



VA BIOREPOSITORY BRAIN BANK NEWS

A YEAR IN REVIEW



CELEBRATES 15 YEARS IN SERVICE TO VETERANS!

THE VABBB: 2019-2020

STAFFING

The VABBB has seen significant staffing growth these past two years. Zachariah Foster took over for Keith Spencer as the project coordinator of the Amyotrophic Lateral Sclerosis (ALS) Brain Bank. Our beloved Keith went on to pursue medicine at Eastern Virginia Medical School. Derek Collins, our resident veteran and recruitment coordinator went on to pursue a masters in public health at Boston University. We know that his military experience will serve him well in the field.

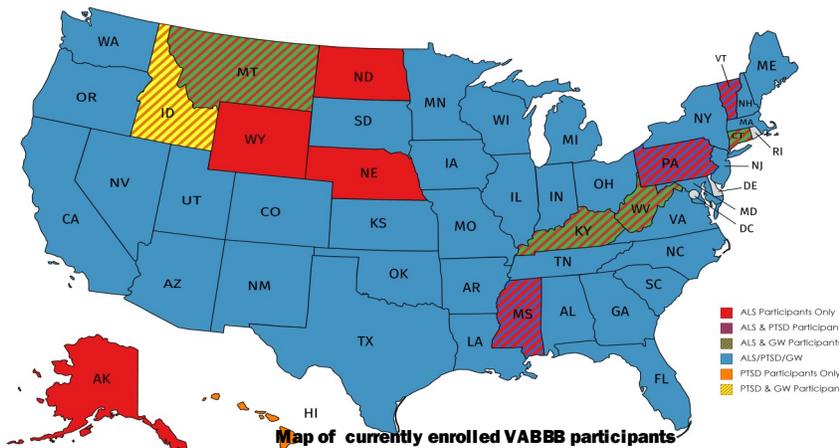
In January 2020, we welcomed Alexandra Riedel, a project research assistant helping on multiple projects, but primarily the ALS brain bank studies. Shortly following Alexandra's arrival, Olivia DeJoie joined us as the new PTSD Brain Bank project coordinator. Jessica Riley is the new Gulf War Veterans Illness Brain Bank coordinator. Finally, our newest staff member is Kendall Carr, a project research assistant for the PTSD Brain Bank. These fantastic four came in with a bang and have gone above and beyond adjusting to working remotely, as the nation grapples with the effects of the COVID-19 pandemic.

In December, we had to bid farewell to our fearless leader/Principal Investigator, Dr. Neil Kowall. Dr. Kowall served as Chief of Neurology at VA Boston Healthcare System for over two decades, while also holding a Professorship at Boston University in Neurology and Pathology. Although he has retired from VA, he will continue his role as the Director of the NIH-funded Boston University Alzheimer's Disease Center. He will be sorely missed!

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VABBB IS CURRENTLY ENROLLING



Who can join the VABBB?

- **Veterans** with ALS, PTSD, Gulf War Veterans Illnesses (GWVI), or those without neurological disorders.
- **Non-Veterans** with PTSD may also enroll.

How can I sign up?

You can enroll in this study by calling:

866-460-1158

VETERAN'S VIEW
GULF WAR VETERANS ILLNESSES BIOREPOSITORY
BY: LORI AND ERIC AHLNESS



My husband and I have always been proud of and humbled by our combined 53 years of active, reserve, and National Guard service. Now that we are retired from military duty and are getting older, we are especially thankful for having access to medical treatment at the VA Medical Center in our community. During our earlier lives, when we received our medical care from the private sector, we occasionally heard medical professionals give acknowledgement to the many medical research discoveries and newly developed treatments that first came through the military and VA medical centers. This was always something we found interesting, and we eagerly read articles in various veteran-related publications, such as from the American Legion, DAV and VA, that discussed VA medical treatments and programs for veterans. And through the years we could see how the VA was moving its medical treatment in a direction of being more proactive, focusing on prevention and research.

When we learned of the opportunity to participate in the VA's Brain Bank study, we signed right up. This is a long-term study and research program committed to researching brain disorders that affect veterans. Both my husband and I have dealt with service-related mental or emotional issues, from anxiety to PTSD to sexual trauma during my earlier military career in the 1970's. These conditions affect you in ways you never realize, but when more PTSD awareness and education became available by the US military and VA, it made us want to do whatever we could to help other veterans who may one day deal with brain disorders to have the best care possible.

