



VA BIOREPOSITORY BRAIN BANK NEWS

A YEAR IN REVIEW

VABBB CELEBRATES 11 YEARS IN SERVICE TO VETERANS!

THE VABBB: 2016 SUMMARY

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ADULTS** 1

As the VA Biorepository Brain Bank goes into its eleventh year, we would like to bid farewell to two very important personnel: Max Stewart and Shannon Murphy. Max is working for a local biotech company while Shannon continues to pursue her educational endeavors by going to nursing school. We'd like to thank them for their commitment to the Veterans and the

Department of Veteran's Affairs. They will both be missed, and we wish them the best of luck with their pursuits.

With the departures of Max and Shannon, two new members joined our ranks bringing their experience to the team. We'd like to introduce Keith Spencer and Derek Collins who were selected from a competitive field of applicants to join the VA

Biorepository Brain Bank. Keith graduated from Wesleyan University in the spring of 2016 with a degree in Neuroscience. Prior to working at the Brain Bank, he worked as a medical assistant at a drug detoxification clinic. Derek graduated from the University of Pittsburgh with a degree in Health Services and a certificate in Community Health Assessment. Prior to working at the brain bank, he worked in Parkinson's Disease research for VA Boston and served over eleven years in the U.S. Navy as a Hospital Corpsman.

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Pictured from left to right:
Derek Collins, Keith Spencer,
Hannah Burris, Gabriel Walt,
Dr. Neil Kowall, Latease Guil-
derson, Nazifa Abdul-Rauf,
Tarnjit Singh, and Dr. Christo-
pher (Kit) Brady

CURRENT VABBB PARTICIPANTS

- ◆ Do you have a new phone number?
- ◆ Are you moving?
- ◆ Have a major health change?

PLEASE LET US KNOW!

Call toll free at
866-460-1158



VABBB IS CURRENTLY ENROLLING !

The VABBB is continuing to accept donations from individuals with no neurological conditions (control participants) to complement our ongoing studies. Comparing brain tissue from a control participant to tissue donated by persons affected with brain disorders is an important tool for studying neurological problems. These comparisons help provide unique insights into the causes of brain diseases and disorders. If you do not have any neurological diagnosis and have thought about donating after your death, please feel free to contact us.

HELP US SPREAD THE WORD:

Learn more about the need for adult participants at:

http://www.research.va.gov/programs/tissue_banking/control/

TUCSON'S BIG MOVE!

The Southern Arizona VA Healthcare System (SAVAHCS) is the main VABBB facility where tissue donations for our ALS and Gulf War Illness brain banks are stored and released to researchers. Recently, the building housing the Molecular Analysis Laboratory underwent extensive remodeling and construction of additional lab space to allow for the strengthening of research activities. From start to finish, the construction and move took 15 months. The new facilities will position SAVAHCS to maintain and expand our research, providing an infrastructure resource to effectively seek additional researchers and funding. The new facility now includes a molecular analysis wet lab, a histology laboratory, a grossing and tissue preparation laboratory, a microscopy and digital im-

aging space, a storage area for a 150 sq. ft. walk-in 4°C cold room for quality storage of formalin-fixed tissues and paraffin-embedded tissue blocks (capacity for 500,000 blocks), a -80°C freezer room for 15 freezers with emergency power access, a space for formalin-fixed tissue, paraffin-embedded blocks, and tissue slides (650 sq. ft.), and six offices. The total square footage of the new facility

is approximately 6,000 sq. ft. (from 2,400 sq. ft. previously). The greatest challenge of this process was coordinating the effort with the many different departments that played a role in its development. The project progressed in manageable stages due to excellent communication between all those involved. The new facility now holds \$2-3 million worth in research equipment that had been previously

dispersed throughout the SAVAHCS campus. The new building will be the subject of a VA Central Office site visit in September 2017. We are looking forward to showcasing the facilities and gain greater attention to our important work in the VA system. The Tucson brain bank started in 2008. The operation has increased in size and sophistication since then. Our inventory is growing, our methods for handling the tissue are always improving, and our data collection practices are expanding. More than enhancing our research function, the new facility serves as a benchmark to the brain bank's maturation in its capacity and expertise. This will ultimately have a positive impact on future donations as the bank develops in esteem.



