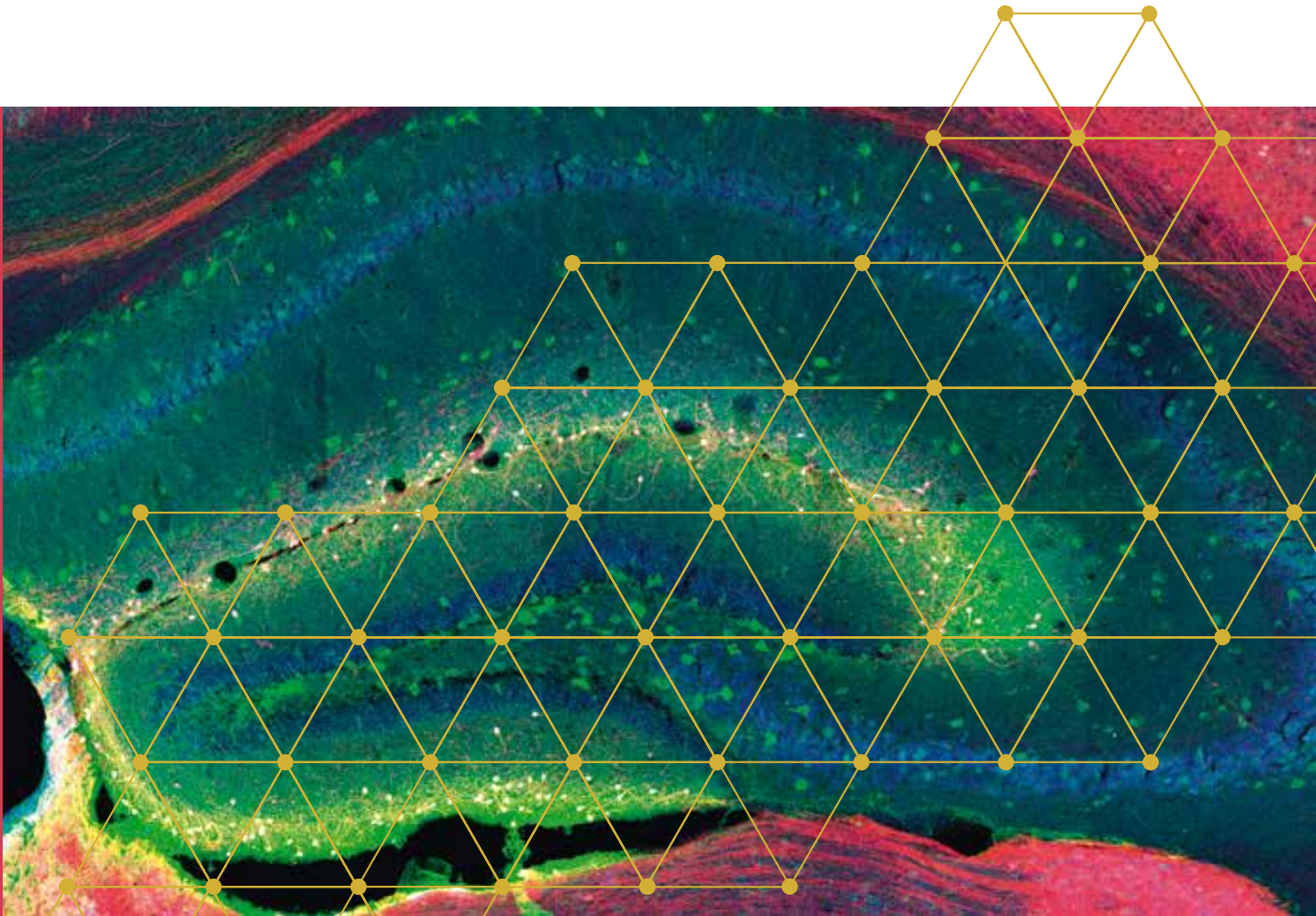
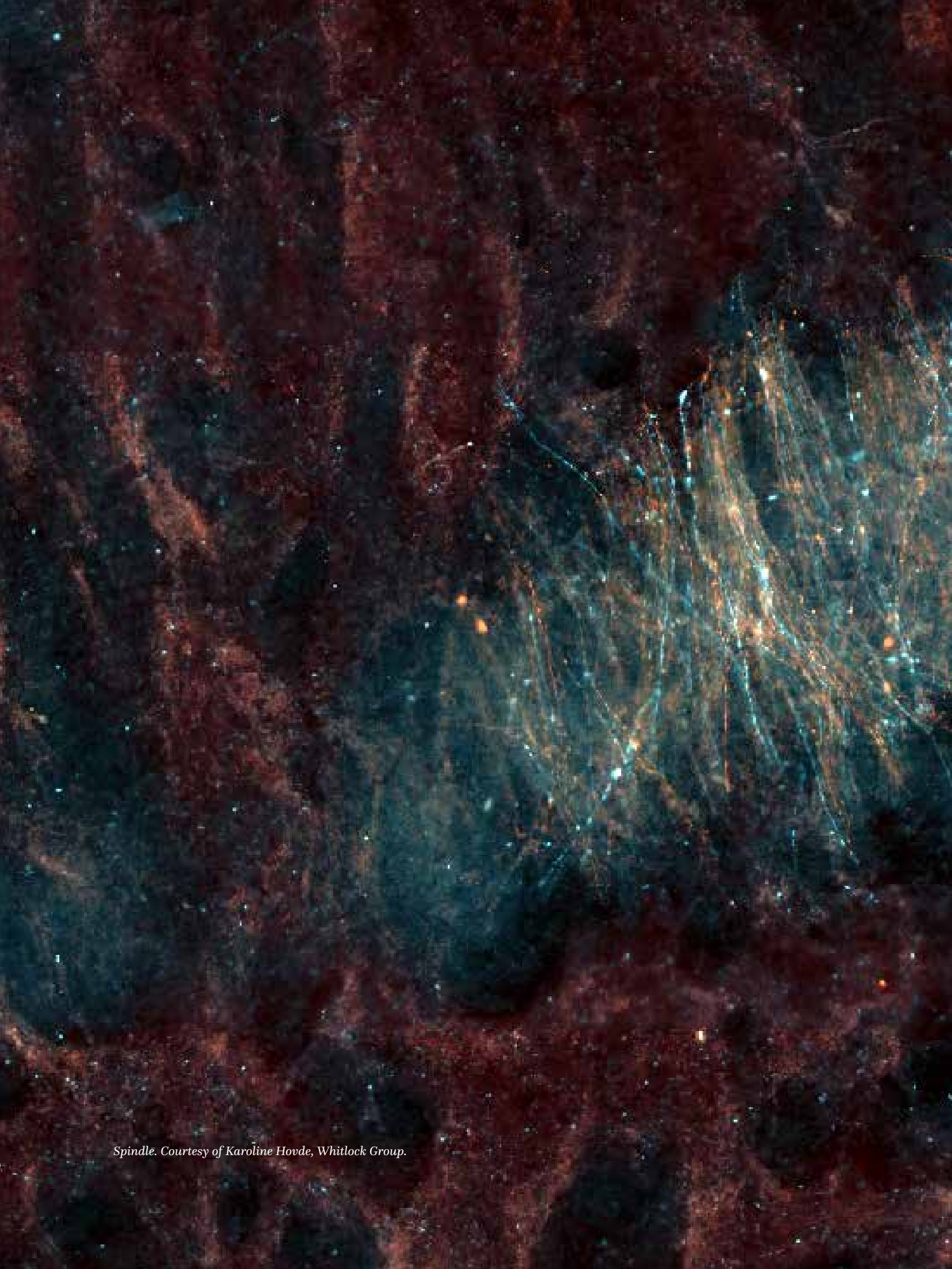


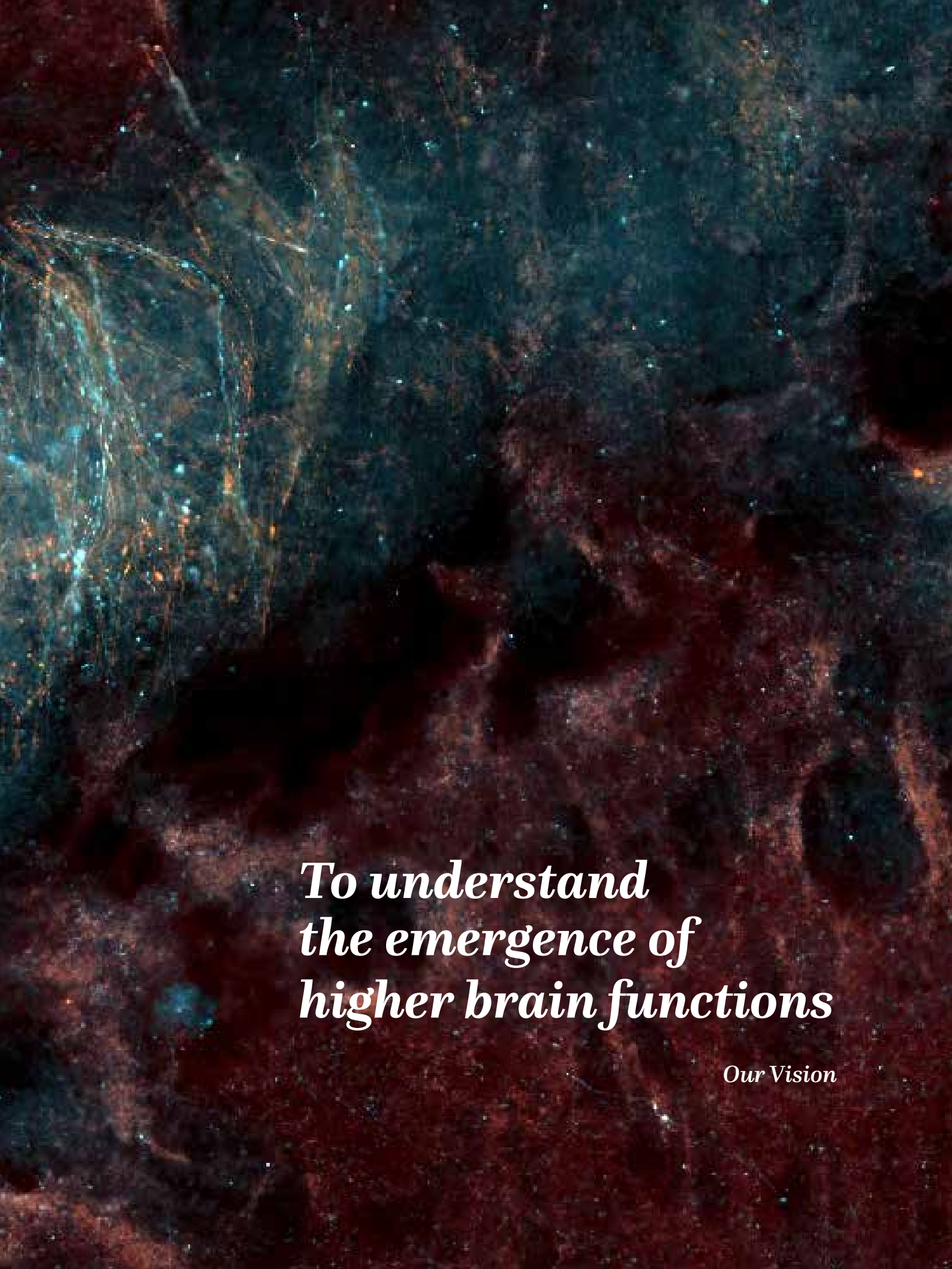
Kavli Institute  
for Systems Neuroscience

*Annual Report 2018*





*Spindle. Courtesy of Karoline Hovde, Whitlock Group.*



*To understand  
the emergence of  
higher brain functions*

*Our Vision*

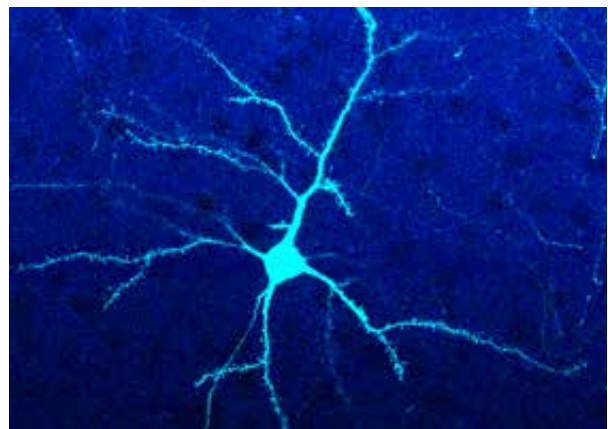


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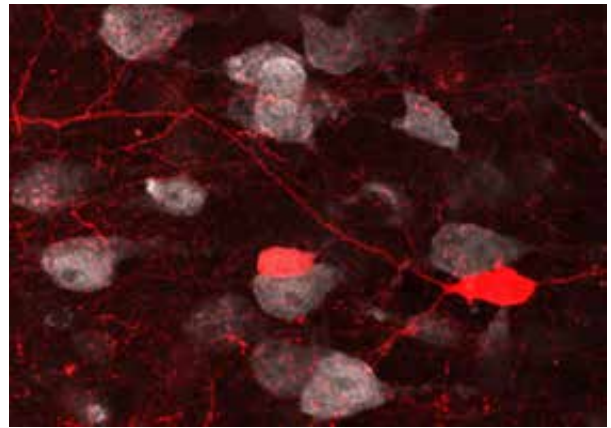
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# *Foreword by the Directors*

2018 was an exciting year for the Kavli Institute for Systems Neuroscience. The institute is still growing and we represent now, with a total of 133 employees from 27 countries, a powerful and truly international neuroscience community in Trondheim. Our Scientific Advisory Board evaluated the institute this year and concluded: “the Kavli Institute is a national treasure in Norway. (...) What has been built here is a unique resource that exists nowhere else in the world and would be difficult if not impossible to duplicate. This consideration applies both to the scientific themes under study, as well as to the extraordinary infrastructure (space, equipment, resources) that has been developed to facilitate exciting and cutting-edge research.” This evaluation makes us proud and inspires us to further realize our newly developed institute strategy.

Our scientific vision is “to understand the emergence of higher brain functions”. In 2018, we have been coming closer to realize this vision. This is apparent in this year’s publication record from the institute, and from each individual group. The institute had one paper in *Nature* and one in *Science*: The Moser group marked a new milestone with the discovery of the mechanism for episodic time that appeared in a *Nature* paper in August. The Whitlock group discovered neural codes for posture in the cortex – which was published in *Science*. The discovery of a posture code is a scientific breakthrough remarkable for a group leader who started his independent lab only 4 years ago.

The new achievements within basic science generate a moral responsibility to strengthen the translational aspects of the institute’s research, since the entorhinal cortex is the area in the brain first affected by Alzheimer disease. The Witter and Kentros group are focusing stronger on the translational aspects of their research fields. The Doeller group has in the last 2 years successfully build the fundament for translation to human patients. Translational research is a strategic priority for the institute. Christian Doeller accepted this summer a position as director at Max Planck institute for Human Cognitive and Brain Sciences in Leipzig. Doeller’s replacement will be an important task for the next year. Meanwhile we have employed a promising young scientist, Raphael Kaplan, to lead the group.

Technological development has seen big progress in 2018. Neuropixel probes developed in cooperation with a consortium led by IMEC in Belgium are now tested in the lab and will be the new standard for electrophysiological registration in the animal facility. Furthermore, 2Photon microscopy is starting to take over as imaging technique for calcium imaging of brain cells. Both techniques have superior resolution in their domains and will increase the number of brain cells registered and their interaction dramatically. Because of the large amount of data, new data processing models are highly demanded. The Roudi group, with core competence in this area, becomes thus more and more important. Equally, big data require new data processing pipelines and storage strategies.



*May-Britt Moser*  
Scientific Director



*Edvard Moser*  
Scientific Director



*Kay Gastinger*  
Managing Director

To be able to stay in the technological forefront the institute has submitted a new proposal to the infrastructure initiative of the Research Council of Norway (RCN) for the 3. stage of the NORBRAIN project. NORBRAIN 2 is about to be realized and in 2018 we have established the organisation that will manage and operate the 7T MR scanner to be installed in 2019. This sophisticated and promising tool is dedicated for translational research.

The international Master program in Neuroscience headed by the Kavli institute has become a recognised study program for neuroscience in Norway, and also abroad. Emre Yaksi has, besides his excellent research on zebrafish, been the leader of the study program board and significantly contributed to the development of the program and the satisfaction of the students. Our alumni are desired candidates for PhD positions in the institute but also around the world.

Also, the administration of the institute has made major progress. The former Managing Director Rannveig Storeng, who left the institute last summer, has contributed greatly to this development. The institute recruited Kay Gastinger to replace her from last fall. Our aim is now to implement the institute further in the university structure and professionalize the service to scientists and students. To achieve this, we will recruit three new administrative positions in 2019 to strengthen the staff.

The Kavli institute has the ambition to be a showcase for NTNU. However, scientific progress would not be possible without our sponsors and funding sources. The Kavli foundation, Pauline Braathen, and the other sponsors, and the support from the RCN and the European Research Council, provide a valuable contribution to the success of the institute. Also, the goodwill and support from our Rector and Dean is highly appreciated. Finally, our biggest treasure are the people working at the institute, Master and PhD students, post docs, group leaders, administrative staff and in particular our technicians running our laboratories with world-class quality and high animal-ethical standards. A big 'thank you' to all of you.

The SAB report also revealed some challenges to be addressed in the next three years. A major challenge is to develop and implement a more reliable financing model for the institute, and the establishment of stronger scientific co-operations inside NTNU. These will be a main focus in the next year. Scientifically, we have very promising new research results making us full of expectations for the years to come.

