McGOVERN INSTITUTE
FOR BRAIN RESEARCH AT MIT

Brain SCAN

FALL 2018 ■ Issue no. 46

Is It Worth the Risk?

How the brain balances risk and reward to make decisions

FROM THE **DIRECTOR**

It's the beginning of the semester and around the MIT campus, including at the McGovern Institute, our new intake of students and postdoctoral trainees are making decisions. The brain is constantly evaluating potential costs and benefits to help decision-making, and small alterations in neural circuit function can shift the balance between wise choices and catastrophic risk-taking. In psychiatric disorders, such as depression and bipolar disorder, decision-making can become highly skewed. In this issue, we look at research from around the McGovern Institute, particularly in Ann Graybiel's lab, into the brain regions that are emerging as key players in such decision-making. Our scientists are not only able to observe the critical circuits in operation, but also alter them in ways that affect decision-making in predictable ways.

In other news, congratulations to Jonathan Wilde, our inaugural J. Douglas Tan postdoctoral fellow, a position made possible by the generosity of K. Lisa Yang. Congratulations are also due to our recently named graduate fellows. You can read more about these fellows and other recent McGovern Institute events in the following pages.

Bob Desimone, Director
Doris and Don Berkey Professor
of Neuroscience

On the cover: How do we evaluate cost and benefit in decision making? McGovern investigators are making new inroads into the basis of choice.
Image: shutterfly

Image: National Park Service

During the Klondike Gold Rush, thousands of prospectors climbed Alaska's dangerous Chilkoot Pass in search of riches. McGovern scientists are exploring how a once-overlooked part of the brain might be at the root of cost-benefit decisions like these.

Is it worth speeding up on the highway to save a few minutes' time? How about accepting a job that pays more, but requires longer hours in the office?

Scientists call these types of real-life situations cost-benefit conflicts. Choosing well is an essential survival ability—consider the animal that must decide when to expose itself to predation to gather more food.

Is It Worth the Risk?

McGovern researchers are studying how the brain balances risk and reward to make decisions.

Now, McGovern researchers are discovering that this fundamental capacity to make decisions may originate in the basal ganglia—a brain region once considered unimportant to the human experience—and that circuits associated with this structure may play a critical role in determining our state of mind.

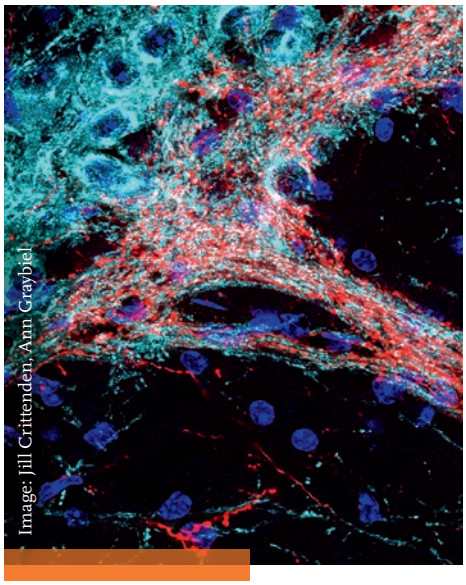
Anatomy of Decision-Making

A few years back, McGovern investigator Ann Graybiel noticed that in the brain imaging literature, a specific part of the cortex called the pregenual anterior cingulate cortex or pACC, was implicated in certain psychiatric disorders as well as tasks involving cost-benefit decisions. Thanks to her now classic neuroanatomical work defining the complex anatomy and function of the basal ganglia, Graybiel knew that the pACC projected back into the basal ganglia—including its largest cluster of neurons, the striatum.

The striatum sits beneath the cortex, with a mouse-like main body and curving tail. It seems to serve as a critical way-station, communicating with both the brain's sensory and motor areas above, and the limbic system (linked to emotion and memory) below. Running through the striatum are striosomes, column-like neurochemical compartments. They wire down to a small, but important part of the brain called the substantia nigra, which houses the huge majority of the brain's dopamine neurons—a key neurochemical heavily involved, much like the basal ganglia as a whole, in reward, learning, and movement. The pACC region related to mood control targeted these striosomes, setting up a communication line from the neocortex to the dopamine neurons.

