

VISN 3 MIRECC Report

News From the NY/NJ MIRECC
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Mount
Sinai



VISN 3 MIRECC Mission Statement

The mission of the VISN 3 MIRECC is to investigate the causes and treatments of Serious Mental Illness (SMI) in order to enhance the recovery of Veterans.

The VISN 3 MIRECC focuses on domains of psychological function that are demonstrable impediments to healthy function and recovery. These domains include: reality testing, cognitive function, affective processing, and aggression / impulse regulation and contribute to: psychosis, cognitive impairment, affective lability, and impulsive aggression. We focus on these dimensions as refracted through the categorical SMI diagnoses of Schizophrenia, Bipolar Disorder, and Borderline Personality Disorder which require extensive systemic resources and are complex to treat. We apply translational research efforts and clinical/system interventions to address one or more of these domains to promote the mental health wellness that Veterans deserve.

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Marianne Goodman, MD	Erin Hazlett, PhD	Vahram Haroutunian, PhD	Deborah Kayman, PhD
Bruce Levine, MD	Margaret McClure, PhD	Effie Mitsis, PhD	Antonia New, MD
Deborah Perlick, PhD	Stella Plevan, PhD	Larry Siever, MD	

Translational Research

From Bench to Bedside

The VISN3 MIRECC fulfills its mental health mission through multiple translational research avenues. One of the approaches being aggressively followed is postmortem brain studies of the neurobiology of schizophrenia. For the MIRECC, these studies began in 1999 when MIRECC investigators, led by Dr. Haroutunian, were among the two laboratories in the world to first use DNA-chip technology to study the brains of persons with schizophrenia. These pioneering studies pointed convincingly to abnormalities in brain cells called oligodendrocytes. These cells provide the fatty membranes, myelin, that coat the axons (principal appendages) of nerve cells and enhance their capacity to conduct the electrical currents that underlie communication between nerve cells and between different parts of the brain. These and subsequent studies have provided the biological context for one of the mechanisms through which communication between nerve cells and different regions of the brain may fail in schizophrenia.

It has been known for a long time that the cells of the brain can be roughly divided into two classes: nerve cells, also called neurons, and glia (a term derived from the Greek word for glue). Oligodendrocytes, the myelin producing cells, are classified as glia. Glia have traditionally been thought to serve a supportive role for the nerve cells and have been largely ignored as the principal agents that may be involved in brain diseases such as schizophrenia. The translational and genetic studies being conducted by the research team of the VISN3 MIRECC are shedding new light on the importance of these glial cells in serious mental illness and are beginning to suggest that far from serving a supportive or ancillary role, abnormal functioning of these cells may be at the heart of disease processes such as schizophrenia.

VISN3 MIRECC investigators are following-up on these initial findings with new studies that take advantage of a unique VISN3 MIRECC resource, the postmortem

Brain Bank. Through the generous and altruistic support of Veterans and non-Veterans, the VISN3 MIRECC has amassed a collection of over 1,700 postmortem human brains. This postmortem collection serves as a resource for the study of the brain not only by VISN3 MIRECC investigators, but by laboratories studying brain diseases world-wide. Using this resource, we have pinpointed some of the specific proteins associated with myelin and how it adheres to the nerve cell that may be malfunctioning in the brain of persons with schizophrenia.

The human brain is the most complex organ in the body and mental illnesses are among the most complex and difficult to understand problems that confront us. Studying the postmortem brain is not enough, or is maybe too complex, for a detailed understanding of how the different abnormally expressed proteins that we have identified in schizophrenia may affect neuronal communication and behavior. To gain a better and more detailed knowledge of the roles of these various proteins, VISN3 MIRECC investigators are creating simpler mouse model systems that directly mimic the schizophrenia-related changes in these different proteins individually and identifying the changes that they produce in brain function and behavior.

