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Evaluation of Tissue Collection for Postmortem Studies of Bipolar Disorder

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Abstract

Objectives—Postmortem human brain is a valuable resource for studying the neuropathology, neurochemistry, and molecular pathways of genes associated with bipolar disorder (BPD), yet available well-characterized BPD brain tissue appears scarce. We set out to evaluate BPD postmortem brain collections in order to identify both successful methods as well as barriers to collection.

Methods—We conducted a literature review of postmortem studies of BPD over the past 30 years, compared and contrasted characteristics of established BPD collections, and identified possible barriers specific to BPD brain collection based on our experience at the NIMH Brain Collection.

Results—Currently, 80% of postmortem BPD studies were derived from just two brain repositories worldwide: the Stanley Brain Collection (69%) and Harvard Brain Tissue Resource Center (HBTRC) (11%) (Combined subjects n=72). The NIMH Brain Collection collected BPD cases four times less frequently than cases with schizophrenia, despite similar prevalence rates for these disorders. Only 53% of cases referred to the NIMH collection as BPD met DSM-IV criteria, with inadequate documentation and comorbid substance abuse as primary confounds for diagnosis in the remaining 47% of cases.

Conclusions—Accurate identification and diagnosis of BPD is a central obstacle to BPD brain collection. Comorbid substance abuse and manner of death are two of many critical factors to consider in BPD postmortem studies. Difficulties in BPD brain collection, coupled with the cessation of brain collection by the Stanley Brain Collection, make the need for alternative BPD brain sources imperative. Recommendations for future BPD tissue collection are offered.

Keywords

bipolar disorder; brain; postmortem; Stanley Foundation Neuropathology Consortium; Stanley Array Collection; Harvard Brain Tissue Resource Center; NIMH Brain Collection

INTRODUCTION

Bipolar disorder affects 1–2% of the world population, is associated with high rates of psychiatric comorbidity, including substance abuse (1), and anxiety, eating, and personality disorders (2), with rates of suicide completion between 10–15% (3). Age of onset for BPD varies across studies, ranging from adolescence into later adulthood (3,4). Family, twin, and

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association studies have indicated that BPD has a strong genetic component (5,6), with a 10-fold increased risk for BPD in first-degree relatives as compared to controls (7).

As possible candidate genes continue to be identified (8–10), postmortem brains of BPD subjects and controls will become increasingly important for determining how risk alleles affect mRNA expression, splice variants and protein levels, receptor binding and/or enzymatic activity. Such research can pave the way for understanding the function of susceptibility genes and their pathways, leading to novel therapeutic targets and improved treatments. Insofar as BPD is probably a complex genetic disorder involving not just genes, but environmental factors, BPD brains may also prove useful for other lines of research including neuropathology and neurochemistry.

Brain collection through medical examiners' offices and nationwide donations are two methods for gathering BPD brains. Proper diagnosis of BPD in living subjects presents a challenge (11), and thus, may be even more difficult in postmortem samples (12), given the episodic nature of the illness. Furthermore, potential confounds such as comorbid substance abuse may contribute to difficulties in assembling postmortem BPD collections.

We first set out to identify existing postmortem BPD brain collections in order to understand successful approaches for collecting BPD brains. Using data from established collections along with our own experience, we describe roadblocks to sample acquisition unique to BPD brain collection. We predicted that identification and subsequent diagnosis of subjects would be the rate-limiting steps in collecting BPD brains.

METHODS

Established BPD Brain Collections

A PubMed search was conducted on studies with "bipolar disorder" and "postmortem" as key words, (studies in English, with cross-references to "manic depressive" and "autopsy", including e-publications) from 1976–2006. We summarized samples characteristics for each collection and reviewed demographic/ clinical characteristics of the most widely-utilized BPD brain collections.

NIMH BPD Brain Collection

Informed consent was obtained from next-of-kin according to NIMH protocol #90-M-0142. A telephone screening and medical examiners' documents provided preliminary diagnoses. Clinical histories were obtained through available psychiatric records and family interviews. Details of the diagnostic process (12) and brain processing are described elsewhere (13). We examined all BPD cases referred to the NIMH Brain Collection, excluding no cases based on tissue characteristics, and including no cases with schizoaffective disorder. After determining which cases with a preliminary BPD diagnosis met DSM-IV criteria (14), we examined possible reasons why remaining cases did not. Lastly, we compared and contrasted our experience collecting BPD tissue at NIMH with already-established BPD brain collections in an effort to understand potential obstacles to BPD tissue acquisition.