After we registered with the VA Brain Bank and completed applications about our military service, we were accepted. The next step was to conduct over-the-phone interviews with a Brain Bank researcher about any trauma or injuries we may have experienced that may have affected the brain. Additionally, we were asked to rate on a scale how we believe an event had affected us. Interviews are concluded with memory quizzes over the phone, which are always both a bit frustrating and fun at the same time. Then periodically, researchers follow up with phone calls months later to repeat memory exercises and rating questions. Eric and I have been impressed with the compas-

sion, care, and respect of privacy these researchers show during each of our phone interviews, and if we had a question, how we can always contact the program via email or phone.

With our personal participation in this program, my husband and I are proud to make a positive contribution for future veterans and their care. Through our participation, researchers can discover patterns of brain behavior that may change over time. And in addition to the interview sessions of the research, my husband and I consented, when one day we pass, to have samples of our brain tissue be added to the study for additional research and development of treatments for veterans dealing with brain trauma. What a positive way for any veteran who has ever dealt with a condition that may affect the brain to contribute to the medical care for our military service members who have served, are serving, or will one day join our ranks.

Lori Ahlness, Major, Retired
 1977-1986 USMCR
 1987-2002 MN ARNG

Eric D. Ahlness, Colonel, Retired
 1986-2014 US Army & MN ARNG

IN THIS SECTION

Each newsletter, we highlight stories from VABBB participants or caregivers, who would like to share their experiences and perspectives.

HAVE A STORY TO TELL?

We would like to thank Eric and Lori Ahlness for sharing their story with us!

If you would like to contribute to the next installment of other newsletters, 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)



VABBB HOSTS NATIONAL MEETING WITH ALS EXPERTS

In June, 2020, the VABBB hosted a national meeting, titled, "Utilization of the VA National ALS Biorepository Brain Bank for Multi-omic Molecular Studies and Biomarker Discovery" during which a panel of international experts in ALS and related motor neuron diseases discussed the current and future state of the art in ALS research. Due to the COVID-19 pandemic, the meeting was a virtual one, which provided opportunities for input and discussion from many experts on ways in which the resources of the VABBB can be maximized to support ALS research.

This 2-day meeting identified future initiatives for the VABBB for data and tissue collection, collaboration and harmonization with other ALS biorepositories, and strategies for enhancing the outreach of the VABBB. The meeting was hosted by **Dr. Neil Kowall**, past Principal Investigator of the VABBB and Chief of Neurology at the VA Boston Healthcare Center, and Professor of Neurology & Pathology, Boston University School of Medicine; and **Dr. Eric Huang**, Professor & Vice Chair for Research, Department of Pathology, University of California San Francisco. Presentations were made by: **Drs. Brady, Robey and Stein**, from the VABBB; **Dr. John Ravits**, University of California, San Diego; **Drs. Richard Bedlack, Dawn Provenzale and Kellie Sims**, Duke University and Durham VA; **Dr. Peter King**, University of Alabama at Birmingham; **Dr. Bryan Traynor**, National Institutes on Aging; and **Dr. Lyle Ostrow**, Johns Hopkins University, who also led a panel discussion among the attendees about how the VABBB can be maximized to support future ALS research.

Department of Veterans Affairs Biorepository Brain Bank



The main issues identified and discussed during the meeting were:

- The VABBB is unique among ALS biorepositories in its collection of extensive health and cognitive information from both our regular contact with living enrollees (our regular phone calls and written surveys we send to you) and through access to the VA electronic health record
- In the future it will be important for biorepositories such as the VABBB to be bigger, better and broader – bigger in terms of the number of samples collected; better in terms of improving the molecular and pathological examination of collected tissue; and broader in terms of collecting different tissue samples (for example, muscle, bone) and samples from those without ALS (controls) to better understand the causes and progression of ALS
- Information about disease progression collected while enrollees are living provides important clues to brain and spinal cord pathology seen in samples donated upon enrollees' passing
- It is important to link genetic and neuropathological data to understand the pathology seen in ALS
- Collecting biofluids such as blood from enrollees while living will be important in developing biomarkers of disease and symptom progression for treatment studies
- Collaboration among ALS biorepositories across the world is essential in order to have large samples needed to discover rare ALS variants and genetic markers
- Finally, and most importantly, make all data, samples and analyses broadly available to researchers

The collective expertise of the presenters and commentary of other scientists at the meeting were used to guide the grant proposal that we submitted to the VA in February for continued funding for the VABBB. We thank the attendees for providing their expertise to help the VABBB collaborate and support the scientific community. Of course, none of this research is possible without the generous participation and tissue donations from the hundreds of Veterans and their families in the VABBB over our 15-years of existence. We honor

The meeting presentations may be found at:

https://www.research.va.gov/programs/tissue_banking/als/default.cfm#natl-meeting

VA BIOREPOSITORY BRAIN BANK: HEALTHY BRAINS- WHY DONATE?