Graybiel discovered these striosomes early in her career, and understood them to have distinct wiring from other compartments in the striatum, but picking out these small, hard-to-find striosomes posed a technological challenge—so it was exciting to have this intriguing link to the pACC and mood disorders.

Working with Ken-ichi Amemori, then a research scientist in her lab, she adapted a common human cost-benefit conflict test for macaque monkeys. The monkeys could elect to receive a food treat, but the treat would always be accompanied by an annoying puff of air to the eyes. Before they decided, a visual cue told them exactly how much treat they could get, and exactly how strong the air puff would be, so they could choose if the treat was worth it.



Klondike prospectors took many risks in search of gold (top) and McGovern researchers believe this kind of cost-benefit decision-making stems from activity in basal ganglia circuits (above).

Normal monkeys varied their choices in a fairly rational manner, rejecting the treat whenever it seemed like the air puff was too strong, or the treat too small to


Photo: R. Charnov

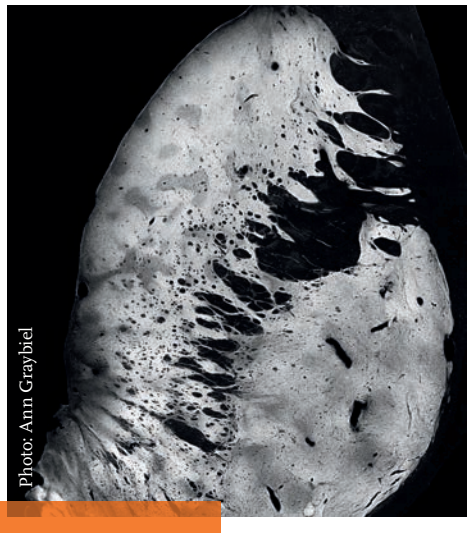


Photo: Ann Graybiel

Early in her career, McGovern Investigator Ann Graybiel (left) discovered striosomes, or column-like neurochemical compartments in the striatum (right).

be worth it—and this corresponded with activity in the pACC neurons. Interestingly, they found that some pACC neurons respond more when animals approach the combined offers, while other pACC neurons fire more when the animals avoid the offers. "It is as though there are two opposing armies. And the one that wins, controls the state of the animal." Moreover, when Graybiel's team electrically stimulated these pACC neurons, the animals begin to avoid the offers, even offers that they normally would approach. "It is as though when the stimulation is on, they think the future is worse than it really is," Graybiel says.

Intriguingly, this effect only worked in situations where the animal had to weigh the value of a cost against a benefit. It had no effect on a decision between two negatives or two positives, like two different sizes of treats. The anxiety drug diazepam also reversed the stimulatory effect, but again, only on cost-benefit choices. "This particular kind of mood-influenced cost-benefit decision-making occurs not only under conflict conditions but in our regular day to day lives. For example: I know that if I eat too much chocolate, I might get fat, but I love it, I want it."

Glass Half Empty

Over the next few years, Graybiel, with another research scientist in her lab, Alexander Friedman, unraveled the circuit behind the macaques' choices. They adapted the test for rats and mice, so that they could more easily combine the cellular and molecular technologies needed to study striosomes, such as optogenetics and mouse engineering.

They found that the cortex (specifically, the pre-limbic region of the prefrontal cortex in rodents) wires onto both striosomes and fast-acting interneurons that also target the striosomes. In a healthy circuit, these interneurons keep the striosomes in check by firing off fast inhibitory signals, hitting the brakes before the striosome can get started. But if the researchers broke that cortical-striatal connection with optogenetics or chronic stress, the animals became reckless, going for the high-risk, high-reward arm of the maze like a gambler throwing caution to the wind. If they amplified this inhibitory interneuron activity, they saw the opposite effect. With these techniques, they could block the effects of prior chronic stress.

This summer, Graybiel and Amemori published another paper furthering the story and returning to macaques. It was still too difficult to hit striosomes, and the researchers could only stimulate the striatum more generally. However, they replicated the effects in past studies.

Many electrodes had no effect, a small number made the monkeys choose the reward more often. Nearly a quarter though made the monkeys more avoidant—and this effect correlated with a change in the macaques' brainwaves in a manner reminiscent of patients with depression. But the surprise came when the avoidant-producing stimulation was turned off, the effects lasted unexpectedly long, only returning to normal on the third day.