# Organizational chart

## GROUP LEADERS



**MAY-BRITT MOSER**  
Moser Lab  
Scientific Director



**EDVARD MOSER**  
Moser Lab  
Scientific Director



**MENNO WITTER**  
Witter Lab

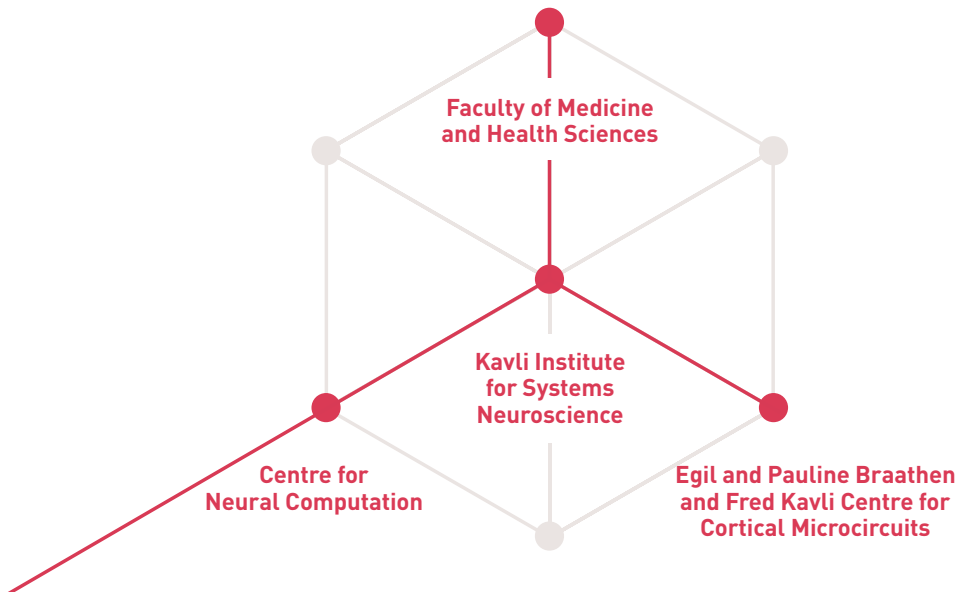


**JONATHAN WHITLOCK**  
Whitlock lab



**KAY GASTERINGER**  
Managing Director





**YASSER ROUDI**  
Roudi Lab



**CLIFFORD KENTROS**  
Kentros Lab



**EMRE YAKSI**  
Yaksi Lab



**RAPHAEL KAPLAN**  
Doeller - Kaplan Lab



# Moser Group

*To determine neural mechanisms for space,  
time and memory in the brain.*



*First row from left: Sebastian Ola Andersson, Richard Gardner, Soledad Gonzalo Cogno, Giulia Quattrocolo, Rita Elmkvist Nilsen, Flavio Donato, Ann Mari Amundsgård, Emilie Ranheim Skytøen, Endre Kråkvik. Second row from left: Jan Sigurd Beddari Blackstad, Ragnhild Irene Jacobsen, May-Britt Moser, Torgeir Waaga, Abraham Zelalem Vollan, Ingvild Ulsaker Kruge, Kyrre Haugen. Third row from left: Horst Obenhaus, Jørgen Sugar, Debora Ledergerber, David Clayton Rowland, Valentin Normand, Øyvind Arne Høydal, Edvard Moser, Miguel Carvalho, Klaus Jenssen. Also in the group but not present when the photo was taken: Weijan Zong, Torstein Slettmoen, Anne Nagelhus, Maria Mørreaune, Nenitha Dagslott.*



## BACKGROUND

As mammals evolved and grew more complex, so too did specific parts of their brain. These regions are termed “association cortices” or “higher cortex” (indicating a highly evolved region) and are thought to be the reason humans exhibit advanced cognition compared to other mammals. Neuroscientists have come a long way in understanding different parts of these cortices, which are often named after the function they support. For example, the part of the brain important for seeing is aptly termed “primary visual cortex” while the part of the brain important for hearing is termed “primary auditory cortex”. Thanks to decades of research, scientists have a pretty good understanding of how incoming sensory signals, such as visual or auditory stimuli, are converted into activity patterns in the brain. However, this characterization is generally limited to describing the earliest stages of sensory processing. Cortical areas that are higher up the chain often receive and make sense of multiple streams of incoming sensory information, and – importantly – they create their own neural codes – codes that cannot be traced back to any region earlier in the chain. The Moser group is interested in identifying such codes in one of the highest-order association cortices, the entorhinal cortex. The presence of a number of functionally specific cell types in this region makes neural coding more accessible in this area than anywhere else in high-order cortices.



## KEY RESEARCH QUESTIONS

What are the neural codes used in advanced, multisensory cortical brain regions, such as entorhinal cortex?



## TOOLS & METHODS

The Moser group implements and develops tools for large-scale brain recordings using standard tetrode recording as well as recently introduced high-site-count silicon probes (meaning they can sample from a particular brain area with high-resolution). In addition, they use portable two-photon microscopes for high-resolution optical imaging

of neuronal activity. This means they can record the brain signal of many neurons, while the mice are allowed to freely move through the environment.



## RESEARCH IN 2017

Previous Nobel-prize winning research from the Moser group identified the existence of grid cells – cells that fire in hexagonal lattices across the available spatial environment – within the medial entorhinal cortex. Since these cells were discovered in 2005, the group has discovered a number of functional elements of the entorhinal space circuit as well as mechanisms likely to explain how these elements are formed and how they are used to form a sense of where you are. During the past year, the group has focused on identifying the mechanisms underlying formation of this grid pattern, expressed during varying conditions, such as during sleep. Since the brain receives minimal sensory input from the outside world when an animal is sleeping, recording from neurons during this time will provide important information about the relationship between the grid pattern and its degree of dependence on incoming sensory signals from the external world. Their research revealed that the grid cell network remained intact – even during sleep – indicating that this neural code works independently of external signals or behavioral state.

One of the most notable research discoveries of the past year was the identification of a neural signal for “episodic time” in the lateral entorhinal cortex (LEC), a sister region of the medial entorhinal cortex (MEC) for spatial coding. Rather than coding for the absolute passage of time, the way we do with the minute hands on a clock, the LEC marks the passage of time based on the order and organization of an experience. Neuroscientists call these experiences “episodes” and thus use the term “episodic time” when describing how this brain region expresses the passage of time. Because the hippocampus receives inputs from both LEC and MEC, partly onto the same cells, it is likely that the time signal is integrated with spatial information when the inputs merge in the hippocampus. This discovery has numerous implications for our human experience of time and its relationship to space. Indeed, in looking to the new year, the group will be exploring coding mechanisms for space and time in large neural networks.

# *How your brain experiences time*

*Researchers at the Kavli Institute for Systems Neuroscience have discovered a network of brain cells that keeps track of time as we experience it.*

Clocks are devices created by humans to measure time. By social contract, we agree to coordinate our own activities according to clock time. Nevertheless, your brain does not perceive the duration in time with the standardized units of minutes and hours on your wristwatch. The signature of time in our experiences and memories belongs to a different kind of temporality altogether.

Over the course of evolution, living organisms, including humans, have developed multiple biological clocks to help us keep track of time. What separates the brain's various timekeepers is not only the scale of time that is measured, but also the phenomena the neural clocks are tuned to.

Some timekeepers are set by external processes, like the circadian clock that is tuned to the rise and fall of daylight. This clock helps organisms adapt to the rhythms of a day.

Other timekeepers are set by phenomena of more intrinsic origins, like the hippocampal time cells that form a domino-like chain signal that tracks time spans up to 10 seconds precisely. Today we know a great deal about the brain's mechanisms for measuring small timescales like seconds. Little is known, however, about the timescale the brain uses to record our experiences and memories, which can last anywhere from seconds to minutes to hours.

## **A NEURAL CLOCK FOR EXPERIENCED TIME**

A neural clock that keeps track of time during experiences is precisely what Albert Tsao and his colleagues

at the Norwegian University of Science and Technology's Kavli Institute for Systems Neuroscience believe they have discovered. By recording from a population of brain cells the researchers identified a strong time-coding signal deep inside the brain.

- Our study reveals how the brain makes sense of time as an event is experienced, says Tsao. - The network does not explicitly encode time. What we measure is rather a subjective time derived from the ongoing flow of experience.

- This network provides timestamps to events and keeps track of the order of events within an experience, says Professor Moser.

The neural clock operates by organizing the flow of our experiences into an orderly sequence of events. This activity gives rise to the brain's clock for subjective time. Experience, and the succession of events within experience, are thus the substance of which subjective time is generated and measured by the brain.



*Albert Tsao took his PhD at NTNU's Kavli Institute and was supervised by the Mosers. Tsao is now postdoc at Stanford University. Photo: Private*





#### *A Neural Clock for Time in Experience and Memories*

*The illustration depicts episodic time in a 4-hour-long ski trip up and down a steep mountain. The skier starts out with climbing the mountain hill. The hill is steep, her head is turned downwards. Time during the repetitive activity is experienced as slow and looping. The trip downhill is far more enjoyable, and the skier feels like time's flying. As she suddenly stumbles, her alert state makes details of the event seem to unfold in slow motion. Until she recovers her balance, upon which her experience of time normalizes. By changing the activities that the skier engages in and thus the content of her experience, the skier can actually change the way she perceives time.*

*The area of the brain where time is experienced, is located in the lateral entorhinal cortex, here seen as the turquoise bean in the centre of the figure. The neighbouring orange coloured structure is the hippocampus, where information about content (what) time (when) and space (where) come together to form episodic memories. Infographic: Kolbjørn Skarpnes & Rita Elmkvist Nilsen / NTNU Communication Division & Kavli Institute for Systems Neuroscience*



## TIME, SPACE AND MEMORY IN THE BRAIN

The area of the brain where time is experienced, is located in the lateral entorhinal cortex or (LEC) the sister-region to the area that codes for space, the medial entorhinal cortex (MEC).

- Today, we have a fairly good understanding of the way our brains process space, whereas our knowledge of time is less coherent, Professor Moser says.

- Space in the brain is relatively easy to investigate. It consists of specialized cell types that are dedicated to specific functions. Together they constitute the nuts and bolts of the system, he says.

In 2005, May-Britt and Edvard Moser discovered grid cells, which map our environment at different scales by dividing space into hexagonal units. In 2014, the Mosers shared the Nobel Prize in Physiology or Medicine with their colleague and mentor John O'Keefe at University College London for their discoveries of cells that constitute the brain's positioning system.

In 2007, inspired by the Mosers' discovery of spatially coding grid cells, then-Kavli Institute PhD candidate Albert Tsao set out to crack the code of what was happening in the enigmatic lateral entorhinal cortex (LEC). This area of the brain is right next to the medial entorhinal cortex (MEC), where his supervisors, the Mosers, had discovered grid cells.

- I was hoping to find a similar key operating cell that would reveal the functional identity of this neural network, Tsao says. The task proved to be a time-consuming project.

- There didn't seem to be a pattern to the activity of these cells. The signal changed all the time, says Professor Moser.

It was only in the last couple of years that the researchers began to suspect that the signal was indeed changing with time. Suddenly the recoded data started to make sense.

- Time is a non-equilibrium process. It is always unique and changing, Professor Moser says.

- If this network was indeed coding for time, the signal would have to change with time in order to record experiences as unique memories.

## *A brief primer on the brain and time*

### WHAT IS EPISODIC MEMORY?

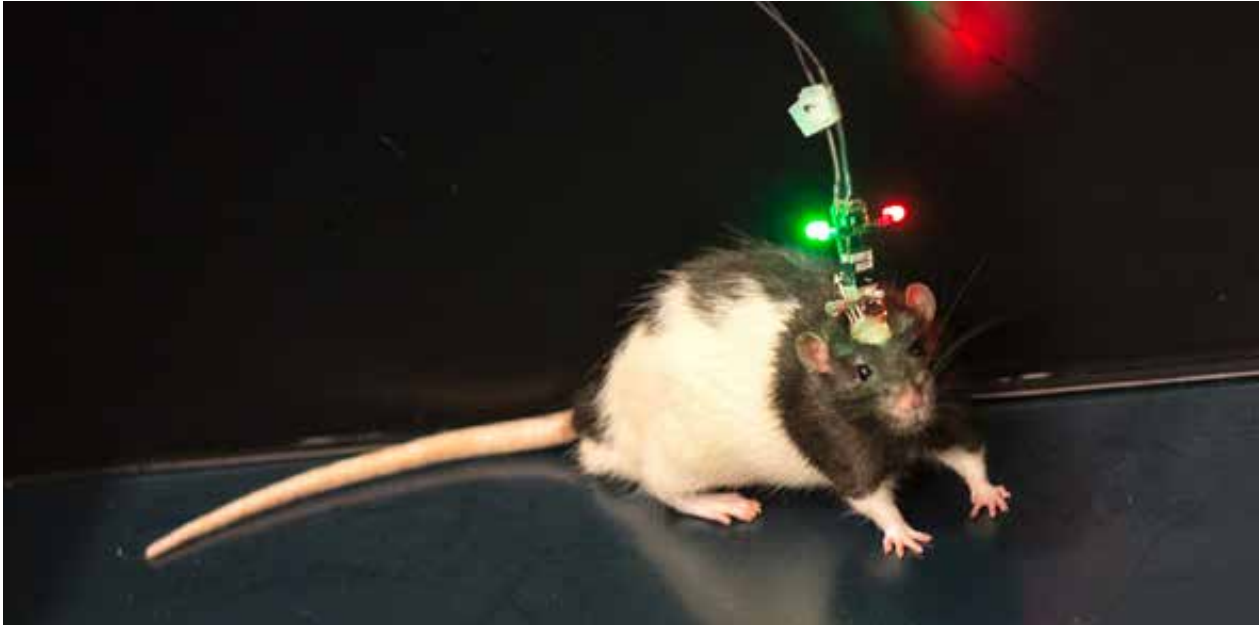
Your ability to recall and mentally relive specific episodes from your past is called episodic memory. This is the type of memories that you can visualize and talk about. The episodic memory is explicit in the way that its content is always anchored to a time and a place. Simply stated, episodic memories are a composition of what (content), where (position) and when (time). The brain area called medial entorhinal cortex is particularly important for mapping positions in space. This study suggests that the lateral entorhinal cortex may be important for putting experience into a temporal context. Information from both of these structures come together in the hippocampus to form episodic memories.

### WHERE IS THE BRAIN'S SUBJECTIVE CLOCK LOCATED?

The researchers recorded the time signal from a neural network in the lateral entorhinal cortex (LEC). LEC, the medial entorhinal cortex (MEC) and hippocampus (Hipp) are components of the hippocampal formation, which are located in the cortices of the left and right temporal lobes of the brain.

### WHAT IS EXPERIENCED TIME?

Subjective experience is the very substrate from which our concept of time arises. Time as we perceive it. Subjective time. Psychological time. Experienced time. Mind time. Episodic time. That time which flies when you're having fun, which stretches when you are waiting, and which nearly comes to arrest in the split seconds of a catastrophe unfolding, is in its essence relational and relative to the multiple aspects of experience it is woven into.



*Marco the rat chasing bits of chocolate during a test. In order to test how our sense of time alters with changing experiences, the researchers at the Kavli Institute in Trondheim let rats run around in different test arenas, while thin electrodes recorded the simultaneous neural activity of hundreds of cells in the lateral entorhinal cortex (LEC). The first experiment was a series of open-space environments that allowed for a wide range of options for action. The time-coding signal recorded from LEC revealed to the researchers that during these experiences of free exploration, the rats kept good track of time and the order of unique events.*

*Photo: Erlend Lånke Solbu/Norwegian Broadcasting Corporation, NRK*

### TECHNOLOGICAL ADVANCEMENTS

The Mosers needed only to decode the signal of one single grid cell to discover how space is encoded in the medial entorhinal cortex. Decoding time in the lateral entorhinal cortex proved to be a more complex task. It was only when looking at activity from hundreds of cells that Tsao and his colleagues were able to see that the signal encoded time.

- The activity in these neural networks is so distributed that the mechanism itself probably lies in the structure of connectivity within the networks. The fact that it can be shaped into various unique patterns implies a high level of plasticity, Professor Moser says. - I believe distributed networks and the combination of structures of activity may deserve more attention in the future. With this work, we have found an area with activity so strongly relating to the time of an event or experience, it may open up a whole new research field.

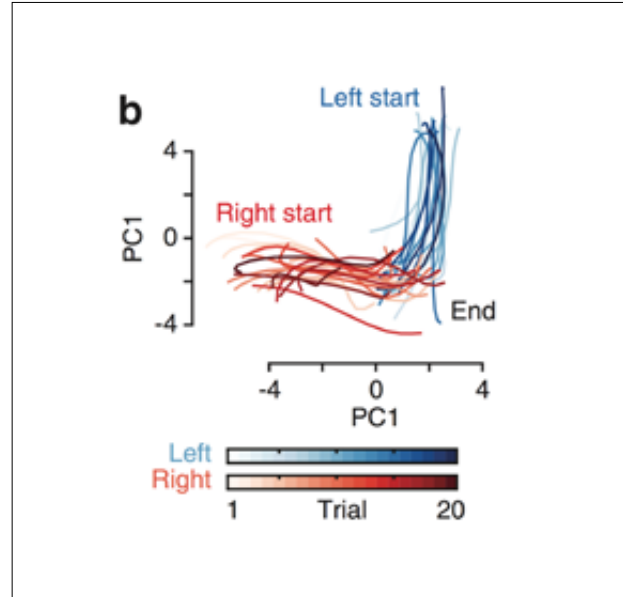
### THE SHAPE OF TIME

The structure of time has long been a disputed topic by philosophers and physicists alike. What can the newly discovered brain's mechanism for episodic time tell us about how we perceive time? Is our perception of time linear resembling a flowing river, or cyclical like a wheel or a helix? Data from the Kavli study suggest both are correct, and that the signal in the time-coding network can take on many forms depending on the experience.

In 2016, PhD candidate Jørgen Sugar joined the Kavli project to perform a new set of experiments that would test the hypothesis that the LEC network coded for episodic time. In one experiment a rat was introduced to a wide range of experiences and options for action. It was free to run around, investigate and chase bits of chocolate while visiting a series of open space environments.



Professor Edvard Moser, Jørgen Sugar, a postdoc at the Kavli Institute, and Professor May-Britt Moser. The Kavli scientists believe that this discovery will bring us one leap closer to solving the challenge of brain diseases such as Alzheimer's. The neural clock for subjective time serves a critical function in memory and learning, in our ability to organize experiences as a succession of events, and to form memories, to learn, and in the shaping of who we are. Photo: Erlend Lånke Solbu/Norwegian Broadcasting Corporation, NRK



The recorded data from the repetitive tasks of the figure-8 maze show that the rat's encoding of time relative to each lap time (left or right turn) improved, while time coding across laps were overlapping and thus reduced. Illustration: Albert Tsao

- The uniqueness of the time signal during this experiment suggests that the rat had a very good record of time and temporal sequence of events throughout the two hours the experiment lasted, Sugar says. - We were able to use the signal from the time-coding network to track exactly when in the experiment various events had occurred.

In the second experiment, the task was more structured with a narrower range of experiences and options for action. The rat was trained to chase after bits of chocolate while turning left or right in a figure-8 maze.

- With this activity, we saw the time-coding signal change character from unique sequences in time to a repetitive and partly overlapping pattern, Tsao says. - On the other hand, the time signal became more precise and predictable during the repetitive task. The data suggest that the rat had a refined understanding of temporality during each lap, but a poor understanding of time from lap to lap and from the start to end throughout the experiment.

Professor Moser says the study shows that by changing the activities you engage in, the content of your experience, you can actually change the course of the time-signal in LEC and thus the way you perceive time.

