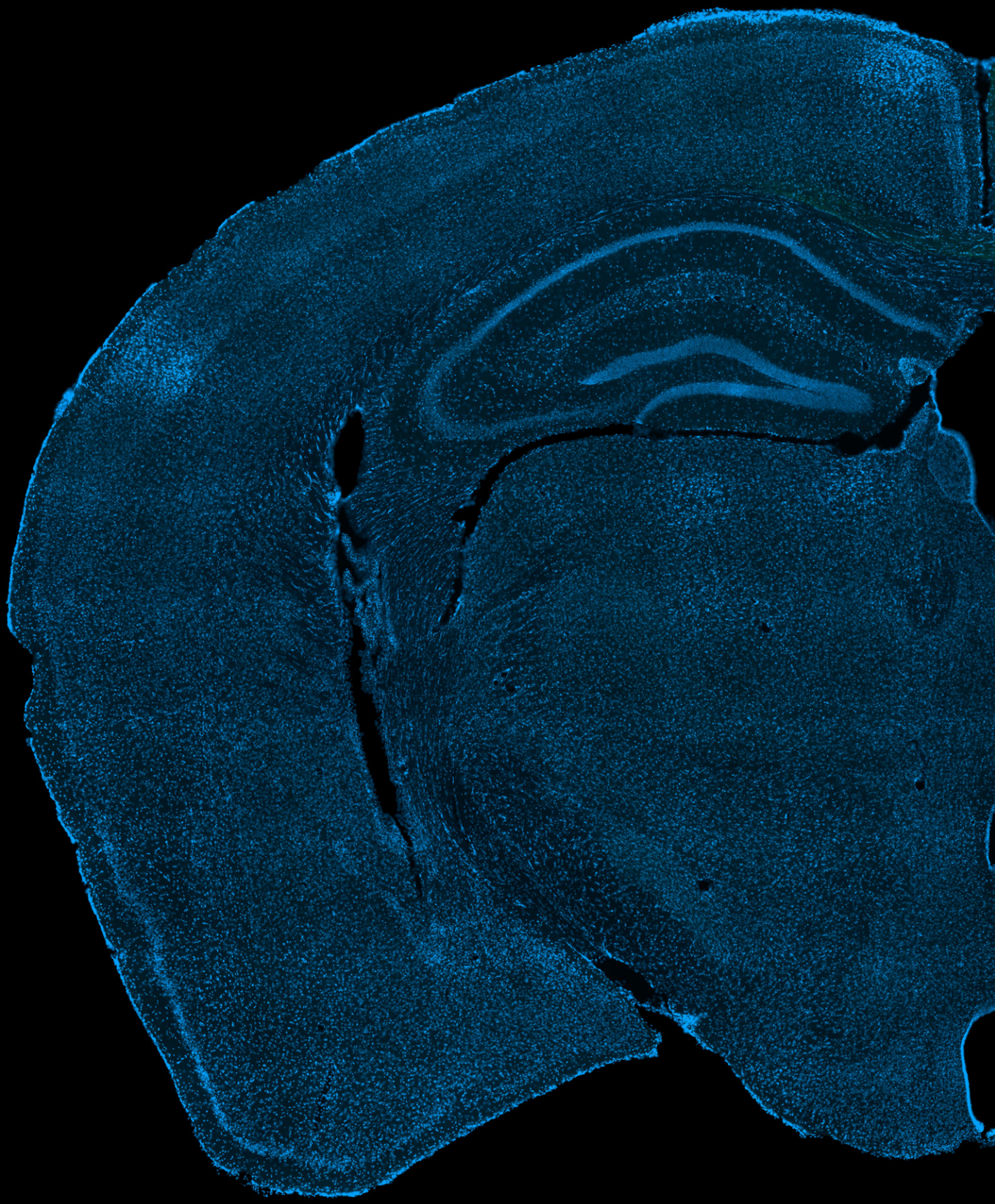
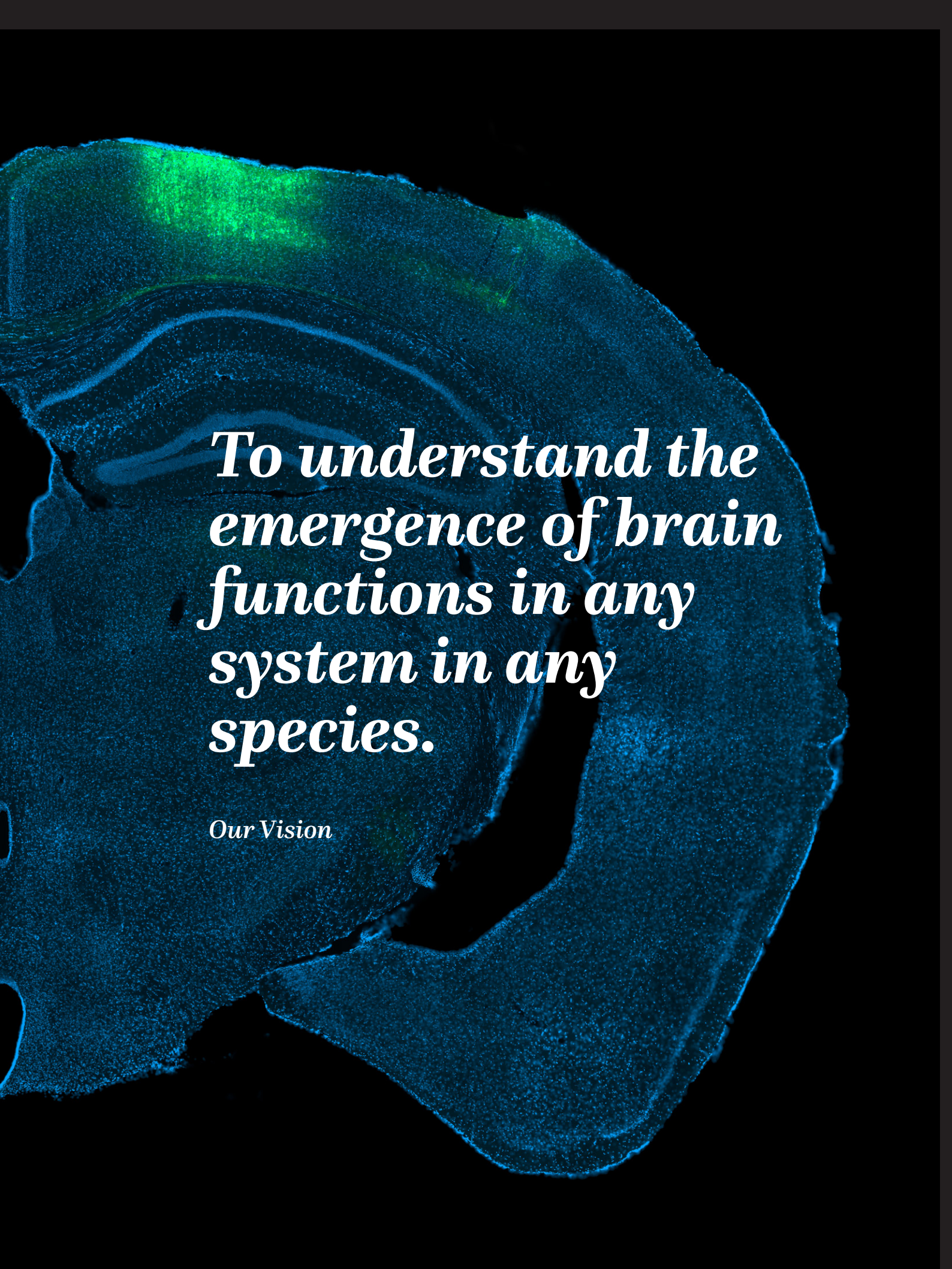
Annual Report | 2016

Kavli Institute for Systems Neuroscience and Centre for Neural Computation

Norwegian Centre of Excellence

NTNU
Norwegian University of Science and Technology





To understand the emergence of brain functions in any system in any species.

Our Vision

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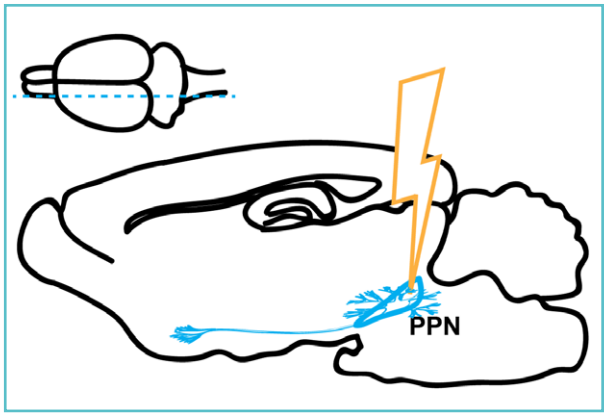

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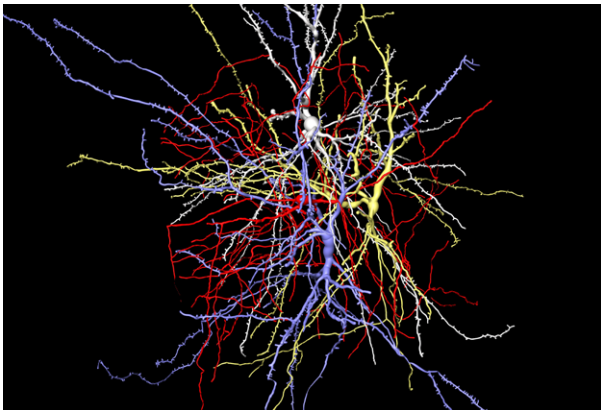

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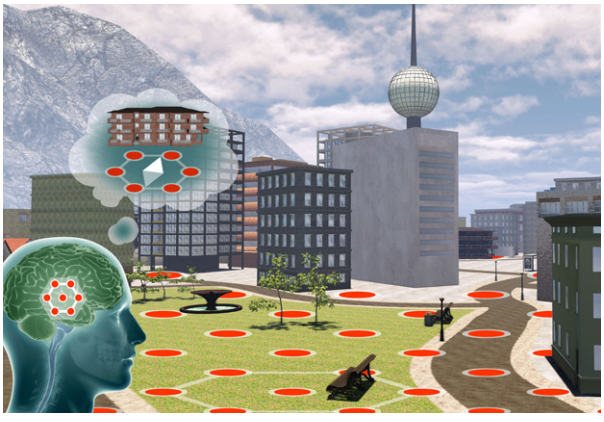

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May-Britt Moser

By embracing curiosity and encouraging creativity, Director May-Britt Moser leads the scientists at KI/CNC through high-gain, high-risk research projects.

The joy of discovery

SCIENTIFIC FRONTIERS

If you ever ask a scientist why they do what they do, pay close attention to the answer. No matter what the research topic you're likely to find that a scientist is motivated by a joy of discovery. The very process of posing a question into the unknown, testing that question and arriving a little bit closer to the truth is, for most scientists, an exciting journey. The unknown frontiers of science continue to shift over time, but each journey of discovery is marked by the same drive: to understand the world a little bit better. Today, a new scientific frontier pulls at adventuring hearts and inquisitive minds: the world of the brain. In just the past century, pioneering work in neuroscience has fundamentally changed the way we view ourselves. As our technologies grow more sophisticated and our datasets grow more complex, so too do our questions about the human mind.

How do we perceive the world around us and how do we navigate through that world? How do we keep track of where we are, where we are going, and how fast we move? How are social interactions represented in our brain? Why do we sometimes suffer at the hands of memory diseases that threaten the very core of who we are? Can a better understanding of the brain help us develop more efficient therapies for these diseases? These are just some of the questions scientists at the Kavli Institute for Neuroscience-Centre for Neural Computation (KI/CNC) are trying to answer, with Director May-Britt Moser at the helm.

Since its initial founding, the institute has been a paragon of scientific discovery and productivity for neuroscientists worldwide. The insights and discoveries that have been published in high-impact journals have pushed the boundaries of scientific understanding – and since the recent Nobel Prize win in 2014, the global attention on the research conducted at KI/CNC has only increased. Dr. Moser reflects on the prize as "a gift for the people who believed in us and supported us."

As the director of the KI/CNC, Dr. Moser works diligently to extend that spirit of support to the scientists who work at the institute. She also emphasizes a few other qualities: openness, cooperativity, risk-taking and creativity. Her spirit is one of adventure – not unlike the explorers of the uncharted waters in the early 15th century – and the joyful tone she sets for all the researchers is sincere but it also serves a purpose. "We know that if there are a lot of negative emotions in an environment," she says, "then creativity goes down. We want to have a brainstorming institute where people feel happy and passionate about their work."

ANIMAL CARE

The care in her leadership extends beyond the people, to the animals. To ensure the highest level of care, the animal caretakers at KI/CNC are selected based on their skill and, just as importantly, based on the caring attitude they have toward the animals. "We feel the responsibility to treat our animals and our co-workers the best that we can," says Dr. Moser. The animals at the institute are given large housing, and provided with lots of toys. As such, they grow and live their lives in "enriched" environments – well above the standard minimum laboratory requirements. Because of this, explains Dr. Moser, the animals are also smarter and learn complicated tasks quickly.

It is also important to recognize when certain research questions can be answered just as well (if not better!) using animals lower on the phylogenetic tree, such as a fish or a fly. In 2015, Dr. Emre Yaksi, a leading sensory physiologist joined the KI/CNC as a group leader, to continue his research on how cellular networks generate psychological functions using zebrafish. Since they are transparent creatures and have a relatively small number of neurons, it is possible to visualize the entire brain. The team can then pursue questions about brain computation that would not be tractable in a rat or mouse.

THE HUMAN IMPACT

In fact, in just the past couple of years, the institute has greatly increased its breadth of research methods: "We have expanded down from rodents to zebrafish, and now we are going to expand up to humans, hopefully to people with dementia," says Dr. Moser. In the autumn of 2016, Dr. Christian Doeller, a human researcher joined the KI/

CNC. Prior to joining the team as a group leader in Trondheim, Dr. Doeller used functional magnetic resonance imaging (fMRI) – a brain scanning technique – to identify physiological predictors of disease in individuals who were asymptomatic at a young age, but went on to develop Alzheimer's disease later in life.

Indeed, many group leaders at the KI/CNC have joined forces to obtain a clearer picture of how and where Alzheimer's first starts in the brain. Drs. Cliff Kentros and Menno Witter, for example, are combining their respective molecular, physiological and neuroanatomical expertise to determine whether a specific group of cells, in a very specific part of the brain, contribute to the emergence and development of the disease.

HATCHING CENTRE FOR EXCELLENCE

As the Director, and a research group leader herself, Dr. Moser has a lot to think about: the research questions, training the next generation of scientists and ensuring that staff feel supported and connected, and setting a tone of openness in research. It seems like a lot to pull off successfully – and she'll be the first to tell you that she doesn't go it alone. Citing the excellent group of individuals she works with, Dr. Moser shares: "It is really a luxury situation to have so many skilled scientists at the centre – both at the group leader level but also within each of the groups. The post docs, students and technicians are fantastic and so skilled. Our supportive group – the administration – does more than expected to support the activity at the centre. We are truly spoiled with excellent quality at all levels."

Across all these levels, people at the KI/CNC come together often, in both formal and informal settings. "We have a tiny kitchen," says Dr. Moser, "where people come just to have a cup of coffee, and that promotes interactions between different groups." This is one of many examples which illustrates the spontaneous spirit of collaboration that emerges at the institute. On a more formal note, group leaders meet every Tuesday to update each other on their research, to help each other think about their work, and to assess the potential for collaboration between projects.

Another goal of the institute, says Dr. Moser, is to make the institute a "hatching place of excellence for developing scientists. We want to be a showcase for excellent science and, at the same time, we want to train people to have excellent attitudes toward science and toward how they treat animals and people. Our slogan is: *Excellent science through happy people and happy animals."* By encouraging inquisitiveness and creativity, explains Dr. Moser, trainees grow into independent investigators who ask impactful scientific questions throughout their career. By emphasizing care toward colleagues and research animals, she hopes to grow a cadre of scientists who will disseminate the centre's values of excellent science, throughout the world.

The institute provides graduate students and post-docs several training opportunities for development. On Thursdays, for example, the KI/CNC hosts a weekly "Journal Club" in which students present and discuss publications from leading scientific journals. These regular and interactive discussions encourage students to learn from already-published research, to deepen their understanding of the strengths and limitations of current techniques, and to craft their own research questions in a thoughtful and impactful manner.

On Wednesdays, the KI/CNC hosts "Data Club" meetings in which students share their data with the community of scientists within the institute. By bringing their unfinished work to the table for discussion, they are challenged to think deeply and critically about their work within an open and supportive environment. To encourage independent thinking and direct interaction with the scientific community outside of the KI/CNC, the students are also given the opportunity to invite guest speakers to the institute.

THE KI/CNC VISION

In the following pages, you can read more about the latest discoveries that have come from the research groups at KI/CNC and, at the same time, get a sense for the values that permeate the institute.

When group leaders are building a lab group, diversity is emphasized and learning from others is encouraged. When the current tools are insufficient to answer the research questions at hand, commitment to excellence is not sacrificed. Instead, time and energy are spent creating tools in-house, ultimately setting a higher standard for the entire field. When someone upstairs can help with the research that is ongoing downstairs, bright minds do not sit apart from each other; they meet in collaboration. When new questions emerge, curiosity and play are embraced, and whenever possible, the impact of research findings on human life and health is considered carefully and wholeheartedly. Each of the stories that follow echo a different piece of Dr. Moser's larger vision.

"Our vision," says Dr. Moser, "is to understand how brain cells work together in complex networks to generate higher mental functions. As a group, we are always aiming to conduct original, high risk – high gain research." Reflecting on the team that makes this research possible she shares: "we have an institute where it's important for our staff, as we work together, to hold a vision higher than ourselves. That means people are eager to help each other. When visitors come, see our team and witness their skills, I think they see that it's a goldmine of scientific discovery."