While understanding the functioning of the brain in schizophrenia is important, our mission is to help Veterans with serious mental illness directly. Using the knowledge gained from these initial translational studies, MIRECC staff are beginning drug trials that aim to “correct” some of the myelin-related changes that we have observed in the postmortem brain of persons with schizophrenia. Drs. Byne, Levine, and Haroutunian are at the beginning stages of clinical trials to determine the potential of a drug, 4-aminopyridine, that is already FDA approved for the treatment of multiple sclerosis, for the treatment of schizophrenia.

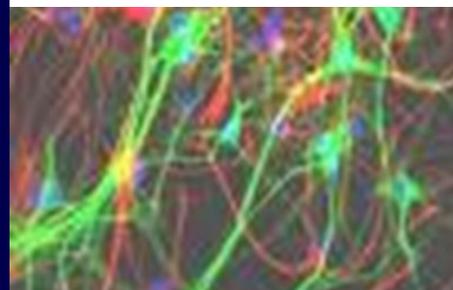


Letter From the Director

I welcome you to a new edition of the VISN3 MIRECC newsletter. This is an exciting time in the VISN3 MIRECC in our continued efforts to investigate the causes and treatments of Serious Mental Illness and enhance recovery of veterans. This newsletter highlights some of our efforts in investigating new mechanisms and treatments of schizophrenia, in establishing evidence based practices in VISN3, and some of the new MIRECC staff that has joined us to further these efforts. We want to keep you informed of our progress, our programs both new and ongoing, and introduce you to some of our investigators. Please feel free to take a look at our webpage (www.mirecc.va.gov/MIRECC/VISN3) or contact us with your ideas and suggestions.

There have been a number of changes in the MIRECC over the last year and while we are saying hello to many new persons we say goodbye to others. Two of our fellows have graduated. Dr. Miklos Losonczy, ACOS of MH for VAHCS -NJ, and the Clinical Director of the VISN3 MIRECC has retired. Dr. Losonczy was a tireless advocate for veterans and for recovery oriented services and he will be missed in all of his roles. But changes are also opportunities to revamp and reevaluate to better meet the needs of veterans and VISN3 and we look forward to working with all of you to make the most of our efforts.

- Larry Siever



Glia and nerve cells intermix in the brain to produce a beautiful mosaic of interconnected and interdependent networks.

Dialectical Behavior Therapy

Research and Training

Dialectical Behavioral Therapy (DBT), developed by Marsha Linehan, PhD, is an empirically validated treatment approach emphasizing the role of *emotion regulation* in the treatment of suicidal and self-destructive behaviors in borderline personality disorder (BPD). It has gained considerable popularity and is included as a component of the American Psychiatric Association guidelines for treatment of BPD. This approach stresses skills and techniques for emotional regulation, and encourages cognitive control over maladaptive behavioral patterns.

The VISN 3 MIRECC, through its pilot grant program, supported the development of the James J. Peters VA DBT ten years ago in 2002. Over the last decade, a vibrant DBT clinical and research program has been developed by VISN 3 MIRECC investigator, Marianne Goodman, MD.

This program is comprised of three components—clinical care, education/training, and research. Clinically, the DBT program targets self-destructive, aggressive and personality disordered Veterans requiring more intensive treatment. Over 125 veterans have participated in the clinical program since its inception. Starting in 2005, the James J. Peters VA DBT program initiated 6-month training experiences for psychology interns and third year psychiatric residents rotating through the mental health outpatient department. The training mission has continued to grow and now includes opportunities for medical student electives, fellowship training, and 4th year psychiatry residency electives.

In 2005, the VISN 3 MIRECC hosted a Behavioral Technology intensive DBT training for over 65 clinicians from across the nation and included DBT teams from the James J Peters VA and Mount Sinai School of Medicine, the academic affiliate. In 2012, the VISN 3 MIRECC was proud to host the

first ever "VA-only" intensive DBT training, initiated by Drs. Marianne Goodman and Christie Jackson from the Manhattan VA. 45 clinicians with representatives from every VA in VISN 3 and a Vet Center team spent an intensive week in training with Dr. Marsha Linehan in January, learning the basics of DBT. A second training week with Dr. Korslund followed in June 2012, with presentations and consultation, after DBT teams were developed at each site. The VISN 3 currently has operative DBT programs at the Manhattan, Bronx, Montrose/Castlepoint, Northport, Brooklyn, New Jersey campuses, and a Vet Center team. They are leaders nationwide in implementing this treatment approach across the VA system.

