# CHEN TIANQIAO & CHRISSY INSTITUTE

# 2018: A YEAR OF PROGRESS AND MILESTONES

The Tianqiao & Chrissy Chen Institute 2018 Annual Report

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www.cheninstitute.org

## Founder's Letter: 2018: A Year of Progress and Milestones

When we created the Tianqiao and Chrissy Chen Institute (TCCI) in late 2016, we had a vision: to improve the human experience by better understanding how the human brain perceives, learns and interacts with the world.

Our approach is multifaceted, focusing on brain discovery with our Caltech partnership and on brain treatment with the creation of the Tianqiao and Chrissy Chen Institute for Translational Research in Shanghai. Brain development is our "third pillar." We made good progress in this area last year and look forward to sharing our thinking with you in 2019.

TCCI is a young organization but we're pleased with the progress we've made to date. As you will see in this report, 2018 was a very productive year. Caltech has been prolific issuing a steady drumbeat of breakthrough research and many TCCI-affiliated scientists were recognized for their work, receiving prestigious prizes throughout the year.

As momentum grows for TCCI, so too, does the sense of community. We enjoyed attending and supporting many key meetings and conferences around the world and rallying support for brain science with the release of our award-winning documentary, "Minds Wide Open." Community remains an important focus for us and we look forward to welcoming more scientists into the TCCI fold in the year ahead.

We hope this report paints a colorful picture of 2018 and also gives you a hint of what's to come.

Thanks always for your ongoing support and partnership.

Tianqiao Chen

Chrissy Luo



# **Our Vision:**

Improving the human experience by understanding how our brains perceive, learn and interact with the world.

Supporting brain research focused on:

- 'Understanding the sensation-perception mechanisms and related systems of memory, attention, learning and expectations.
- Advancing discoveries and applications that minimize the negative and enhance the positive impact of perceptions.

The ability to shape and refine perception will help us better understand our world, be it through more targeted therapies to alleviate negative psychological states such as depression or seamless brain-machine interfaces to enhance the utilization of mental capacity and capabilities.

#### **TCCI Major Milestones:**

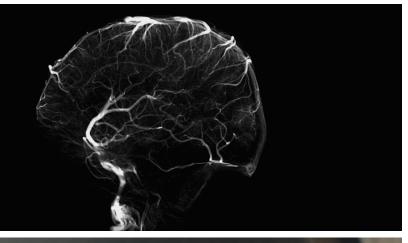
Nov 2016	Tianqiao and Chrissy Chen announce their <b>\$1 billion commitment</b> to brain science
Dec 2016	Tianqiao and Chrissy Chen Institute for Neuroscience at Caltech created with <b>\$115 million donation</b>
Nov 2017	Tianqiao and Chrissy Chen Institute for Translational Research created with <b>\$76 million commitment</b> – a partnership with the Zhou Liangfu Foundation and Huashan Hospital.
Dec 2017 (	Groundbreaking for TCCI Research Building at Caltech
Jun 2018	Shanghai Mental Health Center joins TCCI Translational Research partnership
Sep 2018	Minds Wide Open documentary debuts on Discovery Channel

# **Our Focus:** Supporting fundamental research into brain function and how perceptions are formed

We are committed to bringing together the world's most talented researchers to investigate the complex interactions governing sensation, perception and cognition. We have three core areas of interest:

#### **Brain Discovery**

Supporting interdisciplinary research that enables us to understand the fundamental brain at the level of the individual neuron and synapse. How does the brain gather, organize and retain information? How is this input then translated into thoughts, emotions, decisions, actions and memories?



#### **Brain Treatment**

We seek to translate improved understanding of brain mechanisms and processes into breakthrough treatments for physical and psychological suffering such as mental disorders and neurodegenerative diseases.

#### **Brain Development**

An acute understanding of fundamental brain processes will allow us to perfect the brain-machine interface, use technologies such as AR or VR to improve neurorehabilitation and inform the next generation of artificial intelligence.

# Cornerstone Partnerships:

The large-scale partnerships we create with leading institutions around the world serve as the foundation for TCCI. These partnerships allow us to go deep into specific areas of interest.

# Tianqiao and Chrissy Chen Institute for Neuroscience at Caltech

In December 2018, the Tianqiao and Chrissy Chen Institute for Neuroscience at Caltech turned two years old. This important partnership supports our focus on Brain Discovery, bringing together a cross-disciplinary team of scientists and engineers to investigate and better understand the brain and how it works.

David J. Anderson, the Seymour Benzer Professor of Biology at Caltech and a Howard Hughes Medical Institute Investigator, serves as the director of TCCI at Caltech. He is at the forefront of developing and applying new technologies for neural-circuit manipulation. Mary King Sikora provides operational leadership as TCCI's Executive Director.

TCCI at Caltech comprises six interdisciplinary Centers:





From left to right: Professors Viviana Gradinaru, Doris Tsao and Ralph Adolphs, Chrissy Luo, Professor David Anderson, Tianqiao Chen, Professor Colin Camerer, Mary Sikora and Professor Richard Andersen.

### The Center for Molecular and Cellular Neuroscience unites a

contingent of Caltech researchers who are making discoveries about the brain's anatomy and development, how neurons communicate, and how processes in the brain can go wrong.

#### The Caltech Brain Imaging

**Center** makes available state-ofthe-art instruments and expert staff to provide detailed measurements of the working brain.

#### The T&C Chen Center for Systems Neuroscience is addressing the challenge of understanding how a large group of peurops

ing how a large group of neurons firing in concert gives rise to cognition. The Caltech researchers working in this center explore the neural circuits and computations that underlie perception, thought, emotion, memory, decision making, and behavior.

#### The T&C Chen Center for Social and Decision Neuroscience

is investigating two important higher-order functions of the human brain: making decisions, and processing and guiding social interactions.

#### The T&C Chen Brain-Machine Interface Center is advancing

Caltech's work on a new generation of devices that can communicate with and stimulate the brain.

#### The Chen Center for Neuroscience Education offers a number of opportunities for graduate students in neuroscience. It provides fellowships to exceptional firstyear graduate students in neuroscience options at Caltech, it recognizes the importance of fostering graduate student participation and enriches the graduate student experience through the activities it sponsors.



A rendering of the Chen Neuroscience Research Building.

#### From Vision to Reality: Chen Neuroscience Research Center

Our vision for interdisciplinary collaboration will soon be made a reality at the Chen Neuroscience Research Center at Caltech. Much progress has been made since the ground-breaking ceremony in December 2017 and the building is due to be completed in Fall 2020. The Center will house labs and offices for more than a dozen principal investigators, studying everything from the basic biology of the brain to sensation, perception, cognition and human behavior.