Organisational chart

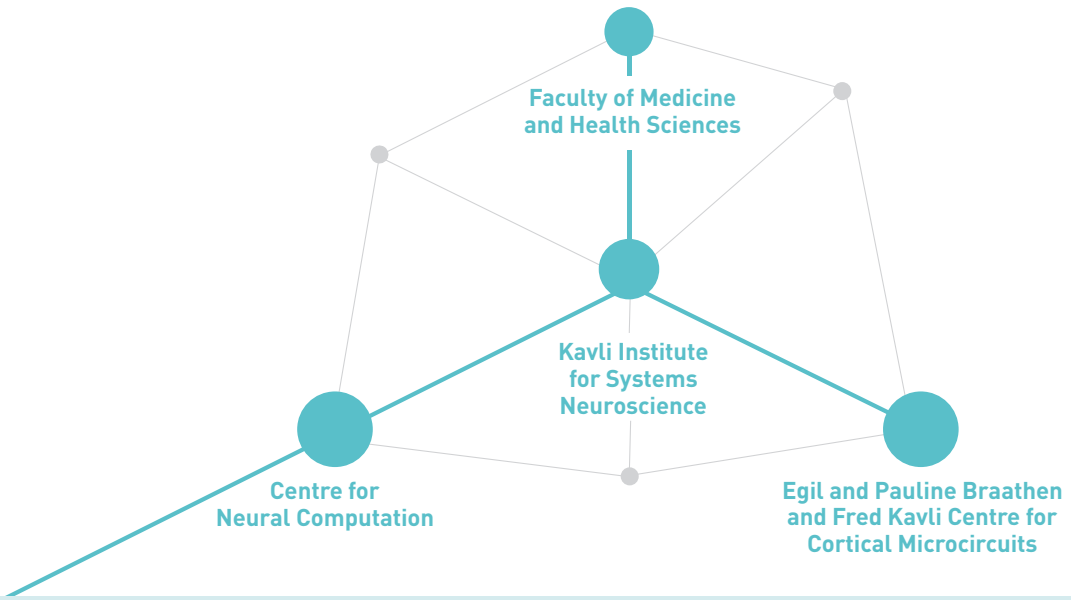
GROUP LEADERS

MAY-BRITT MOSER
Professor
Moser Lab

EDVARD MOSER
Professor
Moser Lab

MENNO WITTER
Professor
Witter Lab

CHRISTIAN DOELLER
Professor
Doeller Lab



CLIFFORD KENTROS
Professor
Kentros Lab

JONATHAN WHITLOCK
Researcher
Whitlock lab

YASSER ROUDI
Professor
Roudi Lab

EMRE YAKSI
Associate professor
Yaksi Lab

Navigating through Space

To successfully navigate through space, you need to know where you are, where you are going, and how you plan on getting there.

AN ENVIRONMENTAL ANCHOR

Imagine how difficult it would be to navigate through the streets of your city if buildings were moving around all the time. In order to navigate to your home, your car, or doctor's office successfully, you need a stable environment to move through. You need some way to anchor to the environment so that you know where you are in reference to buildings, walls, and other cues in your external world.

It turns out this isn't an entirely straightforward problem to solve. However due to the stable "grid-like" firing pattern of grid cells, it was originally proposed that these cells might play a critical role in the anchoring process. In early 2015, Stensola et al, discovered a specific mechanism that may underlie this anchoring process. The answer, it seems, lies in a specific number: 7.5 degrees. Dr. Edvard Moser elaborates: "it's extremely specific, there's usually not that much precision in our field."

It turns out that 7.5 degrees is the angle which allows animals to distinguish boundaries of different orientation. This wasn't immediately apparent, because the Stensolas had already shown that grid cells fire in with a symmetrical distribution around the cardinal axes of the test environment, but looking more closely the research team realized there was a slight (7.5 degree) offset from these axis. Even more interestingly, this offset only appeared when animals were placed in a familiar environment, indicating that this effect developed as a result of an animal's experience.

Dr. Moser explains that since grid cells are effected by the boundaries in the environment, it is likely that border cells (cells that are selectively active at borders or edges in an environment) may be influencing grid cells. In the future, he hopes to manipulate these border cells using optogenetics (a technique that allows selective turning "on" or "off" of cells) to see what effect, if any, this may have on grid cells.

PLANNING MOVEMENTS THROUGH SPACE

In order to successfully navigate through space, you need two pieces of information: where you are *currently* and where you are *planning on going* next. While we know that the former relies on activity from the CA1 region of the hippocampus – where "place cells" signal an animal's current location, less is known about how the hippocampus receives any information about planned movements through space.

A recent study from the Moser group, conducted by Dr. Hirisoho Ito, shed some light on how this information reaches the hippocampus. According to Dr. Moser "the prefrontal cortex (PFC) is a structure that helps in planning the next move". However, there are no direct connections from the PFC to the hippocampus. There is, however, an indirect connection *via an intermediary structure:* the nucleus reuiniens – a midline structure of the thalamus.

Due to this circuitry (PFC – nucleus reuniens – hippocampus), Ito decided to investigate what happens to the hippocampal representation of planned movements if the nucleus reuniens was disrupted. Specifically, he inactivated this region using optogenetics, a temporally precise method which silences active cells using laser light and with ibotenic acid, a common way to inactivate cells with a drug.

He then set up a T-shaped-maze to test the effect of NR disruption on navigation behavior. Rats were trained on the following task: run up the arm of the T-maze, and when

at the stem/choice point: choose the correct arm (left or right) for a food reward. The location of the food reward changes on every trial, such that the rats are trained to alternate between the left and right arms. If the food reward is on the left arm in trial 1, then it will be in the right arm on trial 2, and so on. This T-maze task is a test of navigation because it requires the animal to hold on to information about where it is currently – and where it was on the previous trial – so that it can accurately plan its future movements to the correct arm.

Consistent with the prediction that the PFC is required for the hippocampus to properly signal the *"where am I headed next?"* question, Ito found inactivating nucleus reuniens resulted in a disruption of the loop (PFC – nucleus reuniens – hippocampus) and ultimately in the loss of the hippocampal navigation signal.

RATS IN CARS: THE FLINTSTONE EXPERIMENT

While scientists have wondered about the existence of cells that code specifically for speed, or *speed cells*, for over 20 years, Dr. Edvard Moser says their team remained "open to the possibility that the code could be a mixed code where one particular cell correlates with both speed and many other things." In other words: you don't necessarily need *speed cells* to successfully encode speed. It's possible that the signal is embedded in the neural activity some other way.

To test this question directly, the team placed rats in floorless box cars, on top of a moving linear track, and recorded from the rat brain. At KI/CNC, this experiment is referred to as "the Flintstone experiment". As the rats traversed the 4-meter-long track at various different speeds, an interesting pattern emerged: a subset of the recorded cells seemed to respond preferentially to changing speeds; the faster the speed of travel along the track, the higher the firing rate of the associated speed cells in the rat brain. Scientists refer to this kind of direct relationship between two variables as "linear" and, Dr. Moser shares: "it was extremely gratifying to find that there are cells that linearly encode the speed of the animal."

To make sure that this finding wasn't artificially induced by forcing the rats to "drive," the team also allowed the rats to move spontaneously (i.e. not at pre-determined speeds) and found that the speed cells still showed up. Whether the experimenter or the rat decides the speed of travel is irrelevant – either way, the brain contains cells that code specifically for instantaneous speed.

Currently, Dr. Moser's research team is working on figuring out where exactly in the brain the incoming speed signal to these cells is coming from.

LOOKING FORWARD: A WHOLE NEW WORLD

In addition to unearthing an impressive series of discoveries, the team at KI/CNC has acquired a few key pieces of equipment which will allow them to continue expanding the scope of their research. For example, in 2015, the team acquired a 2-photon microscope – unique in its ability to obtain high-resolution images. Additionally, Dr. Edvard Moser explains that this microscope, "opens a whole new world because you can suddenly image many hundreds of cells as well as the topography of functionally characterized cells." This stands in contrast to traditional imaging with electrodes, where scientists typically take their best guess about where the cells are, relative to each other.

Back row from left: Klaus Jenssen, Kyrre Haugen, Ann Mari Amundsgård, Ailin Moser, Abraham Zelalem Vollan, Torstein Slettmoen, Edvard Moser, Tanja Wernle, May-Britt Moser, Torgeir Waaga, Tale Litleré Bjerknes, Richard Gardner, Valentin Normand, Tor Grønbech, Emilie Ranheim Skytøen. Front row from left: Jarle Bruseth, Anne Nagelhus, Øyvind Arne Høydal, Endre Kråkvik, Alice Burøy, Nouk Tanke, Miguel Carvalho, Horst Obenhaus, Debora Ledergerber, David Clayton Rowland, Vadim Frolow, Flavio Donato, Jørgen Sugar and Ingvild Ulsaker Kruge. Qichen Cao, Nenitha Dagslott, Diana Deca, Martin Hägglund, Kei Igarashi, Ragnhild Irene Jacobsen, Li Lu, Bjarte Bye Løfaldli, Chenglin Miao, Maria Mørreaunet, Tor Stensola and Jing Ye are also in the group, but were not present when the photo was taken.

Additionally, you can label specific types of cells, image them, and compare them to other cells in the network allowing researchers to "study the interaction of complex networks in a way that is quite novel," says Dr. Moser. The high resolution afforded by the 2-photon microscope may even provide the team with the ability to visualize behaviour-related activity in parts of the neurons that weren't easily visualized in the past.

While the 2-photon microscope affords the team many new advantages, it does come with some limitations. The largest limitation: the imaging works only if the animals are head-fixed. What this means is that the microscope is attached to a non-moving arm, which is attached to the head, while the animal is allowed to run freely on a rotating Styrofoam ball.

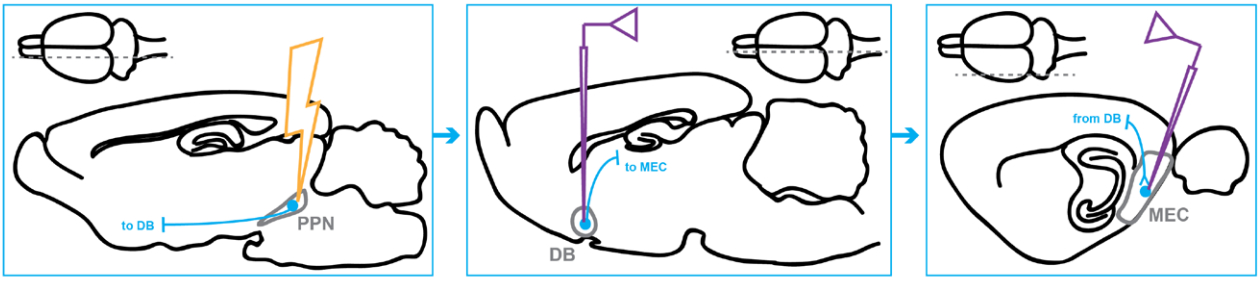
Specifically, this restriction of movement results in a loss of vestibular information – the signal that your brain receives when you (or a rat) navigates through an environment to stay balanced. Interestingly, Dr. Moser shares, when the rats are able to navigate freely on a linear track, place fields show up just fine. However, "at the moment, these virtual environments do not produce place cells or grid cells in two-dimensional space," Dr. Moser says. Well, they do – but they fire everywhere and don't carry any specific information. Presumably this is due to the loss of vestibular information.

When I ask Dr. Moser if there is a way to "trick" the brain into thinking it is receiving vestibular input, he agrees that it might work in theory – and is probably one solution to the problem – but this would require figuring out how to calibrate a vestibular input that is biologically relevant. "We haven't succeeded yet but it's an important problem, so we are still trying and hope we manage to solve it," he says earnestly.

Somehow, I have no doubt that they will.

Tracking down the speed signal

How does your brain keep track of how fast you're moving? Drs. May-Britt and Edvard Moser and their team have identified a brain circuit that may be responsible.



Sagittal brain sections illustrating the functional circuitry identified by Nouk Tanke and Miguel Murteira de Carvalho during their search for the speed cell signal. ***The circuit:*** *A nucleus in the brainstem (PPN) connects to the MEC (where speed signal was first discovered) via a pathway through the DB in the basal forebrain.* ***The protocol:*** *Nouk and Miguel stimulated the PPN with a laser light (yellow lightning bolt) and simultaneously recorded response signals from the DB and the MEC.*

Since the discovery of speed cells in the medial entorhinal cortex (MEC), the Moser team has been wondering: *where, in the brain, do these speed signals originate exactly?* To answer this question, post-doctoral researchers Nouk Tanke and Miguel Murteira de Carvalho began their search by looking for direct connections between the brainstem, specifically the PPN (short for "penduncolopontine nucleus") and the MEC. Since previous research has shown the PPN is important for locomotion – the ability to move from one place to another – it seemed a likely suspect.

In their search, no direct connection between these two regions was identified. However, they did find an indirect connection; a pathway from the PPN to the MEC, coursing through an area of the basal forebrain known as the *diagonal band of Broca* (DB). Having then identified the physical circuit, Nouk and Miguel set out to determine whether these brain regions were also functionally connected (i.e. does activity in one region affect activity in another?). To investigate this circuit (illustrated above), they implemented a dual approach: electrode recordings and optogenetics.

Optogenetics is a technique that makes cells responsive to light. Using this tool, researchers can turn neurons "on" or "off" by stimulating them with a laser and they can then observe how this affects the neural circuit being studied. By combining optogenetics with standard electrode recording procedures, it is possible to simultaneously (1) stimulate (turn on/off) cells in a specific brain region and (2) record from one or more connected brain areas to study the effect of this stimulation. If the areas are functionally connected, then stimulating one brain region should change the firing patterns of neurons in the connected brain area(s). On a first step Nouk and Miguel used electrode recordings and identified speed cells in PPN and DB, confirming that such cells exist in MEC. Subsequently, they optogenetically stimulated the PPN (illustrated by the yellow lightning bolt) and simultaneously recorded from the MEC and DB (illustrated by the purple recording electrodes). They observed a change in neuronal firing rate of speed cells in both the DB and the MEC, in response to the light stimulation. This, explains Nouk, demonstrates "a clear functional connection between the three areas.". Moreover, it shows how the PPN can modulate the activity

of speed cells in both DB and MEC, supporting its relevance for how the brain encodes speed.

While this data fell in line with their predictions, to some degree, it was still a gratifying result, explains Miguel. "We didn't know what to expect with the optogenetic experiment and it was amazing that the speed cells responded to the light pulses," he says. Having established this functional connection, Nouk and Miguel are now looking forward to investigating how (and if) this circuit may be interacting with grid cells in the MEC. For now, the identification of the circuit has brought the team one step closer to better understanding how self-motion cues, such as speed, helps us navigate through our environment.

Becoming a navigator

The short story of how our ability to navigate develops in the brain, featuring a game of Chinese whispers in a vulnerable network, and a clockwork cell dancing to its own beat.

FROM NEURAL CIRCUITS TO MENTAL FUNCTION

During brain development, neurons have to be in contact with each other. They do this by extending their long axons until they are in touch with the other neurons they need to communicate with. Connected neurons form a circuit for communication by chemical and electrical signals. Specialized neural circuits form the structural basis from which the brain's many functional capacities arise.
Understanding how these neural circuits develop and organize into functional networks, can give crucial information for identifying developmental origins of neuropsychiatric illnesses, and in turn developing effective treatments.

A group of researchers consisting of postdocs Flavio Donato and Irene Jacobsen, and the professors May-Britt and Edvard Moser, recently discovered how neurons in the higher mental cortices organize into a functional circuit. The neural circuits in the entorhinal-hippocampal network of the brain, which enable us to navigate in our environment, was their point of departure.

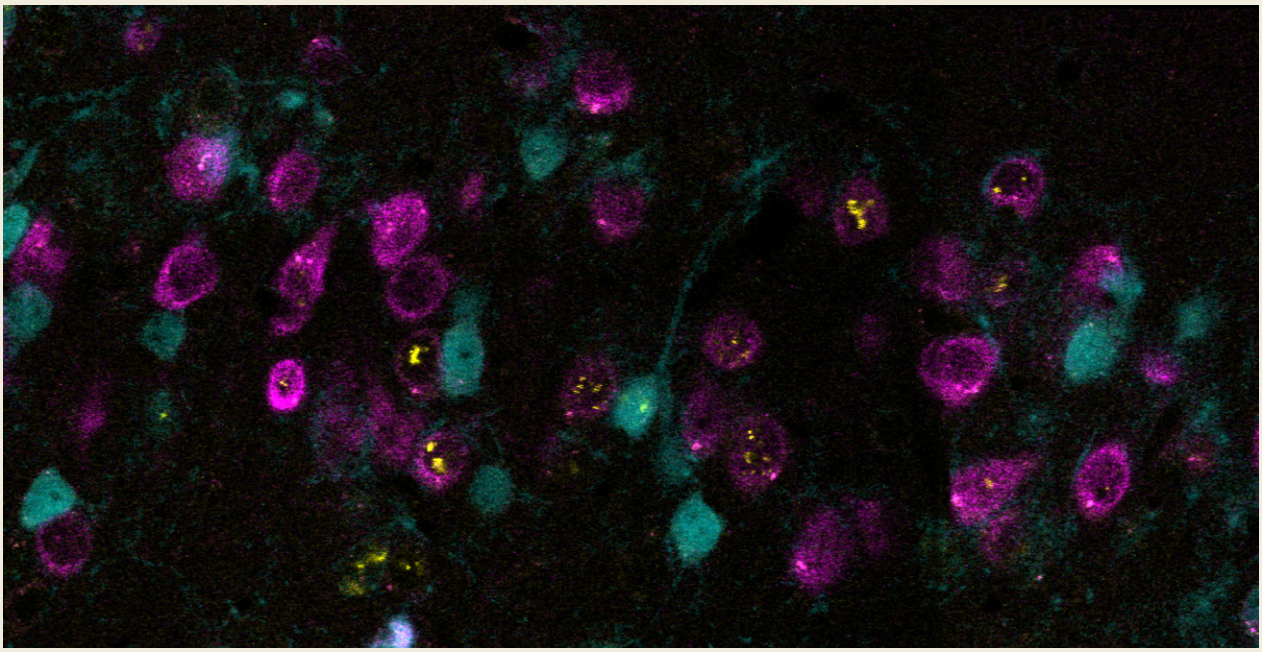
"If you have a machine and you don't know what it does or how it does it, you pick it apart" Flavio explains. "Much of what we know in neuroscience is learned by reduction. But the analogy between the machine and the brain ends there. With a machine, you can re-build and make it work again. You cannot do this with the brain. The only time neural circuits are put together, is during development. We study the development to learn how the brain does what it does."

