency for tissue processing and sampling protocols to reduce potential "noise" -State-of-the-art stereological methods for tissue dissection to enable quantitative assessment and detection of subtle abnormalities, avoid false positive or negative findings due to variable sampling
<p>ACCESSIBILITY</p> <ul style="list-style-type: none"> -A streamlined process, particularly web-based, for requesting tissue -Interactive web-accessible annotated databases for investigators and collaborators that captures demographic, clinical, neuropsychiatric and neuropathological data, as well as digital photography of samples, and genomic data, with public access to some results in the future -Access for investigators and collaborators to adequate sample sizes and resources for studying tissue
<p>ADAPTABILITY</p> <ul style="list-style-type: none"> -Adaptability in how tissue is preserved, dissected, stored -Adaptability or "retooling" of how tissue is aliquoted and disseminated (DNA, RNA, protein) to maximize the use of each individual donation -Adaptability in scientific methods for study (e.g., the shift from case-control studies to high-throughput gene expression studies) and/or to anticipate novel and future tissue uses

Figure 1.
Summary Recommendations for Psychiatric Brain Banking

Table 1

Tissue Acquisition Across Three Brain Bank Settings

	NIMH Brain Tissue Collection *	Mt. Sinai School of Medicine Alzheimer's Disease and Schizophrenia Brain Bank	Harvard Brain Tissue Resource Center
Primary Source(s) of Donations	Medical examiners' offices	Prospective recruitment	U.S. - Nationwide
Founder(s)	Dr. Joel E. Kleinman	Drs. K.L. Davis, D.P. Perl and V. Haroutunian	Dr. Edward D. Bird
Source of Funding	NIMH Intramural Research Program	NIMH, NIA, VA	National Institutes of Health
Date Collection Started	1977	1986	1978
Total Cases in Current Collection	1026 *	1589	2,000 – 3,000
Average Annual Donations	67	55–75	300
Total Cases with Schizophrenia	150	332	276
Average Schizophrenia Cases Per Yr	9	16	10
Total Cases with Bipolar Disorder	50	52	149
Average Bipolar Cases Per Yr	3	2	6
Total Adult Control Cases	226	240	618
Average Adult Controls Per Yr	13	15	34
Primary Focus of Bank	Schizophrenia, Normal Development	Alzheimer's, Schizophrenia, Psychiatric and Neurological Disorders	Neurodegenerative disorders, Psychotic disorders, Non- Neuropsychiatric Controls
Average Age of Cases	43.4 years	77.8	68.0 (range 1–108)
Sex Ratios	65% male	49% male	54% male
Primary Manner of Death	49% Natural; 22% Suicide; 16% Accident	99% Natural; 1% Suicide	80% Natural; 20% Suicide
Racial Data	48% Caucasian; 48% African-American	78% Caucasian; 14% African American; 5.5% Hispanic; 1% Asian	95% Caucasian; 5% Asian or Hispanic
Average tissue pH	6.4	6.4	6.6
Average PMI	34.3 hours	12.1 hours	18.6 hours

*
NIMH data from 1992-present