#### Fast facts about the Chen Building:

- Construction of the building had to be scheduled around the breeding season of the lamprey, a jawless fish used for research on campus. Any vibrations caused by construction could have disrupted their summer breeding.
- 67,000 cubic yards of dirt were excavated from the site to make room for the building's basement and sub-basement.
- A subterranean tunnel will connect the Chen building and the Broad building to the south.
- In recognition of Pasadena's architectural heritage, Caltech relocated seven 1920's era buildings called the Wilson Court bungalows. Once renovated, they will serve as campus housing!

# The Tianqiao and Chrissy Chen Institute for Translational Research



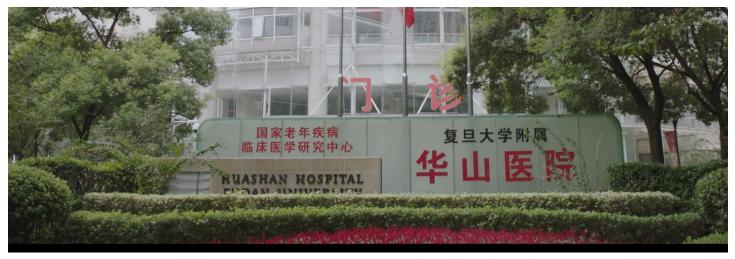
In June 2018, Shanghai Mental Health Center joined the Tianqiao and Chrissy Chen Institute for Translational Research, a partnership established in 2017 with Fudan-affiliated Huashan Hospital and the Zhou Liangfu Foundation to support our focus on brain treatment.

Both hospitals are leaders in their fields. Huashan Hospital, for example, has extensive clinical experience, with the Department of Neurology treating more than 450,000 patients and performing nearly 17,000 operations each year. Shanghai Mental Health Center, has more than 2,100 beds and an annual outpatient capacity of 860,000 visits.

Although currently centered in Shanghai, we envision other teaching hospitals from around the world eventually joining this partnership.



Professor Mao Ying shakes hands with Professor Xu Yifeng, President of the Shanghai Mental Health Center at the June 2018 signing ceremony.



Fudan-affiliated Huashan Hospital in Shanghai, China.

# **PEOPLE:**

As important as our institutional partnerships are the individual scientists working to unlock the mysteries of the human mind. We are building an interdisciplinary community of Principal Investigators and Graduate Fellows and look forward to introducing new programs in the near future that support talented young scientists.

#### **TCCI Principal Investigators:**



#### Professor Zhou Liangfu, PhD Mentor

#### Vice Chairman of TCCI Translational Research, Academician of Chinese Academy of Engineering, Director of Neurosurgery Department of Huashan Hospital

Professor Zhou is a leading Chinese neurosurgery doctor. He graduated from Shanghai Medical University in 1965 and has worked in the field of neurosurgery for over 50 years. He is the honorary president of the Chinese Neurosurgical Committee and a member of the international liaison & advisory panel for Neurosurgery (USA), Europe and Japan. Professor Zhou has won the Chinese National Science & Technological Progress Award three times, and more than 20 other important awards. His fields of interest include vascular neurosurgery, skull-based surgery, minimally invasive neurosurgery and brain tumors.



#### **David Anderson**

#### Director of the Tianqiao and Chrissy Chen Institute for Neuroscience

David Anderson is Caltech's Seymour Benzer Professor of Biology and an investigator of the Howard Hughes Medical Institute. He received his AB from Harvard University (biochemical sciences, summa cum laude) and his PhD in cell biology from the Rockefeller University, where he trained with Nobel Laureate Günter Blobel, and did his postdoctoral training at Columbia University with Nobel Laureate Richard Axel.

Anderson's research focuses on the study of neural circuits that control emotional behaviors in animal models. He has been at the forefront of developing and applying new technologies for neural-circuit manipulation, such as optogenetics and pharmacogenetics, to the study of emotional behaviors such as fear, anxiety, and aggression in both mice and the fruit fly Drosophila melanogaster. His work in mice is currently focused on limbic circuits, including the amygdala and hypothalamus, and their role in aggression.



#### Professor Mao Ying, PhD Mentor, MD

## Director of TCCI Translational Research, Vice President of Huashan Hospital, President of West Huashan Hospital

Professor Ying Mao is Vice President at Huashan Hospital, Fudan University. Concurrently, he is President of the Chinese Neurosurgical Committee and President of the Congress of Neurological Surgeons within the Shanghai Medical Doctors Association. Professor Mao received his Medical Doctor's degree at Shanghai Medical University and was a postdoctoral researcher at the Crosby Neurosurgical Laboratories, University of Michigan. In 2017, he was conferred the "Shanghai Medical Excellence Contribution Award." Professor Mao focuses his research on cerebrovascular disease, minimally invasive brain tumor microsurgery and functional neurosurgery.



#### **Ralph Adolphs**

#### **Director of the Caltech Brain Imaging Center**

Ralph Adolphs studies the neural and psychological basis for human social behavior. His work has focused on examining how people recognize, perceive, and process emotions and other social cues in facial expressions. Some of the questions his lab is trying to answer are: How do people make social and moral judgments? How do they make emotionally charged decisions? Why do people with autism have difficulties with social behavior? The goal is to better understand how both healthy and atypical brains work.

Adolphs uses various techniques in his lab, such as functional magnetic resonance imaging, eye tracking, and recording electrical activity in the brain. He studies neurological patients with focal brain damage, those with neuropsychiatric diseases such as autism and Williams syndrome, and neurosurgical patients who have electrodes in their brains. From these experiments, he's investigating how data from individual brain cells can be connected to neuroimaging data and, ultimately, to behavior.



#### **Richard Andersen**

#### Director of the T&C Chen Brain-Machine Interface Center

Richard Andersen, the James G. Boswell Professor of Neuroscience at Caltech, studies the neural mechanisms of sight, hearing, balance, touch, and action, and uses these insights to inform the development of neural prosthetics. Andersen obtained his PhD from UCSF and completed a postdoctoral fellowship at the Johns Hopkins University School of Medicine. He was a faculty member at both the Salk Institute and MIT before coming to Caltech.

Among Andersen's discoveries is the finding of neural signals of intention, and proving that these are not sensory in nature but rather reflect the planning of the subject. He has recently applied this discovery of intention to advance research on brain-machine interfaces. He and his group have shown that paralyzed patients' intents can be decoded from brain activity and used to control assistive devices such as robotic limbs.



