

# NEUROSCIENCE TRAINING PROGRAM

## Spring Newsletter

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The NTP's Students And Faculty.

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(Image to Right) NTP Student Michael  
Devinney in Gordon Mitchell's Lab.



# 2012



# Implanted Neurons, Grown in the Lab, Take Charge of Brain Circuitry

by Terry Devitt

# 01

**A**mong the many hurdles to be cleared before human embryonic stem cells can achieve their therapeutic potential is determining whether or not transplanted cells can functionally integrate into target organs or tissues.

Writing today (Monday, Nov. 21) in the Proceedings of the National Academy of Sciences, a team of Wisconsin scientists reports that neurons, forged in the lab from blank slate human embryonic stem cells and implanted into the brains of mice, can successfully fuse with the brain's wiring and both send and receive signals.

Neurons are specialized, impulse conducting cells that are the most elementary functional unit of the central nervous system. The 100 billion or so neurons in the human brain are constantly sending and receiving the signals that govern everything from walking and talking to thinking. The work represents a crucial step toward deploying customized cells to repair damaged or diseased brains, the most complex human organ.

"The big question was can these cells integrate in a functional way," says Jason P. Weick, the lead author of the new study and a staff scientist at the University of Wisconsin-Madison's Waisman Center. "We show for the first time that these transplanted cells can both listen and talk to surrounding neurons of the adult brain."

The Wisconsin team tested the ability of their lab grown neurons to integrate into the brain's circuitry by transplanting the cells into the adult mouse hippocampus, a well-studied region of the brain that plays a key role in processing memory and spatial navigation. The capacity of the cells to integrate was observed in live tissue taken from the animals that received the cell transplants.

Weick and colleagues also reported that the human neurons adopted the rhythmic firing behavior of many brain cells talking to one another in unison. And, perhaps more importantly, that the human cells could modify the way the neural network behaved.

A critical tool that allowed the UW group to answer this question was a new technology known as optogenetics, where light, instead of electric current, is used to stimulate the activity of the neurons.

"Previously, we've been limited in how efficiently we could stimulate transplanted cells. Now we have a tool that allows us to specifically stimulate only the transplanted human cells, and lots of them at once in a non-invasive way," says Weick.

Weick explains that the capacity to modulate the implanted cells was a necessary step in determining the function of implanted cells because previous technologies were too imprecise and unreliable to accurately determine what transplanted neurons were doing.