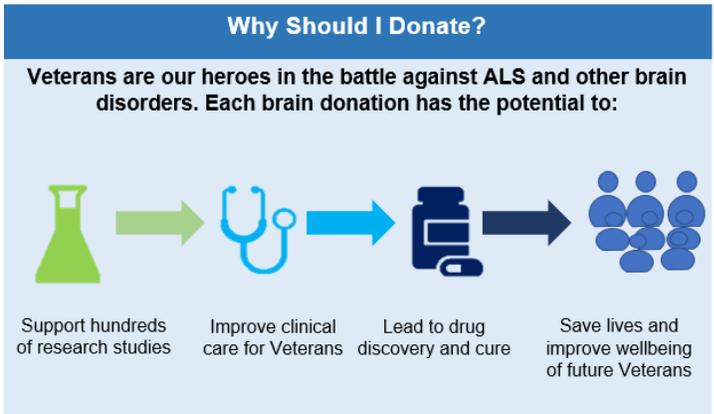


Since its inception the VABBB has dedicated itself to better understand neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), disorders associated with Veterans of the 1990-91 Gulf War, and people experiencing posttraumatic stress disorder (PTSD). Our Veteran participants play an integral role in order for researchers to have access to brain tissue needed to make discoveries. Brain donors with neurological diseases are incredibly important; however, equally meaningful are our healthy controls.

“Brain tissue donations from relatively healthy Veterans are essential to VABBB research.”

As a healthy Veteran, you can make an impact to help advance research

findings for fellow Veterans who experience these diseases. In this way, it is a team effort. Researchers rely on healthy controls to make comparisons between the differences in each population. Over the years the VABBB has continued to make efforts in order to create more opportunities for healthy Veterans to join this noble cause. Currently the VABBB enrolls Veterans with ALS, as well as Veterans without, also known as controls. In our Gulf War Veterans Illnesses study, we recruit Veterans who served during the years 1990-91, regardless of health status. PTSD offers the opportunity for Veterans with this condition to make a donation and, at times, non-Veterans.



“Donating Brain Tissue can help to support fellow Veterans”

Military Veterans are more likely to develop neurodegenerative diseases such as ALS, for reasons unknown. When a relatively healthy Veteran donates their brain tissue, they help their fellow Veterans through the potential of understanding differences between healthy and unhealthy Veterans.

“Donated tissue also gives hope to families of Veterans”

Veterans are not the only ones affected by the impacts of neurodegenerative diseases such as ALS, or other adverse health conditions. Families of Veterans often share the burden of these symptoms acting as the caretakers for our heroes.

Dr. Ann McKee, Chief of Neuropathology, VA Boston Healthcare System; Director Boston University Center for the Study of Traumatic Encephalopathy © 2017

Learn more about the need for adult participants at:
http://www.research.va.gov/programs/tissue_banking/control/

PTSD BRAIN BANK HOSTS EDUCATIONAL BRAIN DISSECTIONS

The PTSD Brain Bank has begun educational brain dissections at VA Boston. The goal of the brain dissection is to educate students and faculty at VA and local academic institutions about neuroanatomy and different neuropathological features of various illnesses. These regular dissection meetings enhance the value of brain donations beyond the traditional use in research by also serving a role in educating future clinicians and researchers. No personally identifying information is revealed during these dissections to preserve the confidentiality of those who make these precious donations. No tissue is lost during educational dissections, all tissues continue to be used for research. Displaying tissues does not affect their integrity or quality.

Published Studies Using VABBB Tissue

The following studies were published in research journals between 2018-2020. Each study used tissue provided by the VABBB. Links to the studies are provided below and in the online version of this newsletter on our website (https://www.research.va.gov/programs/tissue_banking/als/ - see "Issue 7"). The articles are very technical in nature, but in general, the research being conducted using VABBB tissue and data are examining how motor neurons, which directly or indirectly control muscles and glands, are affected by ALS. Motor neurons are located in the motor cortex or brainstem of the brain and the spinal cord. These neurons can be damaged by processes that affect the structure of the neuron, communication of information or other cellular processes within the neuron, or damaging effects that occur outside the neuron. Many of the studies noted below examine how mutations in specific genes, or other neuron dysfunction, may be related to ALS pathology. This research cannot be conducted without the precious tissue donations made by Veterans in the VABBB. Thank you.