#### Reference:

Tsao, Albert; Sugar, Jørgen; Lu, Li; Wang, Cheng; Knierim, James J.; Moser, May-Britt; Moser, Edvard Ingjald (2018). **Integrating time from experience in the lateral entorhinal cortex.** *Nature* 561 (57-62). Kavli Institute for Systems Neuroscience, NTNU, Trondheim Norway

*If you think this article was too long, these researchers know where in the brain you think so.*

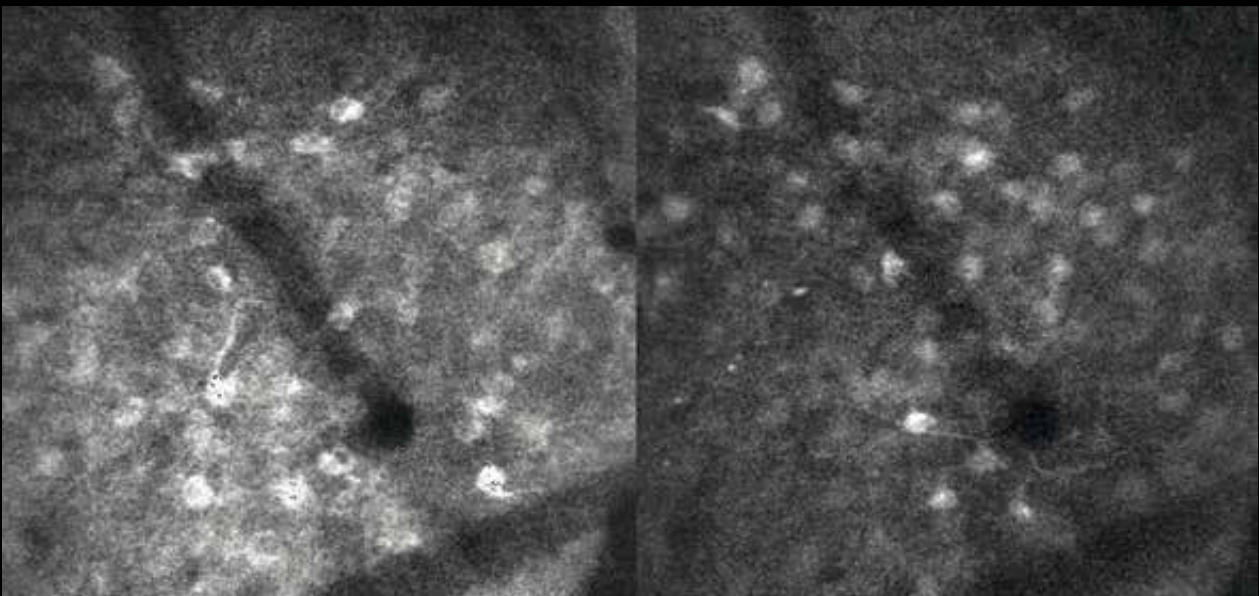


*The rats were trained to run laps in a figure-eight shaped track. This task was more structured with a narrower range of experiences and options for action. With this activity, the researchers saw the time-coding signal change character from unique sequences in time, to a repetitive and partly overlapping pattern of sequences. The time signal in effect zoomed in by becoming more precise and predictable within each lap, while it became very difficult for the rats to maintain a sense of time across laps and from start to end of the experiment. Professor Edvard Moser is seen here with the rat Borghild.*

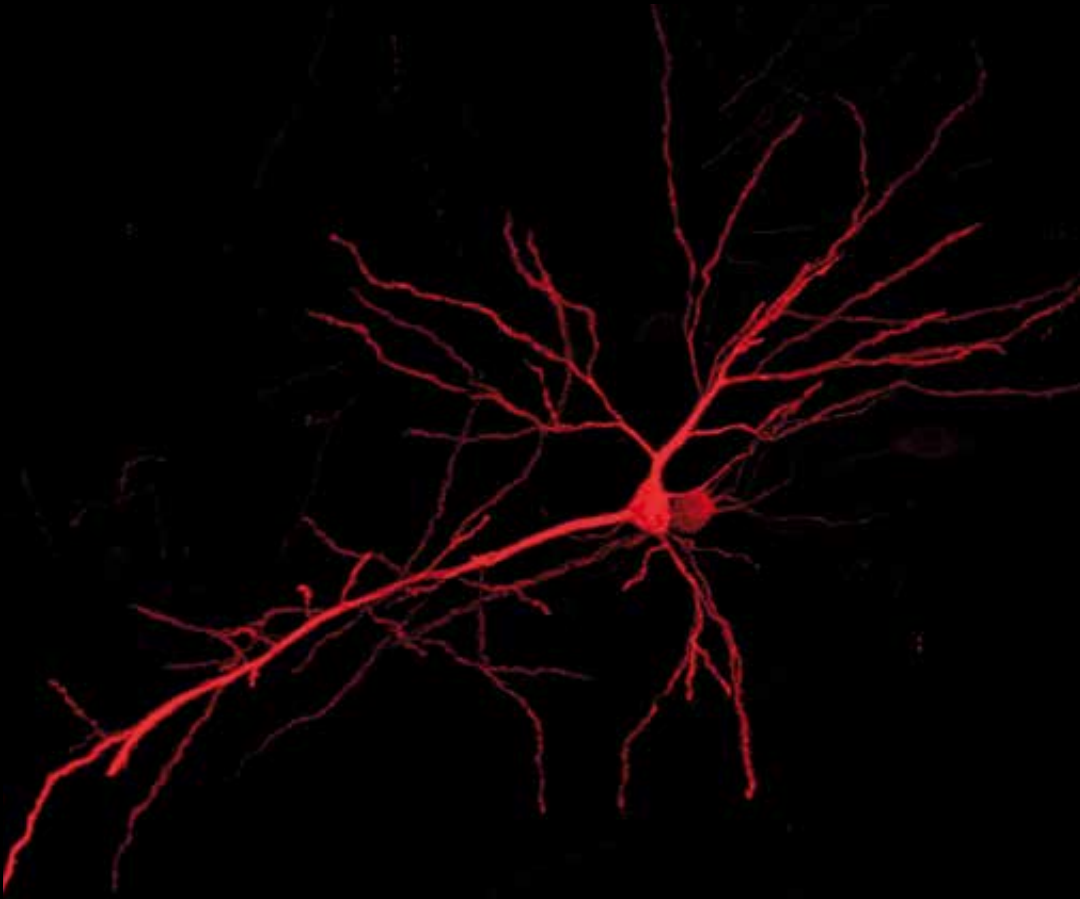




*Tom, the mouse. In vivo twophoton calcium imaging of neural network activity in freely behaving real-life navigating mouse. Enables unprecedented insights into the anatomical and functional network architecture. Image courtesy Horst Obenhaus and Weijian Zong, Moser Group.*







*Confocal microscope image of two CA1 pyramidal cells that were born when the mouse embryo was around 13 days old (image was taken in the adult mouse brain). Image courtesy Ragnhild Irene Jacobsen, Moser Group.*



*Confocal microscope image of cells in hippocampus (predominantly pyramidal cells). Cells are labelled with a variety of viruses and antibodies, giving rise to the different colours. Red (and blue) cells provide monosynaptic input to cells that are both green and red. Important to know which cells are connected to which to get an idea of how information is flowing through the mouse brain. Image courtesy Ragnhild Irene Jacobsen, Moser Group.*



## BACKGROUND

When neuroanatomist Menno Witter sets out to learn more about a brain region, such as the entorhinal cortex, his approach is not unlike that of a landscape surveyor. Rather than survey the shape, contour, location and dimensions of a piece of land, however, Witter investigates neural real estate. He surveys the large-scale connections between brain regions and characterizes the features of the small-scale, local neural circuits within each region. The ultimate goal of a landscape surveyor is to accurately describe the land so that others can begin construction or engineering projects based on that information. Similarly, Witter's ultimate goal as a neuroanatomist is to accurately describe the connectivity of brain regions so that he and other scientists can plan experiments to explore the functions of these networks and ultimately design tools and therapies to treat diseases that disrupt healthy neural landscapes.



## KEY RESEARCH QUESTIONS

- Do underlying anatomical differences in neural circuitry between the lateral and medial entorhinal cortex explain why they function differently?
- Of the neurons in the entorhinal cortex, which ones are key players in the initiation and development of Alzheimer's disease?



## TOOLS & METHODS

Witter's team uses genetically engineered animals and non-infectious viral tracers to fluorescently visualize specific cell types and connections within the entorhinal cortex. After identifying cell types and connections, the team can turn specific cells on and off with laser beams (a technique known as optogenetics) and then study the effect of this manipulation on the rest of the circuit.



## RESEARCH IN 2018

Researchers have previously shown that the sub regions of the entorhinal cortex (EC) – lateral (LEC) and medial (MEC) – play different functional roles, no one really knew why. Witter's research group was interested in seeing if the neuroanatomical differences could provide an explanation. However, in 2017, local circuit analysis revealed striking similarities rather than differences, between the two sub-regions. At the time, this was surprising. Now, new data from the lab suggests that it's the larger-scale connections driving the differences between the sub-regions. By studying how the brain areas develop their connections over time (from birth to adulthood), the team was able to obtain a clearer picture on how connections between MEC and different cortical areas come to be. Studying how different areas hook up to each other can tell us more about the role that these different areas might play.

The Witter group further discovered an interesting relationship between the large-scale and small-scale connections. Using their tracing techniques, they discovered connections from different cortical brain areas converged on single neurons, in the LEC, and specifically within a small band or layer (named "layer II") of LEC. This means that a single neuron in this very small slice of LEC is receiving, and likely integrating, information from many different brain regions. These layer II neurons, in turn, are directly connected to and send information to the hippocampus – a brain area critical for memory. Given that layer II of EC is one of the first brain areas to be affected by Alzheimer's disease, a better understanding of this circuitry is essential. Finally, Witter interacted with his close colleague Cliff Kentros, resulting in a recently patented new tool which makes it possible to manipulate the activity of specific neuron cell types. Future work will use these tools to manipulate the activity of layer II neurons and further clarify the role they play in the healthy and the diseased brain.

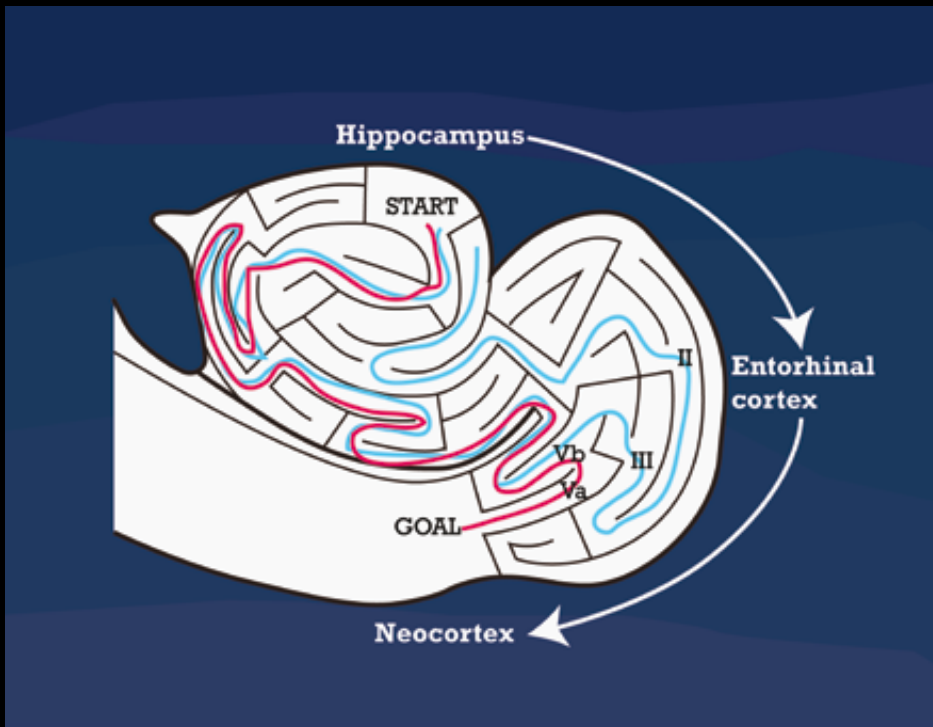
# Witter Group

*To characterize the properties of the entorhinal cortex, one of the first brain regions affected by Alzheimer's disease.*

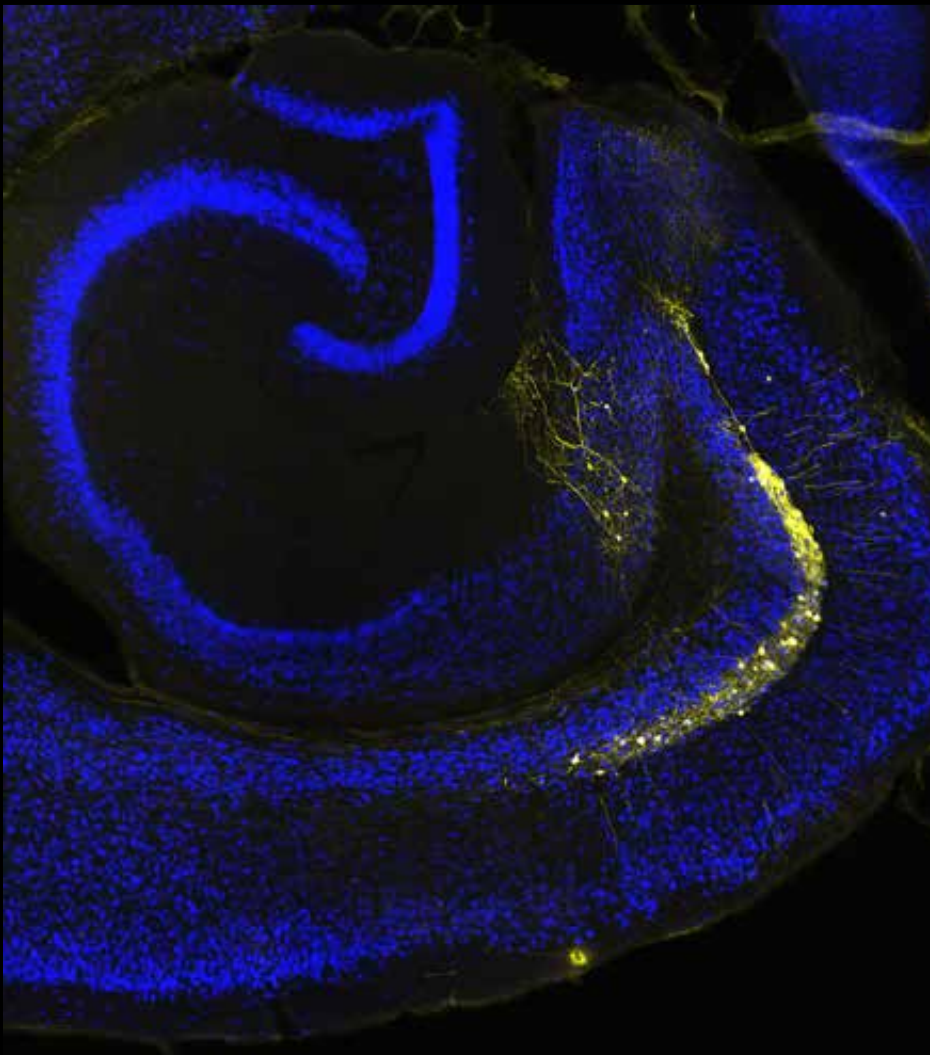


*From left: Thanh Pierre Douan, Bente Jacobsen, Asgeir Kobro-Flatmoen, Arthur Laja, Shinya Ohara, Grethe Mari Olsen, Tina Kleven, Kasper Kjeldsberg, Kathrine Sjaastad Hansen, Paulo Girão, Menno P. Witter, Maximiliano Jose Nigro. Also in the group but not present when the photo was taken: Hanne Tegnander Soligard, Bruno Monterotti, Eirik Stamland Nilsen, Ingrid Ingeborg Riphagen, Tore Bryn-tesen Lund.*





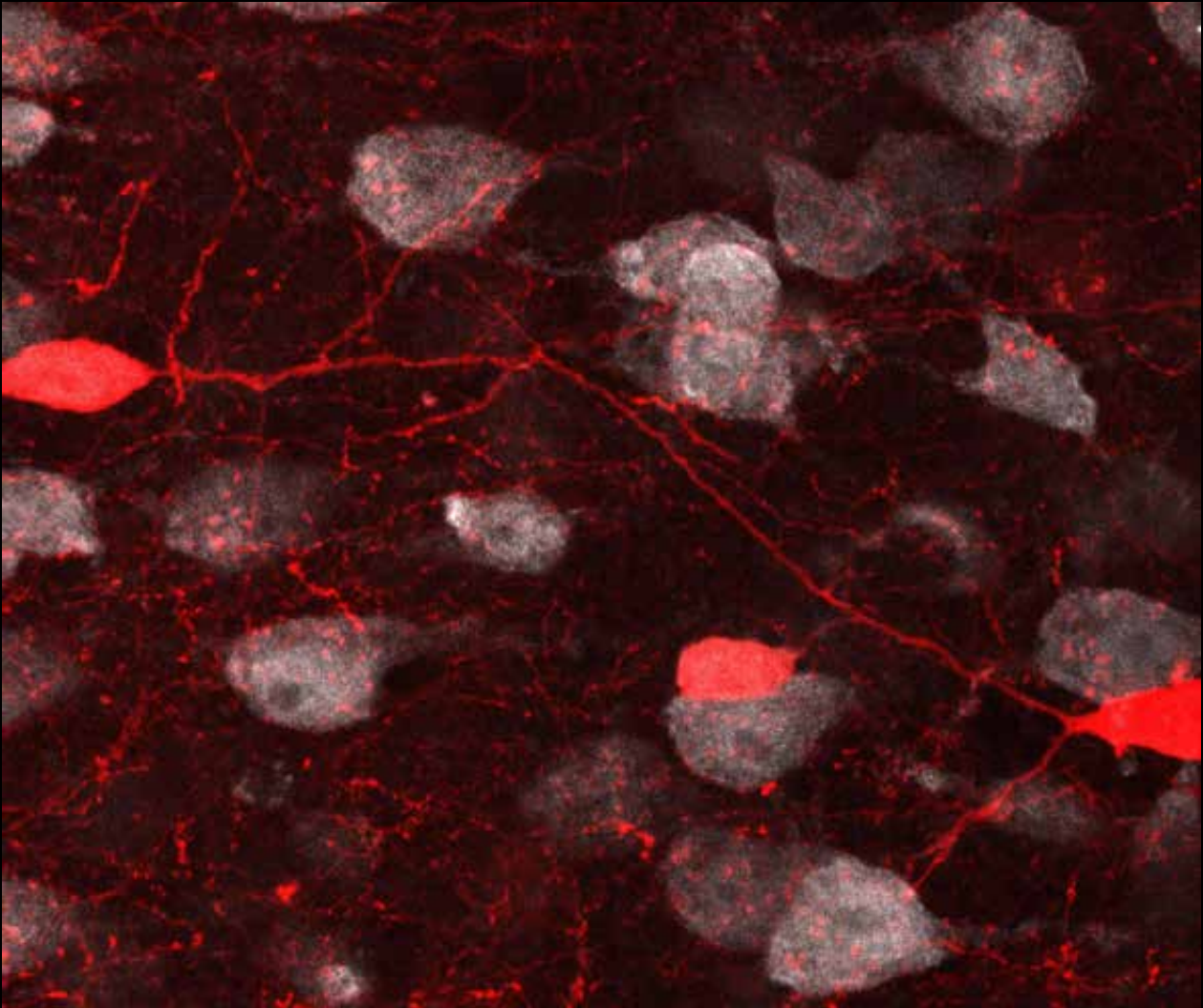
The Witter group is finding its way in the entorhinal-hippocampal circuitry maze. Courtesy of Shinya Ohara, Witter Group.