RESULTS

Established BPD Collections

A literature review yielded 203 relevant publications on BPD in postmortem brain over 30 years, with the majority (69%) originating from one source: the Stanley Foundation Neuropathology Consortium (n=15) and Stanley Array Collection (n=35) (herein jointly referred to as the Stanley Brain Collection). Collectively, subjects were primarily from medical

examiner sources, predominantly Caucasian (94%), 52% male, with average ages of 42–45 at death, and 48% died via suicide. Average age of onset was 21.5 and 25.0 years old, respectively for each Stanley sample (Table 3) [www.stanleyresearch.org; (15,16)].

The Harvard Brain Tissue Resource Center (HBTRC) (also known as the McLean 66 collection) yielded 21 studies from this search (with 18–22 subjects), for which tissue was gathered via nationwide donations. This sample (n=18) was 89% Caucasian, 67% male, with an average age of 64 years at death, 22% died by suicide, with an average age of "psychological" onset of 11 years (Table 2) [www.brainbank.mclean.org].

The Canadian Tissue Bank is comprised of tissue from four sources (n=10), with 12 studies (17). The Rebecca L. Cooper Institute in Victoria, Australia had 10 publications on eight BPD subjects (18). In summary, a literature review yielded the identification of 15 BPD brain collections, with 203 studies of 167 BPD subjects (19–31) (Table 1).

NIMH BPD Brain Collection

From 831 brain donations gathered from 1993–2006 at NIMH, 53 cases were referred with a preliminary BPD diagnosis from medical examiners' documents and/or telephone screenings. Half of these cases (53%) met DSM-IV Axis I lifetime criteria for BPD, while the remaining 47% of subjects fell into other diagnostic groups (56% mood disorders, 36% schizophrenia/schizoaffective disorder, and 8% undetermined) (Table 2). Among the 14 cases with other mood disorders, confounding comorbid substance abuse and inadequate symptom documentation were the most common reasons that cases did not meet BPD criteria.

Six additional cases presenting with other DSM-IV Axis I diagnoses met criteria for BPD. In summary, just 4.1% of the 831 samples collected over 13 years resulted in BPD cases, in contrast to 17.7% cases with schizophrenia from this time period.

A resulting sample of 34 BPD subjects met DSM-IV criteria for a lifetime diagnosis of BPD (BPD-I or II) (Table 3). Most subjects (94%) were obtained from medical examiners' offices, were 65% male, 79% Caucasian, with an average age of 44.0 ± 14.9 years at death. 59% of cases reported having at least one first-degree relative with a mood disorder (24% with BPD). The average age of onset of BPD (i.e., mania) was 32.0 ± 10.3, and the average age of onset for depression was 25.5 ± 11.3 years. Most subjects (82.4%) were depressed at the time of death.

Most subjects (65%) died via suicide, were significantly younger than those who did not (39.5 vs. 52.3, $t=-2.56$, $p<0.02$), and were significantly more likely to be diagnosed with BPD-I (Fishers exact test, $p<0.001$). Comorbid substance abuse was common (74%), with 68% of subjects diagnosed with alcohol abuse/dependence, and 29% diagnosed with substance abuse/dependence. Other psychiatric comorbidities were anxiety disorders (23.5%), eating disorders (11.8%) and borderline personality traits (5.9%).

Comparison of NIMH Sample to Existing BPD Collections

Subjects collected from medical examiners (i.e., Stanley Brain Collection) were similar to the NIMH Brain Collection on many demographic characteristics, including age, pH, PMI, race, and on clinical features such as BPD subtype and rates of psychosis (Table 3).

Three of the collections (HBTRC, Canada, and Rebecca L. Cooper) had subjects who were 10–20 years older at death (range 57–64) than the Stanley or NIMH cases. It appeared that HBTRC and the Canadian Tissue Bank had slightly higher brain pH and lower PMIs. Ages of onset varied (range 11–37). Rates of comorbid substance abuse were generally not found (although they may be available), with the exception of the Stanley Brain Collection

(approximately 54%). High rates of suicide were common to all three collections: HBTRC (22%), Stanley (48%), and NIMH (65%).

DISCUSSION

The majority (80%) of published studies on BPD in postmortem brain were derived from just two U.S. collections, comprised of 72 individuals: Stanley Brain Collection and HBTRC. While many other collections appear to have access to BPD tissue, and studies of additional cases may be in progress, sample sizes for published studies tended to be small.

In our experience, diagnostic difficulties were the first challenge we encountered in the collection of BPD brains. We found that 47% of NIMH Brain Collection cases initially referred as possible BPD did not fulfill DSM-IV criteria for BPD. Among these cases, 56% were instead diagnosed with other mood disorders. Within this subgroup, inadequate documentation of BPD symptoms and comorbid substance abuse were the two biggest barriers to making the BPD diagnosis. As opposed to our experience with schizophrenia, where the illness is unremitting, and thus, records are lengthy and often sufficient to make the diagnosis after death (12), BPD is episodic, and we often required two clinical sources (i.e., family interviews and psychiatric record reviews) to verify symptoms. Diagnosis, particularly BPD-I, was most challenging because of the inability of family informants to describe a discrete period fulfilling DSM-IV criterion A for mania or hypomania, or failure of clinicians to back up discharge summary diagnoses with symptom documentation.