The new SAVAHCS brain bank facility

VETERAN'S VIEW

WHY DONATION IS IMPORTANT TO ME

BY: ELIZABETH A. BLACKFORD, CW03, USCGR, RETIRED

Call it extreme blood donation. Ever since I can remember, my father gave blood regularly, and when I was old enough, I began donating too. It seemed especially important to me that I give because I had the power to help those who needed blood. And when it came time to get my driver's license, it just seemed natural to check that little box and sign up as an organ donor, as well.

That mentality of wanting to help people in need led me to volunteer for the U.S. Coast Guard, a seagoing military service with a humanitarian mission. Enlisting also gave me the opportunity to learn boat handling and navigation - both nec-

essary skill-sets for pursuing my dream of safely sailing around the world.

I met my future spouse Richard at my first (and his last) duty station in Port Aransas, TX. Richard was the coxswain of a 40-foot small boat, and every fourth day our crew of 4 stood duty, ready to respond to all search and rescue (SAR) alarms that came in. For the next 3 years, he followed me around the country, finally winding up in Yorktown, VA where I transitioned to the reserves, and we put down semi-permanent roots. We began crewing for local sailors during Wednesday night "beer can" regattas and fine-tuned our sailing skills.

At last we felt ready to take the plunge, so we bought and moved aboard our 42-foot Slocum sailboat, SLOW DANCING. For 18 years, we've cruised up and down the East Coast from Maine to the Bahamas, and into the southern Caribbean. We've met lots of foreign travelers in many different anchorages, and

IN THIS SECTION

Each newsletter, we highlight stories from caregivers in *Caregiver Corner* or from participants in *Veteran's View*. In this issue we present the *Veteran's View*. The piece provides a small window into a control patient's donation.



Elizabeth Blackford standing in front of her boat "Slow Dancing"

(Continued on page 3)

VETERAN'S VIEW...CONTINUED

WHY DONATION IS IMPORTANT TO ME

BY: ELIZABETH A. BLACKFORD, CW03, USCGR, RETIRED



Elizabeth and Richard Blackford

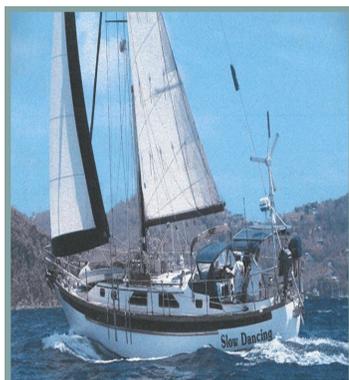
shared short stories and tall tales with strangers who became as close as family. Whenever the conversation turned to harrowing accounts of rescue or assistance, we felt an undeniable glow of pride when our foreign friends told us that in times of emergency, it was always the Americans who came running to help.

Due to my qualifying active duty time, I was eligible for early retirement pay last year. I have to admit, I had my doubts about whether that first retirement check would actually show up on April 1! We both turned 60 last summer and here we are, 39 years later, on the threshold of a new stage of our lives. In January this year, we had our first health scare when my husband was ordered to the emergency room after collapsing in a faint. Six days and countless tests later, he was discharged with reassuring confirmations that his heart, arteries, veins, and colon are all healthy and functioning normally. Doctors surmise the cause of his fainting was low blood oxygen, brought on by a loss of blood in

his lower intestine. That's under control now, but the whole ordeal was a wake-up call for us to put our affairs in order!

