

VA's National PTSD Brain Bank: a National Resource for Research

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Published online: 25 August 2017
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Abstract The National PTSD Brain Bank (NPBB) is a brain tissue biorepository established to support research on the causes, progression, and treatment of PTSD. It is a six-part consortium led by VA's National Center for PTSD with participating sites at VA medical centers in Boston, MA; Durham, NC; Miami, FL; West Haven, CT; and White River Junction, VT along with the Uniformed Services University of Health Sciences. It is also well integrated with VA's Boston-based brain banks that focus on Alzheimer's disease, ALS, chronic traumatic encephalopathy, and other neurological disorders. This article describes the organization and operations of NPBB with

specific attention to: tissue acquisition, tissue processing, diagnostic assessment, maintenance of a confidential data biorepository, adherence to ethical standards, governance, accomplishments to date, and future challenges. Established in 2014, NPBB has already acquired and distributed brain tissue to support research on how PTSD affects brain structure and function.

Keywords Brain banking · Neuropathology · Posttraumatic stress disorder · Diagnostic assessment · Informed consent · Confidential data biorepository

The editors would like to thank Dr. Betty Pfefferbaum for taking the time to review this manuscript.

This article is part of the Topical Collection on *Disaster Psychiatry: Trauma, PTSD, and Related Disorders*

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Introduction

In 2004, an entire issue of the journal *Psychiatry* focused on the need for a national brain bank dedicated to advancing our understanding of posttraumatic stress disorder (PTSD). Osuch and colleagues pointed out that among the 55 US biorepository brain banks currently supporting research on neurological and psychiatric disorders, not a single one focused on PTSD [1]. In the same issue, Torrey argued, “No matter how sophisticated neuroimaging becomes, however, it will always be a bystander on the outside looking in. Understanding normal brain function and disease conditions will ultimately necessitate work with brain tissue itself” (Torrey [2], page 412). Other contributors to that special issue emphasized: (a) within PTSD research, the major epigenetic question is whether stress damages the brain [3]; (b) PTSD is an excellent window through which to investigate a wide variety of gene-environment interactions [3–5]; (c) comprehensive antemortem longitudinal assessment of trauma-exposed individuals with and without PTSD will provide an excellent opportunity to understand what brain tissue risk factors distinguish vulnerable from resilient individuals [4–6]; (d) advances in technology will permit investigation of cytoarchitectonics, neurotransmitters and receptors, neuropeptides, enzyme synthesis, neurotropic factors, neuropeptides, enzyme synthesis, synaptic proteins, signal transduction, pathways, inflammatory markers, cellular architecture, genomics, proteomics, metabolomics, single nucleotide polymorphisms, DNA methylation, and RNA sequencing [1, 4, 5, 7, 8]; and (e) careful curating of tissue from normal and control individuals with other neuropsychiatric disorders, with and without PTSD, (such as depression, substance use disorders, anxiety disorders, and traumatic brain injury) will enable investigators to identify PTSD-specific abnormalities as well as overlapping abnormalities that are present in both PTSD and some associated comorbid disorders [1, 6, 8].

The impetus to establish a PTSD brain bank came when the Stanley Brain Collection, previously established in 1994, moved to The Uniformed Services University of Health Sciences (USUHS) in 1999. Its mission was to supplement existing brain banks committed to promote human brain research in order to develop treatments for schizophrenia and bipolar disorder. When the brain collection moved to USUHS, it had over 300 specimens.

As a result, Robert Ursano, Chair of Psychiatry at USUHS enlisted Matthew Friedman, Executive Director of The Department of Veterans Affairs (VA) National Center for PTSD (NCPTSD), to create a national biorepository brain bank. Despite the persistent efforts of Ursano, Friedman and

colleagues at USUHS, NCPTSD, the National Institute of Mental Health (NIMH) and the Stanley Brain Collection, secure funding was not obtained until 2014. This occurred through the good offices of Senator Patrick Leahy who successfully led a bipartisan legislative initiative to support a biorepository PTSD brain bank under the aegis of NCPTSD.