What the researchers found in this developing circuit was a unidirectional cascade of signals where every cell is dependent on input from the cell uphill from them in the developmental hierarchy. Their method of investigation included a pharmacogenetic tool for muting the communication in one selected cell population at a time, followed by specific markers that identify cells according to type and level of maturation. This strategy would be the equivalence of removing one domino piece at a time from a toppling chain in order to see where in the hierarchy that specific piece is located. All cells (or domino pieces) in the cascade below the one that was silenced (or removed), would not mature (or topple).

This raises the question of who is at the top of the chain, the first mover, and who or what moves him? The only cell type that the researchers could not stop from maturing were the stellate cells. This told them that the stellate cells had to be first mover, the ones that underpin the entire activity throughout the rest of the neural circuit. There must be an intrinsic drive to the stellate cell that enables it to march by its own beat regardless of what goes on in its environment.

"For me the most fascinating discovery is not the one that closes the question, but the one that opens up for a whole new perspective of understanding things", says Flavio.

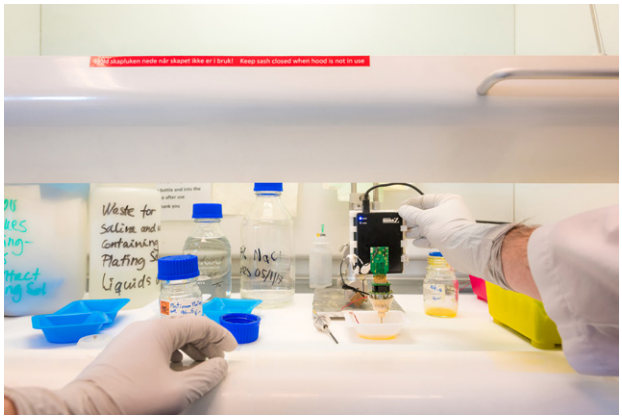
The processes the group uncovered have never before been recorded in the cortices for higher cognitive functions. Their discovery opens an entirely new research field – the development of functional circuits in the non-sensory cortices. They now have valuable first knowledge about the developmental process. And they know that the cascade through the network resembles the connectivity in the adult brain. "Some researchers are studying the function, but not the birth and emergence of connections, others study the birth but not the function" Flavio explains. "At KI/CNC we are now able to follow the developmental process from neural birth to function. This is a matter of bridging two parts of a process that really only makes sense if you see it as a whole."

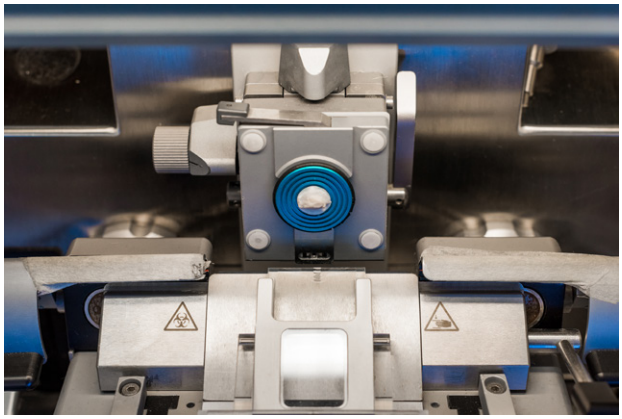


Neurons in layer 2 of the medial entorhinal cortex (MEC). Yellow labelling indicates newly born neurons (BrdU, a thymidine analogue). Magenta labelling indicates stellate cells (immunodetection of reelin). Cyan labelling indicates pyramidal cells (calbindin). Magenta + cyan labelling in the cell body and yellow spots in the nucleus identifies cohorts of neurons born at the time of BrdU labelling. The picture is an optical slice (z=2µm) acquired with a confocal microscope (Zeiss LSM 880, 40× magnification).

Flavio Donato (holding mouse) and Edvard Moser.

ELEMENTS OF LABORATORY LIFE, MOSER LAB



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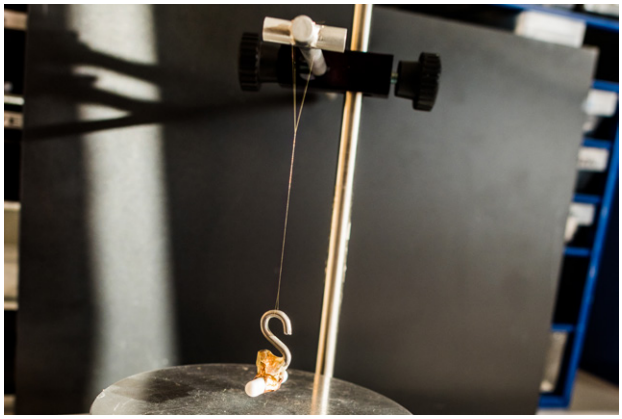
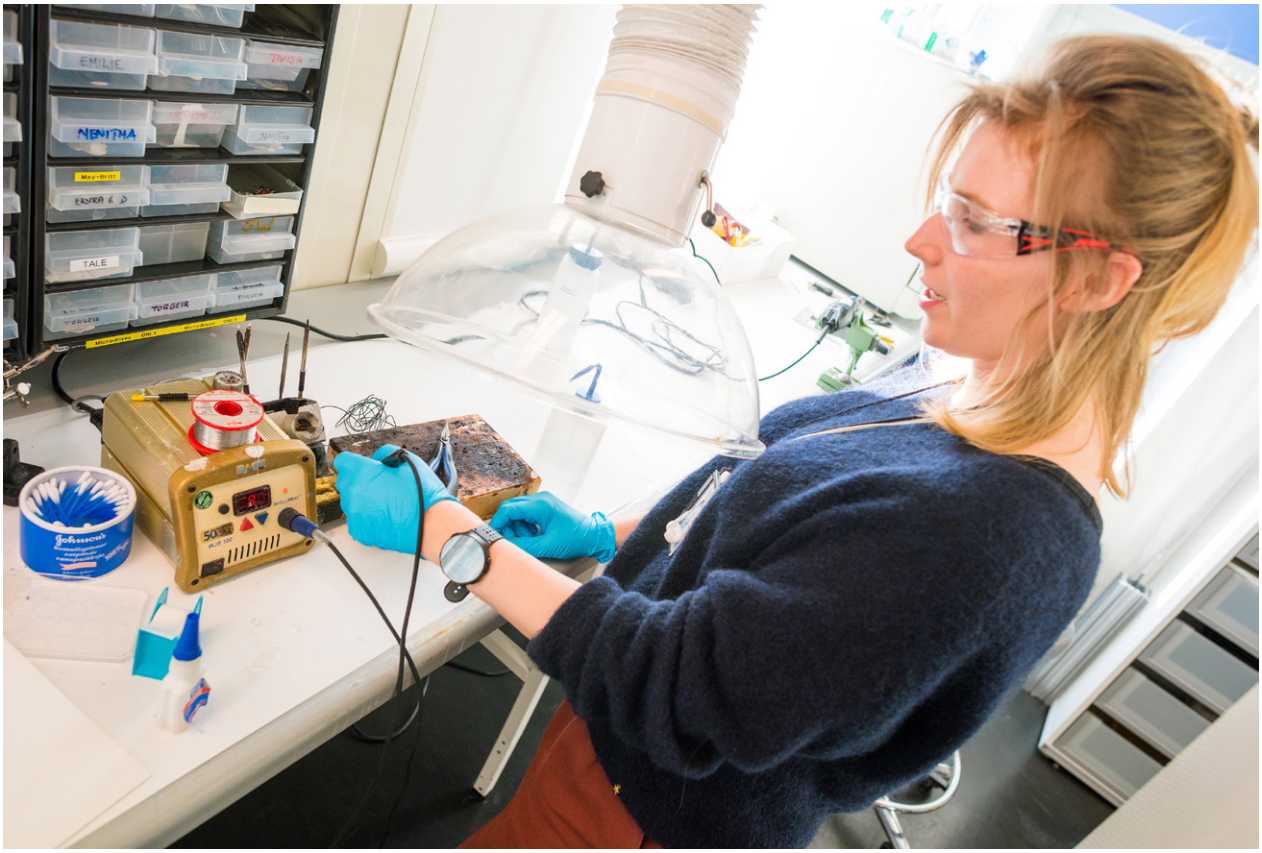



EMILIE
NENITHA
TALE
TORGEIR
Johnsons

Charting the Unknown Terrain

The brain is a structurally diverse landscape. The relationship between structure and function lies at the heart of Dr. Menno Witter's research.

As a functional neuroanatomist, it's fair to think of Dr. Menno Witter as the reliable neural cartographer of the KI/CNC team. In his lab, no project can truly begin without first identifying exactly where you are in the brain – and all other investigators at the center know to follow his lead and take advantage of his expertise. Most neuroscientists rely on standard atlases which are, in Witter's view, not accurate enough. Not only that, but current atlases visualize brains in no more than two standard planes. To get around this, Witter's team has developed its own brain atlases, which are registered in a standardized, virtual space. It is then possible to use this tool to "slice" or visualize the brain at any angle which works best for the analysis. In addition, this tool is shareable. To this end, Dr. Witter says, "you can now hand over that entire dataset to somebody else who can upload his or her data and then you have more data, which hopefully informs the analysis."

Creating useful tools is an important aim of the lab, but it's not the main focus. Dr. Witter's overall research question is about linking brain structure to brain function. "I believe that if neural networks have certain structural features, we might be able to generate functional concepts that can subsequently be tested," he says. To do this, Dr. Witter begins first by obtaining an image of the entire brain, then labeling convergent connections and lastly, using tools and techniques to test the functionality of these connections.

One of these tools is Optogenetics. This is a technique that allows neurons to become light sensitive, and thus responsive to manipulations with laser light. Using this tool, you can "turn on" or "turn off" neurons – and because of their connections to other brain regions, it is then possible to track what effect turning on/off cells has on the rest of the network. This is one way to confirm that areas which are physically connected are also functionally connected. Another tool, quadruple recording, allows researchers to record activity from four cells at the same time, greatly speeding up data collection.

INVESTIGATING ALZHEIMER'S DISEASE

The entorhinal cortex is a brain region of particular interest to the Witter lab. "I chose to study the entorhinal cortex because there seems to be two functional parts," says Dr. Witter. As such, it's a great place to begin exploring the relationships between structure and function. In addition, there are some very important findings about the entorhinal cortex, which are motivating the lab's research on Alzheimer's disease.

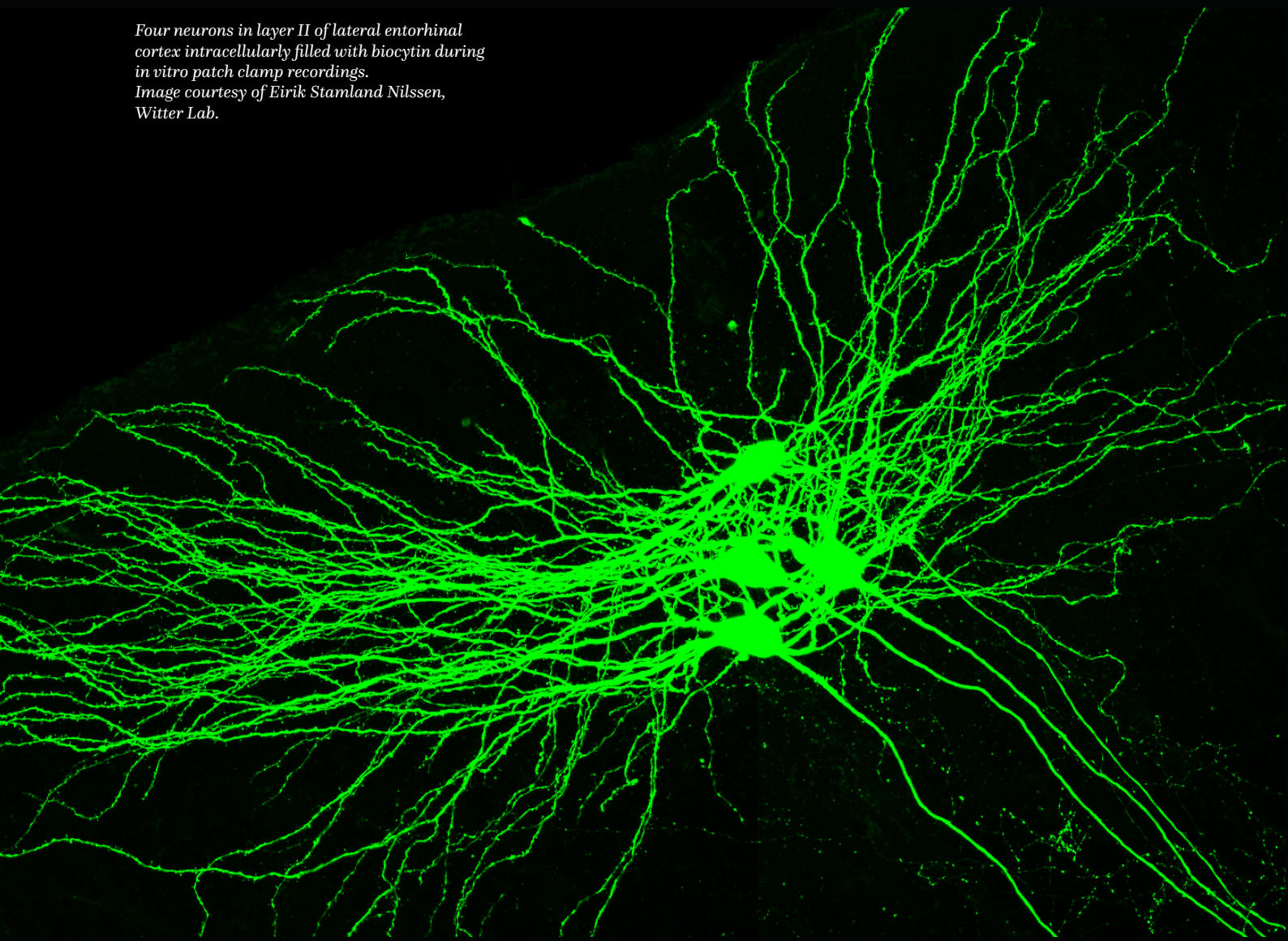
The pathology of Alzheimer's begins in layer two of entorhinal cortex. Currently, many models of Alzheimer's include brains that express the protein amyloid everywhere. However, to get a clearer picture of what's going on over time, it's important to figure out precisely when and where this protein starts to express. Interestingly, Dr. Witter points out, cells that express *amyloid* protein also express the protein reelin, and these cells then send connections to the hippocampus. Despite this knowledge, there are no clear data that explain why *reelin* and amyloid are expressed in the same neurons. The interaction between these two proteins still needs to be further characterized. "Reelin and amyloid matter to each other and we want to understand the causal relationship between the two," says Dr. Witter. To this end, current experiments involve manipulating one protein and studying the effect on the other.

This project is one of many which showcases how basic research findings (i.e. understanding the interaction between reelin and amyloid proteins in entorhinal layer

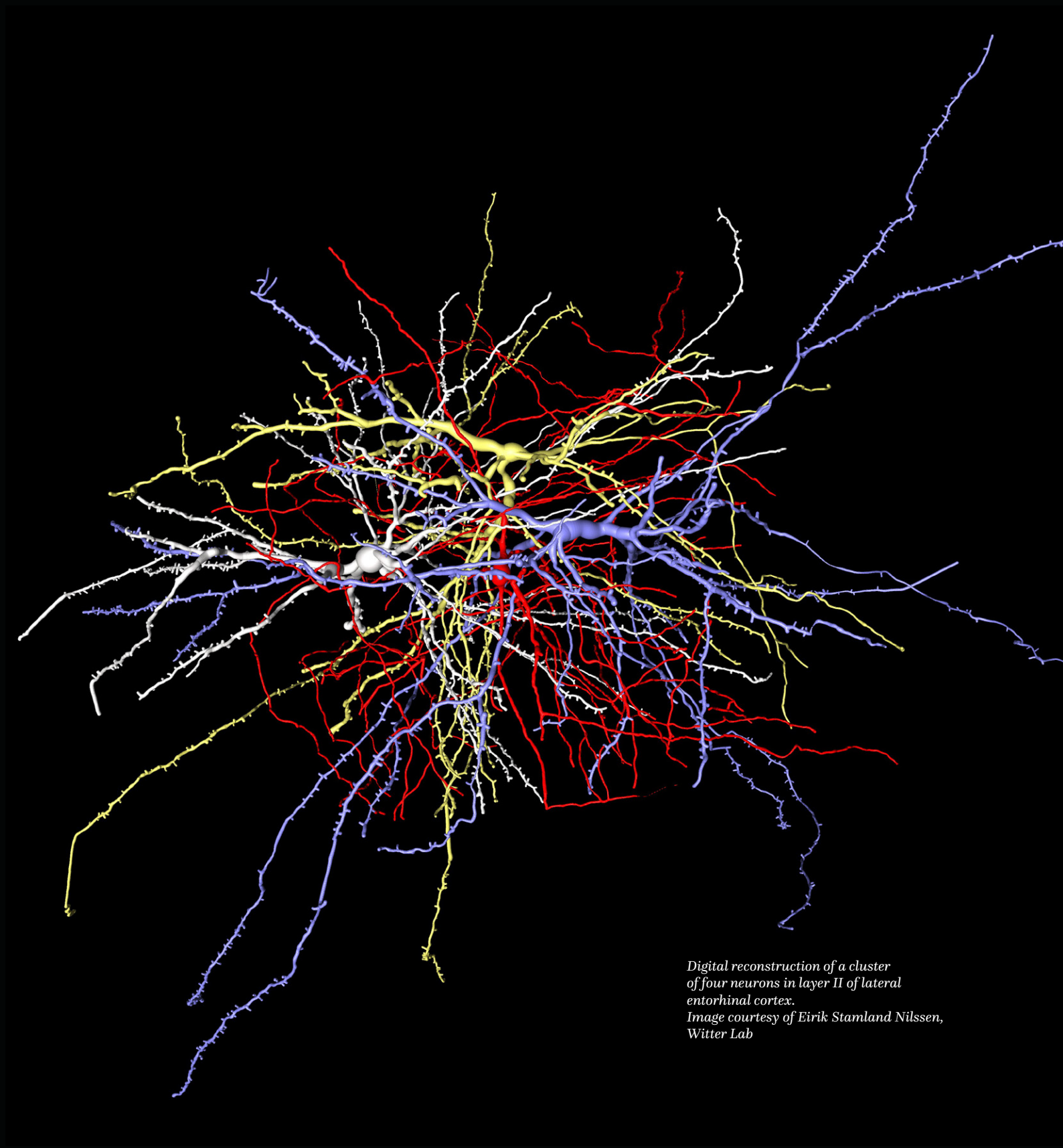
II neurons) translate into a clinical problem (Alzheimer's disease). Additionally, says Dr. Witter, it serves as a "beautiful example of collaboration within the center, because Cliff Kentros and I are both leaders on this project. Cliff and his team are vital to design the viral tools that we need."