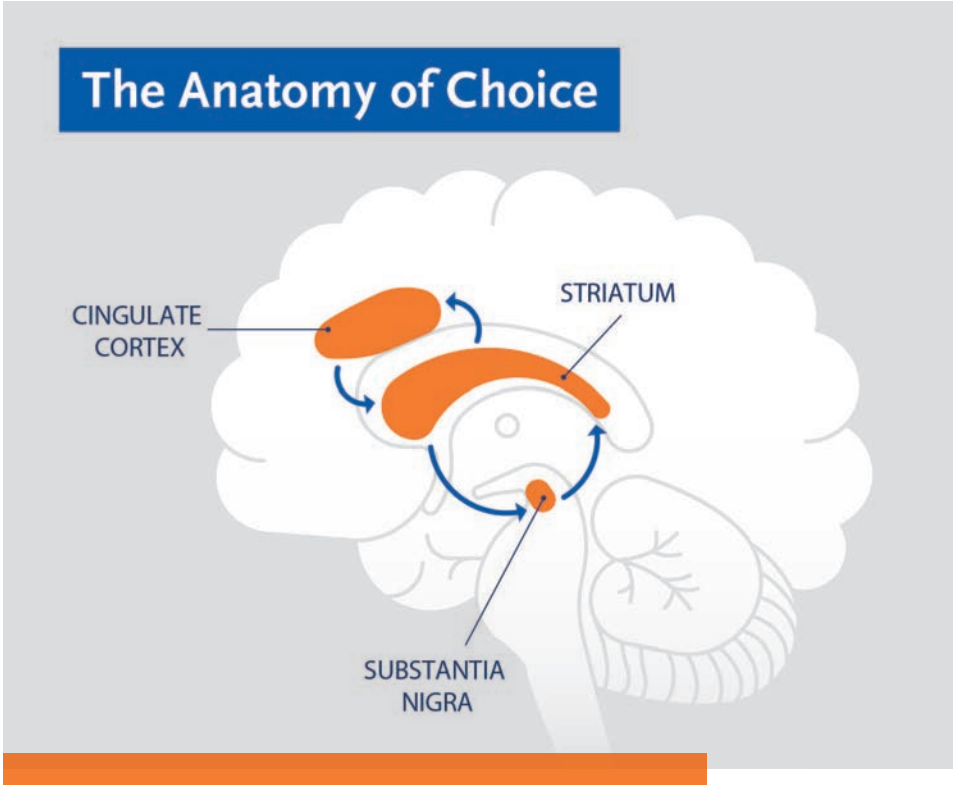
Graybiel was stunned. "This is very important, because changes in the brain can get set off and have a life of their own," she says. "This is true for some individuals who have had a terrible experience, and then live with the aftermath, even to the point of suffering from post-traumatic stress disorder."

She suspects that this persistent state may actually be a form of affect, or mood. "When we change this decision boundary, we're changing the mood, such that the animal overestimates cost, relative to benefit," she explains. "This might be like a proxy state for pessimistic decision-making experienced during anxiety and depression, but may also occur, in a milder form, in you and me."

Graybiel theorizes that this may tie back into the dopamine neurons that the striosomes project to: if this avoidance behavior is akin to avoidance observed in rodents, then they are stimulating a circuit that ultimately projects to dopamine neurons of the substantia nigra. There, she believes, they could act to suppress these dopamine neurons, which in turn project to the rest of the brain, creating some sort of long-term change in their neural activity. Or, put more simply, stimulation of these circuits creates a depressive funk.


Photo: Justin Knight

Postdoc Will Menegas studies dopaminergic inputs from the substantia nigra to the posterior striatum.



The substantia nigra, striatum, and cortex play a role in cost-benefit decision-making.

Bottom Up

Three floors below the Graybiel lab, postdoc Will Menegas is in the early stages of his own work untangling the role of dopamine and the striatum in decision-making. He joined Guoping Feng's lab this summer after exploring the understudied "tail of the striatum" at Harvard University.

While dopamine pathways influence many parts of the brain, examination of connections to the striatum have largely focused on the frontmost part of the striatum, associated with valuations.

But as Menegas showed while at Harvard, dopamine neurons that project to the rear of the striatum are different. Those neurons get their input from parts of the brain associated with general arousal and sensation—and instead of responding to rewards, they respond to novelty and intense stimuli, like air puffs and loud noises.