The VA’s National PTSD Brain Bank (NPBB) is now established with a maturing organization and standard operating procedures for tissue acquisition, diagnostic assessment, tissue preparation, and storage. Procedures are established for review of research proposals and dissemination of brain tissue to investigators, data confidentiality, ethical issues, and governance. In the following, we review these areas as well as NPBB’s accomplishments to date, and important challenges for the future.

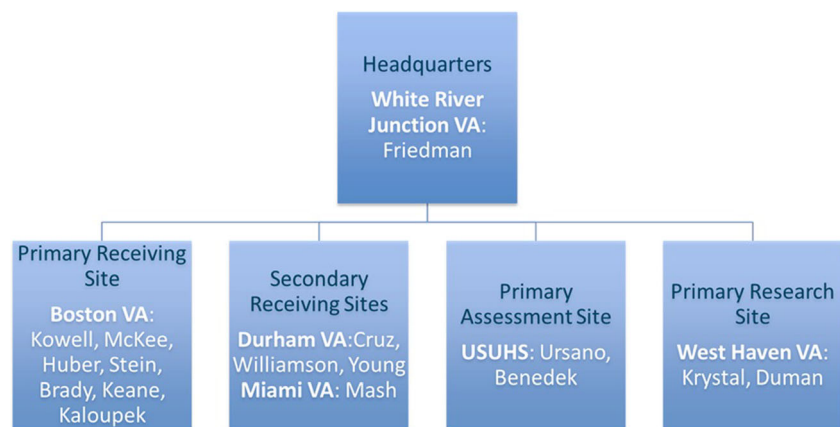
NPBB: Organization and Key Personnel

VA’s National PTSD Brain Bank is a part of VA’s National Center for PTSD. NPBB is a six-part consortium (see Fig. 1) and directed by Matthew Friedman with its headquarters located at NCPTSD’s Executive Division at the VA Medical Center in White River Junction, VT and The Geisel School of Medicine at Dartmouth.

NPBB’s hub is at VA Boston Healthcare System (VABHS) where it is programmatically integrated with VA and Boston University’s other outstanding brain banks dedicated to advancing the understanding and treatment of Alzheimer’s disease, amyotrophic lateral sclerosis (ALS), traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), and Gulf War illness. Leadership at Boston includes Ann McKee, Neil Kowall, Russ Huber, Thor Stein, Christopher Brady, Danny Kaloupek, and Terrence Keane. Boston is NPBB’s primary receiving and storage site for brain tissue specimens. Although brain tissue is obtained posthumously, persons who enroll in the NPBB and personally consent to the donation of their brain tissue are considered “antemortem donors.” Their tissue is referred to as “antemortem tissue.” In situations where consent is obtained from next-of-kin shortly after death, this is referred to as a postmortem donation and the brain tissue is referred to as “postmortem tissue.”

Potential brain donors may contact Boston-based staff through the website (http://www.research.va.gov/programs/tissue_banking/PTSD/default.cfm) or through the toll-free telephone number (1-800-762-6609) where they are given more information about NPBB, asked to review and sign a consent form, and if enrolled, interviewed about demographic facts, trauma history, mental health history, and functional status. All such information is confidential. NPBB is able to enroll both non-veterans and veterans as potential donors. Importantly, in addition to military-related PTSD, donors are also welcome who have previously been exposed to non-

Fig. 1 VA National PTSD Brain Bank: organizational chart



military trauma (such as domestic violence, motor vehicle accidents, terrorist attacks, natural disasters, etc.). Since control participants are essential, NPBB also seeks brain tissue donations from individuals with no psychiatric history (e.g., healthy controls). Indeed, given our interest in resilience, brain tissue from individuals who have been previously exposed to trauma without developing any psychiatric sequelae is extremely important. Since our assessment includes careful documentation of trauma history, we will be able to address the question of resilience by distinguishing healthy controls with a trauma history from those who were never traumatized. Given the high likelihood that an individual with PTSD will also have at least one other psychiatric disorder, we are very interested in donors with depression, substance use disorders, anxiety disorders, and/or traumatic brain injury whether or not they also have PTSD.