Dr. Witter's approach to studying brain function and disease is as broad as it is deep. His ambition (and self-professed hope) is to use information about disease to inform basic research and, likewise, to use the fruits of basic research toward clinical and translational therapies.

From left: Bruno Monterotti, Belma Skender, Thanh Pierre Doan, Maria José Lagartos Donate, Mari Aksnes, Melissa de Reus, Ingrid Heggland, Paulo Girão, Bente Jacobsen, Menno P. Witter, Asgeir Kobro-Flatmoen, Peter Kovachich, Amy Robinson, Øyvind Wilsgård Simonsen, Grethe Mari Olsen, Hanne Tegnander Soligård, Eirik Stamland Nilssen and Agata Anna Staszelis. Michele Gianatti and Kang Zheng are also in the group, but were not present when the photo was taken.



Four neurons in layer II of lateral entorhinal cortex intracellularly filled with biocytin during in vitro patch clamp recordings. Image courtesy of Eirik Stamland Nilssen, Witter Lab.



Digital reconstruction of a cluster of four neurons in layer II of lateral entorhinal cortex.
Image courtesy of Eirik Stamland Nilssen, Witter Lab

Improving drug treatments for brain disease

Dr. Cliff Kentros and his team are using state-of-the-art genetic tools to create better treatments for brain diseases.

The ability to button your shirt, walk down the street, or remember a family member's name depends on your brain's ability to successfully coordinate signals across various circuits and regions. Neuroscientists often describe this patterned activity as an orchestration of signals. To successfully execute a motor command or retrieve a memory, brain signals must be sent and received in the right place and at the right time.

Of course, even the most well-tuned orchestra doesn't always sound perfect. We've all experienced instances when our brain doesn't perform at one hundred percent efficiency. Maybe we don't see the tree branch in our path and trip, or we miscalculate how fast a car is moving towards us as we merge in traffic and get into a minor accident. Sometimes, the consequences of circuit malfunction in the brain are severe, resulting in diseases that threaten our very sense of self, such as with Parkinson's or Alzheimer's. In the words of group leader, Dr. Cliff Kentros: "neurological and neuropsychiatric disorders are circuit imbalances."

Each of these diseases affect different brain regions, circuits, and cell types. In the case of Parkinson's disease, for example, brain cells which normally produce the neurotransmitter dopamine, begin to die in the midbrain. This results in tremors and an inability to move with ease. Current drug treatments for Parkinson's work by increasing the brain's ability to create more dopamine.

However, the problem, says Dr. Kentros is that "drugs often do the right thing in the right circuit, but the wrong thing in the wrong circuit." Current Parkinson's drugs are no exception. While they do correct levels of dopamine in the midbrain, they also increase levels of dopamine across other brain regions, thus resulting in some undesirable side effects. Yet, this is the compromise that doctors and clinicians must make for their patients all the time. It's better, they reason, to remove the most severe symptoms and suffer some side effects than to do nothing at all. The ideal scenario would be to target circuits that are malfunctioning, without altering the balance of neurotransmitters in circuits that are working just fine.

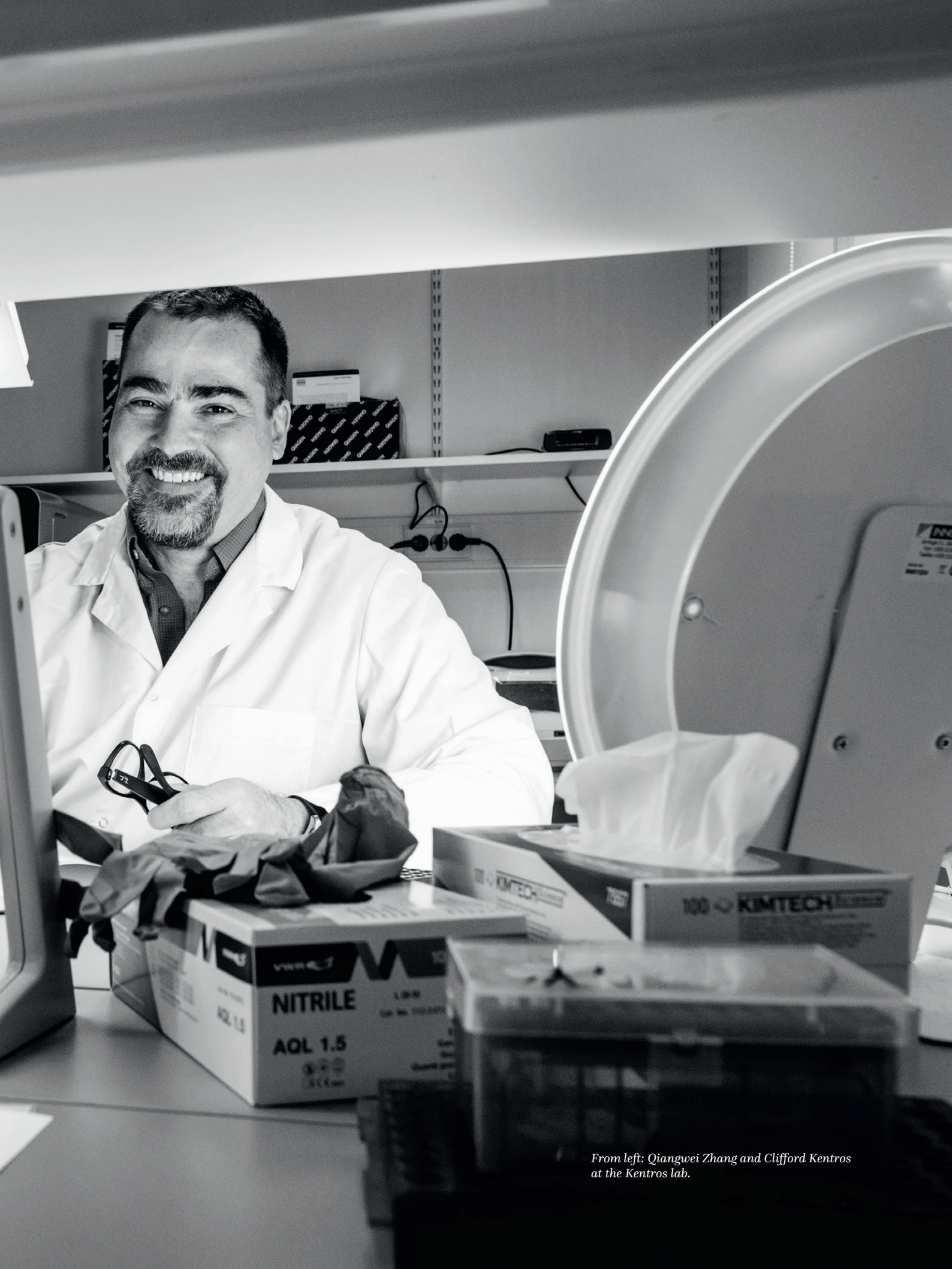
From left: Stefan Mattias Adriaan Blankvoort, Benjamin Kanter, Joachim Schweder Grimstvedt, Vilde Aamodt Kveim, Christine Lykken, Kadjita Asumbisa, Rajeevkumar Nair Raveendran, Qiangwei Zhang, Thomas Doublet, Christina Schrick,Christin H. Berndtsson, Dongkyun Lim and Clifford Kentros. Nils Borgesius is also in the group, but was not present when the photo was taken.

This, explains Dr. Kentros, is exactly what their research team has been working on – and it's no small task. The brain contains more cell types than the entire rest of the body. To identify, and then target, the unique cell types that are contained within diseased brain circuits, the team has developed transgenic mice which express target genes in specific cell types. Next, they combined the improved transgenic mice with another molecular tool called "Designer Receptors Activated by Designer Drugs" – or "DREADDs" for short. DREADDs, developed by Dr. Bryan Roth, are bioengineered receptors (the part of the cell which responds to different molecules) that respond only to a designed drug. In other words, it's a way to make cells responsive to a drug, in a controlled way.

To date, DREADDs have mostly been used as a tool in research laboratories, to study how increasing or decreasing neural activity affects the rest of the brain circuits being studied. By injecting DREADDs into different brain regions, for example, it is possible to restrict which parts of the brain will respond to the drug. However, even specific brain regions are made up of many different cell types. Thus, by combining the genetic engineering tools used to create cell-specific transgenic mice with the existing DREADDs technology, the Kentros team has come up with a new – and potentially more effective – method of drug treatment.

So, what does this mean for our Parkinson's example? In theory, a patient could go to the doctor's office, receive a simple injection (in the arm) which will deliver the DREADDs to the dopaminergic cells in the midbrain. Now, when a patient takes a pill (the designer drug), only the diseased dopaminergic cells in the midbrain will be affected. Using this specific approach, you can treat the movement disorder, without producing any undesired side effects. "This," says Dr. Kentros optimistically, "is how you fix people."


KENTRON5



From left: Qiangwei Zhang and Clifford Kentros at the Kentros lab.

Finding signal in the noise

Dr. Yasser Roudi's team has found meaning in firing patterns that were once considered 'just noise.'

Things aren't always what the seem and in the world of the brain this is especially true. Take grid cells, for example. Grid cells are so named because they respond or "fire" in characteristic grid-like patterns as an animal moves through its environment. The points that make up the grid represent where the cells fire the most strongly and these points are often referred to as peaks.

Until recently, scientists thought these peaks fired at the same frequency – and any of the variability previous observed was simply chalked up to "noise" in the signal. To test this assumption, Dr. Yasser Roudi's research team decided to take a closer look at this property and quantify the variability. What they found: the variability was actually pretty reliable, indicating that it wasn't due to noise but was actually a meaningful signal. This finding, explains post-doctoral researcher Benjamin Dunn, is key as it has "a lot of consequences for the kinds of models you can use [to describe grid cells]."

In fact, one of the most popular models used to describe grid cells was considered partially flawed. The Roudi group, however, suspected that if the variable peaks of grid cells (previously ignored) were accounted for, the model would better match the actual data. They were correct. An updated model, integrating varability of grid cell peaks, better matched the collected data.

Things aren't always as they seem – and experimental neuroscientists who collect brain data know this well. Furthermore, Benjamin reflects, many theoreticians might not have known that grid cells have variable peaks if they hadn't had the chance to see actual data. "That's the benefit of being at this center," he shares. "If you're doing theory at an experimental center then you see the real thing and not the watered down version that other theorists tell each other."

FINDING HIDDEN NEURONS

Graduate student, Claudia Battistin, has developed a new algorithm that accounts for cells which can't be observed with current tools.

The brain is a very active organ, packed with cells that are highly interconnected and active in unique patterns, at different points in time. If you could observe all the cells in the brain at the same time, you would see that some cells are on (active) and some are off (silent). Ideally, you would also see the connections between the active and silent cells. Neuroscientists call this pattern of activity and connections a "neural network". If you observe that same brain, even just a few seconds later, you will likely observe a different pattern of activity between the cells. The cells that were once active may now be silent and vice versa. The brain is a constantly changing world, which responds to (1) inputs from the outside world and (2) inputs from its own internal connections. As such, mathematicians often refer to the brain as a dynamic system.

While modern research tools are improving neuroscientists' ability to investigate this dynamic system, they still have limitations. For example, you can only record from so many cells for a finite amount of time. Because of this, it is important to use the tools of mathematics to model (with an algorithm) what kinds of inputs – internal and external to the brain – may possibly be generating the patterns of neural activity observed.

Claudia Battistin, a PhD student working in Dr.Yasser Roudi's lab, has recently developed an algorithm which does just that. By using the principles from a model, known as the Kinetic Ising (KI) model, she was able to apply her algorithm and reconstruct the functional connectivity from neural network data. Impressively, the algorithm accounted for the contribution of both observed cells and also hidden cells; cells that are part of the network but that scientists can't see with their current tools.

It all begins by setting up a theoretical neural network with random connections and strengths. Then, the algorithm is run in two main steps: (1) estimation and (2) maximization. The estimation step is run to estimate the mathematical parameters (representing the connections between neurons) that are needed to generate the theoretical network in the first place. The second step, maximization, then compares the theoretical pattern of activity to the experimental pattern and updates the strength of the connections between the cells accordingly. Over time, the algorithm goes back and forth between these two steps until the output of the model matches the observed data. In mathematical terms, the algorithm stops when it reaches convergence.

While the principles of this two-step algorithm have been used for decades, it usually takes a great deal of time to run to completion. The current version, written by Claudia Battistin, is more rapid, without any compromises in accuracy. This tool gives neuroscientists a new and useful way to ask questions about the entire neural network.

From left: Yasser Roudi, Claudia Battistin, Nicola Bulso, Stojan Jovanovic, Ryan John Abat Cubero and Benjamin Dunn. Daniel Wennberg is also in the group, but was not present when the photo was taken.

From left: Nicola Bulso, Yasser Roudi and Claudia Battistin.

The neuroscience of social learning and behavior could be 'the next big thing' says Dr. Jonathan Whitlock. His team studies how animals learn through observation and has designed cutting-edge tools to study their natural behavior in 3D.

Rodent see, rodent do

OBSERVATIONAL LEARNING AND PING-PONG BALLS
First, slice open a ping pong ball. Second, insert a motion sensitive device and an LED light. Third, hang that ball in a mouse cage. Now, cue the LED light. If the mouse taps the ball within three seconds, it will receive a liquid reward. All the while, an "observer mouse" will be in a nearby cage watching, and learning from, the "performer" mouse. This, says group leader Dr. Jonathan Whitlock, is what his creative research team has designed to study how the brain facilitates *observational learning*.

Observational learning is exactly what it sounds like: learning by observing someone else. As humans, we are social creatures, quite familiar with the process of watching and learning from others. Some neuroscientists believe that this process is made possible by a specialized set of cells in the brain, called "mirror neurons". These neurons were originally discovered in monkeys in the early 1990s. When a monkey picks up a piece of food, neurons in the motor cortex (the brain region important for movement) are activated. Interestingly these very same neurons were also activated when a monkey observed someone else pick up the piece of food, thus "mirroring" the activity of the observed behavior.

Since their initial discovery, there have been numerous philosophical and sociological studies on what it might mean for humans to have a mirroring system in the brain. There has been a lot of interest, speculation and theory. How neural cirtuits in the brain actually implement observational learning, however, is not well understood. "We really don't know how the brain does it!" says Dr. Whitlock, "It's a basic feature just like any other, just like spatial navigation and we want to know: how is this possible?"

To answer this question, the research team needs to combine their observational learning task with the ping pong to some metrics of animal behavior. The goal is to capture how the brain represents natural behavior, in its natural context, while it is freely moving through an environment. To do this, the team has spent a great deal of time building the appropriate 3D tools and behavioral platforms.