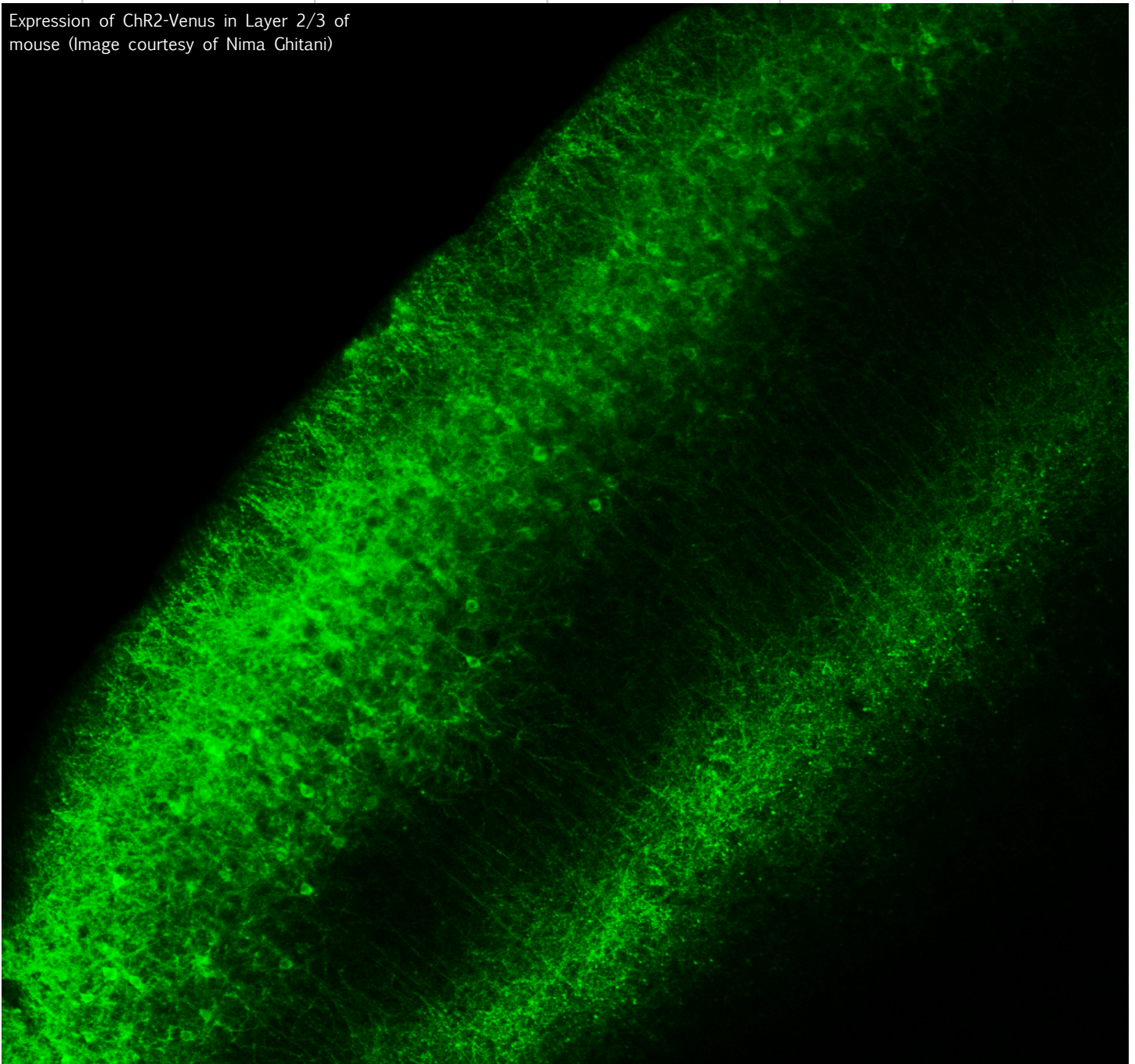
Embryonic stem cells, and the closely related induced pluripotent stem cells can give rise to all of the 220 types of tissues in the human body, and have been directed in the lab to become many types of cells, including brain cells.

The appeal of human embryonic stem cells and induced pluripotent cells is the potential to manufacture limitless supplies of healthy, specialized cells to replace diseased or damaged cells. Brain disorders such as Parkinson's disease and amyotrophic lateral sclerosis, more widely known as Lou Gehrig's disease, are conditions that scientists think may be alleviated by using healthy lab grown cells to replace faulty ones. Multiple studies over the past decade have shown that both embryonic stem cells and induced cells can alleviate deficits of these disorders in animal models.

The new study opens the door to the potential for clinicians to deploy light-based stimulation technology to manipulate transplanted tissue and cells. "The marriage between stem cells and optogenetics has the potential to assist in the treatment of a number of debilitating neuro-degenerative disorders," notes Su-Chun Zhang, a UW-Madison professor of neuroscience and an author of the new PNAS report. "You can imagine that if the transplanted cells don't behave as they should, you could use this system to modulate them using light."

In addition to Weick and Zhang, the new PNAS report was co-authored by Yan Liu, also of UW-Madison's Waisman Center. The study was funded by the U.S. National Institutes of Health.

Expression of ChR2-Venus in Layer 2/3 of mouse (Image courtesy of Nima Ghitani)



## UW-Madison, UW-Milwaukee Award Inter-Institutional Research Grants by Chris Barncard

Twelve hybrid teams of faculty from the University of Wisconsin-Milwaukee (UWM) and the University of Wisconsin-Madison have been awarded the second batch of Intercampus Research Incentive grants, awards designed to foster inter-institutional collaboration.

The awards, announced today by UW-Milwaukee and UW-Madison, total \$600,000 and will support projects such as testing new materials for improved lithium-ion batteries and investigating whether Lake Michigan is a sink or source for carbon dioxide. Each award, chosen from a pool of 60 proposed research programs, is in the range of \$50,000 for one year.

The Intercampus Research Incentive Grants Program is an initiative to foster research projects and scholarship undertaken jointly by researchers at the two institutions. The program is funded by UW-Madison and UW-Milwaukee donors. Projects were selected by a committee of faculty and administrators from both institutions.