Because the Boston VA also houses several other brain banks, NPBB has been fortunate to benefit from its excellent existing neuropathological facilities and leadership from Ann McKee, Neil Kowall, and their colleagues. Most of NPBB's brain tissue is processed and stored at the Boston VA. Finally, since NCPTSD's Behavioral Science Division is also located at the Boston VA, NPBB benefits greatly from the diagnostic and psychological assessment expertise of Terry Keane, Danny Kaloupek, and their colleagues.

NPBB also has two distant sites at the Durham, NC and Miami, FL VA Medical Centers. These accept postmortem brain tissue (i.e., tissue requested and obtained after death with consent of next-of-kin). Whereas the Boston site obtains postmortem brain tissue from donors who are enrolled before death, the Durham and Miami sites receive brain tissue from donors enrolled after death by their next-of-kin. Such tissue is referred from medical examiner offices in North Carolina and Florida, as well as from the Duke University Autopsy Program where existing protocols allow for posthumous brain donation with the consent of next-of-kin. The Durham VA site is led by Douglas Williamson and Dianne Cruz and is closely affiliated with Duke University School of Medicine. Keith

Young, at Texas A&M and The Waco, TX VA Medical Center works closely with NPBB investigators at Durham. The Miami VA site is led by Deborah Mash and colleagues and is closely affiliated with the University of Miami Medical School. Since Miami is also one of the six designated NIMH NeuroBioBanks which are the leading US psychiatric brain biorepositories, it provides an important link between NPBB and NIMH.

Our fifth site, located at USUHS, has primary responsibility for diagnostic protocols and practices regarding all donated brain tissue; it is led by David Benedek and Robert Ursano. Finally, the hub of our intramural research program is located at NCPTSD's Clinical Neuroscience Division at the West Haven, CT VA Medical Center and The Yale School of Medicine; it is led by Ronald Duman and John Krystal.

This organizational structure is extremely flexible and there is a great deal of cross-site collaboration between neuropathologists at Boston, Durham, and Miami, neuroscientists at West Haven, Durham, and Boston, and diagnostic assessment research at USUHS and Boston.

NPBB: Operations

The major functions of the brain bank include (1) tissue acquisition (ante/postmortem), (2) strict criteria for tissue processing and preservation, (3) strict criteria for accurate ante/postmortem diagnosis, (4) rigorous review of research proposals and disseminating brain tissue to approved investigators, (5) maintenance of a confidential data biorepository, (6) strict adherence to ethical standards, and (7) effective governance and oversight. All study procedures are under the oversight of the Institutional Review Board at VABHS.

1. Tissue Acquisition

We have previously discussed our approach to tissue acquisition (see above). Boston is our antemortem tissue acquisition site where potential donors contact us through our

website or toll-free phone number. Such donors receive information about the brain bank, provide informed consent, and receive a thorough assessment (see below). Enrolled donors receive annual abbreviated follow-up assessments until their death. At the time of this writing, we have 50 enrolled donors; two donors have died and donated their brains to NPBB. National recruitment and enrollment into NPBB is ongoing. The advantage of this approach to tissue acquisition is that it is possible to do a thorough assessment of potential donors while living. The disadvantage is that it can be difficult to differentiate stress-related from age-related brain changes. We enroll appropriate control donors and conduct annual follow-up assessments on enrollees to assist in differentiating stress versus age-related effects on the brain.