We want to highlight "Neuropathological profile of long duration amyotrophic lateral sclerosis in military veterans," which was published by the VABBB research team in *Brain Pathology* and featured in *ALS New Today* on July 20th, 2020 (<https://alsnewtoday.com/news-posts/2020/07/20/slow-progression-seen-us-veterans-living-longer-than-als-norm/>).

Brain Pathology (2020): Neuropathological profile of long duration amyotrophic lateral sclerosis in military Veterans

<https://onlinelibrary.wiley.com/doi/full/10.1111/bpa.12876>

VABBB researchers examined similarities and differences in clinical presentation and neuropathology in Veterans with long (>10 years) vs. those with standard duration ALS. Those with long-duration ALS were younger at disease onset, had a slower initial ALS symptom progression on the ALS Functional Rating Scale-Revised, and took longer to diagnose than standard duration ALS. One marker of ALS pathology (TDP-43) was reduced in those with long-duration ALS compared with standard duration. Long-duration ALS participants had less severe

degeneration of the lower motor neuron system (*nerve cells of the brain stem and spinal cord that connect to skeletal muscles and glands*). Upper motor neuron (*neurons extending from various areas of the brain or brainstem that connect with lower motor neurons*) degeneration was similar. Notably, many other neuropathological markers of ALS were similar between the standard and long-duration groups and there was no difference in the frequency of known ALS genetic mutations. These findings suggest that the lower motor neuron system is relatively spared in long-duration ALS and that pathological progression is likely slowed by as yet unknown genetic and environmental modifiers.

Nature Communications (2018): A complex of C9ORF72 and p62 uses arginine methylation to eliminate stress granules by autophagy

<https://www.nature.com/articles/s41467-018-05273-7>

Genes and Development (2018): A C9ORF72-CARM1 axis regulates lipid metabolism under glucose starvation-induced nutrient stress

<http://genesdev.cshlp.org/content/early/2018/10/26/gad.315564.118.short?rss=1>

Journal of Neuropathology and Experimental Neurology (2019): Increased ISGylation in Cases of TBI-Exposed ALS Veterans

<https://academic.oup.com/jnen/article/78/3/209/5292580>

Molecular Brain (2019): Loss of endosomal recycling factor RAB11 coupled with complex regulation of MAPK/ERK/AKT signaling in postmortem spinal cord specimens of sporadic amyotrophic lateral sclerosis patients

<https://pubmed.ncbi.nlm.nih.gov/31196199/>

Molecular Brain (2019): RT₂ PCR array screening reveals distinct perturbations in DNA damage response signaling in FUS-associated motor neuron disease

<https://molecularbrain.biomedcentral.com/articles/10.1186/s13041-019-0526-4>

Human Molecular Genetics (2019): Amyotrophic lateral sclerosis-associated TDP-43 mutation Q331K prevents nuclear translocation of XRCC4-DNA ligase 4 complex and is linked to genome damage-mediated neuronal apoptosis
<https://academic.oup.com/hmg/article-abstract/28/15/2459/5424346?redirectedFrom=fulltext>

Proceedings of the National Academy of Sciences (2019): Motor neuron disease-associated loss of nuclear TDP-43 is linked to DNA double-strand break repair defects

<https://www.pnas.org/content/116/10/4696>

Nature Neuroscience (2019): L3MBTL1 regulates ALS/FTD-associated proteotoxicity and quality control

<https://www.nature.com/articles/s41593-019-0384-5/>

Neuron (2020): Pathogenic Huntingtin Repeat Expansions in Patients with Frontotemporal Dementia and Amyotrophic Lateral Sclerosis

<https://pubmed.ncbi.nlm.nih.gov/33242422/>

Additional Current Research Projects Using VABBB Tissue:

In addition to the projects noted above, these projects have received VABBB tissue and data and are currently conducting research that may result in future published results.

