

Brain Waves

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NTP student Scott Vermilyea at the Wisconsin Science Festival 2013

How Early Experience Impacts Brain Development

Madison, Wisconsin - Biologists, engineers, physicists, and neuroscientists are joining forces to uncover the mechanisms by which early experience impacts the development and function of the human brain.

The distinguished group of researchers today announced a five-year, \$10 million award from the National Institute of Mental Health (NIMH) to establish a new Silvio O. Conte Center for Basic and Translational Mental Health Research on the University of Wisconsin-Madison campus, which will support their efforts.

The new center gives the diverse team an opportunity to work together to reveal the pathological pathways that lead to mental disorders such as anxiety and depression.

Bringing insights and tools from each scholarly perspective, they will be able to trace the roots of mental disorders from their cellular basis to brain function and structure and then examine how these variations in brain circuits later affect emotion and behavior.

While the medical community recognizes a correlation between early-life stress and emotional health, no one has ever described the way in which early adversity affects the way the brain works. The new Conte Center focuses on illuminating the circuitry that connects the amygdala, a brain region important for the 'fight or flight' response, with sectors of the prefrontal cortex, which are associated with the regulation of emotion. The strength of the network and communication between the two areas appears to play a key role in the development of anxious temperament, a known precursor to mental illness.

Based at the Center for Investigating Healthy Minds at the Waisman Center, the new Conte center grant supports three major efforts:

- Non-invasive studies, using functional, diffusion and structural MRI and other tools, to measure response to stressors in the developing brain beginning in infancy

- Molecular studies to characterize anxious temperament at a cellular level, using induced pluripotent stem cells derived from adolescent skin or blood cells

- A study of genetically identical twins to describe how experience and environment cause differences in how the brain functions and in which genes are differentially expressed

Continued on pg. 2

Brain Development Article Cont'd

This work will uncover new targets for early interventions to prevent anxiety-related disorders, which exact enormous social, emotional and economic burdens in adolescence and early adulthood," says Dr. Richard J. Davidson, who is leading the effort. "Ultimately, this new knowledge will inform the diagnosis and treatment of mental disorders and lead to new neurally-inspired interventions."

The path that leads to anxiety and other mental disorders has been shrouded in mystery, says Su-Chun Zhang, a stem cell researcher at the UW-Madison's Waisman Center and one of the lead scientists on the program.

"Anxiety is a high-order – or high disorder – brain function, and we've never really understood how it develops," Zhang says, pointing out that you can't just sample the brain cells of an anxious patient. "Using stem cells, now we can finally get to the bottom of it: the cellular and molecular level."

Using induced pluripotent stem cells derived from skin or blood cells, Zhang says his team will be able to put amygdala cells and cells from the prefrontal cortex together in a petri dish, and watch them communicate.

On another level of the study, the researchers will be able to "see" into the brain as it develops over the first two years of life, non-invasively, using state-of-the-art imaging techniques, like functional MRI. The study will use two groups of new mothers, one happy and healthy, one more stressed; and follow their children as they develop.

"We're going to be looking at how these very early experiences literally get under our skin and affect our brains and bodies," Davidson says.

On yet another level, by observing pairs of genetically identical twins who experience differing levels of stress, researchers will be able to determine some of the epigenetic causes of mental illness. Looking at the pathology from all of these different vantage points ultimately will lead to more effective interventions, including drugs or other therapies.

Dr. Ned Kalin, chair of the Department of Psychiatry, will lead a center project focusing on the development of anxious temperament in a large sample of rhesus monkeys. They will be studied using non-invasive imaging and epigenetic methods. The expression of anxious temperament in rhesus monkeys and human toddlers is remarkably similar and the inclusion of the non-human primate project provides an important opportunity to study the developing brain in a species that shares a lot with humans, but develops considerably more rapidly.

The new studies build upon findings from an earlier Conte Center grant that focused on adolescent anxiety traits. Researchers in those studies found that high levels of family stress during infancy were linked to differences in brain function and anxiety in teenage girls. That group also found that girls with higher levels of cortisol, a stress hormone, showed less communication between the amygdala and the prefrontal cortex.

The Conte Center also supports an undergraduate summer research program and workshop. The program gives exceptional young scholars from around the country the opportunity to work directly with leaders in the burgeoning fields of neuroscience, stem cell research, neuroimaging, medical physics, and biological psychiatry, to solve real-world problems.