The research mission for the JJPVA DBT program spans multiple domains ranging from identification of biomarkers and randomized clinical trials of DBT treatment response (PI: Goodman) to health services research on DBT implementation (PI: Goldstein). Currently two Department of Defense funded studies exist examining DBT for high-risk suicidal veterans (PI: Goodman/New) and Affective Startle as a Biomarker for Suicide Risk (PIs: Goodman/Hazlett) along with a completed VA Advanced Career Development Award (Goodman) on neuroimaging and physiological predictors of DBT treatment response.

Future directions include continued study of DBT implementation, piloting of DBT adaptations and Friends and Family DBT groups (PI: Perlick).



What is DBT?

- A system of therapy originally developed by Marsha M. Linehan to treat people with borderline personality disorder (BPD).
- DBT combines standard cognitive-behavioral techniques for emotion regulation and reality-testing with concepts of distress tolerance, acceptance, and mindful awareness.
- DBT strives to have the patient view the therapist as an ally rather than an adversary in the treatment of psychological issues.
- All DBT involves individual therapy sessions and group meetings.
- The four modules of DBT are Mindfulness, Distress Tolerance, Emotion Regulation, and Interpersonal Effectiveness.



Left: Participants of the VA-only intensive DBT Training Program. Above: Dr. Linehan lecturing to the group.

Spotlight: Psychophysiology with Dr. Erin Hazlett

MIRECC Report (MR): What is psychophysiology? Psychophysiology is a discipline within the larger field of biological psychology/psychiatry. The scientific approach focuses on the interaction between behavior, brain, and the human body's physiology. The main principle of psychophysiology is that cognitive, emotional, behavioral, and social events are all reflected in physiological processes. I think of it as a "window" into the brain.

MR: What are some of the advantages of using psychophysiological methods in research? There are many but I will focus on just a few key strengths. For experimental research, recording of bodily responses may reveal effects of mental states not observable in verbal reports or overt behavior. It allows for the investigation of "mental chronometry", that is, the time course and the waxing and waning of cognitive and emotional processing as physiological responses can be recorded continuously over time. Although psychophysiological research involves human participants, many paradigms can also be employed in animal research making the research translational.

MR: How do you use psychophysiology in your research? I am currently working on two federally-funded studies that involve psychophysiology.

Both record muscle activity under the eye (electromyography or EMG) as a measure of the amplitude of the eyeblink response to a brief static noiseburst. While the eyeblink response is a reliable component of the startle reflex, its amplitude can be modified (potentiated or inhibited) by cognitive/attentional and emotional processing. For example, in healthy people, startle eyeblink amplitude is smaller during an attended tone than an ignored tone. While viewing an unpleasant picture, startle eyeblink amplitude is potentiated relative to that observed during a pleasant picture. My VA Merit award is a proof-of-concept study using a psychophysiological measure of cognitive processing as a potential biomarker for predicting treatment response to an anti-psychotic medication (risperidone) in Veterans with schizophrenia. Secondly, I'm working with my MIRECC colleague, Dr. Marianne Goodman on a DOD-funded study that uses a psychophysiological measure of emotion processing (affective modulation of the startle eyeblink



One of the MIRECC research assistants volunteers for a photo in the MIRECC Psychophysiology Lab.

response, briefly described earlier) in Veterans at low- and high-risk for suicide. The goal is to use affective startle to determine which high-risk patients will best respond to Dialectical Behavioral Therapy.

MR: How do you think psychophysiology will impact clinical care in the future? My hope is that in the future, psychophysiological methods will be translated from the research lab into the clinic. Ideally, we will discover psychophysiological measures or biomarkers that can be reliably used in the clinic to better diagnose, monitor, and treat patients suffering from serious mental illness, e.g., by predicting the best treatment choice for a given patient. I'm working with Drs. Goodman and Erik Langhoff on a new initiative that will begin to explore the use of psychophysiology as a "telehealth" measure of emotional wellness.