Harvard Medical School : Function of ALS-causative RNA binding proteins

University of Western Ontario : Matrin3 mislocalization and aggregation in spontaneous ALS

Columbia University : Brain-derived extracellular vesicles as a novel source of biomarkers for disease progression and environmental exposure in ALS

Massachusetts General Hospital/The Healey Center for ALS: Assessing mitochondrial dysfunction in ALS

VA San Diego/UC San Diego: Identifying Caveolin-1 expression profile in brain and spinal cords in post-mortem veterans ALS samples

Massachusetts General Hospital : Validation in Post-Mortem Tissue of iPSC-Identified ALS Phenotypes

Medical University of South Carolina, RJ VA Medical Center : Ceramide-Mediated Mitochondrial Stress Response in ALS

HIGHLIGHTING WOMEN OF BB IN HONOR OF 100TH ANNIVERSARY

In honor of the 100th anniversary of women's suffrage, we wanted to highlight the women in the VA Biorepository Brain Bank. We asked them to provide a little summary of what they do and what they enjoy most about working in the Brain Bank!

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



Latease Adams Guilderson: I've been with VA for eight years, serving previously as a Project Coordinator and now Administrative Officer. I'm humbled to serve those who have borne the battle and appreciate your wealth of experiences. I also enjoy the task of purchasing intricate equipment used for examining brain specimens that could potentially lead to improving the lives of those suffering from PTSD and ALS.



Dr. Ann McKee: She is the chief of Neuropathology at the VA Boston Healthcare System as well as the Director of the Boston University Center for the Study of Traumatic Encephalopathy. Much of her work focuses on mild traumatic brain injuries that result from contact sports and military experience, and their long term effects.



Dr. Grace Rosen: I have been a health science specialist at the VA since late 2019 after finishing a PhD in biophysics and biochemistry. At the VA I have been working on developing tissue treatment and microscopy techniques to characterize CTE. It is an honor to work here with tissue from brain donors to gain real insight into mechanisms of human disease.



Nazifa Abdul Rauf: I have had the honor of serving our Veterans in the last five years through my work as a Project Coordinator of the VA Brain Bank. In addition to meeting Veterans and learning about their experiences, I enjoy being part of our diverse team that understands Veterans, who come from varied military service and conflicts, and loves taking care of them. With every brain donation that I coordinate, there is a great reward in knowing that I helped honor a Veteran's wish to donate their tissues to advance science and improve the lives of future generations.



Olivia DeJole: I have worked as the PTSD Brain Bank Project Coordinator for about a year now. One of the best parts of the job is hearing from our participants about the various reasons why they choose to participate in such research. We work with a population so dedicated to helping their fellow veterans, and it really is inspiring.



Kendall Carr: I have worked at the Brain Bank as the PTSD Research Assistant for over six months now. I have enjoyed getting to know our veterans during this time as well as working with a great group of people. One of my favorite parts about working here is how committed our veterans are to the Brain Bank, and I love hearing their reasons why they have decided to join. Every story is unique and that is what makes the Brain Bank so special.



Jessie Riley: In March of 2020 I started with the VABBB as a Project Coordinator. One of the reasons I love my job is that I get to have the privilege to serve our Veterans. Something I value most is the vast amount of people and backgrounds I get to work with, both with our Veteran participants as well as our VABBB team. I am honored to be part of a group that is pursuing research to better understand ALS, PTSD and GWVI.

Alexandra Riedel: I have been with the Brain Bank for over a year now and have mainly been working on the ALS study, although I do enjoy contributing to the PTSD and Gulf War Brain Banks as well. My favorite part of my job is collecting data in an efficient manner while also being able to connect and learn about the veteran's service history and life. My partner is in the military and so I have seen the sacrifices involved in military service, as well as the joys. I also enjoy answering questions and relaying information in a way that people can understand. I am honored to be able to contribute in some way to advancing the science on numerous diseases in order to improve the health of veterans.

Interested in participating?