In a new study published in *Nature Neuroscience*, Menegas used a neurotoxin to disrupt the dopamine projection from the substantia nigra to the posterior striatum to see how this circuit influences behavior. Normal mice approach novel items cautiously and back away after sniffing at them, but the mice in Menegas' study failed to back away. They stopped avoiding a port that gave an air puff to the face and they didn't behave like normal mice when Menegas dropped a strange or new object—say, a lego—into their cage. Disrupting the nigral-posterior striatum seemed to turn off their avoidance habit.

"These neurons reinforce avoidance the same way that canonical dopamine neurons reinforce approach," Menegas explains. It's a new role for dopamine, suggesting that there may be two different and distinct systems of reinforcement, led by the same neuromodulator in different parts of the striatum.

This research, and Graybiel's discoveries on cost-benefit decision circuits, share clear parallels, though the precise links between the two phenomena are yet to be fully determined. Menegas plans to extend this line of research into social behavior and related disorders like autism in marmoset monkeys.

"Will wants to learn the methods that we use in our lab to work on marmosets," Graybiel says. "I think that working together, this could become a wonderful story, because it would involve social interactions."

"This a very new angle, and it could really change our views of how the reward system works," Feng says. "And we have very little understanding of social circuits so far and especially in higher organisms, so I think this would be very exciting. Whatever we learn, it's going to be new."

Human Choices

Based on their preexisting work, Graybiel's and Menegas' projects are well-developed—but they are far from the only McGovern-based explorations into ways this brain region taps into our behaviors. Maiya Geddes, a visiting scientist in John Gabrieli's lab, has recently published a paper exploring the little-known ways that aging affects the dopamine-based nigral-striatum-hippocampus learning and memory systems.

In Rebecca Saxe's lab, postdoc Livia Tomova just kicked off a new pilot project using brain imaging to uncover dopaminestriatal circuitry behind social craving in humans and the urge to rejoin peers. "Could there be a craving response similar to hunger?" Tomova wonders. "No one has looked yet at the neural mechanisms of this."

Graybiel also hopes to translate her findings into humans, beginning with collaborations at the Pizzagalli lab at McLean Hospital in Belmont. They are using fMRI to study whether patients with anxiety and depression show some of the same dysfunctions in the cortico-striatal circuitry that she discovered in her macaques.

If she's right about tapping into mood states and affect, it would be an expanded role for the striatum—and one with significant potential therapeutic benefits. "Affect state" colors many psychological functions and disorders, from memory and perception, to depression, chronic stress, obsessive-compulsive disorder, and PTSD.

For a region of the brain once dismissed as inconsequential, McGovern researchers have shown the basal ganglia to influence not only our choices but our state of mind—suggesting that this "primitive" brain region may actually be at the heart of the human experience. ■

Jonathan Wilde Named J. Douglas Tan Postdoctoral Fellow

Jonathan Wilde, an early career neuroscientist in Guoping Feng's lab, has been named the first J. Douglas Tan Postdoctoral Fellow at the McGovern Institute. The endowed J. Douglas Tan Postdoctoral Fellowship Fund was recently created by K. Lisa Yang, co-founder of the Hock E. Tan and K. Lisa Yang Center for Autism Research, in honor of her son Douglas. Each year a full postdoctoral fellowship will be awarded to a promising young scientist in the Feng Lab studying the molecular genetics and neurobiological mechanisms that contribute to autism spectrum disorders.


Photo: Justin Knight


Photo: Douglas Tan

Jonathan Wilde (left) is the first recipient of the J. Douglas Tan Postdoctoral Fellowship. Tan is pictured on right in Antarctica.

Wilde, who became interested in the brain after being diagnosed with a rare brain malformation in college, focused his graduate studies on developmental neurobiology at the University of Colorado Denver. He joined the Feng lab as a postdoc in 2016, where his research has combined cellular, molecular, genetic, and physiological techniques to explore the root causes of neurodevelopmental and neuropsychiatric disorders. Wilde is specifically interested in autism spectrum disorders, and how disruptions in development may shape neural circuit formation and function and influence behavior. His ultimate goal is to understand the developmental mechanisms of autism and to develop new and effective genetic therapies for people with severe autism spectrum disorders. ■

McGovern Institute Names Nine Graduate Fellows

Nine McGovern Institute graduate students have been awarded fellowships for the 2018–2019 academic year. They include:

McGovern Friends Fellows

Han Altae-Tran (Zhang lab) is developing a computational pipeline for the discovery of novel biological systems with therapeutic potential.