"We call it the Seinfeld task – a task about nothing," Whitlock shares humorously. Animal bespeckled with circular markers on their bodies can run on a wheel, climb over branches, explore a reward mountain (apparently, mountains come with juice rewards in the rodent world!). The key is to get the mice exploring so that the 3D tracking

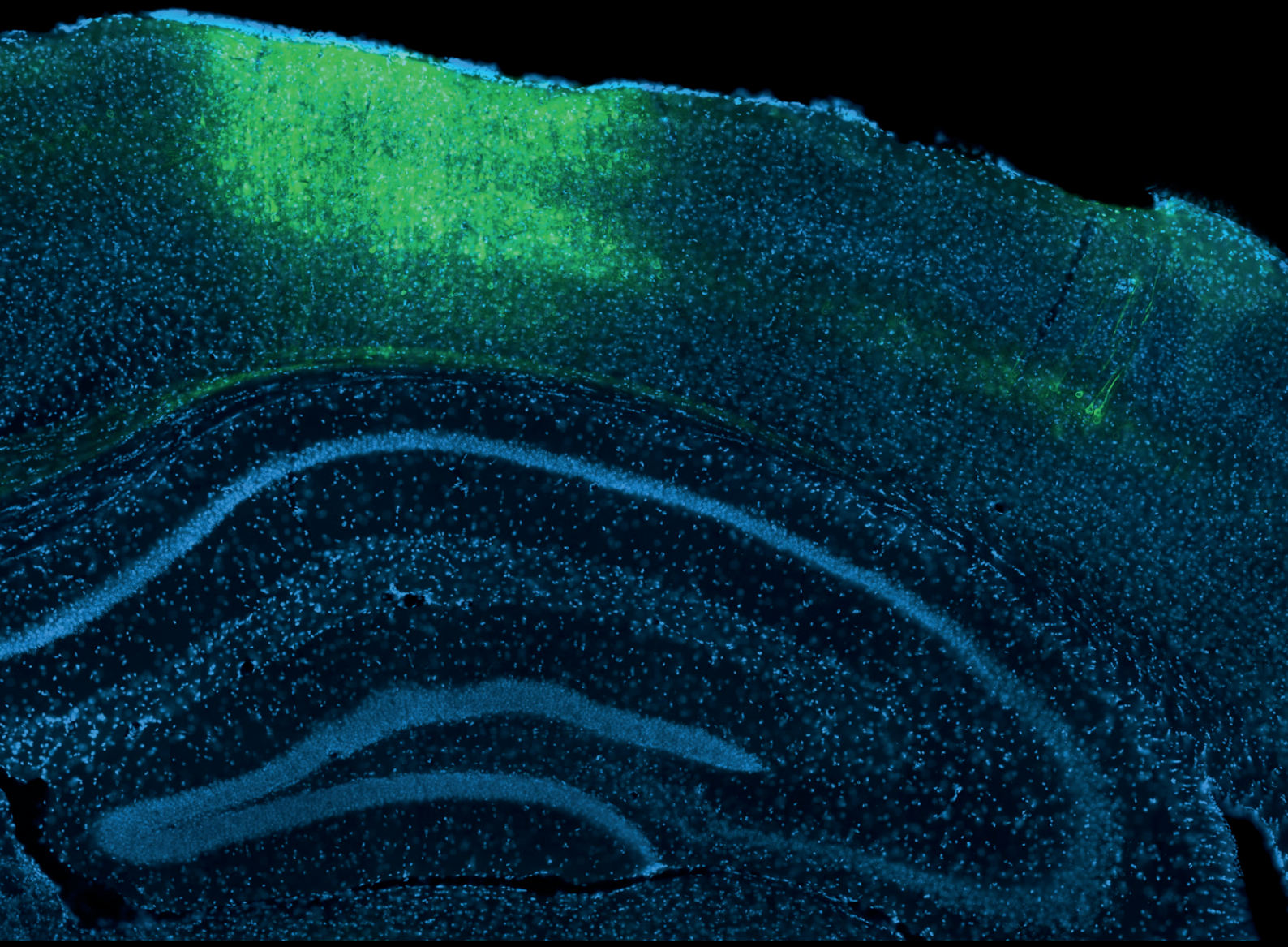
From left: Tuce Tombaz, Bartul Mimica, Ida Välikangas Rautio, Naomi Hanemaaijer, Benjamin Dunn,Jonathan Whitlock, Heidi Kleven and Karoline Hovde. V.P.T.N.C Srikanth Bojja is also in the group, but was not present when the photo was taken.

system can collect as much data on the animal movements as possible. From there, the group applies an automatic algorithmic-based approach which labels the movements of the animal in different categories, for example the various degrees of head movement, shoulder blade and hip position, and so on.

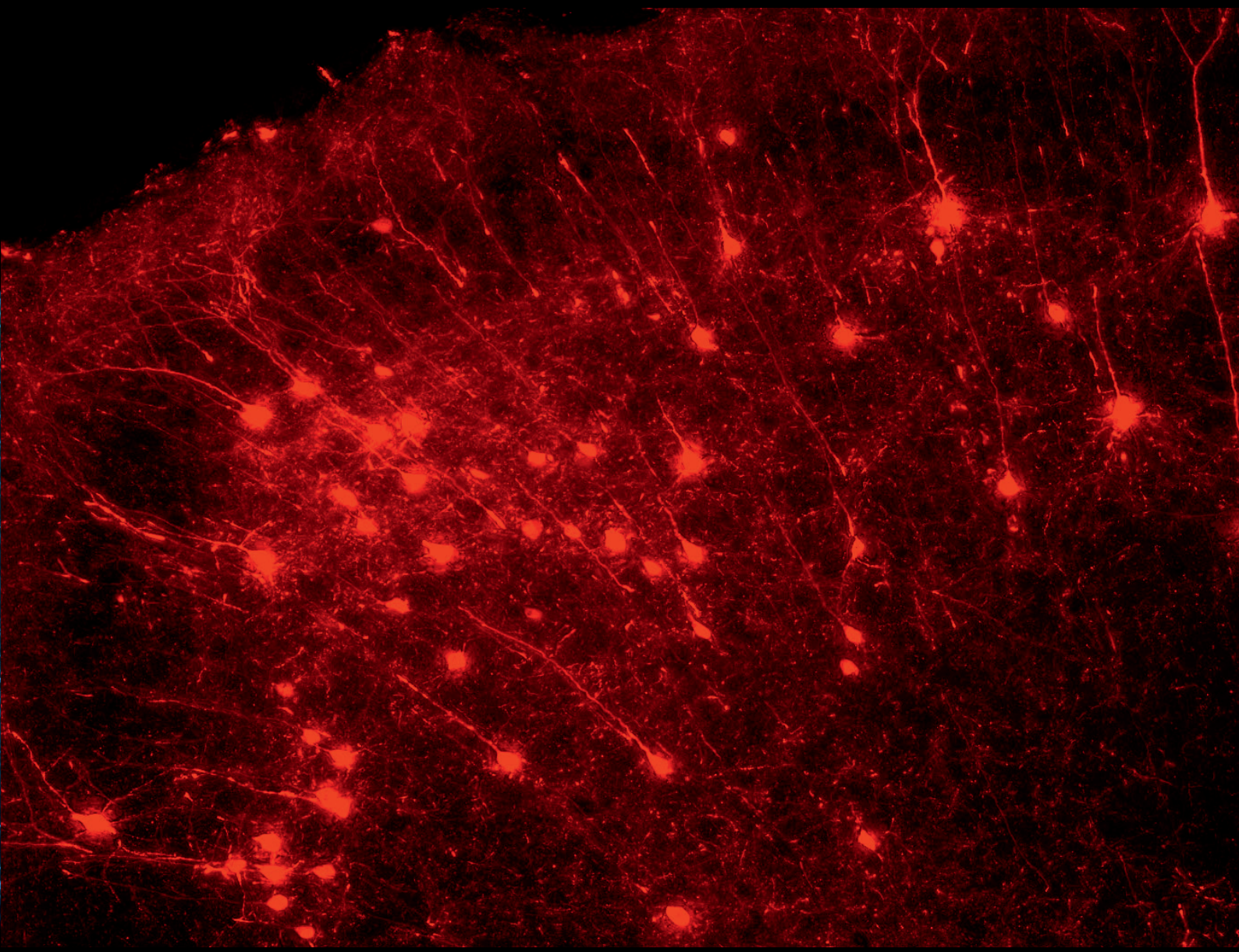
While the tool itself is impressive, the scope of application is even more so. For one, says Whitlock, it will now be possible to study social interactions between two animals that are being tracked by the software. In such a condition, the brain networks activated by social learning can be correlated to the actual behavior – whether it's two mice facing each other, two mice about to fight, two mice simply closer together in space, and so on. The possibilities are only as limited as the number of various animal behaviors there are – and it's not limited to social behavior, either.

Dr. Whitlock's team is also actively investigating spatial navigation. With this new tool, he explains, they are able to independently track the head and the body of the animal. "This gives us a crystal-clear picture of which way an animal is moving and where it is looking relative to a goal location," explains Whitlock. "We can see even subtle changes across many cells during different modes of behavior, such as exploration or homing to a goal."

On his perspective of working at KI/CNC in Trondheim, Whitlock has certainly felt supported in his efforts to delve into new research territory. "Drs. May-Britt and Edvard Moser encourage us to be original and explore." This culture stands in contrast to many current models of scientific training and research. However, Whitlock shares, "it's certainly following the Mosers' vision. They see the value of starting out that way – of truly exploring and trying something new."



Glowing green histology section
Neurons in the mouse posterior parietal cortex and secondary visual cortex express the fluorescent green calcium indicator GCaMP6m, which permits the visualization of neuronal activity in freely-behaving subjects. This section is unique since it comes from a mouse where the first mirror-like responses were recorded in a non-primate mammal. Image credit to Tuce Tombaz and Karoline Hovde, Whitlock Lab.



Neurons labeled by a rabies virus
Cells in secondary motor cortex which were labeled trans-synaptically by a rabies virus injected in posterior parietal cortex. The glowing red cells provide monosynaptic input into parietal cortex, constituting the front-end of the parieto-frontal pathway in the mouse. Image credit to Karoline Hovde, Whitlock Lab.

What do a developmental biologist, engineer and neuroscientist have in common? They were among the first individuals hired by Dr. Emre Yaksi when he first set up his research lab. This diversity of expertise was not accidental. Reflecting on the research team he's built, Yaksi shares: "It's really nice to be surrounded with people from different backgrounds. I am proud to work in an environment, where I can learn from my lab members and they can learn from each other too. I think this is very important for progress." These days, the team also includes physicists and medical doctors. "It's one of the things I like most about my lab," Yaksi shares. The group is working hard to push the traditional boundaries of their individual fields to combine approaches, to exchange ideas, to come up with new models and technologies, and ultimately discover new principles about the brain.

It's more than just a nice idea. The discoveries that have emerged from this meeting of minds have already resulted in some notable publications. For example the team showed that neurons with a similar genetic background are the ones that tend to synchronize together both during on-going and sensory driven neural activity. "In a sense", explains Yaksi, "on-going neural activity predicts the anatomical and molecular organization of the brain." Most recently, the team combined principles from fluid dynamics, mathematics and sensory physiology to explain how zebrafish, which is the lab's model organism, smell different odors. Using propeller-shaped hairs on their nostrils, zebrafish can control fluid dynamics to both intake and expel odors, and consequently navigate through their environments more efficiently.

Though the fish brain is not as complex as the human brain, the basic architecture is preserved across species. "You won't find the exact same structure, but you will find a miniature form of these brain regions in the fish," says Yaksi. In fact, because zebrafish are transparent creatures, it is possible to image the entire brain. Questions about the activity of the entire neural network are more tractable and directly measurable than they are in humans or in rodents. "One major advantage of working with zebrafish," says Yaksi, "is that you can look at the local computations together with the global computations and try to understand, for example, not only how individual brain regions do what they do, but how they interact with each other, in different contexts."

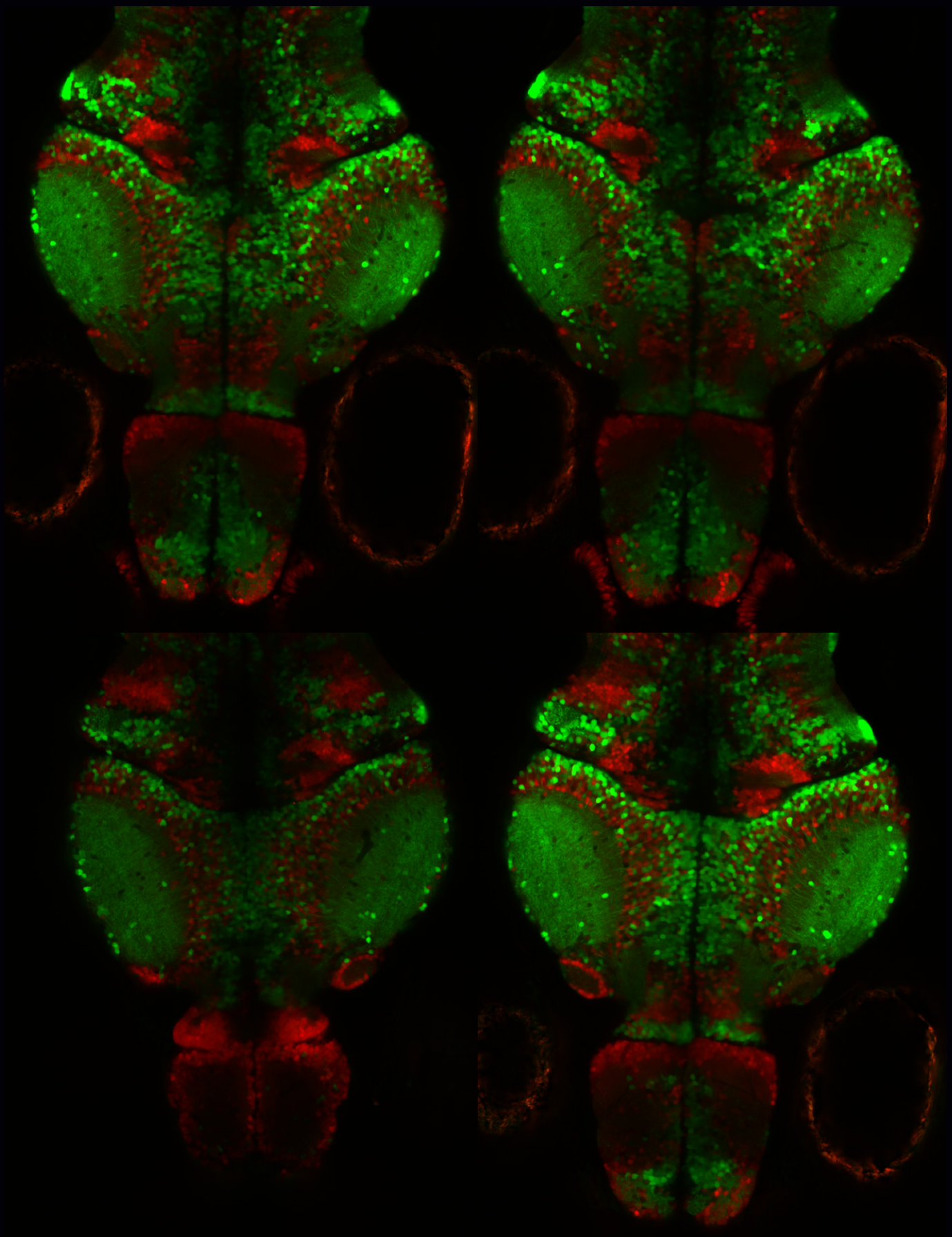
Direct measurements of brain activity can tell us more about how our internal states are corresponding to events in the external world. Hunger is an internal state that is represented in the brain as a certain pattern of activity. When we interact with the external world by eating, this pattern changes. Understanding these internal states in normally-functioning brains is the first step to developing more effective therapies for related brain diseases.

When I ask Yaksi about his dream experiment, he says that what he most wants to develop in his lab is a perfect virtual reality environment, where he can monitor brain activity while fish perform different behaviors. "The dream is to have a happy, comfortable animal so that it can interact with its environment as naturally as possible," he says. Once such a tool is in place, a whole new world of questions can be explored – from spatial navigation to social interactions, perhaps even to studying brain diseases. Given the energetic quality of his leadership and the diverse team he has assembled, it seems a matter of time before he makes that dream a reality.

Simple creatures, complex networks

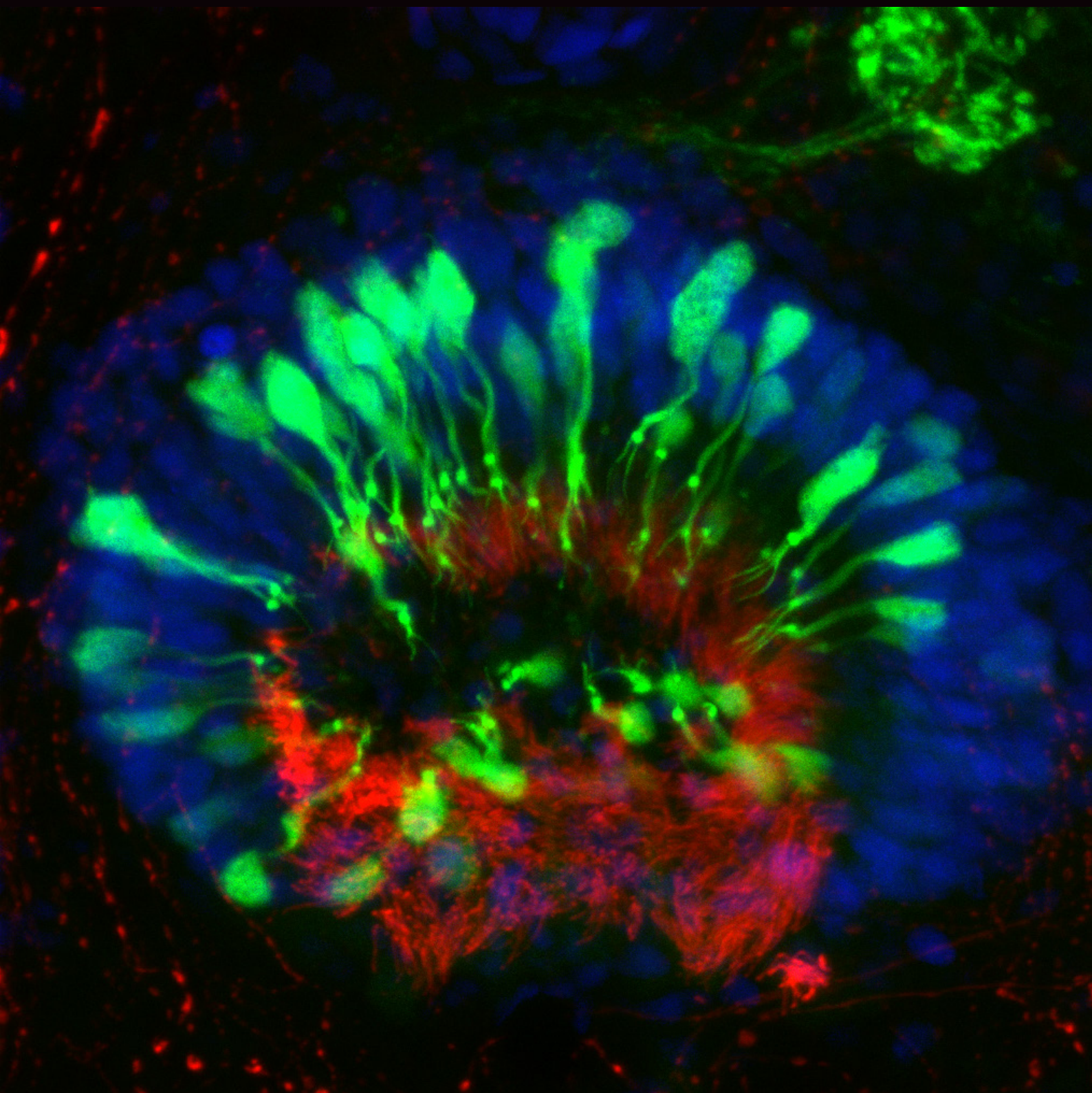
A diverse group scientists take advantage of transparent zebrafish to tackle some of neuroscience's most complex problems.