#### **Colin Camerer**

#### Director of the T&C Chen Center for Social and Decision Neuroscience

Colin Camerer is Caltech's Robert Kirby Professor of Behavioral Economics. He earned a PhD from the University of Chicago in 1981 and was at Northwestern University, Pennsylvania State University, and the University of Chicago before joining the Caltech faculty in 1994. He was the past president of the Economic Science Association and the Society for Neuroeconomics, was elected a member of the American Academy of Arts and Sciences, and was named a MacArthur Fellow in 2013. He has published more than 180 peer-reviewed articles and book chapters and authored or edited four books.

The Camerer group uses a wide variety of lab and field methods to study the computations that result in goal-directed human economic and social decisions, including strategic interactions and market trading. His group's functional magnetic resonance imaging (fMRI) projects have isolated the basis of self-control when faced with tempting foods, emotional regulation in dealing with financial loss, how curiosity increases learning, and the neural circuitry underlying the life cycle of stock market bubbles. Their group has also used transcranial magnetic stimulation (TMS) to causally influence choice, eyetracking to measure attention, behavior of patients with brain lesions to understand altruism and fear.



#### Liang Chen, MD, Ph.D.

#### Professor of Neurosurgery at Huashan Hospital

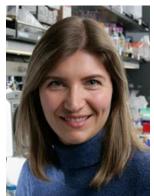
Professor Chen received his Medical Doctor's Degree at Shanghai Medical University and studied as a visiting scholar at various US and European Universities. He performs about 500 neurosurgeries each year. His research areas include minimally invasive surgical treatment and functional rehabilitation or neuromodulation of brain diseases.



#### Li Chunbo, PhD Mentor, MD

#### Vice President, Shanghai Mental Health Center; Vice President, Institute of Psychology and Behavioral Science, Shanghai Jiao Tong University, Professor of Psychiatry and Neuroscience

Professor Li received his MD at Shanghai Second Medical University and studied as a visiting scholar at Harvard University and UCSD. He is the president or committee member of several important Chinese academic associations including Vice President, Geriatric Psychology Branch, Chinese Psychological Society; President and the Shanghai Association of Behavioral Medicine. He is also an editor of the Cochrane Schizophrenia Group at The Cochrane Library. Professor Li's research interests include basic and clinical studies of anxiety disorders, the plasticity of the aging brain and evidence-based psychiatry. He has published over 360 peer-reviewed papers.



#### Viviana Gradinaru

#### Director of the Center for Molecular and Cellular Neuroscience

Viviana Gradinaru completed her BS at Caltech and did her PhD research at Stanford University. She is now a professor of neuroscience and biological engineering and Heritage Medical Research Institute Investigator at Caltech.

Gradinaru's research focuses on investigating the mechanisms underlying neurodegeneration, its affected behaviors, and relevant interventions such as deep brain stimulation. Her group also develops tools and methods for use in neuroscience, such as optogenetic actuators and sensors, tissue clearing and imaging, and genedelivery vehicles.



#### Yanyan Huang, Master Mentor

#### Professor, Deputy Director of Geriatrics Department at Huashan Hospital

Professor Huang graduated from Shanghai Medical University and studied as a visiting scholar at Harvard University, Stanford University, UCLA and UCSF. She is a standing member of the Chinese Rehabilitation Medicine Association's Rehabilitation Committee for Alzheimer's Disease and Other Cognitive Disorders, the Chinese Society of Geriatric Hierarchical Diagnosis and Treatment Committee, the Chinese Medical Association Behaviorial Medicine Committee and a member of The Gerontological Society of America. Her research areas include the prevention, intervention and diagnosis of Alzheimer's disease.



#### **Markus Meister**

#### Director, Chen Center for Neuroscience Education

Markus Meister is Caltech's Anne P. and Benjamin F. Biaggini Professor of Biological Sciences and Executive Officer for Neurobiology. The Education Center offers a number of opportunities for graduate students in neuroscience providing fellowships to exceptional first-year graduate students in neuroscience at Caltech, and fostering graduate student participation in order to enrich the student experience.



#### Doris Tsao

#### Director of the T&C Chen Center for Systems Neuroscience

Doris Tsao is a professor of biology at Caltech and an investigator with the Howard Hughes Medical Institute. She joined the Caltech faculty in 2009; prior to that, she was head of an independent research group at the University of Bremen in Germany.

Tsao seeks to understand how visual objects in space are represented in the brain, and how these representations are used to guide behavior. She employs techniques such as functional magnetic resonance imaging (fMRI), electrophysiology, optogenetics and electrical stimulation, behavior, and mathematical modeling to study species that include both rodents and nonhuman primates. Tsao is widely recognized for pioneering the use of fMRI to target electrodes for studying visual processing in monkeys, and in particular for her discovery of the macaque facepatch system, a network of six regions in the brain's temporal lobe dedicated to face processing.



#### Wei Zhu, MD,

#### Professor of Neurosurgery at Huashan Hospital

Professor Zhu received his Medical Doctor's Degree at Shanghai Medical University and studied as a visiting scholar at UCSF, the Mayo Clinic and the Barrow Neurological Institute. He performs more than 500 neurosurgeries each year. His research areas include cerebrovascular etiology and nerve regeneration.

#### Chen Graduate Fellows at Caltech: Class of 2018-2019



**Weilun Ding** Social and Decision Neuroscience

Weilun is interested in using neural and computational tools to study how naturalistic decisions are formed in the brain from initial sensory input, to intermediate cognitive state and then final action code. Prior to Caltech, he was a research assistant at the Neuroeconomics Lab at UC, Berkeley. He has an MSc in Data Science from the University of Rochester and a BA in Economics from Fudan University in China.



**Marcus Gallo** Social and Decision Neuroscience

Marcos holds a masters in Economics from Shanghai Jiao Tong University in China - for which he received a full scholarship from the Shanghai Government. He also holds a BA in Economics from Brigham Young University, where he was a commencement speaker at his graduation.



Sanghyun Yi Social and Decision Neuroscience

Sanghyun is interested in bi-directional research: understanding brains by machine learning techniques and solving machine learning problems with brain science. He earned his undergraduate degree in mathematics from Seoul National University. He has research experience in applying machine learning algorithms to solve various problems including human decision-making and conversational A.I.



Annie Erickson Neurobiology

Annie graduated from Cornell University with a bachelors in Human Biology, Health and Society. Prior to starting her PhD at Caltech, she spent two years at UCSF researching the neural circuity underlying emotional behavior. At Caltech, Annie is looking forward to studying the neural circuits that drive motivated behavior.