Since our postmortem tissue acquisition sites at the Durham VA and Miami VA, respectively, have only been established recently, almost all of NPBB's current tissue collection from postmortem donors, obtained after informed consent from next-of-kin, has been acquired through a collaborative arrangement with the Lieber Institute for Brain Development (LIBD). The clinical characteristics of the LIBD PTSD collection are described in a recent letter to the editor [9•].

When donor death occurs or is very imminent, the donor's family or caretaker pages VABHS staff. A researcher is on-call 24 h a day, 7 days a week. Once paged, the on-call researcher coordinates the tissue recovery with the enrollee's family and the VABHS-contracted national tissue recovery organization. A VA pathologist or contracted diener conducts the tissue recovery. The tissue is packed in a special shipping container and a medical courier service provides door-to-door delivery from the recovery site to the respective departure and arrival (i.e., Boston) airports and then to VABHS with the minimal postmortem interval possible. Similar tissue recovery procedures are used at the Durham and Miami sites.

Additional assessment challenges include the high prevalence of comorbid disorders associated with PTSD, periaxonal events that may affect brain tissue (such as use of medication or medical procedures), whether death was sudden or occurred after a protracted illness, and the method of death (e.g., suicide versus natural causes) [1, 2, 4].

Table 1 shows our current inventory by gender, diagnosis, veteran status, and whether suicide was the cause of death.

2. Tissue Processing

Since NPBB has been integrated with other Boston-based brain banks, it has adopted the state-of-the-art tissue processing procedures that were already in place. A good description can be found in the published article (plus published supplementary materials) on the Boston-based ALS Biorepository Brain Bank [10•] which is programmatically integrated with

NPBB. All tissue that will be distributed by NPBB must meet standards for pH (e.g., range 5–7) and RNA integrity number (e.g. RIN > 5 to < 9) [11•]. Brain pH and RIN reflect premortem factors such as duration of the agonal period and adverse, often hypoxic events that adversely affect the quality of brain tissue [12, 13].

In brief, each brain is hemisected, with one hemisphere of the brain and cerebellum fixed in periodate-lysine-paraformaldehyde (PLP) and cut into tissue blocks that are paraffin embedded for histological and immunohistochemical staining and for neuropathological analysis. Brain tissue to be frozen is cut into 1–1.5-cm slabs and is rapidly cooled on aluminum plates suspended in dry ice. This protocol freezes tissue quickly and uniformly without ice artifact. Frozen tissue is used for genomic and proteomic analyses such as RNA sequencing, DNA methylation, and a wide variety of genes and gene expressions regarding myelination, protein trafficking immune responses, apoptosis, cell adhesions, and ubiquitin-mediated protein degradation [12].

3. Diagnostic Protocols

The best prepared tissue in the world has limited usefulness in research without confidence in the donor's psychiatric diagnosis. In the case of antemortem donors who enroll in NPBB before death, the antemortem assessment protocol (AAP) is quite similar to other PTSD studies. After informed consent is obtained, donors are assessed via telephone with state-of-the-art structured clinical diagnostic interviews (e.g., the Clinician-Administered PTSD Scale, CAPS, and Mini International Neuropsychiatric Interview, MINI) and a brief cognitive screening (Telephone Interview of Cognitive Status-modified, TICS_m). Information is obtained on demographic factors, medical history, social history, lifestyle factors, and functional achievements via mail-based surveys and medical record review. While most clinical trials rely on in-person administration of these assessments, they have been increasingly administered via telephone, mail-in, and web-based formats in epidemiological and longitudinal studies. These assessments determine current versus lifetime PTSD diagnosis along with other psychiatric comorbidities such as major depressive disorder. Annual follow-up assessments are conducted to update health information and track PTSD symptomatology (PTSD checklist) and cognitive function (TICS_m).

The AAP utilizes a standardized verification procedure to confirm and integrate multiple sources of enrollee information to determine a current and/or lifetime PTSD diagnosis for enrollees. Furthermore, we have developed data-based rules for determining a Diagnosis Confidence Index for PTSD diagnoses determined via the AAP. A detailed discussion of this is beyond the scope of this paper, but our Diagnosis Confidence Index ranges from 1 (PTSD Unlikely) to 5 (PTSD Definite).