In addition to Davidson and Zhang, the leaders of the Wisconsin team include Dr. Andrew Alexander, Dr. Rasmus Birn, Dr. Marilyn Essex, Dr. H. Hill Goldsmith and Kalin.

Since 1988, the NIMH has encouraged scientists to seek funding for projects in which a unifying, well-defined scientific question would be approached from many angles and at many levels (for example, genetic, molecular, clinical, and behavioral) via its Centers for Neuroscience of Mental Disorders and Centers for Neuroscience Research. In 1993, these centers were renamed in memory of Rep. Silvio O. Conte, a champion of neuroscience research and the severely mentally ill. The NIMH Silvio O. Conte Centers are aimed at understanding the neuroscience of severe mental disorders, such as schizophrenia and mood disorders.

A Shot of Anxiety and the World Stinks By: Terry Devitt

In evolutionary terms, smell is among the oldest of the senses. In animals ranging from invertebrates to humans, olfaction exerts a primal influence as the brain continuously and subconsciously processes the steady stream of scent molecules that waft under our noses.

And while odors — whether the aroma of stinky socks or the sweet smell of baking bread — are known to stir the emotions, how they exert their influence of the human brain, evoking passion or



Wen Li Photo: Jeff Miller

Now, however, researchers using powerful new brain imaging technologies are peeling back some of the mystery, revealing how anxiety or stress can rewire the brain, linking centers of emotion and olfactory processing, to make typically benign smells malodorous.

Writing today (Sept. 24, 2013) in the *Journal of Neuroscience*, a team led by Wen Li, a professor of psychology at the UW-Madison Waisman Center, reports that the brains of human subjects experience anxiety induced by disturbing pictures and text of things like car crashes and war transform neutral odors to distasteful ones, fueling a feedback loop that could heighten distress and lead to clinical issues like anxiety and depression.

The finding is important because it may help scientists understand the dynamic nature of smell perception and the biology of anxiety as the brain rewires itself under stressful circumstances and reinforces negative sensations and feelings.

"After anxiety induction, neutral smells become clearly negative," explains Li, who conducted the study with UW-Madison colleagues Elizabeth Krusemark and Lucas Novak, and Darren Gitelman of Northwestern University's Feinberg School of Medicine. "People experiencing an increase in anxiety show a decrease in the perceived pleasantness of odors. It becomes more negative as anxiety increases."

Julio Diaz
University of Miami
Rotating

Do Tromp
Utrecht University
Major Prof. Ned Kalin

Corinne Jones
Boston University
Major Profs. Michelle Ciucci & Marina Emborg

Andrew Sheldon
UC-Berkeley
Major Prof. Brad Postle

Scott Vermilyea
UW-Madison
Rotating

Joe Wszalek
UW-Madison
Major Prof. Lyn Turkstra



NTP faculty member Corinna Burger at BOPS 2013 faculty panel



NTP students Christian La and Sisi Li at the Wisconsin Science Festival 2013

Welcome New Faculty



Heather Abercrombie

Associate Professor
Ph.D. Univ. of Wisconsin-Madison
Affective neuroscience & Psychoneuro-endocrinology



Ozioma Okonkwo

Assistant Professor
Ph.D., Univ. of Alabama at Birmingham
Preclinical Alzheimer's disease, Cognitive Reserve, Physical Activity, Genetics



Krishanu Saha

Assistant Professor
Ph.D. University of California-Berkeley
Integrative Engineering of Stem Cells with Biomaterials and Synthetic Biology



Jill C. Wildonger

Assistant Professor
Ph.D. Columbia University
Role of Microtubule Cytoskeleton in creating and maintaining Neuronal Polarity during development

Congratulations Recent Graduates

Ishmael Amarreh graduated from M. Elizabeth Meyerand's lab and is now working as a postdoc.

Michael Devinney graduated from Gordon S. Mitchell's lab and will be returning to medical school.

Kyunghee Kim graduated from Robert Fettiplace's lab and is now working as a postdoc.

Bornali Kundu graduated from Bradley R. Postle's lab and is returning to medical school.

Aaron Nelson graduated from Chiara Cirelli's lab and **Abha Rajbhandari** graduated from Vaishali P. Bakshi's lab and will be working as a postdoc at UCLA.

Chelsey Smith graduated from Ian D. Duncan's lab and will be working in the Cytogenetics lab at St. Francis Hospital.