Alexander Farhang Neurobiology

Alexander was a Staff Research Associate in the Feinberg Lab at UCSF. He conducted research on sensorimotor processing. He earned a bachelors in Biology from Cornell University.



Tae Han Kim Neurobiology

Han holds a bachelors in Philosophy of Science and Molecular Genetics from the University of Toronto. As a graduate student, he is interested in using molecular genetic tools for studying systems neuroscience.



**Isabelle Rosenthal** Computation and Neural Systems

Isabelle worked at the National Eye Institute for two years studying color vision in primates after getting her BA in Neuroscience at Wellesley College. At Caltech, she is pursuing research at the nexus of neuroscience and computer science, including brain machine interfaces, A.I. and the pathway from perception to decisionmaking.

#### Chen Graduate Fellows at Caltech: Class of 2017-2018



**Anastasia Buyalskaya** Social and Decision Neuroscience

Anastasia is interested in the neural basis behind economic decision-making involving risk and reward. Prior to starting her PhD at Caltech, Anastasia was VP of Behavioral Finance at BlackRock Asset Management, where she helped investors improve their processes with learnings from behavioral finance. She holds a MSc from Imperial College London and a BA from Hunter College in New York.



**David Brown** Computation and Neural Systems

David graduated from the University of Michigan with a degree in Computer Science. He volunteered in a variety of labs at Caltech working on projects bridging neuroscience and A.I. Most recently, David joined the Jet Propulsion Laboratory's A.I. group. In Caltech's Computation and Neural Systems program, David will pursue his passion for understanding how the brain works and how to replicate its functionality in software.



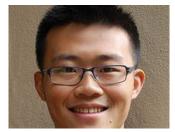
**Jialiang Lu** Computation and Neural Systems

Jialiang grew up in Wuhan, China. Funded by a full DAAD-scholarship from the German government, he received a Bachelor and Master's degree in Biology in Freiburg and Munich, respectively. He became interested in the mechanisms of brain activity and was attracted by the unique environment of Caltech. He is now a graduate student in the Computation and Neural Systems Program, focusing on the encoding and processing of information in the brain.



Varun Wadia Neurobiology

Vaurun was born in India and studied at Bowdoin College. After getting a BA in Physics, he worked in Vikaas Sohal's lab at UCSF. studying mouse models of schizophrenia and autism using optogenetics and in vivo calcium imaging. At Caltech, he hopes to combine wet lab experiments with computational techniques to either dissect the neural systems responsible for visual perception, or improve our understanding of disease-related neural degeneration.



Xinhong Chen Neurobiology

Xinhong worked on the Genetic impact of Alzheimer's disease whilst at Tongji University, China. He spent his senior year at MIT working on alcohol addiction. He became an iGEMer in his freshmen year. Xinhong is passionate about the mystery underlying social interaction and the development of new research techniques.



Yuelin Shi Neurobiology

Yuelin did her undergrad at Shanghai Jiao Tong University in China. She had a year-long research experience at Yale University working on functional neural circuits in the mouse retina.



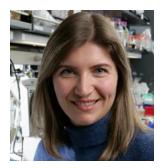
**Dylan Bannon** Biology

Dylan completed his undergraduate degrees at MIT and holds a Bachelors' in both Biology and Economics. Prior to joining the Biology graduate program, he worked in the Kennedy lab at Caltech.

## **Recognition:** Our congratulations to TCCI's 2018 award winners



David Anderson Director of the Tianqiao and Chrissy Chen Institute for Neuroscience at Caltech Winner of the 2018 Edward M. Scolnick Prize in Neuroscience



Viviana Gradinaru Director of the T&C Chen Center for Molecular and Cellular Neuroscience Winner of the 2018 NIH Pioneer Award



#### Professor Mao Ying Director of Translational Research, Vice President of Huashan Hospital, President of West Huashan Hospital

Winner: 2018 Chinese Science and Technology Progress Award, Second Class, Wu Jieping Medical Innovation Award, 2018 Chinese Ministry of Education Science and Technology Progress Award, First Class



#### Doris Tsao Director of the T&C Chen Center for Systems Neuroscience

Winner of the 2018 Perl-UNC Neuroscience Price and a 2018 MacArthur Genius Grant

# **ACTIVITY:**

Last year presented two significant opportunities to bring TCCI-affiliated scientists together for community building and informationsharing.

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#### TCCI Chen Institute Retreat 2018

In February 2018, the Tianqiao and Chrissy Chen Institute for Neuroscience at Caltech hosted its first annual Chen Institute Retreat at the beautiful Bahia Resort on Mission Bay in San Diego. The retreat brought together the Caltech neuroscience community with a mix of scientific talks and social activities.

Attendees at the retreat included six Chen Graduate Fellows, 15 first-year graduate students, 30 faculty, 41 graduate students, 38 postdocs and 10 scientific staff members. All students, postdocs and scientific staff attending the retreat presented a poster during the opening night – these can be found on the Caltech website.



Caltech Graduate Students, Faculty and TCCI staff attend the annual Chen Institute Retreat in San Diego, Feb 23-25. Professor Ralph Adolphs presents.

#### **TCCI Translational Research Symposium**

In August 2018, TCCI was happy to host an international meeting in Shanghai, bringing together top scientists and doctors working on brain-related topics. Attendees from Huashan Hospital, Shanghai Mental Health Center and the Tianqiao and Chrissy Chen Institute for Neuroscience at Caltech, the Shanghai Institute of Neuroscience and others explored opportunities for collaboration and several possible projects were identified.



Professors Richard Andersen (top) and Doris Tsao (below left) address the Symposium audience in Shanghai, China.

#### **TCCI Caltech Director's Award**

#### Computation



#### Awarded to: Frederick Eberhardt and Ralph Adolphs

#### Causal Discovery Algorithms for Neuroimaging Data

Eberhardt and Adolphs apply new computational methods to determine whether it is possible to extract causal inferences from large, resting-state fMRI datasets in humans. These "causal discovery algorithms" leverage temporal sequencing and other factors to infer whether activity in one brain region is driven by activity in another brain region, or vice-versa. If successful, this method could have a transformative effect on the interpretation of correlative fMRI data.