In April, we worked with our VA clinic social worker and primary care providers to execute VA Form 10-0137 Advance Directive, Durable Power of Attorney for Health Care, and Living Will for each of us. On page 5 of the form, in Section C - Additional Preferences, we carefully worded our requests as follows: "First priority is to be Organ/Tissue Donor (all that can be harvested) and specifically that the Veterans Affairs Biorepository Brain Bank shall receive brain and spinal cord tissue as agreed."

We expect to contribute "control tissue", because neither of us has symptoms or a family history of amyotrophic lateral sclerosis (ALS). Control tissue is critically important because it helps researchers understand the causes of brain disorders by contrast to diseased brain tissue. Having our advance directives and registration with VABBB completed will remind



"Slow Dancing" at sea.

our families of our wishes, and make it much easier to keep our status up-to-date, if and when our conditions change.

But back to the extreme blood donation idea: we want to be both organ donors for transplant purposes, and whole body donors for medical research and education - we don't have to choose one or the other. Maybe that's something you support, too, and maybe for the same reasons as the two people featured in the outstanding British program Body Donors. Either way, it beats being doused with a bucket of ice water!

HAVE A STORY TO TELL?

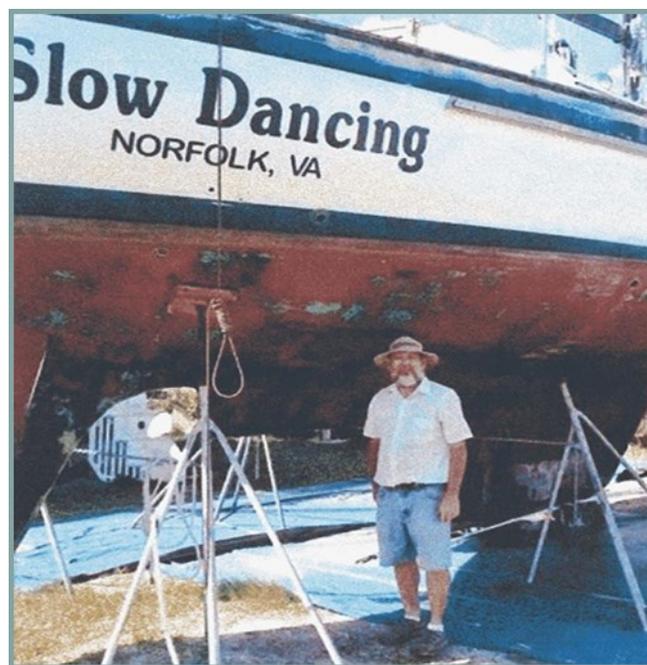
We would like to thank Elizabeth Blackford for sharing her story with us!

If you would like to contribute to the next installment of Caregiver Corner or Veteran's View, please contact us at 866-460-1158.



Let us keep looking, in spite of everything. Let us keep searching. It is indeed the best method of finding, and perhaps thanks to our efforts, the verdict we will give such a patient tomorrow will not be the same we must give this man today."

- Charcot (1889)



Richard Blackford in front of "Slow Dancing".

NEW RESEARCH PROJECTS USING VABBB TISSUE AND DATA

The VABBB exists to supplement research efforts in ALS, Gulf War Veteran's Illnesses, and Post-Traumatic Stress Disorder so that we gain a better understanding of diseases to help prevent and treat future cases. In 2016, we had six new research projects utilizing tissue donated to the VABBB by the generous Veterans enrolled in our studies. Below we've highlighted all six projects contributing to the research efforts in pursuit of a cure and better treatment and therapies.

DNA repair and the role of binding protein-43 (TDP-43). TAR-DNA binding protein-43 (TDP-43) is a protein in humans that binds to RNA and DNA which are two important molecules for gene expression. TDP-43 aids our genes in successfully creating proteins. Improperly processed proteins are a characteristic of many illnesses. Errors in TDP-43 function can lead to protein build-up causing the development of ALS and frontotemporal lobar dementia (FTLD). DNA repair protein 'Ku' associates with TDP-43 suggesting that TDP-43 is involved in DNA repair. The goal of this project is to determine if TDP-43 dysfunction prevents DNA repair in neurons, which is believed to contribute to the development of ALS. Findings from this study can potentially lead to an increase in understanding how ALS develops, opening up new opportunities for treatments.