Sara Beach (Gabrieli lab) is using neuroimaging to understand the brain basis of language, including language-learning aptitude, aphasia, and dyslexia.

Lou Beaulieu-Laroche (Harnett lab) studies the physiological features of human neurons and how they influence information processing in the brain.

Changyang Linghu (Boyden lab) studies super-resolution physiological imaging and is developing new molecular tools to observe living brain tissue.

Morteza Sarafyazd (Jazayeri lab) is studying the neural computations underlying causal reasoning about errors, a skill central to intelligent behavior.

Joshua Saul (Horvitz lab) focuses his research on the genetic maintenance control of neuronal cell-identity.

Jacob Simon (Jasanoff lab) is developing nanoscale probes to detect neurophysiological processes in the brain.

Tan-Yang Center Fellow

Michael Reed (Choi lab) uses mouse models to gain a mechanistic understanding of the relationship between immune function and autism spectrum disorders.

Janet and Sheldon Razin '59 Fellow

Marie-Sophie van der Goes (Harnett lab) studies how visual landmarks can reset the internal sense of direction in the mammalian brain. ■

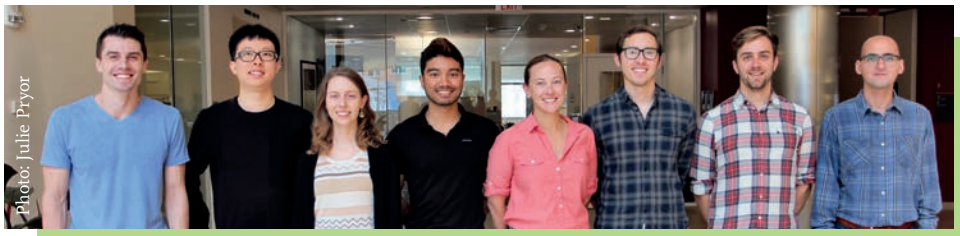


Photo: Julie Pryor

McGovern graduate fellows from left to right: Lou Beaulieu-Laroche, Changyang Linghu, Marie-Sophie van der Goes, Han Altae-Tran, Sara Beach, Joshua Saul, Michael Reed, and Morteza Sarafyazd. Not pictured: Jacob Simon.

RESEARCH NEWS

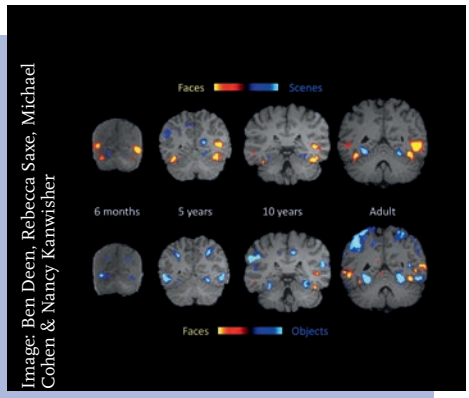
Studies have shown that musical training can enhance language skills, and a new study out of the **Desimone** lab has found that while piano lessons do not appear to affect overall cognitive ability, they do have a very specific effect on kindergartners' ability to distinguish different pitches. This translates into an improvement in discriminating between spoken words, which is believed to aid in learning to read.

In an unrelated study, the **Desimone** lab found that microsaccades precede modulation of specific brain regions associated with attention, suggesting that small shifts of the eyes may be linked to covert attention.

When we look at an object like a tree or a bush from almost any angle, we recognize it as a tree or a bush. However, such recognition has traditionally been a challenge for artificial visual recognition systems. Researchers in the **DiCarlo** lab have now directly examined and shown that artificial object recognition is quickly becoming more primate-like, but still lags behind when scrutinized at higher resolution.