#### Awarded to: Lior Pachter and Marianne Bronner

#### *Tensor-Based Modelling of Nervous System Development Using Multi-Plexed Single-Cell RNA-Sequencing*

Pachter and Bronner, in collaboration with Profs. Joel Tropp and Venkat Chandrasekaran in CMS, are developing algebraic methods to try to infer developmental sequences ("time-lapse" models) in the differentiation of cells in the peripheral nervous system, based on single-cell RNA sequencing carried out on cell mixtures from zebrafish embryos at different developmental stages, where all cells from each stage are labeled by a DNA "bar-code." This will convert conventional 2D matrices of cells x genes into 3D tensors of cells x genes x developmental stages. Developing these tensor computational methods should allow this approach to be extended to many different settings.

#### **Technology Development**



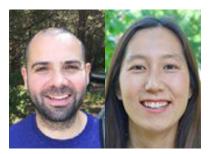
#### Awarded to: Prof. Axel Scherer and Prof. Henry Lester

#### Measuring Brain and Interstitial Nicotine with Wireless Sensors

Scherer and Lester collaborate on the development and application of novel wireless sensors for measuring brain and interstitial levels of nicotine. This technology, if successful, would greatly facilitate within-animal studies of the pharmacokinetics and pharmacodynamics of nicotine, with high temporal resolution (100 ms). It has potentially important implications for the treatment of nicotine addiction in humans, and is potentially extensible to measuring other types of brain chemicals as well.

#### The T&C Chen Center for Systems Neuroscience

#### Interfaces Between Systems



#### Awarded to: Asst. Prof. Joe Parker and Asst. Prof. Betty Hong

#### Dissecting the Neural Interface by a Symbiotic Animal and its Host

Parker and Hong dissect the neural interface between ants and beetles in social symbiosis by identifying the chemicals and chemoreceptors beetles use to locate and successfully interact with ants. Techniques they will use include: neurotranscriptome profiling, phylogenetic analysis, gas chromotography-mass spectroscopy, and electrophysiology.



#### Awarded to: Prof. Henry Lester and Asst. Prof. Matt Thomson

#### Molecular Basis for the Antidepressant Effects of Ketamine

Lester and Thomson dissect the interface between depression, neural network excitability, and gene expression, by studying the effects of ketamine and other anti-depressants on neural activity and gene transcription in neuronal cell culture. Techniques they will use include: single-cell RNA-sequencing, electrophysiology, calcium imaging, and computational analysis.

#### **Mathematical Modeling**



#### Awarded to: Prof. John Doyle

#### *Mathematical Foundations for Understanding Human Sensorimotor and Homiostic Control*

Doyle is exploring how a new mathematical theory of layered architectures can be applied to the brain, with a focus on the role of feedback in the visual system. He will clarify the similarities and differences between the theory and the actual anatomy and physiology of vision.



#### Awarded to: Prof. Michelle Effros

Effros will explore the phenomena of memory in a network of simple, biologically realistic model neurons. She will apply information theory to understand what the optimal code is for information storage, how storing new memories affects old memories, how memories can be sequentially updated, and what the capacity limits are.

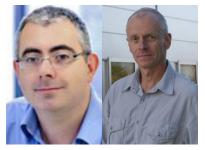
#### The T&C Chen Center for Social and Decision Neuroscience



#### Awarded to: Asst. Prof. Dean Mobbs

#### *Attack or Escape: The Role of the Human Hypothalamus in Reflexive Switching in Survival States*

Mobbs uses MVPA methods to analyze fMRI activity in human hypothalamus at high-resolution, 1.5-1.7mm, using the new, upgraded 3T Prisma awarded by NSF. Using a lifelike, simplified attack-escape, they hope to identify changes in the hypothalamus and other regions as subjects switch from artificial predator to prey.



#### Awarded to: Prof. John O'Doherty and Prof. Ralph Adolphs

#### Using Reinforcement-Learning as a Window into Between-Subject Variability in the Neural Computations Underlying Psychiatric Dysfunction

O'Doherty and Adolphs are conducting fMRI during four, well-characterized human choice tasks, involving reward, model-based and model-free learning, exploration, and mentalizing. Behavior of brain activity of populations of patients with diagnosed OCD and autism spectrum disorder (ASD) will be compared to control subjects to search for novel, functional biomarkers of these disorders.





**Awarded to:** Prof. Steven Quartz, Prof. Christopher Hitchcock and Prof. Shin Shimojo

#### A Novel Paradigm to Investigate Human Intention and Agency: A Neuroscience and Philosophy Collaboration

Quartz, Hitchcock and Shimojo are investigating a motor illusion. Subjects move their thumb at any time then choose, which then triggers an external stimulation-induced (TMS) thumb twitch. Subjects report feeling that the machine can 'read their mind', because their thumb movement feels involuntary. This result challenges the traditional philosophical view that introspection is direct, suggesting instead that the feeling of personal agency is an inference.

#### The T&C Chen Brain-Machine Interface Center

#### Invasive or Non-Invasive Recording Technology



#### Awarded to: Prof. Markus Meister

## *Electrode Pooling: A Method to Boost the Yield of Multi Neuron Record-ings*

Being able to record from large numbers of neurons is essential for brainmachine interface (BMI) studies as well as systems neuroscience research. Meister, in collaboration with Dr. Tim Harris from Janelia, has proposed a novel design for silicon probes that can increase channel counts by drastically reducing the number of wires needed on these multi-channel probes.

#### **Computational Neural Prosthetics**



Awarded to: Professor Azita Emami

## *Efficient Machine Learning Algorithms for Closed-Loop Brain-Machine Interfaces*

Real-time and fast learning algorithms are required to decode neural signals for BMI applications. Emami is developing efficient machine learning algorithms for closed-loop BMIs. She plans to implement these learning algorithms on a single integrated circuit, and will be collaborating with Prof. Yisong Yue.

#### **Neural Plasticity for BMI learning**

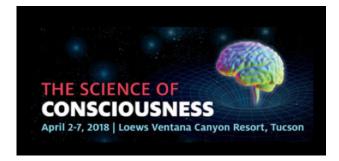


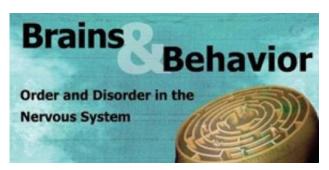
#### Awarded to: Prof. Joel Burdick

#### A Pilot Study of Joint Cortical and Spinal Plasticity During Spinally Stimulated Recovery of Voluntary Control in a rat model of severe SCI

Burdick and colleagues have shown, in rats and humans, that spinal cord stimulation below an incomplete lesion can enhance volitional control. He proposes, in rat studies, combined spinal cord and motor cortex stimulation to see if plasticity is enhanced by affecting both ends of the cortico-spinal pathway.