The role of HDAC6 in ALS pathogenesis. Build-up of misfolded proteins, defective cellular transport to and from a neuron (nerve cell), and death of motor neurons due to loss of neuromuscular junctions are features of ALS. Familial ALS is caused by mutations in superoxide dismutase 1 (SOD1) and TAR-DNA binding protein 43 (TDP-43); superoxide dismutase 1 (SOD1) is an enzyme that breaks down toxic byproducts of normal cell processes to prevent cell damage. Excess clumping of these proteins are found in neurons of sporadic ALS patients also. Histone deacetylase 6 (HDAC6) is an enzyme that influences the transport of harmful protein clusters. HDAC6 interacts with SOD1 and TDP-43. Studies in ALS mouse models have shown that inhibition of HDAC6 protects neurons from degeneration and restores neuromuscular junctions and motor neuron function. Therefore, HDAC6 activity may be involved in ALS pathology. This study will confirm whether HDAC6 expression is increased in human ALS tissue. This would support the use of a medication that targets HDAC6 to treat ALS.

Human endogenous retrovirus contributes to motor neuron disease. Human endogenous retrovirus-K (HERV-K) has been detected in the nerve cells located in the outer layer of the brain in patients with ALS. When expressed in neuronal cultures, HERV-K caused death to neurons, and when the HERV-K envelope protein was expressed in genetically engineered mice they developed features characteristic of ALS. The study will evaluate the expression of HERV-K envelope proteins in specific regions of the brain where ALS is present. Outcomes from this study will improve understanding of the role of HERV-K in how ALS develops.



Mechanisms of ALS/FTD Pathogenesis. ALS is a neurodegenerative disease characterized by gradual death of motor neurons. Protein toxicity is common in ALS and influences defects in transporting molecules to and from neurons. These transport defects are related to stress of the nucleolus, which is the largest structure within the nucleus and is composed of DNA, RNA, and proteins. This stress causes damaging effects in cellular processes. A number of genes have been linked to familial ALS, including C9ORF72. This gene appears to be prominent in nucleolar stress, a feature of neurodegenerative disease. This study will help determine if nucleolar stress is a general response that is activated in familial and sporadic ALS. Advances made in this project will deepen our understanding of the mechanisms in all ALS cases.

Novel pathways of TDP-43 aggregate clearance. A hallmark of ALS is the increase of certain proteins in motor neurons. TDP-43 is an

excess protein regularly observed in ALS. Build-up of TDP-43 may damage nerve cell function. Efforts are underway to understand how cells either limit formation of, or aid the clearance of TDP-43 protein clusters. This study identified a new cellular pathway that clears accumulated proteins. Although this pathway plays a minor role, preliminary data in yeast and human cell lines strongly suggests that TDP-43 accumulations are cleared in a manner dependent on endocytic trafficking, a process by which molecules are engulfed by cells and transported. Materials harmful to the cell are eventually transported to vacuoles/lysosomes, which are structures within each cell that degrade the unwanted material. It is proposed that endocytic trafficking to vacuoles/lysosomes is a previously unexplored means by which cells clear collections of TDP-43, which could lead to the identification of novel therapeutic targets in ALS.

Cryptic exon evaluation in human tissue. TDP-43 plays a role in controlling how specific genes are expressed. One of its primary functions is to repress the expression of RNA sequences known as 'cryptic exons'. In ALS, TDP-43 is mislocalized, which leads to the build-up of abnormally processed proteins in motor neurons. Therefore, cryptic exons may serve as a biomarker in ALS. This will help determine the degree of TDP-43 loss of function. Cryptic exon regions in two key genes were recently found in TDP-43 positive ALS brain tissue from disease. This finding highlights the need for additional studies determining the robustness, reliability, reproducibility and anatomical distribution of cryptic exon expression in ALS.