### Projects funded that include NTP Faculty:

An EEG Triggered Robotic Stroke Rehabilitation Device — Ying-Chih Wang and Brooke Slavens (Milwaukee, occupational science and technology), Justin Williams (Madison, biomedical engineering), Vivek Prabhakaran (Madison, radiology), and Dorothy Edwards (Madison, kinesiology)

Effects of Sleep Deprivation on the Activity of Hippocampal Neurons and Cortico-Hippocampal Coordination — Kamran Diba (Milwaukee, psychology) and Chiara Cirelli, Giulio Tononi and Vladyslav Vyazovskiy (Madison, psychiatry)

# 02



# Study Pinpoints Ritalin's Influence

by Chris Barncard

# 03

**M**illions of individuals diagnosed with attention deficit hyperactivity disorder (ADHD) are helped by methylphenidate, the stimulant better known as Ritalin. Now researchers at the University of Wisconsin-Madison have pinpointed the area of the brain in which Ritalin does its work.

"These drugs are highly effective at controlling the symptoms of attention deficit and hyperactivity disorder for the great majority of patients," says Craig Berridge, a UW psychology professor. "And they've been around since the 1930s, which makes it all the more amazing that we didn't understand until recently how they worked in the brain."

A study conducted by Berridge and graduate student Robert Spencer has identified the upper portion of the brain's prefrontal cortex as the key area in which the drug works.

Spencer delivered Ritalin to rats through tiny needles routed directly into different parts of the prefrontal cortex and into parts of the nearby striatum. The striatum is linked to the prefrontal cortex as part of the frontostriatal circuit, a neural pathway vital to motor and cognitive function.

"Brain imaging studies show that both the prefrontal cortex and striatum aren't responding normally in ADHD patients, and there was much speculation that the striatum plays a role in the way Ritalin worked," says Berridge, whose newest research was published online recently by the journal *Biological Psychiatry*. "This is the first study to show unambiguously that the drug acts in the prefrontal cortex to improve cognition."

Rats in the study performed much better in a maze that tests working memory after small Ritalin doses were applied to the top of the prefrontal cortex, but larger doses and other entry points for the drug failed to help the rats.

"This mirrors what we see with oral administration of this drug to ADHD patients," Berridge says.

This cognition-enhancing action was only observed when infused into the upper region of the prefrontal cortex. No significant changes were found when Ritalin was introduced in the lower prefrontal cortex, an area that processes emotional information.

Earlier studies showed the striatum receiving direction from the prefrontal cortex. And when Spencer deactivated the striatum, the animals could not complete the working memory task at all. However, despite the striatum's importance to cognitive function, Ritalin added directly to the striatum also resulted in no improvement in the maze.

The study provides new information about how methylphenidate works to produce therapeutic effects, which may well be useful for developing new treatments.

"In particular, when we're screening new compounds to treat ADHD, we will want to know if they are acting on the prefrontal cortex," says Berridge, whose work is funded by the National Institute of Mental Health. "And we know that if [the compounds] are acting outside the prefrontal cortex, they have the potential for addictive or other deleterious effects."

Though most people with attention deficit symptoms benefit a great deal from Ritalin, the drug has a sketchy reputation. It is popular without prescription as a "study aid" — sharpening the focus of people without ADHD issues. And it is a powerful stimulant that, at doses higher than those used to treat ADHD, can have addictive and detrimental effects.

"There is concern with prescribing an addictive medication to children," Berridge says. "However, our work and work of others indicates that at clinically relevant doses, Ritalin acts fundamentally different than when used at higher doses associated with drug abuse. At these lower doses, it boosts cognition dependent on the prefrontal cortex and appears to be quite safe and effective."

## Recent Graduates



### Hilary Gerstein

Hilary graduated from Corinna Burger's Lab and will continue as a post-doc in the Burger Lab.



### Jesus Mena

Jesus graduated from Brian Baldo's Lab and will continue to work there as he explores post-doc opportunities.

## Successful Prelim Exams

Aaron Nelson  
Samantha Wright  
Valerie Joers  
Michael Devinney  
Kimberly Farbota  
Sarah Baisley

## Faculty

Edwin Chapman received the Kellett Award and had an unusually productive year with many of papers receiving write-ups and press releases (e.g. the 2011 Cell paper got a three page write up in Cell, and many of these other papers were written up and were also selected for the Faculty of 1000)

Michelle Ciucci received the Michael J. Fox Foundation Grant.