Specific labeling of neurons in layer Va allow us to study their functional connectivity. Blue: neurons in the hippocampus and entorhinal cortex, stained with the neuronal marker NeuN. Yellow: Fluorescently labeled projecting neurons in layer Va of entorhinal cortex. They were labeled by injecting a retrograde AAV expressing Cre in a part of the cortex that receives entorhinal projections (retrosplenial cortex). In the same animal, another AAV virus was injected in the entorhinal cortex which shows Cre-dependent expression of a fluorescent label (AAV-flex-mCherry). Courtesy of Shinya Ohara, Witter Group.

CCK-GABAergic interneurons (red) in layer 5 of the perirhinal cortex were targeted with an intersectional viral approach. An AAV carrying a floxed tdTomato (red fluorescent protein) under the control of the mDLX enhancer was injected in the perirhinal cortex of CCK-cre mice. The mDLX enhancer restricts the expression of the tdTomato to interneurons, among which only the ones expressing Cre-recombinase will express

tdTomato. This strategy has allowed the identification of the largest GABAergic population in perirhinal cortex and will be adapted to manipulate these cells with opto- or chemogenetic tools, as well as with modified rabies viruses. The tissue was stained against NeuN, a neuronal marker (white neurons), to define cytoarchitecture of perirhinal cortex. Courtesy of Max J. Nigro, Witter Group.





# *Whitlock Group*

*AIM To understand the role that posterior parietal cortex (PPC) and other cortical areas play in representing bodily posture, and to characterize their anatomical boundaries.*



*From left: Ece Gözde Demirci, Tuce Tombaz, Benjamin, Dunn Karoline Hovde, Jonathan Whitlock, Andrea Marie Hegstad, Bartul Mimica, Ida V. Rautio.*



## BACKGROUND

On the largest scale, the goal of any neuroscientist is to link brain activity to behavior. As a complex organ, the brain offers no shortage of areas and sub-circuits to investigate. Likewise, a large repertoire of behaviors can be studied. While the Whitlock lab has chosen to investigate the specific link between rodent postural behavior (standing, rearing, reaching, etc.) to cortical brain activity, his team's research provides a window into answering a larger question about how the brain computes and supports behavior in the first place.



## KEY RESEARCH QUESTIONS

- What role do the posterior parietal cortex (PPC) and frontal motor cortex (M2) of rats play in coding posture?
- What is the anatomy of the posterior parietal cortex (PPC) in the mouse?



## TOOLS & METHODS

The Whitlock group uses several tools to tackle their research questions: (1) a tracking and visualization software (developed in-house), which follows and records a rat's movement through three-dimensional space and (2) electrophysiological recordings of the rat's brain while it moves through that three-dimensional space. These two pieces of information (behavior and neural activity) are then analyzed using statistical methods. The parallel anatomical work in mice used tracers and markers to map out the circuits of the PPC.



## RESEARCH IN 2018

Over the course of the past year, the Whitlock team published a series of tantalizing findings on the relationship

between body posture and cortical activity. The first study, published as a Science Report by Mimica, Dunn and colleagues, reported that neural activity in posterior parietal cortex (PPC) and the frontal motor area (M2), was driven largely by 3D head and body posture, and less so by an animal's actual movements. This finding was somewhat surprising; movements are considered more active by nature. Thus, one might predict that the active features of movement, such as velocity and acceleration, would be the key drivers of neural activity in PPC and M2. Instead, the mere postures of the animal turned out to be the key signal that drive neural activity in these areas. Furthermore, by identifying this neural code for posture, the team was able to reconstruct an animal's ongoing behavior. This latter finding is one common way that neuroscientists can confirm that the brain signal they are claiming is important for behavior X is actually causative. In this case, it confirms that the cortical brain activity identified as "postural" is important for behavior. Most recently, the research group has begun collecting data from other cortical brain regions not typically considered important for postural coding and that data so far suggests that postural tuning may not be a feature restricted to the PPC and M2 areas. "While it is still early days," says Whitlock, "2019 just might come to show postural tuning is a universal feature of cortex—a finding that may have been hiding in plain sight all along."

In addition to these findings, Hovde and colleagues carefully characterized the anatomy of the PPC region in the mouse. Currently, neuroscientists disagree when it comes to deciding what parts of the brain should be deemed "parietal" and which parts are more "visual" in nature, particularly so in mice. Using combinations of colorful tracers, Hovde carefully characterized the inputs and outputs of PPC and identified which parts overlap with nearby visual areas. The work was published in late 2018 in the European Journal of Neuroscience and it "stands to settle some ongoing dispute in the field," says Whitlock.

# *Scientists record posture-coding neurons in the cortex*

Even the most basic moves in life, like getting out of bed in the morning, require far more coordination than one might think. Neuroscientists may have just uncovered key aspects of how the brain controls body posture during these kinds of everyday movements.

On October 31, 1905, a British surgeon named Sir Victor Horsley removed a 6-cm diameter ball of tissue and tumour from the brain of a man called George M.

George M.'s surgery gave him some relief from the seizures caused by the tumour. Yet he probably would be forgotten except that two curious medical doctors and neurologists named Henry Head and Gordon Holmes followed up on George M. and dozens of other patients like him.



*Medical doctor and neuroscientist Henry Head, who undertook studies in the early 1900s to understand how different parts of the brain work. Photo: G. C. Beresford, Wikimedia Commons, CC-BY-4.0*

Their goal was to learn how the brain worked by observing what didn't work in patients who had had different parts of the brain damaged or removed.

As they examined patient after patient, the two doctors began to see that when a part of the brain called the parietal cortex was damaged, the patients could lose their sense of where certain body parts were in space.

The patients weren't blind. They could see a body part, like an arm or a hand or a leg. But when they closed their eyes, they were unable to tell where it was.

This may seem trivial, yet it's anything but. Your mostly unconscious sense of where you are in space is formed in your brain from the integration of all your senses. It allows you to touch type, scratch your head, get a beer from the fridge, and move from one position to the next.

Without this sense of the body in space, which Head and Holmes called "body schema," the researchers wrote in a paper in 1911, "we could not probe with a stick, nor use a spoon unless our eyes were fixed upon the plate."

More than 100 years after this idea of body schema was first described, researchers at NTNU's Kavli Institute for Systems Neuroscience have found that the areas of the brain responsible for movement planning and spatial navigation — the posterior parietal cortex and the frontal motor cortex — are hugely responsive to the posture of the body.

In other words, the researchers believe the neurons they recorded are sending signals the brain uses to help create the body schema, that sense of self in space.

Their paper, "Efficient Cortical Coding of 3D Posture in Freely Behaving Rats," has just been published in *Science*.

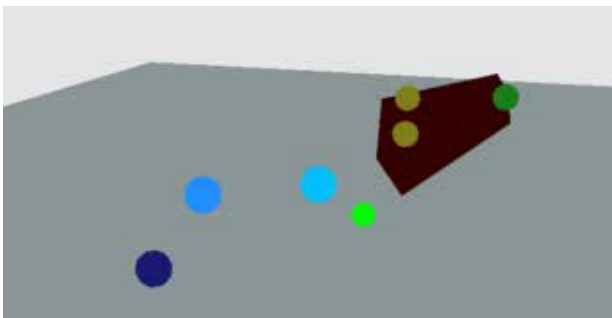


When rats are exploring their environment, they spend time on all fours — a default, or neutral, position — but also raised up on their hind legs. When researchers at the Kavli Institute for Systems Neuroscience recorded the firing of neurons in rats exploring a 2 m by 2 m box they found that many fewer neurons fired when the rat was in its default position compared to when it was in a posture less often visited, such as rearing up on its hind legs. Illustration: Goran Radosevic.

### SIX CAMERAS AND SEVEN INFRARED TRACKING POINTS

The researchers were interested in understanding more about what happens in the posterior parietal cortex and the frontal motor cortex.

They set up a 2-metre octagonal box with six cameras and outfitted 11 rats with special 3-D printed drives, which allowed the researchers to record a total of 800 neurons in one region and 700 in the other. The rats also had seven infrared tracking points, four on the animal's head and three spaced along their backs to their tails.



Benjamin Dunn devised a computer model that researchers used to couple the information that they collected from the rat's brain while it was moving around to 3-D recordings of the rat's movements. The movements were captured with seven infrared sensors, and then visualized as a simplified rat, as shown above. Illustration: Kavli Institute for Systems Neuroscience.

The rats spent 20 minutes in the box where they were allowed to roam around and explore, and occasionally to find a piece of chocolate cookie, all while their movements were recorded visually and while the probes on their heads sent information about which neurons were firing when.

The set-up allowed the researchers to measure the animal's movement in 3-D — not only where it went in the box in its quest for treats, but whether it was turning its head, or rearing up, or twisting in a particular direction.

What they found was when the rats were in a “default position,” roaming on all fours with the head lowered, not that many neurons were engaged in keeping track of what body position the animal was in. But when the rat moved out of this default position, such as when it would rear up on two legs to sniff something, many more neurons fired up to take on the task.

### A 3-D VIEW OF BEHAVIOUR

- This experimental set-up allowed us to see for the first time how these neurons responded during 3-D behaviour in a freely moving animal, said Jonathan Whitlock, senior author of the paper and head of a research group at the Kavli Institute. - The most detailed knowledge we have about these areas has come from head-fixed paradigms, in which animals make simple movements of their hand, arm or eyes. Here we could see for the first time how the brain responded during unrestrained movement of the body, in its native 3-D.

The researchers also conducted some of the tests in the darkness, during which the researchers (but not the rats) wore night-vision goggles to see what the rat was doing. This last effort was to make sure that the information they were recording from the rats was not solely based on what the rat saw, but from how the rat actually moved.

- We wanted to be certain that what these cells were relying on was not just vision, said Bartul Mimica, the first author of the paper and a PhD candidate in the Kavli Institute's Whitlock group.

### STATISTICAL MODEL HELPED CLARIFY PATTERNS

In the end, the researchers used the data to match the firing of the neurons to the movement and postures they had recorded with the infrared sensors and the six cameras. They then developed a statistical model that allowed them to sort through and interpret all the data.

The model “allowed us to see what the neurons were responding to,” said Benjamin Dunn, who developed the model and is starting as an associate professor in data science at NTNU's Department of Mathematical Sciences. They tested the robustness of the model by turning the data around and seeing if the neuron firing data they had collected could “predict” what the rat would be doing without actually looking at the move-

ments they had recorded with the cameras — and it did.

Whitlock said it was especially exciting to see their findings support the 100-year-old observations by early neuroscientists.

- It was a real 'aha-moment' reading over the work of Head & Holmes, Balint, and other neurologists—since to me it seemed very clear that the neural signals we were seeing in our rats was probably what was missing in these patients, he said.

The analysis also allowed the researchers to discover an unexpected detail. Because neutral positions, such as walking around on all fours, didn't require nearly as many neurons to fire as more uncommon postures, such as rearing up, the researchers understood this as a way for the brain to actually conserve energy. That matters because the brain can consume as much as 25 per cent of the body's daily energy budget.

- It is very efficient for the metabolic consumption of the cells, said Tuce Tombaz, one of the paper's co-authors and also a PhD candidate at the Kavli Institute's Whitlock group. - Why would we have cells firing all the time for postures that we occupy all the time? This way the neurons don't have to expend a lot of energy to code for every posture.



*Tennis player: When a tennis player hits a ball, she moves through a series of postures to ensure that her racquet connects with the ball. The ability to hit the ball requires the brain to be aware of your body's position in space, a concept called "body schema". A new paper published in Science shows that many more neurons in two parts of the brain called the posterior parietal cortex and the frontal motor cortex, fire when the body is in certain postures or positions versus when the body is in a more neutral position. Illustration: Goran Radosevic.*

## FROM BASIC RESEARCH TO LEARNING AND ROBOTICS

The Kavli researchers are interested in understanding how the brain works, without any specific clinical or applied goal in mind. But understanding how hard the brain works when it comes to posture as compared to movement might help inform a range of disciplines, the researchers said.

- The clearest application could be in understanding how to better treat stroke patients whose strokes have damaged this area of the brain, Dunn said. - You can't fix a problem if you don't understand it, he said.

Another application might be in robotics, he added.

- The brain has always been an inspiration for artificial intelligence, Dunn said.

- Knowing how we represent the relationship of our bodies as we move around could push the next generation of robots closer to human-like learning of movement and interaction in an ever-changing environment.

- But then there's also the larger question of why the brain is organized in this way, Mimica said.

- Why would this most sophisticated part of the brain care so much about this? he said.

- There must be a reason for this. Uncovering this reason, maybe by finding some little detail, we can learn some deeper truths about the brain and how it is organized. What we're doing is homing in on a precise account of what is going on in the brain.

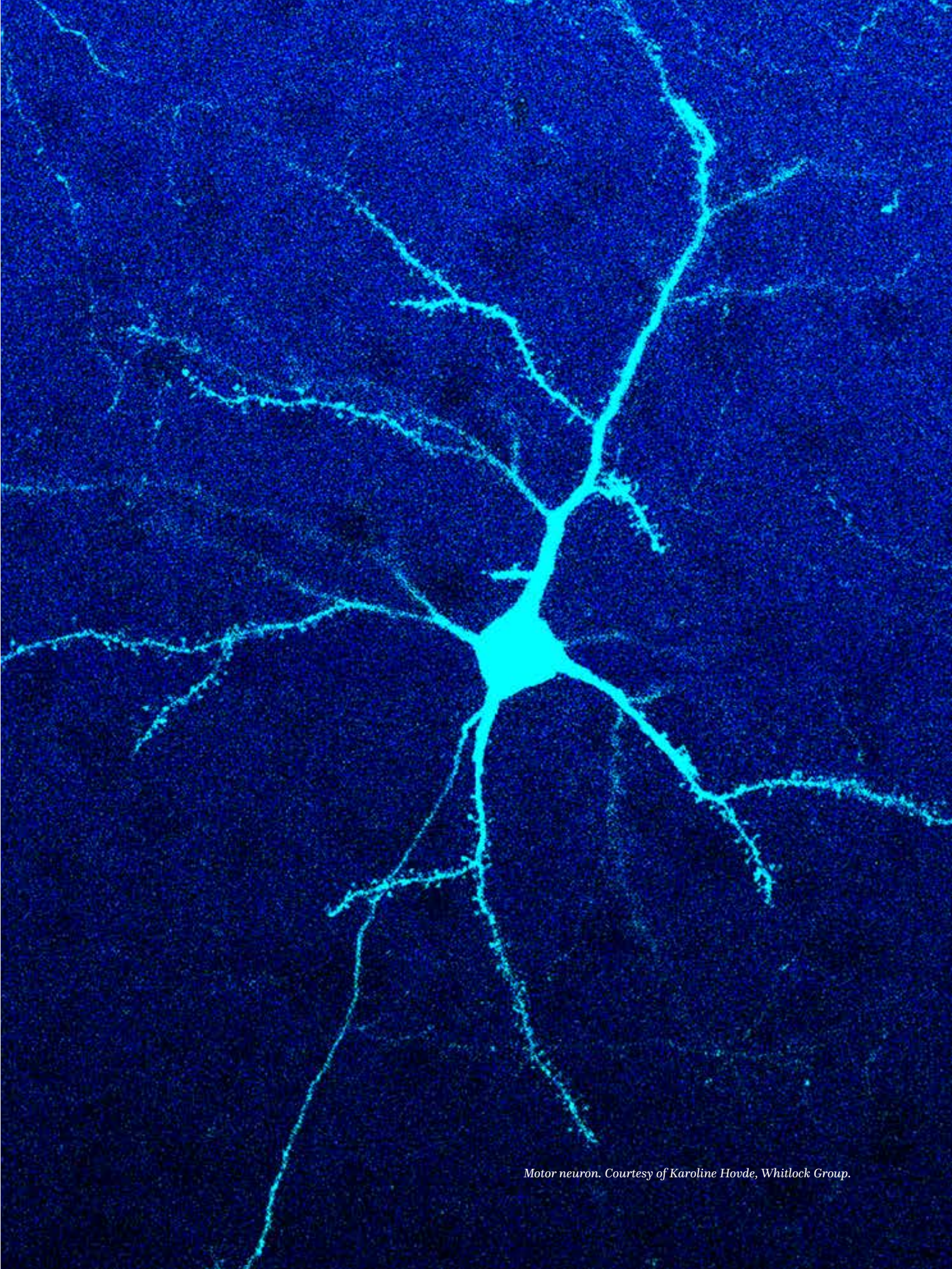


From left: Benjamin Dunn, Bartul Mimica, Tuce Tombaz, Jonathan Whitlock.

## Reference:

Mimica, Bartul; Dunn, Benjamin Adric; Tombaz, Tuce; Bojja, V.P.T.N.C. Srikanth; Whitlock, Jonathan (2018): **Efficient cortical coding of 3D posture in freely behaving rats.** *Science* vol 362 (6414), Kavli Institute for Systems Neuroscience, NTNU, Trondheim.





*Motor neuron. Courtesy of Karoline Hovde, Whitlock Group.*





## BACKGROUND

As technologies are growing more sophisticated, neuroscientists are gathering larger and larger datasets with recordings from hundreds up to thousands of neurons at a time. On their own, large data sets are not very informative. However, match them with a theoretician, and it is possible to extract relevant patterns, mechanisms and universal principles from the data, that will enable scientists to explain behaviour across several scales in a meaningful way. The Roudi group is interested in understanding properties of information transmission and coding in neuronal systems at a general level in biological systems.



## KEY RESEARCH QUESTIONS

- What can global patterns of neuronal activity tell us about how the brain works?
- What are the principles governing network communications?



## TOOLS & METHODS

Roudi's team uses mathematical tools from the field of theoretical physics to analyse big datasets, to develop models that draw out neural mechanisms in big datasets, and to identify and describe universal principles in biological systems.