POST-TRAUMATIC STRESS DISORDER BRAIN BANK



Anyone living with PTSD in the United States may enroll in the PTSD Brain Bank

Beginning in December of 2016, the PTSD brain bank saw a change in the role of project coordinator. Tarnjit Singh, formerly the coordinator of the Gulf War Veteran's Illnesses Brain Bank, continues her work for the VABBB as the new PTSD project coordinator. Latease Guilderson, the former PTSD brain bank project coordinator, has moved into the role of administrative officer of the VABBB. The PTSD brain bank, founded in the summer of 2015, continues to enroll participants and bring awareness to PTSD affecting many veterans and non-veterans. For an interview with Bertrand Huber, one of the PTSDBB neuropathologists see p. 7-8



Learn more about the PTSD Brain Bank at:

http://www.research.va.gov/programs/tissue_banking/PTSD/default.cfm

GULF WAR VETERAN'S ILLNESSES BRAIN BANK

The Gulf War Veterans' Illnesses (GWVI) Brain Bank has also seen many promising developments within the last year. Hannah Burris and Gabriel Walt are now coordinating the GWVI Brain Bank. The Research Advisory Committee on Gulf War Veterans' Illnesses Conference was recently held in Boston, and GWVI Brain Bank staff were able to attend, which allowed the bank to stay updated on latest research and to network with Veterans with GWVI who shared

the things that they were looking for from the VA and from researchers within that community. The GWVI Brain Bank also continues to collaborate with other researchers in the field in an attempt to best raise awareness of GWVI, promote research developments, and to best serve the community.

ABOUT ONE-THIRD OF GULF WAR VETERANS — OR 175,000 TO 250,000 HAVE GULF WAR ILLNESS. USA TODAY



Cognition, Behavior, and Caregiver Burden in ALS

As the "Cognition, Behavior, and Caregiver Burden in ALS" (CBCB-ALS) entered its second year, we saw some exciting changes in recruitment and additions to our team. Hannah Burris, who worked as a Research Assistant on the project, transitioned to work with the VABBB ALS Brain Bank as a Project Coordinator. We welcomed Derek Collins to join our team as a Health Science Specialist. Derek brings many unique skills and qualities from his previous experiences working in Parkinson's Disease Research and as a US Navy combat veteran.

CBCB-ALS is examining whether some persons with ALS experience changes in thinking and behavior, and how these changes affect their caregivers' ability to care for them. As this is an ongoing study, we are excited to continue recruiting new PALS and their caregivers to help us illustrate new ways to slow the rapid progression of the disease and address the needs of caregivers that would allow them to provide effective care for longer periods.



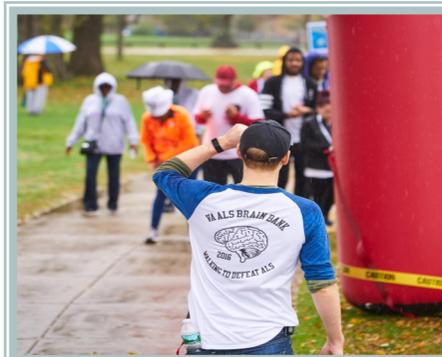
Cognition, Behavior and Caregiver Burden in ALS

ALS BRAIN BANK UPDATE

The ALS Brain Bank has had a year full of exciting changes and progress. Hannah Burris and Gabriel Walt have transitioned into the role of Project Coordinators for the ALS Brain Bank. They are excited to be able to work with the 111 generous Veterans who are currently enrolled in the ALS bank, as well as with the families of those who have donated. Since last summer, 21 new Veterans have enrolled in the bank, and we are excited by this continuation of growth. From the Walk to Defeat ALS to VA Boston's Research Week, we are always looking for new ways to connect with the community of those who have been affected by ALS, as well as by the community of ALS researchers working to find a cure.

Interested in participating?