Table 1 The NPBB currently holds tissue from 168 brains from seven diagnostic categories plus healthy controls. The numbers in parentheses are the number of male donors with the listed diagnosis

Primary diagnosis	Gender		Total	Veteran	Suicide
	Male	Female			
Posttraumatic stress disorder	34	22	56	28(26)	10(3)
Major depressive disorder	27	19	46	4(2)	16(4)
Depression not otherwise specified	10	1	11	4(4)	3(2)
Schizoaffective disorder	0	1	1	1(1)	0
Bipolar disorder	1	4	5	2(1)	1(1)
Anxiety	1	0	1	0	0
Alcohol	1	0	1	0	0
Control	32	15	47	5(5)	0
Total	106	62	168	44(39)	30(10)

A much bigger challenge is postmortem diagnostic assessment. As noted earlier, next-of-kin may not be aware of important subjective symptoms because the deceased never discussed them due to PTSD avoidance, stigma, lack of trust, or other factors. NPBB's postmortem diagnostic assessment protocol (PAP) (a) provides a standardized approach to conducting a comprehensive psychiatric and medical record review; (b) tracks and registers the range of previously documented clinical diagnoses, behaviors, and symptoms as well as psychosocial functioning; (c) queries for lifetime history of exposure to potentially traumatic stressors; (d) catalogs results of psychological assessment reports and medical and neurological testing; and (e) provides corroboration of medical record information via interviews with next-of-kin and/or healthcare providers familiar with the donor's life history. As with the AAP, diagnoses determined via the PAP are given a Diagnosis Confidence Index ranging from 1 (PTSD Unlikely) to 5 (PTSD Definite).

For tissue donated by next-of-kin, after the death of a family member, there is an obvious problem in diagnostic assessment, especially with respect to subjective symptoms. Although this is a challenge for any brain bank enrolling postmortem donors, there are unique challenges for PTSD. Individuals with PTSD are especially reluctant to discuss their symptoms with anyone, since such discussions often re-trigger painful traumatic memories. Furthermore, next-of-kin may be unaware of the deceased's non-behavioral PTSD symptoms because of their subjective nature, reluctance to discuss them because of PTSD avoidance symptoms, and reluctance to acknowledge psychiatric symptoms because of the stigma often associated with such disclosures. These problems can be offset to a great extent when hospital records can be obtained that will enhance diagnostic accuracy.

Peer Review of Research Proposals

At the time of this writing, NPBB has just received Institutional Review Board approval to convene a Tissue

Access Committee (TAC). As with other brain banks, the NPBB TAC will review the scientific merit of each proposal, the investigator's productivity, institutional resources available to the investigator, availability of appropriate federal/other funding, and the nature/magnitude of the tissue request. With regard to the latter, most PTSD tissue requests include the amygdala, which is a very small nucleus. Therefore, evaluation of such a request for scarce tissue that is in great demand must necessarily balance available tissue inventory with the quality and importance of the request. Furthermore, there may be tissue requests which duplicate investigations that have already been initiated (such as RNA sequencing of key brain nuclei that mediate or moderate PTSD symptoms). Establishment of a data biorepository is one way to approach this matter (see below). Once approved, requested brain fixed and/or frozen tissue is disbursed to investigators.

Among the many principles and regulations for operation of brain banks, it is important to have a code of conduct that governs the many complex steps needed for successful operations. With regard to tissue disbursement, a number of documents are needed such as tissue application forms, material transfer agreements, confidentiality agreements, and personal data protection measures [14•, 15].

4. Maintenance of a Confidential Data Biorepository

Confidentiality and data security are essential. Privacy must be maintained regarding all collected data. This is especially true for a PTSD NeuroBioBank, given the stigma associated with psychiatric disorders. Since NPBB is located within VA, the VA firewall and safeguards for confidentiality provide an extra layer of protection for any data generated from tissue donations to NPBB [16–18].