# Supporting the community:





#### 7-11 July 2018 | Berlin, Germany







#### April 2-7, 2018: The Science of Consciousness

We think about the brain and mind holistically so we were happy to kick off the year supporting this well-established conference focused on the study and understanding of conscious awareness at University of Arizona.

#### May 30 – June 4, 2018: 83rd Cold Spring Harbor Laboratory Symposium on Quantitative Biology

The 2018 Symposium on **Brains & Behaviour: Order & Disorder in the Nervous System** was a perfect fit for us and we were happy to support this event. We were excited to introduce the Chen Travel Fellows program which made it possible for 10 young scientists to attend the event in New York.

#### July 7-11, 2018: 11th FENS Forum of Neuroscience

With over 4,000 scientists from Europe, US and Asia in attendance, this annual event was a hotbed of activity and discussion. We were honored to support the Presidential Plenary Session which featured biologist and ethologist, Frans de Waal, speaking on the **"Evolution of Emotions and Empathy in Primates."** 

## Oct 1-2, 2018: Neuropsychiatry Symposium and Workshop

Organized by Steve Hyman, M.D., Harvard University, Huda Zoghbi, Balor College and Orla Smith, PhD and Editor, Science Translational Medicine, this meeting focused on key issues that must be addressed in order to develop effective therapies for neuropsychiatric disorders.

#### Nov 3-7, 2018: Neuroscience 2018

A staple for the neuroscience community, we sponsored a Presidential Special Lecture at SfN's annual meeting in San Diego. Catherine Dulac, PhD, Harvard University, Howard Hughes Medical Institute. Dr. Dulac spoke on the **"Neurobiology of Social Behavior Circuits."** 

# Advocacy:

Debuting on the Discovery Channel in September 2018, we commissioned this film to help make the case that more support is needed if we are to realize the unparalleled breakthroughs scientists are so close to achieving.

# MINDS WIDE OPEN

AWARDED:

**2018 Cannes Corporate Gold Awards** Winner in Educational, Medical & Science Film Categories

2018 Gold Standard Award for Broadcast & Video Public Affairs Asia

FINALIST:

**2019 New York Festivals TV & Film Awards** Science & Technology Film, Feature Documentary, Branded Documentary Production



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# **RESEARCH:**

TCCI Researchers at Caltech were prolific in 2018, releasing significant research findings spanning perception, fear, intelligence and much more.

#### 2018: A Year of Breakthrough Research at Caltech



**THIRST:** "You get Thirsty and Drink. How Does Your Brain Signal You've Had Enough?"

Yuki Oka, Assistant Professor of Biology and Biological Engineering and TCCI-affiliated faculty member



**FEAR:** "You Don't Think Your Way Out Of A Tiger Attack"

Dean Mobbs, Assistant Professor of Cognitive Neuroscience

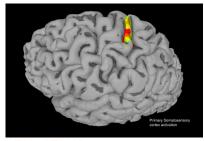


**EVOLUTION:** "How Insects Can Help Us Understand Evolution"

Joe Parker, Assistant Professor of Biology and TCCI-affiliated faculty member Neural circuits for appetites are regulated by both homeostatic perturbations and ingestive behaviour. However, the circuit organization that integrates these internal and external stimuli is unclear. Here we show in mice that excitatory neural populations in the lamina terminalis form a hierarchical circuit architecture to regulate thirst. Among them, nitric oxide synthase-expressing neurons in the median preoptic nucleus (MnPO) are essential for the integration of signals from the thirst-driving neurons of the subfornical organ (SFO). Conversely, a distinct inhibitory circuit, involving MnPO GABAergic neurons that express glucagon-like peptide 1 receptor (GLP1R), is activated immediately upon drinking and monosynaptically inhibits SFO thirst neurons. These responses are induced by the ingestion of fluids but not solids, and are time-locked to the onset and offset of drinking. Furthermore, loss-of-function manipulations of GLP1Rexpressing MnPO neurons lead to a polydipsic, overdrinking phenotype. These neurons therefore facilitate rapid satiety of thirst by monitoring real-time fluid ingestion. Our study reveals dynamic thirst circuits that integrate the homeostatic-instinctive requirement for fluids and the consequent drinking behaviour to maintain internal water balance.

Flight initiation distance (FID), the distance at which an organism flees from an approaching threat, is an ecological metric of cost-benefit functions of escape decisions. We adapted the FID paradigm to investigate how fast- or slow-attacking "virtual predators" constrain escape decisions. We show that rapid escape decisions rely on "reactive fear" circuits in the periaqueductal gray and midcingulate cortex (MCC), while protracted escape decisions, defined by larger buffer zones, were associated with "cognitive fear" circuits, which include posterior cingulate cortex, hippocampus, and the ventromedial prefrontal cortex, circuits implicated in more complex information processing, cognitive avoidance strategies, and behavioral flexibility. Using a Bayesian decision-making model, we further show that optimization of escape decisions under rapid flight were localized to the MCC, a region involved in adaptive motor control, while the hippocampus is implicated in optimizing decisions that update and control slower escape initiation. These results demonstrate an unexplored link between defensive survival circuits and their role in adaptive escape decisions.

Not many people get to turn their childhood hobby into a career, but when Joe Parker began collecting insects at the age of 7, he simply never stopped. Parker took his childhood fascination with insects to the next level, amassing a diverse and pristine collection from the Welsh countryside surrounding his hometown of Swansea in the United Kingdom. It was only natural for him to turn this love of insects into a career and, in 2017 2017, Parker arrived at Caltech as an assistant professor of biology and an affiliated faculty member of the Tianqiao and Chrissy Chen Institute for Neuroscience. He now focuses on small species of beetle that have the potential to answer fundamental questions of evolution. Watch our conversation with Parker on the Caltech Website.



**SENSATION:** "Paralyzed Patient Feels Sensation Again"

Richard Andersen, Professor of Neuroscience, T&C Chen Brain-Machine Interface Center Leadership Chair, and director of the T&C Chen Brain-Machine Interface Center.