Call us toll-free at 866-460-1158 for more information



Bottom Left: Members of the VABBB and their families at the finish line

Top Left: Members of the VABBB during the "Walk to defeat ALS"

Top Center: Gabriel Walt of the VABBB approaches the finish line

Right: Gabriel Walt and Hannah Burris of the VABBB during the walk

THIRD TIME IS A CHARM!

VABBB Researchers Participate in the "Walk to Defeat ALS"

On October 22, 2016 members of the VA Biorepository Brain Bank research team at the VA Boston Healthcare System participated in their third "Walk to Defeat ALS" hosted by the ALS Association.

The walk, which takes place at Carson Beach, is a 3-mile walk that is open to the general public. People choose to walk for various reasons. They walk "For the Fight" to motivate and educate others about ALS while being hopeful to find a cure. People choose to walk "For Care Services" to connect with others for social support and to ensure that families of patients with ALS have access to loaner equipment and supplies to bet-

ter accommodate them. Lastly, People walk "For Public Policy" to raise awareness and to garner support from legislators in our nation's capital to introduce and pass bills that will increase funding for ALS research.

Joined by family and friends, our team walked to commemorate Veterans enrolled in our research studies and in memoriam of deceased Veterans who made tissue donations to make our research efforts possible.

The "Walk to Defeat ALS" raised over \$390,000, which is approximately 95% of the proposed goal, to the ALS Association.



ASK A NEUROPATHOLOGIST



Bertrand (Russ) Huber, M.D., Ph.D. is a neuropathologist at the VA Boston Healthcare System and Boston University. He is also the director of the PTSD Brain Bank at the Boston VA.

Can you tell us about what you do for the brain bank?

I'm a neuropathologist. I work with Ann McKee, Thor Stein, and Victor Alvarez; all neuropathologists who work across the different brain banks. Once we get a brain donation my role, along with the other neuropathologists, is to prepare the brain for examination and perform the analysis of the brain tissue. We first take the brain and cut it into two pieces. We freeze one half of the brain and fix the other half so that we can perform histology on it. We then conduct the histological workup on those cases. This allows us to analyze the brain on a microscopic level.

Could you tell us a bit about the PTSD brain bank?

The bank was started by collaboration with Dr. Matt Friedman and Senator Patrick Leahy. They put together the funding to start the PTSD brain bank. Since then we've been collecting the brains of people with a history of PTSD or other conditions such as manic depressive disorder. We also collect the brains of those willing to donate as controls. One of the reasons we're collecting all these brain types is because we want to see if there are any neuropathological features that will allow us to differentiate between the different conditions and PTSD.

What led to your interest in neurological conditions such as PTSD?

It goes back to when I was in the military. While I was serving in the military, understanding different diseases such as PTSD and Gulf War Veteran's Illness was put on the backburner of research. People weren't really paying attention to a lot of the information about these diseases that we're just discovering now. Following the first Persian Gulf War, veterans started coming with different symptomologies. That's when people began to find out about Gulf War illness and other disease states. This always stayed in the back of my mind while I was training and I always wanted to come back and do something about these diseases. As I went through my trainings in medical school and onto my neuropathology fellowship, the opportunity to study those kinds of diseases made itself available and that's what I've been working on ever since.

How long were you in the military and what duties did you perform during your service?

I was in the Army and was involved with air defense. I was in for three years (8 years active ready reserves) and stationed in Germany at an airbase called Bitburg Airbase, which is in southern Germany. The first Persian Gulf War happened when I was stationed in Germany, and the aircraft at the airbase I was at were deployed. Most conflicts today are of course a lot longer compared to the Persian Gulf War, where ground combat only occurred for about five days.

It seems that PTSD research has become a much more prominent issue since the beginning of OEF/OIF. How do you think PTSD research has changed since the first Persian Gulf War to the end of OEF/OIF?