A major goal for NPBB is that all raw data derived from research on brain tissue, that it has banked and disbursed to investigators, should be archived in a data biorepository. Such data must be de-identified before it can be shared with authorized investigators. As noted by Haroutunian and Pickett [19],

such data sharing “makes it possible for different tissue recipients and researchers to be cognizant of related research efforts and to maximize the gains from each research project by collaborating with each other” ([19], page 413). Furthermore, authorized investigators requesting NPBB tissue for a research project that has already been completed may be eligible to receive de-identified data from the data biorepository rather than precious brain tissue. Given the magnitude of data sets developed from brain banks (especially if brain imaging data is also included), cloud technologies are needed to provide adequate capacity. VA is currently working to develop such capacity that also meets its stringent requirements for privacy and data security. NPBB is part of that process and will utilize such cloud technology when it becomes available.

5. Strict Adherence to Ethical Standards

The NPBB is cognizant of ethical issues and challenges associated with operating a brain bank. First, given the sensitivity and altruism involved in making a donation to a brain bank, a thorough and rigorous informed consent process must be provided for next-of-kin who might consider the donation of a loved one’s brain tissue in the immediate aftermath of their loss, and in some jurisdictions must provide consent even if their loved one has previously provided his or her consent. Similarly, there must be processes for donors who enroll in the NPBB and consent to assessment and eventual donation of their brain tissue to involve their next-of-kin in informed discussions about their decision. Furthermore, in the case of antemortem donors, families need to know, before death, that their loved one’s brain will be used for scientific research (as opposed to organ transplant). Whether it is an antemortem or postmortem brain donation, donors and families alike must have an opportunity to adequately review and understand (usually with the help of an informational brochure) about the research purposes and organization of the brain bank. Living enrollees and their families must also understand that they can withdraw consent at any time. As antemortem donors may be enrolled years before their death, longitudinal follow-up to allow for up-to-date medical assessment over time and to ensure that the NPBB is notified at the time of donor death, requires a balance of tactfulness and persistence that upholds ethical standards of respect for the dignity and autonomy of enrollees and their families, yet allows for timely collection of data and tissue. To the extent that enrollment may be sought by or offered to elderly and/or medically ill persons, care must be taken to insure that potential donors are competent to provide informed consent. Donors and their families need to know how any data generated from their family member’s tissue are protected by privacy and confidentiality safeguards, an increasing concern with the development of techniques for postmortem genetic analyses that may have privacy implications for living relatives [16, 20, 21]. Finally, to the extent that

the NPBB receives brain tissue from other existing collections or brain banks, the NPBB must take appropriate measures to insure that this tissue was also obtained under IRB-approved protocols, with appropriate safeguards to insure informed consent from donors and appropriate privacy safeguards.

6. Effective Governance and Oversight

VA’s National PTSD Brain Bank is a section of VA’s National Center for PTSD, which, organizationally, operates under the aegis of VA Mental Health. NPBB is directed by one of us, (MF), who chairs the Steering Committee consisting of key personnel from each of the six sites (see Fig. 1). In addition, there are NPBB subcommittees that focus on major brain bank functions such as diagnostic assessment, tissue preparation, logistics, networking, and sustainability. The Tissue Access Committee reviews all research applications and oversees disbursement of tissue. A recently convened, Scientific Advisory Board will meet annually to review policies, procedures, current challenges, and future priorities. Finally, to the extent that the NPBB receives brain tissue from other existing collections or brain banks, the NPBB takes appropriate measures to insure that this tissue was also obtained under IRB-approved protocols, with appropriate safeguards to insure informed consent from donors and appropriate privacy safeguards.