From left: Tord Aronsen,Thomas, Sommers, Filip Janiak, Florence Kermen, Nancy Saana Banono, Christa Ringers, Merethe Andresen, Nathalie Jurisch-Yaksi, Emre Yaksi, Sverre Myren-Svelstad Pradeep Lal, Stéphanie Foré, Christoph Wiest and Fabrizio Palumbo. Ewelina Bartoszek, Maximilian Hoffmann, Robbrecht Pelgrims and Carmen Diaz Verdugo are also in the group, but were not present when the photo was taken.



Left: Zebrafish brain, excitatory neurons (in red), inhibitory neurons (in green).
Confocal microscopy image is generated by Carmen Diaz Verdugo, Yaksi Lab.

Under: Olfactory neurons in transgenic zebrafish nose.
Confocal microscopy image is generated by Christa Ringers, Yaksi Lab.



Cognitive neuroscientist Christian Doeller is the newest recruit to KI/CNC and his lab is hard at work discovering the neural building blocks of human cognition and taking the first steps toward unravelling Alzheimer's disease.

Imaging memory and predicting disease

In the autumn of 2016, Prof. Dr. Christian Doeller moved parts of his laboratory from the Netherlands to join the KI/CNC and work side-by-side with the world's foremost physiologists, extending his research on memory and spatial navigation. As a cognitive neuroscientist, he has focused his research on investigating space and memory processing using functional brain imaging, or fMRI, in healthy humans. This work, supported partly by grants from the European Research Council (ERC), is a necessary step to understanding the neural building blocks of human cognition and to developing more effective therapies for diseases, such as Alzheimer's.

Having always kept an eye toward physiological research findings, Dr. Doeller explains that joining the centre has opened new lines of research questions that he can now follow in collaboration with other group leaders at the institute. Specifically, the potential to conduct translational research is greatly improved. The goal, he says, is to translate "the fundamental, Nobel-prize winning coding principles discovered in animal models to the human brain."

Within the Centre of Excellence (COE), collaborations between Doeller's group and other leaders are already underway. Together with the Moser group, for example, the plan is to investigate and compare the virtual reality data between animals and humans to better understand spatial navigation. A collaboration with the Kentros lab involves combining the molecular tools used in rats to study cortical dynamics with rodent fMRI to obtain a clearer picture of brain function in spatial navigation. Lastly, says Doeller, his lab has begun working with leading neuroanatomist Dr. Menno Witter. Using Witter's anatomical expertise, it will be possible to perform fine-grained, anatomically inspired analysis of the human fMRI data and consequently "better understand the link between brain structure and function." These tools have their individual strengths and weaknesses, and thus combining strengths across methods becomes a powerful research strategy.

This is "a big advantage of doing fMRI research at a world-class physiology institute. We can always go back into an animal model and look at data [collected using physiological methods]." In addition to going back and forth between methods more seamlessly, it is possible to align experimental paradigms across human and animal technologies to make better sense of the data. For example, fMRI scans require that humans lay still in a brain scanner. Thus, to study something like spatial navigation – which requires movement – researchers take advantage of virtual reality environments to mimic movement through space. Similarly, the latest animal technologies of spatial navigation have begun using virtual reality environments. "This is especially exciting," says Dr. Doeller, "because you can translate between the human and the animal more easily when the methods are similar."

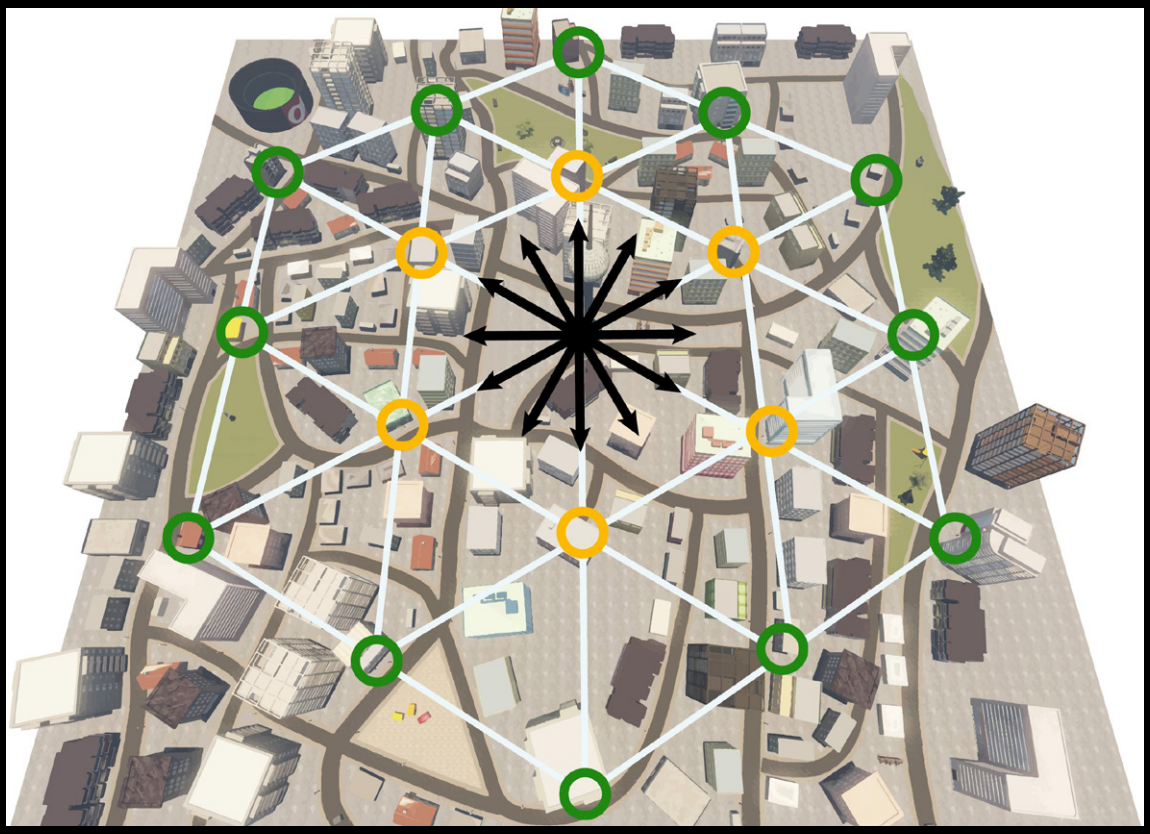
On the clinical side, Doeller is also working actively with clinicians at Trondheim University Hospital within the newly established Egil and Pauline Braathen and Fred Kavli Centre for Cortical Microcircuits, of which Doeller is the Acting Director. Here, they are studying patients with dementia and Alzheimer's to relate traditional clinical tests and outcomes to fMRI brain measures. "The problem with

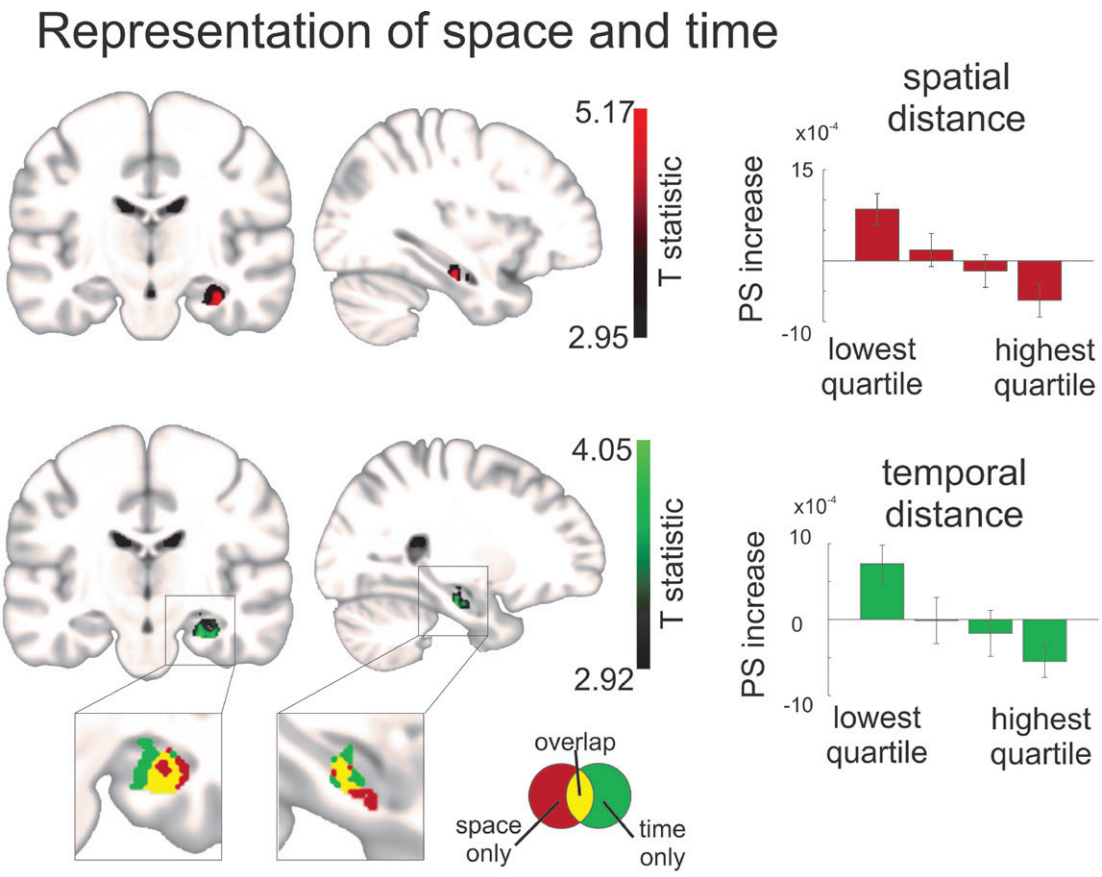
current Alzheimer's research is that there is no reliable early diagnostic marker," says Doeller. In 2010, however, Doeller's team discovered a spatial grid-like code in the human brain that was very reminiscent of the grid cells discovered in rodents by the Mosers, and in 2015 the group determined that impairments in these grid-like codes predicted the development of Alzheimer's in later life.

This finding is a promising indication of how physiological changes in the brain can be used as early diagnostic tools.

Says Doeller, "this is a top environment and it's super exciting for our research team."

From left: Christian Doeller, Tobias Navarro Schröder, Tom Arend Ruiter, Anne Merete Lie, Jacob Bellmund, Britt Veldman and Matthias Nau.

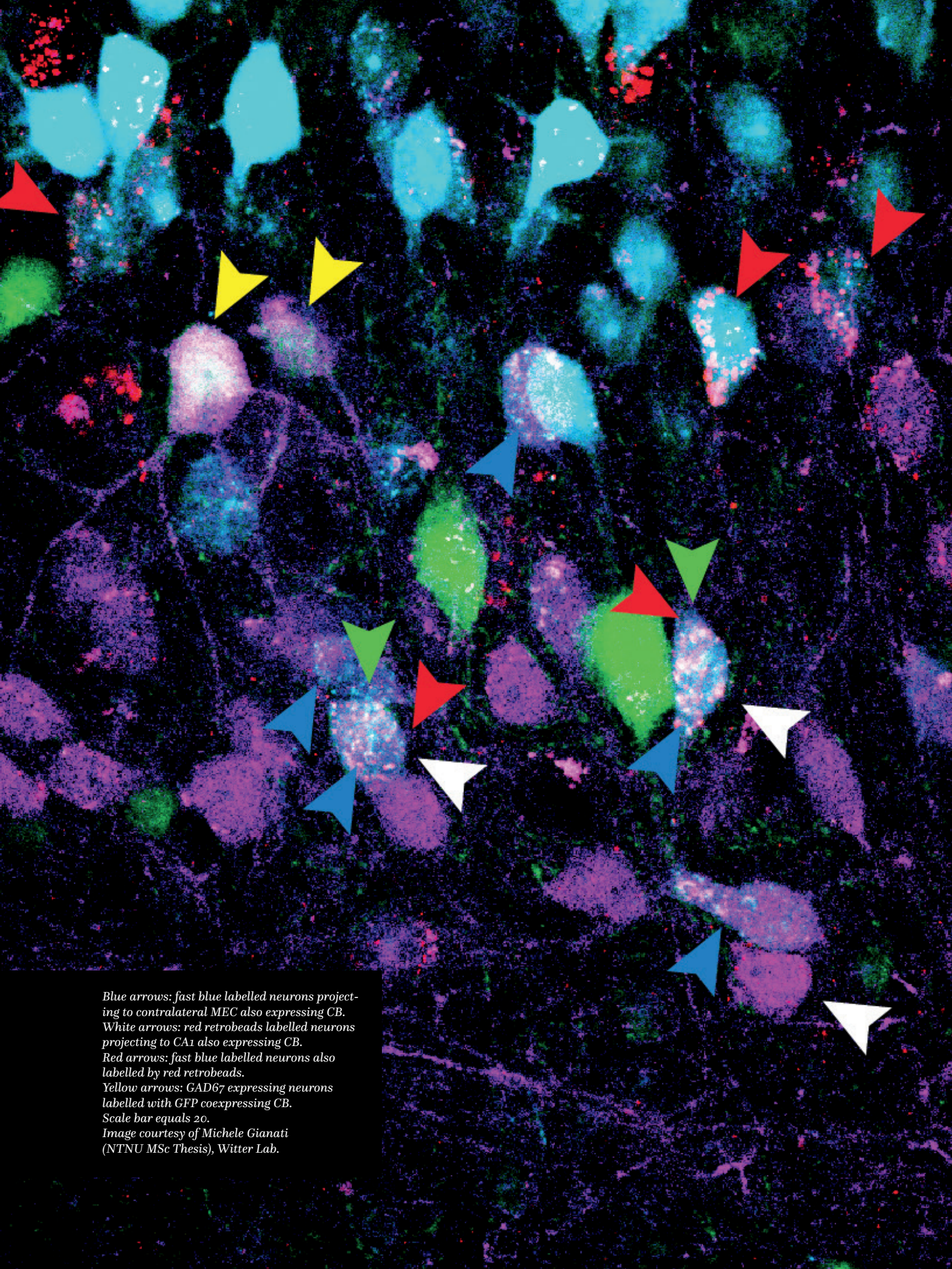




Top left: Grid-cell representations in mental simulation.
Healthy volunteers learned the positions of buildings in a virtual city during training before undergoing an fMRI scan during which they imagined directions between these buildings. The entorhinal grid system was active during imagination of these directions. Image credits: Bellmund, J.L., Deuker, L., Schröder, T.N., and Doeller, C.F. (2016), Doeller Lab.

Lower left: The brains inner metric
Participants imagined views facing different directions from positions in a virtual city while in the fMRI scanner. Specific patterns of brain activity indicated that the head direction and grid cell system were active during this task. The red pattern illustrates how the firing pattern of a grid cell might look like in the virtual city. Bellmund, J.L., Deuker, L., Schröder, T.N., and Doeller, C.F. (2016), Doeller Lab.

Above: An event map of memory space in the hippocampus.
Human participants navigated a virtual city on a fixed route along which they encountered objects. Pattern similarity analysis of the fMRI data showed that the similarity of object representations in the hippocampus reflected how far apart participants remembered these objects. The hippocampus represented both the distance in space in the city and time along the route. Deuker, L., Bellmund, J.L., Schröder, T.N., and Doeller, C.F. (2016), Doeller Lab.



Blue arrows: fast blue labelled neurons projecting to contralateral MEC also expressing CB.
White arrows: red retrobeads labelled neurons projecting to CA1 also expressing CB.
Red arrows: fast blue labelled neurons also labelled by red retrobeads.
Yellow arrows: GAD67 expressing neurons labelled with GFP coexpressing CB.
Scale bar equals 20.
Image courtesy of Michele Gianati (NTNU MSc Thesis), Witter Lab.