## Students

Michael Devinney received the Caroline Tum Suden/Frances Helleberrandt Professional Opportunity Awards for the abstract he submitted to the 2012 Experimental Biology Meeting.

Ginny Hu was awarded the Vilas international travel award for her dissertation and was invited by Dr. Stefan Hell's Group at the Max Planck Institute of Biophysical Chemistry to collaborate on a research project in Goettingen, Germany.

Julian Motzkin was awarded the Anne Kelley Fellowship in Behavioral Neurosciences. This fellowship, honoring the legacy of Ann E. Kelley, supports the training of future generations of Behavioral Neuroscientists that embody Ann Kelley's passion for understanding the brain with the ultimate goal of using this knowledge to reduce human suffering.

Angela Navarrete Opazo was invited to be member of the Golden Key International Honour Society due to academic excellence. They will give a diploma during the year.

Christine Swanson is a recipient for this year's Graduate Student Peer Mentor Award, sponsored by the Multicultural Graduate Network as well as the Graduate Student Collaborative.

## Awards & Achievements

# 04



# Psychopaths' Brains Show Differences in Structure and Function

UW Health Marketing  
and Public Affairs

# 05

Images of prisoners' brains show important differences between those who are diagnosed as psychopaths and those who aren't, according to a new study led by University of Wisconsin-Madison researchers.

The results could help explain the callous and impulsive antisocial behavior exhibited by some psychopaths.

The study showed that psychopaths have reduced connections between the ventromedial prefrontal cortex (vmPFC), the part of the brain responsible for sentiments such as empathy and guilt, and the amygdala, which mediates fear and anxiety.

Two types of brain images were collected. Diffusion tensor images (DTI) showed reduced structural integrity in the white matter fibers connecting the two areas, while a second type of image that maps brain activity, a functional magnetic resonance image (fMRI), showed less coordinated activity between the vmPFC and the amygdala.

"This is the first study to show both structural and functional differences in the brains of people diagnosed with psychopathy," says Michael Koenigs, assistant professor of psychiatry in the University of Wisconsin School of Medicine and Public Health. "Those two structures in the brain, which are believed to regulate emotion and social behavior, seem to not be communicating as they should."

The study, which took place in a medium-security prison in Wisconsin, is a unique collaborative between three laboratories, UW-Madison psychology Professor Joseph Newman has had a long term interest in studying and diagnosing those with psychopathy and has worked extensively in the Wisconsin corrections system.

Dr. Kent Kiehl, of the University of New Mexico and the MIND Research Network, has a mobile MRI scanner that he brought to the prison and used to scan the prisoners' brains. Koenigs and his graduate student, Julian Motzkin, led the analysis of the brain scans.

The study compared the brains of 20 prisoners with a diagnosis of psychopathy with the brains of 20 other prisoners who committed similar crimes but were not diagnosed with psychopathy.

"The combination of structural and functional abnormalities provides compelling evidence that the dysfunction observed in this crucial social-emotional circuitry is a stable characteristic of our psychopathic offenders," Newman says. "I am optimistic that our ongoing collaborative work will shed more light on the source of this dysfunction and strategies for treating the problem."

Newman notes that none of this work would be possible without the extraordinary support provided by the Wisconsin Department of Corrections, which he called "the silent partner in this research." He says the DOC has demonstrated an unprecedented commitment to supporting research designed to facilitate the differential diagnosis and treatment of prisoners.

The study, published in the most recent Journal of Neuroscience, builds on earlier work by Newman and Koenigs that showed that psychopaths' decision-making mirrors that of patients with known damage to their ventromedial prefrontal cortex (vmPFC). This bolsters evidence that problems in that part of the brain are connected to the disorder.

"The decision-making study showed indirectly what this study shows directly - that there is a specific brain abnormality associated with criminal psychopathy," Koenigs adds.



Patrick Kerstein and Miguel Santiago-Medina in Timothy Gomez's Lab.

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## CONTRIBUTIONS TO THE PROGRAM

Funds given to the program are used to support recruiting activities, guest speakers, the undergraduate award in neurobiology research 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: [www.uwfoundation.wisc.edu](http://www.uwfoundation.wisc.edu)

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

### Article Credits:

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