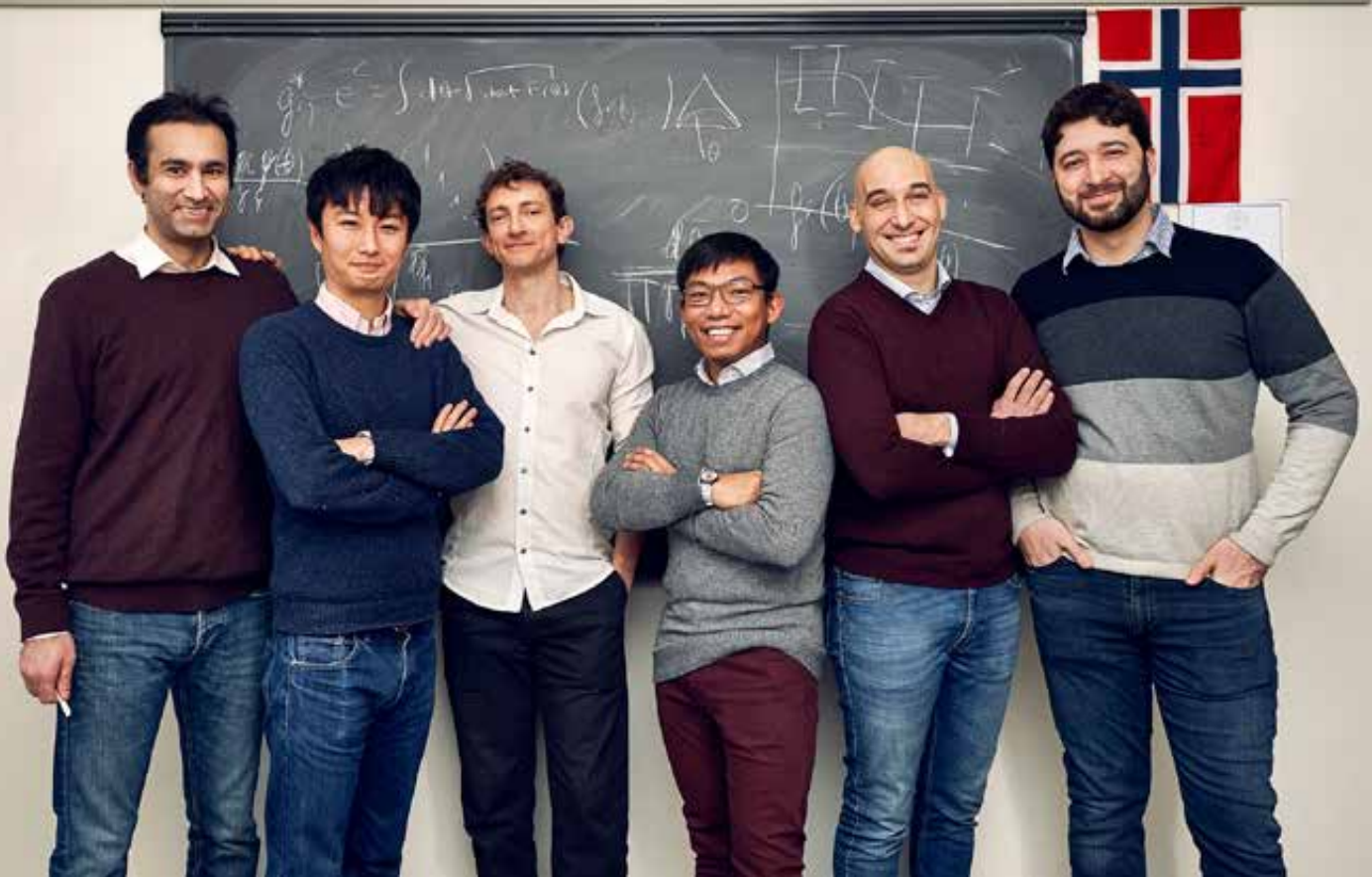
## RESEARCH IN 2017

**Shouting or listening: How living systems grapple with noisy conversations.**

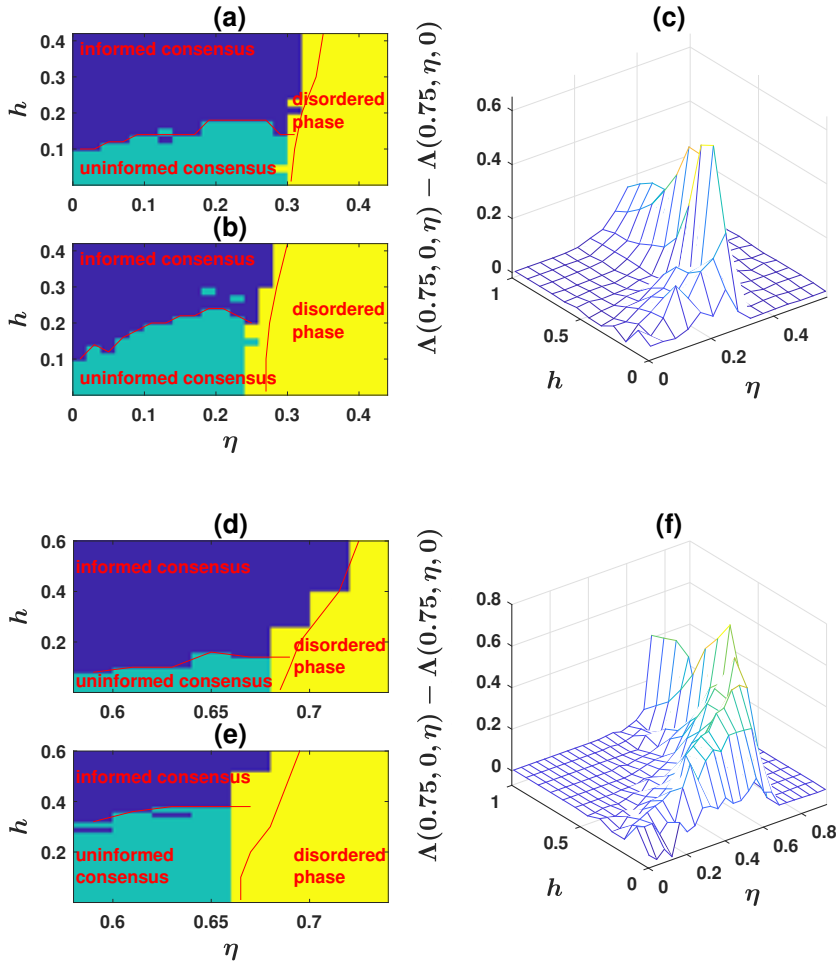
Whether we consider neurons communicating through electrical impulses, bacteria communicating through quorum sensing, or humans communicating through language – all biological populations rely on clear communication. In the past year, the Roudi Group published a study on the properties of a biological communication network. Firstly, let's think about a biological population in the terms of network of interacting agents. The network of agents could stand for a neural population, a bacterial culture, a human society, or another biological population. All agents want to understand their environmental conditions, from temperature, pH, and nutrients, to more complex features. Agents can gather information about their environment by sensing the external world directly and by communicating with other sensing agents. They communicate by signalling to each other what they think the state of the world is. Based on the information received from other agents and from their own sensory information apparatus tuned to the world, the agents continuously make decisions about the current state of the environment, and communicate this to other agents. Alas, in this system there is also noise. Signals on all levels are prone to noise: the sensory information signal that the agent acquires from the environment may be incorrect; the agent may miscommunicate its information signal to other agents; or the communicated information signal may be misinterpreted by the agent on the receiving end. Roudi's team set out to identify these rules of noise

# Roudi Group

*To understand the properties of neural communication on a network level.*



*From left: Yasser Roudi, Yu Terada, Piero Mana, Ryan John Abat Cubero, Nicola Bulso, Ivan Andres Davidovich. Also in the group but not present when the photo was taken: Abel Sagodi.*

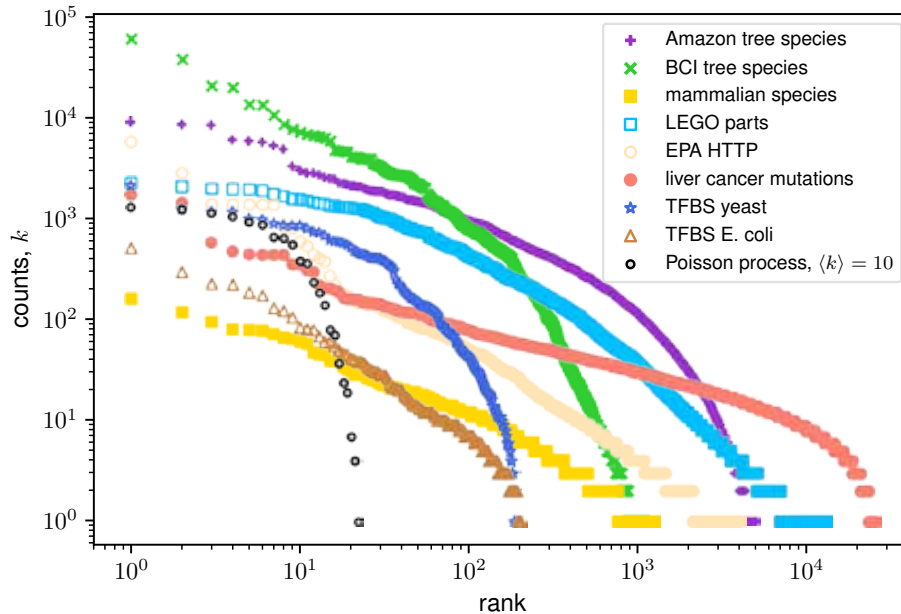


A phase diagram of the model, showing that it is more important that the communicated information is correct than that the interpreted communication is correct, for a system's ability to arrive at the correct conclusion. The evolutionary pressure is thus higher towards reducing noise in signal production, than towards reducing noise in signal comprehension. In the first nearest neighbour network: noisy comprehension (a) vs. noisy production (b), and the comprehension-production symmetry defined as L (c). In the second nearest neighbour network: noisy comprehension (d) vs. noisy production (e), and the comprehension-production symmetry defined as L (f). Figure by Mohammad Salahshour, Shahin Rouhani and Yasser Roudi.

in various stages of signal, in order to identify under what circumstances the network as a whole will arrive at the correct conclusion about its environment, circumstances leading to the wrong conclusion, or circumstances leading to conflicting belief spread randomly across agents without any general consensus in the network. They found that the most important factor is where in the flow of communication that the noise arises. Noise that arise in the agent's production of signal (speech) is more harmful than noise in an agent's comprehension of signals (listening). Since biological organisms have limited resources to devote to

noise reduction, Roudi's team propose that evolutionarily, it is more advantageous to make oneself understandable than to understand. So, where in nature would we expect to observe this asymmetry between being understandable and understanding others? Their model points to populations that are living in smaller groups with high connectivity, like primate populations and early human societies. This phenomenon has already been reported on, for instance in signalling games and in human language learning, where children tend to produce correct language signals before they themselves can correctly comprehend speech.





The research group showed that the MDL-optimal codes exhibit broad distributions for several well-known statistical models: 4962 species of trees across 376 genera and 89 families sampled across a 50 hectare plot in the Barro Colorado Island, Panama; Counts indicating the inclusion of each 13,001 LEGO parts on 2613 distributed toy sets; The number of genes that are regulated by each of the 203 transcription factors (TFs) in *E. coli* and 188 TFs in yeast, through binding with transcription factor binding sites (TFBS).

### Proposing a universal explanation to a frequently observed pattern in nature.

In another recent work, the Roudi Group provides a novel explanation to broad distribution patterns. Broad distribution patterns show up time and time again across different natural systems – from the co-activity of neurons, to the distribution of tree species, or the size of cities. It is a highly debated topic in the field, and the ubiquity of these patterns begs for a universal explanation. Ryan Cubero et al propose that they are the results of a mathematically

well-defined notion for optimal information transmission called Minimum Description Length (MDL). The notion reads that the best description of data is the one that compresses the data the most. In other words, the broad distribution patterns happen so often in nature because they are the best way to transfer information.



# Kentros Group

*To better understand the neural circuitry underlying learning and memory and to develop powerful tools to precisely investigate questions relevant to brain disease.*



## BACKGROUND

In order to understand (1) how neural circuits contribute to normal functioning of complex processes, such as learning and memory and (2) what breaks down in these circuits in pathologies and diseases of learning and memory, neuroscientists need highly precise tools to interrogate these circuits. The Kentros team has taken a two-fold approach in their investigation by generating state-of-the-art tools with unprecedented precision and by applying these tools to the interrogation of neural circuits, which are important for learning and memory.



## KEY RESEARCH QUESTIONS

- How do the different neuron types in a neuronal circuit contribute to the complex process of learning and memory?
- Is it possible to develop highly precise tools and therapies by targeting specific cell types in the brain?



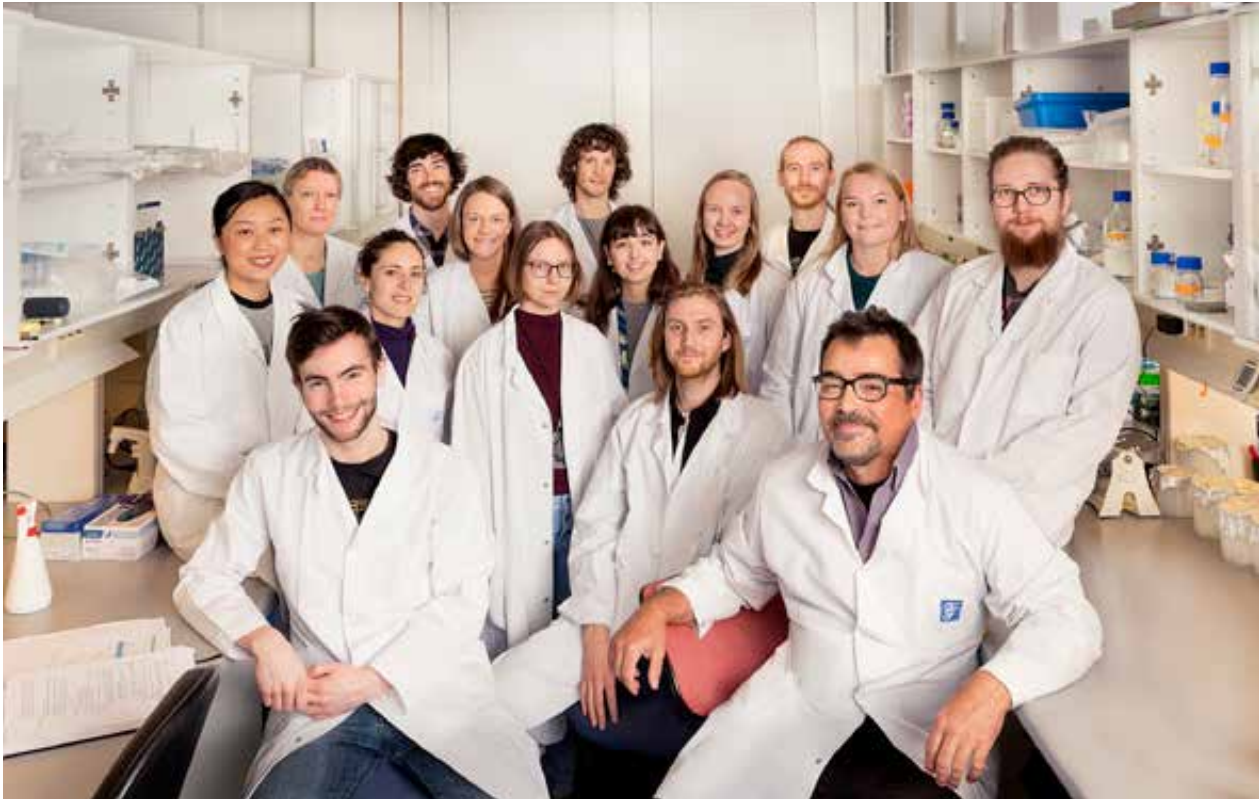
## TOOLS & METHODS

The Kentros group is investigating the neural circuitry of learning and memory by applying – and creating – tools based in principles of molecular genetics and electrophysiology (recording from neurons) in awake, behaving animals.



## RESEARCH IN 2017

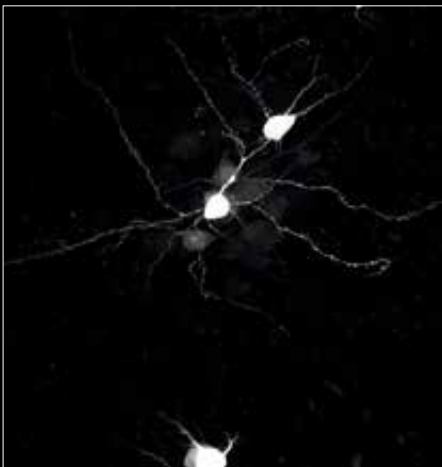
Genetically altered – or transgenic – mouse models are one of the most commonly used tools in a neuroscientist's toolbox. They are often used to answer questions like: how do these cells contribute to this neural circuit and how does activity in this circuit, in turn, relate to behavior? However, even within a given neural circuit, there are an astounding number of cell types, distinguished from one another based on the unique combination of proteins and genes they express. Thus, to really understand how the smallest parts of the circuit contribute to something as complex as learning and memory, it is important to have



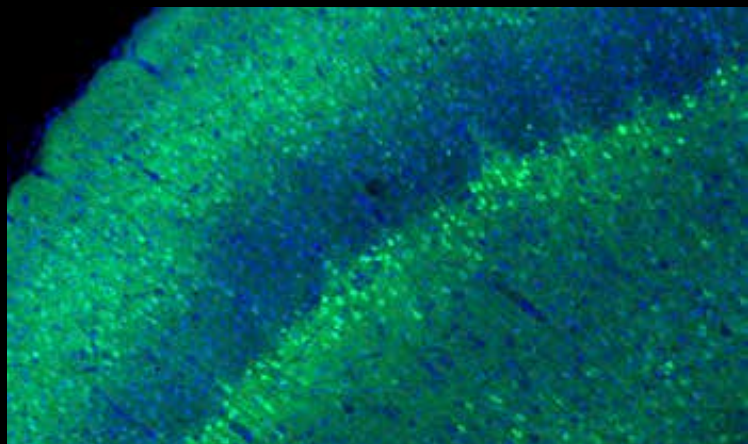
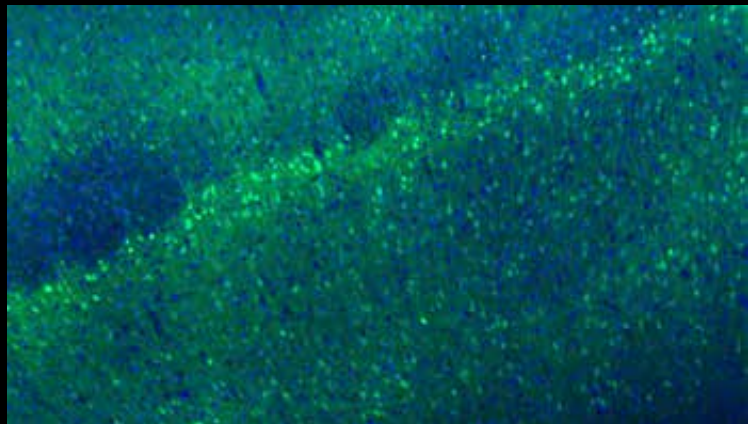
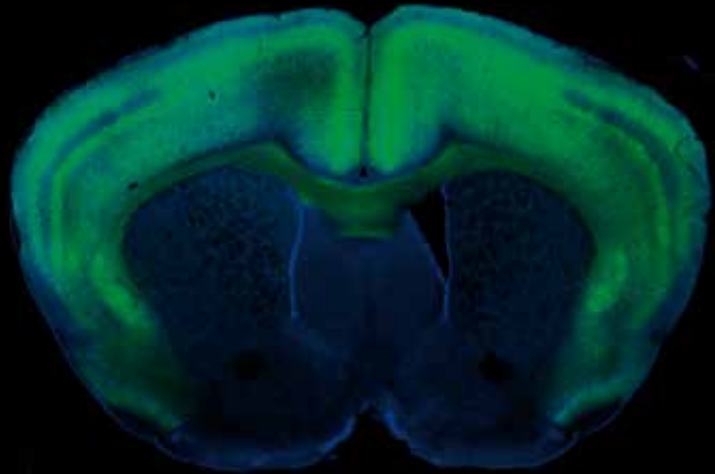
From left: Qiangwei Zhang, Christina Schrick, Joachim Schweder Grimstvedt, Maria Jose Donate Lagartos, Benjamin Kanter, Christine Lykken, Annika Utz, Miguel Carvalho, Lucie Descamps, Oscar Chadney, Vilde Aamodt Kveim, Stefan Mattias Adriaan Blankvoort, Clifford Kentros, Ada Nilsen Nordeidet, Marcus Sandbukt. Also in the group but not present when the photo was taken: Valentina Di Maria, Tania Winter Gjøvik.

a tool which can identify and ultimately manipulate the circuit on the level of these different cell types. To address this challenge, Stefan Blankvoort and colleagues from the Kentros group created with a tool known as “Enhancer-Driven Gene Expression” or “EDGE”. Enhancers are the small sequences of DNA which help control which genes are translated into proteins. It is worth noting that while “promoters” also drive gene expression – and indeed, although most transgenic mouse models that are currently developed are based on different promoter types – enhancers are 1) much more specific to particular cell types than promoters (which can be used to drive many different types of genes) and 2) are smaller than most promoters, making them amenable to drug development. If we can develop therapies that more precisely target just the diseased parts of a neural circuit, then we increase the chances of more effectively treating diseases and minimizing their undesirable side-effects.