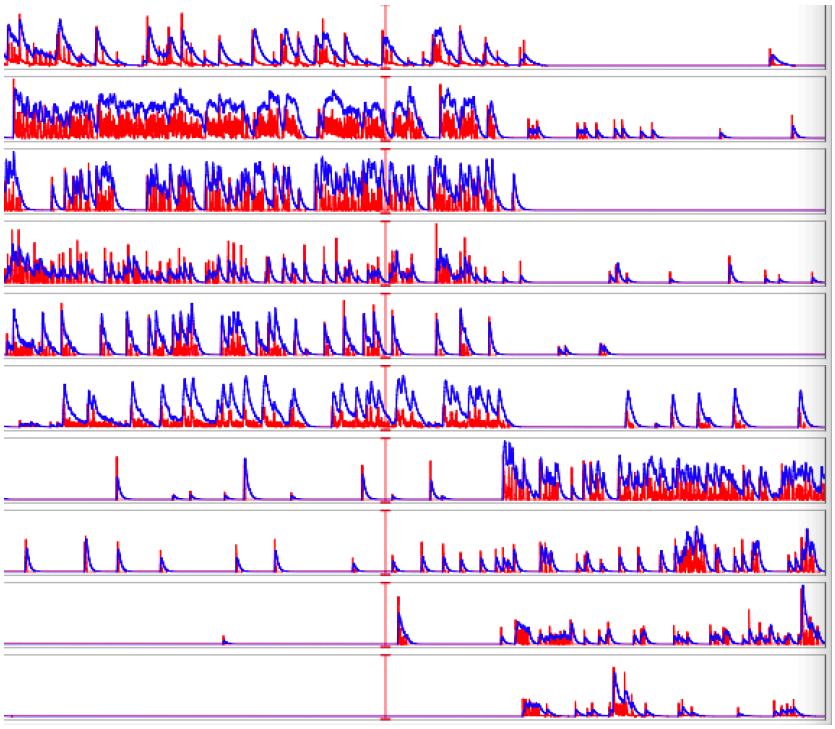
The hippocampus of KI/CNC

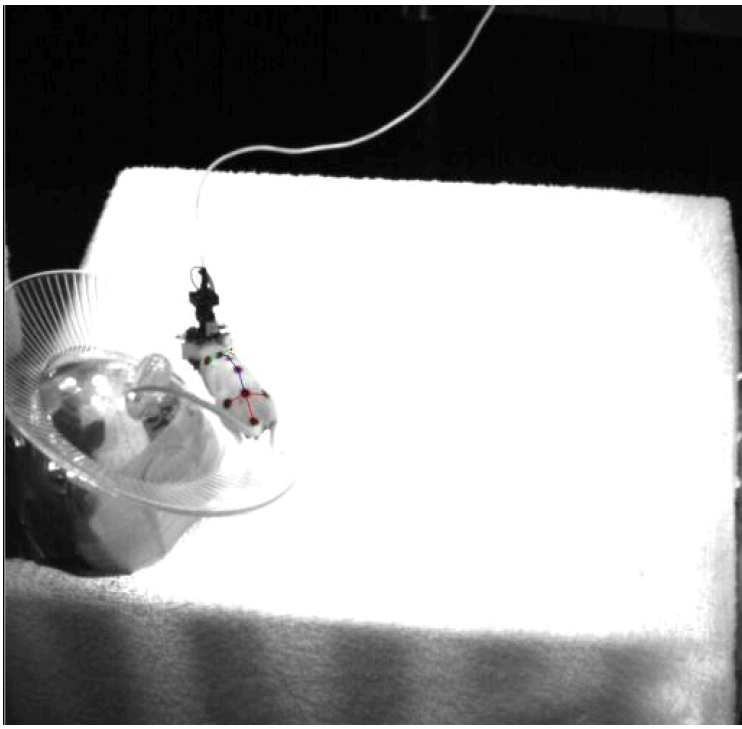
Excellent support enables excellent science – this is the mantra of the Support group and the Technical staff.

A staff of highly dedicated technicians, administrators and specialists are providing their knacks to the research groups across the centre. Diversified in skill and training, the individuals of these groups attend to the animals' welfare, assist scientists in designing tools and practical solutions for the novel experiments they envision, they help organize conferences and events, nurture local and international relations, keep track of economical and organizational matters as well as digital solutions.

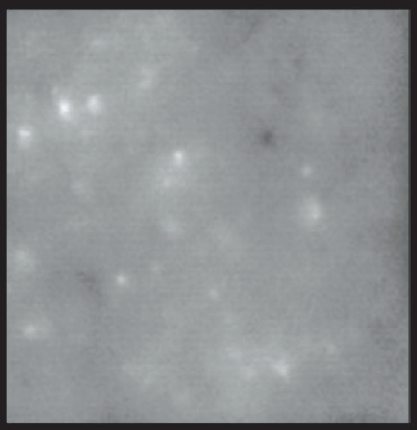
These are the workers the Director fondly refers to as the hippocampus of the Centre, archiving information from short-term memory, retrieving knowledge from long-term memory, establishing long-term potentiation of preparedness based on recent activities, and in general providing cues used for navigation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

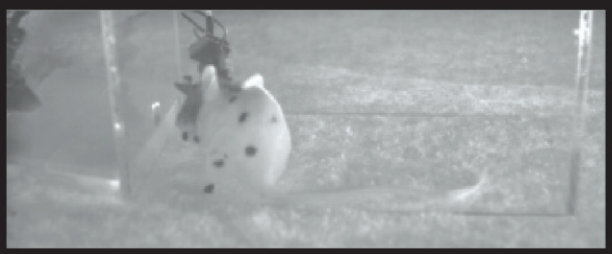
From left: Eirin Hårstad, Lisbeth Normann Mitlid, Alice Burøy, Haagen Waade, Rita Elmkvist Nilsen, Siv Eggen, Mussie Debesai, Hanne Mali Møllergård, Dina Hestnes, Håvard Tangvik, Lisbeth Aune and Grethe Jakobsen.
Jens Fredrik Andersen, Linda Eikegard, Cecilie Kristiansen, Claudia Melis, Anne Lise Stamnes and Linda Katalin Veres are also in the group, but were not present when the photo was taken.





Neural activity during 3D tracking
Different patches of neurons in posterior parietal cortex are co-activated when the animal runs in different directions on the running wheel. The top 6 rows are cells which preferred counter-clockwise running, while the bottom rows are from 4 cells which preferred clockwise running. Image credit to Ben Dunn and Tuce Tombaz, Whitlock Lab.





I was watching recordings from the Mouse Mirror Cell project at home and felt inspired by one of Gertrude Stein's poems, "If I told him", an homage to her dear friend Pablo Picasso. The poem was written in what feels like verbal cubism. The repetitions and distortions in the poem seemed to jive with the repeating but shifting camera angles in the experiment, and the behaviors of the performer mouse being recapitulated in the brain cells of the observer.
Image credit to Jonathan Whitlock, Whitlock Lab.

"Exact resemblance
to exact resemblance
the exact resemblance
as exact as a resemblance
exactly as resembling,
exactly resembling,
exact in resemblance
exactly a resemblance,
exactly and resemblance,
For this is so. Because."

Gertrude Stein
from: *If I Told Him*
(A complete Portrait of Picasso)

Highlights

2013

Start of CNC

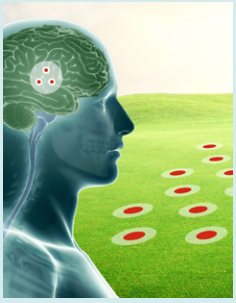
Start up Kentros Lab

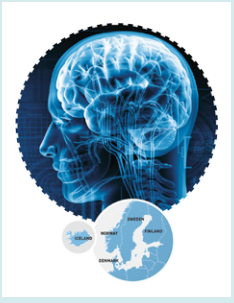
2014

Neural Networks in the Arctic.
Conference in Svalbard

Nobel Prize in Physiology
or Medicine

Start up Yaksi Lab





2015

Creation of Egil and Pauline Braathen and Fred Kavli Centre for Cortical Microcircuits

1st Nordic Neuroscience Conference in Trondheim

2016

Announced Starmus to Trondheim

Start up Doeller Lab

KI/CNC:

Research and collaboration across the centre

10 work packages reflect collaborations between research groups in the centre:

1. To determine the algorithms by which grid signals are transformed to place signals
   Participants: Moser group, Kentros group, Witter group, Roudi group.

2. To determine the computational mechanisms by which the grid signal is generated
   Participants: Moser group, Roudi group, Treves.

3. To determine the mechanisms and functions of modularity in the grid map
   Participants: Moser group, Witter group, Kentros group, Roudi group

4. To identify structural and computational subcircuits in medial and lateral entorhinal cortex
   Participants: Kentros group, Witter group, Moser group, Roudi group.

5. To identify structural and computational subcircuits in the hippocampus
   Participants: Moser group, Witter group, Kentros group, Roudi group.

6. To determine how the elements of the space circuit are coordinated
   Participants: Moser group, Witter group, Kentros group.

7. To determine how entorhinal-hippocampal space codes are used for navigation
   Participants: Roudi group, Moser group.

8. To identify neural circuit computations underlying learning and navigation in mini brains
   Participants. Yaksi group, Witter group.

9. To determine how parieto-frontal circuits enable action planning, action perception, and social learning
   Participants: Whitlock group, Witter group, Roudi group

10. Entorhinal codes in human cognition and its breakdown in Alzheimer's disease
    Participants: Doeller group, Kentros group, Witter group, Moser group

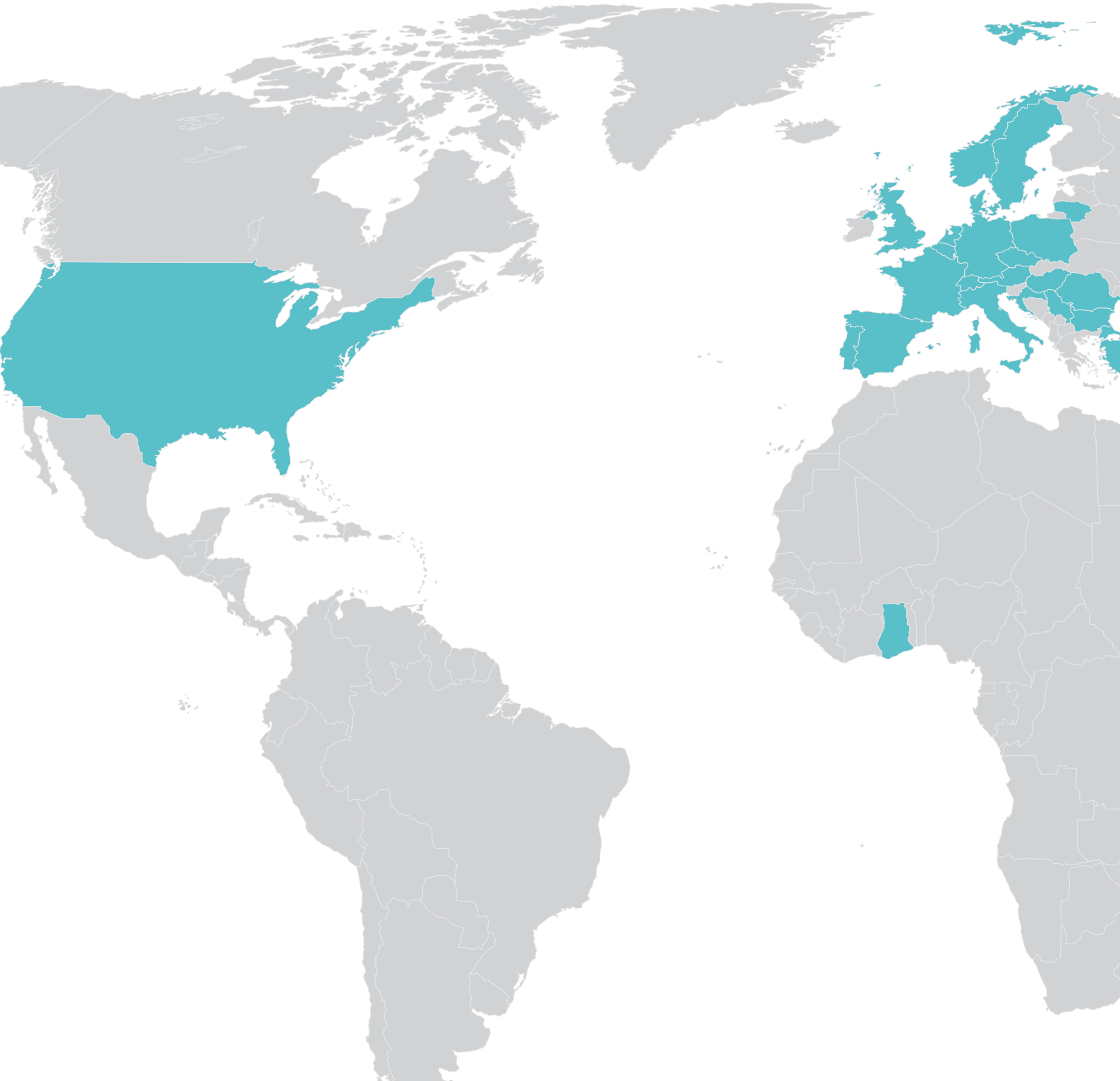
KI/CNC:

International collaborations

The group leaders at KI-CNC initiate and develop collaborations with leading research groups across the world. The opportunity to share knowledge, expertise and innovative technological solutions, is enhancing the quality of research as well as the capacity to address global challenges. Examples of active research collaborations include:

Al Quds University, Pelstine (Moser)
Charite University Hospital, Berlin, Germany (Moser)
Collège de France, Paris, France (Doeller)
Columbia University, New York (Moser)
Dresden University, Dresden, Germany (Doeller)
Friedriech Miescher Institute, Basel, Switzerland (Moser)
Hebrew University, Jerusalem (Moser)
Humboldt University, Berlin, Germany (Moser)
Instituto Leloir, Buenos Aires, Argentina (Moser)
International Centre for Theoretical Physics, Trieste, Italy (Roudi, Moser)
Janelia Farm Research Campus, Ashburn VA, USA (Moser)
Kings College, London, United Kingdom (Roudi)
Koc Universitesi, Turkey (Yaksi)
Massachusetts General Hospital, Boston, USA (Moser)
Max Planck Florida Institute, Jupiter FL, USA (Moser)
Max Planck Institute for Neurobiology, Martinsried, Germany (Moser)
National Institute of Genetics, Shizuoka, Japan (Yaksi)
National Institute of Health, USA (Doeller)
New York University, New York (Moser)
Nordic Institute for Theoretical Physics, Stockholm (Roudi)
Northwestern University, Illinois, USA (Roudi)
Pfizer, Cambridge MA, USA (Moser, Doeller)
Princeton University, New Jersey, USA (Roudi, Doeller)
Ruhr-University Bochum, Germany (Doeller)
Technische Universität München, Munich, Germany (Roudi)
Romanian Institute of Science and Technology, Cluj-Napoca, Romania (Whitlock)
Stanford University, California, USA (Moser)
Tohoku University, Sendai, Japan (Witter)
University College London, London, United Kingdom (Doeller, Moser)
University of Arizona, Tucson, USA (Moser)
University of Birmingham, United Kingdom (Doeller)
University of California, Irvine, USA (Moser)
University of California Santa Barbara, USA (Roudi)
University of Guelph, Ontario, Canada (Whitlock)
University of Heidelberg, Germany (Moser)
University of Texas, Austin (Moser)
University of Zurich, Zurich, Switzerland (Yaksi)
Weizmann Institute, Rehovot, Israel (Moser, Witter)

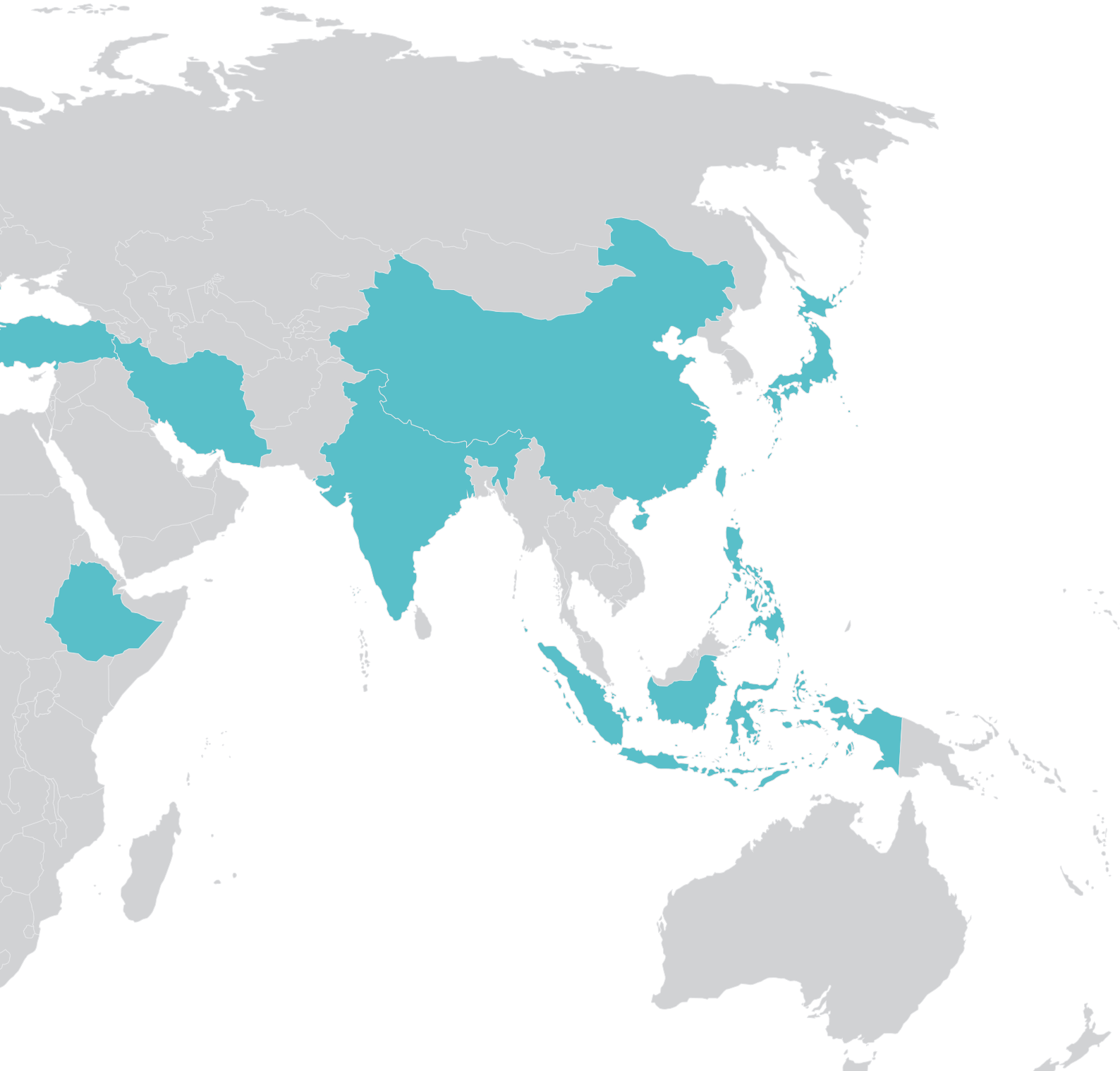
Facts



32
nationalities represented
in CNC's workforce

3000
estimated number
of requests pr. year

4.5 kg
weight of
autograph cards sent



Dissemination and communication

The scientists at KI/CNC take part in various activities for communicating science to the public.

The tools of the trade for communicating within the science community, like peer-reviewed journals and conference proceedings, are not good sources of knowledge for the public. Rather it's through popular media, like online video platforms, television, social media, radio, podcasts, newspapers and magazines, as well as popularized talks and debates taking place in the public, that the majority of citizens gain knowledge and advice about science.