Call us toll-free at

866-460-1158 for more information

POST-TRAUMATIC STRESS DISORDER BRAIN BANK

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

Learn more about the PTSD Brain Bank at:

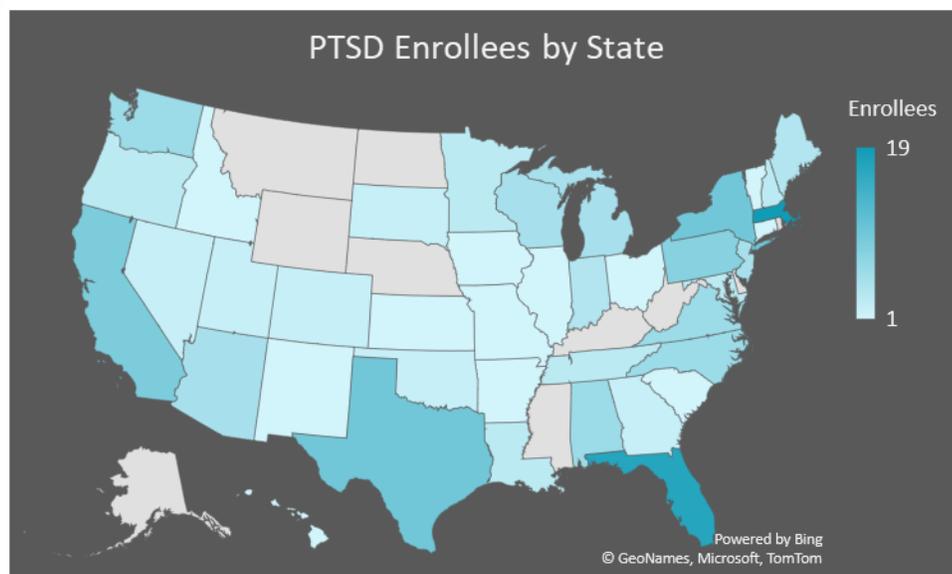
http://www.research.va.gov/programs/tissue_banking/PTSD/default.cfm

The PTSD Brain Bank (PTSDBB) has experienced rapid growth in enrollment over the past year. The PTSDBB began a collaboration with PINKConcussions to increase the number of female Veteran and non-Veteran participants. PINKConcussions, is a non-profit organization with a mission to “improve the pre-injury education and post-injury medical care for women and girls challenged by brain injury including concussion incurred from sport, violence, accidents or military service. Additionally, the PTSDBB began collaboration with USUHS at the VA Seattle this year and Please call the PTSDBB Coordinator, Olivia De Joie, at 857-364-4198, with any questions or updates regarding the PTSDBB.

Our PTSD Brain Bank colleagues at Yale recently published an article in Nature Neuroscience titled “Transcriptomic organization of the human brain in posttraumatic stress disorder”. Using postmortem RNA-sequencing data from four prefrontal cortex subregions, researchers analyzed molecular data to determine how psychological trauma impacts the brain’s molecular landscape in deceased participants with PTSD and/or MDD. Marked differences in gene expression patterns were found in those diagnosed with PTSD and those who had not. This crucial dataset will pave the way for better understanding of PTSD genetic risk and “identifying molecular pathways that are significantly involved in mediating the effects of trauma.”

“This is a new beginning for the PTSD field,” noted Yale’s John Krystal, the Robert L. McNeil, Jr. Professor of Translational Research, professor of psychiatry, neuroscience, and psychology, and co-senior author of the paper. “We need new treatments for PTSD, and studies like this will provide the scientific foundation for a new generation of medication development efforts.” (<https://news.yale.edu/2020/12/21/brain-tissue-yields-clues-causes-ptsd>).

The full article can be read at <https://www.nature.com/articles/s41593-020-00748-7>



Map of 2021 VABBB PTSD Enrollees

The VABBB would like to thank all of our participants for their patience during this unprecedented time. In spite of limited resources internally and beyond, the team continues to work feverishly to meet your expectations. Rain, snow, or COVID, we will always be a 24/7 operation, available to serve the needs of our participants who have willed their organs to VABBB for research.

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)
- Michelle Becker, (Licensed Dietician)
- Bernadette Cummings, (Licensed Occupational Therapist)
- Anne Lamberts, (Major Medical Committee)
- Dawn Medeiros, (Clinical Nurse Coordinator)
- Caitlan E. Keane, (Licensed Speech & Language Pathologist)
- Denise Hayes, (Nurse Practitioner)

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The views expressed in this newsletter are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

FAREWELL TO DR. KOWALL!



Pictured here is Dr. Neil Kowall (right) pictured with Dr. David McCarthy at Dr. Kowall's farewell ceremony.

The VABBB staff greatly appreciates the many contributions Dr. Kowall has provided during his two decades of commitment to the VABBB. In the words of Dr. McCarthy "Dr. Kowall's leadership and mentorship will be missed." On behalf of the VABBB staff we want to recognize him for all of his accomplishments, and thank him for his leadership of the VABBB for over a decade.

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.