Michael Zorniak graduated from John S. Kuo's lab and will be a research associate at the Scripps Research Institute in the Barbas lab.

Kile Mangan graduated from Mathew V. Jones' lab and will be working as an Applications Scientist at Cellular International.

Shilpashree Balakrishnan graduated from Robert A. Pearce's lab.

Introducing NTP's New Website!

If you haven't seen it already, the new NTP website is officially live! Check it out at <http://ntp.neuroscience.wisc.edu/>

Awards & Achievements

Seth Blair

won the Chancellor's Award for Distinguished Teaching last spring.

Robin Fropf, David Ruhl, & Rick Wolf

were all awarded the NSF GRFP.

Abigail Zdrale Rajala

was awarded the SFN student travel award and her presentation poster was accepted in the media book for SFN.

Ryan Herringa

received the NARSAD Young Investigator Grant and the ICTR Type 1 Translational Pilot Grant Award.

Anne Racine & Martina Ly

were accepted for pre-doctoral slots on the IOA T32 Biology of Aging and Age-Related Diseases Training Grant.

Josh LaRocque & Brittany Young

received Clinical Neuroengineering Training Program slots.

Kate Sprecher received a ICTR pre-doctoral TL1 program slot.

Congratulations to the students who have passed their preliminary examinations.

Ewa Bomba
Sharon Dubois
Robin Fropf
Tristan Lee
Martina Ly
Cliff Rodgers
Lisa Sudmeier
Anne Tanenhaus
Jingxin Wang
Jiabin Zhang

Angela Navarrete Opazo

Anxiety Article Cont'd

Using behavioral techniques and functional magnetic resonance imaging (fMRI), Li's group looked at the brains of a dozen human subjects with induced anxiety as they processed known neutral odors.

Functional MRI is a technology that enables clinicians and researchers to observe the working brain in action. Before entering the MRI where screens cycle through a series of disturbing pictures and text, subjects were exposed to and rated a panel of neutral smells.

In the course of the experiment, the Wisconsin team observed that two distinct and typically independent circuits of the brain — one dedicated to olfactory processing, the other to emotion — become intimately intertwined under conditions of anxiety. Subsequent to anxiety induction and the imaging process, subjects were asked again to rate the panel of neutral smells, most assigning negative responses to smells they previously rated as neutral.

"In typical odor processing, it is usually just the olfactory system that gets activated," says Li. "But when a person becomes anxious, the emotional system becomes part of the olfactory processing stream."

Although those two systems of the brain are right next to each other, under normal circumstances there is limited crosstalk between the two. However, under conditions of induced anxiety, the Wisconsin team observed the emergence of a unified network cutting across the two systems.

The results may have clinical implications in the sense that it begins to uncover the biological mechanisms at play during periods of anxiety. "We encounter anxiety and as a result we experience the world more negatively. The environment smells bad in the context of anxiety. It can become a vicious cycle, making one more susceptible to a clinical state of anxiety as the effects accumulate. It can potentially lead to a higher level of emotional disturbances with rising ambient sensory stress."

Cortex, Consciousness and Anesthesia 2013

On November 1, 2013 from 8 AM-6 PM there will be a conference on the cortico-thalamic mechanisms of consciousness and their disruption in clinical and non-clinical settings, to be held in the DeLuca Forum at Wisconsin Institutes for Discovery.

Registration and further information is available at <http://anesthesia.wisc.edu/events/CCA>

This event is co-sponsored by the Departments of Anesthesiology and Neuroscience and the Neuroscience Training Program.



CONTRIBUTIONS TO THE PROGRAM

Funds given to the program are used to support recruiting activities, guest speakers, the graduate travel award for professional conferences and the annual program picnic. For additional information, please contact the program office at (608)262-4932. To contribute, please contact the UW Foundation at: <https://secure.supportuw.org/MultiPage/processStep1.do?seq=17268>

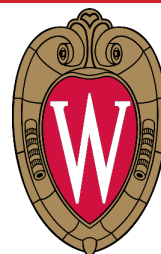
Thank you to all those who have contributed and continue to support the Neuroscience Training Program and its students.

Neuroscience
Training Program
7225 Medical Sciences Center
1300 University Ave.
Madison, WI 53706
(608) 262-4932

ntp@mhub.neuroscience.wisc.edu

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