The group has already begun making discoveries using this newly-developed tool. “We have found that stimulating the same neurons in the medial entorhinal cortex leads to the same hippocampal response multiple times, suggesting that there is more “hard-wiring” in the circuitry underlying memory than previously thought,” says Kentros. Other groups at the KISN already recognize the power of this tool and have been applying it to their own work. For example, a collaboration between Kentros and Witter has led to the application of EDGE to identify and manipulate the cells within layer II of the entorhinal cortex to further clarify the role they play in the onset and pathophysiology of Alzheimer’s Disease (AD).



*Cells in the claustrum from one of our transgenic EDGE lines. Courtesy of Kentros Group.*

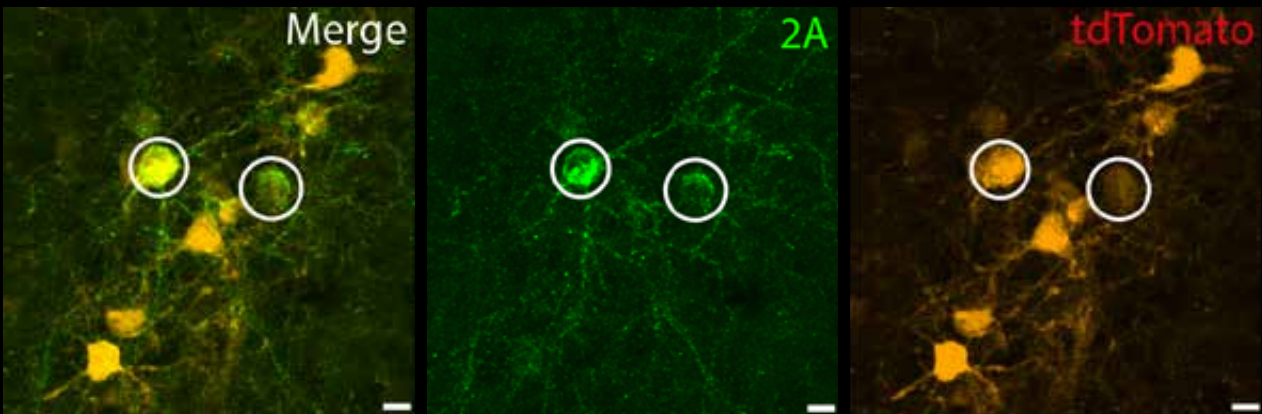


*Confocal images taken from the transgenic mouse line using for calcium imaging. Coronal slice of a mouse brain acquired with a confocal microscope. Cells are stained in blur with DAPI and excitatory cells expressing the calcium indicator GCaMP6s are green. Courtesy of Kentros Group.*





Implanted mice eating biscuits. Courtesy of Kentros Group.



Starter cells in claustrum: Confocal image showing intrinsic monosynaptic input cells in the claustrum of a CC-tTA transgenic mouse. The 2A-peptide is conditionally expressed in transgene expressing cells, allowing targeted transfection of the claustral complex. Cells infected with a modified rabies virus are visualized by the fluorescent label tDTomato. White circles indicate starter cells – cells that express both 2A and rabies. Cells that only express rabies are monosynaptic inputs to the starter cell population. Courtesy of Kentros Group.

# Yaksi Group

*To better understand how sensory information is encoded in the brain and how it is modulated by learning and by an animal's internal states.*



*From left: Ahmed Jamali, Kadir Aytac Mutlu, Vy Thuy Nguyen, Robbrecht Pelgrims, Evelien Laura H Van Hoeymissen, Pradeep Lal, Julie Hélène Vancraeynest, Daniela Weth-Malsch, Stéphanie Forè, Anna Ostenrath, Emre Yaksi, Sverre Myren-Svelstad, Khac Thank Phong Chau, Nathalie Jurisch-Yaksi, Christa Ringers, Fabrizio Palumbo, Ecem Aydin, Bram Serneels, Silke Anny Vanderhaeghe. Also in the group but not present when the photo was taken: Ewelina Bartoszek, Emilie Willoch Olstad, Andreas Moe Nygaard, Wojciech Marcin Swiergon, Kevin Eriksen, Jong-hee Hon.*



## BACKGROUND

The habenula is an evolutionary conserved brain region that has caught the attention of neuroscientists in recent years, due to its strong link to depression, addiction, sleep and social interactions. It receives multiple inputs from different brain regions, which provide information about an animal's sensory world and internal state, such as reward expectation.

Additionally, the habenula regulates key neurotransmitters, such as serotonin, dopamine and acetylcholine – all of which play critical roles in learning, memory, motivation and mood. Interested in the connection between sensory processing and higher-level functions such as experience-dependent learning and memory, the Yaksi lab has been investigating the relationship between the habenula and other brain regions such as the hippocampus and the amygdala, which have known roles in mood regulation, learning and memory.



## KEY RESEARCH QUESTIONS

- What drives ongoing activity in the brain and how does this ongoing activity relate to internal states and experience-dependent learning in brain regions known to be important for emotional processing and learning?
- How do changes in ongoing brain activity modify sensory computations in these brain regions?



## TOOLS & METHODS

The Yaksi group uses two-photon microscopy, electrophysiology, genetic and applied mathematical tools to measure and analyze neural activity across the whole brain of awake, behaving juvenile zebrafish in naturalistic and virtual reality environments.



## RESEARCH IN 2018

Previous work from the Yaksi group showed that the habenula integrates olfactory and visual information. The team further demonstrated that depriving the zebrafish of this multisensory input altered the corresponding multisensory representations in the habenula establishing the important link between incoming information from the outside world to its corresponding representation inside the brain. In parallel, a separate study from the group showed that the habenula integrates multisensory information with internally generated brain activity – that is to say, signals that are generated from inside the brain itself.

Wanting to build upon these results, the team has been investigating where inside the brain these signals are coming from and what role these signals play, in experience-dependent learning, different behavioral states of the animal, and sensory information processing. After extensive analysis of brain activity, the team discovered that numerous distinct brain regions (hippocampus, amygdala, hypothalamus) are the main driver of habenular activity. “Our unpublished findings suggest that cortico-limbic brain regions and the habenula cooperate with each other and that the coherent interactions of this distributed brain-wide network are the main source of ongoing brain activity,” says Yaksi.

Finally, because the habenula controls the release of key neurotransmitters involved in learning, memory and mood, Yaksi hypothesizes that these brain interactions “are essential for regulating experience dependent changes in sensory computations and animals’ emotional states.” To test this, the group has recently optimized methods which can record neural activity from multiple brain regions, simultaneously. By recording this neural activity from the brains of juvenile zebrafish while they are behaving and exploring in a virtual reality environment, the team will learn how experience-dependent learning and emotional states (internally represented in the brain) can affect neural connectivity and sensory information processing.





# Doeller & Kaplan Group

*To understand the general principles of cognition, and to identify neural signals or biomarkers that can predict the onset of neurodegenerative diseases of learning and memory.*



## BACKGROUND

Grid cells play a well-established role in map-like coding and spatial navigation. Less well understood, however, is the potential role that these map-like codes contribute to general cognition and complex processes such as learning, memory and decision making. The Doeller and Kaplan group is interested in investigating the idea that the brain uses map-like representations for cognition that extends beyond spatial navigation.

brain systems that support learning, memory, and decision making. The former technique boasts relatively good “spatial resolution” (the ability to detect where a signal is coming from) while the latter boasts good “temporal resolution” (the ability to detect when a signal occurs). By combining this data with electrophysiological recordings from rodents, the team is able to paint a more comprehensive picture of the link between entorhinal brain signals and general cognition.



## KEY RESEARCH QUESTIONS

- Are map-like learning mechanisms, that are already known to play a role in spatial cognition, also important for cognition in general?
- What are the cognitive-level biomarkers that predict the onset of neurodegenerative diseases such as Alzheimer’s Disease?



## RESEARCH IN 2017

Recent work in the Doeller and Kaplan lab has focused on the entorhinal cortex, the part of the brain where grid cells reside. In comparing data from human MEG recordings to electrophysiological recordings of grid cells in rodents, the group found a “grid-like” signal in the MEG recordings during a visual exploration/tracking task. This discovery demonstrates that “grid coding” applies not only to spatial navigation tasks, as originally described, but may also play a critical role in other behaviors such as visual exploration or locomotion. The group proposes that the same systems which represent literal space are responsible for representing abstract/mental space. The idea of cognitive space actually dates back to the 1940s, when Edward Tolman first proposed that goal-directed behavior was made possible through “cognitive maps”. Over two decades later, when place cells – cells that fire when an animal is in a particular region of space – were discovered by scientists O’Keefe



## TOOLS & METHODS

The Doeller and Kaplan group uses neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) to investigate

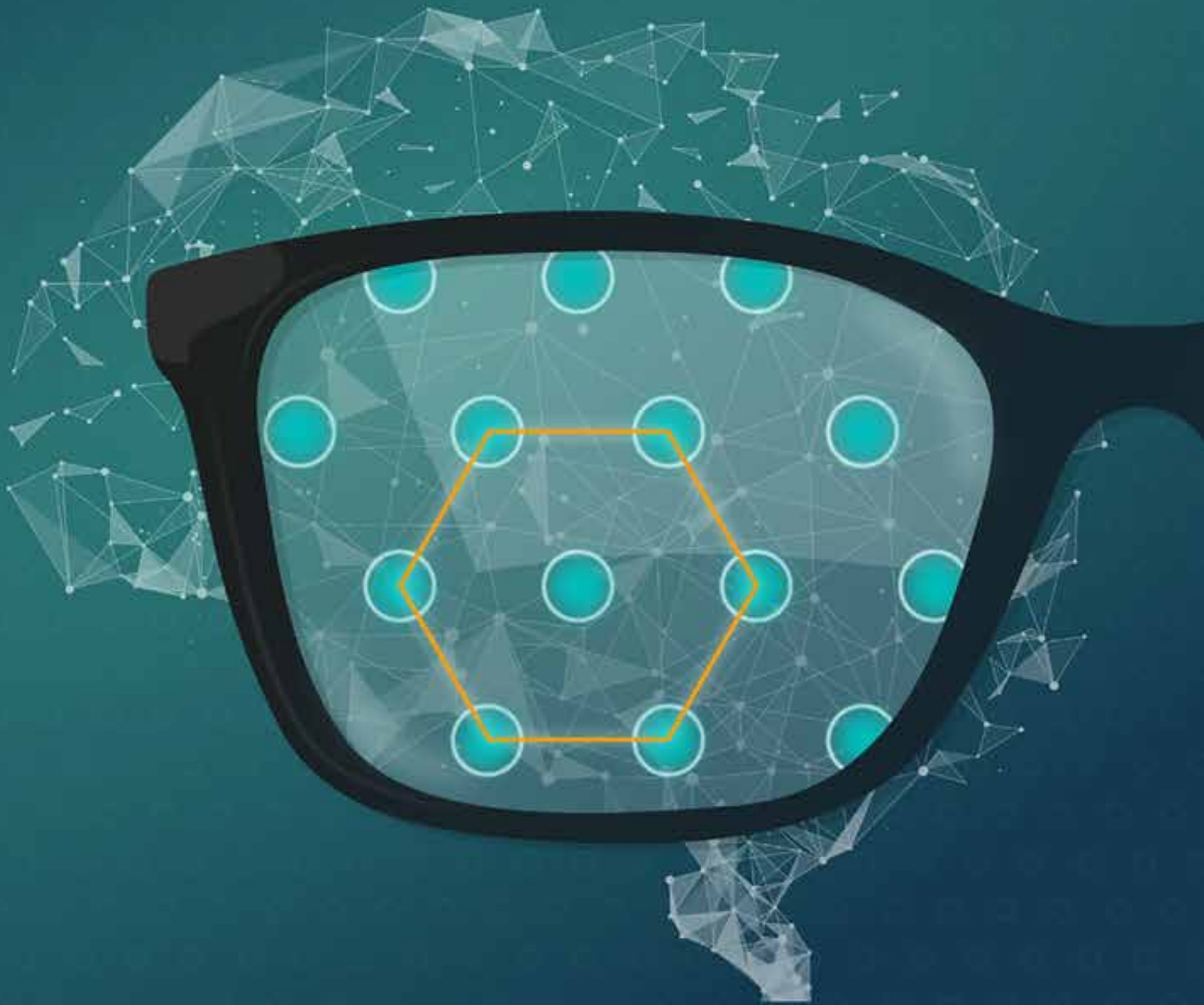


and Nadel, many credited the discovery as a validation of Tolman's cognitive map theory. Yet, since the discovery of spatially-selective cells (place cells, grid cells, head-direction cells, border cells, etc.), scientists have focused more on the use of these codes for physical navigation through space, and less so on the psychological space that is supported by these codes.

Research by the Doeller and Kaplan group is bringing attention and experimental validation back to the cognitive map theory of psychological function. Whether we are discussing how to get from the grocery store back home, or whether we are figuring out how two ideas might be connected, we use the same map-like brain systems to fulfill our goal.

*First row from left: Dörte Kuhrt, Stian Jensen Framvik, Merethe Andresen, Ignacio Polti, Lydia Brunvoll Sandøy, Tobias Navarro Schroeder. Second row from left: Ingrid Framås Syversen, Renil Mathew, Annelene Gulden Dahl, Marcus Frey, Raphael Samuel Matthew Kaplan, Matthias Nau, Nathalie St. John, Joshua Julian, Anne Merethe Winther. Also in the group but not present when the photo was taken: Christian Doeller, Lillith Sommer, Gøril Rolvseng Grøntvedt, Christiana Bjørkli.*





*Hexadirectional coding of visual space in human entorhinal cortex.  
Courtesy of Doeller and Kaplan Group.*



Raphael Kaplan, Associate Professor  
Kavli Institute for Systems Neuroscience

# *The Kavli Institute's translational neuroscience initiative*

*To make new knowledge from basic science discoveries available for research on brain diseases and patient treatment in the clinic.*

The mission of the institute's translational neuroscience initiative is to make our neuroscience findings available in two primary ways. First, we translate promising results from basic animal research to humans, where we use findings at the level of individual neurons to inform research on human brain networks. Second, we aim to transform these cross-species basic research findings into clinical knowledge.

Locally, the research activities are performed in close collaboration with the St. Olav's Hospital. Nationally, the initiative is part of a network including hospitals, research facilities, patient organizations, and other relevant stakeholders. The network is established to implement a national research agenda on prevention, diagnosis, treat-

ment and care of people with dementia, with the aim of strengthening research capacity on national priorities for research into dementia in a sustainable and cost-effective manner.

In order to develop and implement a more reliable financing model for the translational neuroscience initiative, the institute has submitted a new proposal that, given its success, will provide the fundamental structures necessary for growth and impact on a national and international scale in the fight against dementia and other brain diseases. Our multifaceted approach will allow us to continue to gain key insights into the function of neural systems, while at the same time facilitating patient treatment in the clinic.

## **WHAT IS TRANSLATIONAL NEUROSCIENCE?**

Using in-vivo intracellular recordings in behaving animals to inform our human behavioral and neuroimaging experiments gives us a solid foundation to develop potential behavioral and imaging diagnostics for clinical brain disorders. In particular, investigating the grid cell system and map-like coding in humans and how it extends beyond

navigation allows us to understand how spatial coding principles could form the building blocks of learning and memory. By better understanding the brain's internal map of the world, we can uncover specific internally driven symptoms related to psychiatric illness and neurodegenerative disease like intrusive memories and memory difficulties



# *The hippocampus of KISN*

*Excellent support enables excellent science.*

A staff of highly dedicated technicians, administrators and specialists is providing their knacks to the research groups across the institute. Diversified in skill and training, the individuals of these groups operate the laboratories, train young researchers on advanced technologies, attend to the animals' welfare, assist scientists in designing practical solutions for novel experiments, they help organize conferences and events, mediate science to the public, coordinate the institutes Master program, support project proposals and keep track of economical and organizational matters.

These are the workers the Directors fondly refers to as the hippocampus of the institute, archiving information from short-term memory, retrieving knowledge from long-term memory, establishing long-term potentiation of preparedness based on recent activities, and in general providing cues used for navigation and speed by the leaders.





First row from left: Nina Wold Johansen, Anne Lise Starnes, Alice Burøy, Qiangwei Zhang, Tonje Aarsand, Vy Thuy Nguyen, Rita Elmkvist Nilsen, Ingvild Ulsaker Kruge. Second row from left: Endre Kråkvik, Lisbeth Normann Miltid, Maria Gangstø, Merethe Andresen, Eirin Hårstad, Hanne Mali Møllergård, Kay Gastinger, Paulo Girão, Third row from left: Solfrid Nordtug, Ann Mari Amundsgård, Kyrre Haugen, Haagen Waade, Klaus Jenssen, Grethe Jakobsen, Siv Eggen, Safa Ali Mohamad. Also in the group but not present when the photo was taken: Hanne Soligard, Grethe Mari Olsen, Mussie Debesai, Dina Hestnes, Janani Jeyachandran, Bruno Monterotti, Christina Schrick.