The National Comorbidity Survey Replication recently reported that lifetime prevalence estimates for BPD-I and BPD-II are 1% and 1.1% respectively (32). Insofar as the vast majority (82.3%) of BPD subjects in our collection are BPD-I, it would support the idea that less severe BPD cases are disproportionately missed by postmortem collections.

Suicide as a manner of death is also over-represented in medical examiner BPD samples (48–65% in Stanley and NIMH collections vs. 22% in HBTRC) relative to 10–15% lifetime estimates in BPD. This further supports the notion that medical examiner collections may be sampling from a severely ill subset of BPD, not only BPD-I, but subjects dying younger, via suicide, and those experiencing depressive episodes at time of death. The relatively low number of natural deaths in the Stanley and NIMH collections regardless of BPD subtype may result from one of two other possibilities: BPD subjects dying from natural causes are not autopsied and/or they tend to be BPD-II, which are not being recognized.

Comorbid substance abuse was somewhat higher within the NIMH sample (74%) than in community/clinical samples (30–71%) (2), with alcohol being the most common substance abused. While other comorbidities such as anxiety disorders and eating disorders are prevalent in the NIMH BPD sample, these diagnoses generally do not hinder the diagnosis of mania/BPD, and thus do not create diagnostic dilemmas. While high rates of substance abuse and psychiatric comorbidities may result from a medical examiner sampling bias, exclusion of BPD subjects on the basis of comorbidity would be a case of the cure being worse than the disease. Instead, two possible strategies can be employed. First, in the case of substance abuse, postmortem researchers can consider using non-psychiatric substance abuse cases as controls. Second, subjects can be subdivided by the presence/ absence of comorbidities, by clinical features like psychosis, or by postmortem toxicology results.

Recommendations for Future BPD Brain Collection

The greatest success in BPD brain banking to date has been the Stanley Brain Collection, which set out specifically to collect from patients with schizophrenia and BPD. Although a centralized mechanism for collecting, diagnosing, and processing BPD brain tissue would be ideal to

minimize variability, it is impractical given differing institutional guidelines, resources, and barriers across settings. It would instead seem that one solution to the problem is to fund a collection whose designated mission is the collection of BPD brains.

Although medical examiners' offices have been the most abundant source for gathering BPD cases, an alternative strategy would be to utilize the Veteran's Administration hospital system, which had over 56,000 registered BPD cases in 1998 (33), and computerized medical records. Certainly the Veteran's Administration is not immune from the institutional barriers or other difficulties inherent in brain collection (i.e., finding next-of-kin and obtaining their informed consent, lack of incentive to perform autopsies). Nevertheless, it is a relatively untapped resource for BPD brains.

Postmortem human brains are an absolute necessity for elucidating how allelic variation in genes increase risk for BPD. Studies involving allelic variation cannot be done with samples of 12–20 cases as were used in the past; numbers in the hundreds (controls plus index cases) will be required. Whatever the methodologies or exclusion criteria (e.g., pH or RNA quality cut-offs, exclusions based on comorbidity or toxicology), more stringent standards require larger numbers of bipolar subjects to choose from. Insofar as risk genes for BPD have already been discovered (34), the time for increasing the available numbers of BPD brains is now. This will undoubtedly require a bipolar disorder-centered effort, not unlike what was accomplished with the Stanley Brain Collection.

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Table 1

Existing Bipolar Disorder Brain Collections

Name of Center	Location of Collection	# Subjects*	Published Studies+
United States			
Stanley Neuropathology Consortium	Bethesda, MD	15	124
Harvard Brain Tissue Resource Center (McLean)	Belmont, MA	22	21
Stanley Array Collection	Bethesda, MD	35	17
NIMH Brain Collection**	Bethesda, MD	8	4
University of California, Irvine Brain Repository	Irvine, CA	9	2
Cuyahoga County Coroner's Office	Cleveland, OH	5	1
University of Michigan/ Battle Creek VA Hospital	Ann Arbor, MI	2	1
Canada			
Canadian Tissue Bank++		10	12
Europe			
University of Geneva School of Medicine	Geneva, Switzerland	21	1
Forensic Institutes-Bilbao & Geneva	Bilbao, Spain; Geneva, Switzerland	6	1
University of Madgeburg/ Department of Psychiatry	Madgeburg, Germany	11	4
Moscow Psychiatric Hospitals/ Medical School	Moscow, Russia	6	1
Newcastle General Hospital	Newcastle, United Kingdom	6	1
Netherlands Brain Bank	Amsterdam, Netherlands	2	2
Semmelweis University Medical School	Budapest, Hungary	1	1
Australia			
Rebecca L. Cooper Research Laboratories	Victoria, Australia	8	10
	Total	**167**	**203**