Popular science communication demands a translation of both complexity, language and dissemination form, without compromising central scientific aspects. By explaining scientific relationships in a straight-forward language and contextualizing scientific facts within issues of public interest and concern, our scientists aim at not only translating information and facts into publicly accessible knowledge and understanding, but also at providing a vocabulary that allows the broader public to engage in and join discourses about local and global issues that involve both risks and benefits, and in which every citizen is a stakeholder.

These insights represent the fundament upon which KI/CNC's communication plan is built. The photos on this page show some examples of our recent public outreach activities.

Coverage in national printed media can be assembled from Media Retriever upon request. Internationally the Centre has been covered by extensive articles in New York Times, Huffington Post, the Guardian, and Scientific American – to name a few.

Edvard Moser, Christian Doeller and Menno Witter have contributed to the upcoming popular science TV-series Evig Ung (Eng. Forever Young) by the Norwegian Public Broadcasting Corporation (NRK), to be aired in 2017.

Christian Doeller, Solveig Hareide (TV reporter, NRK) and Edvard Moser discussing recent insights from basic science on brain health.

Christian Doeller explaining to Solveig Hareide the use of VR-technology in Alzheimer research.

Science is not just about generating concepts and facts. Science is curiosity – opening ones' eyes – wondering. Another way of inspiring interest in science, is by sharing the untapped beauty of our scientific pursuit.
Unveiling the grandeur of nature as it transpires through our research tools. Through science images, revealing a vastness of systems and principles, codes, mysteries or even seemingly chaos, we are aiming to inspiring a way of knowing and approaching nature that goes beyond words. The visuals displayed in this report is an example of this approach.

May-Britt Moser explaining how grid cells and place cells contribute to goal-directed navigation at her Presidential Lecture at Society for Neuroscience in Chicago 2015, the conference was visited by about thirty thousand people of which more than five thousand were from the broader public.

PhD students and postdocs engaging school children to become brain investigators during the Research Fair in Trondheim 2016.

The Trondheim Soloists, May-Britt Moser and musical composer Bertil Palmar Johansen, during a media screening of the innovative art/science project Lost Memory (2016/17), aiming at communicating insights from basic neuroscience research at KI/CNC in the context of Alzheimer's disease for a general audience.

Edvard Moser from his popular science lecture at the Starmus III festival in Tenerife (2016). Starmus represents an innovative approach to boosting public understanding of science, inviting citizens to engage with and participate in scientific discourses, by bringing together the very best of science and art into a weeklong popular science dissemination festival. The festival is pulling thousands of visitors, and is covered by major media houses across the world. Edvard and May-Britt Moser have since been instrumental in bringing the Starmus initiative to Trondheim (2017).

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 KI/CNC
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 international conferences. Some PhD students co-supervise MSC students.

List of PhD defences so far carried out at KI/CNC:
2013: No dissertations
2014: There were four dissertations in 2014. Tora Bonnevie (f), Charlotte Boccara (f), Tor Stensola (m) and Alessandro Luchetti (m)
2015: There were six dissertations in 2015. Mathias L. Mathiasen (m), Charlotte B. Alme (f), Albert Tsao (m), Li Lu (m), Chenglin Miao (m) and Mehdi Fallahnezhad (m)
2016: There were six dissertations in 2016. Stefan M. A. Blankvoort (m), Ingrid Heggland (f), Benjamin A. Dunn (m), Hanne Stensola (f), Jørgen L. Sugar (m), Ingvild U. Kruge (f).

There are 22 active PhD-candidates at KI/CNC per 31.01.2017.

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 and the Norwegian University of Life Sciences. NRSN aims to add UIT as partner in 2017.

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 .KI/CNC.

The NRSN organize a weeklong summer school each year at various locations in Norway. These are intensive events that combine theoretical and hands-on activities. The sum-

mer school in 2016 was hosted at KI/CNC and was considered a great success with very positive feedback from the participants. One of the summer schools in 2017 will again be hosted by KI/CNC.

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 the 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 for 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 KI/CNC we have had 2 MSRP students defending their PhD theses.

POST-DOCTORAL
Post-doctoral researchers are employed at KI/CNC based on either writing a proposal for projects relevant for 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 within 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 INVESTIGATORS
There are currently seven research groups at KI/CNC 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 have spent time and effort at KI/CNC 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. KI/CNC recruits independently of nationality or origin. Since CNC's inauguration in 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 CNC and its predecessor, the Centre for the Biology of Memory (2002-12), 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.

SELECTED GRANTS

2016-21 NORBRAIN stage 2. Large-scale infrastructure program of the Research Council of Norway (E. Moser)
2016-21 ERC Consolidator Grant (C. Doeller)
2016 Norwegian Research Council "Toppforsk" (C. Kentros)
2015 Egil and Pauline Braathen and Fred Kavli Center for Cortical Microcircuits (E. Moser, M.B. Moser).
2015-19 FRIPRO Young Investigator Grant (E. Yaksi)
2014-19 European Research Council Advanced Investigator Grant (E. Moser)
2014-18 FRIPRO Young Research Talents Grant (J. Whitlock)
2013-22 Centre of Excellence, Appointment by Research Council of Norway (E. Moser, M.B. Moser)
2013-18 ERC Starting Grant (J. Whitlock)
2013-15 European Commission Framework VII Coordinator. (E. Moser)
2013-18 NFR funded Advanced Investigator Grant (M. Witter)
2013-19 ERC Starting Grant (E. Yaksi)
2011-16 NORBRAIN stage I. Large-scale infrastructure program of the Research Council of Norway, Coordinator. (E. Moser)
2011-16 European Research Council Advanced Investigator Grant (M.B. Moser)

SELECTED HONOURS AND AWARDS

CHRISTIAN DOELLER

2016 Radboud Science Award

CLIFFORD KENTROS

2015 Elected Member, Royal Academy of Arts and Letters, Norway

EDVARD MOSER

2016 Elected Foreign member of the Royal Swedish Academy of Sciences
2016 Elected International member of the German National Academy of Sciences Leopoldina
2015 Elected International member of the National Academy of Medicine (USA)
2015 Elected Foreign Member of the Max Planck Society
2015 Elected International Member of the American Philosophical Society (USA)
2014 Nobel Prize in Medicine or Physiology
2014 Elected Foreign Associate of the National Academy of Sciences (USA)
2014 30th Koerber European Science Prize
2014 59th Karl Spencer Lashley Award
2013 47th Louisa Gross Horwitz Prize for Biology or Biochemistry (prize)
2013 102nd annual Fridtjof Nansen Award of Outstanding Research in Science and Medicine
2013 13th Perl/UNC Neuroscience Prize

MAY-BRITT MOSER

2016 Elected Foreign member of the Royal Swedish Academy of Sciences
2016 Elected International member of the German National Academy of Sciences
2015 Elected International Member of the American Philosophical Society (USA)
2015 Elected International member of the National Academy of Medicine (USA)
2014 Nobel Prize in Medicine or Physiology
2014 Elected Foreign Associate of the National Academy of Sciences (USA)
2014 30th Koerber European Science Prize
2014 59th Karl Spencer Lashley Award
2013 47th Louisa Gross Horwitz Prize for Biology or Biochemistry prize
2013 1'Best female leader' award from Trondheim Business Society (Madame Beyer Award)
2013 102nd annual Fridtjof Nansen Award of Outstanding Research in Science and Medicine,
2013 13th Perl/UNC Neuroscience Prize

YASSER ROUDI

2015 Elected Starr Foundation Member, Institute for Advanced Study, Princeton (2015-)
2015 Bright Young Minds, a list of 10 junior scientists selected from across the world by Science News.
2015 Eric Kandel Young Neuroscientist Award
2014 Fridtjof Nansen Young Researcher Award
2013 Young Investigator Award, The Royal Norwegian Society for Sciences and Letters

EMRE YAKSI

2015 Association for Chemoreception Sciences (AChemS) Young investigator award
2014 Elected FENS/Kavli Network of Excellence
2014 Federation of European Neuroscience Young Investigator Prize 2014

Publications

Selected Publications from KI-CNC since its inauguration in 2013

We have chosen to highlight four experimental publication and a joint theoretical paper involving all research groups present at the Centre at the time of writing. All work on these papers is performed at CNC, with CNC funding. All authors are, or have been, members of CNC.

EXPERIMENTAL PAPERS:

1. Stensola T, Stensola H, Moser M-B, Moser EI (2015). Shearing-induced asymmetry in entorhinal grid cells. **Nature**, 518, 207-212 (Article).
   This paper provides fundamental information about how grid patterns interact with geometric reference boundaries of the local environment. We show that the axes of the grid are offset from the walls of the test environment by an angle that minimizes symmetry with the borders of the enclosure. This rotational offset is invariably accompanied by an elliptic distortion of the grid pattern. Reversing the ellipticity analytically by a shearing transformation removed the angular offset, suggesting, together with the near absence of rotation in novel environments, that rotation emerges through non-coaxial strain as a function of experience. The systematic relationship between rotation and distortion points to shear forces arising from anchoring to specific geometric reference axes as a major element of the mechanism for alignment of grid patterns to the external world.

2. Ito HT, Zhang S-J, Witter MP, Moser EI, Moser M-B (2015). A prefrontal-thalamo-hippocampal circuit for goal-directed spatial coding. **Nature**, 522, 50-55 (Article).
   Hippocampal place cells provide accurate information about the animal's current location but it has remained unclear how the place-cell map is used to navigate from the current position to a goal location elsewhere in the environment. This study identifies a prefrontal-thalamic circuit required for hippocampal representation of routes or trajectories through the environment. Trajectory-dependent firing was observed in cells in medial prefrontal cortex, nucleus reuniens of the midline thalamus, and CA1 of the hippocampus. Silencing the nucleus reuniens substantially reduced trajectory-dependent firing in CA1, suggesting that projections from medial prefrontal cortex, via the nucleus reuniens, are crucial for representation of the future path during goal-directed behavior. The findings point to the thalamus as a key node in networks for long-range communication between cortical regions involved in navigation. Like the early work on grid cells, the study also illustrates the power of combining neuroanatomy (Witter group) with multi-site neurophysiological recordings (Moser group).

3. Kropff E, Carmichael JE, Moser M-B, Moser EI (2015). Speed cells in medial entorhinal cortex. **Nature**, 523, 419-424 (Article).
   When animals move, activity is translated between grid cells in accordance with the animal's displacement in the environment. For this translation to occur, grid cells must have continuous access to information about the animal's instantaneous running speed. Until 2015, a powerful speed signal had not been identified, however. The present study reports the discovery of cells that provide this information. We shows that running speed is represented in the firing rate of a ubiquitous but functionally dedicated population of medial entorhinal neurons distinct from other cell populations of the local circuit, such as grid, head direction and border cells. These speed cells are characterized by a context-invariant positive linear response to running speed. The findings point to speed cells as a fundamental component of the dynamic representation of self-location in the medial entorhinal cortex.

4. Donato, F., Jacobsen, R.I., Moser, M.-B., Moser, E.I. (2017). Stellate cells drive maturation of the entorhinal-hippocampal circuit. **Science**, In press (Research Article).
   To determine how the entorhinal-hippocampal space network is set up during early postnatal development, we monitored markers of structural maturation in developing mice, both in naïve animals and after temporally restricted pharmacogenetic silencing of specific cell populations. We found that entorhinal stellate cells provide an activity-dependent instructive signal that drives postnatal maturation sequentially and unidirectionally through the intrinsic circuits of the entorhinal-hippocampal network. The findings raise the possibility that a small number of autonomously developing neuronal populations operate as intrinsic drivers of maturation across widespread regions of cortex. The study is under final revision for Science (third revision) and we expect it to be published in March-April 2017. The findings open an entirely new research field – the development of functional circuits in the non-sensory cortices. Understanding development of these circuits may put us on the track of how cortical circuits are wired in adult brains and how they give rise to neural representations.

THEORETICAL PAPER:

5. Moser EI, Roudi Y, Witter MP, Kentros C, Bonhoeffer T, Moser M-B (2014). Grid cells and cortical representation. **Nature Reviews Neuroscience**, 15, 466-481.
   We have chosen to highlight one theoretical paper resulting from collective discussions among the five group leaders working at CNC at the time of writing (2013-2014), as well as one external member of the Centre. The study uses grid cells to comprehend principles of neural computation in the cortex. We use grid cells as a gateway to understand network computation at a stage of cortical processing in which firing patterns are shaped not primarily by incoming sensory signals but to a large extent by the intrinsic properties of the local circuit. The paper explains how grid pattern may arise out of attractor properties of entorhinal circuits, as well as competitive learning mechanisms in individual cells. Challenges of existing computational models are discussed in depth, and critical avenues for future exploration are identified. The study is a direct outcome of the interactive trans-disciplinary nature of the CNC environment.

For a complete list of publications and output from KI/CNC please visit PubMed at https://www.ncbi.nlm.nih.gov/pubmed/ and search the following names: Moser MB, Moser EI, Witter MP, Kentros CG, Roudi Y, Yaksi E, and Doeller CF. It would also be possible to search in the same database for "Centre for Neural Computation" AND "Kavli".

Annual accounts

INCOME	
Norwegian Research Council: Centre of Excellence	21 000 000
Norwegian Research Council: Other	22 151 000
International Funding	16 223 000
Other Public/Private	4 135 000
Norwegian University of Science and Technology	68 172 000
TOTAL INCOME	131 681 000

EXPENSES	
Payroll and indirect expenses	89 430 000
Equipment	14 607 000
Other operating expenses	27 644 000
TOTAL EXPENSES	131 681 000

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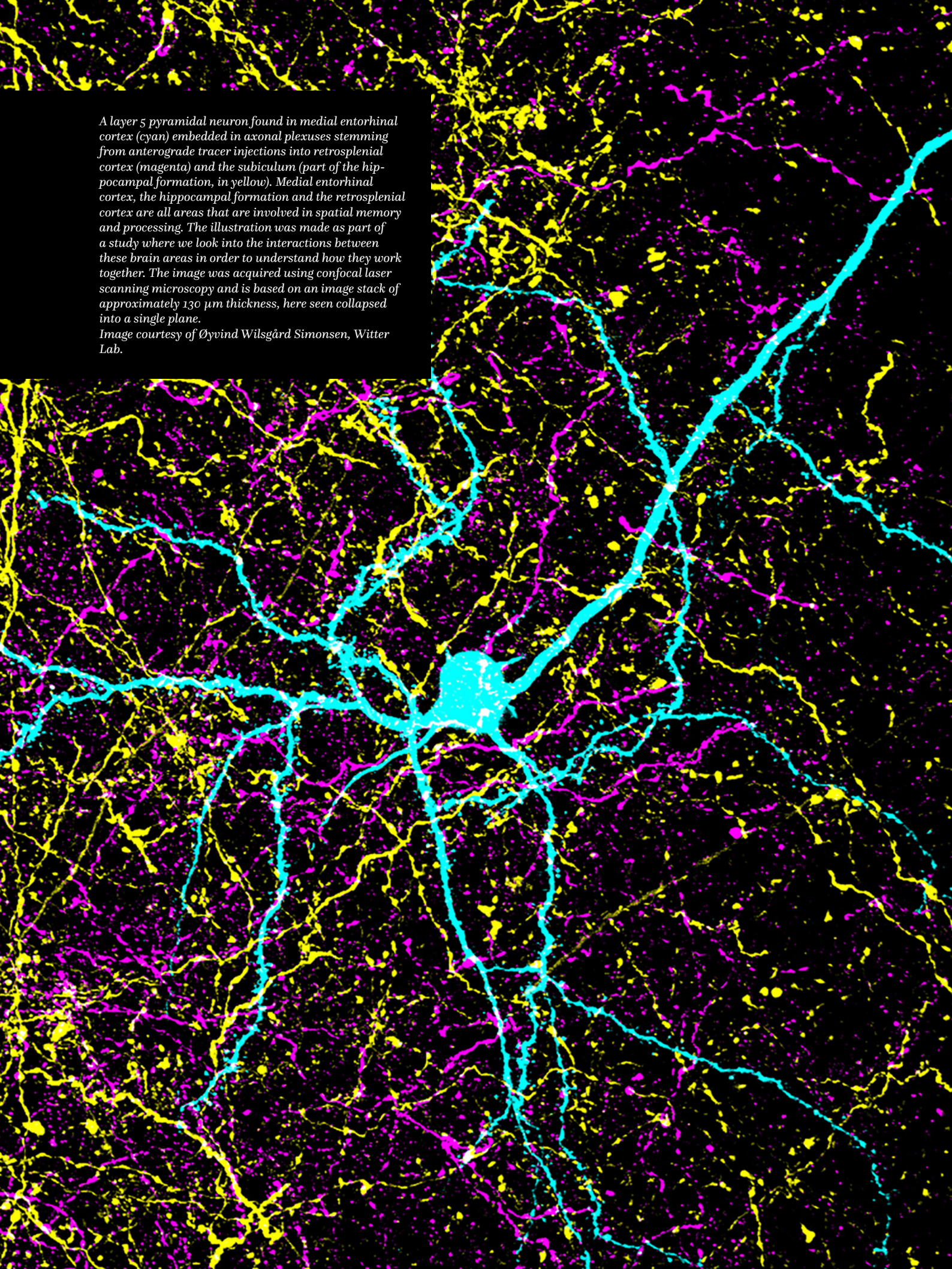

A layer 5 pyramidal neuron found in medial entorhinal cortex (cyan) embedded in axonal plexuses stemming from anterograde tracer injections into retrosplenial cortex (magenta) and the subiculum (part of the hippocampal formation, in yellow). Medial entorhinal cortex, the hippocampal formation and the retrosplenial cortex are all areas that are involved in spatial memory and processing. The illustration was made as part of a study where we look into the interactions between these brain areas in order to understand how they work together. The image was acquired using confocal laser scanning microscopy and is based on an image stack of approximately 130 µm thickness, here seen collapsed into a single plane.
Image courtesy of Øyvind Wilsgård Simonsen, Witter Lab.

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