# *Egil and Pauline Braathen and Fred Kavli Centre for Cortical Microcircuits*



*Mrs. Pauline Braathen and Prof. Edvard Moser in February 2019.*

*Alzheimer's disease is one of the biggest health challenges to society, but for the last 15 years no new drug has seen the light of day in a clinical study.*

Disorientation and memory loss are hallmarks of Alzheimer's disease. We know very little about what causes the disease, nor of the mechanisms behind its rapid progression and destruction of brain tissue.

#### **KNOWLEDGE FROM FOUNDATIONAL RESEARCH**

Today, we know where in the brain these higher mental functions are generated. Our ability to orient ourselves in space and in time as well as our ability to remember from our experiences, all arise from three brain areas that are tightly interconnected.

The area called hippocampus is the brain's memory hub. The neighbouring brain structure entorhinal cortex is functionally divided between spatial awareness and navigation abilities (in the medial part), and temporal awareness and ability to organize our experiences in chronological sequences (in the lateral part).

It is not surprising that the entorhinal cortex, our brain's hub for space and time, is the very first area where Alzheimer's disease causes massive cell death. The loss of brain cells in this area is found as early as a decade before clinical symptoms of the disease start to manifest.

Alzheimer's works by disrupting communication between the neurons, causing cells in the brain to lose their function and eventually die. The result of this silent death is a decline in cognitive abilities, like disorientation, gradual loss of memory and even personality changes.

Only by understanding how these brain regions work before they are broken, will we be in a position to find

the cause of the disease, and further to develop diagnostic tools and treatments.

#### **THE EGIL AND PAULINE BRAATHEN AND FRED KAVLI CENTRE FOR CORTICAL MICROCIRCUITS**

The Braathen-Kavli Centre is a basic research centre studying neural mechanisms affected by Alzheimer's disease. The Centre conducts research on the neural codes and mechanisms underlying cognitive functions, in particular memory; the ability to organize experiences in time; and to find one's way.

The Centre's aim is to understand how brain functions that are the first to be affected by Alzheimer's work in the normal brain, before the onset of neurodegeneration. We believe that these foundational studies will help us understand what triggers the onset of deterioration and cell death in the entorhinal cortex - insights that will be essential for developing a cure for this disease.

**FOUNDATIONAL NEUROSCIENCE RESEARCH ON SPACE, TIME AND MEMORIES IN THE FIGHT AGAINST ALZHEIMER'S DISEASE**

The Centre will use its research on cortical microcircuits to investigate how physiological processes might set the stage for Alzheimer's. During the year of 2018, researchers at the Centre discovered a neural code that expresses time in the lateral entorhinal cortex - a code that may be among the very first higher brain functions that are impaired by Alzheimer's disease.

The activity at the Centre may form a fundament for recruitment of internationally renowned researchers working with human patients on mechanisms of cortical dysfunction discovered through the basic-research programme at the Centre.



# In Mrs. Braathen's words



- With this grant, I want to recognize and encourage the world leading neuroscience research in Trondheim which is led by the remarkable Nobel Prize Winners May-Britt and Edvard Moser. At the same time, I wish to honor my deceased husband, Egil Braathen, who had a lot to be grateful to St. Olav's Hospital for. The research led by May-Britt and Edvard Moser has great importance for a world in need of increased knowledge about how the brain works, in order to prevent and cure disease and illness related to the brain. I believe that this unique combination of research and clinical excellence has the prerequisites to find the answers to the Alzheimer mystery.

Pauline Braathen, on the donation realizing the new Egil and Pauline Braathen and Fred Kavli Centre for Cortical Microcircuits at the Kavli Institute for Systems Neuroscience.



Egil Braathen's nieces Anita Lien and Mona Arnesen, and his nephew Erik Ruud.

- His eyes were empty, but his words "Are you my wife?" filled mine with tears.

Pauline Braathen, on slowly losing her beloved husband to Alzheimer's disease.

- I know there are millions who suffer with Alzheimer's and many millions more who suffer in another way caring for their loved ones, but just at the time I felt uniquely tortured and truly alone.

Mrs. Braathen lost her husband of 46 years in 2009, after a prolonged period of advanced Alzheimer's disease.





*– We are morally obliged to help solve one of the greatest challenges for global health of our time.*

Edvard Moser

Pauline Braathen is a philanthropist in the great Anglo-American tradition. Like Bill Gates and Warren Buffet, she has decided that her fortune will channel back to the community providing lasting value for those coming after her.

Value, not in terms of money, but in terms of securing stable, long term funding for basic research that is devoted to solving the mysteries of the brain and alleviating some of the most heartbreaking sufferings that afflict humankind.

Mrs. Braathen has since long been wanting to express her gratitude to the medical team at the hospital in Trondheim, who once saved her husband, Egil Braathen's life by performing world class pioneering surgery. As she later learned about the research done at the Institute run by

May-Britt and Edvard Moser, and about the gift trusted to them by the Kavli Foundation, and further about the Nobel Prize in Physiology or Medicine 2014 awarded to them for their groundbreaking discoveries – things had come full circle for Pauline. Within the same innovative research environment that once had come to her husband's rescue all those years ago, a new world class research community had developed, holding the potential for saving millions of people worldwide.

Pauline Braathen is donating most of her remaining assets in the effort to realize a new center for brain research at the Kavli Institute that will cooperate with St. Olav's Hospital in Trondheim. She is joined by three of her late husband's nephew and nieces Anita Lien, Mona Arnesen and Erik Ruud in making this substantial donation, and thus provide one of the largest philanthropic contributions in the history of Trøndelag County.

Harald Ellefsen

*Attorney of Law*

Stig Slørdahl

*CEO at the Central Norway  
Regional Health Authority*



# *The Kavli Foundation and Fred Kavli*



FRED KAVLI (1927-2013) was born in Norway in 1927. As a young scientist, he received his basic education in Physics from The Norwegian Institute of Technology, the predecessor of our University NTNU. Kavli was an excellent entrepreneur, business leader and innovator, and brought his company Kavlico Corporation to great success. His vision was to support basic research and education with a positive, long-term impact for the human society.

In 2000, he established the Kavli Foundation, in particular to promote basic science in the fields of astrophysics, nanoscience, neuroscience and theoretic-

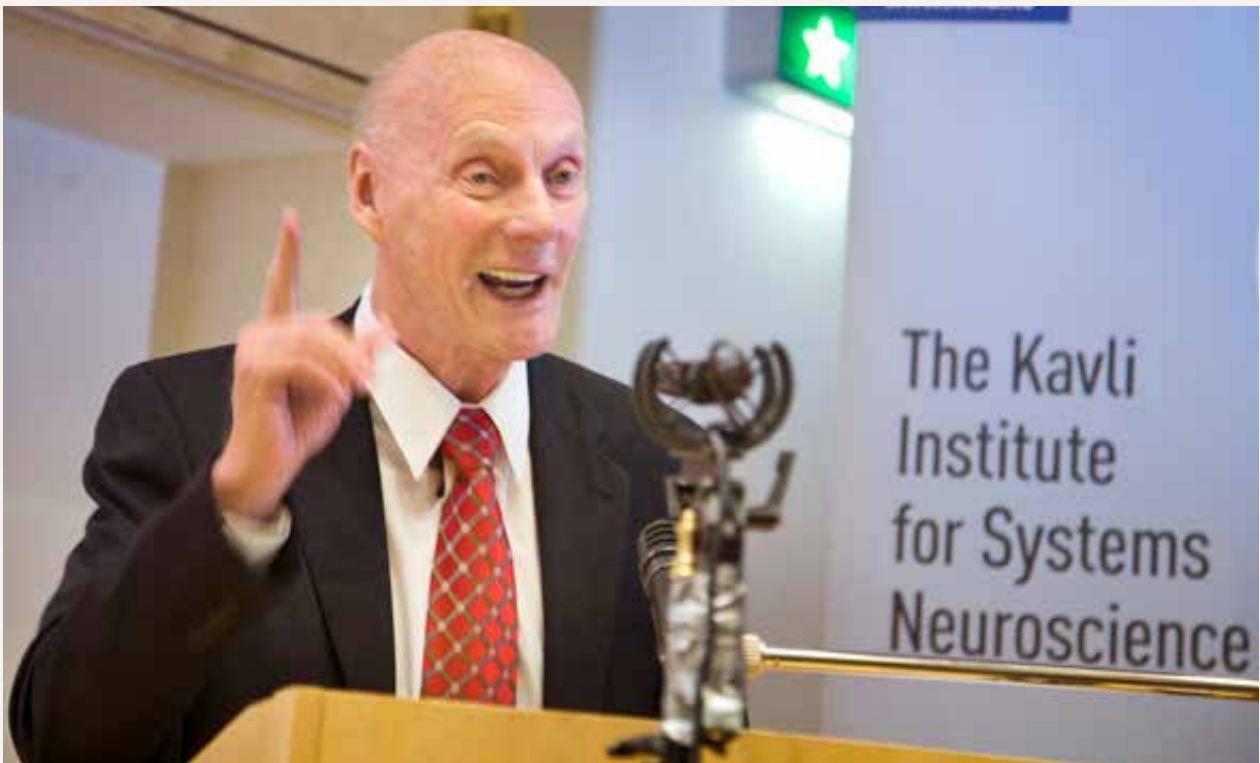
cal physics - "from the biggest, to the smallest, to the most complex". He selected these fields because he thought these are the most exciting scientific fields for the 21st century. The mission of the Kavli foundation is to "advance science for the benefit of humanity and to promote public understanding and support for scientists and their work".

To realize this mission, the Kavli Foundation supports excellent scientists around the world. Today, sixteen Kavli institutes are established on three continents, collecting some of the best scientists in their fields. Besides the Kavli institutes, the Kavli Foundation supports science conferences, symposia and seminars around the globe, and has initiated the biennial Kavli Prize Awards honouring important scientific achievements in the research areas: astrophysics, nanoscience, and neuroscience.

The Kavli institute for Systems Neuroscience (KISN) at NTNU was established in 2007 and is one out of only three European Kavli Institutes. We are obliged to the mission Fred Kavli assigned to us. The status as a Kavli institute gives us free, long-term financing and international recognition. This was an important pillar for the Nobel prize to May-Britt and Edvard Moser in 2014. The continued support from the Kavli Foundation contributes decisively to novel discoveries at the Kavli Institute for Systems Neuroscience, like the time code for experience and memories in the brain, and object vector cells for navigation.



First row from left: The 2018 laureates in neuroscience: James Hudspeth, Rockefeller University, New York, USA; Robert Fettilplace University of Wisconsin, Madison, USA; Christine Petit, Collège de France, Institut Pasteur, Inserm and Sorbonne Université, Paris, France. Second row from left: May-Britt Moser, Scientific Director, Kavli institute for Systems Neuroscience, NTNU; Christopher Martin, Director Science Operations, The Kavli Foundation; Bob Conn, President and CEO, The Kavli Foundation; Bjarne Foss, Pro-Rector for Research, NTNU; Eric Marshall, Vice President of Prizes & Public Programs, The Kavli Foundation; Edvard Moser, Scientific Director, Kavli institute for Systems Neuroscience, NTNU.



Kavli Institute for Systems Neuroscience and NTNU are co-organizers of the Kavli Prize ceremony in Trondheim. The laureates in neuroscience give their Kavli Prize lectures in a joint program with the laureates in nanotechnology. In addition, the Kavli institute organizes a symposium together with the neuroscience community at NTNU.

# NORBRAIN

## - The Norwegian Brain Initiative

*NORBRAIN is a large-scale infrastructure for 21st century neuroscience.*

### Mission

*NORBRAIN enables research to determine neural mechanisms of behavior and crack the neural codes of the brain.*

### Facilities

*NORBRAIN is hosted by the Norwegian University of Science and Technology (NTNU), with University of Oslo (UiO) as partner. NORBRAIN facilities are shared between UiO and NTNU.*

### ABOUT NORBRAIN

NORBRAIN provides nationwide access to cutting-edge neuro-technology, and offers services to researchers from universities in Norway and other national users.

### KEY GOALS

- To provide state-of-the-art research tools with a capacity for enabling novel insight into how complex mental functions and dysfunctions emerge from distributed neuronal activity in local brain circuits.
- To apply knowledge from basic science for the development of new diagnostic tools and treatments for neurological and neuropsychiatric disorders.

### PARTNERS

- Kavli Institute for Systems Neuroscience, Centre for Neural Computation, Egil and Pauline Braathen and Fred Kavli Centre for Neural Computation, NTNU.
- Medical Imaging Laboratory for Innovative Future Healthcare (MI-Lab), NTNU.
- Centre for Molecular Biology and Neuroscience (CMBN), UiO



**EDVARD I. MOSER**

Scientific Director of NORBRAIN  
Kavli Institute for  
Systems Neuroscience

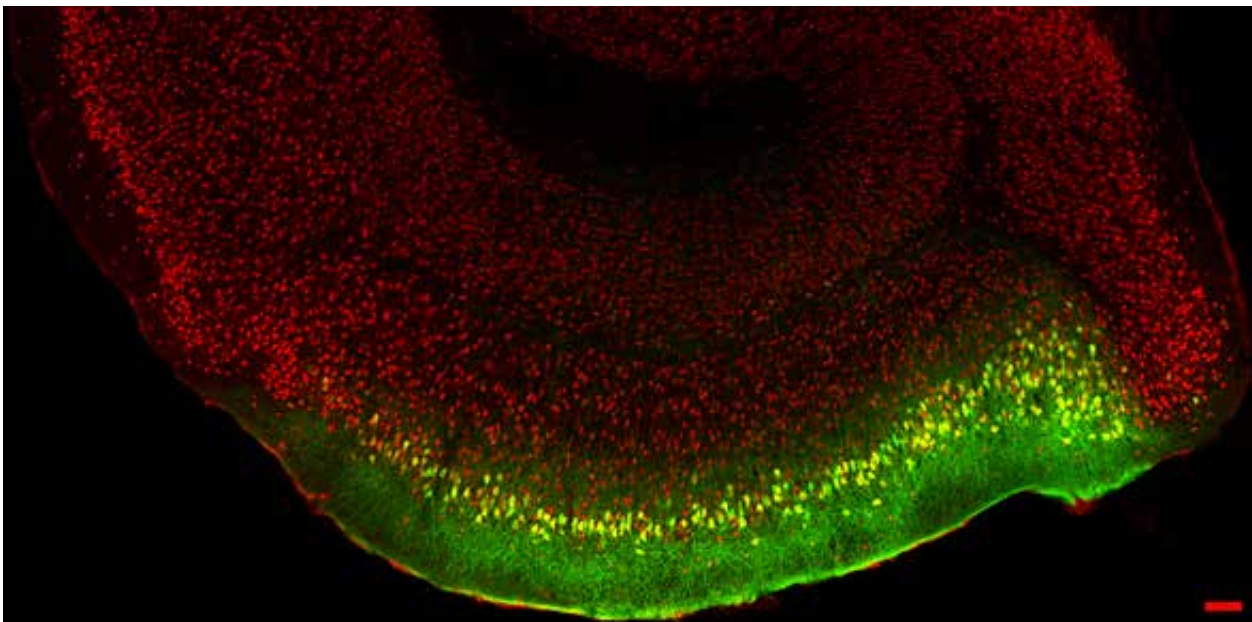


**KAY GASTERINGER**

Administrative Director of NORBRAIN  
Kavli Institute for  
Systems Neuroscience







Adeno-associated virus mediated transgene expression (yellow and green color) in medial entorhinal cortex of rat brain. A medial entorhinal cortex specific enhancer drives this region/cell type-specific gene expression. All the neurons are shown in red color. BioRxiv 606467. Image: Rajeevkumar R. Nair / Kavli Institute for Systems Neuroscience].

# *The Kavli Institute's Viral Vector Core*

Viruses are tiny parasitic particles that require a host cell to reproduce. Once a virus enters its host, it injects its DNA or RNA into the cell, effectively hijacking the cellular machinery of the host to reproduce itself.

It is hard to imagine viruses as being anything other than harmful because they usually don't receive favorable coverage in the news. The viruses we typically hear about are the ones that we are taught to actively avoid like polio, the flu, measles and small pox. We do everything in our power to keep these disease-carrying viruses at bay. We vaccinate ourselves, we sanitize surfaces, we wash our hands and we cover our coughs and sneezes.

However, these viruses can only be harmful if they are injecting their DNA or RNA into host cells. Without its own genetic material, the virus is essentially an empty cargo van. Recognizing that viruses are powerful vehicles for gene delivery, scientists have devised engineering strategies to remove the viral genes and replace them with genes of their own choosing. In this way, researchers can deliver selected genes to cells, to

treat genetic disease or to study biological processes in the lab. Researchers who engineer these viruses always take special precautions when doing so by ensuring that the process is conducted in sterile and confined environments.

## **LEARNING FROM VIRUSES**

The well-known Rabies virus is by nature a master of exploiting the biology of the host organism it infects. It jumps across the connections between neurons, but only backwards and upstream the neural chain of communication. These characteristics makes the rabies virus interesting for questions about how the brain is connected. If the virus could share its path through the nerve tissue, it would provide the scientist with a cartography over the circuits of the brain.

But how to make a virus work for researchers? And how to get a virus to communicate where it is at any given time? This is where Viral Vector Cores enter the story. Core Manager Rajeevkumar R. Nair produces tamed versions of viruses. For the rabies virus, the taming restricts its ability to jump across neural gaps.



Core Manager Rajeevkumar Raveendran Nair creates toolboxes of defanged viruses that makes chatting nerve cells glow. Photo: Rita Elmkvist Nilsen / Kavli Institute for Systems Neuroscience].

Thus, the tamed version of the virus is able to make only one single jump from the nerve cell it entered and over to its first upstream neighbours. The virus also carries with it a marker protein that causes infected neurons to glow when researchers shine a special light on them. This is how the researchers trick the virus into revealing which neurons are connected and chatting with each other.

#### VIRAL VECTOR CORE FACILITIES

Engineered viruses are made in viral vector core facilities around the world, from where they are shipped out to scientists, upon request for research purposes. Currently, Norwegian scientists pay significantly for production and shipping costs and wait long time to obtain viral tools from viral vector facilities abroad. The wait is extended further if a scientist requires a custom-made virus tailored to a specific research question. The quality of the viruses may also deteriorate due to less than optimal storage conditions during transport.

To address the need, Kavli recently established its own Viral Vector Core. The core is a non-profit facility that offers consultation, design and construction of a wide variety of high-quality viral vectors to supply for scientific research in Norway and abroad.