*The number of subjects listed for each collection reflects only those found in published studies via a PubMed search through 2006, and may not reflect the total BPD brains available for study;

+Collaborative studies between two banks were counted for the bank contributing the majority of samples;

** These publications resulted from a previous NIMH BPD cohort for which tissue has since been depleted and is to be considered entirely separate from the current NIMH Brain Collection;

++ Consists of tissue from four sources: Boston Brain Bank, Canadian Brain Tissue Bank, National Neurological Tissue Bank, Montreal Brain Bank.

Table 2

Breakdown of Preliminary vs. Final DSM-IV Diagnoses for NIMH Bipolar Disorder Brain Collection (n=34)

Preliminary Diagnosis (phone screen/MEO documents)		**Final Consensus Review Diagnosis (records, interviews, narrative, all info)**		
n=53 Bipolar (n=38) R/O Bipolar (n=15)	--->	**Bipolar (n=28)** MDD (n=10) Depression NOS (n=4) Schizophrenia (n=5) Schizoaffective, Bipolar (n=4) Undetermined (n=2)	--->	**Final BPD Cohort** **n=34** 82.4% had BPD or R/O BPD preliminary diagnoses 17.6% had other preliminary diagnoses 47.2% of BPD preliminary cases did not meet criteria for cohort
n=6 MDD (n=4) Schizophrenia (n=1) Substance Abuse (n=1)	--->	**Bipolar (n=6)**	--->	

BPD=bipolar disorder; MEO=medical examiners' office; R/O=rule out; MDD=major depressive disorder

Table 3

Comparison of Demographic and Clinical Data for Existing Bipolar Disorder Brain Collections

	Stanley Array Collection	Stanley Foundation Neuropathology Consortium	Harvard Brain Tissue Resource Center/ (McLean)	Canadian Tissue Bank	Rebecca L. Cooper/ Victorian Brain Bank	NIMH Brain Collection
Total Subjects	35	15	18*	10	8	34
Mean age (range)	45.3 (19–64)	42.3 (25–61)	64	56.7 (27–94)	59 (38–74)	44.0 (20–79)
pH (range)	6.4 (5.8–7.0)	6.2 (5.8–6.5)	6.48 (6.03–7.06)	6.56 (6.24–6.81)	6.28 (5.68–6.46)	6.2 (5.8–6.5)
PMI (range)	37.9 (12–84)	32.5 (13–62)	20.8	17.8 (8–33)	40 (17–58)	30.3 (5.5–71.5)
Sex	17M, 18F	9M, 6F	12M, 6F	4M, 6F	4M, 4F	22M, 12F
Race	33C, 1AA, 1NA	14C, 1AA	16C, 2 UK			27C, 6AA, 1AS
Manner of Death	15S, 16N, 4A	9S, 4N, 1A, 1Other	4S, 1A, 7N, 6UK	4S, 5N, 1UK	2S, 4N, 1A, 1UK	22S, 6N, 3A, 2 UD, 1UK
Age at Onset	25.0 (14–48)	21.5 (7–39)	11 "psychological"		36.6 (21–48)	32 (15–53)
Subtypes	26BPI, 4BPII, 4BPNOS, 1BP-SA			7 BPI, 3 Other		28BPI, 6BPII
Psychosis	20+/11−, 4 "unclear"	11+/4−				21+/13−
Comorbid Substance Use	20 “current” – moderate to heavy	7+/8−				25+/ 9−
Primary Tissue Source	MEO	MEO	Nationwide	4 Tissue Banks	MEO	MEO

	Stanley Array Collection	Stanley Foundation Neuropathology Consortium	Harvard Brain Tissue Resource Center/ (McLean)	Canadian Tissue Bank	Rebecca L. Cooper/ Victorian Brain Bank	NIMH Brain Collection
Demographic Data	Stanley website, 2007	Torrey et al., 2000	Harvard website, 2007	Young et al., 1993	Dean et al., 2005	This manuscript

* The HBTRC website reported demographic and clinical data on a sample of 18 subjects; however it should be noted that some publications included a sample size of up to 22 subjects.

PMI=postmortem interval (hours); C=Caucasian; AA=African-American; NA=Native American; AS=Asian; S=suicide; N=natural; A=Accident; UK=unknown; UD=undetermined; BPI=bipolar disorder type I; BPII=bipolar disorder type II; BPNOS=bipolar disorder not otherwise specified; BP-SA=schizoaffective, bipolar type; MEO=medical examiners' office