Many patients with neuropsychiatric disorders such as anxiety or depression experience negative moods that lead them to focus on the possible downside of a given situation more than the potential benefit. **Ann Graybiel**'s lab has now pinpointed a brain region, the caudate nucleus, that can generate this type of pessimistic mood in animals. In a separate study, Graybiel uncovered the plan underlying the development of the striatum, the largest nucleus of the basal ganglia in the vertebrate brain. They showed that different functions of the striatum, such as execution of actions as opposed to evaluation of outcomes, are defined early on as part of the blueprint that constructs this brain region, rather than sculpted through a later mechanism.

The human cerebellum has primarily been considered to impact motor control and coordination. Two parallel studies from the **Martinos Imaging Center** have recently converged to support an unexpectedly complex level of non-motor cerebellar organization, that would not have been predicted from known motor representation regions.

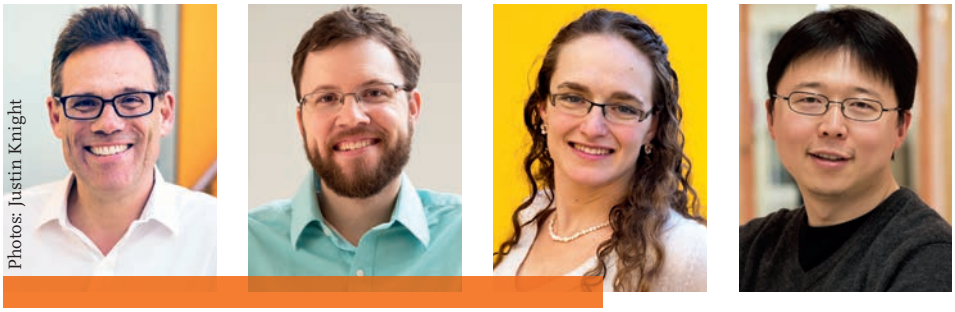


Brain scans showing face- and scene-preferring regions across human development.

When interacting with an infant you have likely noticed that the human face holds a special draw from a very young age. **Rebecca Saxe** and her team have considered two emerging theories regarding early face recognition, and come up with a third proposition, arguing that when a baby looks at a face, the response is also social, and that the resulting contingent interactions are key to subsequent development of organized face recognition areas in the brain. ■

AWARDS & HONORS

Michale Fee has been selected to receive a McKnight Technological Innovations in Neuroscience Award, which supports scientists using novel and creative approaches to understanding brain function.



McGovern investigators (from left to right) Michale Fee, Mark Harnett, Rebecca Saxe, and Feng Zhang.

Mark Harnett has been named a 2018 Vallee Foundation Scholar and a Klingenstein-Simons Neuroscience Fellow for his work dissecting dendritic contributions to associative cortical computations.

Rebecca Saxe has been named the inaugural John W. Jarve (1978) Professor in Brain and Cognitive Sciences.

Feng Zhang has been named one of Fortune Magazine's 40 under 40 for his work pioneering the use of CRISPR in human cells. ■

EVENTS

Photo: Justin Knight

Caltech neurobiologist David Anderson delivers the 2018 Scolnick Prize lecture.


Photo: Kris Brewer

The CBMM summer course has grown to include 35 students, 15 teaching assistants, and many guest lecturers.

David Anderson Delivers Scolnick Prize Lecture

On September 17, David J. Anderson (HHMI, Caltech) delivered the 2018 Edward M. Scolnick Prize in Neuroscience. Anderson was awarded the prize for his contributions to the isolation and characterization of neural stem cells and for his research on neural circuits that control emotional behaviors in animal models.

CBMM Summer Workshop

The Center for Brains, Minds and Machines (CBMM) hosted an intensive three-week course at the Marine Biological Laboratory in Woods Hole this summer to give advanced students a "deep end" introduction to the problem of intelligence. Videos of select lectures are available on the CBMM website.

The McGovern Institute for Brain Research at MIT is led by a team of world-renowned neuroscientists committed to meeting two great challenges of modern science: understanding how the brain works and discovering new ways to prevent or treat brain disorders. The McGovern Institute was established in 2000 by Lore Harp McGovern and the late Patrick J. McGovern, with the goal of improving human welfare, communication and understanding through their support for neuroscience research. The director is Robert Desimone, who is the Doris and Don Berkey Professor of Neuroscience at MIT and former head of intramural research at the National Institute of Mental Health.

Further information is available at: http://mcgovern.mit.edu

Brain SCAN
Quarterly Newsletter of the McGovern Institute

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