Erin Hazlett, PhD

Research Professor

Director of the Cognitive Psychophysiology Laboratory, Mount Sinai and JJPVAMC MIRECC. She received her Ph.D. in Psychology from the University of Southern California. Her research involves an examination of cognitive and emotional processing abnormalities in serious mental illness (e.g., schizophrenia) using neuroimaging and psychophysiological approaches.

Introducing New MIRECC Staff

Lisa Dixon, MD, MPH

Director of the Center for Practice Innovations at Columbia University and the Director of Health Services Research and Education Development at the VISN 3 MIRECC. She has published more than 170 articles in peer-reviewed journals and received the 2009 American Psychiatric Association Health Services Senior Scholar Award, as well as the Wayne Fenton Award for Exceptional Clinical Care. Dr. Dixon's clinical work and



research focuses on people with severe mental illnesses such as schizophrenia who have co-morbid medical and substance use disorders, and other vulnerabilities. Dr. Dixon is a graduate of Harvard College and the Cornell University Medical School. She received a Master's in Public Health at Johns Hopkins.

Effie Mitsis, PhD

Director of the post-doctoral training program at the VISN 3 MIRECC. She is a licensed neuropsychologist, Assistant Professor of Psychiatry at Mount Sinai School of Medicine, James J. Peters VA Medical Center affiliate within the Department of Rehabilitation Medicine, and Vice Chair of the JJPVA IRB. Dr. Mitsis received her doctorate in neuroscience/neuropsychology at the Graduate School and University Center of the City University of New York and conducted her dissertation research at Columbia University. She completed pre- and post-doctoral fellowships at Yale University School of Medicine and the Veterans Affairs Connecticut Healthcare System. At the JJPVAMC, she is investigating the cognitive and neurobiological consequences of blast-exposure traumatic brain injury.



David Banthin, PhD

Dr. Banthin graduated from the Clinical Psychology Ph.D. program at the New School for Social Research. Dr. Banthin is presently a JJPVAMC VISN 3 MIRECC Postdoctoral Fellow in Psychology. Concurrently, he is a Psychoanalytic fellow at Columbia University. Dr. Banthin's current research focuses on therapeutic alliance between patient and therapist. The aim is to develop and establish evidence-based interventions for maintaining the therapeutic alliance.



Fiona Graff, PsyD

Dr. Graff received her doctorate in Clinical Psychology with a concentration in Community Psychology, from the Rutgers Graduate School of Applied and Professional Psychology and completed her internship at NYU-Bellevue Hospital Center. Her research interests include treatment development and receipt for individuals with serious mental illness and substance use disorders. She joins the MIRECC as a Postdoctoral Fellow.



Mercedes Perez-Rodriguez, MD, PhD

Dr. Perez-Rodriguez received her medical and doctorate degrees from the Autonoma University of Madrid. She joined the Department of Psychiatry in July 2008, as one of the two founding members of the Physician-Scientist Research Track at Mount Sinai. She joins the MIRECC as a Postdoctoral Fellow. Her research focuses on suicidal behaviors, impulsivity, and aggression in patients with serious mental illness.



Panos Roussos, MD, PhD

Dr. Roussos received his MD and PhD from the University of Crete and completed his residency training in psychiatry at Mount Sinai School of Medicine. His research includes investigating the genetic mechanisms of molecular intermediate phenotypes that underlie the pathophysiology of schizophrenia. Dr. Roussos joins the VISN 3 MIRECC as a Postdoctoral Fellow.





What to Look for in the Next Issue

Spotlight on Health Services Research and Evaluation

Recent Publications

Dixon L, Lewis-Fernandez R, Goldman H, Interian A, Michaels A, Kiley MC. Adherence disparities in mental health: opportunities and challenges. *J Nerv Ment Dis.* 2011, 199:815-820.