INTELLIGENCE: "Caltech Scientists Can Predict Intelligence from Brain Scans"

Ralph Adolphs, Professor of Psychology, Neuroscience, and Biology and Chair of the Caltech Brain Imaging Center. Pioneering work with nonhuman primates and recent human studies established intracortical microstimulation (ICMS) in primary somatosensory cortex (S1) as a method of inducing discriminable artificial sensation. However, these artificial sensations do not yet provide the breadth of cutaneous and proprioceptive percepts available through natural stimulation. In a tetraplegic human with two microelectrode arrays implanted in S1, we report replicable elicitations of sensations in both the cutaneous and proprioceptive modalities localized to the contralateral arm, dependent on both amplitude and frequency of stimulation. Furthermore, we found a subset of electrodes that exhibited multimodal properties, and that proprioceptive percepts on these electrodes were associated with higher amplitudes, irrespective of the frequency. These novel results demonstrate the ability to provide naturalistic percepts through ICMS that can more closely mimic the body's natural physiological capabilities. Furthermore, delivering both cutaneous and proprioceptive sensations through artificial somatosensory feedback could improve performance and embodiment in brain-machine interfaces.

Personality neuroscience aims to find associations between brain measures and personality traits. Findings to date have been severely limited by a number of factors, including small sample size and omission of out-of-sample prediction. We capitalized on the recent availability of a large database, together with the emergence of specific criteria for best practices in neuroimaging studies of individual differences. We analyzed resting-state functional magnetic resonance imaging (fMRI) data from 884 young healthy adults in the Human Connectome Project database. We attempted to predict personality traits from the "Big Five," as assessed with the Neuroticism/Extraversion/Openness Five-Factor Inventory test, using individual functional connectivity matrices. After regressing out potential confounds (such as age, sex, handedness, and fluid intelligence), we used a cross-validated framework, together with test-retest replication (across two sessions of resting-state fMRI for each subject), to quantify how well the neuroimaging data could predict each of the five personality factors. We tested three different (published) denoising strategies for the fMRI data, two intersubject alignment and brain parcellation schemes. and three different linear models for prediction. As measurement noise is known to moderate statistical relationships, we performed final prediction analyses using average connectivity across both imaging sessions (1 hr of data), with the analysis pipeline that yielded the highest predictability overall. Across all results (test/retest; three denoising strategies; two alignment schemes; three models), Openness to experience emerged as the only reliably predicted personality factor. Using the full hour of resting-state data and the best pipeline, we could predict Openness to experience (NEOFAC\_0: r=.24, R^2=.024) almost as well as we could predict the score on a 24-item intelligence test (PMAT24 A CR: r=.26, R^2=.044). Other factors (Extraversion, Neuroticism, Agreeableness, and Conscientiousness) yielded weaker predictions across results that were not statistically significant under permutation testing. We also derived two superordinate personality factors (" $\alpha$ " and " $\beta$ ") from a principal components analysis of the Neuroticism/Extraversion/Openness Five-Factor Inventory factor scores, thereby reducing noise and enhancing the precision of these measures of personality. We could account for 5% of the variance in the  $\beta$  superordinate factor (r=.27, R^2=.050), which loads highly on Openness to experience. We conclude with a discussion of the potential for predicting personality from neuroimaging data and make specific recommendations for the field.



**CIRCUITS:** "Switching Brain Circuits On and Off Without Surgery"

Mikhail Shapiro, Assistant Professor of Chemical Engineering and TCCI-affiliated faculty member



NAVIGATION: "Guiding Flight: The Fruit Fly's Celestial Compass"

Michael Dickinson, Professor of Bioengineering and Aeronautics and TCCI-affiliated faculty member



CHOICE: "Scientists Uncover Why You Can't Decide What to Order for Lunch"

Colin Camerer, Professor of Behavioral Economics and the T&C Chen Center for Social and Decision Neuroscience

Neurological and psychiatric disorders are often characterized by dysfunctional neural circuits in specific regions of the brain. Existing treatment strategies, including the use of drugs and implantable brain stimulators, aim to modulate the activity of these circuits. However, they are not cell-type-specific, lack spatial targeting or require invasive procedures. Here, we report a cell-type-specific and non-invasive approach based on acoustically targeted chemogenetics that enables the modulation of neural circuits with spatiotemporal specificity. The approach uses ultrasound waves to transiently open the blood-brain barrier and transduce neurons at specific locations in the brain with virally encoded engineered G-protein-coupled receptors. The engineered neurons subsequently respond to systemically administered designer compounds to activate or inhibit their activity. In a mouse model of memory formation, the approach can modify and subsequently activate or inhibit excitatory neurons within the hippocampus, with selective control over individual brain regions. This technology overcomes some of the key limitations associated with conventional brain therapies.

Despite their small brains, insects can navigate over long distances by orienting using visual landmarks [1], skylight polarization [2, 3, 4, 5, 6, 7, 8, 9], and sun position [3, 4, 6, 10]. Although Drosophila are not generally renowned for their navigational abilities, mark-and-recapture experiments in Death Valley revealed that they can fly nearly 15 km in a single evening [11]. To accomplish such feats on available energy reserves [12], flies would have to maintain relatively straight headings, relying on celestial cues [13]. Cues such as sun position and polarized light are likely integrated throughout the sensorymotor pathway [14], including the highly conserved central complex [4, 15, 16]. Recently, a group of Drosophila central complex cells (E-PG neurons) have been shown to function as an internal compass [17, 18, 19], similar to mammalian head-direction cells [20]. Using an array of genetic tools, we set out to test whether flies can navigate using the sun and to identify the role of E-PG cells in this behavior. Using a flight simulator, we found that Drosophila adopt arbitrary headings with respect to a simulated sun, thus performing menotaxis, and individuals remember their heading preference between successive flights—even over several hours. Imaging experiments performed on flying animals revealed that the E-PG cells track sun stimulus motion. When these neurons are silenced, flies no longer adopt and maintain arbitrary headings relative to the sun stimulus but instead exhibit frontal phototaxis. Thus, without the compass system, flies lose the ability to execute menotaxis and revert to a simpler, reflexive behavior.

Modern societies offer a large variety of choices, which is generally thought to be valuable. But having too much choice can be detrimental if the costs of choice outweigh its benefits due to 'choice overload'. Current explanatory models of choice overload mainly derive from behavioural studies. A neuroscientific investigation could further inform these models by revealing the covert mental processes during decision-making. We explored choice overload using functional magnetic resonance imaging while subjects were either choosing from varying-sized choice sets or were browsing them. When choosing from sets of 6, 12 or 24 items, functional magnetic resonance imaging activity in the striatum and anterior cingulate cortex resembled an inverted U-shaped function of choice set size. Activity was highest for 12-item sets, which were perceived as having 'the right amount' of options and was lower for 6-item and 24-item sets, which were perceived as 'too small' and 'too large', respectively. Enhancing choice set value by adding a dominant option led to an overall increase of activity. When subjects were browsing, the decision costs were diminished and the inverted U-shaped activity patterns vanished. Activity in the striatum and anterior cingulate reflects choice set value and can serve as neural indicator of choice overload.