#### A TOOLBOX OF VIRUSES

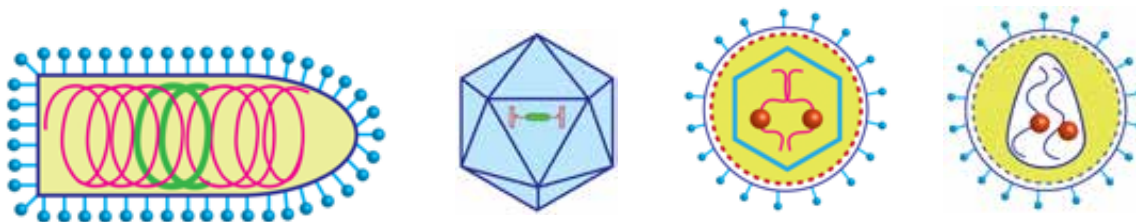
Whereas the rabies virus helps scientists map the neural circuitry of the brain, other research questions may call for other tools. Thanks to the great diversity of viruses nature offers us, scientists can choose the virus with the distinct characteristics that makes them best suited for their particular research question.

For example, Recombinant adeno-associated viruses (AAVs) are formerly infectious viruses now engineered into non-hazardous delivery vehicles. They are capable of long-term expression of chosen genes in the host cell, and they keep away from the host organism's own DNA. These characteristics make them ideal for gene therapy and many other research uses.

Moloney murine leukemia viruses only work in dividing cells, making them well-suited for research questions about dividing cells with no concerns of affecting the mature cell population. One could for example use them to see hippocampal neurogenesis in adult brain: dividing neurons in the brain's memory hub (also for studying the developing brain). The Lenti virus is conversely used by researchers for targeting non-dividing cells.

All these viral vectors are currently being engineered and produced at the Kavli Institute's Viral Vector Core for research. The facility is also ready to design and develop new, custom-made vector tools in collaboration with scientific partners.

For more information please visit Viral vector core's webpage and web shop featured at the Kavli Institute's website.



Illustrations of viruses, from the left: Rabies virus, Adeno-associated virus, Moloney murine leukemia virus and Lenti virus. Illustrations: Rajeevkumar R. Nair / Kavli Institute for Systems Neuroscience].



# Researcher Training

## MASTER OF SCIENCE IN NEUROSCIENCE

The Master of Science (MSc) in Neuroscience at NTNU provides an in-depth study of brain structure and function, reaching from the molecular to systems level. A central aim for students is to understand how neural systems may contribute to sensory experiences, thoughts, emotions and behaviour, and learn to adopt experimental methods to gain new knowledge in the field.

The MSc in Neuroscience is a two-year, full-time programme. The teaching includes lectures, laboratory work/demonstrations and supervised project work. The language of instruction is English. Both Norwegian and international students are welcome to apply for a seat.

## NEUROSCIENCE PHD PROGRAMME AT KISN

The objective of the Neuroscience PhD Programme is to provide theoretical and methodological training in neuroscience research and to contribute to increased understanding about basic biological principles for neural structure and activity and their importance for movement, sensory and autonomic functions, emotions, behaviour and cognitive processes in animals and human beings. Studies of normal function as well as elucidation of mechanisms for neurological and psychiatric illnesses are relevant. Through own research the students will learn to formulate and solve scientific questions and at the same time they will acquire basic skills and methods in parts of neuroscience.

PhD-candidates receive supervision from their principal investigator as well as from a relevant co-supervisor, either within or externally of the institute. They present at internal journal clubs, data clubs and are encouraged to submit abstract and present poster at national and inter-

national conferences. Some PhD students co-supervise MSc students.

## LIST OF PHD DEFENSES CARRIED OUT AT KISN IN 2018:

There were three dissertations in 2018: Tale L. Bjerknes (f), Tanja Wernle (f), Claudia Battistin (f).

There is currently 30 active PhD candidates and 14 post-docs at KISN.

## NORWEGIAN RESEARCH SCHOOL IN NEUROSCIENCE

The Norwegian Research School in Neuroscience (NRSN) is an initiative aimed to bring together the research training expertise in the field of neuroscience from NTNU, University of Oslo, University of Bergen, the Norwegian University of Life Sciences, and University of Tromsø.

By combining the specific expertise of the participating institutions, the NRSN aims to facilitate the PhD research training that will enable the next generation of Norwegian-trained neuroscientists to face the great challenges and opportunities in the field.

The NRSN is funded by the Norwegian Research Council, with an annual budget of around 3 Mill NOK. The NRSN board is composed of representatives from all partner institutions. The daily management is hosted by the Faculty of Medicine, NTNU, and the scientific director is a PI at KISN.

## THE MEDICAL STUDENT'S RESEARCH PROGRAMME (MSRP)

The Medical Student's Research Programme (MSRP) is a national research education and grant scheme for medical students who wish to carry out research in parallel with



their studies. The Medical Student's Research Programme is offered to a group of the medical students (10%), who are interested in medical research, and willing to do research besides their studies.

The students at the MSRP follow the ordinary medical study. In addition to this, they achieve an organized research education and get to perform their own research activity, which might be the beginning of a PhD.

The students are affiliated at the MSRP after second or third year of their medical study. To be a student at the MSRP involves that their regulated medical study syllabus will be prolonged by one year, from 6 to 7 years. The students at the MSRP are affiliated at the research programme in 4,5 years. In two semesters and two summers they are full time researchers, the rest of the time period they are part time researchers. Fulfilled MSRP will give a total of 120 ECTS, in addition to the ordinary study. Many of these students will subsequently enter a fast-track PhD program which takes an additional 2 years. At KISN we have had 1 MSRP students defending their PhD theses.

### POST-DOCTORAL

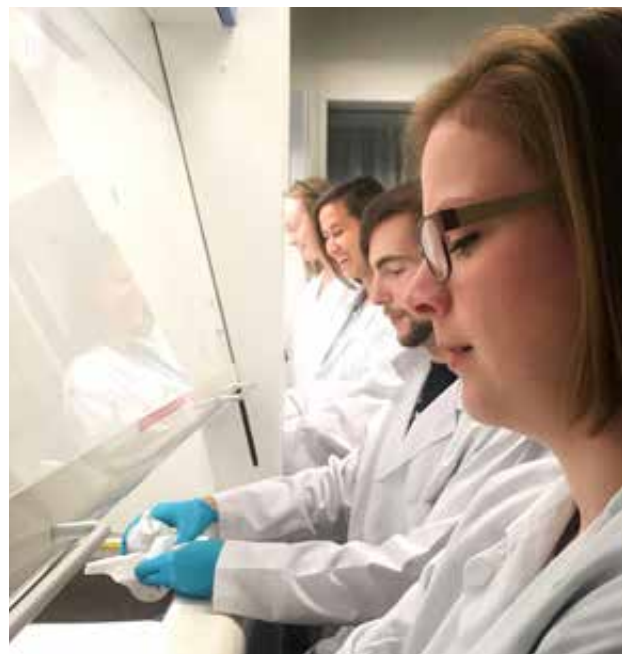
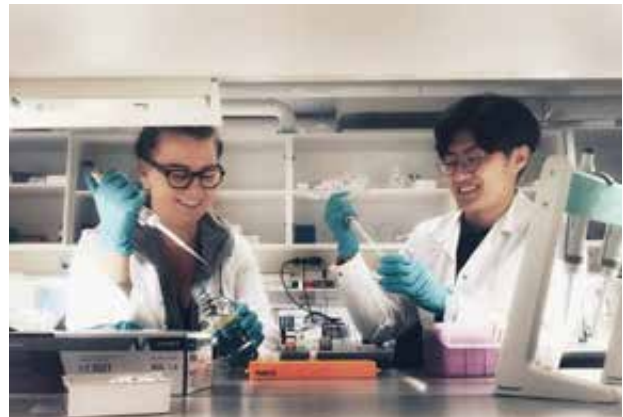
Post-doctoral researchers are employed at KISN based on either writing proposal for part-projects relevant of already funded research projects, or by applying for funding themselves within their research group. Access to infrastructure such as the national infrastructure scheme NORBRAIN (equipment), administrative and technical help is provided. Our post-docs are fully integrated with the institute and they receive supervision from their principal investigator as well as from a relevant co-supervisor, either within or externally of the institute. They present at internal journal clubs, data clubs and are encouraged to submit abstract and present poster at international conferences. Abroad stay and collaboration is highly encouraged and supported. Some will co-supervise PhD students or MSc students as part of their responsibilities.

### PRINCIPAL INVESTIGATOR

There are currently seven research groups at KISN with in total eight principal investigators. It is a requirement that new principal investigators have at least one mentor in the start-phase to give advice and support in the next step of their career. Young PIs now receive two mentors, one internal, familiar with the Norwegian University system, and one external.

### ALUMNI

Our alumni of trained researchers who has spent time and effort at KISN tells us we are succeeding in our ambition of being a nurturing and developing nest for young minds to grow and expand their work-environment to stay international. KISN recruits independently of nationality or origin. Since 2013 we have had more than 30 different nationalities represented among employee staff. For a given period, the international researcher is located in Trondheim, side by side with other internationals, learning, developing and exploring, before returning home, continuing their research careers as PhDs, post-doctors, or researchers, or



even forming their own research group and becoming principal investigators. Numerous PhD students and postdocs of KISN have achieved faculty and group-leader positions at internationally well-recognized universities and institutes such as Stanford University, University of California in San Diego, University of California at Irvine, University of Texas at Austin, the Max Planck for Brain Research in Frankfurt, and the University of Oslo, among others.

# *Grand Cross of St. Olav's Order*

*His Majesty King Harald of Norway has awarded May-Britt Moser and Edvard I. Moser The Royal Norwegian Order of St. Olav – Grand Cross, for their outstanding efforts in neuroscience research.*





- It is very rare that the Grand Cross of the Royal Norwegian Order of St. Olav is awarded other than royalty and Heads of State, said Chancellor Mette Tverli.



Chancellor Mette Tverli, Rector Gunnar Bovim, Edvard Moser, May-Britt Moser and Dean Björn Gustafsson.

On behalf of His Majesty the King, the Order was given to Moser and Moser in recognition of their research; their social involvement; and their commitment to animal welfare in research.



- This award is a recognition of the issues we are working on: firstly to figure out how the brain works, and secondly to acquire a public understanding of how research and especially basic science work.

*May-Britt Moser and Edvard I. Moser*



**THE GRAND CROSS**

The Grand Cross is the highest grade within the Order of Saint Olav, instituted by King Oscar I in 1847.

The Order of St. Olav rewards individuals for remarkable accomplishments on behalf of the country and humanity.

The Orders motto is Justice and Truth.

# *Facts*



**27**

nationalities represented in  
KISN's workforce of

**133**

employees

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**73**

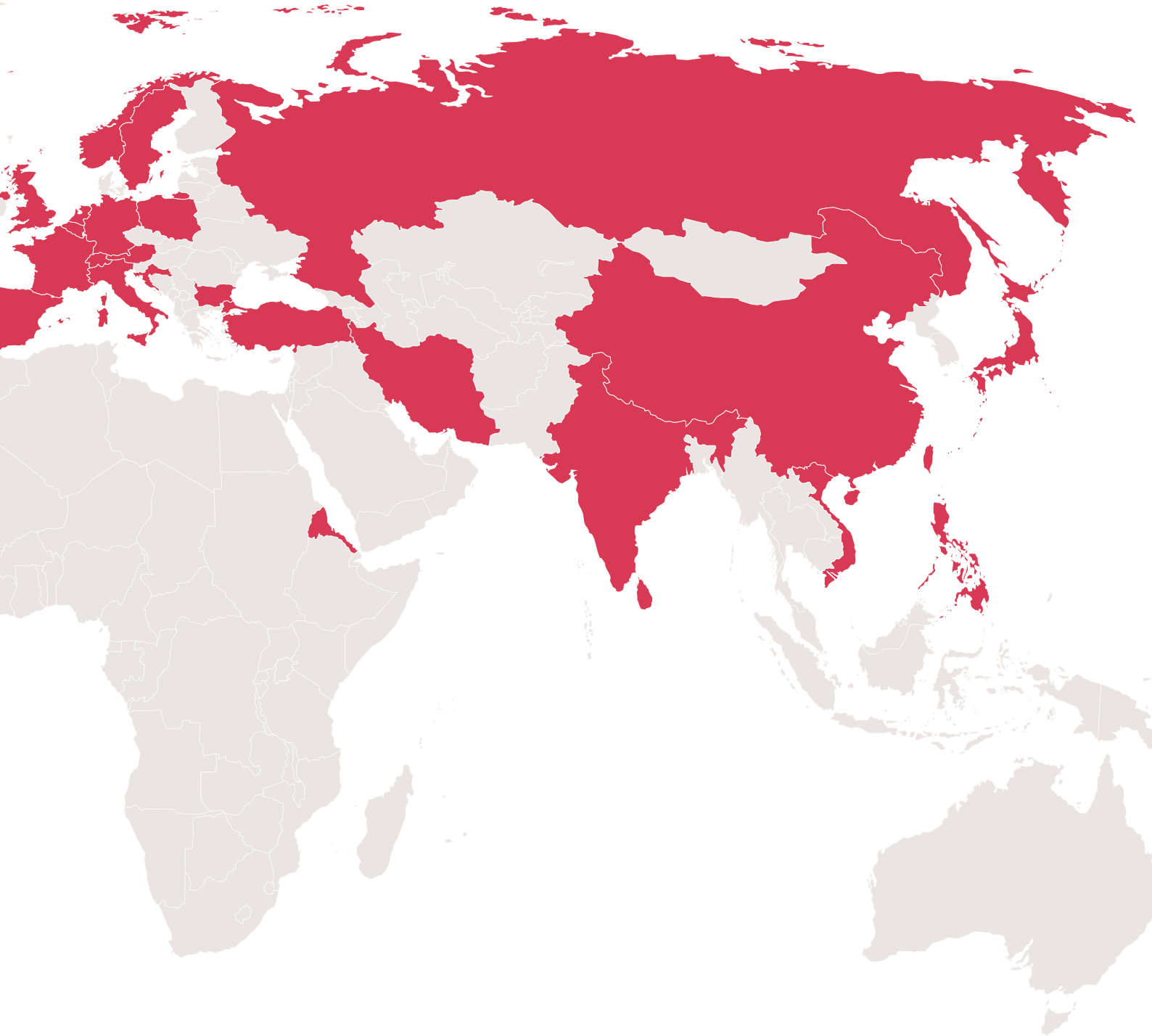
international employees

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**60**

Norwegian employees





# Annual accounts

## INCOME

Norwegian Research Council: Centre of Excellence	18 000 000
Norwegian Research Council: Other	14 616 000
International funding	32 040 000
Other public/private	9 822 000
Norwegian University of Science and Technology	65 918 000
<b>TOTAL INCOME</b>	<b>140 396 000</b>

## EXPENSES

Payroll and indirect expenses	105 322 784
Equipment	4 162 627
Other operating expenses	30 910 589
<b>TOTAL EXPENSES</b>	<b>140 396 000</b>

## ECONOMY MODEL

The Kavli Institute for System Neuroscience had in 2018 a budget of 142 MNOK. This budget consists of (i) the budget reported for the Center for Neural Computation (140 MNOK; copied above) and (ii) the NTNU internal budget and a few funding smaller sources not associated with the Centre of Excellence (2 MNOK).

The Kavli institute for System Neuroscience (142 MNOK) had in 2018 the following financing sources:

- Basic funding - NTNU (19MNOK)
- TFSR Trondheim Foundation for Scientific Research, NTNU (= Kavli Foundation endowment) (15MNOK)
- Funding from Ministry of Education and Research (16MNOK)
- Centre of Excellence - RCN (32MNOK)
- Other external funding - Research Council of Norway, EU, Central Norway Regional Health Authority, NTNU own financing, other private financing (60 MNOK)

### NTNU KAVLI INSTITUTT FOR SYSTEM NEUROSCIENCE – 142 MNOK



The left side of the diagram (blue boxes) show long-term basic funding of the institute (35% of the total funding), the right side (red and violet boxes) show competitive funding (65%). This funding distribution is untypical for a basic research institute and shows that our researchers are highly competitive on calls of the Research Council of Norway as well as the European Research Council. As an example, the eight group leaders at the institute had in 2018 five

active ERC projects and six projects within RCN's highly competitive program of Independent projects (FRIPRO). Yet the dependence on variable external funding sources, and the fact that there are few of these sources, puts the institute in a vulnerable financial situation that makes long-term planning difficult.

# 2018 Highlights

## HIGH IMPACT PUBLICATIONS

1. Høydal et al (2018). Object-vector coding in the medial entorhinal cortex. *BioRxiv (Nature, 2019)*

2. Mimica et al (2018). Efficient cortical coding of 3D posture in freely behaving rats. *Science*

3. Tsao et al. (2018). Integrating time from experience in the lateral entorhinal cortex. *Nature*

Bellmund et al (2018). Navigating cognition: Spatial codes for human thinking. *Science*

Bjerknes et al (2018). Path integration in place cells of developing rats. *Proc. Natl Acad. Sci. U.S.A.*

Blankvoort et al (2018) Marked Diversity of Unique Cortical Enhancers Enables Neuron-Specific Tools by Enhancer-Driven Gene Expression. *Current Biology*

Cubero et al (2018). Minimum description length codes are critical. *Entropy*

Gardner et al (2018). Correlation structure of grid cells is preserved during sleep. *BioRxiv (Nature Neuroscience, in press)*.

Grøntvedt et al (2018). Alzheimer's disease. *Current Biology*

Hovde et al (2018). Architecture and Organization of Mouse Posterior Parietal Cortex Relative to Extrastriate Areas. *European Journal of Neuroscience*

Ito et al (2018). Supramammillary nucleus modulates spike-time coordination in the prefrontal-thalamo-hippocampal circuit during navigation. *Neuron*

Lal et al (2018). Identification of a neuronal population in the telencephalon essential for fear conditioning in zebrafish. *BMC Biology*

Nau et al (2018). How the Brain's Navigation System Shapes Our Visual Experience. *Trends Cognitive Science*

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*If we didn't  
post about it,  
it didn't  
happen*

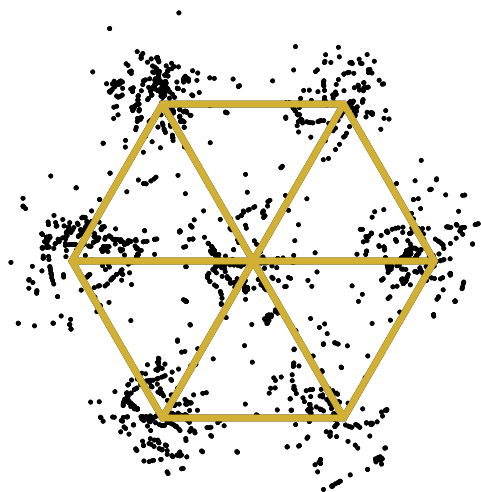
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