Goodman M, Roiff T, Oakes AH, Paris J. Suicidal risk and management in borderline personality disorder. *Curr Psychiatry Rep.* 2012, 14:79-85.

Hazlett EA, Zhang J, New AS, Zelmanova Y, Goldstein KE, Haznedar MM, Meyerson D, Goodman M, Siever LJ, Chu, KW. Potentiated amygdala response to repeated emotional pictures in borderline personality disorder. *Biol Psychiatry.* 2012, 72:448-56.

Hazlett EA, Collazo T, Zelmanova Y, Entis JJ, Chu KW, Goldstein KE, Roussos P, Haznedar MM, Koenigsberg HW, New AS, Buchsbaum MS, Hershowitz JP, Siever LJ, Byne W. Anterior limb of the internal capsule in schizotypal personality disorder: Fiber-tract counting, volume, and anisotropy. *Schizophrenia Res.* In press.

Katsel P, Byne W, Roussos P, Tan W, Siever L, Haroutunian H. Astrocyte and glutamate markers in the superficial, deep and white matter layers of the anterior cingulate gyrus in schizophrenia. *Neuropsychopharmacology.* 2011, 36:1171-7.

Kayman DJ, Goldstein MF. Cognitive deficits in schizophrenia. *Curr Translational Geriatric Exper Geontology Rep.* In press.

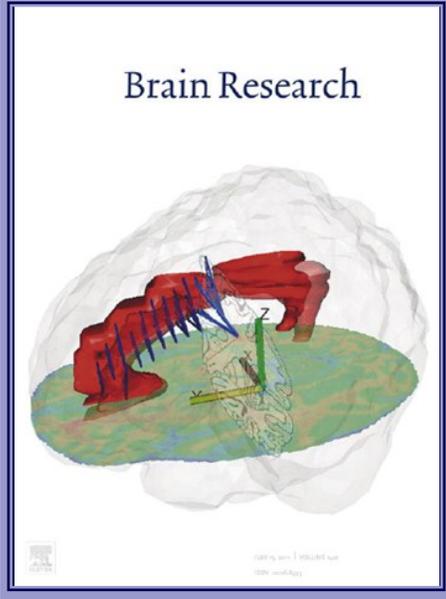
Moehle MS, Luduena RF, Haroutunian V, Meador-Woodruff JH, McCullumsmith RE. Regional differences in expression of beta tubulin isoforms in schizophrenia. *Schizophrenia Res.* 2012, 135:181-6.

New AS, Aan Het Rot A, Ripoll LH, Perez-Rodriguez MM, Lazarus S, Zipursky E, Weinstein SR, Koenigsberg HW, Hazlett EA, Goodman M, Siever LJ. Empathy and alexithymia in borderline personality disorder: clinical and laboratory measures. *J Pers Disord.* In press.

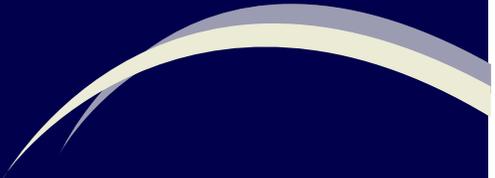
Perez-Rodriguez MM, Hazlett EA, Rich EL, Ripoll LH, Weiner DM, Spence N, Goodman M, Koenigsberg HW, Siever LJ, New AS. Striatal activity in borderline personality disorder with comorbid intermittent explosive disorder: sex differences. *J Psychiat Res.* 2012, 46:797-804.

Perlick DA, Gonzalez J, Michael L., Huth M, Culver J, Kaczynski R, Calabrese J, Miklowitz DJ. Rumination, gender, and depressive symptoms associated with caregiving strain in bipolar disorder. *Acta Psychiatr Scand.* In press.

Roussos P, Katsel P, Davis KL, Bitsios P, Giakoumaki SG, Jogia J, Rozsnyai K, Collier D, Frangou S, Siever LJ, Haroutunian V. Molecular and genetic evidence for abnormalities in the nodes of Ranvier in schizophrenia. *Arch Gen Psychiatry.* 2012, 69:7-15.



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