Accomplishments to Date

1. To those of us who have been working to establish a national PTSD brain bank since 1999, the actual existence and exuberance of NPBB is a dream come true. We have assembled an enthusiastic and productive group of pre-eminent neuropathologists, neuroscientists, psychologists, and psychiatrists who enjoy working together and have already initiated a number of intramural projects.
2. As noted earlier, we are programmatically linked with the highly regarded Boston-based brain bank dedicated to Alzheimer’s disease, ALS, TBI, CTE, and Gulf War illness.
3. We are currently engaged in productive strategic partnerships and collaborative relationships at host academic institutions such as Boston University, Dartmouth, Duke, University of Miami, USUHS, and Yale, as well as with the Lieber Institute for Brain Development, the University of Pittsburgh, and the NIMH NeuroBioBank.
4. Our first publication, since NPBB was established, demonstrated that decreased serum and glucocorticoid regulated kinase 1 (SGK1) expression and function contributes to behavioral deficits induced by traumatic stress. These findings with human brain tissue were corroborated by preclinical studies with rats exposed to uncontrollable stress [22••].

5. Prior to formal establishment of NPBB, the group that began to meet by phone in 1999 (the Traumatic Stress Brain Research Group):
 - a. Began developing assessment and tissue protocols
 - b. Jointly contributed to the special issue of Psychiatry in 2004, cited previously [1–8]
 - c. Published two articles using tissue from the Stanley Brain Collection:
 - i) Identifying upregulation of the protein, p11 in human pre-frontal cortex (PFC), of PTSD patients and in that of stressed rats [23]
 - ii) Identifying specific PTSD-related gene expression patterns in postmortem dorsolateral PFC mitochondria [24]

Challenges for the Future

1. As with most brain banks, sustainability will remain a major challenge, as we expand the intensity and scope of our activities.
2. Establishment of a cloud-based data biorepository within the VA firewall that maintains privacy and confidentiality.
3. Improving antemortem recruitment at Boston.
4. Improving postmortem recruitment at Durham and Miami with collaborating medical examiners and with The Duke Autopsy Program.
5. Fortifying existing strategic partnerships and collaborative arrangements (e.g., LIBD and U. Pittsburgh) and developing new ones.
6. Serving as a major resource in support of neuropathological and neuroscientific research with brain tissue from individuals who had PTSD, with healthy controls and with appropriate neuropsychiatric controls who suffered from some other disorder (with or without PTSD) when they were alive.

Conclusions

VA's National PTSD Brain Bank provides a unique resource for advancing research on the pathophysiology of PTSD at genomic, proteomic, cellular, synaptic, histological, and many other levels. This work will facilitate the search for biomarkers that distinguish PTSD from other neuropsychiatric disorders. NPBB offers a platform for advancing our understanding of resilient versus pathological responses to traumatic stress. Most importantly, it raises realistic hopes for discovering novel pharmacological approaches for treating PTSD.

Acknowledgements NPBB is supported by VA's National Center for PTSD. It also receives institutional support at each participating site including VA medical centers in Boston, MA; Durham, NC; Miami, FL; West Haven, CT; and White River Junction, VT along with the Uniformed Services University of Health Sciences.

In addition to the authors, there are a number of other key participants in NPBB who are known collectively as the Traumatic Stress Brain Research Group. They are Victor Alvarez, M.D., Dianne Cruz, M.S., David Davis, PhD, Ronald Duman PhD, Linda Duque MS, CAP, Latease Guilderson MSW, Melanie Hardegree RN, Danny Kaloupek PhD, John Krystal MD, Deborah Mash MD, Christina Romani CTBS, Tamjit Singh MA, Thor Stein, M.D., PhD., Douglas Williamson PhD, and Keith Young PhD.

Compliance with Ethical Standards

Conflict of Interest Matthew J. Friedman is a section editor for *Current Psychiatry Reports*.

Bertrand R. Huber, Christopher B. Brady, Robert J. Ursano, David M. Benedek, Neil W. Kowall, Ann C. McKee, and The Traumatic Stress Brain Research Group each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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