LOCOMOTION: "Gut Bacteria Influence Movement in Flies"

Sarkis Mazmanian, Professor of Microbiology and a TCCI-affiliated faculty member



AGGRESSION: "Picking Fights with Fruit Flies"

David Anderson, Professor of Biology, TCCI for Neuroscience Leadership Chair and director of the Tianqiao and Chrissy Chen Institute for Neuroscience.



**SIGHT:** "Helping the Blind to Navigate"

Markus Meister, Professor of Biological Sciences, executive officer for neurobiology, and TCCIaffiliated faculty member. While research into the biology of animal behaviour has primarily focused on the central nervous system, cues from peripheral tissues and the environment have been implicated in brain development and function. There is emerging evidence that bidirectional communication between the gut and the brain affects behaviours including anxiety, cognition, nociception and social interaction. Coordinated locomotor behaviour is critical for the survival and propagation of animals, and is regulated by internal and external sensory inputs. However, little is known about how the gut microbiome influences host locomotion, or the molecular and cellular mechanisms involved. Here we report that germ-free status or antibiotic treatment results in hyperactive locomotor behaviour in the fruit fly Drosophila melanogaster. Increased walking speed and daily activity in the absence of a gut microbiome are rescued by mono-colonization with specific bacteria, including the fly commensal Lactobacillus brevis. The bacterial enzyme xylose isomerase from L. brevis recapitulates the locomotor effects of microbial colonization by modulating sugar metabolism in flies. Notably, thermogenetic activation of octopaminergic neurons or exogenous administration of octopamine, the invertebrate counterpart of noradrenaline, abrogates the effects of xylose isomerase on Drosophila locomotion. These findings reveal a previously unappreciated role for the gut microbiome in modulating locomotion, and identify octopaminergic neurons as mediators of peripheral microbial cues that regulate motor behaviour in animals.

Threat displays are a universal feature of agonistic interactions. Whether threats are part of a continuum of aggressive behaviors or separately controlled remains unclear. We analyze threats in Drosophila and show they are triggered by male cues and visual motion, and comprised of multiple motor elements that can be flexibly combined. We isolate a cluster of ~3 neurons whose activity is necessary for threat displays but not for other aggressive behaviors, and whose artificial activation suffices to evoke naturalistic threats in solitary flies, suggesting that the neural control of threats is modular with respect to other aggressive behaviors. Artificially evoked threats suffice to repel opponents from a resource in the absence of contact aggression. Depending on its level of artificial activation, this neural threat module can evoke different motor elements in a threshold-dependent manner. Such scalable modules may represent fundamental "building blocks" of neural circuits that mediate complex multi-motor behaviors.

To restore vision for the blind, several prosthetic approaches have been explored that convey raw images to the brain. So far, these schemes all suffer from a lack of bandwidth. An alternate approach would restore vision at the cognitive level, bypassing the need to convey sensory data. A wearable computer captures video and other data, extracts important scene knowledge, and conveys that to the user in compact form. Here, we implement an intuitive user interface for such a device using augmented reality: each object in the environment has a voice and communicates with the user on command. With minimal training, this system supports many aspects of visual cognition: obstacle avoidance, scene understanding, formation and recall of spatial memories, navigation. Blind subjects can traverse an unfamiliar multi-story building on their first attempt. To spur further development in this domain, we developed an open-source environment for standardized benchmarking of visual assistive devices.



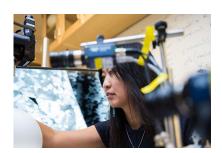
**DECISION-MAKING:** "Cracking Open a Cold One with the Flies"

Michael Dickinson, Professor of Bioengineering and Aeronautics and TCCI-affiliated faculty member



LEARNING: "Learning from Mistakes"

Ralph Adolphs, Professor of Psychology, Neuroscience, and Biology and Chair of the Caltech Brain Imaging Center.



PERCEPTION: "The Face Detective"

Doris Tsao, Professor of Biology; T&C Chen Center for Systems Neuroscience Leadership Chair; Investigator, Director, T&C Chen Center for Systems Neuroscience Carbon dioxide is produced by many organic processes and is a convenient volatile cue for insects that are searching for blood hosts, flowers, communal nests, fruit and wildfires. Although Drosophila melanogaster feed on yeast that produce CO 2 and ethanol during fermentation, laboratory experiments suggest that walking flies avoid CO 2. Here we resolve this paradox by showing that both flying and walking Drosophila find CO 2 attractive, but only when they are in an active state associated with foraging. Their aversion to CO\_2 at low-activity levels may be an adaptation to avoid parasites that seek CO 2, or to avoid succumbing to respiratory acidosis in the presence of high concentrations of CO 2 that exist in nature. In contrast to CO 2, flies are attracted to ethanol in all behavioural states, and invest twice the time searching near ethanol compared to CO 2. These behavioural differences reflect the fact that ethanol is a unique signature of yeast fermentation, whereas CO 2 is generated by many natural processes. Using genetic tools, we determined that the evolutionarily conserved ionotropic co-receptor IR25a is required for CO 2 attraction, and that the receptors necessary for CO2 avoidance are not involved in this attraction. Our study lays the foundation for future research to determine the neural circuits that underlie both state- and odorant-dependent decision-making in Drosophila.

Humans can self-monitor errors without explicit feedback, resulting in behavioral adjustments on subsequent trials such as post-error slowing (PES). The error-related negativity (ERN) is a well-established macroscopic scalp EEG correlate of error self-monitoring, but its neural origins and relationship to PES remain unknown. We recorded in the frontal cortex of patients performing a Stroop task and found neurons that track self-monitored errors and error history in dorsal anterior cingulate cortex (dACC) and pre-supplementary motor area (pre-SMA). Both the intracranial ERN (iERN) and error neuron responses appeared first in pre-SMA, and ~50 ms later in dACC. Error neuron responses were correlated with iERN amplitude on individual trials. In dACC, such error neuron-iERN synchrony and responses of error-history neurons predicted the magnitude of PES. These data reveal a human single-neuron correlate of the ERN and suggest that dACC synthesizes error information to recruit behavioral control through coordinated neural activity.

Doris Tsao unlocked the brain's code for recognizing faces. Now she wants to work out how we see everything else.

Read the full article in the *December 13, 2018 issue of Nature*.





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