When I went into the military there hadn't been a war in a long time so there weren't a lot of people who had the exposure that would lead to PTSD outside of the Special Forces. People that had PTSD were mainly Vietnam vets, which of course was a longer conflict compared to when I served in the Gulf War. Now as people are getting these repeated exposures and going into longer conflicts like the ones that we have in Iraq and other areas of the Middle East, they're getting deployed multiple times so they're getting exposure that can lead both to PTSD and chronic traumatic encephalopathy (CTE). The exposure we're seeing in our troops nowadays is very different from that of previous conflicts and when I served.

Do you see any similarities in the development of PTSD in veterans from older military conflicts such as the Vietnam War and veterans returning from more recent conflicts such as OEF/OIF?

One of the biggest differences has been how veterans are perceived when they came back from war. I think that when the Vietnam veterans came back they weren't welcomed the way soldiers nowadays are. The fact that veterans are accepted more now has led to increased willingness to reach out for help. This might be aiding our abilities to help veterans because they know that the VA wants to help them out in any way it can.

Can you tell us about the history of brain donation?

The history of preserving tissue starts in the Civil War. What happened during the Civil War is soldiers would be killed far away from their families. At that time it was very important for the families to view the bodies of their loved ones before they were buried. That is when they started using the process of formalin fixing, and the process of embalming the brain became mainstream. Once the brain is embalmed you can look at it under a microscope. A lot of early microscopy was started after the discovery of aniline dyes in the 1800s. Nowadays we only formalin fix half the brain and freeze the other half because a lot of new technology works better on unfixed tissue.

Can you tell us how brain donations have led to any new medications of therapies for other veterans who might be suffering from similar illnesses?

What we find with our studies are new mechanisms that other people can use to design drugs for or find better uses for available drugs. For PTSD they're looking at using certain depression medications to treat patients. For CTE, these donations help us find treatments for tauopathies. I think we're making the most headway in finding markers for disease progression that allow us to see the presence of tau as it goes through the brain. Once we are able to do that we have a way of monitoring people who develop diseases and monitoring treatment as well.

What would you say to encourage people who might be reluctant to donate?

The one thing this field has really been lacking is tissue research. What we're learning from tissue research utilizing donations cannot be learned from any other type of study. When people are willing to donate their brains it gives us a chance to study diseases and determine the factors involved. This gives us the opportunity to make new therapies and find ways of tracking brain diseases, which are both, extremely important. Those who are willing to donate their brains help all different kinds of research and help us fully understand diseases in a way that we can't understand by any other means.

Special thanks to the ALS Clinic Team at the Boston VA for their hard work for the clinic!

- Manisha Thakore-James, MD
- Naomi Turbidy, LICSW (Social Work)
- Elizabeth Bowers, RNP (Palliative Care)
- Melissa Toulan, (Licensed Dietician)
- Bernadette Cummings, (Licensed Occupational Therapist)
- Anne Lambersg, (Major Medical Committee)
- Jacqueline Deppen, RNP
- Caitlan E. Keane, (Licensed Speech & Language Pathologist)

Call Us Toll Free!

If you're interested in participating in any of our studies, please call any of these numbers toll free. Participants can enroll in more than one study .

ALS Brain Bank

(866) - 460 - 1158

PTSD Brain Bank

(800) - 762 - 6609

Gulf War Brain Bank

(855) - 561 - 7827

Caregiver Study

(857)- 364-2136

THANK YOU!

We are deeply grateful to all the Veterans who have decided to make this generous after-death organ donation supporting the VA's commitment to ALS research. While no one can say when ongoing scientific investigations will discover the magical key that unlocks the secret of this destructive disease, it is certain that without the very precious gift of neurologic tissues, progress would be much slower. We are also deeply grateful to Veterans' families and caretakers who have done everything in their power to fulfill the Veterans' wishes of organ donation.

DEPARTMENT OF VETERANS AFFAIRS BIOREPOSITORY BRAIN BANK

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Department of Veterans Affairs Biorepository Brain Bank

